HbA1c AS A PREDICTOR OF PROGNOSIS FOLLOWING ACUTE CORONARY SYNDROME (ACS) AND ST ELEVATION MYOCARDIAL INFARCTION (STEMI) COMPARED TO FASTING AND ADMISSION GLUCOSE

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ABSTRACT

Background: Glycosylated hemoglobin (HbA1c) is a marker of long-term glycemic control and elevated HbA1c is associated with an increased risk of cardiovascular diseases in patients with diabetes. Moreover, HbA1c is also associated with all-cause mortality and cardiovascular disease even in the absence of diabetes. Both plasma glucose levels and HbA1c were implicated as predictors of prognosis. Methods: This study was conducted as a prospective study, wherein written informed consent was taken prior to the investigation after detailed information given to the participants regarding the study. Non diabetic patients in the age group 22 to 60 years; presenting with Acute Coronary Syndrome or ST Elevation MI was taken for the study. Patients were stratified into four groups based on HbA1c levels as low (<5%), intermediate (5.1-5.6%), high (5.7-6.4%) and diabetic (>6.5%). They were subjected to follow up after one year by a telephone and/or clinical interview; and checking medical records in case of another visit to hospital. Pre-specified clinical endpoints were defined as cardiac death; nonfatal MI; revascularization / rehospitalisation due to attack of ACS. Results: Heart failure, non-fatal MI, repeat PTCA/TLT, attack of ACS, cardiac death, and heart failure plus ACS were respectively seen in 15.9%, 4.5%, 15.9%, 22.7%, 15.9% and 6.8% of patients with HbA1c between 5.7-6.4%. The independent CV outcome of our combined variable outcomes of one year were statistically significant for HbA1c with odd s ratio=4.36 (95% CI of 2.17 – 8.74, p<0.0001). However, neither admission glucose nor FBS were associated with increased risk (p=0.055 and P=0.07 respectively). Conclusion: We concluded that in ACS patients without known diabetes mellitus, long term abnormalities in glucose control assessed by HbA1c is a better predictor of poor CV outcome compared to admission glucose and FBS.


INTRODUCTION

Coronary Artery Disease, a non- communicable disease is the leading cause of death worldwide currently. It tops the list released by World Health Organization (WHO) and kills around 7 million per year.[1] Experts have predicted that the percentage can raise up to 40 around 2020. Though the occurrence is sudden in most of the individuals, the disease progresses silently without any signs and symptoms for decades. Considering this, it is mandatory to dig out all the tools to screen susceptible patients. In rapidly developing countries like India, the percentage of feedlot syndrome is quite high due to life style changes and stress.

Hyperglycemia on admission in patients with acute myocardial infarction (MI) is a negative predictor of short and long term clinical outcomes.[2-3] Hyperglycemia is also associated with poor clinical outcomes among non-diabetic patients and the risk of mortality is higher in hyperglycemic patients without diabetes than those with diabetes.[6-11] Glycosylated hemoglobin (HbA1c) is a marker of long-term glycemic control and elevated HbA1c is associated with an increased risk of cardiovascular diseases in patients with diabetes.[12] Moreover, HbA1c is also associated with all-cause mortality and cardiovascular disease even in the absence of diabetes.[13,14] Both plasma glucose levels and glycosylated hemoglobin (HbA1c) were implicated as predictors of prognosis.[15-16]

Moreover, among the first, there is currently no consensus about the precise glucose value (or range of values) that should be considered abnormal on admission. Second, there is no consensus about the most suitable method to initially measure and subsequently...
monitor blood glucose levels in the acute setting of ACS. Third, the benefits of treating hyperglycemia have not been established definitively, and the target value of blood glucose to be achieved with treatment remains undefined. Although several randomized trials have attempted to study the effects of glucose control with a variety of therapeutic approaches, because of their many limitations, the results have been mixed and at times confusing. Therefore, we evaluated the effect of fasting, admission glucose and HbA1c values on long-term clinical outcomes in non-diabetic patients following acute coronary syndrome (ACS) and ST elevation myocardial infarction (STEMI) compared to fasting and admission glucose.

**AIMS & OBJECTIVES**

**Aims**

HbA1c as a predictor of prognosis following acute coronary syndrome (ACS) and ST elevation myocardial infarction (STEMI) compared to fasting and admission glucose.

**Objectives**

1. To evaluate the significance of HbA1c as a predictor of prognosis following ACS and STEMI
2. To identify whether HbA1c is a better predictor compared to fasting and admission glucose following ACS and STEMI.

**REVIEW OF LITERATURE**

Acute coronary syndrome (ACS) describes the range of myocardial ischemic states that includes unstable angina (UA), non-ST elevated myocardial infarction (NSTEMI), or ST-elevated myocardial infarction (STEMI). The diagnosis and classification of ACS is based on a thorough review of clinical features, including electrocardiogram (ECG) findings and biochemical markers of myocardial necrosis. UA is defined by the presence of ischemic symptoms without elevations in biomarkers and transient, if any, ECG changes. The term myocardial infarction (MI) is used when there is evidence of myocardial necrosis in the setting of acute myocardial ischemia. STEMI is differentiated from NSTEMI by the presence of persistent ECG findings of ST segment elevation.

**Scope of the problem**

Coronary artery disease (CAD) is responsible for more than half of all cardiovascular events in individuals less than 75 years of age. The prevalence of CAD is estimated to be 6.4% in United States (US) adults greater than or equal to 20 years of age, which represents approximately 15.4 million Americans.

During the past several years, the rates of hospitalization for MI and mortality associated with CAD have decreased in developed countries. The decline in CAD mortality is partially reflective of the change in the pattern of clinical presentations of ACS. There has been a substantial reduction in the incidence of STEMI and a subsequent increase in the incidence of NSTEMI. An analysis of 46,086 hospitalizations for ACS in a study conducted by Kaiser Permanente demonstrated that the percentage of STEMI cases decreased from 48.5% to 24% between 1999 and 2008. Despite the improvement in survival associated with ACS, this medical condition continues to have an association with fatal outcomes and places a burden on the entire health care system. A diagnosis of MI was responsible for approximately 125,000 deaths in the US in 2009, and ACS was associated with an estimated 625,000 hospital discharges in 2010. It is evident that there is room for improvement in the prevention and management of ACS.

CAD occurs in Indians 5–10 years earlier than in other populations around the world and the major effect of this peculiar phenomenon is on the productive workforce of the country aged 35–65 years. The prevalence of CAD and the incidence of ACS also are very high among Indians. India has the highest burden of ACS in the world. The rising incidence of ACS in Indians may be related to the changes in the lifestyle, the westernization of the food practices, the increasing prevalence of diabetes mellitus and probably genetic factors.

**Diagnosis**

**Clinical presentation**

A diagnosis of ACS should be considered in all patients presenting with ischemic symptoms. Clinical signs and symptoms of ischemia include various combinations of chest pain, upper extremity, mandibular or epigastric discomfort, dyspnea, diaphoresis, nausea, fatigue, or syncope. The pain and discomfort associated with an ACS event may occur with exertion or at rest and is often diffuse rather than localized. Pain radiating to the left arm, right shoulder, or both arms is more likely to be associated with MI, as is pain associated with diaphoresis. These symptoms are not specific for MI and do not occur in all patients experiencing an ACS event. Atypical symptoms of ACS may occur in certain patient populations such as women, the elderly, diabetics, or postoperatively. In these situations, ACS may be associated with palpitations, cardiac arrest, or with an asymptomatic clinical presentation.

**Past medical history**

Obtaining a thorough past medical history in patients with suspected ACS is essential in assuring appropriate diagnosis and management. Factors that should be evaluated include the nature of a patient’s angina symptoms, prior history of coronary artery disease (CAD), sex, age, and presence of risk factors for ACS.
For patients who do not have these factors, consideration should be given to an alternative disease process.\(^{[18]}\)

### Differential diagnosis

It is important to remember that MI represents myocardial necrosis due to myocardial ischemia. Other clinical conditions, such as pericarditis, dissecting aortic aneurysm, and mitral valve prolapse represent non-ischemic, cardiac causes of myocardial injury and thus do not fall within the definition of ACS. In addition, there are several non-cardiac conditions that may manifest with similar symptoms of ACS, including musculoskeletal pain, esophageal discomfort, pulmonary embolism, or anxiety. It is essential to determine the correct etiology of a patient’s signs and symptoms to determine an appropriate management plan.\(^{[17,18]}\)

### Cardiac biomarkers

Cardiac troponins are biochemical markers of myocardial damage.\(^{[26]}\) Increases in cardiac biomarkers, notably cardiac troponin (I or T), or the MB fraction of creatine kinase (CKMB), signify myocardial injury leading to necrosis of myocardial cells. Elevated cardiac biomarkers in and of themselves do not indicate the underlying mechanism of injury and do not differentiate between ischemic or non-ischemic causes.\(^{[1]}\) There are several clinical conditions that have the potential to result in myocardial injury and cause elevations in cardiac biomarkers, including acute pulmonary embolism, heart failure (HF), end-stage renal disease, and myocarditis.\(^{[23]}\) As a result, cardiac biomarker elevations cannot be utilized in isolation to make a diagnosis of MI.\(^{[17]}\)

