Prevalence and prognostic significance of chronic hyperglycaemia post acute myocardial infarction in a multiethnic UK population

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Prevalence and Prognostic Significance Of Chronic Hyperglycaemia Post Acute Myocardial Infarction In A Multiethnic UK Population

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Abstract

Background:
Coronary heart disease (CHD) and chronic hyperglycaemia (type 2 diabetes (T2DM) and impaired glucose regulation) are highly prevalent and associated with premature and excess mortality in the South Asian (SA) compared with the White European (WE) population. Further knowledge about chronic hyperglycaemia in SA patients with acute myocardial infarction (AMI) would help develop strategies to reduce the burden of CHD in this ethnic group.

Aims:
1) To undertake a systematic review and meta-analysis to establish the association between diabetes and long-term mortality post AMI.
2) To investigate the relative prognostic significance of admission hyperglycaemia and prior diabetes in SA and WE patients admitted with AMI.
3) To compare survival in SA and WE patients presenting with AMI
4) To compare the prevalence of undiagnosed chronic hyperglycaemia in SA and WE patients admitted with AMI.
5) To evaluate the diagnostic yield and utility of oral glucose tolerance test (OGTT) versus HbA1c in screening for chronic hyperglycaemia in AMI.

Key findings:
1) Diabetes increased long-term mortality post AMI by 50%.
2) Admission glucose was strongly associated with short- and long-term mortality post AMI, irrespective of prior diabetes diagnosis.
3) Adjusted survival following AMI was similar for SA and WE patients in the UK.
4) SA patients with AMI had up to six-fold higher risk of having undiagnosed T2DM than WE patients.
5) In AMI, use of HBA1c increased the prevalence of undiagnosed T2DM by over 1.5 fold (6.0% to 8.5%) in comparison with OGTT.

Conclusion: This thesis established the higher prevalence of T2DM (diagnosed and undiagnosed) in UK SA patients presenting with AMI. This programme of work will help establish methods of screening for chronic hyperglycaemia in the setting of AMI. Early detection of T2DM in the SA population is extremely important to curb the higher incidence of CHD and related mortality in this population.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
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<td>AMI</td>
<td>Acute myocardial infarction</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
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<tr>
<td>FPG</td>
<td>Fasting plasma glucose</td>
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<tr>
<td>2hrPG</td>
<td>2-hour post glucose challenge plasma glucose</td>
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<tr>
<td>HbA1c</td>
<td>Glycated haemoglobin</td>
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<tr>
<td>IGR</td>
<td>Impaired glucose regulation</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<td>NSTEMI</td>
<td>Non-ST elevation myocardial infarction</td>
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<td>OGTT</td>
<td>Oral glucose tolerance test</td>
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<td>PVD</td>
<td>Peripheral vascular disease</td>
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<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<td>SA</td>
<td>South Asian</td>
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<td>STEMI</td>
<td>ST elevation myocardial infarction</td>
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<td>T2DM</td>
<td>Type 2 diabetes mellitus</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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<td>WE</td>
<td>White European</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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Chapter One: Introduction and guide to the thesis

1.1 Diabetes, Hyperglycaemia and Coronary Heart disease

Coronary heart disease (CHD) is the main cause of morbidity and mortality in most European countries (Allender et al. 2008). Diabetes mellitus is also a common long-term condition and it is estimated that around 6% of the UK population (Diabetes UK 2016) is currently suffering from this condition. Approximately 90% people with diabetes have type 2 diabetes (T2DM) and CHD-related mortality and morbidity is significantly increased in such individuals (Haffner et al. 1998, Bulugahapitiya et al. 2009, Emerging Risk Factors Collaboration. 2010). Furthermore, abnormalities of glucose metabolism at a level below the current threshold for diagnosis of T2DM, also known as impaired glucose regulation (IGR: pre-diabetes, impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) defined using World Health Organization 1999 criteria) or high-risk state (defined as per recommendations from UK Expert committee (John et al. 2012) of Glycated haemoglobin (HbA1c) levels 42-47 mmol/mol) are also associated with increased cardiovascular risk compared with normal glucose metabolism (Tominaga et al.1999, Coutinho et al 1999, Danaei et al. 2006, Selvin et al. 2010). Moreover, there seems to be a continuous relationship between hyperglycaemia and cardiovascular risk (Coutinho et al.1999, Danaei et al. 2006, Gerstein et al 1999, Khaw et al 2001, Selvin et al 2010). With the predicted exponential rise in obesity and T2DM and IGR, there will be a parallel and significant rise in associated CHD (Diabetes UK 2016). Urgent actions are therefore needed exploring various strategies to tackle this challenge.
In people with T2DM, early and aggressive management of blood glucose, blood pressure and lipids is associated with reduced cardiovascular complications (Gæde et al, 2008, Holman et al 2008). Similarly, in those with IGR, lifestyle and pharmacological interventions markedly reduce the progression to T2DM (Gilles et al 2007), and may also reduce the associated risk of CHD (Chiasson et al, 2003). On this basis, a policy of early detection and aggressive management of T2DM and IGR is considered as a key to preventing CHD in people with these disorders (Diabetes UK 2009, NICE 2012, UK NSC 2012, Rydén et al. 2013).

