Prevalance of glucometabolic disorders in acute coronary syndrome and their prognostic influence in long term cardiovascular outcome.

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Dedicated

To

My wife Grace, my daughter Tanya and son, Nathan

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List of abbreviations

ACCF: American College of Cardiology Foundation

ACE-I: Angiotensin Converting Enzyme-Inhibitor

ACS: Acute Coronary Syndrome

AHA: American Heart Association

AIR: Acute insulin secretory response

APG: Admission plasma glucose

ARB: Angiotensin receptor blocker

BP: Blood Pressure

CABG: Coronary Artery Bypass Grafting

CCF: Congestive cardiac failure

CHD: Coronary heart disease

CHS: Cardiovascular Health Study

CKD: Chronic kidney disease

CMIA: Chemiluminescent Microparticle ImmunoAssay

COPD: Chronic obstructive pulmonary disease

CRP: C-reactive protein

CVD: Cardiovascular disease

DAPT: Dual anti-platelet therapy

DECODE: Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe

DES: Drug eluting stent

DESIR: Data from the Epidemiological Study on the Insulin Resistance Syndrome

DM: Diabetes Mellitus

EDTA: Ethylenediaminetetraacetic acid

ESC: European Society of Cardiology

EST: Exercise stress test

FFA: Free Fatty Acid

GAMI: Glucose Tolerance in Patients with Acute Myocardial Infarction

G-6-PDH: Glucose-6-phophate dehydrogenase

HbA1c: Glycated haemoglobin A1c

HDL: High density lipoprotein

HDS: Hypertension in Diabetes Study

HR: Hazard ratio

ICD: International classification of diseases

IDF: International Diabetes Federation

IFG: Impaired Fasting Glucose

IGT: Impaired Glucose Tolerance

IL-6: Interleukine-6

IMT: Intima-media thickness

IPCH: Isolated post-challenge hyperglycaemia

KM: Kaplan-Meier

LDL: Low density lipoprotein

LIMIT-AMA: Limitation of myocardial infarction following thrombolysis in acute myocardial infarction

LV: Left ventricle

LVEF: Left ventricular ejection fraction

MACE: Major adverse cardiac events

MACCE: Major adverse cardiac and cerebrovascular events

MAP: Mitogen Activated Protein

MCP-1: Monocyte chemo-attractant protein-1

MI: Myocardial Infarction

MINAP: Myocardial Infarction National Audit Project

NADP: Nicotinamide Adenine Dinucleatide Phosphate

NADPH: Nicotinamide Adenine Dinucleatide Phosphate Reduced

NDA: National Diabetes Audit

NDM: Newly diagnosed Diabetes Mellitus

NEFA: Non-esterase free fatty acid

NGT: Normal glucose tolerance

NHANES: National Health and Nutrition Examination Survey

NIDDM: Non-insulin dependent diabetes mellitus

nRNA: nuclear Ribonucleic acid

NSTE-ACS: Non ST-segment elevation acute coronary syndrome

NSTEMI: Non ST-segment elevation myocardial infarction

OGTT: Oral glucose tolerance test

OPUS: Optimal angioplasty versus primary stenting

OPUS-TIMI: Orbofiban in Patients with Unstable Coronary Syndromes-Thrombolysis in Myocardial Infraction

OR: Odd's ratio

PCI: Percutaneous coronary intervention

PPCI: Primary percutaneous coronary intervention

PCPG: Post-challenge plasma glucose

PET: Photon emission tomography

PI-3: Phosphatidylinositol 3-kinase

RBC: Red blood cell

RLU: Relative light units

ROC: Receiver-operating characteristics

SPSS: Statistical Package for the Social Sciences

STE-ACS: ST-segment elevation acute coronary syndrome

STEMI: ST-segment elevation myocardial infarction

UA: Unstable angina

TACTICS-TIMI: Treat Angina with Aggrastat and Determine the Cost of Therapy with an Invasive or Conservative Strategy-Thrombolysis in Myocardial Infraction

TIMI: Thrombolysis in myocardial infarction

TIS: Total ischaemic score

TNF-α: Tumour Necrosis Factor-α

UA: Unstable angina

UK: United Kingdom

UKPDS: United Kingdom Prospective Diabetes Study

VLDL: Very low density lipoprotein

WHF: World Heart Federation

WHO: World Health Organization

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Publications and abstracts

- George A, Bhatia RT, Buchanan GL, Whiteside A, Moisey RS, Beer SF, Chattopadhyay S, Sathyapalan T, John J. Impaired glucose tolerance or newly diagnosed diabetes mellitus diagnosed during admission adversely affects prognosis after myocardial infarction: An observational study. PLoS One. 2015; 10(11): e0142045.
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Chapter 1: Introduction

1.1 Acute coronary syndrome and glucometabolic status

Acute Coronary Syndrome (ACS), despite advances in management, remains a life threatening condition with high mortality and morbidity rates. The long term mortality for patients presenting with ACS is around 25% [1, 2]. The mortality rate for patients with diabetes mellitus (DM) presenting with acute coronary syndrome is even higher. Over the past 30 years, there has been a 27 percent decrease in age-adjusted heart disease mortality in non-diabetic women. In contrast, women with diabetes have experienced a 23 percent increase in age-adjusted heart disease mortality [3, 4].

The relationship between ACS and glucometabolic disorders was noted as far back as 1931, when an unusually high prevalence of glycosuria was observed in patients without diabetes presenting with acute myocardial infarction (MI) [5]. Subsequent studies have shown a positive relation between the glucose level at admission and long-term mortality in patients without diabetes presenting with ACS [6]. Similarly post-prandial hyperglycaemia is an important predictor of cardiovascular risk, even within non-diabetic threshold [7, 8].

Evidence of macro and micro-vascular disease involving the cardiovascular system has been observed with hyperglycaemia [9, 10]. These findings suggest a more complex relationship between glucometabolic status and cardiovascular disease than previously thought, especially in the context of ACS. However the exact nature of this correlation has not been adequately explored or validated.

1.2. Definitions

Diabetes is primarily a clinical condition associated with hyperglycaemia, which results in an increased risk of micro and macrovascular complications. Since 1965 the World Health Organization (WHO) has published multiple guidelines to aid the diagnosis and management of diabetes and related conditions. The most recent update to the guidelines was published in 2005 following a joint WHO and International Diabetes Federation (IDF) technical advisory group meeting in Geneva.

The purpose of this meeting, in addition to reviewing the definition of diabetes mellitus, was to define intermediate hyperglycaemic conditions such as Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT). In view of the cardiovascular and systemic vascular risk associated with these conditions it was felt that the diagnostic criteria needed to be robust and in keeping with the latest clinical evidence. The panel also considered whether diabetes represented a discrete clinical entity or the upper end of a continuous distribution of glycaemia. Furthermore, the panel reviewed the diagnostic tests used for the diagnosis of these conditions [11].

The panel reviewed the available clinical evidence and considered the occurrence of diabetes specific complications to identify the cut off ranges for the diagnostic interpretation of diabetes and other glucometabolic conditions. The panel noted that while there was abundant data; confirming that the presence of hyperglycaemia has an adverse effect on patient's health, there was insufficient information to identify the demarcation point at which this level of harm categorically increases, in order to clearly differentiate 'diabetes' from 'non-diabetes'.

In order to identify this, the panel used the incidence and prevalence of diabetic retinopathy to establish the threshold for diagnosing diabetes. The WHO panel highlighted the PIMA Indian, NHANES III and an Egyptian study cited in the 1997 American diabetes association (ADA) report to establish the diagnostic criteria for diabetes. The cut-off values identified in these 3 studies were 10.3mmol/l, 8.5mmol/l and 8.6mmol/l respectively for 2-hr plasma glucose and 6.1mmol/l, 5.9mmol/l and 6.0mmol/l respectively for fasting plasma glucose (FPG). However, the results for the same population, when patients with known diabetes were excluded, showed a 2-hr plasma glucose of 9.0mmol/l, 9.9mmol/l and 8.9mmol/l respectively and fasting plasma glucose of 6.0mmol/l, 6.4mmol/l and 6.1mmol/l respectively [11, 12].

The panel also reviewed the study by Ito et al (2000), which examined the relationship between Oral Glucose Tolerance Test (OGTT) results and the incidence and prevalence of diabetic retinopathy. The study examined 12,208 people who underwent OGTT between 1965 and 1997 and noted that the incidence of retinopathy increased above a fasting plasma glucose level of 7.0mmol/l and a 2–h post-glucose load plasma glucose of 13.3mmol/l [11, 13]. There is however an argument that the presence of macrovascular complications, in particular, that of cardiovascular disease, should also be taken into consideration in order to identify the categorical cut-off points used for defining glucomatabolic conditions since it is the presence of macrovascular complications that result in the morbidity and mortality commonly encountered in patients with diabetes and intermediate hyperglycaemia.

Multiple prospective observational studies have examined the relationship between plasma glucose levels and risk of cardiovascular disease, cancer, all-cause mortality and risk of

developing diabetes. While some studies have shown a clear threshold above which the risk categorically increases, other studies appear to suggest that the relationship is more linear. A meta-analysis of 30 studies by Levitan et al (2005) showed that the cardiovascular risk increases in linear fashion with the 2-hour post-prandial glucose even at levels below the diabetic range; and without a clear threshold [14, 15, 16]. Furthermore, studies looking at the physiological functions in people with non-diabetic plasma glucose levels (<7.0 mmol/l) have noted various abnormalities. In particular, Godsland et al (2004) noted that the first phase insulin response in non-diabetic individuals begins from a fasting plasma glucose (FPG) level of 5.0-5.4mmol/l, and the late phase insulin response decreases above a FPG>6.0 mmol/l [17].

1.2.1 Fasting plasma glucose

Fasting plasma glucose assessment is one of the standard ways of assessing a patient's gluco-metabolic status. It provides better standardization and reproducibility compared to random plasma glucose evaluation and is typically performed following an overnight fast. The test enables the diagnosis of diabetes and IFG.

The WHO/IDF panel hence recommended that the current criteria for diagnosis should be retained- i.e., a fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) or 2-hr plasma glucose ≥ 11.1mmol/l (200mg/dl). The panel also felt that there were insufficient data to define normal glucose levels accurately, and hence the term normoglycaemia should be considered for glucose levels associated with low risk of cardiovascular disease or of developing complications [11].

1.2.2 Impaired glucose tolerance

The concept of a separate category of impaired glucose tolerance was first put forward by the US National Diabetes Data Group in 1979 to describe a cohort of patients with glycaemic status that increased the risk of progressing to type 2 diabetes [18]. Pathophysiological studies appear to suggest that patients with IGT have muscle insulin resistance and defective insulin secretion, resulting in less efficient disposal of the glucose load during the OGTT [19]. IGT is associated with a 6-fold increase in the risk of developing type 2 diabetes; with a relative risk of all-cause mortality and cardiovascular mortality that is 1.48 and 1.66 fold higher than patients with normal glucose tolerance respectively [20].

The diagnostic cut-off values for 2 hour post challenge serum glucose levels were primarily based on the Pima Indian study data which examined the risk of incident diabetes [11, 21]. While the study failed to show a clear cut off value; the risk of developing future type 2 diabetes was markedly higher in the upper 10% of the glycaemic spectrum. The 5 year incidence of diabetes was 24% for patients with a post challenge glucose of > 7.8 mmol/l compared to 4% for those with levels< 7.8 mmol/l. As mentioned earlier there was no clear threshold for post challenge plasma glucose level above which the risk of adverse outcome was categorically increased. Instead the risk of adverse cardiovascular outcome was noted to increase in a linear fashion across the diabetic and non-diabetic range of 2 hour plasma glucose levels.

The WHO/IDF panel recommended that the current diagnostic criteria for the diagnosis of IGT should be maintained, i.e. - fasting plasma glucose of <7.0mmol/l (126mg/dl) and 2-hr plasma glucose level of ≥7.8mmol/l (140mg/dl) and <11.1mmol/l (200mg/dl) [11].

1.2.3 Impaired fasting glucose

The concept of impaired fasting glucose was first introduced in 1997 by the American Diabetes Association expert committee to describe the glycaemic range between the upper limit of normal fasting plasma glucose and lower limit of diabetic fasting plasma glucose [21]. Like IGT, IFG is not a distinct clinical condition but an intermediate state of abnormal glucose regulation, which is associated with increased risk of progressing into diabetes in the long term. Studies suggest that patients with IFG have a 4.7 fold increased risk of developing DM-2 compared to those with normal fasting glucose. As with diabetes and IGT, the threshold for defining IFG is difficult to establish. While both the ADA and WHO consider fasting glucose level ≥ 6.1mmol/l as abnormal, they differ in the definition of IFG. The ADA felt that the cut-off point for IFG should be 5.6mmol/l; based on the ROC curve analysis of the PIMA Indian and Hoorn study data, which showed that a cut-off point of 5.4-5.5 had the highest sensitivity and specificity for predicting the future development of DM [21, 22].

Forouhi et al (2006) reviewed the association between fasting plasma glucose levels and type 2 diabetes from the published data and found that the magnitude of association was higher for FPG between 6.1-6.9 mmol/l, compared to FPG between 5.6-6.0 mmol/l. Furthermore the DESIR (Data from the Epidemiological Study on the Insulin Resistance Syndrome) study showed that the incidence of type 2 diabetes per thousand person year was 1.8, 5.7, 43.2 for males and 0.7, 6.2, 54.7 for males when FPG was categorized into <5.6 mmol/l, 5.6-6.0 mmol/l and 6.1-6.9 mmol/l respectively [23]. Reviewing these and other similar studies the WHO panel concluded that there is no consistent evidence for the threshold to define IFG. It was felt that while the risk of progression to diabetes was important, there were reservations against using this as the only consideration for defining IFG. They felt that the risk of

cardiovascular disease or premature mortality should also be taken into account, and studies appear to suggest that the risk of these conditions increase in a linear fashion and a cut-off to define IFG needs to reflect this [11].

The WHO/IDF panel's recommendation for the diagnosis of IFG differed from the ADA recommendations- fasting plasma glucose ≥6.1mmol/l (110mg/dl) and <7.0mmol/l (126mg/dl) and a 2-hr plasma glucose (if done) of <7.8mmol/l (140mg/dl) [11].

1.2.4 Glycated haemoglobin and diagnosis of diabetes mellitus

Although the WHO/IDF panel in 2006 did not consider HbA1C a suitable marker for the diagnosis of diabetes or intermediate hyperglycaemia, a subsequent consultation was held in March, 2009 to reassess this position. As a result, the WHO recommended the use of HbA1C for the diagnosis of diabetes, provided that strict quality assurance tests were in place and assays were standardised to the international reference values, and there were no conditions that precluded its accurate measurement [11, 24].

The recommendation states that an HbA1C of 6.5% is recommended as a cut-off value for diagnosing diabetes, although a value less than 6.5% does not exclude the diagnosis of diabetes using glucose measurement. Furthermore, the expert group concluded that currently there is inadequate evidence to recommend the interpretation of HbA1C below 6.5% [24].

1.2.5 Summary of WHO recommendations

Table 1. WHO recommendation for diagnosis of diabetes and intermediate hyperglycaemia.

Recommendation	Statement
1	The current WHO diagnostic criteria for diabetes should be maintained -: Fasting plasma glucose ≥ 7.0mmol/l (126mg/dl) **or** 2-hr plasma glucose ≥ 11.1mmol/l (200mg/dl).
2	Since there is insufficient data to define normal glucose levels accurately, the term 'normoglycaemia' should be used for glucose levels associated with low risk of developing diabetes or cardiovascular disease, that is levels below those used to define intermediate hyperglycaemia.
3	The current WHO definition for Impaired Glucose Tolerance (IGT) should be maintained -: Fasting plasma glucose < 7.0mmol/l (126mg/dl) **and** 2-hr plasma glucose ≥ 7.8mmol/l (140mg/dl) and < 11.1 mmol/l (200mg/dl).
4	The current definition for Impaired Fasting Glucose (IFG) should be maintained -: Fasting plasma glucose: 6.1 to 6.9mmol/l (110mg/dl to 125mg/dl) and (if measured) 2-hr plasma glucose < 7.8mmol/l (140mg/dl).
5	HbA1c can be used as a diagnostic test for diabetes providing the WHO recommended criteria are met-: HbA1c ≥ 6.5%.

1.3 Pathogenesis of cardiovascular disease in patients with glucometabolic disorders

Cardiovascular complications are the most common cause of morbidity and mortality in patients with glucometabolic disorders including diabetes and intermediate hyperglycaemia. A large Canadian population-based retrospective cohort study, inferred that diabetes confers an equivalent risk of 15 years of aging in term of cardiovascular disease [25]. It is important to understand that diabetes is no longer regarded as a disease associated solely with hyperglycaemia; instead it is an integral part of a spectrum of disorders of metabolism; which includes an increased risk of cardiovascular diseases. In the vast majority of patients, this increased risk precedes the formal development of a clinical state by many years; with the development of insulin resistance.

The concept of insulin resistance was first introduced in the 1960s when it was noted that a significant proportion of patients presenting with acute myocardial infarction had elevated insulin levels. In a prospective study of Pima Indians, a group at high risk of developing DM, various parameters including insulin secretion, insulin action, body composition, and endogenous glucose output were monitored over several years. In patients who subsequently developed DM there was 27% reduction in the acute insulin secretory response (AIR) at the time of transition from normal to impaired glucose tolerance, while there was a further 57% reduction at the time of transition from IGT to type 2 diabetes [26, 27].

1.3.1 Insulin resistance

The primary function of insulin is to facilitate the uptake of glucose by various tissues, especially the skeletal muscles and to regulate hepatic gluconeogenesis. Insulin resistance is a

clinical state that precedes the development of type 2 diabetes by many years, and is characterized by decreased ability of peripheral organs, especially liver, fat and skeletal muscles, to respond to the effects of insulin. In the initial stage there is a compensatory increase in insulin secretion by the pancreatic ß-cells resulting in a state of chronic hyperinsulinaemia. However in due course, with an increasing peripheral demand the pancreas becomes unable to sustain the increased secretion of insulin and a clinical state of diabetes (type 2) characterised by hyperglycaemia, ensues [28].

In addition to its primary role as a regulator of hepatic gluconeogenesis, and enabling glucose uptake in skeletal muscles and other tissues, insulin has other functions. It suppresses free fatty acid release from adipose tissue; controls triglyceride synthesis in hepatic cells, promotes endothelial functioning and is involved in regulating the thrombotic cascade. Hence insulin resistance is associated with a wide variety of other systemic and metabolic changes including central obesity, dyslipidaemia (characterized by low HDL to cholesterol ratio and hypertriglyceridemia), oxidative stress, endothelial dysfunction, hypertension and hypercoagulability [29]. Although the mechanism remains unclear, insulin resistance is associated with elevated acute-phase inflammatory markers like C-reactive protein. Furthermore, elevated CRP (C-reactive protein) is a predictor of the development of diabetes and adverse cardiovascular outcome [30, 31]. It is also important to note that the risk of atherosclerotic disease begins several years before a clinical state of diabetes (type 2) manifests.

Insulin suppresses free fatty acid release from adipose tissue and lipolysis. In insulin resistance, the adipose tissue is less responsive to the effects of insulin resulting in lipolysis

and increased secretion of nonesterified free fatty acid (NEFA) and pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6) and monocyte chemo-attractant protein-1 (MCP-1). Higher concentrations of circulating NEFA inhibits insulin nRNA (nuclear Ribonucleic acid) expression and can also lead to β-cell dysfunction. The β-cells would hence be unable to produce insulin rapidly enough in the event of a glucose challenge. Furthermore higher concentrations of free fatty acids (FFA) interfere with the anti-inflammatory properties of insulin by blockade of phosphatidylinositol 3-kinase (PI-3). This is especially the case with visceral fat compared to peripheral fat [32, 33].

Blockage to the PI-3 pathway results in hyperstimulation of the alternate pathway involving mitogen activated protein kinase (MAP-kinase). However the unopposed activation of the MAP-kinase pathway leads to pro-inflammatory changes, vascular hypertrophy and hypertension [33].

1.3.2 Dyslipidaemia in glucometabolic disorders

The usual lipid profile abnormalities noted in glucometabolic disorders are elevated levels of triglycerides, low high density lipoproteins (HDLs) and small dense low density lipoproteins (LDLs). The presence of elevated levels of FFA in the portal circulation, released as a result of insulin resistance, stimulates the synthesis of very low density lipoproteins (VLDLs). This in turn leads to an exchange of triglycerides from the VLDLs to HDLs or LDLs in return for their cholesterol esters. The elevated level of cholesterol ester rich VLDLs, result in the delivery of more cholesterol per particle into the atherosclerotic plaque. The triglyceride enriched HDLs however are targets for the hepatic lipase, whose activity is enhanced in

insulin resistance, resulting in increased breakdown and dysfunction of the HDL molecules [34, 35, 36].

In glucometabolic disorders the LDL levels show minimal change, due to a decrease in the production as well as catabolism of these proteins. As mentioned earlier, insulin resistance is associated with an increased concentration of triglyceride enriched LDLs, which in turn is hydrolyzed into small dense LDLs. These enter the arterial intima easily due to their smaller size, and are more likely to be retained by the proteoglycans, where they are oxidized. Oxidized LDL molecules are antigenic and mediate the release of chemicals that attract monocytes and macrophages leading to the formation of foam cells, thereby accelerating the process of atherosclerosis [35, 36].

1.3.3 Hypertension in glucometabolic disorders

The association between hypertension and glucometabolic disorder is not as clear-cut as the association between dyslipidaemia and glucometabolic disorders. However, there is conclusive evidence that the incidence of hypertension is higher in patients with diabetes and intermediate hyperglycaemia when compared to the general population. The Hypertension in Diabetes Study (HDS) revealed that 39% of patients with type 2 diabetes were hypertensive [37]. Studies by Ferrari and Weidmann demonstrated that patients with hypertension are more likely to have insulin resistance and hence abnormal responses to oral glycaemic challenge [38]. Although the causative mechanism for hypertension in patients with diabetes and intermediate hyperglycaemia is unclear, it is likely to be multifactorial. The potential contributing factors could include endothelial dysfunction, adipocyte release of vasoactive

substances, hyperinsulinaemic activation of the sympathetic nervous system and renal reabsorption of sodium [39].

1.4. Coronary artery disease and glucometabolic disorders

Patients with glucometabolic disorders are at a higher risk of developing atherosclerosis as a result of the various mechanisms described above, which could contribute towards the development of coronary artery disease. Furthermore, case controlled studies have shown that diabetic patients have smaller caliber coronary arteries, even in the absence of coronary artery disease [40]. The prognosis of patients after ACS has been noted to be worse if they have diabetes, both in the short and long term.

Multiple explanations have been put forward to explain the relatively poor outcome of these patients, but it is now generally accepted that the cause is multifactorial. In the short term, the primary cause for increased mortality is secondary to heart failure which could be due to a combination of diabetic cardiomyopathic process, the severity of the involvement of coronary arteries, decreased vasodilatory reserve and possibly abnormal metabolism of myocardial substrates [41].

The increased longer term mortality is secondary to the increased incidence of re-infarction in these patients. This could be due to the diffuse nature of atherosclerotic disease that is commonly seen in these patients, and the pro-thrombotic nature of the circulatory system. The mechanism for the latter includes platelet hyperactivity, autonomic neuropathy and endothelial dysfunction, all which are more likely to be noted in patients with diabetes [40].

Furthermore, diabetic patients are more likely to develop subacute and late stent thrombosis [42].

1.4.1 Prevalence of acute coronary syndrome in patients with glucometabolic disorders

The prevalence of diabetes, both type 1 and type 2, is on the rise. It is estimated that by 2030, the global diabetic population will reach 366 million. The number of patients with type 2 DM far exceeds that of type 1 DM [43]. Although the exact figures are unavailable, the prevalence of intermediate hyperglycaemia is also increasing. As described previously the risk of coronary artery disease secondary to atherosclerosis is increased in patients with glucometabolic disorders, and thereby that of acute coronary syndrome. This increase in risk starts even before the establishment of diabetes (type 2) [44]. The precise prevalence rate for acute coronary syndrome in patients with diabetes is unclear, since most studies measure cardiovascular disease (ICD-9:410-414) which includes acute MI, old MI, angina and other chronic ischaemic heart conditions. Furthermore the results from these studies seldom differentiate between ST-elevation ACS (STE-ACS) and Non ST-elevation ACS (NSTE-ACS).

The DECODE (Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe) study was initiated to evaluate the prognostic impact of the fasting and 2 hour plasma glucose levels that define diabetes and intermediate hyperglycaemia. A total of 13 centres provided cause specific mortality data, and included 22,515 patients (15,388 males, 7126 females) between the age of 30-89. 796 patients were previously known to have diabetes. Fasting plasma glucose levels and 2 hour plasma glucose levels were measured for all the remaining patients who were classified into DM, IGT, IFG and normoglycaemic as per the

standard WHO criteria. Patients were followed up for a median duration of 8.8 years, achieving an accumulated 208,203 person-years in men and 52,536 person-years in women. The study examined the mortality rates and cause of mortality in each of these groups. In particular the mortality rate secondary to coronary heart disease (CHD) which includes new MI, old MI, angina or other forms of chronic ischaemic heart disease (ICD-9: 410-414) was studied. The prevalence of known DM in the study population was, as mentioned earlier, 796; with an additional 656 (506 male, and 150 females) patients diagnosed as having diabetes based on FPG levels. 2,279 patients (1907males and 372 females) were noted to have impaired fasting plasma glucose, while 2,557 patients (1,633 males and 924 females) were noted to have IGT. The mortality rate secondary to coronary heart disease was 5.4% for males and 1.8% for females in the IGT group; 3.5% for males and 0.8% for females in the IFG group; 5.5-6.3% in males and 6.0-6.1% in females for the DM group. The study however did not consider the overall prevalence rate of coronary heart disease or MI for these patients; however it demonstrated that the incidence of mortality secondary to coronary heart disease was significantly higher for patients with diabetes and IGT, but not for IFG. Furthermore the mortality rates of males were considerably higher than females, especially in patients with intermediate hyperglycaemia [45].

The National Diabetes Audit (NDA), UK, monitors the prevalence of diabetes-related complications of nearly 2.5 million diabetic patients across 88 GP surgeries in England and Wales. The most recent report published in November 2013 examined the 2 year prevalence of diabetes related complications between 1st April, 2010 and 31st March, 2012. This demonstrated a 2-year prevalence of myocardial infarction of 28,812, indicative of a crude prevalence rate of 1.467% [46]. The recently published LEADER trial, comparing the

cardiovascular outcome between Liraglutide and placebo in 9340 patients with diabetes, noted myocardial infarction in 6.8% of patients over a 3.8 year median follow-up period with an incidence rate of 1.9 events per 100 patient years [47].