The preferred cardiac biomarker is troponin, which has high clinical sensitivity and myocardial tissue specificity. An elevation in troponin concentration is based on specific assays and is defined as a value exceeding the 99th percentile of a normal reference population. At this level, sensitive cardiac troponin I assays have a positive likelihood ratio (LR) of 11–14 and a negative LR of 0.06–0.15.\(^{[26]}\) It is essential to detect a rise and/or fall in cardiac biomarkers to distinguish acute from chronic elevations in troponin concentrations, which may be associated with structural heart disease. Troponin levels should be measured on first assessment, within six hours of the onset of pain, and in the 6–12 hour time frame after onset of pain, due to the delayed increase in circulating levels of cardiac biomarkers (strength of recommendation A). In addition, it is important to understand that elevations in troponin may be seen for up to two weeks after the onset of myocardial necrosis. If troponin concentrations are unavailable, then CKMB should be measured.\(^{[17]}\) Ideally, both troponin and CKMB should be obtained during evaluation for ACS due to the different concentrations of these biomarkers over time and the added diagnostic value of serial testing (strength of recommendation A).\(^{[18,19]}\) For example, serial measurement of CKMB has a positive LR of 20 and negative LR of 0.22.\(^{[23]}\)

### ECG changes

ECG abnormalities that are potentially reflective of myocardial ischemia include changes in the PR segment, the QRS complex, and the ST-segment. A meticulous evaluation of ECG changes can assist in estimating time of the event, amount of myocardium at risk, patient prognosis, and appropriate therapeutic strategies. ST-segment elevation found on an ECG is the hallmark sign of a STEMI.\(^{[17]}\) Similar to cardiac biomarkers, the ECG alone is often insufficient to make the diagnosis of an acute MI, and the sensitivity and specificity of ECG are increased by serial assessments.\(^{[29]}\) ECG changes such as ST deviation may be present in other conditions, such as left ventricular hypertrophy, left bundle branch block, or acute pericarditis.\(^{[17]}\)

ACS is a potentially life-threatening condition that affects millions of individuals each year. Despite declining rates of hospitalization for MI, the identification and prevention of ACS continues to be an important public health concern. Over the past several years, studies have led to an improved understanding of the pathophysiology of ACS and advancements have been made in the medical management of this condition. Initial ACS management should include risk stratification, appropriate pharmacologic management including DAPT, anticoagulation and appropriate adjuvant therapies, and a decision to pursue an early invasive or conventional treatment strategy. Long-term management following an ACS event should follow evidence-based recommendations and should be individualized to each patient.
Suspected diagnosis of UA or NTSEMI based on clinical symptoms, history, cardiac biomarkers, and ECG

Administer aspirin (162-325 mg, non-enteric coated)

Select initial treatment strategy: conservative vs. invasive

Conservative Strategy:
- Initiate a second antiplatelet agent (clopidogrel or ticagrelor) with a loading dose followed by a daily maintenance dose.*
- Initiate anticoagulation with UFH†, or enoxaparin or fondaparinux‡

Invasive Strategy:
- Initiate a second antiplatelet agent (clopidogrel, ticagrelor, prasugrel, with or without an IV GP IIb/IIa inhibitor). A loading dose of a P2Y12 receptor inhibitor is recommended in patients for whom PCI is planned followed by a maintenance dose.*
- Initiate anticoagulation with UFH†, or enoxaparin or fondaparinux‡, or bivalirudin§

Consider need for acute anti-ischemic and analgesic therapies:
- Supplemental oxygen
- Nitroglycerin
- IV morphine sulfate
- Beta blocker
- ACE inhibitor or ARB
- Statin

Consider the following medications for long-term management:
- Aspirin (continue 75-162 mg indefinitely)
- P2Y12 receptor inhibitor (continue for up to 12 months)
- Statin (initiate regardless of LDL or dietary modifications)
- Beta Blocker∥
- ACE inhibitor or ARB∥
- Aldosterone Antagonist∥

*Refer to Table 2 for recommended dosage regimens
† Continue for up to 48 hours, then discontinue
‡ Continue for duration of hospitalization or up to 8 days, then discontinue
§Discontinue bivalirudin or continue at 0.25 mg/kg/hour for up to 72 hours at the physician’s discretion
∥∥ Recommended for select patients if contraindications are not present
UFH: unfractionated heparin; IV: intravenous; GP: glycoprotein; PCI: percutaneous intervention; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker

Figure 1: Pharmacologic management of patients with Unstable Angina (UA)/Non-ST Elevation Myocardial Infarction (NSTEMI).[36]
Relationship between admission glucose level and outcomes in ACS patients with and without preexisting Diabetes Mellitus

Numerous prior studies have established that hyperglycemia on admission is common in patients with ACS and is a risk factor for death and in-hospital complications.\textsuperscript{31-35} Although the exact definition of hyperglycemia has not been established, the prevalence of admission hyperglycemia in prior epidemiological studies ranges from 25% to >50% of patients admitted with ACS.\textsuperscript{31,33,44} In a meta-analysis of 15 relatively small and mostly older studies that evaluated the association between admission glucose level and death, Capes et al.\textsuperscript{33} demonstrated that the relative risk of in-
hospital death in nondiabetic patients with acute myocardial infarction (AMI) with admission glucose more than or equal to 110 mg/dl was 3.9 compared with nondiabetic AMI patients who were normoglycemic. Among AMI patients with diabetes, those with admission glucose more than or equal to 180 mg/dl had a 70% relative increase in the risk of in-hospital death compared with diabetic patients with normal admission glucose values. Similarly, Foo et al.[34] demonstrated a near-linear relationship between higher admission glucose levels and higher rates of left ventricular failure and cardiac death among 2127 patients with ACS. Meier et al.[55] showed higher long-term mortality rates and larger infarct size (measured by creatine kinase MB-fraction levels) among hyperglycemic AMI patients both with and without diabetes. Studies by Wahab et al.[44] and Stranders et al.[50] have also suggested that the admission hyperglycemia associated risk is the highest in AMI patients without previously known diabetes.

The Cooperative Cardiovascular Project, the largest retrospective study of this subject to date, which examined the outcomes of 141680 elderly AMI patients, demonstrated a significant 13% to 77% relative increase in 30-day mortality and a 7% to 46% relative increase in 1-year mortality depending on the degree of hyperglycemia (Figure 3).[33] This higher risk of both short- and long-term mortality persisted after controlling for higher burden of comorbidities (such as prior AMI and heart failure) and greater disease severity (higher Killip class, higher peak creatine kinase and creatinine levels, and lower ejection fraction) observed in patients with elevated glucose levels. Importantly, the glucose-associated risk of increased mortality was not restricted to patients with preexisting diabetes. As can be seen in Figure 4, higher glucose levels were associated with a significantly greater increase in the risk of 30-day mortality in patients who did not have preexisting diabetes. In fact, in patients without known diabetes, the risk of 30-day mortality started to rise once admission glucose exceeded 110 mg/dl, whereas the threshold was higher among diabetic patients.

Figure 3: Mortality by admission glucose level.

Figure 4: Mortality by admission glucose level in patients with and without diabetes.
Data from several randomized clinical trials also confirm a powerful association between higher glucose levels and death in ACS populations. In the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment and Evaluation–Estudios Clinicos Latino America (CREATE-ECLA), which evaluated patients with ST-elevation AMI, the 30-day mortality rate was 6.6% among control group patients with baseline glucose in the lowest tertile, whereas those in the highest glucose tertile experienced a mortality rate of 14%.[56] In the Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study, the 6-month mortality rate was significantly higher among AMI patients with mean 24-hour glucose levels ≥144 mg/dl.[57]

**Relationship between persistent hyperglycemia during hospitalization for ACS and mortality**

Most prior studies have focused predominantly on the prognostic value of admission glucose; however, admission glucose represents only a single measurement in time. Three prior studies suggest that hyperglycemia after hospital admission is more important prognostically than admission hyperglycemia alone. Suleiman and colleagues[58] have demonstrated in a sample of 735 nondiabetic AMI patients that the addition of a fasting glucose level within 24 hours of hospitalization to the admission glucose values improved the ability of the model to predict 30-day mortality rates. Svensson et al.[59] showed that patients whose lowest blood glucose reading during hospitalization for ACS was >120 mg/dl had a 46% increase in relative risk of 30-day mortality compared with patients whose lowest values were between 56 and 119 mg/dl; this relationship was present regardless of admission glucose values. Goyal et al.[60] evaluated the effect of the change between 24-hour and admission glucose levels and death and found that an increase in glucose values during the first 24 hours of hospitalization was associated with higher 30- and 180-day mortality rates, whereas a fall in the glucose level was associated with improved survival; this relationship was present in patients without diabetes but not in those with diabetes. Importantly, this study was not able to differentiate between spontaneous and insulin-mediated decreases in glucose values.