Furthermore, in those with established CHD, diabetes is common and significantly increases the risk of adverse outcomes including mortality (Rydén et al. 2013). There is therefore a greater need to optimise care of people with CHD and diabetes to improve their prognosis. This also warrants screening and early detection of previously undiagnosed T2DM and IGR in people with established CHD and early initiation of intervention to address atherosclerotic risk factors. However, knowledge in this area is still evolving. For example, the prevalence and prognostic significance of chronic hyperglycaemia in patients with acute myocardial infarction (AMI) from UK multiethnic population are less known and further research in this area is much needed.

1.1.1 Chronic hyperglycaemia and Acute Myocardial Infarction

Acute Myocardial Infarction is an acute and potentially fatal presentation of CHD, and AMI is a major contributor to the overall CHD mortality. Abnormalities of glucose metabolism are very common in people with AMI. The data from
various registries show that in patients hospitalised with AMI, 20 - 25% have a prior diagnosis of diabetes (Rydén et al. 2013). Additionally, in those previously not known to have diabetes, about 40-45% have newly diagnosed T2DM or IGR on screening with an oral glucose tolerance test (OGTT) (Rydén et al. 2013, Norhammer et al. 2002).

Among the patients presenting with AMI, compared with those without, those with established or newly detected diabetes have a worse prognosis post AMI (Donahoe et al. 2007, Lenzen et al. 2006, Aguilar et al. 2004). The excess risk associated with diabetes can be mitigated with evidence-based interventions, including early use of reperfusion and revascularization therapies in the acute stage, and thereafter secondary prevention with statins, antiplatelet agents, renin–angiotensin blockers and beta-blockers (Anselmino, 2008). The absolute benefits of these interventions can be greater in people with diabetes (Anselmino et al. 2008). However, various acute and long-term evidence-based therapies may be inadequately used in people with diabetes and this could partly explain their adverse prognosis post AMI (Anselmino et al. 2007, Gale et al. 2011). There is a need for developing strategies and care models to improve the use of evidence-based therapies and adherence to medications among patients with diabetes following AMI.

Furthermore, among those previously not known to have diabetes, screening and early diagnosis of T2DM would enable aggressive management of cardiovascular risk factors, and additionally, allow the use of specific coronary interventions and antiplatelet agents which are shown to be more effective in
the diabetes population (Rydén et al. 2013). Impaired glucose regulation carries a significant risk of progression to T2DM and increased cardiovascular morbidity and mortality (de Vegt, 2001). Early diagnosis of impaired glucose regulation would allow initiation of lifestyle interventions, including diet and exercise, and in some cases pharmacotherapy to prevent T2DM and associated complications (NICE 2012). However, effective screening strategies and care pathways for people with AMI and at risk of T2DM or IGR are lacking.

Diabetes is a long-term condition and an event of AMI represents an acute episode in the chronic and accelerated process of atherosclerosis seen in diabetes. Several pathogenic mechanisms continue to promote chronic, diffuse, multi-vessel coronary atherosclerosis in diabetes, resulting in the formation of large unstable plaques. This along with adverse thrombogenic environment further increases the risk of recurrent ischaemic events and fatal outcomes in people with diabetes over their course of life (Beckman et al. 2002, Nicholls et al. 2008, Gale et al. 2011). While many studies have examined survival following AMI among patients with diabetes, the focus has been mainly on short-term mortality. There is a paucity of studies examining long-term mortality post AMI, and further research in this area particularly involving multi-ethnic population is necessary.