The Cardiovascular Health Study (CHS) examined the prevalence of cardiovascular complications in 5877 (3383 females and 2494 males) Medicare beneficiaries >65 years of age in the USA. The presence of CVD and sub-clinical CVD was ascertained at baseline by measuring the common and internal carotid artery wall thickness, ankle-arm index, looking for carotid artery stenosis, ECG changes and clinical history suggestive of angina and leg claudication. FPG and 2-hour PG were performed to categorize patients into normal, IGT and DM. 1343 patients were diabetic and 1433 patients had IGT. The presence of clinical and sub-clinical CVD was higher in patients with DM and IGT. The incidence of CHD (MI and angina) was higher in patients with both DM and IGT. The prevalence rate (rate per thousand years) was 75.5 for patients with normal glucose, 97.2 for patients with IGT and 126.5 for patients with DM [48].

Similarly the UKPDS 38 (United Kingdom Prospective Diabetes Study) considered the microvascular and macrovascular complications in patients with type 2 diabetes with and without tight blood pressure (BP) control. The study involved 1148 patients (758 in the tight BP control and 390 in less tight control group) with a median follow up of 8.4 years. The total number of MIs (including fatal and non-fatal) for both these groups were 110 and 71 respectively with no significant difference between the group. The combined prevalence rate of MI in this group would be around 15% for the 8 year period [49].

A Spanish study comparing the long-term outcome of non-diabetic patients with MI with that of diabetic patients with no previous history of MI, examined the prevalence of cardiovascular complications in 2260 patients between 30-74 years. The diagnosis of diabetes was made as per the WHO definition which includes FPG and OGTT results. Patients were followed-up for a period of 10 years. The incidence rate of MI was 7.1% (161) and that of unstable angina was 8.1% (184). The limitations of the study included non-differentiation of NSTE-ACS and STE-ACS, and the limitation in the demographic (patients outside the age group of 30-74 were excluded). The latter is of significance since, we would expect a higher incidence of MI in the older diabetic population; and hence these rates may not be reflective of the prevalence rate of the general population where a higher rate would be likely [50].

A Japanese study performed by Fujishima et al (1996), comprised 2427 individuals, aged 40-79 years, with no previous history of cerebro-vascular accident (CVA) or myocardial infarction (MI) who were followed up prospectively for 5 years after performing a standard OGTT. The test showed that 260 patients were diabetic and 474 had IGT. The incidence of myocardial infarction was significantly higher in the diabetic group (5.0 per 1000 patient years) and the IGT group (3.0 per 1000 patient years) compared to patients with NGT. The study however did not differentiate between NSTE-ACS and STE-ACS and did not appear to have included patients with unstable angina [51].

The National Health and Nutrition Examination Survey (NHANES) 1999-2004, conducted in America, studied the prevalence of diabetes related complications and reported an estimated prevalence of myocardial infarction among the diabetic population in America of 9.8% (12.2% for males and 7.1% for females) [52]. Similarly, Haffner et al (1998) studied the

incidence rate of ACS in patients with diabetes during a follow up period of 7 years and noted that it was 20.2% for patients with type 2 diabetes and no previous history of ACS. For patients with diabetes and a previous history of ACS the incidence rate for the 7 year period was 45.0% [53]. It is however worth noting that none of the above mentioned studies differentiated between STE-ACS and NSTE-ACS in their findings. Furthermore these studies did not examine into the prevalence rate of MI in patients with intermediate hyperglycaemia or glucose intolerance.

1.4.2 Prevalence of glucometabolic disorders in STE-ACS

The prevalence rate of diabetes in the UK general population is 4.6%, while that of impaired glucose tolerance is around 15% [54, 55]. However, the prevalence of glucometabolic disorders including diabetes and intermediate hyperglycaemia is significantly higher in patients presenting with ACS compared to the general population. This is also true for patients presenting with STE-ACS. One meta-analysis studied the cohort of STE-ACS patients from three large trials; the Thrombolysis In Myocardial Infarction (TIMI)-10A/B trial, the Limitation of Myocardial Infarction Following Thrombolysis in Acute Myocardial Infarction (LIMIT-AMI) study and the Optimal Angioplasty versus Primary Stenting (OPUS)-TIMI-16 trial. The total number of STE-ACS patients from these trials was 4224. The number of patients, whose plasma glucose levels were in the diabetic range was 2092 (49.5%); of whom 738 (17.5%) were known to be diabetic [56].

A subgroup analysis of patients with diabetes enrolled in 11 independent TIMI study group clinical trials from 1997 to 2006, performed by Donahoe et al (2007), included 46,577 patients. The prevalence rate of diabetes was 15.4% (7146 patients). The study however only

included patients previously known to have diabetes, and patients who were diagnosed following the index presentation were not included. It would hence be reasonable to assume that the prevalence rate derived is an underestimate [57]. A similar increase in the prevalence rate of diabetes in STE-ACS population has been described across the world. A retrospective study considering the effectiveness of tenecteplase in STEMI population in India revealed that 435 (45%) out of 968 patients who presented with an STE-ACS were diabetic. A diagnosis of diabetes was made if they were known to have diabetes or if their fasting plasma glucose (or 2 hour plasma glucose levels) was in the diabetic range. Similar findings were also noted in a Thai study, where 37.15% of patients presenting with STE-ACS were noted to be diabetic [58, 59].

The SWEETHEART registry examined the incidence of diabetes and intermediate hyperglycaemia and associated long-term prognosis in patients presenting with acute coronary syndrome, including STE-ACS. 2749 patients with ACS were enrolled out of which 1,549 had STE-ACS. 20.1% of these patients were known to have DM. An OGTT was performed on the 4th day for the remaining patients and this identified new DM in 16.0% and impaired glucose tolerance in 22.1% [60].

1.4.3 Prevalence of glucometabolic disorders in NSTE-ACS

In keeping with the high rate of prevalence of diabetes and intermediate hyperglycaemia in the STE-ACS population, the prevalence rate is also increased in patients presenting with NSTE-ACS. The SWEETHEART registry, as mentioned above, examined the incidence of diabetes and intermediate hyperglycaemia in patients presenting with ACS. The study included 1200 patients who were admitted with NSTE-ACS of whom 30.4% patients were

diabetic, while the remainder were revealed to have DM (17.8%) and IGT (21.3%) following OGTT [60].

Donahoe et al (2007) studied the outcome of diabetic patients who participated in the 11 TIMI study groups between the years 1997 to 2006. The data from the two trials that specifically considered the NSTE-ACS patients was OPUS-TIMI and TACTICS-TIMI (Treat Angina with Aggrastat and Determine the Cost of Therapy with an Invasive or Conservative Strategy- Thrombolysis in Myocardial Infraction). In total there were 12,487 patients who presented with a diagnosis of NSTE-ACS in both these studies, out of whom 2,777 patients were diabetic, which corresponds to a prevalence rate of 22.24% [57]. A similar prevalence rate was observed in the Global Registry for Acute Coronary Events (GRACE) registry which analyzed the baseline characteristics of patients presenting with ACS in 94 hospitals across 14 counties. Out of 10,713 patients who presented with NSTE-ACS (4725 with NSTEMI and 5988 with UA) 2760 (25.7%) were diabetic. It was also noted that most of these patients were more likely to be older and female. Furthermore these patients tended to have multiple co-morbidities and were less likely to be treated with standard cardiac medications compared to the non-diabetic group [61]. Both of these trials, however, only considered the prevalence of known DM.

Few studies have examined the role of glucose tolerance in these patients and most of them involved small cohorts of patients. Norhammar et al (2002) prospectively enrolled 181 patients, admitted to the coronary care units in two Swedish hospitals with acute MI, with no previous diagnosis of DM and a plasma glucose level of less than 11.1 mmol/l. Standardised OGTT was performed on these patients (n=181) at the time of admission and 3 months after

discharge (n=144). This demonstrated that 58 (35%) patients had impaired glucose tolerance and 51 (31%) patients had new DM at baseline, and 58 (40%) patients had IGT and 36 (25%) had DM 3 months after discharge. The study however did not differentiate between NSTE-ACS and STE-ACS [62].

A similar study, performed in the UK, examined the prevalence of glucose intolerance and diabetes in patients with NSTE-ACS, and included 49 patients with no history of DM. OGTT was performed at a median duration of 36 hours after admission and again at 3 months. Undiagnosed abnormal glucose tolerance was noted in 61% (49% for IGT, 12% for DM) patients at admission and 41% (31% for IGT and 10% for DM) at 3 months. Both the above mentioned studies excluded patients with chronic or acute renal impairment (creatinine ≥200 μmol/L), age>80 and an admission blood glucose ≥ 11.1mmol/l [63]. Since a significant proportion of diabetics with ACS are elderly and have co-morbidities including renal impairment it is likely that the prevalence of those with impaired glucose tolerance in the general NSTE-ACS population would be higher than identified in these studies [61].

1.5. Assessment of glucometabolic status in patients with ACS

As described previously, patients presenting with acute coronary syndrome have a higher prevalence rate of glucometabolic disorders compared to the general population. Different studies however use different tests to assess the glycaemic status of these patients, yielding different results. The common tests used in the various studies include admission plasma glucose (APG), fasting plasma glucose, OGTT and HbA1C.

1.5.1 Admission plasma glucose in ACS

A significant proportion of patients presenting with ACS have elevated plasma glucose levels. Hyperglycaemia, in patients with no previous history of DM, may reflect undiagnosed DM, pre-existing glucose intolerance or stress related glucose intolerance. While the exact mechanism of stress related hyperglycaemia is not clear, it is largely regarded as a response to stress resulting from catecholamine induced glycogenolysis [64]. There is some evidence that relative insulin deficiency also plays an important role [65]. Studies have also indicated that presence of admission hyperglycaemia is an indicator of adverse outcome.

A subgroup analysis of the Zwolle study, a randomized study comparing primary percutaneous coronary intervention (PCI) with thrombolysis, followed the outcome of patients with elevated APG, with no history of DM. The Zwolle study cohort consisted of 395 patients of whom 32 (8%) patients had DM and 7 had no admission blood glucose assessment and hence were excluded from the sub-analysis. The remaining 356 patients were classified into 3 groups based on the admission glucose level. The first group comprised patients with admission glucose level <7.8 mmol/l (n=163); the second group consisted of patients with admission glucose level 7.8-11.0 mmol/l (n=151); and the third group patients with admission glucose level of ≥ 11.1 mmol/l (n=42).

The mean follow-up period was 8±2 years. The mortality rate in group 1 was 19.0% (31), group 2 was 26.5% (40) and group 3 was 35.7% (15). Mortality rates were significantly higher in patients with highest APG levels ($p<0.05$). Occurrence of Major Adverse Cardiac Events (MACE), which was a combined end-point of death and non-fatal re-infarction, was noted in 53 (32.5%), 58 (38.4%) and 17 (40.5%) patients in group 1, group 2 and group3

respectively. Furthermore, higher admission glucose levels were associated with reduced left ventricular ejection fraction (LVEF) and enzymatically derived infarct size irrespective of the reperfusion strategy used. The study however only had a limited number of patients from single centre and there was no assessment to ascertain if elevated APG levels represented a glucometabolic disorder including DM and IGT. Similarly medical management of these patients did not include some of the standard medications used currently including clopidogrel, glycoprotein IIb-IIIa inhibitors and drug eluting stents (DES) [66].

A similar study compared the long-term outcome for patients based on their APG and HbA1C levels, after presentation with STE-ACS. The study recruited 4698 non-diabetic patients who presented with STE-ACS, from which 522 patients (11%) were excluded. The remaining 4176 patients were divided into quartiles based on their APG (QR1 ≤6.9 mmol/l, QR2: 7.0-8.1 mmol/l, QR3:8.2-9.5 mmol/l, QR4 ≥9.6 mmol/l) and HbA1C (QR1≤ 5.35%, QR2: 5.36-5.54%, QR3: 5.55-5.80%, QR4≥5.81%). The corresponding 30 day mortality for the HbA1C quartiles were 2.0, 2.3, 2.3 and 3.1; differences which were not found to be statistically significant. The one year mortality figures, however demonstrated a strong correlation between HbA1c levels and mortality; with a progressive increase in the mortality rate with higher HbA1c levels (3.1, 4.1, 4.9 and 6.8). On the other hand, the 30 day mortality rate for the APG showed a significant co-relation between them with progressive rise in mortality rate with increase in APG levels (1.3, 1.0, 2.6 and 4.9), however with a relative increase in mortality at the hypoglycaemic lower levels compared to the normoglycaemic values indicating a 'U' shaped relationship. The 1 year mortality also followed a similar pattern (3.8, 2.3, 4.9 and 8.0). However when the 30 day mortality patients were excluded from analysis the increase in the 1 year mortality rates at higher glucose levels was not statistically

significant. This is presumably because patients with elevated APG tend to more sick and unstable and hence have high 30 day mortality. Admission glucose also demonstrated a positive correlation with the enzymatic infarct size and the presence of multivessel disease [67]. The major limitation of the study was the inability to discover the glucometabolic status of the patients, especially considering the fact that HbA1C levels used to classify the cohort were lower than the WHO recommended range for diagnosis of DM.

Another study, by Norhammar et al (1999), examined the relationship between APG and long term outcome in non-diabetic patients admitted with ACS. This was a retrospective study involving 197 patients who were admitted with ACS and whose APG levels were available. Patients were followed up for at least 2.5 years. Of 197 patients 60 (30%) died, of whom 30 died during the index hospital admission and 30 died during follow up. Out of this mortality figure of 60, 58 were attributed to cardiovascular causes. During follow up there were 79 MACE, 20 patients developed congestive cardiac failure (CCF), and 12 had non-fatal reinfarction. The results suggest that APG levels above the median range are associated with increased mortality and major cardiovascular events. However when adjusted for other baseline characteristics including age, history of previous MI or CCF, smoking and sex and using the multivariate analysis using Cox regression model, the association between mortality and admission glucose was not statistically significant ($p=0.097$). There was however a strong relationship between APG and hospitalization for CCF ($p=0.003$) and non-fatal reinfarction ($p<0.001$). The study was limited by the retrospective design and a lack of clarification of the glucometabolic status of these patients. Furthermore being a tertiary referral hospital most of the patients admitted were transfers from other hospitals and hence could be expected to be unwell. This might be reflected in the higher mortality figures [68].

Similarly a Canadian study examined the prevalence rate and long term mortality of patients admitted with ACS. There were 1,664 patients admitted with ACS during a 12 month period in Nova Scotia of whom 1,103 (66.3%) presented with NSTE-ACS, while 561 (33.7%) had STE-ACS. The overall in-hospital mortality rates for STE-ACS and NSTE-ACS were 12.9 and 10.9 respectively; and at 1 year were 18.1% and 13.3% respectively. 72.9% were not known to have DM at the time of admission. Patients were classified into four groups based on a history of DM and APG levels. Group one included non-diabetics with APG of ≤11.0 mmol/l (n=1078), while group 2 comprised of non-diabetic with APG of > 11.0 mmol/l (n=135). Groups three and four consisted of diabetic patients with APG of ≤ 11.0mmol/l and > 11.0 mmol/l respectively.

Although diabetic status irrespective of the APG was a predictor of adverse prognosis (OR: 1.91, CI: 1.16-3.14, p=0.0105), patients with hyperglycaemia with no history of diabetes did even worse, with a twofold increase in risk (OR: 2.44, CI: 1.42-4.2, P=0.0013). The in-hospital mortality rates for the four groups were: group1: 8.1%, group 2: 23.7%, group 3: 18.3% and group 4: 18.8%. Similarly, the one year mortality rates were: group1: 3.1%, group 2: 8.1%, group 3: 6.5%, group 4: 5.7%. The major limitation of the study was that a significant proportion of these patients with elevated APG could have had underlying undiagnosed DM or IGT and the increased mortality could be representative of this [69].

An east London study examined the relationship between APG and outcome post-ACS in 2,127 patients and noted an almost linear relationship between higher APG and left ventricular impairment and cardiovascular mortality [70].

1.5.2 Fasting plasma glucose and ACS

Similar to APG, fasting plasma glucose is an important indicator of prognosis, both short term and long term, for patients presenting with ACS. Unlike admission glucose levels which could be elevated secondary to stress hyperglycaemia, fasting hyperglycaemia is a more reliable representation of the patient's glucometabolic status. Studies looking at the relationship between cardiovascular mortality and morbidity and fasting plasma glucose have shown a positive relationship between them.

A study by Suleiman et al (2005) compared prospectively the prognostic value of fasting plasma glucose and APG in patients with ACS. Patients not known to have DM were classified into those having normal FPG (<5.6mmol/l, n=409) and having elevated FPG (≥5.6mmol/l) based on the ADA criteria. The latter group was further classified into tertiles based on FPG; FPG:5.6-6.7mmol/l (n=109), FPG: 6.8-7.6mmol/l (n=109), and FPG≥7.8mmol/l (n=108). Similarly patients were classified, based on APG, into normal admission glucose group (APG<7.8mmol/l, n=436), APG: 7.8-8.7mmol/l (n=100), APG: 8.8-10.2mmol/l (n=100), and APG: >10.3mmol/l (n=99). There were 65 (8.8%) mortalities within the first 30 days. Both FPG and APG were noted to be significant independent predictors of 30 day mortality (p<0.0001 and p=0.001 respectively) and heart failure (p<0.0001 and p=0.0002 respectively). The adjusted odds ratios (ORs) for 30 day mortality in tertiles of elevated FPG compared with normal FPG were 2.3 (95% CI: 0.63-8.7; p=0.021), 7.3 (95% CI: 2.3-22.8; p=0.0006); and 11.7 (95% CI: 4.0-34.7; p=0.0001) respectively. The adjusted OR for 30 day morality in tertiles of APF compared with normal APG were 1.1(95% CO: 0.5-2.44; p=0.87), 2.7 (95% CI: 1.4-5.2; p=0.004) and 3.0 (95% CI: 1.6-5.7; p=0.001) respectively. Furthermore, compared with patients with normal FPG and APG the OR for 30

day mortality for patients with normal FPG and elevated APG was 0.71 (95% CI: 0.15-3.4, p=0.67), elevated FPG and normal APG was 3.4 (95% CI: 1.1-10.4,p=0.03), and for patients with elevated FPG and APG was 9.6 (95% CI: 3.5-26, p<0.0001). Log likelihood ratio tests to compare the nested models showed that addition of APG did not significantly improve the prediction of 'a model' based on FPG; however the addition of FPG significantly improved the prediction of 'a model' based on APF for both 30 day mortality and for heart failure. The study inferred that FPG was a better predictor of 30 day mortality and heart failure than APG. However, it was limited by the lack of data to establish longer-term mortality or morbidity correlation [71].

Another study that examined the relationship between impaired fasting glycaemia and outcome following ACS, categorized fasting glucose levels based on the WHO recommended thresholds. 999 patients were enrolled in the study of whom 53% (n=526) had abnormal glucose metabolism and 473 (47%) had normal fasting glucose. Of the 526 patients with impaired FPG, 381 (38%) were known to have DM or had FPG≥7.0 mmol/l, while the remaining 145 (15%) had IFG (FPG: 6.1-6.9mmol/l). Amongst the non-diabetic group, patients with IFG were associated with twice the number of in-hospital mortality when compared to patients with normal fasting glucose (p=0.049), however when adjusted for possible confounding factors this was not an independent predictor for in-hospital mortality. It was however a predictor for cardiogenic shock (p=0.005) [72].

The majority of studies described above involved patients with STE-ACS or did not differentiate between STE-ACS and NSTE-ACS. Since the prevalence of STE-ACS is on the decline and that of NSTE-ACS on the rise, it is essential to ensure that the assumed risk of

long term mortality and morbidity in patients with DM also extends to the NSTE-ACS population. The GRACE registry was designed to collect the risk profile of patients with ACS. It is a multi-centre registry involving 113 hospitals from 14 countries. Of the 57,406 patients enrolled between 1999 and 2005, 22,001 had APG and 13,526 had FPG measured. The FPG values showed that 5,507 (40.7%) had normal FPG (<5.6mmol/l), 4268 (3.5%) had IFG (FPG: 5.6-6.9mmol/l) and 3751 (27.8%) had DM (FPG≥7.0 mmol/l). 60.3% of patients with an elevated FPG in the diabetic range were known to have DM.

The results demonstrate that, when considered as a continuous variable, increasing FPG was associated with an increase risk of in-hospital death, without any identifiable threshold, even in patients not previously known to have DM. In patients with FPG ≥16.7mmol/l (300mg/dl) mortality was 8-fold higher than patients with normal FPG. On the other hand, the increase in mortality with APG was less modest, with increased risk at the lower end of the spectrum compared to the mildly hyperglycaemic group (2.39% vs. 2.09%). The in-hospital mortality rate for APG ≥ 16.7mmol/l (300 mg/dl) was 2-fold higher than for patients with normal APG. The results for the post discharge 6-month mortality, however, were less predictable. While the mortality risk was significantly higher in patients with FPG between 7.0-11.0mmol/l and ≥ 16.7mmol/l those for patients with FPG between 11.1-16.6mmol/l were not significantly different. Furthermore the APG was not associated with an increased mortality risk at 6-months post discharge, irrespective of the type of ACS.

This study appears to suggest that compared to FPG, APG is a weak predictor of mortality in patients with NSTE-ACS, especially 6-months post discharge. The study appears to have adopted the ADA threshold for the diagnosis of IFG, which is lower than the WHO

recommended threshold. The authors were unable to explain the reduced mortality risk in patients with FPG between 11.1-16.6mmol/l. The study shows a very weak association between both in-hospital and post discharge mortality rates and FPG in patients presenting to the hospital following unstable angina [73].

1.5.3 HbA1c and ACS

Recent change in the WHO guidelines has led to the use of HbA1c for the diagnosis of diabetes. This is a significant deviation from the traditional method of diagnosis using the measurement of plasma glucose levels either randomly, after fasting or post glucose challenge. Glycated haemoglobin, which was discovered over 40 years ago, is a normal variant of haemoglobin and is formed when haemoglobin is glycated with plasma glucose. Measuring the concentration of HbA1c is hence a reliable way of assessing the patient's glycaemic status over the previous 8-12 weeks; which is the normal life span of a red blood cell (RBC). The major limitations of HbA1c include conditions that affect the haemoglobin concentrations and the strict technical specification that needs to be met for performing the analysis. The cut off point for HbA1c was identified largely based on the presence of microvascular complications especially retinopathy and micro-albuminuria [24]. As with plasma glucose levels this does not necessarily reflect the threshold point beyond which macro vascular, especially cardiovascular, complications occur. The clinical evidence for the long term cardiovascular outcome in patients with DM and ACS is limited.

As described previously, Timmer et al (2011) demonstrated that HbA1c was a predictor of long term mortality in patients following STE-ACS, however the association with 30-day mortality was not found to be significant. The study also used a lower threshold for the

diagnosis of DM than recommended by WHO. Furthermore patients with NSTE-ACS were not included [67]. A study by Chan et al (2011) examined the relationship between HbA1c and ACS (including NSTE-ACS and STE-ACS) in 317 consecutive diabetic patients who presented to a hospital in Hong Kong during a 2-year period. Only patients with HbA1c levels checked either during admission or within the previous 2-months were included. Of the 317 patients, the majority were diabetic (94%), while 20 were newly diagnosed. There were 83 patients with STE-ACS (26.2%) and 234 (73.8%) patients with NSTE-ACS. Patients underwent APG, FPG and HbA1c following admission. The results revealed an HbA1c level >7.0% for about 44% (139) patients, while 178 (56%) had HbA1c≤7.0%. When compared, there was no significant difference between these 2 groups with regard to in-hospital mortality (p=0.856) or 6-month occurrence of MACE (p=0.803). Similarly the 6-month cardiovascular and all-cause mortality rates were non-significantly different (p=0.856 and 0.417 respectively). A MACE-free Kaplan-Meier survival curve also revealed no significant difference between these 2 groups. When assessed as a continuous variable HbA1c was a poor predictor of occurrence of MACE (HR: 1.013, 95% CI: 0.876–1.170, p= 0.866) and 6-month cardiovascular mortality (HR: 0.814, 95% CI: 0.582–1.137, p = 0.227). This study appears to suggest that in diabetic patients, the level of HbA1C does not confer any additional prognostic value. However it did not include patients with intermediate hyperglycaemia. The study was also limited by its relatively small size, and the fact that only patients with HbA1c performed during or 8 weeks prior to index admission were included [74].

By contrast a study by Cakmak et al (2008), showed a strong association between HbA1c levels and short term mortality. They examined the 4 week mortality rates of a 100 consecutive patients who presented with acute MI. Patients were divided into three groups;

HbA1c:4.5-6.4% (n=25), HbA1c 6.5-8.5% (n=28) and HbA1c>8.5% (n=47). All patients underwent a photon emission tomography (PET) scan and coronary angiography, except for seven patients who died before these tests. There was a statistically significant correlation between HbA1c levels and the mortality rate at 4 weeks (p=0.006). Significant association (p=0.001) between HbA1c level and post MI exercise stress test (EST) was also noted. Furthermore, HbA1c levels correlated with the PET scan (p=0.0001) derived total ischaemic score (TIS) and the number of coronary vessels involved (p=0.0001), identified during coronary angiography. The major limitation of the study was that patients with certain key demographics were excluded which including patients undergoing primary PCI, patients with delayed presentation of MI, renal impairment and patients on anti-diabetic medications. Furthermore, the study only involved a small number of patients and the results cannot be extrapolated to the larger population [75].

Amore recent study examined the role of HbA1c and OGTT in predicting long-term cardiovascular outcome in patients presenting with ACS. 548 patients were prospectively enrolled. All patients underwent measurement of HbA1c, while patients without a previous diagnosis of diabetes underwent OGTT. Interestingly the criteria used for diagnosis of glucometabolic disorders following OGTT were not in keeping with the recent guidelines. Normal glucose tolerance was defined as FPG<5.6 mmol/l and 2h-PG of <7.8mmol/l, while IFG was defined as FPG between 5.6-6.0 mmol/l. Likewise IGT was defined as FPG < 6.1 mmol/l and 2h-PG between 7.8-11.0 mmol/l; and newly diagnosed DM was defined as FPG ≥ 6.1 mmol/l or 2h-PG ≥ 11.1 mmol/l. The study noted that 23% (99) of patients who were not known to have diabetes were noted to have diabetes based on the OGTT results, however had HbA1c<6.5%. Patients were followed-up for a median period of 9.8 years. The findings

demonstrated that patients with newly diagnosed DM by OGTT and with an HbA1c < 6.5% had similar mortality when compared to patients with an HbA1c > 6.5% [76].

Although studies appear to suggest that elevated HbA1c levels are associated with poor long term outcome following ACS, the relation between HbA1c and short term outcome however is not clear. The current WHO definition only provides a threshold for diagnosis of DM and hence patients with intermediate hyperglycaemia, who are also likely to be associated with adverse outcome, may not be identified.