These studies used glucose values that were based on a single measurement after hospital admission and thus were not indicative of overall hyperglycemia throughout the hospitalization. No prior study has used multiple glucose values obtained in a real-world clinical setting to define the prognostic value of persistently elevated glucose during the entire ACS hospitalization.

**Physiological link between elevated glucose and adverse outcomes in patients with ACS: is hyperglycemia a marker of high risk or a mediator of adverse outcomes**

It is important to define the possible underlying pathophysiological mechanisms that might be responsible for the adverse prognostic impact of hyperglycemia in the setting of ACS. Multiple physiological studies demonstrate that hyperglycemia may have a direct detrimental effect on ischemic myocardium through a variety of mechanisms. Kersten and colleagues[59,60] have shown decreased collateral circulation and increased infarct size in the setting of severe hyperglycemia. Studies in animals have shown that acute hyperglycemia abolishes ischemic preconditioning and promotes apoptosis.[61] Hyperglycemia is also associated with elevated systolic and diastolic blood pressures and QT prolongation, changes that were alleviated with hyperglycemia correction.[62] Marfella et al.[63] have reported similar hemodynamic and electrocardiogram changes, as well as elevated catecholamine levels, in healthy human volunteers with artificially induced hyperglycemia (glucose >270 mg/dl).

In diabetic patients, postprandial hyperglycemia is associated with development of myocardial perfusion defects due to microvascular dysfunction, a condition that improves with better glucose control.[64,65] Hyperglycemic patients with ST-elevation AMI have lower rates of spontaneous reperfusion.[66] Microvascular dysfunction was also demonstrated in hyperglycemic patients with AMI undergoing reperfusion. Specifically, Iwakura et al.[67] showed a higher incidence of the no reflow phenomenon by myocardial contrast echocardiography in patients with elevated glucose levels after successful reperfusion. Human studies have also linked elevated glucose levels with endothelial dysfunction, as measured by endothelium-mediated brachial artery vasodilation,[68] in which the level of endothelial dysfunction was correlated with the level of hyperglycemia.

Several studies have shown that hyperglycemia is associated with a prothrombotic state. Acutely hyperglycemic rats exhibit lower tissue plasminogen activator activity and higher plasminogen activator inhibitor levels.[69] Hyperglycemic but not euglycemic clamp conditions in patients with type 2 diabetes mellitus were found to be associated with increased platelet aggregation and higher thromboxane A2 and Von Willebrand factor activity.[69] Acute hyperglycemia induces a shortening of the half-life of fibrinogen and platelet aggregation and results in increased levels of fibrinopeptide A, prothrombin fragments, and factor VII, all phenomena that suggest increased activation of prothrombotic factors.[70,71]

Higher glucose levels have also been shown to be associated with increased markers of vascular inflammation. Both in vitro and in vivo studies have linked hyperglycemia with elevated levels of C-reactive protein, interleukin-6, and tumor necrosis factor-α.[75,76] Tumor necrosis factor-α has been shown to extend infarct size in laboratory animals and to induce myocardocyte apoptosis.[77,78] In vitro and in vivo studies
also demonstrated induction of the proinflammatory transcription factor nuclear factor-κB in a setting of elevated glucose. Glucose ingestion in healthy human volunteers is also associated with increased production of other proinflammatory factors, such as activator protein 1 and early growth response 1, and increased expression of the genes regulated by them, including the genes for matrix metalloproteinases-2 (MMP-2) and 9 (MMP-9) and tissue factor (TF). Hyperglycemia has also been shown to be associated with increased generation of reactive oxygen species, which can induce tissue injury. Interestingly, recent data from human studies suggest that acute fluctuations in glucose levels may have an even more powerful impact on oxidative stress than chronic, sustained hyperglycemia.

Higher glucose levels in patients with ACS have also been associated with higher free fatty acid concentrations, insulin resistance, and impaired myocardial glucose utilization, thus increasing the consumption of oxygen and potentially worsening ischemia. Higher free fatty acid concentrations have been linked to increased incidence of malignant ventricular arrhythmias. Finally, hyperglycemia has been linked to an impaired immune response. Figure 5 summarizes the detrimental effects of glucose on cardiovascular and other organ systems.

![Figure 5: Detrimental physiological impact of hyperglycemia. Modified from Clement et al. FFA indicates free fatty acids; tPA, tissue plasminogen activator; and PAI, plasminogen activator inhibitor.](image)

Given the multiple detrimental effects of elevated levels of glucose on the cardiovascular system, it is possible that poor glucose control during hospitalization may have a direct effect on outcomes in patients hospitalized with ACS. As demonstrated by several investigators, insulin-mediated normoglycemia may attenuate some of the detrimental effects of elevated glucose; specifically, it may have anti-inflammatory effects (such as reducing C-reactive protein levels) in both AMI and post-coronary artery bypass grafting patients. Insulin may also inhibit generation of reactive oxygen species, may have profibrinolytic and antiapoptotic effects, and may improve myocardial blood flow. Whether the possible beneficial effects of glucose control in the setting of ACS could be attributed primarily to glucose normalization, insulin administration, or both remains debatable; however, the preponderance of evidence suggests that insulin therapy alone, without achievement of normoglycemia, does not improve outcomes. Whether insulin-mediated normoglycemia will improve survival and reduce complications in patients with ACS remains to be established.
The differential impact of hyperglycemia on outcomes in patients with and without known diabetes has been a consistent finding by several investigators. Specifically, elevated glucose appears to be a much stronger predictor of adverse events in patients without previously recognized diabetes than in those with established diabetes. Although the specific pathophysiological mechanisms behind this phenomenon are not well understood, several potential explanations exist. Some hyperglycemic patients without known diabetes (particularly those with severe hyperglycemia) likely have diabetes that was neither appropriately recognized nor treated before hospitalization; these patients may, therefore, represent a higher-risk cohort. Furthermore, hyperglycemic AMI patients without known diabetes are much less likely to be treated with insulin than those with diabetes, even when glucose levels are markedly elevated. Given the possible beneficial effects of insulin in a setting of myocardial ischemia, this therapeutic difference may account in part for the disparity in outcomes. Finally, it is also possible that a higher degree of stress (or severity of illness) is required to produce a similar degree of hyperglycemia in patients without known diabetes than in those with diabetes. A better understanding of this important interaction between hyperglycemia, the presence of diabetes, and adverse outcomes is needed and should be the subject of further research.

**Metrics of glucose control during hospitalization and their prognostic association with outcomes in ACS**

Although hemoglobin A1c (HbA1c) is a useful tool in assessing average glucose control in the outpatient setting, it has limited prognostic value in predicting inhospital and short-term mortality rates in ACS patients.\(^{[49,97]}\) In the inpatient setting, where the duration of care is relatively brief, there is no single laboratory test (such as HbA1c) that can accurately assess the degree of glucose control during the entire hospitalization or part of the hospitalization. Instead, multiple glucose results must be analyzed; these results may be obtained either from plasma samples or from capillary blood (“finger sticks”) and represent a variety of fasting and nutritional conditions. The development of a summary measure of average glucose control from multiple inpatient glucose measurements is likely to be of critical importance if the nature of the relationship between glucose control and death in ACS is to be determined accurately. Several candidates for this measurement exist, such as mean glucose level,\(^{[98,99]}\) time-averaged glucose level, hyperglycemia index,\(^{[100]}\) and patient-day glucose level.\(^{[101]}\) No prior studies have systematically evaluated the prognostic association of these metrics with outcomes in ACS.

Another dimension of measuring glucose in the inpatient setting deserves brief mention. Some prior epidemiological studies and randomized clinical trials have used plasma glucose, whereas others used whole-blood glucose measurements. These are not identical; in fact, plasma glucose is around 10% higher than whole-blood glucose. Care should be taken to account for this difference when the results of prior studies are interpreted and applied in clinical care.

New technologies, such as continuous glucose monitors, are currently emerging that may simplify the task of multiple glucose measurements in the inpatient setting; however, there are currently no data on the use of these technologies in patients hospitalized with ACS. Whether these devices will have a role in future management of hyperglycemic ACS is therefore unclear.