1.1.2 Acute hyperglycaemia in Acute Myocardial Infarction

Acutely elevated blood glucose levels, irrespective of underlying chronic hyperglycaemia, is a common finding at admission with AMI and is associated with adverse prognosis regardless of pre-existing glycaemic status (Capes et
al. 2000, Goyal et al. 2006, Kosiborod et al. 2008). Furthermore, acute hyperglycaemia has a differential effect on post-AMI outcomes and patients with newly diagnosed diabetes suffer from worst outcomes compared to those with established diabetes (Petursson et al. 2007, Stranders et al. 2004, Wahab et al. 2002). While admission hyperglycaemia may indicate a stress-related epiphenomenon, in some patients it can also be related to undiagnosed glucose intolerance (Okosieme et al. 2008). Nonetheless, correlation between acute and undiagnosed chronic hyperglycaemia seems to be poor (Ishihara et al. 2006, de Mulder et al. 2012). With regard to its prognostic significance, some believe that only the acutely elevated glucose is important (Cao et al. 2005), while others speculate that the impact of acute and chronic hyperglycaemia on outcomes following AMI may be differential and time dependent (Ishihara et al. 2007, Tenerz et al. 2003).

Various mechanisms have been proposed to explain the adverse prognostic influence of acute hyperglycaemia and trials such as DIGAMI (Diabetes mellitus Insulin-Glucose infusion in Acute Myocardial Infarction) have been undertaken to assess the effect of intensive glucose lowering on clinical outcomes (Malmberg et al. 1995, Malmberg et al. 2005) after AMI. There was a paucity of non-diabetic subjects in these studies and the results were inconclusive. The guidelines from professional societies in this area differ in their recommendations and the strategy of intensive glucose control with insulin infusion in patients with significant acute hyperglycaemia is not universally supported in these guidelines (Deedwania et al. 2008, NICE 2011, Vergès et al. 2012, Tardif et al. 2013, Rydén et al. 2013).
These controversies and inconsistencies in the recommendations from various guidelines may be potentially affecting patient care. Currently, the majority (>65%) of patients presenting with acute hyperglycaemia in the context of AMI and not previously known to have diabetes, do not receive active management of blood glucose (Weston et al. 2007). Further knowledge on the relative strength of association of chronic versus acute hyperglycaemia with outcomes after AMI would help improve clinical practice and patient care.

1.1.3 Diabetes and CHD in the South Asian population

People of South Asian (SA) origin (countries of the Indian subcontinent, originating from India, Pakistan, Sri-Lanka, Bangladesh and Nepal) form the largest ethnic minority population in the UK comprising 4% of the UK population (ONS 2013). Compared with White European (WE), SA people bear a larger burden of CHD (Harding et al. 2008) with AMI occurring at a younger age and in some studies, being associated with premature and high mortality (McKeigue et al. 1989, Wilkinson et al. 1996). Much of the excess CHD risk in SA is thought to be related to the high prevalence of T2DM and insulin resistance in this population (Forouhi et al. 2006, Mather et al. 1998, McKeigue et al. 1991, Wilkinson et al. 1996). Prevalence of T2DM is 2 to 6 fold higher and develops 12 years earlier in people of SA compared with those of WE origin (Wild et al. 2009, Holman et al. 2011, Paul et al. 2017). Furthermore, SA individuals have a higher rate of IGR and three times greater risk of progression to T2DM than their WE counterparts (Srinivasan et al. 2007, Oldroyd et al. 2007, Wild et al. 2009). In the INTERHEART study, a large global case-control study investigating risk factors for AMI, diabetes was found to be one of the three
metabolic risk factors significantly associated with occurrence of MI at a younger age (less than 60 years) in SA compared with non-SA people (Joshi et al. 2007). Moreover, in SA people with established CHD but without T2DM, a higher degree of abnormalities of glucose metabolism was observed compared with their WE counterparts and the authors speculated that such abnormalities could also be contributing to the increased CHD risk in the SA population (Arabi et al. 2004).