1.5.4 OGTT and ACS

The oral glucose tolerance test which was introduced in 1922 has long been regarded as the gold standard test to diagnose DM and intermediate hyperglycaemia, due to its high sensitivity [77]. It is the only test available to assess the post challenge response of gluco-metabolic status. This represents the post-prandial hyperglycaemic spikes encountered following meals during daily life. While it is fair to argue that 75gm or 100 gm of glucose solution cannot reproduce the glucometabolic response following a mixed meal, studies have shown that the glycaemic levels reached post OGTT closely relate to the glycaemic levels reached following a standardized meal [78]. Despite this only a small proportion of patients have OGTT done for diagnosis of DM due to the complicated nature of the test. A study by Ealovega et al examined the screening practices of physicians and noted that <1% of patients underwent OGTT for diagnosing DM [79].

OGTT is the only test that can reliably categorize patients into appropriate glucometabolic groups (NGT, IFG, IGT, and DM). A study by Ishihara et al examined 200 non-diabetic

patients who presented following ACS. Post challenge glucose assessment was done using standard OGTT and FPG was also checked. OGTT identified DM in 53 (27%) patients, IGT in 78 (39%) and normal glucose tolerance in the remaining 69 (35%). However when the FPG level was used for diagnosis only 14 (7%) patients were diabetic. When OGTT results were compared with APG, 15 (19%) patients with APG <7.8mmol/l were diabetic, 21 (25%) patients with APG ≥7.8 mmol/l and <11.1 mmol/l were diabetic, and APG≥11.1 mmol/l were diabetic. The study suggests that OGTT has better sensitivity in assessing the glucometabolic status of patients compared to FPG and APG, since a significant proportion of patients would not have been diagnosed as diabetic in the absence of OGTT [80].

IGT was first defined in 1980 by WHO as a metabolic state between normal glycaemia and DM [81]. While it was considered as a high risk state for developing DM, the condition itself was not regarded as a disease or of any clinical relevance outside this context. The current diagnostic criterion of IGT as described previously was established by the WHO in 1999 [82]. In current clinical practice IGT is regarded as a part of the metabolic syndrome with an increased risk of developing DM in the future and associated with increased cardiovascular morbidity and mortality [83].

Epidemiological studies such as the Whitehall study [84], the Baltimore longitudinal study [85], the Chicago heart study [86] and the DECODE study [7]; have clearly demonstrated that elevated PCPG is a strong predictor of cardiovascular risk. Similarly Isolated Post-Challenge Hyperglycaemia (IPCH), which has been described as an elevated post-challenge plasma glucose level (≥11.1 mmol/l) with a normal FPG (<7.0 mmol/l), is associated with a two-fold increase in mortality. [87, 88, 89]

Various studies have used the OGTT to assess glucometabolic status following ACS and following the long-term prognosis associated with these patients. As described previously patients with DM have a poor long term prognosis following ACS, however it is not clear if this risk extends to patients with intermediate hyperglycaemia. While there have been various studies examining this, the results have not been consistent, with some showing an increased risk in patients with IGT, while others have shown this risk only in patients with DM.

The glucometabolic response to OGTT following admission with ACS has been examined, not only during the index admission but following discharge and has noted that in a small but significant proportion of patients, the glucose levels during the repeat OGTT were lower compared to the initial test. In some cases this resulted in a change in the glucometabolic category from DM to IGT or IGT to NGT. This could be secondary to the stress induced glucometabolic response from ACS [62].

The Glucose Tolerance in Patients with Acute Myocardial Infarction (GAMI) study was a Swedish investigation, during which 181 patients post ACS had OGTT performed during the index admission, 3 months and 12 months post discharge to ascertain their glucometabolic status. A control group of 185 patients with no significant cardiovascular disease was also recruited for comparison. Patients were followed up for a median duration of 11.6 years with a final study population of 167 study and 184 control patients. At the end of follow-up 54 patients (32%) had NGT, 58 (35%) had IGT, and 55 (33%) had DM. Interestingly HbA1c did not differ between these two groups of patients. The total mortality rate was 32% of which 58% was due to a cardiovascular cause and 43% experienced a major cardiovascular event. Following univariate analysis AGT was related to cardiovascular event (HR: 2.46; 95% CI

1.37–4.42; p = 0.003), while FPG and HbA1c were not. Following multivariate analysis using the Cox proportional-hazard regression model AGT remained a predictor of cardiovascular events. Interestingly univariate analysis of the control group showed that AGT was a predictor of MACE, however following multivariate analysis AGT was no longer a significant predictor [62, 90].

Similarly a study by Tamita et al (2007) enrolled 275 patients following presentation with ACS of whom 85 had previously been diagnosed with DM. The remaining patients underwent OGTT at the time of discharge which revealed that 78 had NGT while 77 had IGT and 35 had new diagnosis of DM. Patients were followed up for a median duration of 5.3 years. The incidence of MACE events were as follows: 12 for patients with NGT of which 5 occurred during the first year; 33 for patients with IGT with 8 cases occurring in the first year; and 36 for the group with DM in which 17 cases occurred during the first year. The presence of abnormal glucose tolerance and previous diagnosis were both significant predictors of adverse cardiovascular outcome following multivariate analysis with a p value of 0.004 and 0.0005 respectively. The relative risk of MACE was 2.65 (95% confidence interval (CI): 1.34–5.15, p=0.004) in the group with abnormal glucose tolerance and 3.27 (95% CI: 1.68-6.38, p=0.0005) in the group with previously diagnosed DM when compared with NGT group. The study however had some limitations. It excluded a significant proportion of patients (109, 28%) who presented during the study period with ACS. These patients were at higher risk of cardiovascular events with some requiring emergency in-patient revascularisation. Furthermore, elderly patients (>80 years) and patients with chronic kidney disease (CKD) were excluded [91].

Bartnik et al demonstrated that abnormal glucose metabolism in patients with ACS is associated with poor outcome. The study examined 168 patients, post-ACS, and performed OGTT which revealed that 55 patients had NGT while 113 had abnormal glucose tolerance. Abnormal glucose tolerance post 34 months follow-up was noted to be the strongest predictor of poor cardiovascular outcome hazard ratio (4.18; CI 1.26-13.84; p = 0.019). The study however did not consider the outcome in patients with IGT and DM separately [92].

Kitada et al retrospectively reviewed 422 patients who presented with ACS and classified them based on their glycaemic status into normal glucose tolerance (NGT, n=106), impaired glucose tolerance (IGT, n=140), newly diagnosed DM (NDM, n=68) and previously known DM (n=108). Long term MACE was noted in 120 patients followed up for a period of 2 years. Interestingly there was no significant difference between the MACE rates between patients with NGT and IGT. OGTT was noted to be superior in predicting MACE compared to APG, FPG and HbA1c [93].

A Norwegian study by Knudsen et al considered the glucometabolic response following OGTT in patients who presented with STE-ACS. Patients underwent OGTT following admission and 3 months after discharge. Patients also underwent a SPECT myocardial perfusion scan at 3 months, at rest, to assess left ventricular (LV) volume, ejection fraction (EF), and infarct size. In total 224 patients were enrolled and underwent OGTT, which revealed that 53% (119) had NGT, while 47% (105) had abnormal glucose tolerance, of which 24 (11%) were in the diabetic range. Repeat OGTT was performed in 201 patients which showed NGT in 75% (151) patients, and abnormal glucose tolerance in 25% (50) of which 10 (5%) had a response within the diabetic range. This reduction in patients with abnormal glucometabolic status occurred in the absence of any glucose lowering medications.

Patients were followed up for a median duration of 33 months. The study however did not demonstrate any significant difference between patients with NGT and abnormal glucose tolerance in terms of event free survival period. This was the case for both in-patient OGTT (adjusted HR 0.81, 95% CI: 0.48-1.38, p = 0.44) and out-patient OGTT (adjusted HR 0.68, 95% CI: 0.34-1.36, p = 0.27). The study however had limitations in that it did not include patients presenting with NSTE-ACS, which is the more common type of presentation in the present day clinical setting. Patients who were older than 85 years and who had severe renal impairment were excluded, as were those with clinical instability requiring primary PCI. Patients with persistent hyperglycaemia and heart failure were also excluded. This, almost certainly, would have resulted in the exclusion of patients who were most likely to have had adverse cardiovascular events. Hence excluding them from the study is likely to have skewed the results [94].

A Danish study examined the microvascular function of the myocardium using non-invasive quantification of the coronary flow reserve (CFR) with the aid of Doppler echocardiography. 183 patients, who presented with ACS, were enrolled for the study. Out of 183, 22 patients were diabetic. The remaining 161 patients underwent OGTT which showed normal glucose metabolism in 64(35%) patients, IGT in 58 (32%) and new diagnosis of DM in 39 (22%) patients. CFR was assessed using Doppler echocardiography. In patients with significant left anterior descending (LAD) disease echocardiography was performed after coronary intervention, since the procedure involved intravenous adenosine infusion. Results showed that while the coronary flow reserve was significant reduced (greater than 2 being normal) in patients with known DM (CFR: 1.4) and a new diagnosis of DM (CFR: 1.6), however the CFR was normal for patients with NGT (CFR: 2.2) and IGT (CFR: 2.1) [95].

The Whitehall study was a longitudinal observational study which looked at the long term cardiovascular risk in 18,403 civil servants in London aged 40-64 following OGTT. They were followed up over a period of 33 years. There were 5497 cardiovascular mortalities during the period. The survival curves diverged after 5-10 years with patients with IGT living 4 years less than patients with NGT, and patients with DM living 10 years less than patients with IGT. The relationship between post challenge plasma glucose and survival was linear with the hazard of mortality rising from a level of 4.6 mmol/l (95% CI 4.2–5.3). For the glucose-CHD relationship curve above the 2h-PG level of 4.6 mmol/l and up to the diabetic threshold, the age adjusted HR for CHD was 1.22 (95% CI 1.14 –1.30) per mmol/l (p= 0.001) and 3.62 (2.34–5.56) for 2hBG of 11.1 mmol/l versus values below 4.6 mmol/l [84].

The Baltimore longitudinal study, on the other hand, studied 1236 men following assessment and categorization using OGTT. The study examined the long term all cause mortality, but excluded patients known to have DM or who had a FPG ≥7.8 mmol/l. During the follow up period the mortality rate was 35%. Patients with FPG in the diabetic range of 7.0-7.7 mmol/l and in the IFG range of 6.1-6.9 mmol/l had significantly increased RR for mortality compared with patients with FPG of 4.1-5.2 mmol/l. However the mortality rates for patients with FPG of 5.6-6.0 were not higher than the reference group. Patients with a 2 hour PG of 7.8-9.4, and 9.5-11.0 (IGT range) and patients with 2 hour PG of ≥ 11.1 mmol/l (diabetic range) had significantly higher RR for mortality compared to patients with normal 2 hour PG. The RR associated with a1-mg/dl (0.056 mmol/l) increase in glucose concentration was 1.003 (1.001–1.005, p=0.006). Men with IFG and normal glucose tolerance had the same risk for all-cause mortality, RR 1.0 (95% CI 0.5–2.1), as men with both normal FPG and normal 2hPG. On the other hand men with impaired FPG and diabetic 2hPG had a significantly increased risk for

all-cause mortality, 1.7 (1.0 –2.8). The RR for men with impaired glucose tolerance (IGT) and IFG, 1.5, was however only of borderline significance (p=0.07) [85].

It is well recognized that macrovasular complications including ACS is the most important cause of mortality and morbidity in patients with DM. Furthermore the risk of macrovascular complications is increased in patients with elevated glycaemic parameters including FPG, APG, HbA1c and post prandial glucose levels. While it is not entirely certain which amongst these parameters has the strongest association with the risk of macrovascular complications, some studies seem to indicate that this association is the strongest with post challenge glucose levels. One study examined the incidence of macrovascular risk of atherosclerosis by measuring the carotid intima-media thickness using carotid Doppler ultrasonography. 582 participants, between the age of 40-70, of the Risk Factors in IGT for Atherosclerosis and Diabetes Study were recruited. Patients known to have DM and patients on medications likely to affect glucose tolerance were excluded. Patients had FPG, HbA1c and post-challenge plasma glucose (PCPG) measured, with PCPG measured every 30 minutes for 2 hours. Patients then underwent carotid arterial Doppler ultrasonography to assess the intima-media thickness. Following univariate analysis all the glycaemic parameters were significantly correlated with IMT and remained significant after adjustment for age and sex. Post challenge plasma glucose however showed the strongest association in relation to abnormal IMT. Amongst the various post challenge glucose measurements, all except 30 minute post challenge plasma glucose level, showed significant association. Following multivariate analysis only the post challenge plasma glucose level, and not FPG or HbA1c, were significant determinants of carotid IMT [96].

HbA1c is a reliable measure of the glycaemic status of an individual over a period of 8-12 weeks. It is widely used to assess the glucometabolic status of patients presenting with ACS. The contribution of fasting plasma glucose and post-prandial plasma glucose levels in determining the value of HbA1c is variable. Monnier et al (2006) examined this by analysing the results from previous studies of diurnal glycaemic profiles in patients known to have diabetes. This demonstrated that in patients with well controlled diabetes (HbA1c<7.3%) the contribution of post-prandial plasma glucose was high (70%), while in patients with poorly controlled diabetes (HbA1c>10.2%) the contribution was significantly lower (30%). In contrast, the contribution of fasting plasma glucose showed a gradual increase with increasing levels of HbA1c [97].

1.5.5 OGTT and infarct size

As described in the previous pages, elevated fasting and post-challenge plasma glucose levels are associated with adverse outcomes in patients presenting with ACS, with a correlation which appear to progress in a linear fashion. The exact pathophysiology underlying this relationship is however not entirely clear. The most likely explanation is the adverse biochemical milieu associated with the abnormal glucometabolic state seen in these patients. The resulting prothrombotic state and endothelial dysfunction may have played a role in the increased incidence of cardiovascular events noted in these patients. An alternative argument is that the elevation in plasma glucose levels noted in these patients are secondary to a stress mediated glycaemic response that could have resulted from the activation of the adrenergic system post-infarct. Since a more extensive infarct provokes a more pronounced stress mediated response this could translate to higher plasma glucose levels. It could hence be argued that the relationship between cardiovascular prognosis and plasma glucose levels seen

in these patients is merely a bystander effect. In order to accurately comment on the correlation between plasma glucose levels and cardiovascular outcome, it is important to establish if there is an association between the glucose levels and the extent of myocardial infarction.

There are indeed multiple ways this could be assesed. HbA1c, which is not significantly influenced by the stress mediated response, could be used as a marker to evaluate the glucometabolic status of the patients. However, HbA1c is a poor surrogate for post-challenge glycaemic status, especially in the intermediate hyperglycaemic levels [76].

Another option would be to reassess the fasting and post-challenge plasma glucose levels post discharge and re-evaluate the relationship. This approach however does have various practical limitations. A reasonable number of patients may not return for the repeat tests. Also, patients may change their dietary and life style habits post-ACS, which could influence their repeat plasma glucose levels. An alternative approach would be to use a surrogate marker for the extent of myocardial injury and examine the relationship between this and the plasma glucose levels. If there is a no correlation between the glucometabolic status of patients and the extent of myocardial injury, it is unlikely that relationship between plasma glucose levels and cardiovascular outcome is a bystander effect.

1.6 Rationale for the study

Diabetes and other glucometabolic disorders are on the rise, as is the incidence of acute coronary syndrome. It is fairly common to see patients with both conditions in clinical practice. It has also been noted that patients with abnormal glucometabolic disorders have a

relatively poor outcome compared to the general population and have a higher incidence of macrovascular disorders. While multiple studies have examined the cardiovascular risk in patients with diabetes, the glucometabolic disturbances seen in the ACS patients have not been well established. Similarly, with the existence of different tests to assess glucometabolic disturbances, it is not entirely clear how to assess them reliably in the context of ACS, and how strongly these tests reflect the long-term prognosis in these patients.

The GAMI investigators examined the prevalence of glucometabolic disturbances in patients with ACS; however this study involved a small group of patients (n=181) from a tertiary centre. It is hence very likely that these patients were haemodynamically more unstable compared to the general cohort of ACS patients; a factor that could increase the likelihood of stress induced glucometabolic impairment. The study also excluded patients aged above 80 years with renal impairment and glucose level ≥11.1 mmol/l. This would however constitute a reasonable proportion of patients encountered in routine clinical practice and excluding these patients in a study with limited number of patients could potentially result in a skewed result [62].

Similarly the Euro Heart Survey studied 4196 patients from 110 centers and noted that the prevalence of abnormal glucose tolerance was high. This study however included patients with ACS as well as stable coronary artery disease (CAD). Furthermore a significant proportion of this cohort (n=736) did not undergo OGTT. Hence the true percentage of patients with IGT could be different. Similarly it could also affect the results of the study which appear to suggest that IGT is not associated with long term cardiovascular mortality [98].

Epidemiological studies have shown that IGT is associated with increased mortality and morbidity secondary to CVD. There is however insufficient evidence to comment on the risk of cardiovascular morbidity and mortality following ACS. While some studies have shown that abnormal glucose tolerance is associated with an increased risk of adverse cardiovascular events post ACS [62, 81, 82], other studies have only shown an increased risk in established or newly diagnosed diabetic patients [83, 84, 98].

However most of these studies are limited by their small size [62, 81, 82, 83, 84]. This may be one of the reasons why the results vary so widely between them. Furthermore the follow-up period for most of these studies was short. The atherosclerotic risk associated with IGT probably takes longer to manifest, which could also explain the equivocal results noted in some of the studies with shorter follow-up periods (67, 69, 74, 75). It is also worth mentioning that most of these studies were conducted prior to the establishment of current interventional cardiac care which includes dual anti-platelet therapy (DAPT), drug eluting stent (DES) implantation, aggressive medical management including medications like statins, beta-blockers and angiotensin converting enzyme-inhibitors (ACE-I). Furthermore over the years the diagnostic criteria for ACS has changed, with emphasis on the use of more sensitive cardiac markers such as highly sensitive troponin or third generation troponin.

Interestingly, when some of the studies which only used FPG to categorize the gluco-metabolic status, are revisited the likelihood of intermediate hyperglycaemia especially IGT being an independent predictor of prognosis, can be noted. For example the Zeller et al (2004) study, which has been described previously, categorized 999 patients post ACS using FPG demonstrated that patients with IFG had a mortality rate which was twice that of patients with

normal FPG (8% vs 4%;p=0.049). Similarly a significant increase in the incidence of cardiogenic shock and arrhythmia was seen in the IFG group compared to the group with normal FPG. Considering that none of the studies which used OGTT to categorize the glucometabolic status exhibited a strong correlation between IFG and adverse outcome, one can safely assume that a significant proportion of these IFG patients actually had IGT, which however was not diagnosed since OGTT was not used for the assessment of their glucometabolic status [72].

Some of the studies which show an increased risk of incidence of MACE in patients with AGT, did not differentiate between IGT and newly diagnosed DM. Since AGT is merely a response to a glycaemic challenge it cannot be regarded as a clinical entity, whereas IGT, as mentioned previously, is a distinct entity. Similarly a distinction has not been made between the different types of ACS which include the NSTE-ACS and STE-ACS. Since the underlying pathophysiology for both are different and considering the fact that NSTE-ACS is more commonly associated with high atherosclerotic burden, it would be interesting to observe if there is a difference in the prevalence of glucometabolic disorders between them. There is only limited evidence to state whether coronary intervention makes a difference to the long term prognosis in these patients.

There is also a lack of evidence, examining the role of post-prandial hyperglycaemia and its role in cardiovascular outcome. The underlying pathophysiological process involving fasting hyperglycaemia and post-prandial hyhyperglycaemia is is slightly different, as mentioned previously in the chapter. It is hence not clear if the presence of isolated post-challenge hyperglycaemia, defined as normal FPG and elevated post-challenge plasma glucose (≥ 11.1

mmol/l), constitute a different cardiovascular risk profile. Pararajasingam et al (2016) demonstrated that post-ACS patients with diabetes diagnosed on the basis of OGTT results but with an HbA1c < 6.5% were associated with the similar mortality rates when compared to patients with HbA1c >6.5%. The results are of greater significance in the context of the recent additions in the management options for diabetes including dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like protein-1 (GLP-1) agonists, that are capable of targeting sudden glycaemic load such as post-prandial hyperglycaemia [76].

In summary, there is a lack of adequate data to comment on the prognosis of abnormal glucometabolic following ACS. As discussed above, the literature contains conflicting results. The aim of the following research was therefore to explore this problem in greater detail, while addressing the limitations noted in the aforementioned studies. This thesis has therefore examined the prevalence rate of glucometabolic impairment in patients presenting with ACS and the risk of cardiovascular mortality and morbidity in these patients, while comparing the efficacy of various markers of glucometabolic status including APG, FPG, and PCPG. The thesis also aims to discover whether IGT is a risk factor for adverse events following ACS.

1.7 Hypotheses examined by the thesis

In the subsequent chapters, the thesis will examine the following hypotheses:

- The prevalence of glucometabolic disorders in patients presenting to hospital following acute coronary syndrome is similar to that in the general population. This hypothesis will be examined the chapter 3.

- The presence of glucometabolic disorder in patients presenting to hospital following acute coronary syndrome is not associated with increased incidence of adverse events. This hypothesis will be examined in chapter 4.
- The two hour post load plasma glucose level has the same capacity as fasting plasma glucose and admission plasma glucose to predict adverse events in patients presenting to hospital following acute coronary syndrome. This hypothesis will be examined in chapter 5.
- The presence of isolated post-challenge hyperglycaemia is not associated with increased risk of adverse events in patients presenting to hospital following acute coronary syndrome, compared to patients with normal glucose tolerance. This hypothesis will be examined in chapter 6
- The glucometabolic status as ascertained using OGTT in patients presenting to hospital following acute coronary syndrome is not influenced by the extent of myocardial injury as measured using cardiac enzymes like troponin I. This hypothesis will be examined in chapter 7.

Chapter 2: Methodology

2.1. Defining Acute Coronary Syndrome

The following research examined the glucometabolic status of patients admitted with ACS. A primary diagnosis of ACS was based on the criteria set up for redefining myocardial infarction, by the Global Task Force with joint leadership from among the European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the American Heart Association, and the World Heart Federation (WHF) [99].

Based on these criteria ACS was diagnosed when there was a rise or fall in cardiac markers (which for the purpose of this study was exclusively troponin) with at least one value above the 99th percentile of the upper reference limit, suggestive of myocardial necrosis secondary to myocardial ischaemia; together with one of the following:

- symptoms suggestive of myocardial ischaemia,
- ECG changes indicative of new ischaemia (new onset ST-segment or T wave changes or new left bundle branch block),
- imaging evidence of new loss of viable myocardium or new regional wall motion abnormality,
- development of pathological Q waves in ECG.

Troponin was the cardiac marker exclusively used for the diagnosis of ACS. While Scunthorpe General Hospital used Roche Troponin I (with a cut-off value for 10% imprecision of 0.03ng/ml), the Diana, Princess of Wales, Grimsby site used Siemens Dimension Troponin T (with a cut-off value for 10% imprecision of 0.14 ng/ml).

2.2 Laboratory methods and reagents

2.2.1 Oral Glucose Tolerance Testing

Patients who presented to the hospital with ACS underwent OGTT to assess their glucometabolic status. This was performed while they were an in-patient. The median duration between admission and OGTT was 3 days. Patients were encouraged to eat a normal carbohydrate based diet for 2-3 days prior to the OGTT, where possible. Patients were fasted overnight for at least 10 hours prior to the test, but were allowed to drink small sips of plain water. The OGTT was performed in the morning following the fast.

Fasting plasma glucose was measured at time 0 min, by collecting 1-2 ml of blood in a fluoride oxalate tube to prevent ex vivo glycolysis. Following this, patients were provided with either 75 gm anhydrous glucose solution in 200 ml of cold water or its equivalent, which was 410 ml of Lucozade from a standard Lucozade bottle (70kcal/100mmls). Patients were asked to consume the glucose load within 5 minutes. Patients would remain seated or in bed during the course of the test, and at 120 min post challenge, plasma glucose assessment was done by collecting 1-2 ml of blood using standard venepuncture technique. The exact times of blood collection were clearly documented in the request form to ensure the results were interpreted appropriately.

As per the hospital policy, glucose was assessed from the plasma, which allows the sample to be centrifuged without having to wait for it to clot. Since all the patients underwent the baseline glucose test performed after overnight fasting, the baseline plasma glucose samples were used as fasting plasma glucose. The results were interpreted based on the WHO

guidelines [11]. Further details regarding various glucemetabolic categories assessed in the study are provided in figure 1.

Table 2: Classification of glucometabolic status based on OGTT results.

	Plasma glucose (mmol/L) 0 min	Plasma glucose (mmol/L) 120 min
Normal Glucose Tolerance (NGT)	<6.0	<7.8
Impaired Glucose Tolerance (IGT)	6.1-6.9	7.9-11.0
New Diabetes Mellitus (NDM)	>7.0	≥11.1

2.2.2 Admission plasma glucose

The admission plasma glucose levels (APG) were measured at the time of admission, with no reference to the patient's food intake. This was performed as a part of standard practice in the trust, for patients presenting with symptoms suggestive of ACS. As described previously 1-2 ml of venous blood using standard venepuncture technique was obtained and analyzed in the laboratory. Point of care glucometer reading was not used and only formal laboratory results were used for APG levels.

2.2.3 Laboratory analysis of plasma glucose

An Abbott Architect ci8200 analyzer was used to measure plasma glucose levels. 1-2 ml of blood was collected by standard venepuncture techniques into glass or plastic tubes, usually containing sodium fluoride/ potassium oxalate as the anti-coagulant. Other accepted anti-coagulants were lithium heparin (with or without gel barrier), sodium heparin and

Ethylenediaminetetraacetic acid (EDTA). Plasma was separated from blood cells as per the specimen collection tube manufacturer's recommendations. The reagent used for analysis was Hexokinase/ Glucose-6-phosphate dehydrogenase (G-6-PDH).

The principle behind the analysis is that glucose is phosphorylated by hexokinase in the presence of ATP (adenosine triphosphate) and magnesium ions to produce glucose-6-phosphate (G-6-P) and ADP (adenosine diphosphate). The G-6-PDH in the reagent specifically oxidizes the G-6-P to 6-phosphogluconate with concurrent reduction of nicotinamide adenine dinucleotide phosphate (NADP) to NADPH (nicotinamide adenine phosphate dinucleatide reduced). One micromole of NADPH is produced for every micromole of glucose consumed. NADPH produced absorbs light at 340nm and can be detected using spectrophotometry as an increased absorbance. Hence by quantification of NADPH an accurate measurement of glucose level can be made.

2.2.4 Measurement of troponin

ARCHITECT STAT troponin I assay was used at Scunthorpe General Hospital for determining the presence of cardiac troponin I in the blood. ARCHITECT STAT is a two step immunoassay using the chemiluminescent microparticle immunoassay (CMIA) technology. In the first step the sample, assay diluent and anti-troponin I antibody-coated paramagnetic microparticles are combined. The troponin present in the particle then combines with antibody coated microparticles. After incubation and wash, anti-troponin-I acridinium-labeled conjugate is added in the second step. Following further incubation and wash pre-trigger and trigger solutions are added. The resulting chemiluminescent reaction is measured as Relative Light Units (RLUs). A direct relationship exists between the amount of troponin-I in the

sample and the RLUs detected by the ARCHITECT i* System optics. The concentration of troponin-I is read relative to a standard curve established with calibrators of known troponin-I concentrations.