**Relationship between intensive insulin therapy, glucose control, and outcomes in hyperglycemic patients with ACS and in other critically ill patient populations**

Prior randomized clinical trials of glucose control in ACS have been limited primarily to patients with known diabetes, and their results have been inconsistent (Table 1). The 2 most relevant studies for glycemic control in ACS patients are the DIGAMI (Diabetes mellitus, Insulin Glucose infusion in Acute Myocardial Infarction) studies. The original DIGAMI study from 1995 studied the effects of intensive in-hospital insulin treatment (insulin-glucose infusion for at least 24 hours followed by multi-dose subcutaneous insulin regimen) versus usual care in 620 AMI patients with established diabetes and/or admission glucose of >11 mmol/L (200 mg/dl).\(^{[102]}\) Better glucose control was achieved in the arm receiving more intensive insulin therapy (mean 24-hour posttreatment glucose of 173 mg/dl versus 210 mg/dl in the control group). A significant mortality benefit was seen in the intervention arm at both the 1 and 3.4 year follow-up points.\(^{[103]}\) The original DIGAMI study was the only randomized trial of glucose control in AMI to date to have achieved a significantly lower glucose level in the intervention arm compared with the control arm; it also happens to be the only randomized trial to have demonstrated a survival benefit associated with better glucose control.
Table 1: Summary of clinical trials in ACS patients with hyperglycemia.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size, n</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Glucose Targets</th>
<th>Glucose Contrast Between Groups</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td>DIGAMI</td>
<td>620</td>
<td>AMI with either diabetes or admission glucose &gt;200 mg/dl</td>
<td>Glucose-insulin infusion for at least 24 h, then multi-dose subcutaneous insulin for &gt;3 months vs conventional care</td>
<td>126–196 mg/dl</td>
<td>Mean 24-h glucose was significantly lower in the intervention arm than in the control arm (173 vs 210 mg/dl, respectively)</td>
<td>19% Mortality in intervention arm vs 26% in control arm (P&gt;0.011) at 1 year</td>
</tr>
<tr>
<td>DIGAMI-2</td>
<td>1253</td>
<td>AMI with either diabetes or admission glucose &gt;200 mg/dl</td>
<td>Group 1: Glucose-insulin infusion for at least 24 h, then multi-dose subcutaneous insulin for &gt;3 months Group 2: Glucose-insulin infusion for at least 24 h, then conventional care. Group 3: Conventional care.</td>
<td>126–180 mg/dl</td>
<td>Overall, no significant difference in glucose control between the 3 groups. Long-term fasting glucose target was not achieved in group 1.</td>
<td>No difference in mortality at 2 years between the 3 groups</td>
</tr>
<tr>
<td>HI-5</td>
<td>244</td>
<td>AMI with either diabetes or admission glucose &gt;140 mg/dl</td>
<td>Dextrose-insulin infusion for at least 24 h vs conventional Care</td>
<td>72–180 mg/dl</td>
<td>No significant difference in mean 24-h glucose between groups</td>
<td>No difference in mortality (in-hospital, 3 and 6 months) between intervention and control groups. Intervention group had lower rate of post-MI heart failure (12.7% vs 22.8%, P&gt;0.04) and reinfarction (2.4% vs 6.1%, P&gt;0.05)</td>
</tr>
<tr>
<td>CREATE-ECLA</td>
<td>20201</td>
<td>STEMI; no requirement for diabetes or hyperglycemia on admission</td>
<td>GIK infusion for 24 h vs conventional care</td>
<td>None</td>
<td>Mean 24-h glucose 155 mg/dl in GIK group vs 135 mg/dl in control group</td>
<td>No difference in 30day mortality between intervention and control arms</td>
</tr>
</tbody>
</table>
The DIGAMI-2 trial attempted to study 3 alternative treatment regimens: acute insulin-glucose infusion followed by insulin-based long-term glucose control; insulin-glucose infusion followed by standard glucose control on discharge; and routine metabolic management in both inpatient and outpatient settings. Although there were no differences in outcomes among the 1253 randomized AMI patients, this may be attributable to the similar short-term glucose control and identical longer-term glucose control obtained among the 3 groups. Most importantly, the longer-term fasting glucose target of 90 to 126 mg/dl was never achieved in the intensive-treatment group. Thus, despite its intent, DIGAMI-2 ended up comparing different insulin-treatment strategies, not different intensities of glucose control. Furthermore, like the original DIGAMI trial, DIGAMI-2 did not include any hyperglycemic patients without previously known diabetes, the group with the highest risk of glucose-associated death.

The HI-5 study attempted to rectify some of the issues that were encountered in DIGAMI-2. It was the first randomized clinical trial of intensive insulin infusion that included hyperglycemic AMI patients without previously established diabetes. Patients assigned to the intensive insulin-infusion arm received standard insulin and dextrose infusion that was then adjusted to maintain glucose levels between 72 and 180 mg/dl. Patients in the conventional arm received their baseline diabetes medications (including subcutaneous insulin); additional short-acting subcutaneous insulin was permitted for those with a glucose level >288 mg/dl. There were only 244 patients randomized in the study. There was no difference in mortality rates among the groups during hospitalization or at 3 or 6 months. There were, however, statistically and clinically significant reductions in post–myocardial infarction heart failure during hospitalization (10% absolute risk reduction) and in reinfarction at 3 months (3.7% absolute risk reduction).

There are several very important issues that need to be considered in the interpretation of this study. First and most importantly, the HI-5 study suffered from the same issues that complicated the DIGAMI-2 trial. Specifically, the mean 24-hour glucose values were similar in the intensive-treatment arm (141 mg/dl) and the conservative-treatment arm (153 mg/dl). Thus, as with the DIGAMI-2 study, the HI-5 investigators ended up comparing 2 different insulin strategies but not 2 different intensities of glucose control. In addition, no provisions for tight glucose control were made after the initial 24 hours of hospitalization, and the study never recruited the intended number of patients (244 patients recruited instead of the 850 patients planned for on the basis of the power calculations). CREATE-ECLA, a multinational, randomized clinical trial, compared the impact of glucose-insulin-potassium (GIK) infusion and placebo on mortality in 20,201 AMI patients. From the outset, CREATE-ECLA was not designed to be a study of intensive glucose control in AMI. There was no requirement for admission hyperglycemia for study entry, and patients with both normal and elevated glucose levels on admission were included. Unlike DIGAMI-1 and 2, glucose control was not the primary intervention target. There were also no prespecified targets for glucose control with GIK infusion, and in fact, posttreatment glucose levels (24 hours after randomization) were higher in the GIK group (155 mg/dl) than in controls (135 mg/dl). There were no differences in rates of 30-day mortality, cardiac arrest, cardiogenic shock, or reinfarction between the GIK and placebo groups. However, studies in other critically ill patient populations show that successful strict glucose control, regardless of diabetes status, may result in better outcomes. Specifically, a landmark study by van den Berghe and colleagues has demonstrated that target-driven glucose control with intensive insulin therapy (goal of whole-blood glucose level of 80 to 110 mg/dl) reduced intensive care unit (ICU) mortality rates from 8.0% to 4.6% in surgical patients and in-hospital mortality rates from 10.9% to 7.2%. This improvement was entirely attributable to the decrease in the mortality rate seen in patients who remained in the ICU for >5 days. The relative risks of ICU complications, such as renal failure, sepsis, and transfusion requirements, were also markedly reduced by 41% to 50%. Importantly, the benefit was achieved with few adverse events (such as hypoglycemia). The findings from this study clearly suggest that control of hyperglycemia may be more critical than the dose of insulin administered. In a recent follow-up study by the same group, which involved medical ICU patients, intensive glucose control reduced morbidity but not mortality in the intention-to-treat analysis; however, the mortality rate was lower in the intervention arm among those patients who required ICU care for ≥3 days. Analysis of pooled data from both surgical and medical ICU studies by van den Berghe and colleagues demonstrated that intensive glucose control in the intention-to-treat analysis was associated with significant reductions in mortality (24% relative risk reduction) and morbidity (42% relative risk reduction in kidney injury); patients who achieved mean whole-blood glucose levels <110 mg/dl had the lowest mortality and complication rates but also had the highest rate of hypoglycemia (10.7%). The mortality and morbidity benefit of intensive glucose control, once again, was not seen in the subgroup of patients who stayed in the ICU <3 days. Interestingly, the benefit of intensive glucose control was also not observed among patients with established diabetes, which again suggests that the relationship between glucose control and outcomes may be very different in patients with and without preexisting diabetes.

Because of significant differences in patient populations, the results of these studies by van den Berghe et al. cannot simply be extrapolated to patients with ACS, particularly because many patients with ACS have ICU stays shorter than 3 days. Whether strict glucose control in hyperglycemic patients with ACS will result in similar
reductions in mortality and in-hospital complications remains to be established and needs to be investigated in well-designed randomized clinical trials.

Current patterns of glucose management during ACS hospitalisation
A paucity of data exists regarding current patterns of glucose management across hospitals. Prior studies have shown that even among patients with severe hyperglycemia on admission (glucose >240 mg/dl), 78% of patients without known diabetes and 27% of patients with diabetes do not receive any insulin. However, an important limitation of these prior studies was their inability to determine how many patients with elevated glucose on admission also had persistent hyperglycemia during hospitalization. It is possible that some AMI patients were not treated with insulin because their hyperglycemia resolved. Because of this limitation, it is still unknown how many patients with persistent hyperglycemia during hospitalization receive insulin therapy and how many receive intensive therapy. Addressing these knowledge gaps would help determine whether significant variations in regard to glucose control exist among hospitals and whether these variations are associated with different outcomes in patients hospitalized with ACS.