2.3 Study parameters

2.3.1 Patient selection

The study was conducted at the two major hospitals sites in North Lincolnshire and Goole hospitals NHS foundation trust; the Scunthorpe general hospital and the Diana, Princess of Wales hospital, Grimsby. Both hospitals are located in eastern England and each have a catchment population of 75-85,000.

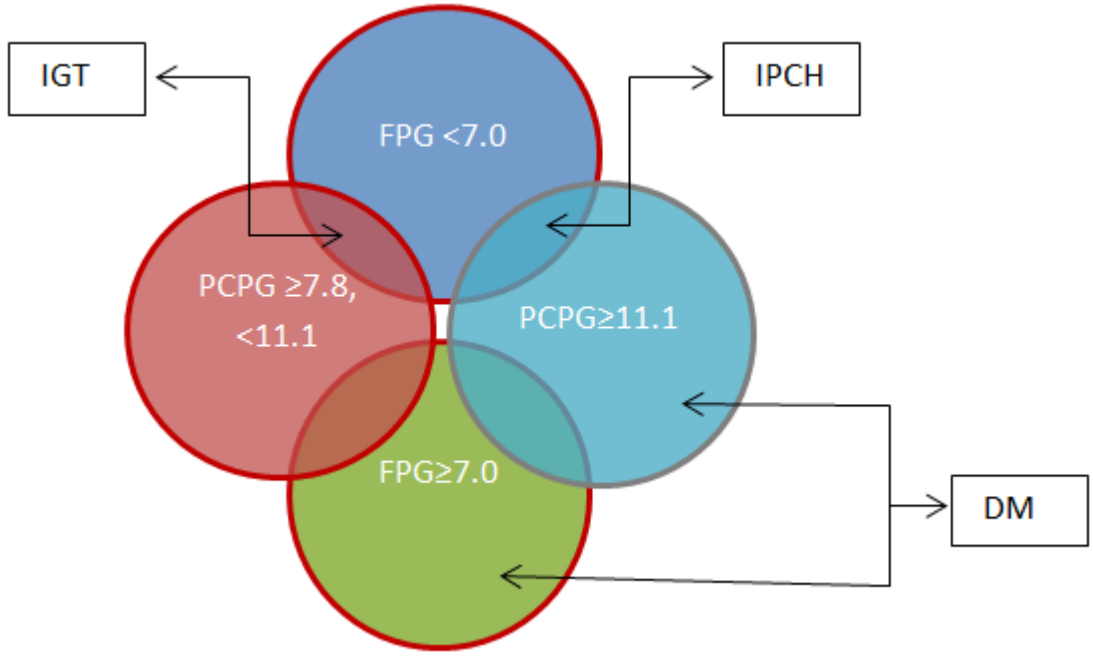
Patients admitted with a diagnosis of acute coronary syndrome from November 2005 to October 2008 were included. Patients had baseline blood parameters, including admission plasma glucose, assessed immediately following admission. Patients underwent OGTT between 3-14 days (median 3 days) post admission. If patients required emergency transfer for percutaneous intervention prior to their OGTT, this was performed following their return. Patients with known diagnosis of diabetes, patients who died before the OGTT or did/could not have an OGTT were excluded. Details regarding the number of patients screened and how many were excluded are provided in figure 2.

Baseline characteristics including demographics, risk factors or coronary artery disease, pre-admission and discharge medications, cardiac markers were recorded. These were obtained from the MINAP (Myocardial Infarction National Audit Project) database and patient case

records. Details of coronary angiography were obtained from patient case records where performed. If not clearly documented in the case records this was obtained from the database in the local interventional centers at the Hull Royal Infirmary and Castle Hill Hospital, Hull. The details collected included the number of coronary arteries involved, type of coronary intervention which included PCI, Percutaneous Balloon Angioplasty or coronary artery bypass grafting (CABG) surgery.

Patients were followed up for a median period of 48 months. Follow-up data was complete for all the patients. Completeness of follow-up was ensured by manual review of patient care records in the hospital and at the general practice. Details of discharge medications were also collected especially with regard to Dual Anti-Platelet Therapy (DAPT), statin, beta-blocker and Angiotensin Converting Enzyme-Inhibitor (ACE-I). This information was collected to discover if the increased incidence of adverse events associated with glucometabolic disturbances noted in previously mentioned studies, persist despite appropriate medical management.

Figure 1: Venn diagram describing the different sub-groups of glucometabolic disorders



2.3.2 End points for the study

The primary end point was composite outcome defined as the first occurrence of a major adverse cardiac event including cardiovascular death, non-fatal reinfarction, severe heart failure or non-haemorrhagic stroke. The secondary end-points were all cause mortality, cardiovascular mortality, non-fatal re-infarction, severe heart failure or stroke. Mortality information was obtained from the Primary Care Trust (PCT) mortality database and the hospital patient care record. Follow-up data were complete for all patients.

2.3.3 Definitions

As described previously acute coronary syndrome was defined as per the recommendations of the Global Task Force comprising representation from the ESC, ACCF, AHA and the WHF.

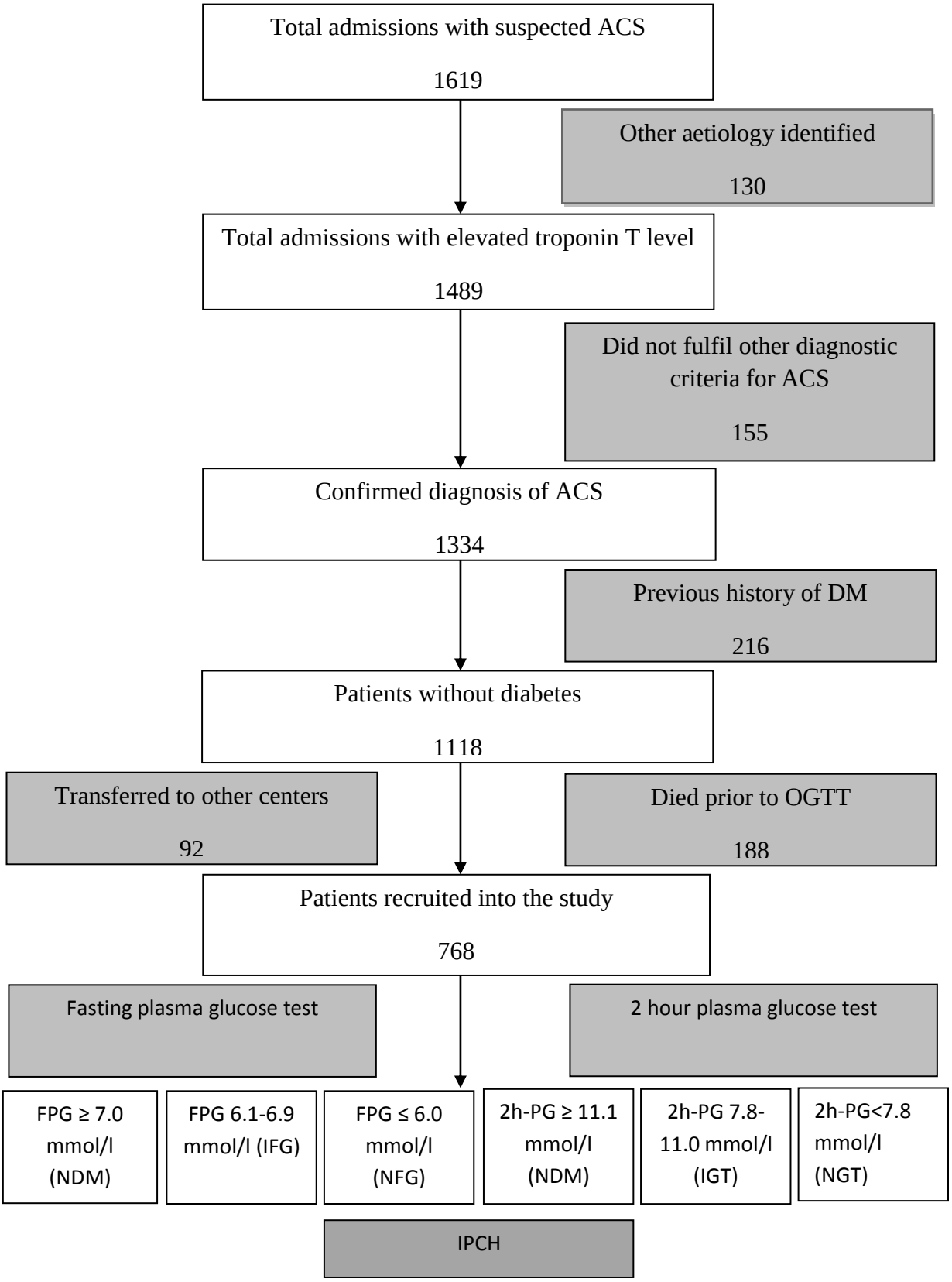
Family history of coronary artery disease was defined as the presence of premature coronary artery disease in a first degree relative before the age of 60. A patient was categorized as a smoker if he or she was smoking at the time of admission or has stopped within the last 2 years. Patients were classified as hypertensive if they had been diagnosed as hypertensive prior to admission; were newly diagnosed with hypertension following admission as per the National Institute of Health and Clinical Excellence (NICE) diagnostic criteria [100]; or were on anti-hypertensive medications at the time of admission. Patients were classified as hypercholesterolaemic if their total cholesterol level was > 5 mmol/l or if they were being treated for this condition. Patients were considered to have a history of coronary artery disease if there was a history of ACS in the past or had undergone PCI or CABG in the past.

2.4 Statistical analysis

2.4.1 Sample size

A power calculation for the sample size was performed based on the findings of the GAMI trial; in order to identify a significant difference in the incidence of primary as well as secondary end points. The incidence of major adverse cardiac events after 24 months in the GAMI study population [92] was 7.2% for patients with NGTand 30.9% for patients with IGT. Therefore, for a 90% power and significance level of 5%, a sample size of 115 was required. A similar calculation based on the study by Tamita et al [91] population showed that a sample size of 320 patients would be required. Considering the likely high attrition rate, and to enable performing further subgroup analysis if required a population size of 500 was felt to be appropriate. Eventually it was felt that patients admitted with ACS over a 3 year period would provide an adequate sized population for the study.

Figure 2: Consort diagram describing details regarding patient screening and recruitment.



2.4.2 Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 22 was used to perform statistical analyses. Continuous variables were presented as medians (lower and upper quartiles), while categorical variables were presented as counts or proportions (percentages). The differences in the baseline characteristics between the groups (NGT, IGT, NDM) were compared using one way analysis of variance and Kruskal- Wallis test for parametric and non-parametric data respectively for continuous variables and the chi-squared test for categorical variables. Kaplan-Meier curves were computed for event free survival. A log rank test was used for comparing the differences in cardiovascular events and survival. Cox proportional-hazards regression modeling was used to analyse the effects of several variables on event free survival. Results are reported as hazards ratio with 95% confidence intervals. Multivariate logistic regression models were used to calculate odds ratios and 95% confidence intervals for events in each glucometabolic categories after adjustment for the above clinical characteristics.

In order to compare the ability of different glucometabolic assessment tests (APG, FPG and 2h-PG) to predict prognosis following ACS, nested models were compared using the $\chi 2$ likelihood ratio test. Receiver-operating characteristics (ROC) curves were compared to assess the ability of various levels of APG, FPG and 2h-PG to predict MACE.

2.5. Ethics and regulatory approval

The study was discussed with the vice-chairman of Humberside ethics committee Dr Stephen Beer, who felt that it did not require a specific ethics approval, since assessment of patients

glucometabolic status following presentation with acute coronary syndrome was a standard clinical practice and was recommended by the European Society of Cardiology at the time of the study. Hence it was felt that the study could be considered as an evaluation of the clinical practice. The study was hence registered with the North Lincolnshire and Goole hospitals NHS Foundation trust Clinical Governance department.

Chapter 3: The association between acute coronary syndrome and the prevalence of glucometabolic disorders.

3.1 Introduction

The relationship between acute coronary syndrome and glucometabolic perturbations was noted as far back as 1931, when an unusually high prevalence of glycosuria was noted in patients presenting with coronary thrombosis and myocardial infarction [5]. It is well recognized that patients presenting with acute coronary syndrome have an increased incidence of diabetes. While the prevalence of diabetes amongst the UK general population is 4.6%, and that amongst the north Lincolnshire population from where the study cohort was derived is around 7.5% [54], the prevalence of diabetes amongst the acute coronary syndrome population is significantly higher. The Sweetheart registry noted that 24.6% of patients who presented following ACS were diabetic in a study involving 2749 patients [60]. Similarly, a sub-group analysis of the TIMI trials showed that the prevalence of diabetes in ST-elevation acute coronary syndrome (STE-ACS) population of 46,577 patients was 15.4% (7146) [57].

The increased risk of atherosclerosis associated with diabetes precedes the establishment of diabetes [29]. It can hence be assumed that a significant proportion of patients with coronary artery disease who are not known to have diabetes could have other glucometabolic disturbances. This is supported by the findings of studies which demonstrate an increased risk of cardiovascular disease in patients with intermediate hyperglycaemia [7, 84, 101]. A significant number of studies which examined the glucometabolic status in patients with coronary disease have, however, used admission plasma glucose or fasting plasma glucose, which could result in underestimation of the prevalence [66, 67, 70, 71, 72]. The WHO/IDF guidelines recommend the use of the oral glucose tolerance test as the gold standard test for assessing the glucometabolic status of patients [11].

While some studies have examined the incidence of glucometabolic conditions using OGTT in patients with acute coronary syndrome, such investigations recruited only a small number of patients. For example the GAMI trial examined the glucometabolic condition in 181 patients' post-ACS at discharge and after 3 months. The prevalence of IGT at the time of discharge was 35% and at 3 months was 40%, while that of previously undiagnosed diabetes was 31% at discharge and 25% at 3 months [62]. In the following study the prevalence of glucometabolic disorders in patients admitted with acute coronary syndrome is examined using admission plasma glucose, fasting plasma glucose and OGTT.

3.2 Research design and methods

A detailed description of the methodology has been described previously (see chapter 2). In brief, this observational study includes all consecutive adult patients without a diagnosis of diabetes admitted with acute coronary syndrome between November 2005 and October 2008. Baseline demographic data, co-morbidities, risk factors, pre-admission and pre-discharge medications, cardiac markers and revascularisation status were collected. Patients with known diagnosis of diabetes, patients who died before the OGTT or did/could not have an OGTT were excluded.

All patients underwent standard OGTT, following an overnight fast, on or after the third day of admission. Patients were categorized based on the results of OGTT into newly diagnosed diabetes mellitus (NDM), impaired glucose tolerance (IGT) and normal glucose tolerance (NGT) based on the WHO definition. All patients diagnosed with NDM and IGT were provided lifestyle modification advice and referred to the Diabetologist for appropriate management as an outpatient. Patients also had plasma blood glucose measured at the time of

admission as a part of routine care. Admission glycated haemoglobin (HbA1c) was not used since it was not part of the contemporary guideline. All patients were followed up for 48 months. Follow up data was complete for all the patients.

3.3 Results

There were 1489 admissions with elevated cardiac markers during the indexed period, of which 90% were secondary to acute coronary syndrome. Following exclusion of known diabetic patients and, patients who died prior to OGTT, 768 patients were included in the study. The baseline characteristics of the patients were classified into the three groups based on their glucometabolic status and is shown in table 3. Patients in the IGT and NDM group were older; however other baseline characteristics were similar across the three groups.

OGTT was performed on the third day in 63.3% patients, day 4-7 in 33.3% and day 7-14 for the remaining patients. Patients who had their OGTT on day 3 had similar fasting plasma glucose (5.28±0.75 v 5.20±0.89, p=0.17) and 2hour-plasma glucose (8.75±3.07 v 8.76±3.14, p=0.99) to those done later. About 63% of ST-elevation acute coronary syndrome (STE-ACS) and 64% of non-ST-elevation acute coronary syndrome (NSTE-ACS) patients had OGTT done on day three. OGTT was carried out later in STE-ACS patients compared to patients presenting with NSTE-ACS (4.07±1.67 days v 3.82±1.37 days, p=0.02). FPG (5.32±0.80 v 5.21±0.81, p=0.06) and 2h-PG (8.76±3.08 v 8.76±3.11, p=0.99) were similar in patients with NSTE-ACS and STE-ACS respectively.

Table 3. Clinical characteristics of the study population.

	NGT(n=337)	IGT(n=279)	NDM(n=152)	p
Age(years; median; IQR)	62(17)	68(18)	68(19)	<0.001
Male n (%)	236(70)	204(73)	109(72)	0·70
Current smoker	101(30·0)	96(34·4)	46(30·3)	0·46
Hypertension	122(36·2)	117(41·9)	59(38·8)	0·35
Hypercholesterolaemia	151(44·8)	134(48·0)	67(44·1)	0·65
Previous myocardial infarction	51(15·1)	59(21·1)	29(19·1)	0·15
Known IHD	85(25·2)	89(31·9)	50(32·9)	0·10
Family history	138(40·9)	115(41·2)	65(42·8)	0·93
Discharge diagnosis of NSTEMI	196(58·2)	159(57·0)	92(60·5)	0·78
Discharge medications				
Aspirin	308(91·4)	255(91·4)	142(93·4)	0·72
Clopidogrel	280(83·1)	222(79·6)	129(84·9)	0·33
Dual anti-platelet	265(78·6)	207(74·2)	121(79·6)	0·31
Beta-blocker	260(77·2)	211(75·6)	116(76·3)	0·90
ACEI/ARB	270(80·1)	236(84v6)	128(84·2)	0·29
Statin	325(96·4)	264(94·6)	142(93·4)	0·30
Revascularised	147(43·6)	118(42·3)	58(38·2)	0·52
Troponin I (µg/l; median; IQR)	2·8(13·2)	3·2(11.0)	3·0(15·5)	0·82
FPG (mmol/l; median; IQR)	4·9(0.5)	5·1(0·8)	5·7(1.3)	<0.001
2HPG (mmol/l; median; IQR)	6·3(1.6)	9·2(1.9)	12·9(2.7)	<0.001

When fasting plasma glucose was applied for assessing the glucometabolic state, 689 out of 768 (89.7%) patients, were noted to have normal fasting plasma glucose, 48 (6.3%) patients had impaired fasting plasma glucose and 31 (4.%) patients had newly diagnosed diabetes mellitus. Following OGTT, 328 (42.7%) patients had normal glucose tolerance, 9 (1.2%) patients had impaired fasting glucose, 279 (36.3%) patients had impaired glucose tolerance and 152 (19.8%) patients had newly diagnosed DM. However for the purpose of further analysis IFG patients were considered as part of the NGT group. Of the 431 (56.1%) patients with post challenge hyperglycaemia, 361 (83.8%) patients had normal fasting plasma glucose.

Of the 689 patients diagnosed normal on FPG alone, 261 (37.9%) had IGT and 100 (14.5%) had NDM. Of the 48 patients diagnosed IFG on FPG alone, 17 (37.4%) had IGT and 22 (45.8%) had NDM. Of the 431(56.1%) patients with post load hyperglycaemia, 361 (83.8%) had normal FPG.

Although guidelines do not define categorical thresholds for random plasma glucose with which to define various glucometabolic states, we applied the cut-off ranges used for post challenge plasma glucose for this purpose. This demonstrated that out of 768, 499 (65%) patients had APG of < 7.0 mmol/l, 217 (28.2%) patients had APG between ≥ 7.8 and < 11.1, while 52 (6.8%) has APG ≥ 11.1 mmol/l.

3.4 Discussion

This study demonstrates that a significant proportion of patients admitted following ACS have glucometabolic perturbations. The findings show that 36.3% patients had impaired glucose tolerance, while 19.8% patients had newly diagnosed diabetes. Furthermore, 1.2%

patients had impaired fasting glucose. This suggests that more than half of the patients admitted with ACS have abnormal glucose tolerance. This was despite the exclusion of patients who were known to have diabetes. Norhammar et al (2002) have previously demonstrated that the glucometabolic disturbances, noted in a similar but smaller population of patients, persisted when monitored 3 months following discharge [62].

The study also demonstrates that fasting and admission plasma glucose underestimates the prevalence of glucometabolic disorders in patients presenting with ACS. OGTT is more sensitive in identifying these patients. About 90% of our patients were diagnosed as normal when FPG alone was used for determination of the glucometabolic state. Similarly 84% of patients who were noted to have AGT following OGTT had normal FPG. In the DECODE study, about 37% of NDM diagnosed on OGTT were normal on FPG criteria [45]. The reliability of pre-discharge OGTT in reflecting the "true" glucometabolic state may be dependent on the timing of the test in relation to the cardiac event and the severity itself. The pre-discharge glucometabolic category of the patient may [94, 102] or may not [6, 103] change in the medium to long term.

The glucometabolic categories based on OGTT performed within 24 hours of a STE-ACS changed in 46% of patients at 3 months post-discharge [104]. However, OGTT performed at or after 5 days seems to reliably predict long term glucometabolic state. This may be related to the subsidence of the acute response between 2-5 days with no further decrease thereafter [6, 103]. The GAMI study suggested a somewhat better reproducibility of OGTT in patients with subendocardial than transmural infarction [105]. All the present patients had the OGTT performed at least three days (37% ≥ day 4) after the index event, later in STEMI than

NSTEMI. Only about 42% of patients had STEMI. This makes it likely that the results would reliably predict long term glucometabolic state.

The need for identification of this group of patients is becoming increasingly relevant in modern clinical practice, not only because they could develop overt diabetes and associated micro and macrovascular complications, but have an increased risk of cardiovascular morbidity and mortality which studies have shown may follow glucose intolerance [7, 84, 101]. Early identification of these glucometabolic disorders could hence permit risk modification and closer monitoring for the occurrence of associated complications.

This study adds to the current evidence that, glucometabolic disorders are significantly more common in patients with ACS compared to the general population. This could be due to an increased risk of cardiovascular disorders in patients with impaired glucose tolerance, although the study did not examine the causal relationship. Although there are studies that have previously examined the prevalence of glucometabolic disorders, as mentioned earlier, this is the first to examine such a large group of patients. The findings from the study suggest that the use of OGTT may be of added value in order to establish the glucometabolic status of patients admitted with ACS, and to stratify them into categories of risk.

Chapter 4: Prognostic implications of newly diagnosed diabetes mellitus and impaired glucose tolerance in patients presenting with acute coronary syndrome.

4.1 Introduction

Impaired glucose tolerance and newly diagnosed diabetes mellitus based on the oral glucose tolerance test are common in patients with acute coronary syndrome and coronary artery disease, as described in the previous chapter. Similarly the prognosis of patients with acute coronary syndrome (ACS) has been noted to be worse in patients with elevated admission plasma glucose levels. While some studies only observed this adverse prognosis in patients with glucose levels in the diabetic range [10, 107], other studies have shown that this risk also extends to patients with intermediate hyperglycaemia [68, 69, 108]. The risk of adverse cardiovascular events also increases in the diabetic and pre-diabetic states diagnosed on fasting plasma glucose levels following acute coronary syndrome [73, 109].

The effect of glucometabolic disorders diagnosed by OGTT on the incidence of major adverse cardiac events has not been adequately explored. The Euro Heart Survey on diabetes and the heart demonstrated that only new diabetes mellitus, and not impaired glucose tolerance or impaired fasting glucose was associated with an increased incidence of MACE in patients with coronary artery disease [98]. Similarly studies by Kitada et al [93] and Knudsen et al [94] did not reveal an increased incidence of MACE in patients with IGT. However the GAMI trial and a study by Tamita et al (2007) demonstrated that abnormal glucose tolerance was associated with an increased incidence of MACE in the ACS population. However, this study did not differentiate between impaired glucose tolerance (IGT) and new diabetes mellitus (NDM) [62, 90, 91]. Most of the above mentioned studies have major limitations in terms of size of the study population and duration of follow up and a significant proportion were conducted when management of ACS was different and did not involve wide spread use of dual anti-platelet therapy, statin and beta-blocker.

In the current study, data collected on patients admitted with MI who underwent pre-discharge OGTT have been analyzed, to evaluate the relationship between glucometabolic status and long-term prognosis.

4.2 Research design and methods

4.2.1 Patients

A detailed description of the methodology has been described previously in this thesis (chapter 2). In brief, this observational study includes all consecutive adult non-diabetic patients admitted with acute coronary syndrome between November 2005 and October 2008. Baseline demographic data, co-morbidities, risk factors, pre-admission and pre-discharge medications, cardiac markers and revascularisation status were collected. Patients with a known diagnosis of diabetes, patients who died before the OGTT or did/could not have an OGTT were excluded.

All patients underwent standard OGTT, following an overnight fast, on or after the third day of admission. Patients were categorized based on the results of the OGTT into newly diagnosed diabetes mellitus (NDM), impaired glucose tolerance (IGT) and normal glucose tolerance (NGT) based on the WHO definition. All patients diagnosed with NDM and IGT were provided with lifestyle modification advice and referred to the Diabetologist for appropriate management as an outpatient. Patients also had their plasma blood glucose measured at the time of admission as a part of routine care. Admission glycated haemoglobin (HbA1c) was not used since it was not part of the contemporary guideline.

4.2.2 Definitions

Acute coronary syndrome was diagnosed based on the universal definition as defined by the global task force [99]. Interpretation of OGTT results and fasting plasma glucose (FPG) levels and diagnosis of various glucometabolic states were based on the WHO definition for diabetes and intermediate hyperglycaemia [11]. Further details regarding this and the definition of other co-variates and risk factors have been described previously (chapter 2).

4.2.3 Outcome measures

All participants were followed up for 48 months. Follow up data was complete for all the patients. The primary end-point was a composite outcome defined as the first occurrence of a MACE including cardiovascular death, non-fatal re-infarction, severe heart failure or non-haemorrhagic stroke. Secondary end-points were all cause mortality, cardiovascular mortality, non-fatal re-infarctions, severe heart failure or stroke. Each event was considered at its first occurrence only. Cardiovascular death was defined as death from myocardial infarction, heart failure, non-haemorrhagic stroke and sudden death without any obvious reason. A non-fatal re-infarction was defined as a non-fatal MI occurring later than 72 h after the index infarction. Stroke was defined as a neurological deficit persisting >24 hours as observed by a physician with radiological confirmation of haemorrhagic or non-haemorrhagic stroke. Severe heart failure (HF) was recognized when causing hospital admission requiring intensification of or additional treatment.

4.3 Statistical analysis

Continuous variables are presented as medians (inter-quartile range) and categorical variables as counts and proportions (%).Differences in baseline characteristics between the three groups were compared using one-way analysis of variance and Kruskal-Wallis test for parametric and non-parametric data respectively for continuous variables and chi-squared test for categorical variables. Event free survival was estimated in the three glucometabolic categories from Kaplan–Meier curves that were compared using the Log-rank test. Cox proportional-hazards regression modeling was used to analyse the effect of several variables on event free survival. All covariates known to affect prognosis after ACS including age, gender, smoking status, hypercholesterolaemia, hypertension, past history of ACS, discharge diagnosis, discharge prescription for aspirin, clopidogrel, beta-blockers, angiotensin converting enzyme inhibitors and statin, revascularisation status and glucometabolic status were entered into the model. Results are reported as hazard ratios (HRs) with associated 95% confidence intervals (CIs). Multivariate logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for events in each glucometabolic categories after adjustment for above clinical characteristics.

4.4 Results

4.4.1 Patients

There were 1489 admissions with elevated cardiac markers during the indexed period, of which 90% were secondary to acute coronary syndrome. Following exclusion of known diabetic patients and patients who died prior to OGTT, 768 patients were included in the

study. The baseline characteristics of the patients classified into the three groups based on their glucometabolic status are shown in table 3. Following OGTT 337 patients were noted to have NGT, while 279 patients had IGT and 152 patients had NDM. The mean age of patients in the NGT group was 62, while for both the IGT and NDM the mean age was slightly higher at 68. Other baseline characteristics were similar across the three groups. The study population was predominantly male. Similarly majority of patients presented following NSTE-ACS, with 58% of the NGT, 57% of IGT and 60.5% of the NDM having had an NSTE-ACS.

All patients underwent coronary angiography, of which 42% underwent a revascularisation procedure (PCI 37%, CABG 5%). Following FPG assessment 689 (89.7%) had normal fasting glucose, 48 (6.3%) had IFG and 31 (4%) had NDM. However when the results of the OGTT were applied 328 had NGT, 9 had IFG, 279 had IGT and 152 had NDM. As mentioned previously during further analysis, patients with IFG were considered a part of the NGT group, since by definition they did not have post-challenge hyperglycaemia. Of the 689 patients with normal fasting glucose only 328 had normal glucose tolerance; while of the 48 patients with IFG based on FPG, 9 had normal glucose tolerance.

4.4.2 Outcome measures

During the course of the study which included the 47.2± 9.4 months follow up period, a total of 224 events occurred. These included 102 mortalities of all causes, 95 non-fatal myocardial infarctions, 18 admission secondary to heart failure and 9 non-haemorrhagic strokes. Of the 102 all cause mortalities 32 (9.5%) had NGT, 44 (15.8%) had IGT and 26 (17.1%) had NDM. Out of the 102 mortalities, 79 occurred as a first event. The remaining 23 mortalities occurred

during the follow up period after a non-fatal primary end point. Of these, 13 were cardiovascular mortalities (3 in NGT, 8 in IGT and 2 in NDM groups), 4 secondary to malignancies, 3 due to sepsis, 2 due to haemorrhagic strokes, and 1 secondary to chronic obstructive pulmonary disease.

The incidence of adverse events progressively increased from the NGT to the NDM group (Table 4). There was a significant difference in the event free survival between the three groups (Figure 3). After adjusting for the presence of covariates using the Cox proportional hazard modeling (Table 5), IGT and NDM were strong independent predictors of survival free of the primary end-point.

Table 4. First cardiovascular event in relation to glucometabolic status

	NGT (n=337)	IGT (n=279)	NDM (n=152)	P	p for trend	Total (n=768)
Death	24(7·1)	33(11·8)	22(14·5)	0·027	0·008	79(10·3)
Non-cardiovascular	13(3.9)	12(4.3)	8(5.3)	0.778	-	33(4.3)
Cardiovascular	11(3·3)	21(7·5)	14(9·2)	0·015	0·005	46(6·0)
Non-fatal re-infarction	31(9·2)	35(12·5)	29(19·1)	0·009	0·003	95(12·4)
Non-haemorrhagic stroke	1(0·3)	6(2·2)	2(1·3)	0·102	0·163	9(1·2)
Heart failure re-admission	5(1·5)	9(3·2)	4(2·6)	0·351	0·295	18(2·3)
MACE*	48(14·2)	71(25·5)	49(32·2)	<0·001	<0·001	168(21·8)

Summary of events that occurred until death or end of follow up (Feb 1, 2011)

NDM, but not IGT, independently predicted all cause mortality (HR 2.14, 95% CI: 1.17-3.94; p=0.0145), cardiovascular mortality (HR 2.83, 95% CI: 1.24-6.45; p=0.0135), non-fatal MI (HR 1.96, 95% CI: 1.16-3.29; p=0.0121) and combined cardiovascular death or non-fatal MI (HR 2.17, 95% CI: 1.39-3.38; p=0.0007) (Figure 4). The absence of abnormal glucose tolerance was associated with reduced cardiovascular mortality (HR 0.45, 95% CI: 0.23-0.91; p=0.0257), combined cardiovascular death or non-fatal MI (HR 0.62, 95%: 043-0.90; p=0.0125) and combined cardiovascular mortality, non fatal MI or heart failure (HR 0.61, 95% CI: 0.43-0.87; p=0.0069). The adjusted ORs for MACE were significantly higher in the IGT, NDM and abnormal glucose tolerance (AGT) groups compared to the NGT group; however the odds of the secondary end-points increased with NDM and AGT but not with IGT (Table 6).

The log-likelihood ratio tests were used to compare the fit of predictive models using categories based on FPG and OGTT separately and in combination. Comparing the nested models showed that including the OGTT categories significantly improved the predictability of the model based on FPG categories and the above risk factors, for MACE ($\chi 2 = 26.41$, df=3, p=0.00), cardiovascular death ($\chi 2 = 9.1$, df=3, p=0.03), nonfatal MI ($\chi 2 = 11.75$, df=3, p=0.01) and combined end-point of cardiovascular deaths and non-fatal MI ($\chi 2 = 19.18$, df=3, p=0.00). In contrast, the addition of categories, to the model based on FPG, based on OGTT and risk factors did not significantly improve the prediction of the model for MACE ($\chi 2 = 0.44$, df=2, p=0.80), cardiovascular deaths ($\chi 2 = 0.59$, df=2, p=0.74), non-fatal MI ($\chi 2 = 0.08$, df=2, p=0.96) and combined end-point of cardiovascular deaths and non-fatal MI ($\chi 2 = 0.13$, df=2, p=0.94).

Figure 3. Kaplan–Meier estimates for the three groups showing survival free of all-cause mortality (A), cardiovascular mortality (B), non-fatal re-infarction (C), and MACE (D). Numbers below graph are the number of patients at risk.

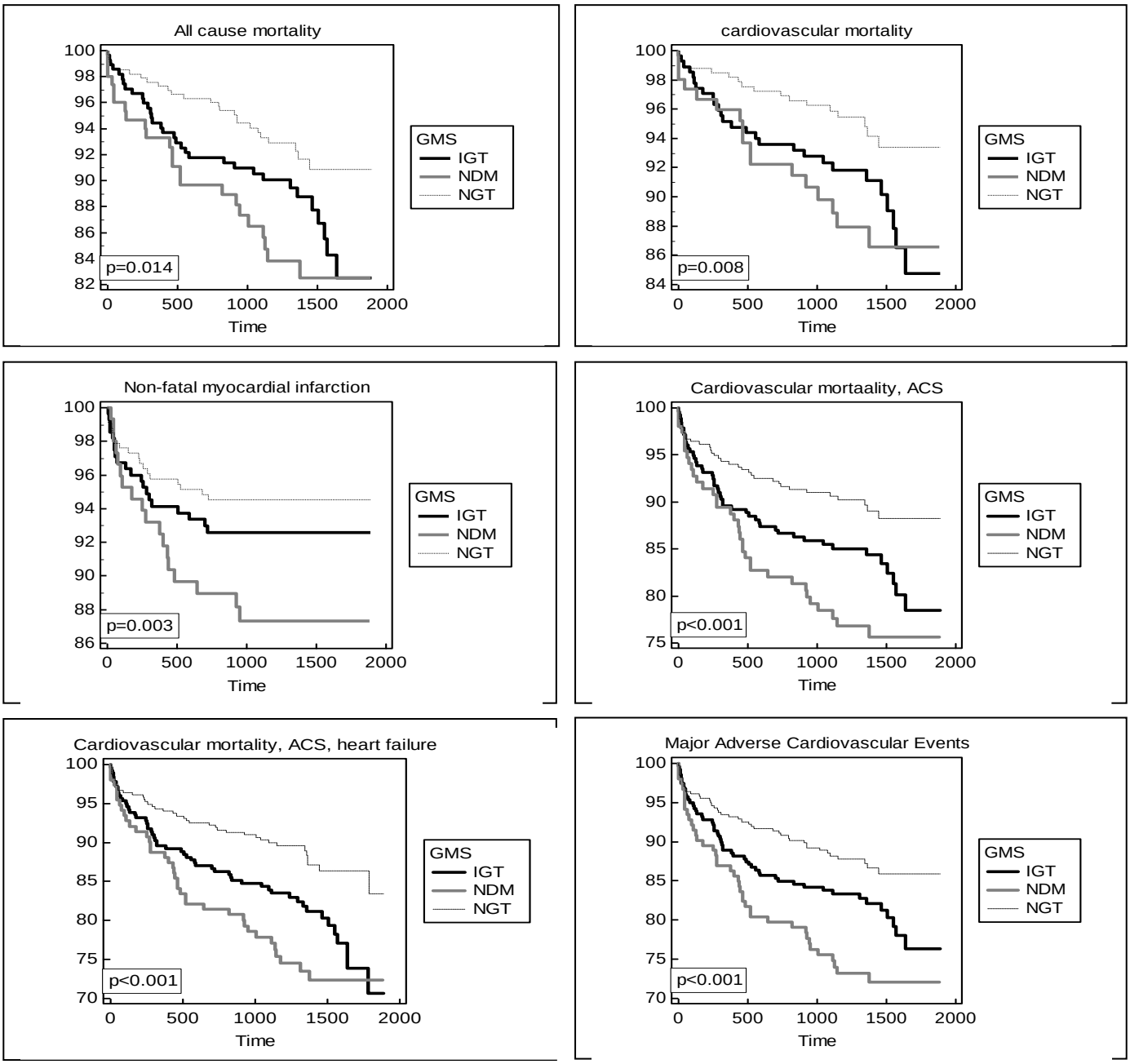


Table 5. Candidate predictors affecting major cardiovascular events for the entire population using Cox proportional hazard modeling.

Covariates	HR	95% CI	p
Age	1·037	1·02-1·05	<0·0001
Previous myocardial infarction	2·281	1·63-3·18	<0·0001
Newly diagnosed DM	2·148	1·42-3·24	0·0003
Absence of Post-challenge hyperglycaemia	0·574	0·41-0·81	0·0016
Newly diagnosed IGT	1·543	1·06-2·24	0·0242
Discharged without beta-blockers	1·446	1·03-2·04	0·0365
Discharge diagnosis of STEMI	1·382	1·01-1·90	0·0475
Discharged without ACEI	1·442	0·98-2·11	0·0614
Hypertension	1·303	0·95-1·78	0·1001
Discharged without Aspirin	1·447	0·90-2·33	0·1297
Revascularised	1·273	0·92-1·75	0·1407
Hypercholesterolaemia	0·860	0·63-1·18	0·3550
Discharged without clopidogrel	1·162	0·80-1·68	0·4246
Female gender	0·879	0·62-1·25	0·4765
Current smoker	0·904	0·62-1·32	0·6055
Discharged without statin	1·152	0·63-2·10	0·6460

Figure 4: Survival curves for patients with NGT, IGT and NDM showing survival free of all cause mortality, cardiovascular mortality, non-fatal myocardial infarction and a combination of the latter two, adjusted for covariates using Cox proportional-hazards regression modeling.

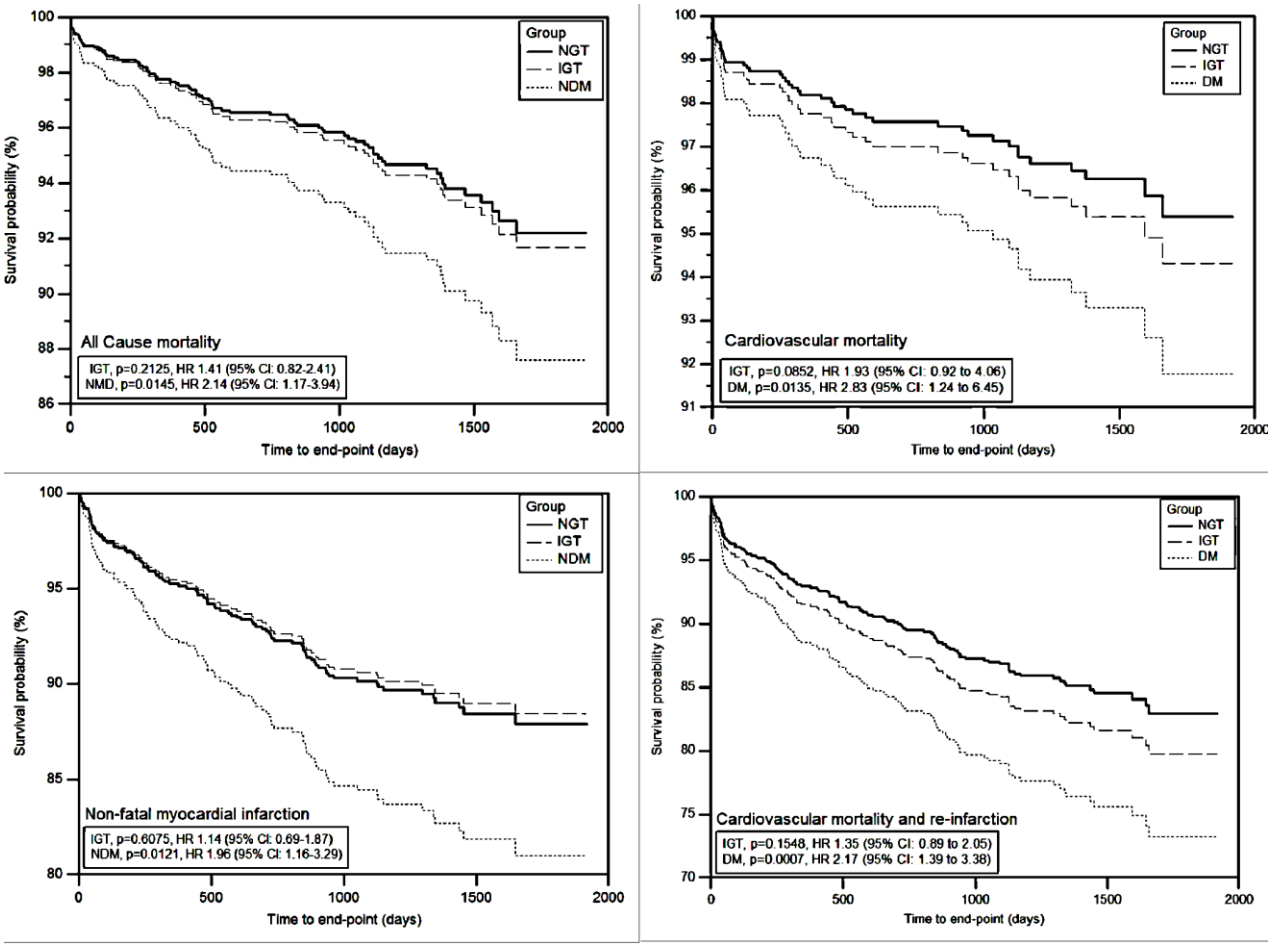


Table 6. Adjusted logistic regression for the primary and secondary end-points at the end of follow up according to glucometabolic state after the oral glucose tolerance test.

	NGT	IGT			DM		
		OR*	95% CI	p	OR*	95% CI	P
All death	1·00	1·28	0·69-2·40	0·436	2·05	0·99-4·28	0·055
CVS death	1·00	1·83	0·81-4·09	0·144	3·40	1·31-8·85	0·012
CVS death or non-fatal MI	1·00	1·41	0·87-2·28	0·159	2·59	1·53-4·40	<0·001
CVS death, non-fatal MI or CCF	1·00	1·52	0·96-2·40	0·071	2·52	1·51-4·20	<0·001
Non-fatal MI	1·00	1·19	0·69-2·06	0·527	2·09	1·17-3·75	0·013
MACE	1·00	1·74	1·11-2·72	0·016	2·71	1·63-4·50	<0·001

4.5 Discussion

This study demonstrates that the incidence of MACE following ACS increases progressively from patients with NGT to those with NDM. The study also showed that the MACE free survival is reduced not just in the NDM group, but in patients with IGT and that both IGT and NDM are strong predictors of MACE. While there are other similar studies examining the incidence of adverse events post-ACS in patients with glucometabolic disorders [91, 92, 93], the present study is by far the largest to assess the effect of AGT in this population. Furthermore, previous studies have given conflicting results with regard to the prognostic effect of IGT. Although both the GAMI study group and the work of Tamita et al (2007)

reported an independent effect of AGT on the incidence of MACE, neither study reported the adjusted hazard of MACE in patients with IGT and NDM separately. The study by Kitada et al (2010) on the other hand reported similar MACE rates for both NGT and IGT patients, while the MACE rate for the NDM group was higher. The Euro Heart Survey [96] reported the prognosis in 2515 non-diabetic patients with CAD, including 1029 with ACS, and 11 classified on the basis of OGTT. Within the whole population, NDM but not IGT independently increased the risk of death but not the other end-points. However the study included patients with both ACS and stable CAD, and since the details of MACE for the ACS patients were not published separately, it is impossible to predict the prognostic effect of the glucometabolic states in these patients. However, the study clearly demonstrates that not only NDM but IGT is also associated with an increased risk of MACE following ACS.

While the MACE rates in present study were similar to those previously reported; the differing definitions of ACS and MACE used in other studies [91, 92, 93, 94], rendered comparison of MACE rates between studies less meaningful. Differences in baseline characteristics may have resulted in higher MACE rates in the NGT group compared to that in others [91, 92]. Contrary to some, the present work demonstrated clinical events rather than target vessel revascularisation as the major adverse event in newly diagnosed IGT or DM patients post-ACS. Furthermore, since both STE-ACS and NSTE-ACS were included, with the latter often diagnosed on the basis of small increases in cardiac markers and symptoms with or without ECG changes, the results imply that newly diagnosed IGT and NDM imposes a worse prognosis even in patients without severe myocardial damage. Although the MACE rates in patients with STE-ACS and NSTEACS were not analyzed separately, a discharge diagnosis of STEACS but not NSTE-ACS independently predicted MACE.

The management of patients in the study was in keeping with contemporary guidelines and published data [92, 96]. The revascularisation rates were similar to those in the GRACE registry [105]. In summary, the findings from the current research indicate that the risk of major adverse cardiac events following ACS is increased not only in patients with NDM but in those with IGT.

Chapter 5: The effect of isolated post challenge hyperglycaemia on prognosis after acute coronary syndrome

5.1 Introduction

Patients presenting with acute coronary syndrome have an increased incidence of glucometabolic perturbations, including that of newly diagnosed diabetes and impaired glucose tolerance. As described previously, such patients have an increased incidence of adverse events and worse prognosis. Epidemiological studies have indicated that patients with abnormal glucose tolerance are at increased risk of cardiovascular events [7, 110, 111]. In addition to impaired glucose tolerance (IGT), post prandial hyperglycaemia may also be an important predictor for cardiovascular mortality. Post-challenge plasma glucose level following an OGTT is the most sensitive method to assess post prandial hyperglycaemia. The Honolulu Heart Programme reported that the risk of fatal coronary artery disease (CAD) and non-fatal acute cirinary syndrome (ACS) in 6394 non-diabetic men of Japanese ancestry during a 12 year follow-up period was significantly higher in those with elevated post-challenge plasma glucose [112]. Similar results were noted with the Diabetes Intervention Study where elevated post-challenge glucose levels were associated with increased risk of all cause mortality and coronary artery disease in patients with type 2 diabetes [113].

Certain epidemiological investigations such as the Rancho-Bernardo and the DECODE studies [114,115] have examined the cardiovascular risk specifically associated with isolated post-challenge hyperglycaemia (IPCH); a glucometabolic category characterized by a normal fasting plasma glucose level but with an elevated post-challenge glucose level, and an increased risk of cardiovascular mortality. On the other hand the Strong Heart Study found that IPCH was not associated with any significant rise in all-cause or cardiovascular mortality [116]. IPCH is known to exaggerate neo-intimal hyperplasia in patients post bare metal stent implantation, suggesting a potential pathophysiological process which could contribute to

increased cardiovascular complications [117]. The effect of IPCH on major adverse cardiac events post-ACS has not been explored. In this study, an analysis was conducted, of prospectively collected data on patients admitted with ACS who were diagnosed with IPCH on pre-discharge OGTT in order to evaluate the relationship between IPCH and long-term MACE in the context of current practice.

5.2 Research design and methods

5.2.1 Patients

A detailed description of the methodology is given in chapter 2. In brief, this observational study includes all non-diabetic patients admitted with ACS during the study period. Baseline demographic data, co-morbidities, risk factors, pre-admission and pre-discharge medications, cardiac markers and revascularisation status were collected. Patients with a known diagnosis of diabetes, those who died before the OGTT or did/could not have an OGTT were excluded. Patients with a fasting plasma glucose > 7.0 mmol/l were also excluded. All patients underwent standard OGTT, following an overnight fast, on or after the third day of admission.

5.2.2 Definitions

Isolated post-challenge hyperglycaemia was defined as fasting plasma glucose level of < 7.0 mmol/l and a 2 hour-plasma glucose level of ≥ 11.1 mmol/l. This is in keeping with the definition followed in the above mentioned clinical studies. Further details regarding this definition and those of other co-variates and risk factors have been described previously.

5.2.3 Outcome measures

All participants were followed up for a median period of 48 months for cardiovascular outcomes. Each event was recorded at the first occurrence only. Follow-up data were complete for all patients. Every death was counted in the all cause mortality but not in the condition that led to the death. Cardiovascular death was defined as death from MI, heart failure (HF) and sudden death without any obvious reason. A non-fatal re-infarction was defined as a non-fatal MI occurring later than 72 h after the index infarction. Stroke was defined as a neurological deficit persisting >24 hours as observed by a physician. Severe HF was recognized when requiring hospital admission for intensification of or additional treatment. The primary end-point was defined as the first occurrence of a MACE including cardiovascular death, non-fatal re-infarction, severe HF or non-haemorrhagic stroke. Secondary end-points were all cause mortality, cardiovascular mortality, non-fatal re-infarctions, severe heart failure or stroke.

5.2.4 Statistical analysis

Continuous variables are presented as mean±SD and median (interquartile range, IR) and categorical variables as counts and proportions (%). Differences in baseline characteristics between the two groups were compared using the t-test and Mann-Whitney test for parametric and non-parametric data respectively for continuous variables and chi-squared test for categorical variables. Kaplan–Meier curves were computed for event free survival. The log-rank test was used for comparing the differences in cardiovascular events and survival, and Cox proportional-hazards regression modeling was used to analyse the effect of several variables on event free survival. Age, gender, smoking status, hypercholesterolaemia,

hypertension, history of previous acute myocardial infarction, diagnosis at discharge, prescription at discharge of aspirin, clopidogrel, beta-blockers, angiotensin-converting enzyme inhibitors and statins, and revascularisation status were "entered" as co-variates into the model. Results are reported as hazard ratios (HRs) with associated 95% confidence intervals (CIs). Multivariate logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for events in each glucometabolic category after adjustment for the above baseline clinical characteristics. A two-sided p value <0.05 was regarded as statistically significant.

5.3 Results

5.3.1 Patients

There were 1489 admissions with elevated cardiac markers during the indexed period, of which 90% were secondary to acute coronary syndrome. Following exclusion of known diabetic patients and patients who died prior to OGTT, 768 patients remained. The fasting plasma glucose level was > 7 mmol/l in 79 patients and they were excluded from further analysis, leaving a cohort of 689 patients. Following 2h-PG, 52% of these patients had IPCH. Patients were hence categorized into 2 groups; the normal glucose tolerance (NGT) group (n= 328) and IPCH group (n= 361). The baseline characteristics of the study patients are shown in table 7. Patients with IPCH were older with a higher prevalence of hypertension, previous MI, IHD and were more likely to be treated with ACE-I/ARB. They also had higher fasting plasma glucose (although < 7.0 mmol/l).

Table 7: Clinical characteristics of the study population

	NGT(n=328)	IPCH(n=361)	p
Age, years	62.6±12.1	67.3±12.3	<0.0001
Male n (%)	229(69.8)	261(72.3)	0.47
Current smoker	140(42.7)	131(36.3)	0.09
Hypertension	118(36.0)	152(21.3)	0.00
Hypercholesterolaemia	150(45.7)	164(45.3)	0.94
Previous myocardial infarction	50(15.2)	77(21.3)	0.04
Known IHD	84(25.6)	119(33.0)	0.03
Family history	134(40.9)	130(36.0)	0.19
Discharge diagnosis of STEMI	134(40.9)	150(41.6)	0.85
Discharge medications			
Aspirin	300(91.5)	331(91.7)	0.91
Clopidogrel	272(82.9)	292(80.9)	0.49
Dual anti-platelet	257(78.4)	273(75.6)	0.39
Beta-blocker	254(77.4)	274(75.9)	0.63
ACEI/ARB	261(79.6)	309(85.6)	0.04
Statin	317(96.7)	339(93.9)	0.09
Revascularised	144(43.9)	145(42.2)	0.32
Troponin I (µg/l; median; IQR)	2.7(12.4)	3.0(12.3)	0.87
FPG (mmol/l; median; IQR)	4.9(0.5)	5.1(0.8)	<0.0001
2h-PG (mmol/l; median; IQR)	6.3(1.6)	10.0(2.6)	<0.0001

5.3.2 Outcome measures

Table 8 summarizes all the events during the 48 month follow up period. A total of 198 events (91 deaths from all cause, 83 non-fatal reinfarctions, 17 heart failure admissions and 7 non-haemorrhagic strokes) occurred during the period. Out of the 91 all-cause mortalities, 31 (9.5%) in the NGT group and 60 (16.6%) in the IPCH group occurred as the first event. Amongst these, 39 were cardiovascular deaths (18 had ACS, 17 had heart failure, 2 sudden cardiac death and 2 non-haemorrhagic strokes). Of the remaining 32 first event all-cause mortalities, 13 were secondary to cancer, 7 due to pneumonia, 5 due to haemorrhagic stroke, 3 due to sepsis, one due to gastro-intestinal bleed and one secondary to chronic obstructive pulmonary disease (COPD). Of the 20 deaths that occurred after the incidence of a composite study end-point, 13 were cardiovascular deaths (3 in the NGT group, 10 in the IPCH group), one due to cancer, 3 due to sepsis, 2 due to haemorrhagic strokes and one due to COPD. 146 major adverse cardiac events were noted, 68.5% of which occurred in the IPCH group.