Prognostic value of hypoglycemia
Another important aspect of glucose control in ACS that deserves mention is the adverse impact of hypoglycemia on outcomes in patients with ACS. Most of the existing data on this issue come from prior epidemiological studies. Specifically, in the study by Svensson et al., a single blood glucose measurement of less than 54 mg/dl during hospitalization was associated with a 93% increase in relative risk of long-term mortality. Other studies also demonstrated that hypoglycemia on admission is associated with increased risk of death or MI at 30 days. Whether this adverse prognostic impact extends to all hypoglycemic events versus only symptomatic/clinically important hypoglycemic episodes is not currently known.

Recommendations
Until the above-mentioned knowledge gaps have been addressed appropriately, specific, evidence-based recommendations will be difficult to make with regard to the diagnosis and management of hyperglycemia during ACS hospitalization. The following set of recommendations should therefore be viewed by clinicians only as a general reference. There is currently insufficient evidence to consider glucose control as a quality measure during ACS hospitalization, although this position may change in the future.

1. Glucose level should be a part of the initial laboratory evaluation in all patients with suspected or confirmed ACS. (Level of Evidence A)
2. In patients admitted to an ICU with ACS, glucose levels should be monitored closely (Level of Evidence B). It is reasonable to consider intensive glucose control in patients with significant hyperglycemia (plasma glucose >180 mg/dl), regardless of prior diabetes history (Level of Evidence B). Although efforts to optimize glucose control may also be considered in patients with milder degrees of hyperglycemia (Level of Evidence C), the data regarding a benefit from this approach are not yet definitive, and future randomized clinical trials in ACS populations will be needed to determine whether it improves patient outcomes. The precise goal of treatment has not yet been defined. Until further data are available, approximation of normoglycemia appears to be a reasonable goal (suggested range for plasma glucose 90 to 140 mg/dl), as long as hypoglycemia is avoided. (Level of Evidence C)
3. Insulin, administered as an intravenous infusion, is currently the most effective method of controlling glucose among patients hospitalized in the ICU. Effective protocols for insulin infusion and glucose monitoring have been developed in other patient populations. Care should be taken to avoid hypoglycemia, which has been shown to have an adverse prognostic impact. (Level of Evidence B)
4. Treatment should be instituted as soon as feasible, without compromising the administration of life-saving and evidence-based treatments. (Level of Evidence C)
5. In patients hospitalized in the non-ICU setting, efforts should be directed at maintaining plasma glucose levels less than 180 mg/dl with subcutaneous insulin regimens. (Level of Evidence C)
6. ACS patients with hyperglycemia but without prior history of diabetes should have further evaluation (preferably before hospital discharge) to determine the severity of their metabolic derangements. This evaluation may include fasting glucose and HbA1C assessment and, in some cases, a post discharge oral glucose tolerance test. (Level of Evidence B)
7. Before discharge, plans for optimal outpatient glucose control should be determined in those patients with established diabetes, newly diagnosed diabetes, or evidence of insulin resistance. (Level of Evidence C)

Future directions and areas of further study
The benefit of insulin infusion in patients with hyperglycemia in ACS has yet to be demonstrated convincingly in a large prospective clinical trial. While there is significant evidence that admission and postadmission hyperglycemia is associated with increased mortality and morbidity in AMI, there is no consensus regarding the targets and the benefits of treating hyperglycemia in this setting. This is illustrated by the 2009 ACC/AHA focused update on STEMI, which makes a rather weak recommendation for the use of an insulin-based regimen to achieve and maintain blood glucose levels below 180 mg/dl (10 mmol/L),
consistent with the 2007 update by Antman and colleagues (level of evidence B).\textsuperscript{111,112} It should be noted this recommendation does not discriminate based on prior diabetes history. Similarly, Kosiborod and colleagues, who performed an extensive review on the topic of hyperglycemia and AMI, have recommended glucose treatment targets within the “conservative range” of 140–180 mg/dl\textsuperscript{113} This falls within the range demonstrated to be beneficial by Lazerri and colleagues, who in 2010 demonstrated in 252 nondiabetic STEMI patients undergoing mechanical revascularization, that peak glycaemia more than 180 mg/dl was associated with the elevated mortality, whereas patients with peak glycaemia comprised between 140 and 180 mg/dl exhibited attenuated mortality rates.\textsuperscript{114} If the lowering of glucose levels with insulin infusion can demonstrate a reduction in adverse cardiac outcomes over and above the benefits provided by reperfusion therapy, it would be a significant improvement in the management of ACS in the reperfusion era. Indeed, this was reflected in a 2008 AHA statement on hyperglycemia in ACS, where the guidelines emphasized the need for a large prospective randomized study examining this issue. Specifically, it recommends randomized multicenter trials which should include hyperglycemic patients both with and without preexisting diabetes (suggested definition is plasma glucose >140 mg/dl at admission), should use safe and effective protocols for glucose control, and should afford sufficient statistical power to assess mortality as a primary outcome.\textsuperscript{115}

**MATERIAL AND METHODS**

This study was conducted in compliance with the protocol; The Institutional Ethics Committee (IEC) clearance was taken. ICH/ GCP guidelines were followed. The present prospective study involved a group of 112 patients presented with Acute Coronary Syndrome or ST Elevation MI. This study was conducted in Department of Medicine with collaboration of Department of Cardiology and Department of Emergency medicine of AJ institute of Medical Sciences, Mangalore.

**Method of collection of data** (including sampling procedure, if any)

This study was conducted as a prospective study, wherein written informed consent was taken prior to the investigation after detailed information given to the participants regarding the study. Non diabetic patients in the age group 22 to 60 years; presenting with Acute Coronary Syndrome or ST Elevation MI was taken for the study. Patients were subjected to follow up after one year by a telephone and/or clinical interview; and checking medical records in case of another visit to hospital. Pre-specified clinical endpoints were defined as cardiac death; nonfatal MI; revascularization / rehospitalisation due to attack of ACS.

**Sample and sampling technique**

- Study design: prospective study.
- Set-up: AJ Institute of Medical Sciences.
- Study Period: September 2014 to September 2015
- Age group: between 22years and 60yrs
- Sample size: All patients(meeting the inclusion criteria) who present to the hospital during the study period

**Study type:** 1 year, single centre, prospective study.

**Inclusion criteria**

- Age:22 to 60 years
- Patients presenting with ACS(Unstable Angina/Non STEMI) or STEMI
  (Presence of typical angina or positive or equivocal results of noninvasive screening tests for myocardial ischemia)

**Exclusion criteria**

- Subjects diagnosed with diabetes mellitus; on oral hypoglycemic agents or on insulin therapy
- Subjects with h/o previous PTC/STUG ; acute MI ; on cardiac medications ; past h/o stroke
- Subjects with severe renal or hepatic insufficienty
- Subjects with stable angina
- Subjects with haematological disorders ; infectious or inflammatory disease

This study requires the following investigations.

- Blood investigations(baseline)
  - Hb, TC, RFT, LFT, Fasting Lipid Profile
  - FBS , RBS , HbA1c
- Cardiac enzymes- CKMB/Troponin I

**STATISTICAL ANALYSIS**

Data will be entered in Microsoft Excel Sheet and the statistical analysis will be carried out with IBM SPSS Version-20(Chicago, IL, USA). Categorical data will be presented as actual numbers and percentages. Categorical variables will be analysed with Chi square test. Continuous variables are presented as Mean (SD). For normally distributed continuous data, between groups analyses was done by one way ANOVA.

To evaluate the multivariate significance of HbA1c, admission FBS and RBS, the binary logistic regression analysis was chosen, where the dependent dichotomous variable was status defined as cardiovascular death or rehospitalisation due to another ACS / heart failure or non-fatal MI. Forward method of variable inclusion was used. For statistical significance, a two tailed probability value of less than 0.05 will be considered.

**RESULTS**

A total of 112 patients satisfying the inclusion criteria were enrolled during the study period. The analysis of data is as follows.
Table 1: Distribution of patients based on HbA1c.

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>&lt;5 % (n=25)</th>
<th>5.1 - 5.6% (n=39)</th>
<th>5.7-6.4% (n=44)</th>
<th>&gt;6.5 % (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>25(22.3%)</td>
<td>39(34.8%)</td>
<td>44(39.3%)</td>
<td>4(3.6%)</td>
</tr>
</tbody>
</table>

HbA1c < 5% was seen in 22.3% of the patients, between 5.1-5.6% in 34.8%, between 5.7-6.4% in 39.3%, and >6.5% in 3.6% of patients.

Table 2: Mean age(years) of patients among groups.