Table 8. First cardiovascular event in relation to glucometabolic status

	NGT (n=328)	IPCH (n=361)	P	Total (n=689)
Death	23(7.0)	48(13.3)	0.007	71(10.3)
Non-Cardiovascular	13(4.0)	19(5,3)	0.418	32(4.6)
Cardiovascular	10(3.1)	29(8.0)	0.005	39(5.7)
Non-fatal re-infarction	30(9.2)	53(14.7)	0.026	83(12.0)
Non-haemorrhagic stroke	1(0.3)	6(1.7)	0.076	7(1.0)
Heart failure re-admission	5(1.5)	12(3.3)	0.128	17(2.5)
MACE[a]	46(14.0)	100(27.7)	<0·001	146(21.2)

Table summarizes events that occurred until death or end of follow up.

The incidence of all cause mortality, cardiovascular mortality, non-fatal MI and overall MACE were higher in the IPCH group. The Kaplan–Meier curves (Figure 5) of the two groups diverge early and continue to do so till end of follow-up. There were significant differences in event-free survival among the groups. After adjustment for important covariates using Cox proportional hazard modeling (Table 9), absence of IPCH was the third strongest predictor of survival free of the primary end-point after age and history of MI.

Table 9. Candidate predictors affecting major cardiovascular events for the entire population using Cox proportional hazard modeling.

Covariate	HR	P	95% CI of Exp(b)
Age	1.04	<0.001	1.02 to 1.05
Previous myocardial infarction	2.48	<0.001	1.74 to 3.54
Absence of IPCH	0.58	0.0037	0.41 to 0.84
Hypertension	1.40	0.0502	1.00 to 1.96
Discharge Diagnosis of "STEMI"	1.42	0.0523	0.10 to 2.01
Discharge without statin	1.79	0.075	0.95 to 3.38
Discharge without aspirin	1.52	0.1015	0.92 to 2.49
Revascularised	1.27	0.1668	0.91 to 1.79
Discharge without ACEI/ARB	1.32	0.2085	0.86 to 2.03
Discharge without beta-blocker	1.25	0.2538	0.85 to 1.82
Hypercholesterolaemia	0.90	0.5664	0.64 to 1.27
Current smoker	0.91	0.6307	0.60 to 1.36
Discharge without clopidogrel	1.07	0.7532	0.72 to 1.59
Female gender	0.98	0.9072	0.67 to 1.42

IPCH also predicted cardiovascular mortality and its combination with non-fatal MI and HF (Figure 6). Within the IPCH group, both IGT (HR 1.55, 95% CI:1.05 to 2.28, p=0.028) and NDM (HR 2.20, 95% CI:1.38 to 3.50, p=0.001) increased the risk of MACE. NDM also increased the risk of all cause mortality (HR 2.10, 95% CI: 1.07 to 4.13, p=0.033), non-fatal MI (HR 1.95, 95% CI: 1.07 to 3.56, p=0.0296) and cardiovascular death and MI (HR 2.07, 95% CI: 1.24 to 3.47, p=0.006). Impaired glucose tolerance (IGT) did not affect these secondary end-points. The adjusted ORs for MACE were significantly higher in the IPCH group, as were the combination of cardiovascular mortality with non-fatal MI and HF (Table 10).

Table 10. Adjusted logistic regression for the primary and secondary end-points at the end of follow up according to glucometabolic state after the oral glucose tolerance test.

	NGT	IPCH		
		OR[a]	95% CI	P
All cause mortality	1.00	1.45	0.38 to 1.24	0.212
CVS mortality	1.00	2.08	0.22 to 1.04	0.063
Non-fatal MI	1.00	1.45	0.42 to 1.14	0.145
CVS mortality or non-fatal MI	1.00	1.69	0.37 to 0.92	0.020
CVS mortality or non-fatal MI or HF	1.00	1.79	0.37 to 0.86	0.009
MACE	1.00	2.00	0.33 to 0.77	0.002

[a] Odds ratio adjusted for age, gender, previous history of myocardial infarction, smoking status, hyperlipidaemia, hypertension, discharge diagnosis (STEMI, NSTEMI), discharge medications i.e. aspirin, clopidogrel, statin, ACEI or ARB and beta-blockers and revascularisation.

Figure 5. Kaplan–Meier curves for patients with NGT and IPCH showing survival free of all cause mortality, cardiovascular mortality, myocardial infarction, and major adverse cardiac events. Survival compared using log-rank test.

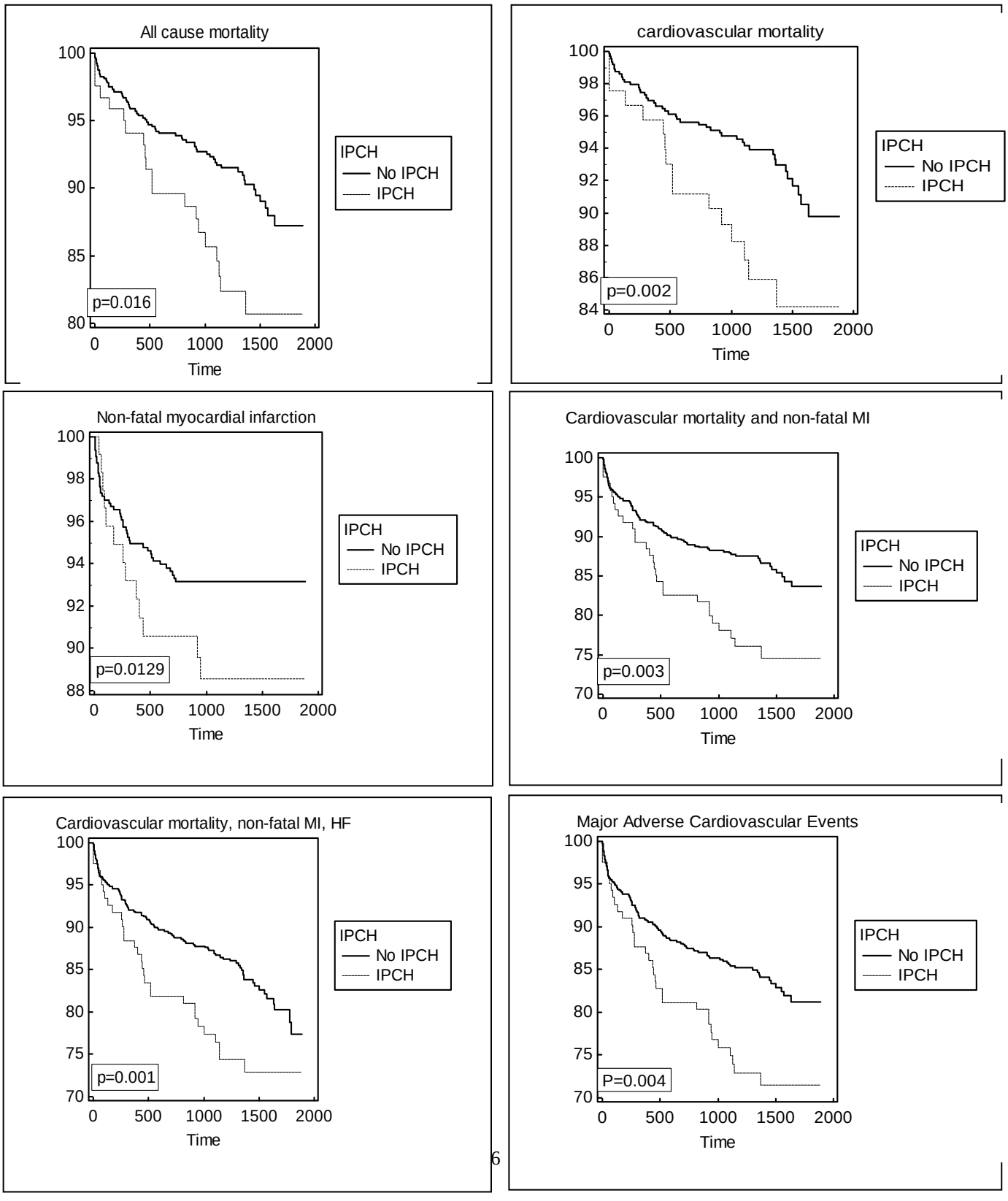
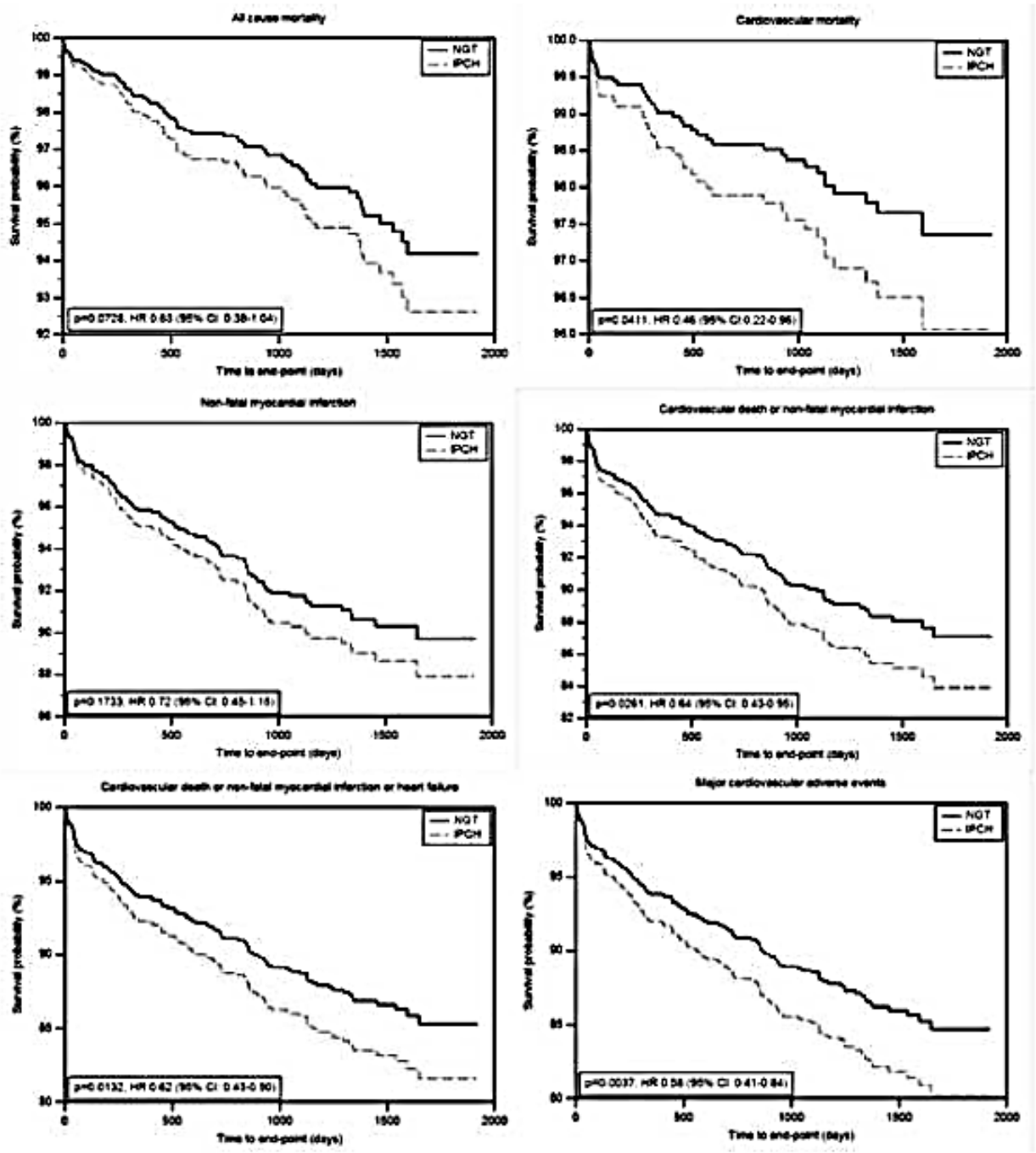


Figure 6. Survival curves for patients with NGT and IPCH showing survival free of all cause mortality, cardiovascular mortality, non-fatal myocardial infarction and a combination of the latter two adjusted for covariates using Cox proportional-hazards regression modeling.



5.4 Discussion

To the best of my knowledge this is the only study assessing the effect of newly diagnosed IPCH on prognosis after ACS in the context of current clinical practice. The data demonstrate that a large proportion of non-diabetic patients admitted with ACS have IPCH, that would remain undiagnosed on FPG assessment alone. Furthermore patients with IPCH have a significantly increased incidence of MACE and poorer event free survival rates.

Although some epidemiological studies have noted that the incidence of cardiovascular complications is higher in patients with IPCH during long term follow up in the general population [114, 115], its relationship with prognosis in patients post-ACS has not been explored. IPCH was defined in these studies as FPG < 7.0 mmol/l and 2h-PG ≥ 11.1 mmol/l. This excludes patients with impaired fasting glucose and patients with IGT. None of the studies on the prognosis after ACS in non-diabetic patients with abnormal glucose tolerance have examined the role of IPCH.

IPCH appears to be an important sub-group that warrants further attention due to the potential for under diagnosis despite a high prognostic risk following ACS. About 66% of the patients, in the current study would have been misdiagnosed as having a normal glucometabolic status on the basis of their FPG levels. More than half of the patients with normal FPG had IPCH. The prevalence of IPCH with normal FPG is much higher in this study, compared to studies like the Rancho-Barnardo study (8%), DECODE study (14%) and the National Health and Nutrition Examination Survey III [114, 115, 118]. This could be due to the highly selected nature of the study population and the effect of stress due to recent ACS.

While studies suggest that the glucometabolic status diagnosed on the basis of pre-discharge OGTT could change in the longer term [6, 104], only a small percent of patients in the IGT or NDM group based on pre-discharge OGTT, change to NGT post-discharge [103]. As described in the previous chapter the timing of OGTT in relation to the ACS event may influence its ability to predict long term glucometabolic status. If performed too soon after the event the results may be affected by acute stress induced hyperglycaemia and insulin resistance hence overestimating the prevalence of IPCH [94, 104]. The acute response decreases significantly after the initial 48 hours [6]. The majority of the patients in the present study underwent OGTT at least 72 hours after the index event, making it likely that the results would reliably predict long term glucometabolic state. Pre-discharge IPCH, independent of its relation to long term glucometabolic status, reliably predicts prognosis in post-MI patients even after adjusting for several covariates.

Using comparable definitions of adverse events, the 14% and 28% MACE rate in the NGT and IPCH groups compares to 3-10% and 4-31% respectively in other studies [91, 92, 93]. The MACE rate in the GAMI study that did not include patients with “isolated” PCH but defined MACE as in the present study, closely matches the present results [92]. Cardiovascular mortality in our IPCH and “normal” patients of 8% and 3% compares to 7.5% and 4% respectively in the DECODE Study that used identical definitions [119]. Comparison with other studies is less meaningful due to the differing definitions of MI and MACE [94]. Differences in the baseline characteristics may have resulted in higher MACE rates in the NGT group compared to that of others [91, 92] and since a more inclusive definition of MI was used the present results may imply that newly diagnosed IPCH imposes a worse prognosis even on patients without severe myocardial damage. Though the MACE rates in

the STEMI and NSTEMI patients were not measured separately, a discharge diagnosis of STEMI did not predict MACE.

Chapter 6: Predictive value of OGTT, FPG and APG for adverse prognosis following acute coronary syndrome in patients without diabetes.

6.1 Introduction

Acute coronary syndrome is associated with an increased incidence of glucometabolic perturbations, characterized by elevated admission plasma glucose (APG) [66, 68, 69, 106], fasting plasma glucose (FPG) [71, 72, 73, 120], glycated haemoglobin A1c (HbA1c) [67] or 2 hour-plasma glucose (2h-PG) [91, 92, 93, 94]; and increased risk of adverse long term prognosis. However, it is not clear, which of these glucometabolic parameters, best predicts long term prognosis following ACS since there is a lack of studies that have examined the relative ability of APG, FPG and 2h-PG to predict prognosis after ACS.

The GRACE registry examined the risk of in-hospital and 6 month mortality in patients following ACS, and noted that while both APG and FPG are associated with an increased risk of in-hospital death, the risk of 6 month mortality was predicted by FPG only [73]. Similarly Suleiman et al (2005) showed that FPG was a better predictor of 30-day mortality than APG. Furthermore, most of the studies demonstrating the adverse effect of APG in post-ACS prognosis did not include 2h-PG levels.

On the other hand, in the studies that did include 2h-PG levels, the results were conflicting with a lack of consistency in the outcome. The GAMI study demonstrated that neither FPS nor 2h-PG were independent predictors of MACE [92]. Kitada et al (2010) reported that a 2h-PG level of $\geq$ 160 mg/dl (8.9 mmol/l) was an independent predictor of long term MACE in post-ACS patients [93]. Tamita et al (2007) demonstrated that APG and FPG did not predict long term MACE, while the presence of abnormal glucose tolerance did so [91]. The study however did not describe the effect of 2h-PG on these events. In the present study the aim

was to examine the relative value of APG, FPG and 2h-PG in predicting the long-term prognosis in this population.

6.2 Research design and Methods

6.2.1 Patients

Detailed description of the methodology is as documented in chapter 2. In brief, this observational study included all non-diabetic patients admitted to the North Lincolnshire and Goole hospitals NHS trust, during a 3 year period with a confirmed diagnosis of acute coronary syndrome. All patients had APG, FPG and 2h-PG documented. Demographic details, co-morbidities and details regarding management including that of coronary intervention were obtained.

6.2.2 Outcome measures

All participants were followed up for a median period of 48 months for the incidence of cardiovascular events. Follow up data was complete for all the patients. Each event was recorded at the first occurrence only. Details regarding how individual events were defined have been described in detail in chapter 2. The primary end-point was a composite outcome defined as the first occurrence of a major adverse cardiac event (MACE) including cardiovascular death, non-fatal re-infarction, severe heart failure or non-haemorrhagic stroke. Secondary end-points were all cause mortality, cardiovascular mortality, non-fatal re-infarctions, severe heart failure or stroke.

6.2.3 Statistical analysis

Continuous variables are presented either as means (±SD) or median (interquartile range, IQR) and categorical variables as counts and proportions (%). Differences in baseline characteristics between the three groups were compared using one-way analysis of variance and Kruskal-Wallis test for parametric and non-parametric data respectively for continuous variables and the chi-squared test for categorical variables.

Event free survival was estimated in these quartiles of 2h-BG from Kaplan–Meier curves that were compared using the Log-rank test. APG, FPG or 2h-PG were "entered" as continuous variables along with age, gender, smoking status, hypercholesterolaemia, hypertension, history of previous acute myocardial infarction, diagnosis at discharge, discharge prescription of aspirin, clopidogrel, beta-blockers, angiotensin-converting enzyme inhibitors and statins and revascularisation status into the Cox proportional-hazards regression models individually and in combination to analyse the effect of several variables on event free survival. Cox proportional hazard models are essentially survival models which relate the time following ACS against various covariates (glucometabolic status). Results are reported as hazard ratios (HRs) with associated 95% confidence intervals (CIs). Multivariate logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for events APG, FPG or 2h-PG as continuous variables after adjustment for above clinical characteristics.

Nested models were compared using $\chi 2$ likelihood ratio tests to determine whether the Cox regression model that included APG, FPG and 2h PG provided a better fit than models limited to each of these variables individually did, both in pairs and vice versa. Receiver-operating characteristics (ROC) analysis was used to assess the ability of various levels of

APG, FPG and 2h PG to predict MACE. An ROC curve is essentially a curve created by plotting the true positive rate against the false positive rate at various threshold settings. The areas under each ROC curves (AUC) were compared to assess the best variable that predicted MACE [121]. Differences were considered statistically significant at the 2-sided P<0.05 level.

6.3 Results

6.3.1 Subject sample and demographics

A total of 674 patients were included for this analysis. The clinical characteristics of the patients according to 2h-PG quartiles are shown in Table 11. The patients in the higher quartiles were older and had higher prevalence of hypertension and ischaemic heart disease. About 76% of patients with ST elevation acute coronary syndrome (STEMI) were thrombolysed of whom 23% needed rescue PCI. Another 2% had primary percutaneous intervention (PCI). Remaining patients were not eligible for thrombolysis and were not reperfused. Among the STEMI patients that did not undergo acute reperfusion, 29% had ischaemia driven revascularisation (PCI in 72%).

All patients with NSTEMI had a coronary angiogram and 41% were revascularised (92% had PCI). The median (IQR) ARPG, FPG and 2h-PG were 6.6 mmol/l (2.4 mmol/l), 5.1 mmol/l (0.8 mmol/l) and 8.2 mmol/l (4.0 mmol/l) respectively. Following the conventional definitions of glucometabolic status, all the patients in the 1st quartile and 126/160(78.7%) in the 2nd quartile had NGT; 34/160(21.3%) in the 2nd quartile, all patients in the 3rd quartile and 39/172(22.7%) in the 4th quartile had IGT and the rest in the 4th quartile had new

diabetes mellitus (NDM). About 319/383 (83.3%) patients with abnormal 2h-PG, had normal FPG.

Table 11. Clinical characteristics of the study population categorized by quartiles of 2h post load glucose.

	Q1,<6.6 (n=165)	Q2,6.6-8.1 (n=160)	Q3,8.2-10.5 (n=177)	Q4,>10.5 (n=172)	p
Age(years; median; IQR)	61(13)	64(17)	67(18)	69(20)	<0·001
Male n (%)	120(72.7)	109(68.1)	131(74.0)	122(70.9)	0.66
Non-smoker n (%)	41(24.9)	48(30.0)	50(28.3)	57(33.1)	0.40
Hypertension n (%)	43(26.1)	69(43.1)	73(41.2)	79(45.9)	<0·001
Hypercholesterolaemia n (%)	73(44.2)	86(53.8)	82(46.3)	79(45.9)	0.32
Previous AMI n (%)	22(13.3)	27(16.9)	39(22.0)	36(20.9)	0.15
Known IHD n (%)	36(21.8)	48(30.0)	55(31.1)	60(34.9)	0.06
Diagnosis STEMI n (%)	67(40.6)	70(43.8)	82(46.3)	70(40.7)	0.66
Discharge medications					
Aspirin n (%)	155(93.9)	144(90.0)	163(92.1)	156(90.7)	0.58
Clopidogrel n (%)	132(80.0)	136(85.0)	137(77.4)	147(85.5)	0.15
Dual anti-platelet n (%)	126(76.4)	128(80.0)	129(72.9)	136(79.1)	0.40
Beta-blocker n (%)	132(80.0)	118(73.8)	136(76.8)	134(77.9)	0.60
ACEI/ARB n (%)	128(77.6)	133(83.1)	148(83.6)	144(83.7)	0.39
Statin n (%)	159(96.4)	155(96.9)	165(93.2)	163(94.8)	0.38
Revascularised n (%)	74(44.9)	70(43.8)	70(39.6)	66(38.4)	0.56
Troponin I (µg/l;median; IQR)	2.5(13.7)	3.2(14.5)	3.5(15.7)	3.1(14.4)	0.90
FBG (mmol/l; median; IQR)	4.9(0.5)	5.0(0.6)	5.2(0.8)	5.6(1.1)	<0·001
RBG (mmol/l; median; IQR)	5.9(1.93)	6.4(1.75)	6.8(2.4)	7.7(2.8)	<0·001
2HBG (mmol/l; median; IQR)	5.6(1.4)	7.4(0.8)	9.3(1.33)	12.3(3.0)	<0·001

3.3.2 Outcomes

A total of 65 (9.6%) deaths occurred during the follow up. Rates of MACE and non-fatal MIs were higher, with a trend towards higher cardiovascular mortality in the upper glucose quartiles (Table 12). Kaplan-Meier survival curves (Figure 7) showed a significant decrease in unadjusted event-free survival with increasing quartiles of 2h-PG suggesting decreased event-free survival not only in diabetics but also in pre-diabetic patients. After adjustment for co-variates using the Cox proportional hazard regression model that included FPG alone, FPG independently predicted MACE free survival (HR 1.25, 95% CI: 1.05-1.49, p=0.0122) along with age, previous MI and absence of discharge beta-blockers. It also predicted survival free of cardiovascular mortality (HR 1.51, 95% CI: 1.11-2.04, p=0.0082) and its combination with MI (HR 1.24, 95% CI:1.03-1.51, p=0.0260).

Table 12. First cardiovascular event in each quartile of 2 hour post load plasma glucose.

	Q1 (n=165)	Q2 (n=160)	Q3 (n=177)	Q4 (n=172)	p	Total (n=674)
Death	9(5.5)	12(7.5)	23(13.0)	21(12.2)	0.052	65(9.6)
Non-cardiovascular	4(2.4)	7(4.4)	9(5.1)	7(4.1)	0.644	27(4.0)
Cardiovascular	5(3.0)	5(3.1)	14(7.9)	14(8.1)	0.051	38(5.6)
Non-fatal MI	13(7.9)	23(14.4)	19(10.7)	32(18.6)	0.021	87(12.9)
Non-hgic stroke	1(0.61)	0(0.00)	4(2.3)	4(2.3)	0.153	9(1.3)
HF re-admission	1(0.61)	6(3.8)	4(2.3)	5(2.9)	0.289	16(2.4)
MACE[a]	20(12.1)	34(21.6)	41(23.2)	55(32.0)	<0·001	150(22.3)

Table summarizes events that occurred until death or end of follow up.

When 2h-PG alone was included, it independently predicted survival free of MACE (HR 1.12, 95% CI:1.06-1.18, p<0.0001), all cause mortality (HR 1.13, 95% CI:1.04-1.23, p=0.0033), cardiovascular mortality (HR 1.19, 9% CI:1.07-1.32, p=0.0009), non-fatal MI (HR 1.09, 95% CI:1.02-1.17, p=0.0133) and their combination (HR 1.12, 95%CI:1.06-1.19, p=0.0001). APG alone did not predict any of the end points. When APG, FPG and 2h-PG were included in the same model, 2h-PG, but neither FPG nor APG, independently predicted MACE free survival (Table 13). It also predicted all cause mortality (HR 1.17, 95% CI: 1.05-1.29, p=0.0039), cardiovascular mortality (HR 1.17, 95% CI: 1.02-1.33, p=0.0205), non-fatal MI (HR 1.10, 95% CI: 1.01-1.19, p=0.0291), cardiovascular mortality or MI (HR 1.12, 95% CI: 1.05-1.21, p=0.0015) and cardiovascular mortality or MI or HF (HR 1.12, 95% CI: 1.05-1.20, p=0.0008).

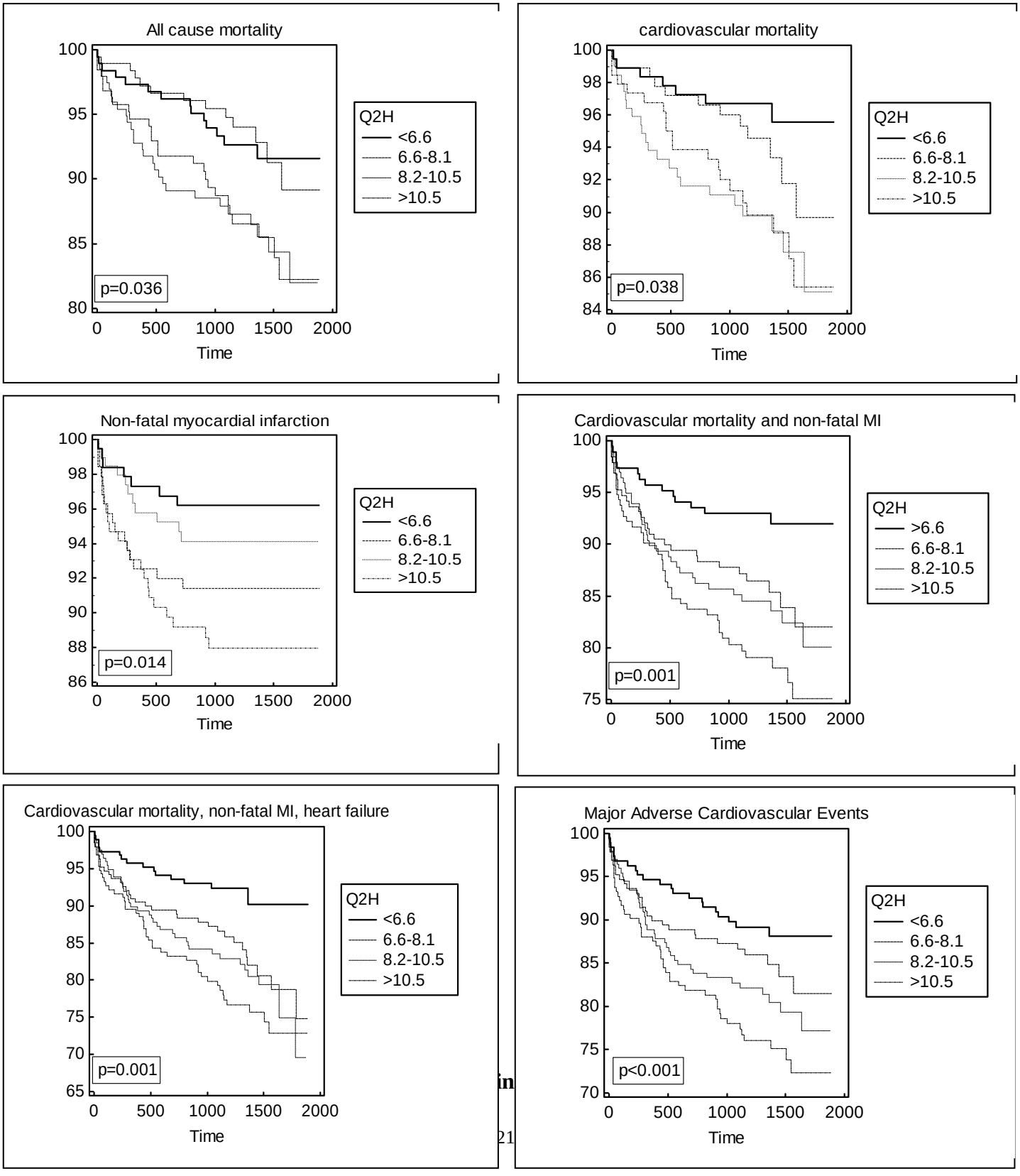
2h-PG alone in a logistic regression model independently predicted the odds of MACE (OR 1.14, 95% CI: 1.07-1.22, p<0.0001), cardiovascular deaths (OR 1.16, 95% CI:1.04-1.30, p=0.0080), non-fatal MI (OR 1.09, 95% CI: 1.01-1.18, p=0.022) and their combination (OR 1.13, 95% CI:1.06-1.21, p=0.0003). Similarly, FPG independently predicted MACE (OR 1.35, 95% CI:1.07-1.69, p=0.0106), cardiovascular deaths (OR 1.55, 95% CI:1.10-2.20, p=0.0131) and its combination with non-fatal MI (OR 1.32, 95% CI:1.04-1.68, p=0.0231). However, entering APG, FPG and 2h-PG into a single model showed that odds of all cause mortality (OR 1.13, 95% CI: 1.01-1.26, p=0.0411), non-fatal MI (OR 1.11, 95% CI:1.02-1.22, p=0.0232), cardiovascular mortality or MI (OR 1.15, 95% CI:1.05-1.25, p=0.0015) and MACE (OR 1.15, 95% CI:1.07-1.25, p=0.0004) significantly increased with increasing 2h PG but not APG or FPG.

Table 13. Candidate predictors affecting major cardiovascular events for the entire population using Cox proportional hazard modeling.

Covariate	HR[a]	95% CI of HR	P
Age	1.04	1.02-1.05	<0.0001
Previous MI	2.43	1.71-3.45	<0.0001
2h post load plasma glucose	1.12	1.05-1.19	0.0006
Discharged without beta-blockers	1.58	1.10-2.26	0.0143
Revascularised	1.32	0.94-1.85	0.1172
Discharged without clopidogrel	1.35	0.91-2.00	0.1338
Hypercholesterolaemia	0.80	0.57-1.12	0.1934
Hypertension	1.24	0.89-1.74	0.2053
Discharged without ACEI	1.26	0.84-1.88	0.2701
Discharge Diagnosis of STEMI	1.18	0.84-1.66	0.3313
Current smoker	0.82	0.55-1.23	0.3382
Discharged without Aspirin	1.26	0.76-2.10	0.3715
Female gender	0.88	0.60-1.28	0.5017
Random plasma glucose	0.97	0.89-1.06	0.5029
Fasting plasma glucose	1.04	0.83-1.31	0.7420
Discharged without statin	1.08	0.55-2.12	0.8231

[a] Hazard ratio adjusted for age, gender, previous history of myocardial infarction, smoking status, hyperlipidaemia, hypertension, discharge diagnosis (STEMI, NSTEMI), discharge medications i.e. aspirin, clopidogrel, statin, ACEI or ARB and beta-blockers and revascularisation.

Figure 7. Kaplan–Meier estimates showing survival free of all cause mortality, cardiovascular mortality, myocardial infarction, and major adverse cardiac events with patients grouped into quartiles of 2h-PG. Survival compared using log-rank test.



The area under the ROC curves predicting MACE were 0.526 for APG (p=0.342), 0.574 for FPG (p=0.005) and 0.633 for 2h-PG (p<0.0001). On pair wise comparison of the AUC predicting MACE there was no difference between APG and FPG (p=0.117), but that for 2h-PG was significantly higher than for both APG (p=0.001) and FPG (p=0.044). The log-likelihood ratio tests were used to compare the fit of predictive Cox regression models that included APG, FPG and 2h-PG together, in pairs and individually. Examination of the nested models demonstrated that including the 2h-PG as a continuous variable significantly improved the ability of a model based on relevant co-variates and APG alone (χ^2 =33.19, df=1, p<0·0001), FBG alone (χ^2 =22.58, df=1, p<0·0001) or APG and FBG (χ^2 =23.21, df=1, p<0·0001) to predict MACE free survival. A similar pattern was observed with all cause mortality when 2h PG was added to APG (χ^2 =14.98, df=1, p=0·0001), FBG (χ^2 =17.12, df=1, p<0·0001) or APG and FBG (χ^2 =16.5, df=1, p<0·0001); cardiovascular mortality when 2h PG was added to APG (χ^2=21.93, df=1, p<0·0001), FBG (χ^2 =10.18, df=1, p=0·0014) or APG and FBG (χ^2 =10.71, df=1, p=0·0011), non-fatal MI when 2h PG was added to APG (χ^2 =10.96, df=1, p=0·0009), FBG (χ^2 =9.41, df=1, p=0·0022) or APG and FBG (χ^2 =9.38, df=1, p=0·0022). Including FPG into models based on APG alone improved their predictability for MACE (χ^2 =10.20, df=1, p=0·0014), cardiovascular deaths (χ^2 =13.37, df=1, p=0·0003) and its combination with non-fatal MI (χ^2 =8.58, df=1, p=0·0034). Adding FPG into models based on 2h-PG alone (χ^2 =0.016, df=1, p=0·8993) or the combination of 2h-PG and APG (χ^2 =0.216, df=1, p=0.6421) did not improve their predictability for MACE or any other end-points. If APG was included in a model based on FPG alone (χ^2 =0.29, df=1, p=0·5902), 2h PG alone (χ^2 =0.72, df=1, p=0.3961) or the combination of FPG and 2h PG (χ^2 =0.92, df=1, p=0.3375) the predictability of these models for MACE did not improve. A similar pattern was noted for all other end-points.

6.4 Discussion

The present study evaluated the prognostic value of APG, FPG and 2h-PG in patients without a history of diabetes, presenting after ACS. The study demonstrated that FPG when considered as the lone glucometabolic marker predicts prognosis independently. However, when considered along with 2h-PG, it was not an independent predictor. On the other hand, post-challenge plasma glucose appeared to be the strongest predictor of MACE, cardiovascular mortality, all cause mortality and non-fatal MI compared to APG and FPG.

While the association between glucometabolic disorders and ACS is well documented, the significance of post-challenge plasma glucose in predicting prognosis, relative to APG and FPG, is not well established. Although multiple studies have reported the adverse prognosis in post-ACS patients using conventionally defined glucometabolic abnormalities diagnosed by APG, FPG and OGTT, these studies did not report the independent effect of 2h-PG on prognosis [91, 92, 93, 94]. The finding that elevated FPG increases the risk of adverse events following ACS is in keeping with the literature [71, 72, 73, 120]. In addition, the study also showed that 2h-PG is superior to FPG in predicting adverse events, while FPG ceases to be an independent predictor when considered along with 2h-PG.

Although there is a lack of studies directly comparing the predictive capacity of APG, FPG and 2h-PG in patients following ACS, some reports have tested the relative performance of these parameters in diagnosing glucometabolic disorders and predicting outcomes in patients with acute and chronic coronary artery disease. De Mulder et al (2012) demonstrated that in 169 patients presenting post-ACS, OGTT was superior to APG, FPG and HbA1c in detecting glucometabolic disturbances [122]. Ishihara et al (2006) showed that FPG and HbA1c were

superior to APG in predicting abnormal glucose tolerance in patients with ACS [80]. Okosieme et al (2008) reported that while FPG had better sensitivity in detecting diabetes in patients with ACS compared to APG, it was less specific. Likewise, although a combination of both APG and FPG was sensitive in diagnosing glucometabolic disorders, its specificity and positive predictive value remained poor [123].

Epidemiological studies have reported that 2h-PG is a better predictor than FPG or APG in predicting adverse outcomes in the general population. In the Cardiovascular Health Study, FPG and 2h-PG individually increased the risk of cardiovascular events in community dwelling elderly adults without a previous history of treated diabetes, ACS or stroke. However when both FPG and 2h-PG were included in the model only 2h-PG level remained predictive of the event risk [124]. Similarly in the DECODE study, patients diagnosed with NDM based on FPG or OGTT, and patients diagnosed with IGT based on the OGTT results had an increased risk of all cause and cardiovascular mortality. In a model which includes FPG and 2h-PG simultaneously the risk of mortality decreased only slightly in individuals diagnosed with IGT or diabetes based on the 2h-PG, but decreased significantly in patients diagnosed with IFG or diabetes based on the FPG [45]. The relative value of the APG, FPG and 2h-PG, in predicting post-ACS prognosis has not been adequately examined. Tamita et al (2007) demonstrated, in a study involving 275 patients admitted following ACS, that neither APG nor FPG independently predicted MACE. While these investigators did not look specifically for the predictive value of 2h-PG, they noted that presence of AGT independently predicted MACE, suggesting that an abnormal OGTT may be a better predictor of MACE than FPG or APG [91,125]. In the GRACE registry, an elevated level of both APG and FPG was associated with an increased risk of in-hospital mortality, but only FPG was associated

with 6-month mortality [73]. The authors felt that FPG was a better marker than APG for predicting prognosis post-ACS, especially in patients not known to have diabetes.

Studies reporting the effect of abnormal glucose tolerance on prognosis in post-ACS patients use glucose levels to categorize patients into various glucometabolic categories. It can reasonably be assumed that increasing glucose levels affect the prognosis in continuum. As described in chapter 1, the cut-offs used for diagnosing the various glucometabolic categories are based on the occurrence of microvascular complications (especially with regard to the incidence of diabetic retinopathic changes) and hence are somewhat arbitrary, especially in the context of macrovascular complications such as atherosclerotic disease and ACS. When tertiles of FPG were used, Suleiman et al (2005) noted that levels even below the conventional thresholds, affected prognosis which again suggests that these thresholds are arbitrary [71]. The present data suggest that 2h-PG as a continuous variable affects prognosis and is associated with adverse long term prognosis.

Chapter 7: The role of myocardial injury in the prognosis of patients with glucometabolic disorders following presentation with acute coronary syndrome.

7.1 Introduction

In addition to being a pre-disposing factor for the development of coronary artery disease, glucometabolic disorders also adversely affect the prognosis in patients with coronary artery disease (CAD) [126].The findings described in the preceeding chapter are consistent with this. The precise patho-physiological mechanism through which glucometabolic disorders influence the prognosis is not clear, especially in the setting of acute coronary syndrome (ACS). The likely explanation is that glucometabolic disorders are associated with an increased risk of micro and macrovascular complications mediated through various mechanisms as detailed in chapter 2. Another potential explanation is that the increased mortality is unrelated to the glucometabolic status but is a reflection of the extent of myocardial injury suffered during the event. Since patients with a larger infarct could potentially have a more pronounced stress mediated hyperglycaemic response it could be erroneously interpreted that the cause of increased adverse events in these patients was related to their glucometabolic status.

The myocardial isoform of Troponin I is a highly sensitive marker of myocardial injury and is released into the systemic circulation shortly after myocardial necrosis occurs. Numerous studies have demonstrated a consistent and positive correlation between troponin level and infarct size [127, 128, 129, 130]. Assuming the mechanism behind the increased prevalence of glucometabolic disorders in patients with ACS is stress mediated and the increased mortality in these patients is due to the infarct size, then it would be reasonable to expect a positive correlation between troponin level and the glucometabolic status. In the current study the aim was to examine the correlation between glucometabolic status and troponin levels.

7.2 Research design and Methods

Detailed description of the methodology was as documented in chapter 2. In brief, this observational study included all non-diabetic patients admitted to the North Lincolnshire and Goole hospitals NHS trust, during a 3 year period, with a confirmed diagnosis of acute coronary syndrome. All patients had admission plasma glucose (APG), fasting plasma glucose (FPG) and 2 hour-plasma glucose (2h-PG) documented. Demographic details, co-morbidities, details regarding management including that of coronary intervention were obtained.

All participants were followed up for a median period of 48 months for the incidence of mortality. Follow up data was complete for all the patients. The primary objective was to examine the relationship between Troponin I level and the glucometabolic status of these patients. Details of potential confounding factors were obtained to ensure they were accounted for.

Statistical analysis was performed using SPSS (IBM Corp, Armonk, NY) version 22. Continuous variables are presented either as means (±SD) or median (interquartile range, IQR) and categorical variables as counts and proportions (%). One way ANOVA was used to examine the correlation between troponin and glucometabolic status of the patients.
Cox proportional-hazards regression model was used to analyse the effect of troponin level on event free survival. Results are reported as hazard ratios (HRs) with associated 95% confidence intervals (CIs).

7.3 Results

There were 1489 admissions with elevated cardiac markers during the indexed period, of which 90% were secondary to acute coronary syndrome. Following exclusion of known diabetic patients, patients who died or were transferred to another center prior to OGTT, 768 patients were included in the study. The baseline characteristics of the patients classified into three groups based on their glucometabolic status are shown in table 3 in chapter 3. Patients were categorized into NGT, IGT and NDM based on the results of OGTT. Troponin I level was measured for all patients following admission and after 12 hours as per the trust policy. A rise of $\geq$ 25% from the baseline value was considered to be positive for the diagnosis of ACS, in patients with appropriate symptoms and clinical presentation.

Following OGTT, 337 patients were noted to have NGT, while 279 were diagnosed with IGT and 152 with NDM. The average trponon I level in the study population was 11.34 ± 17 ng/ml. The average troponin level for patients in the NGT, IGT and NDM groups were 10.92 ± 16.07, 11.21 ± 16.92, and 12.73 ± 19.06 ng/ml respectively. The average troponin level was higher for NDM compared to the NGT and IGT groups, while the average troponin levels for the IGT group was higher than that for the NGT group. Statistical analyses of the differences between the 3 groups were performed using analysis of variance (ANOVA) test, which demonstrated that there was no significant difference ($F(2,765) = 0.620$, $p=0.538$) between troponin results between the 3 glucometabolic groups examined. After adjusting for potential confounders (age, gender, hypertension, dyslipidaemia, smoking status, history of ischaemic heart disease, discharge diagnosis, post-discharge DAPT and revascularisation), further analysis was performed using analysis of covariance (ANCOVA) test. An ANCOVA test is an extension of the ANOVA, but with the added benefit of being able to incorporate

covariates variables. This also did not demonstrate any significant correlation between patient's glucometabolic state and troponin level after adjusting for covariates ($F(2,744)=1.705, p=0.183$) between the 3 groups. A linear regression model involving troponin and post prandial glucose level demonstrated that troponin I levels did not predict post prandial glucose levels ($F(1, 766)=1.212, p=0.271$).

Since troponin level is an indicator of myocardial injury it was reasonable to assume that patients with elevated troponin levels were more likely to have an adverse prognosis. This was tested using multiple regression in a model that included other potential predictors described above which indicated that troponin I was significantly associated with adverse outcome and predicted poor survival in patients with ACS ($F(9,747)=8.575, p<0.001$).

7.4 Discussion

The current study evaluated the relationship between the cardiac marker troponin I and glucometabolic status of patients presenting with ACS. As previously described, the troponin level reflects the extent of underlying myocardial injury in patients with ACS. The findings from the present study did not demonstrate any significant correlation between the extent of myocardial injury and glucometabolic status.

Although the mean troponin level did increase with increasing severity of glucometabolic perturbation, this was not statistically significant. Likewise, the study also showed that increase in troponin I level was associated with reduced survival and is likely to be secondary to the fact that troponin levels are indicative of the extent of myocardial injury. An elevated troponin level therefore suggests a relatively more significant myocardial injury and thereby a

poor outcome. The lack of association between glucometabolic state and troponin I levels suggests that the former was not related to the extent or severity of myocardial injury.

One of the potential arguments for adverse prognosis associated with abnormal glucose tolerance in patients presenting with ACS is that patients with a relatively larger myocardial infarction are likely to produce a greater adrenergic stress response which could drive gluconeogenesis and result in stress induced hyperglycaemia. Hence it could be argued that the adverse prognosis associated with abnormal glucose tolerance (AGT) is largely due to the extent of myocardial damage and not due to the glucometabolic state of the patient. Furthermore it is likely that the glucometabolic state of the patient might be more benign than adjudged on the basis of tests performed post-ACS. However, this would require a correlation between the glucometabolic status of the patient and a surrogate marker of myocardial injury (troponin I) which the current study did not find.

While echocardiography or similar myocardial imaging assessment might be considered to be a better method to assess the extent of myocardial injury directly; this was not considered for two reasons. A significant proportion of patients had a history of previous IHD and hence may have impaired myocardial function as a baseline. An echocardiographic assessment performed post-ACS would not be able to distinguish between long standing myocardial dysfunction from an acute injury. An echocardiographic assessment can only categorize myocardial function as normal, mildly impaired, moderately impaired or severely impaired. However, these categories are very broad and the extent of injury can vary even amongst patients within each of these categories such that troponin I would be a better substrate to define myocardial injury.

The use of troponin I as a surrogate marker for myocardial injury however does carry some limitation due to the pattern of Troponin I release from the myocyte following myocardial injury. The level starts to rise 4-6 hours after the onset of symptoms with a peak between 12-24 hours. The troponin I level can hence vary depending on the time the sample was taken. As per the local guidelines it was recommended that troponin I be measured at 12 hours after the onset of symptoms, although there was considerable variation between symptom onset and troponin measurement. Furthermore, it is possible that some patients presented to the hospital after the 12 hour period.

The majority of the studies assessing the prognostic implications of glucometabolic disorders in post ACS patients have not examined the relationship between troponin and glucometabolic status [91, 93] and hence an element of stress induced glycaemic reaction could have potentially influenced the glucometabolic state of these patients. The lack of association between adverse prognosis and glucometabolic disorders could have been a result of this. The studies that did examine this relationship found no correlation as in the current study. Knudsen et al (2009) examined the prognosis of 200 patties post STE-ACS and did not find any significant difference in the troponin results between patients with NGT and AGT. The study however did not differentiate between IGT and NDM, only examined the ST elevation acute coronary syndrome (STE-ACS) patients and did not include the non-ST elevation acute coronary syndrome (NSTE-ACS) population [104].

The above findings indicate that glucometabolic state is not related to the extent of myocardial injury. The patients in the present study underwent OGTT 72 hours after the index event. The GAMI study demonstrated that glucometabolic status identified by OGTT

performed 3-5 days post ACS is more likely to persist in the longer term [103], suggesting that after this period the influence of stress response on glucose level is not significant. This along with the current findings indicates that glucometabolic states in these patients are not secondary to a response to stress mediated hyperglycaemia.

These findings suggest that the relatively high incidence of OGTT abnormalities noted in patients presenting post-ACS is likely to be a genuine reflection of their glucometabolic state and is more likely to represent an increased risk of coronary disease. Similarly the above finding also suggest that the increased incidence of adverse cardiovascular events noted in these patients is more likely to be secondary to the effects of glucometabolic perturbations rather than a reflection of the extent of stress induced by the index event.

Chapter 8: Discussion

8.1 Introduction

Coronary artery disease and glucometabolic disorders are closely associated, and with changing life styles, the prevalence of both is on the rise. While the role of diabetes in patients with coronary artery disease and ACS has been examined, the role of intermediate hyperglycaemia in this population has not been adequately explored. The risk of vascular complications associated with insulin resistance, that characterizes glucometabolic disorders, precedes established diabetes. Furthermore, considering that the risk of micro and macrovascular complications associated with hyperglycaemia increases in a linear pattern with a rise in plasma glucose levels, it can be assumed that patients with intermediate hyperglycaemia are also at risk of adverse cardiovascular events in the setting of acute coronary syndrome [14, 15, 16]. Research examining this, however has not produced consistent findings; with some studies suggesting an increased risk in patients with intermediate hyperglycaemia while others have not demonstrated any elevated risk. Most of these studies, however, had major limitations especially with regard to sample size and may not have been adequately powered [62, 81, 82, 83, 84].

Most of the work that has examined the role of glucometabolic perturbations in patients with ACS was performed prior to the widespread use of dual anti-platelet therapy, statins, beta-blockers and percutaneous coronary intervention using drug eluting stents [131], and hence is not reflective of current practice. It would hence be of significant merit to establish whether the risk of adverse cardiovascular events associated with glucometabolic disorders is relevant in the context of current clinical practice.

The current study is by far the largest to examine the effect of abnormal glucose tolerance on prognosis in patients presenting with ACS. The management of the patients included was in keeping with contemporary guidelines. Most previous studies [91, 92, 93] recruited fewer patients before the widespread use of statins, clopidogrel and drug eluting stents and the effect of IGT on prognosis remained unclear. Although both the GAMI group [92] and Tamita et al [91] suggested an independent effect of AGT on MACE, neither reported the adjusted hazard ratio of MACE in patients with IGT and NDM separately. Thus it is unclear whether the demonstrated effect of AGT on prognosis was due to the combined effect of IGT and DM, or if largely driven by the MACE rates in the NDM group. Kitada et al [93] reported similar MACE rates in the NGT and IGT groups with higher MACE rates in the NDM. In most of these studies MACE predominantly consisted of revascularisation for restenosis and denovo lesions with very few cardiovascular events. To assume adverse prognosis predominantly based on the need for repeat revascularisation may not indicate an adverse outcome from a survival or quality of life point of view. Euro Heart Survey [98] reported the prognosis in 2515 non-diabetic patients with CAD, which included 1029 patients with ACS, based on the OGTT classification. Within the whole population, NDM but not IGT independently increased the risk of death but not the other end-points. Since the MACE rate for the ACS patients has not been published separately, it is difficult to infer the prognostic effect of the glucometabolic states in this cohort.

8.2 Increased prevalence of glucometabolic disorders in patients with ACS

The prevalence of type 2 diabetes in the North Lincolnshire region, from where the present study cohort was derived, is around 7.5% based on data from the Yorkshire Public Health Observatory [132]. Diabetes UK reports a prevalence rate of 15% for IFG or IGT based on

the WHO definition [133]. In the current study population, the prevalence rate for NGT was 43.9%, while that for IGT was 36.3% and NDM was 19.8% following OGTT. This demonstrates that while the prevalence rate of NDM is higher than in the general population, in keeping with previous literature, the prevalence of IGT is also considerably higher. As mentioned previously, macro-vascular complications can develop years prior to the development of diabetes, and hence could explain the reason for this increased prevalence. Most similar studies examining the prevalence rate of glucometabolic disorders in ACS population used fasting plasma glucose levels to assess the glucometabolic states, which underestimates the prevalence of intermediate hyperglycaemia, while the studies which did use OGTT for assessment recruited small number of patients [91, 92] and the current study findings were consistent with these studies.

Since OGTT was not repeated following discharge, random fluctuation in glycaemia or stress associated hyperglycaemia could potentially have influenced the results and contributed to the increased prevalence of AGT in these patients. While it cannot be stated conclusively whether the pre-discharge glucometabolic state may or may not vary in the medium to long term, the reliability of pre-discharge OGTT in reflecting “true”glucometabolic state could be improved by the timing of the test in relation to the index presentation. Glucometabolic categories based on OGTT performed within 24 hours of STE-ACS changed in 46% patients at 3 months following discharge in some studies [94, 104]. However, OGTT performed after 3-5 days seems to predict long-term glucometabolic abnormality reliably [6, 103]. This may be related to the reduction of the acute responses between 2-5 days with no further decrease thereafter [6]. The GAMI group [105] suggested a somewhat better reproducibility of OGTT in patients with subendocardial than transmural infarction. While performing a repeat OGTT post

discharge would have helped identify the glucometabolic status of these patients with greater sensitivity, since most of the present study patients underwent OGTT at or after 3 days from the presentation, the likelihood of the long term predictability of the glucometabolic state of these patients is likely to be high.

The above conclusion supports the notion that patients presenting with ACS should undergo OGTT as a standard care not just for prognostic purposes, but in order to identify patients with glucometabolic disorders. Since it is logistically inefficient to screen the entire population to identify patients with glucometabolic disorders, screening patients presenting with ACS is likely to improve the detection rate. Established evidence suggest that active intervention in terms of dietary and life style modification reduces the risk of intermediate hyperglycaemic conditions progressing to type 2 diabetes and reduces the risk of micro and macrovascular complications [134, 135].