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>&lt;5 % (n=25)</th>
<th>5.1 - 5.6% (n=39)</th>
<th>5.7-6.4% (n=44)</th>
<th>&gt;6.5 % (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>53.9</td>
<td>52.4</td>
<td>54.9</td>
<td>53.4</td>
</tr>
<tr>
<td>SD</td>
<td>9.1</td>
<td>7.3</td>
<td>6.1</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Mean age (years) of the patient was 53.9(9.1) in HbA1c <5%, 52.4(7.3) in HbA1c between 5.1-5.6%, 54.9(6.1) in HbA1c between 5.7-6.4%, and 53.4(7.2) in HbA1c >6.5%.

Figure 1: Distribution of patients based on HbA1c.

Figure 2: Mean age(years) of patients among groups.
Table 3: Gender of patients among groups.

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 %</td>
<td></td>
</tr>
<tr>
<td>5.1 - 5.6%</td>
<td></td>
</tr>
<tr>
<td>&gt;6.5 %</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>N %</th>
<th>N</th>
<th>N %</th>
<th>N</th>
<th>N %</th>
<th>N</th>
<th>N %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>&lt;5 %</td>
<td>21</td>
<td>84.0</td>
<td>4</td>
<td>16.0</td>
<td>35</td>
<td>89.7</td>
<td>39</td>
</tr>
<tr>
<td>5.1 - 5.6%</td>
<td>35</td>
<td>89.7</td>
<td>4</td>
<td>16.0</td>
<td>39</td>
<td>88.6</td>
<td>5</td>
</tr>
<tr>
<td>&gt;6.5%</td>
<td>3</td>
<td>75.0</td>
<td>1</td>
<td>25.0</td>
<td>1</td>
<td>25.0</td>
<td>1</td>
</tr>
</tbody>
</table>

Males were 84% and females were 16% in HbA1c <5% group. Males were 89.7% and females were 10.3% in HbA1c 5.1-5.6% group. Males were 88.6% and females were 11.4% in HbA1c 5.7-6.4% group. Males were 75% and females were 25% in HbA1c >6.5% group.

Table 4: Diagnosis of ACS among groups.

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>&lt;5 % (n=25)</th>
<th>5.1 - 5.6% (n=39)</th>
<th>5.7-6.4% (n=44)</th>
<th>&gt;6.5% (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>N</td>
<td>N %</td>
<td>N</td>
<td>N %</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>10</td>
<td>40.0</td>
<td>16</td>
<td>41.0</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>2</td>
<td>8.0</td>
<td>2</td>
<td>5.1</td>
</tr>
<tr>
<td>STEMI</td>
<td>13</td>
<td>52.0</td>
<td>21</td>
<td>53.8</td>
</tr>
</tbody>
</table>

UA, NSTEMI, and STEMI was seen in 40%, 8%, and 52% of patients with HbA1c <5% respectively. UA, NSTEMI, and STEMI was seen in 41%, 5.1%, and 53.8% of patients with HbA1c 5.1-5.6% respectively.
Table 5: History of hypertension among groups.

<table>
<thead>
<tr>
<th>H/O of HTN</th>
<th>&lt;5 % (n=25)</th>
<th>5.1 - 5.6% (n=39)</th>
<th>5.7-6.4% (n=44)</th>
<th>&gt;6.5 % (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N %</td>
<td>N</td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>H/O of HTN</td>
<td>10</td>
<td>40.0</td>
<td>12</td>
<td>30.8</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>43.2</td>
<td>50.0</td>
<td>0.65</td>
</tr>
</tbody>
</table>

History of hypertension was seen in 40% of patients with HbA1c <5%, 30.8% of patients with HbA1c 5.1 – 5.6%, 43.2% of patients with HbA1c 5.7-6.4% and 50% of patients with HbA1c >6.5%.

Figure 5: History of hypertension among groups.

Table 5: Prevalence of risk factors among groups.

<table>
<thead>
<tr>
<th></th>
<th>HbA1c</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;5 % (n=25)</td>
<td>5.1 - 5.6% (n=39)</td>
</tr>
<tr>
<td>Sedentary Lifestyle</td>
<td>N</td>
<td>N %</td>
</tr>
<tr>
<td>Smoking</td>
<td>15</td>
<td>60.0</td>
</tr>
<tr>
<td>Alcohol</td>
<td>5</td>
<td>20.0</td>
</tr>
</tbody>
</table>

Sedentary lifestyle was seen in 60% of patients with HbA1c <5%, 59% of patients with HbA1c 5.1 – 5.6%, 63.6% of patients with HbA1c 5.7-6.4% and 75% of patients with HbA1c >6.5%. Distribution of sedentary lifestyle was not statistically significant.

40% of patients with HbA1c <5% were smokers, 41% of patients with HbA1c 5.1 – 5.6%, 27.3% of patients with HbA1c 5.7-6.4% and 25% of patients with HbA1c >6.5% were smokers.

20% of patients with HbA1c <5%, 25.6% of patients with HbA1c 5.1 – 5.6%, and 31.8% of patients with HbA1c 5.7-6.4% had history of alcoholism.

Sedentary lifestyle, history of smoking and alcoholism were equal among groups.

Figure 5: Lifestyle among groups.
Table 6: Distribution of BMI (kg/m²) among groups.

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>HbA1c &lt;5% (n=25)</th>
<th>5.1 - 5.6% (n=39)</th>
<th>5.7-6.4% (n=44)</th>
<th>&gt;6.5% (n=4)</th>
<th>N</th>
<th>N %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>0</td>
<td>0.0%</td>
<td>1</td>
<td>2.6%</td>
<td>2</td>
<td>4.5%</td>
</tr>
<tr>
<td>Normal</td>
<td>21</td>
<td>84.0%</td>
<td>32</td>
<td>82.1%</td>
<td>35</td>
<td>79.5%</td>
</tr>
<tr>
<td>Overweight</td>
<td>3</td>
<td>12.0%</td>
<td>6</td>
<td>15.4%</td>
<td>7</td>
<td>15.9%</td>
</tr>
<tr>
<td>Obese Class I</td>
<td>1</td>
<td>4.0%</td>
<td>0</td>
<td>0.0%</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

2.6% of patients with HbA1c 5.1 – 5.6%, and 4.5% of patients with HbA1c 5.7-6.4% were underweight.

Normal BMI was seen in 84% of patients with HbA1c <5%, 82.1% of patients with HbA1c 5.1 – 5.6%, 79.5% of patients with HbA1c 5.7-6.4% and 50% of patients with HbA1c >6.5%.

12% of patients with HbA1c <5%, 15.4% of patients with HbA1c 5.1 – 5.6%, 15.9% of patients with HbA1c 5.7-6.4% and 50% of patients with HbA1c >6.5% were overweight.

4% of patients with HbA1c <5% were obese.

Dyslipidemia was seen in 16% of patients with HbA1c <5%, 12.8% of patients with HbA1c 5.1 – 5.6%, 31.8% of patients with HbA1c 5.7-6.4% and 25% of patients with HbA1c >6.5%. Distribution of dyslipidemia was not statistically significant.

Figure 6: Distribution of BMI (kg/m²) among groups.

Figure 7: Distribution of dyslipidemia among groups.
Table 8: Family history of IHD among groups.

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 % (n=25)</td>
<td>5.1 - 5.6% (n=39)</td>
</tr>
<tr>
<td>N</td>
<td>N%</td>
</tr>
<tr>
<td>H/O of IHD</td>
<td>5</td>
</tr>
</tbody>
</table>

Family history of IHD was seen in 20% of patients with HbA1c <5%, 12.8% of patients with HbA1c 5.1 – 5.6%, 6.8% of patients with HbA1c 5.7-6.4% and 25% of patients with HbA1c >6.5%.

![Figure 8: Family history of IHD among groups.](image)

Table 9: Distribution of ECHO-RWMA among groups.

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 % (n=25)</td>
<td>5.1 - 5.6% (n=39)</td>
</tr>
<tr>
<td>N</td>
<td>N%</td>
</tr>
<tr>
<td>ECHO-RWMA</td>
<td>15</td>
</tr>
</tbody>
</table>

RWMA in ECHO was seen in 60% of patients with HbA1c <5%, 59.0% of patients with HbA1c 5.1 – 5.6%, 77.3% of patients with HbA1c 5.7-6.4% and 50% of patients with HbA1c >6.5%.

![Figure 9: Distribution of ECHO-RWMA among groups.](image)

Table 10: Distribution of mean ejection fraction (EF %) among groups.

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 % (n=25)</td>
<td>5.1 - 5.6% (n=39)</td>
</tr>
<tr>
<td>EF %</td>
<td>Mean</td>
</tr>
<tr>
<td>53.3</td>
<td>7.2</td>
</tr>
</tbody>
</table>
Mean baseline EF (%) was 53.3(7.2) in HbA1c <5%, 49.5(10.4) in HbA1c between 5.1-5.6%, 49.6(10.6) in HbA1c between 5.7-6.4%, and 50.4(14.1) in HbA1c >6.5%. EF did not vary significantly among groups.