Irrespective of its relation to long term glucometabolic status, pre-discharge OGTT based categorization independently predicts long term prognosis in post-MI patients.

8.3 Stress induced hyperglycaemia and its role in prognosis post ACS

Despite precautions taken with regard to the timing of OGTT, it is possible that the increased incidence of glucometabolic disorders identified in this study could have been partly confounded by stress induced hyperglycaemia. The precise pathophysiology behind stress associated hyperglycaemia is not well understood, but is believed to be due to complex interplay between various hormones including catecholamines, cortisol, growth hormone and cytokines resulting in increased hepatic gluconeogenesis and insulin resistance [136]. While

hepatic gluconeogenesis is largely mediated by glucagon, excess cortisol and adrenaline reduce insulin mediated glucose uptake. The severity of illness is associated with a corresponding increase in the level of cytokines, while the resulting rise in glucose level exacerbates the cytokine response and thereby a vicious cycle ensues [136].

Irrespective of the exact mechanism, the presence of hyperglycaemia post- ACS is associated with poor prognosis. Studies have shown that an acute increase in the glucose level in healthy subjects is associated with significant QT interval prolongation, thereby predisposing them to electrophysiological abnormalities and potentially life threatening arrhythmia [137,138]. Furthermore, a hypoinsulinaemic state noted in these patients results in a reduction in the glycolytic substrate available for the myocyte and excess accumulation of free fatty acids. This could potentially predispose the patient to myocardial dysfunction and arrhythmia in addition to promoting endothelial dysfunction [139]. Another potential explanation for the poor outcome in patients with stress induced hyperglycaemia is that the higher level of plasma glucose is merely a reflection of a more severe myocardial insult compared to patients with lower plasma glucose levels [140]. However the results from the above study indicated that OGTT levels were not related to the extent of myocardial insult as represented by the troponin levels. This might suggest that the elevated OGTT levels noted were not due to a stress response and reflect an underlying glucometabolic disorder. Furthermore, studies examining the relation between stress induced hyperglycaemia and glucometabolic disorders have noted that patients with stress induced hyperglycaemia were more likely to have dysglycaemia even when not stressed [140]. In one study, 60% of patients with admission hyperglycaemia had confirmed diabetes at 1 year [141]. Since a diagnosis of stress hyperglycaemia requires the glucose levels to drop below the threshold for diagnosis of

diabetes once the stress settles, these patients with persistent dysglycaemia could have underlying intermediate hyperglycaemia.

8.4 Fasting plasma glucose under-estimates glucometabolic disorders

The presence of glucometabolic disorders has long term prognostic implications in patients presenting with ACS. Identification of this high risk group enables physicians to manage these patients more aggressively and with closer monitoring. Furthermore, early identification of non-diabetic glucometabolic disorders could enable life style changes which could potentially avert or delay the development of type 2 diabetes. This highlights the importance of appropriate characterization of the glucometabolic status in these patients. While multiple tests, including APG, FPG, HbA1c and OGTT, are used to assess the glucometabolic status in these patients uncertainty remains regarding the most appropriate test for glucometabolic characterisation. It is also important to remember that these different tests examine different facets of glucometabolic disorders. Although convenient and easier to perform APG lacks sensitivity in diagnosis. HbA1c is a relatively new addition to these tests; however its use is primarily to diagnose diabetes mellitus. Use of HbA1c in characterising intermediate hyperglycaemia is not well validated. Fasting plasma glucose is the most commonly used test in this context in most centers and is usually preferred over OGTT due to its convenience in comparison with the latter.

The current study demonstrated that FPG on its own underestimates the prevalence of glucometabolic disorders in patients presenting with ACS. About 90% of the patients were diagnosed normal by FPG and 84% of patients with AGT had normal FPG. Based on FPG, only 31 patients were diagnosed as NDM, while following OGTT 131 (79.6%) patients were

diagnosed as NDM. This suggests that a significant proportion of patients with glucometabolic disorders would have remained undiagnosed in the absence of OGTT. In the DECODE study, about 37% of NDM diagnosed on OGTT were normal on FPG criteria [45]. In the GAMI population, [62] 10% had NDM on FPG criteria compared to 31% on OGTT criteria. In another study, 81% of patients with AGT after AMI had normal FG [91]. Similarly the Euro Heart Survey on Diabetes and the Heart reported that evaluation of glucometabolic status based on FPG only would have resulted in misclassification in 41% of patients [142]. The findings from the present study, which involved a larger number of patients with ACS, is in keeping with these findings and suggests that OGTT is an important tool in categorization of glucometabolic status, while use of FPG on its own is likely to result in significant under diagnosis of glucometabolic disorders. On the other hand performing OGTT can be more complicated and reproducibility is perhaps not as high as for FPG. Nevertheless, based on the above findings I feel it provides better risk characterization than the other tests. Reproducibility can be improved by standardizing the test in terms of the glucose load and the timing of the test.

8.5 Newly diagnosed glucometabolic disorders adversely affects prognosis after acute coronary syndrome

It is well recognized that the vascular risks associated with glucometabolic disorders appear early in the course of the disease spectrum and years ahead of the development of diabetes [67]. Although past studies have examined the relationship between glucometabolic disorders and incidence of adverse events post ACS, these have given conflicting results. As described previously most of these studies had multiple limitations. Although both the GAMI group [92] and Tamita et al [91] suggest an independent effect of AGT on MACE, neither study

reported the adjusted hazard of MACE in patients with IGT and NDM separately. It is therefore not clear if IGT in itself is associated with poor outcome or if the adverse outcome associated with AGT is largely driven by the risk associated with NDM. Kitada et al (2010) noticed that the MACE rates for NGT and IGT were similar, while those for NDM were higher although the higher MACE rates were predominantly driven by revascularisation for restenosis and denovo lesions with very few cardiovascular events.

The Euro Heart Survey on Diabetes and the Heart reported the prognosis in 2515 non-diabetic patients with coronary artery disease which included 1029 patients with ACS. While diabetes (newly detected and previously known) was associated with adverse outcome, intermediate hyperglycaemia was not. The study, however, examined the risk of both IGT and IFG together, and the risk associated with IGT on its own was not reported [98]. Furthermore, patients in the Euro Heart Survey were followed up for 1 year, which is too short to identify longer term adverse events in this cohort. In the present study we noted that out of a total of 102 mortalities only 17 (16.7%) occurred during the first year, while 85 (83.3%) occurred after one year of which 40 (47%) of the patients had IGT. Most of the pathophysiological changes such as neointimal hyperplasia and negative arterial remodeling that influence the incidence of adverse events in these patients occur months to years after the original presentation. Hence adequate duration of follow up is a crucial factor when considering the prognostic significance in this population.

Most previous studies examining this relationship were conducted during an era when management of ACS was not as aggressive as it is today. This therefore raises the question whether the increased risk noted in these studies persists in the context of current practice.

While only 32% of patients in the study by Tamita et al [91], 46% in the study by Kitada et al and 57% of the AGT patients in the GAMI study [92] were on statins, more than 94% of patients in the study were on regular statin therapy. Patients in our study were also slightly older than patients in most other studies reflecting an increased age in the population of patients presenting with ACS [91, 94].

Most of the previously published studies do not differentiate between STE-ACS and NSTE-ACS and hence it is difficult to establish what proportion of these patients had NSTE-ACS. It is well recognized that patients with NSTE-ACS tend to be older with more co morbidities compared to patients with STE-ACS. Furthermore, while patients STE-ACS had a higher short term mortality risk, patients with NSTE-ACS had a higher risk of long term mortality [143]. Majority of the patients in our study had NSTE-ACS (58%), which is in keeping with the prevalence observed in clinical practice. Similarly the incidence of adverse events in our study was predominantly led by clinical events and not due to need for revascularisation. Since only a small proportion of revascularizations are due to re-infraction or other clinical events, an increased incidence of revascularisation need not translate to poor prognosis in the long term, which can sometimes be misleading.

The findings from the present study are more up to date and accurate with regard to the long term outcome in this population of patients. While the majority of the previous studies have only noted increased incidence of adverse events in patients with NDM, we have noted that this risk extends to patients with IGT as well. Since FPG would not be able to identify this group of patients the findings further exemplify the significance of performing OGTT in these

patients and confirm that despite aggressive medical management and revascularisation the risk associated with glucometabolic disorders persists in these patients.

8.6 Isolated post-challenge hyperglycemia (IPCH) and acute coronary syndrome

IPCH is essentially a type of post-prandial metabolic disorder that is characterized by normal fasting plasma glucose and elevated post-prandial plasma glucose level. The study (chapter 5) examined the prognostic implications of IPCH on its own, despite it being well established that patients with diabetes have an adverse outcome post-ACS. The findings of the study are significant primarily because the diagnosis of IPCH requires OGTT and hence screening patients post-ACS with FPG would result in non-identification of these high risk patients. IPCH is defined as a glucometabolic state with FPG < 7.0 mmol/l and a post-challenge glucose level of ≥ 11.1 mmol/l [144].

Following a meal insulin release is characterized by 2 stages. The initial stage which occurs immediately after meal is associated with a small quantity of insulin release in a pre-emptive fashion to blunt the glycaemic load. A secondary and much more sustained phase of release occurs depending on the glycaemic load incurred. One of the earliest changes seen in glucometabolic disorders includes the loss of this first phase of insulin release resulting in a post prandial rise in glucose and free fatty acid level which stimulates a more sustained and delayed second phase of insulin release [145].

Post-prandial metabolic disorder is hence characterized by a transient rise in plasma glucose, free fatty acid and triglyceride levels following intake of a calorie rich meal, particularly if high in refined carbohydrates. This leads to the release of free radicals and subsequent

oxidative stress response. The end result is the activation of an inflammatory response resulting in endothelial dysfunction, sympathetic stimulation and hypercoagulability. Recurrent activation of this pathway increases the risk of atherosclerosis and coronary artery disease [145]. As mentioned previously, HbA1c doesn not reflect changes in post-prandial glucose levels unless in the well controlled range (HbA1c<7.3%). At elevated levels of HbA1c, post-prandial glucose levels exert minimal influence in the HbA1c level.

The prevalence of IPCH is higher than previously assumed. The DECODE study which investigated the glucometabolic status of 7680 males and 9251 females reported that 31% of participants diagnosed with NDM had IPCH [16]. Similarly the DECODA study (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia), the Asian counterpart of the DECODE study noted that 41% of patients with NDM had IPCH [146]. The Rancho-Barnardo study on the other hand reported a much higher prevalence rate, with almost 60% of patients diagnosed with NDM having IPCH [114].

Furthermore, most of these studies have shown that IPCH is a strong predictor for future adverse cardiovascular events. The Rancho-Bernardo study which monitored patients with IPCH for a 7 year duration noticed an increased risk of adverse cardiovascular events [114]. Similarly the Honolulu Heart Programme which monitored around 8000 patients between the age of 44-70 demonstrated an increased risk in the IPCH patients [147]. However there is a lack of evidence with regard to the prognostic implication of IPCH in the context of ACS. Most of the studies that have examined the relationship between glucometabolic disorders and prognosis post-ACS have not considered at the role of IPCH in the outcome. Our findings clearly demonstrate that IPCH is associated with increased risk of adverse events in this

population. This reinforces the significance of measuring OGTT in screening high risk patients, especially in the post-ACS context.

8.7 Predictive value of APG, FPG and 2 hour post load glucose

While the present study and other similar but smaller studies have demonstrated the relationship between glucometabolic disorders and ACS, there remains some ambiguity in the best way of identifying the glucometabolic state in this population. Different tests are available to assess the glucometabolic status including random plasma glucose, fasting plasma glucose, 2 hour post load plasma glucose and HbA1c, while the OGTT uses both FPG and post load glucose levels. The European Society of Cardiology recommends the use of OGTT for this purpose although a majority of centers still use FPG [148]. The American guidelines do not recommend the use of OGTT routinely in this cohort. While it is important to recognize that different tests assess different facets of the disorder, understanding the predictive capacity of these tests will help in their appropriate use. Unfortunately the present study did not include glycated haemoglobin levels and hence we could not incorporate them in the analysis.

Over the last 2 decades around 15 observational studies have reported that elevated post prandial hyperglycaemia, even to IGT levels, can result in a significant increase in the risk of developing a coronary event [149] and this was further confirmed by a meta-analysis of over 20 studies [9]. While the meta-analysis by Coutinho et al (1999) suggested that abnormalities in both FPG and 2 hour plasma glucose are more or less equally associated with the incidence of these events, other studies such as the DECODE and Funagata Diabetes Study suggest that 2 hour plasma glucose is a better predictor [9].

A subgroup analysis of the BIOMARCS2 (Biomarker Study to Identify the Acute Risk of a Coronary Syndrome) glucose study examined the sensitivity of various tests to diagnose glucometabolic disorders in patients post-ACS, and noted that APG, FPG and HbA1c were less sensitive that OGTT. This analysis however did not examine the longer term persistence of the identified glucometabolic abnormality. Furthermore the study only included a relatively small number (n=130) of patients who were selected from a group of patients who participated in a single center randomized control study [122]. A Finnish study involving 6766 patients, who were followed up for 7-10 years, demonstrated that OGTT was a better predictor for cardiovascular events and mortality when compared to FPG [150]. However, very few studies have compared the ability of various glucometabolic tests to predict adverse events post ACS.

The findings from the current study demonstrate that OGTT is a better predictor than FPG or APG not only in identifying glucometabolic disorders but in terms of prognostic assessment. Nakamura et al (2003) demonstrated that the 2 hour plasma glucose level was associated with increased risk of atherosclerotic changes and hence was likely to be a more sensitive test in predicting incidence of coronary disease [117], while the findings from the present study suggest that this also extends to predicting adverse events post ACS.

8.8 The role of HbA1c in predicting prognosis in ACS

The use of glycated haemoglobin has certain advantages when compared to fasting or post challenge plasma glucose measurement. It is much more convenient to perform since it does not require overnight fasting or glucose challenge. It also provides a more accurate long term glycaemic measurement and is less likely to be influenced by glycaemic spikes associated

with illness or stress. However, the use of HbA1c is also associated with some disadvantages. The major limitation includes conditions that affect the haemoglobin concentrations and the strict technical specification that needs to be met for performing the analysis. A study by Olson et al demonstrated that sensitivity of HbA1c for diagnosis of diabetes was lower than that for OGTT. The sensitivity is further reduced when used for the diagnosis of pre-diabetic state [159].

There is a strong correlation between glycated haemoglobin and cardiovascular risk. Selvin et al (2010) compared the prognostic value for HbA1c and FPG in 11,092 non-diabetic patients without a history of coronary artery disease. The study noted that, when compared to FPG, HbA1C was similarly associated with the risk of developing type 2 diabetes and more strongly associated with the risk of cardiovascular disease and mortality [160]. Likewise, the study by Olsson et al demonstrated that HbA1c was strongly associated with the incidence of ACS, although this association decreased over time [161]. In diabetic patients, every 1% increment in HbA1c was associated with a 30% increase in all cause mortality and 40% increase in cardiovascular mortality [162].

Despite the availability of large population-based studies examining the relationship between HbA1c and cardiovascular events, there is limited evidence for patients with ACS. Most studies involved a small cohort and differ widely in patient selection and methodology. The results hence are not consistent. In one study involving 504 consecutive, non-diabetic patients who presented for PCI following STE-ACS, HbA1C was not a predictor for 30 day outcome [75]. Similarly, in another study, 317 patients post ACS (STE-ACS and NSTE-ACS) were classified into 2 groups depending on HbA1c level (HbA1c≤7.0%=178 vs

HbA1C>7.0%=139) and were followed up for 6 months, demonstrating that HbA1c was not associated with cardiovascular outcome or all cause mortality [74]. Lazzeri et al (2012) examined the prognostic effect of HbA1c for mortality in 518 non-diabetic patients with STE-ACS. While patients with an HbA1c level of ≥ 6.5% had higher values of admission and discharge plasma glucose levels, higher incidence of acute insulin resistance, elevated levels of fibrinogen and lower levels of HDL; there was no significant differences in short and long term mortality rates between patients with HbA1c < 6.5% and patients with HbA1c ≥ 6.5%, when followed up for a median period of 40 months [163]. In contrast to the above described findings, a study by Timmer et al (2011) involving 4176 nondiabetic patients with STEACS, noted that with increasing quartiles of HbA1c there was an associated increase in mortality over a 3.3 year follow up [67].

As described previously, a recently published study by Pararajasingam et al, examined the role of OGTT and HbA1c in 548 patients who presented with ACS. Patients under went OGTT and HbA1c assessment following admission and were followed-up for a duration of 9.8 years. HbA1c >6.5% was associated with an increased risk of mortality, however when adjusted for known DM this was not noted to be significant. Likewise, OGTT also did not show a significantly increased mortality when examined separately. A combined estimate showed a significantly increased mortality in patients categorized as newly diagnosed DM by OGTT and HbA1c b 6.5% (HR 1.56 [95% CI 1.07–2.30]) compared to patients categorized as normal/ impaired fasting glycaemia/impaired glucose tolerance by OGTT and HbA1c b6.5%. Approximately 50% of the patients with newly diagnosed DM by OGTT were only detected due to 2-hour post-load glucose values [76].

While the prognostic role of HbA1c in patients presenting with ACS is not entirely clear, it is well recognized that an incremental rise in its level is associated with changes in the vascular milieu which could potentially increase the cardiovascular disease burden. The GAMI study as previously described, demonstrated that HbA1c independently predicted glucose intolerance and correlated closely with the results of the OGTT ($r=0.39$, $p<0.0001$) [62]. Unfortunately HbA1c was not incorporated for glucometabolic assessment in the present study, since this was not in the recommended guidelines available at the time. Furthermore the role of HbA1c in the diagnosis of intermediate hyperglycaemia was not well established at the time of the study, especially with regard to the cut-off values.

8.9 Limitations

The current investigation was an observational longitudinal cohort study and despite being one of the largest to examine the effect of glucometabolic disorders and the role of OGTT in patients presenting with ACS, some limitations are acknowledged. One limitation is that the glucometabolic status of the patients was not examined post-discharge. Repeating OGTT following discharge, could have provided the information as to whether the glucometabolic status noted during admission persisted post-discharge. As described previously in this and the previous chapter, the likelihood that the glucometabolic state is secondary to stress-induced transient perturbation is low in view of the timing of the test and the lack of association with markers of myocardial injury. Furthermore, since elevated pre-discharge post-challenge hyperglycaemia, irrespective of its pathophysiological mechanism, predicted outcomes in post-MI patients, the reproducibility of these measurements and their relation to long term glucometabolic status may be less relevant when assessing prognostic risk.

Similarly the interaction between the post-discharge management of glucometabolic disorders and prognosis was not explored.

Though the revascularisation rate in the NSTE-ACS patients was similar to contemporary registries, it was lower in the STE-ACS patients compared to the EHS-ACS II survey since majority of the STE_ACS patients in the present study did not undergo primary PCI. Revascularisation status did not independently affect MACE in this study [164, 165].

Although the aim was recruit all consecutive admissions with ACS, a small group of patients was excluded. This included patients who were transferred as an emergency to another centre or who died prior to the OGTT. This constituted only a small proportion of patients and I believe that exclusion of this small group does not affect the over-all results. As mentioned in the last section HbA1c was not used for assessment of the glucometabolic state. While, HbA1c would have provided a more comprehensive glucometabolic assessment, especially with regard to long term glycaemic state, this was not a part of the guidelines at the time of study. While acknowledging this limitation, it did not affect the validity of our findings.

8.10 Clinical implications of the study findings

Findings from the current research have demonstrated that patients presenting with ACS have a high incidence of glucometabolic disorders. These patients are associated with increased incidence of adverse cardiovascular events. The study also highlighted that a significant proportion of these patients would not have been identified using fasting plasma glucose alone and would require OGTT for appropriate risk stratification. One of the major findings of clinical relevance from the study is the role of OGTT as a screening tool in this population.

As the findings have demonstrated, patients with IGT and IPCH have an increased risk of adverse events post-ACS. Both IGT and IPCH require OGTT for diagnosis and in the absence of this test patients with these conditions would remain undiagnosed.

Although these findings demonstrated an increased risk of adverse outcome, it is not clear if medical intervention with anti-hyperglycaemic agents improves prognosis. The current study was not designed to assess this aspect and existing literature reports conflicting results. The Euro Heart Survey on Diabetes and the Heart noted that lowering plasma glucose using metformin was associated with a lower incidence of cardiovascular events in patients with DM [151]. Similarly the UKPDS 34 study demonstrated that intensive glucose control using metformin appeared to reduce the risk of diabetes-related endpoints including myocardial infarction and stroke in overweight diabetic patients. The UKPDS study however was designed to examine the incidence of macro and microvascular complications which are higher than for cardiovascular events alone, and hence may have been undersized to detect the latter [152]. The PROactive trial (Prospective Pioglitazone Clinical Trial in Macrovascular events) compared Pioglitazone with placebo and demonstrated a reduced risk for secondary end point (composite end point of all cause death, non fatal ACS and CVA) in the former group [153]. While the above studies examined the risk reduction with oral anti-hyperglycaemic agents in patients with DM, the STOP-NIDDM trial examined the effect of acarbose on the risk of cardiovascular events in 1429 patients with IGT. After 3.3 years the study noted that treatment with acarbose was associated with a 25% reduction in progression to type 2 diabetes. It was also associated with a significant reduction in cardiovascular events (of 49%) and ACS (of 91%). Furthermore it was associated with a significant reduction in development of new hypertension and carotid artery atherosclerosis [154]. Similarly a large

retrospective meta-analysis of 7 long term studies demonstrated that acarbose significantly reduced the risk of ACS and cardiac events in patients with DM [155].

The recently published EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) trial examined the long term cardiovascular outcome in 7020 patients with type 2 DM. This demonstrated that patients on empagliflozin had a lower incidence of adverse events, primarily driven by reduced cardiovascular mortality. This benefit was noted in addition to the standard primary prevention therapy which includes aspirin, statin and ACE-inhibitor. Empagliflozin is an SGLT-2 (Sodium Glucose Co-transporter-2) inhibitor which facilitates urinary excretion of glucose. There is some argument that the cardiovascular benefit noted was due to anti-hypertensive or diuretic effect associated with the medication and not necessarily secondary to ints anti-hyperglycaemic effect [156]. Similarly, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) examined the incidence of cardiovascular events in patients with type 2 diabetes treated with Liraglutide. 9340 patients were randomized in a 1:1 fashion into Liraglutide and placebo; and followed-up for a median period of 3.8 years. At the end of the follow-up period the incidence of primary composite end-point (which included cardiovascular mortality, non-fatal ACS or stroke) was significantly in the Liraglutide group. Liraglutide is a Glucagon-like peptide (GLP-1) receptor agonist, which works by activating the GLP-1 hormone that in turn enables pancreatic beta cells secrete insulin in response to acute glycaemic load. Lixisenetide would hence be useful in managing IPCH and similar post-challenge hyperglycaemic conditions [47].

On the other hand, the ELIXA trial (Evaluation of Lixisenatide in Acute Coronary Syndrome), which was a multi-center double blinded placebo controlled study, examined the incidence of cardiovascular outcomes in patients with type 2 diabetes following an ACS who were treated with lixisenatide (another GLP-1 receptor agonist) or a volume-matched placebo, did not note any significant cardiovascular benefit with the use of lixasenetide. 6068 (3034 in each arm) patients were followed up for a median period of 25 months. Primary end-point events (composite of cardiovascular mortality, non-fatal re-infarction, non-fatal stroke or admission with unstable angina) occurred in 406 (13.6%) patients in the lixasenatide group and 399 (13.2%) in the placebo group. The study further highlights the high incidence of adverse cardiovascular events in these patients; but dissappintingly does not demonstrate any significant cardiovascular benefit with the use of lixisenatide [166].

Likewise, the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptine versus Standard of care) trial, examined the incidence of cardiovascular mortality in patients with diabetes on alopgliptine or placebo, post-ACS. Alogliptine, which is dipeptidyl peptidase-4 (DPP-4) inhibitor, works by blocking the effects of DPP-4 enzyme, which deactivates and hence reduces the levels of incretin which inturn inhibits the release of glucagon and encourages insulin secretion. The study examined the incidence of cardiovascular mortality in 5380 patients randomized in a 1:1 fashion to receive alogliptine or placebo within 15-90 days post-ACS. The study found no significant difference in the incidence of the all cause mortality (alogliptine: 153, placebo: 173, HR: 0.88, 95% CI: 0.71-1.09) or cardiovascular mortality (alogliptine: 112, placebo: 120, HR: 0.85, 95% CI: 0.66-1.10) between the two groups [167].

On the other hand, the ACCORD (the Action to Control Cardiovascular Risk in Diabetes) study, which examined 10,251 patients randomly assigned to standard therapy and intensive therapy for gycaemic control, demonstrated increased mortality and no significant evidence of benefit with regard to cardiovascular event protection in patients on intensive therapy. The study was discontinued prematurely following this finding [157]. Similarly in the ADVANCE (Action in Diabetes and Vascular disease: Preterax and Diamicron MR Controlled Evaluation) study, intensive glucose control although resulted in significant lowering of the glucose levels, it did not result in a reduction in major macrovascular events or death from cardiovascular causes [158].

Irrespective of whether anti-hyperglycaemic agents improve prognosis in patients with glucometabolic disorders, there is evidence to suggest that life style modification and dietary changes reduces the risk of patients with intermediate hyperglycaemia progressing into type 2 diabetes. Tuomilehto et al (2001) examined the effect of life style and dietary change in 522middle aged over weight subjects and noted that the intervention was associated with a significant reduction in progression to diabetes [134]. Similar findings were also noted in the Diabetes Prevention Program where life style intervention in 1079 patients resulted in a 58% reduction in the incidence of diabetes [135].

Based on the findings described in the current thesis, further studies would be recommended to examine whether intervention, either in-terms of life style changes or using pharmacological agents, would reduce the incidence of cardiovascular events noted in these patients. It would also be useful to compare the role of HbA1c and OGTT in predicting the incidence of adverse events in these patients, especially considering the fact that at elevated levels, HbA1c poorly reflects post-prandial glycaemia. Considering the risk of adverse

cardiovascular events associated with isolated post-challenge hyperglycaemia (IPCH) in post-ACS patients; the role of newer anti-hyperglycaemic agents like GLP-1 receptor agonists and DPP-4 inhibitors, which are better suited for managing sudden glycaemic load, in reducing cardiovascular events would need to be examined. At present, it is not entirely clear, how the results of the present study can be applied to clinical practice. Performing OGTT in every patient presenting with ACS can be a challenge, considering the work load in hospitals. Furthermore, in the absence of any clear evidence demonstrating that intervention in these patients (especially with regard to patients with IGT) results in significant reduction of cardiovascular risk, performing OGTT in every ACS patient may not result in any significant clinical benefit. As mentioned previously, it is however important to recognize that different tests examine a different aspect of glucometabolic pathway. It is hence likely that reliance on only one modality could potentially under-diagnose the true extent of these conditions in a high risk cohort of post-ACS patients.

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