Figure 10: Distribution of mean ejection fraction (EF%) among groups.

Table 11: Distribution of SVD, DVD and TVD among groups.

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>&lt;5 % (n=25)</th>
<th>5.1 - 5.6% (n=39)</th>
<th>5.7-6.4% (n=44)</th>
<th>&gt;6.5 % (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N %</td>
<td>N</td>
<td>N %</td>
<td>N</td>
</tr>
<tr>
<td>CAG</td>
<td>19</td>
<td>76.0</td>
<td>23</td>
<td>59.0</td>
</tr>
<tr>
<td>DVD</td>
<td>3</td>
<td>12.0</td>
<td>12</td>
<td>30.7</td>
</tr>
<tr>
<td>TVD</td>
<td>3</td>
<td>12.0</td>
<td>4</td>
<td>10.3</td>
</tr>
</tbody>
</table>

P Value: 0.001

SVD, DVD and TVD were seen in 76%, 12% and 12% of patients with HbA1c <5% respectively.

SVD, DVD and TVD were seen in 59%, 30.7% and 10.3% of patients with HbA1c 5.1 – 5.6%, respectively.

SVD, DVD and TVD were seen in 29.5%, 29.5% and 40.9% of patients with HbA1c 5.7-6.4% respectively.

SVD and DVD were seen in 50% each of patients with HbA1c >6.5%.

This was found to have a significant association. Multiple vessels were involved in patients with HbA1c in intermediate and high range (non-diabetic range of HbA1c).

Figure 11: Distribution of SVD, DVD and TVD among groups.
Table 12: Percentage of patients underwent PTCA/CABG among groups.

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>&lt;5 % (n=25)</th>
<th>5.1 - 5.6% (n=39)</th>
<th>5.7-6.4% (n=44)</th>
<th>&gt;6.5 % (n=4)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>PTCA</td>
<td>1</td>
<td>4.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
</tr>
<tr>
<td>CABG</td>
<td>3</td>
<td>12.0</td>
<td>2</td>
<td>5.1</td>
<td>11</td>
</tr>
</tbody>
</table>

4% and 12% of patients underwent PTCA and CABG in HbA1c <5% group respectively. 5.1% of patients underwent CABG in HbA1c 5.1 – 5.6% group.

Heart failure and attack of ACS were respectively seen in 4% and 4% of patients with HbA1c < 5%. Heart failure, non-fatal MI, repeat PTCA/TLT, attack of ACS, cardiac death, and heart failure plus ACS were seen respectively in 7.7%, 7.7%, 7.7%, 25.6%, 5.1% and 2.6% of patients with HbA1c between 5.1-5.6%.

Heart failure, non-fatal MI, repeat PTCA/TLT, attack of ACS, cardiac death, and heart failure plus ACS were respectively seen in 15.9%, 4.5%, 15.9%, 22.7%, 15.9% and 6.8% of patients with HbA1c between 5.7-6.4%. Non-fatal MI was seen in 25% of patients with HbA1c >6.5%.

Heart failure, non-fatal MI, repeat PTCA/TLT, attack of ACS, cardiac death, and heart failure plus ACS were respectively seen in 15.9%, 4.5%, 15.9%, 22.7%, 15.9% and 6.8% of patients with HbA1c between 5.7-6.4%. Non-fatal MI was seen in 25% of patients with HbA1c >6.5%.

Figure 12: Percentage of patients underwent CABG among groups.

Table 13: One year outcome of patients among HbA1c groups.

<table>
<thead>
<tr>
<th>One Year Outcome</th>
<th>HbA1c</th>
<th>&lt;5 % (n=25)</th>
<th>5.1 - 5.6% (n=39)</th>
<th>5.7-6.4% (n=44)</th>
<th>&gt;6.5 % (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Uneventful</td>
<td>23</td>
<td>92</td>
<td>17</td>
<td>43.6</td>
<td>8</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1</td>
<td>4.0</td>
<td>3</td>
<td>7.7</td>
<td>7</td>
</tr>
<tr>
<td>Non-Fatal MI</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>7.7</td>
<td>2</td>
</tr>
<tr>
<td>Repeat PTCA/TLT</td>
<td>0</td>
<td>0.0</td>
<td>3</td>
<td>7.7</td>
<td>7</td>
</tr>
<tr>
<td>Attack of ACS</td>
<td>1</td>
<td>4.0</td>
<td>10</td>
<td>25.6</td>
<td>10</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>0</td>
<td>0.0</td>
<td>2</td>
<td>5.1</td>
<td>7</td>
</tr>
<tr>
<td>Heart failure + ACS</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>2.6</td>
<td>3</td>
</tr>
</tbody>
</table>

4% and 12% of patients underwent PTCA and CABG in HbA1c <5% group respectively. 5.1% of patients underwent CABG in HbA1c 5.1 – 5.6% group.

25% of patients underwent CABG in HbA1c 5.7-6.4% group.
Mortality and adverse outcome during 1 year follow up were higher among patients with HbA1c in the intermediate and high range (non-diabetic).

Table 14: One year outcome of patients among FBS groups.

<table>
<thead>
<tr>
<th>One Year Outcome</th>
<th>FBS</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;99 mg/dl (n=87)</td>
<td>100-125 mg/dl (n=22)</td>
<td>&gt;126 mg/dl (n=3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Uneventful</td>
<td>37</td>
<td>42.5</td>
<td>11</td>
<td>50.0</td>
<td>3</td>
<td>100.0</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>9</td>
<td>10.3</td>
<td>2</td>
<td>9.1</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Non-Fatal MI</td>
<td>6</td>
<td>6.9</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Repeat PTCA / TLT</td>
<td>8</td>
<td>9.2</td>
<td>2</td>
<td>9.1</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Attack of ACS</td>
<td>17</td>
<td>19.5</td>
<td>4</td>
<td>18.2</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>6</td>
<td>6.9</td>
<td>3</td>
<td>13.6</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Heart failure + ACS</td>
<td>4</td>
<td>4.6</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Heart failure, non-fatal MI, repeat PTCA/TLT, attack of ACS, cardiac death, and heart failure plus ACS were respectively seen in 10.3%, 6.9%, 9.2%, 19.5%, 6.9% and 4.6% of patients with FBS < 99 mg/dl.

Heart failure, repeat PTCA/TLT, attack of ACS and cardiac death were respectively seen in 9.1%, 9.1%, 18.2%, and 13.6 % of patients with FBS between 100-125 mg/dl.

All patients with FBS>126 mg/dl were uneventful on follow up for 1 year.
Table 15: One year outcome of patients among RBS groups.

<table>
<thead>
<tr>
<th>One Year Outcome</th>
<th>RBS</th>
<th>&lt;139 mg/dl (n=84)</th>
<th>140-199 mg/dl (n=20)</th>
<th>&gt;200 mg/dl (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Uneventful</td>
<td>31</td>
<td>36.9</td>
<td>14</td>
<td>70.0</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>9</td>
<td>10.7</td>
<td>2</td>
<td>10.0</td>
</tr>
<tr>
<td>Non-Fatal MI</td>
<td>6</td>
<td>7.1</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Repeat PTCA/TLT</td>
<td>9</td>
<td>10.7</td>
<td>1</td>
<td>5.0</td>
</tr>
<tr>
<td>Attack of ACS</td>
<td>19</td>
<td>22.6</td>
<td>1</td>
<td>5.0</td>
</tr>
<tr>
<td>Cardiac Death</td>
<td>8</td>
<td>9.5</td>
<td>1</td>
<td>5.0</td>
</tr>
<tr>
<td>Heart failure + ACS</td>
<td>2</td>
<td>2.4</td>
<td>1</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Heart failure, non-fatal MI, repeat PTCA/TLT, attack of ACS, cardiac death, and heart failure plus ACS were seen respectively in 10.7%, 7.1%, 10.7%, 22.6%, 9.5% and 2.4% of patients with RBS < 139 mg/dl respectively.

Heart failure, repeat PTCA/TLT, attack of ACS, cardiac death, and heart failure plus ACS were seen in 10%, 5%, 5%, 5% and 5% of patients with RBS 140-199 mg/dl respectively.

Figure 15: One year outcome of patients among RBS groups.

Table 16: Binary logistic regression analysis to predict CV outcome.

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>P Value</th>
<th>Odds ratio/EXP(B)</th>
<th>95% C.I.for EXP(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c</td>
<td>1.472</td>
<td>0.355</td>
<td>17.158</td>
<td>1</td>
<td>&lt;0.0001</td>
<td>4.359</td>
<td>2.172 – 8.747</td>
</tr>
<tr>
<td>FBS</td>
<td>-0.028</td>
<td>0.016</td>
<td>3.116</td>
<td>1</td>
<td>0.078</td>
<td>0.972</td>
<td>0.942 – 1.003</td>
</tr>
<tr>
<td>RBS</td>
<td>-0.011</td>
<td>0.006</td>
<td>3.667</td>
<td>1</td>
<td>0.055</td>
<td>0.989</td>
<td>0.978 – 1.000</td>
</tr>
<tr>
<td>Constant</td>
<td>-3.769</td>
<td>2.091</td>
<td>3.250</td>
<td>1</td>
<td>0.071</td>
<td>0.023</td>
<td></td>
</tr>
</tbody>
</table>

The independent CV outcome of our combined variable outcomes of one year were statistically significant for HbA1c with odd’s ratio=4.36 (95% CI of 2.17 – 8.74, p=<0.0001). However, neither glucose on admission nor FBS were associated with increased risk (p=0.055 and p=0.07 respectively).
DISCUSSION

In this prospective study involving non diabetic ACS patients of south Indian population, we clearly demonstrated that elevated HbA1c levels, even in the pre-diabetic range, was a significant risk factor for the development of cardiovascular disease (CVD) (p < 0.0001). These study groups were evenly matched for age, sex, BMI, family h/o IHD, hypertension, dyslipidemia and other CV risk factors.

Some clinical and population-based cohort studies have shown that increased HbA1c levels were positively associated with the risks of CVDs and mortality.[116-127] In the present study, the risks of CHD was significantly higher even in the subjects with HbA1c levels of ≥ 5.7% compared with those with HbA1c levels of ≤ 5.0%. There has been controversy over whether or not the pre-diabetic levels of HbA1c are associated with CVD risk. Prior cohort studies in Caucasian populations have shown positive associations between the pre-diabetic range of HbA1c levels and the incidence of total CVD or CHD.[116-119,121,128] A clinical study from Japan has revealed that HbA1c is significantly associated with the complexity of coronary lesions even in non diabetic adults.[129] Likewise, such an association was observed for ischaemic stroke in other cohort studies.[118,121] Our findings are in accordence with these studies. On the other hand, some prospective studies have demonstrated that the risk of CVD was increased only in subjects with diabetic levels of HbA1c and not in those with pre-diabetic levels.[120,130] This inconsistency in findings might be caused by differences in population and methodology among the studies.

Why does HbA1c have the potential to predict CVD?

Complex and diverse hypotheses have been proposed to explain the causal relationship between hyperglycaemia with atherosclerosis, and one of the important pathways is recognized as glycosylation. Glycosylation is a nonenzymatic reaction induced by chronic hyperglycaemia, and is process in vivo results in two different products: early and advanced glycation end products (AGEs).

HbA1c is well known as one of the early glycation end products and is a precursor of AGEs.[131] It was reported that AGEs decreased large-vessel elasticity and induced inflammatory and pro-thrombotic responses in the vessel wall, thereby being involved in vascular complications.[132,133] Some clinical studies demonstrated that high AGEs levels were associated with the risk of CVD.[134,135] Therefore, the biological mechanisms of glycosylation may be one of the reasons for the relationship between HbA1c and the risk of CVD observed in our study.

In our study, 3.6% of total sample were diagnosed as new cases of DM, and 43% had HbA1c levels ≥ 5.7%. Another interesting aspect of the prognostic value of HbA1c in ACS is the differences observed in non diabetic and diabetic patients. A meta-analysis by Liu et al. demonstrated that elevated HbA1c level is an independent risk factor for mortality in CAD patients without diabetes, but not in patients with established diabetes.[123]

In our study, both admission glucose and FBS in pre-diabetic range showed long term poor CV outcome following ACS numerically, but was not statistically significant. The prevalence of admission hyperglycaemia (random glucose levels of > 140 mg/dl) in different epidemiological studies ranges from 51% to >58% of patients admitted with ACS.[136] However, in our study, prevalence of admission RBS more than 140 mg/dl was 25%. In patients with ACS, hyperglycaemia at the time of admission regardless of diabetic status has been tied to both long and short term negative outcomes.[137,138] A number of contemporary investigators, however, have challenged this notion and demonstrated that hyperglycaemia after hospital admission may yield a more important prognostic role than admission hyperglycaemia in terms of morbidity and mortality.[119,140] Suleiman and colleagues, for instance, were able to demonstrate that fasting glucose was superior to admission glucose in predicting 30-day mortality in 735 non diabetic AMI patients.[141] Loomba and Arora performed an extensive systemic review and were able to demonstrate that persistent glucose levels offer a better model to predict ACS mortality than on-admission glucose levels.[142] It has been demonstrated that the use of insulin to lower glucose concentrations decreased negative outcomes in patients with hyperglycaemia and myocardial infarction. However, a mechanism by which hyperglycaemia may be a causal factor in poor outcomes in ACS remains a topic of debate. It has been proposed that in ACS patients, decreased levels of blood insulin associated with hyperglycaemia may lead to a decrease of glycolytic substrate for cardiac muscle. As a result, the heart has to depend on alternate substrates such as free fatty acids for its metabolism. The accumulation of excessive free fatty acids results in the reduction of myocardial contractility and increases the risk of pump failure and arrhythmias. This challenges the assumption that hyperglycaemia is simply a “marker” of the stress response mediated by cortisol and noradrenaline.[143] A meta-analysis by Capes and colleagues in 2000 supported this hypothesis by demonstrating that among non diabetic patients, those with glucose concentrations between 110 and 143 mg/dl had a 3.9-fold higher risk of death and that those with glucose values between 144 and 180 mg/dl had a 3-fold higher risk of heart failure or cardiogenic shock. Similarly, diabetics with glucose concentrations between 180 and 196 mg/dL had an increased risk of death (relative risk 1.7).[137] Even though in our study, the CV outcome was poor in patients with FBS and admission glucose in pre-diabetic range, however did not show statistical significance.
In addition to decreased contractility, pump failure, and arrhythmia, hyperglycemia in ACS may affect coronary perfusion prior to and following percutaneous coronary intervention (PCI). A 2005 observational analysis by Timmer and colleagues sought to determine how hyperglycemia affected coronary perfusion prior to revascularization in ST-segment elevation myocardial infarction (STEMI). In 460 consecutive patients with STEMI who were treated with PCI, 70% had serum glucose levels more than or equal to 140 mg/dl (7.8 mmol/L) on admission, but only 14 percent had a history of diabetes. They were able to demonstrate that the patients with hyperglycemia were significantly less likely to have TIMI grade 3 (normal) flow prior to PCI compared to those with normoglycemia. This finding complements those by Lazzeri and colleagues in 2010, who were able to demonstrate that glucose serum levels measured after mechanical revascularization were independent predictors of in-hospital mortality in STEMI patients without previously known diabetes. Indeed, acute hyperglycemia has been associated with increased platelet activation in diabetic and non-diabetic patients coupled with evidence that acute hyperglycemia increases inflammatory responses during STEMI, these findings could explain an impairment in coronary flow that reflects a prothrombotic state and/or endothelial dysfunction associated with hyperglycemia, leading to a greater stress response.

Controlling hyperglycemia during AMI admissions has been the target of a great deal of basic and clinical research, with results primarily trending toward a benefit. The optimal “glucose target” has been elusive, and contemporary guidelines reflect this. A prospective study of 32 patients demonstrated that insulin infusion reduced inflammatory and clotting mediators in the plasma, with a concomitant reduction in enzymatic infarct size in subjects with STEMI receiving fibrinolytics. Recent experimental data also supports the beneficial effects of insulin infusion among patients with ACS. Wong and colleagues were able to demonstrate that insulin started five minutes prior to reperfusion in white rabbits significantly reduced infarct size following regional ischemia and reperfusion in a dose-dependent manner.

The strengths of our study include its longitudinal population-based design, low selection bias at baseline, perfect follow-up of subjects, and accuracy of diagnosis of ACS. However, some limitations of our study should be discussed. First, HbA1c and other potentially confounding factors were based on a single measurement at baseline, although this limitation is typical of most prospective studies. During the follow-up, risk factor levels changed due to modifications in lifestyle or medication, and misclassification of these levels was possible. This could have weakened the association found in this study, biasing the results towards the null hypothesis. Thus, the true association may be variable than that shown in our study. Second, our study included the relatively small number of event cases of ACS. The cardiovascular spectrum ranges much further, including transient ischaemic attack, and peripheral artery disease. Last, our study population was comprised of one ethnic group, and thus, generalizability to other ethnicities may be limited. On the other hand, the use of a monoethnic group in such a study avoids problems relevant to population stratification artifacts. Further studies in other ethnic groups will be needed to determine the applicability of HbA1c levels to the prediction of vascular events.

CONCLUSION

Binary logistic regression analysis in this study showed that in ACS patients without known diabetes mellitus, long term abnormalities in glucose control assessed by HbA1c is associated with poor CV outcome. HbA1c may be used to assess cardiovascular risk in a non-diabetic population with ACS. However, Large population based multicentric studies with long-term follow-up may be needed for further revealing more information regarding the role of HbA1C in non-diabetic patients with ACS.

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