There is a paucity of studies systematically examining the prevalence and associated outcomes of acute as well as chronic (known and undiagnosed) hyperglycaemia in SA patients presenting with AMI. Limited studies from UK and Canada have demonstrated that a significantly higher proportion of SA admitted with AMI had diabetes compared with WE (Gupta et al. 2002, Wilkinson et al. 1996). With regard to previously undiagnosed hyperglycaemia, one study from India showed that majority (84%) of the patients admitted with ACS and previously not known to have diabetes had either T2DM or IGR (Ramachandran et al. 2005) on OGTT conducted prior to their discharge. In another study from the UK involving patients admitted with AMI and not known to have diabetes, an OGTT conducted at 3 months showed a higher rate of T2DM and IGT in SA (66%) compared with WE (25%) people (Salmassi et al. 2006). Only few studies have reported associations between chronic hyperglycaemia and clinical outcomes in SA people presenting with AMI and they have shown conflicting results. While some studies have suggested higher case-fatality rates following AMI in migrant SA compared with WE patients in the UK (Hughes et al. 1989, Wilkinson et al. 1996), others from the UK
(Fischbacher et al. 2007, Mukhtar et al. 1995, Jones et al. 2012, Zaman et al. 2013) and Canada (Raghavan et al. 2008, Khan et al. 2010) have suggested similar (Mukhtar et al. 1995, Jones et al. 2012, Raghavan et al. 2008, Liew et al. 2006) or better (Khan et al. 2010, Zaman et al. 2013) adjusted survival for these ethnic groups in this setting.

It is very likely that in addition to increased prevalence of known T2DM, SA individuals with AMI and other forms of CHD have higher rates of undiagnosed chronic hyperglycaemia, and this may be one of the key factors driving excess CHD mortality in the SA population. Further robust studies systematically examining the prevalence of newly detected T2DM and IGR in SA patients admitted with AMI are therefore required. Similarly, robust studies assessing the impact of any chronic hyperglycaemia on outcomes after AMI in SA and WE populations are needed. This has also been identified as a key research priority in a national report by Diabetes UK (Gholap et al. 2009).

1.1.4 Establishing chronic hyperglycaemia in AMI

The observed high prevalence of undiagnosed chronic hyperglycaemia in patients with AMI warrants accurate characterisation of glucose metabolism disorders following admission with AMI. Commonly used diagnostic tests - fasting plasma glucose (FPG) or the OGTT can have limitations of reliability, inconvenience and resources in the setting of AMI, and can hamper the screening uptake (Gholap et al. 2012). The best approach to screening for glucose intolerance post AMI therefore remains debated. With the recent availability of glycated haemoglobin (HbA1c) as an additional diagnostic test for
diabetes (WHO 2011), there are opportunities for improving screening uptake using the convenient and reliable test of HbA1c and screening strategies in AMI using HbA1c as the preferred diagnostic test requires validation. For this to happen, there is a need to examine the correlation between HbA1c and fasting/2-hour plasma glucose on OGTT and the association between HbA1c and clinical outcomes in patients presenting with AMI.

The programme of work done for this thesis aims to address the various above-mentioned gaps in the current knowledge. The outline of my thesis is provided here as a chapter synopsis.

1.2 Chapter synopsis

Chapter Two provides a broad literature review on the topic of T2DM and CHD including AMI. Furthermore, there is a major focus on the epidemiology, characteristic pathophysiology, and traditional, socio-cultural and novel risk factors associated with these conditions in the SA ethnic population. At the end, the review identifies some of the research priorities in this area. The chapter forms the basis for subsequent chapters describing studies conducted to address these research gaps.

Chapter Three explores the impact of diabetes on long-term mortality following AMI. In this chapter, I present the findings of my systematic review and meta-analysis of studies conducted in the post-thrombolysis era, examining long-term mortality (1-year and longer) following AMI among people with and without diabetes. The findings provide robust estimates of the adverse association
between diabetes and long-term mortality. Reasons for such associations and implications of the findings on clinical practice and policy making are discussed. This study also identifies the need for further research which is addressed by studies described in the subsequent chapters.

Chapter Four describes the findings of a large retrospective cohort study (n=4111), conducted using the national myocardial audit programme (MINAP) database. In a multiethnic UK population of SA and WE patients admitted with ST-elevation myocardial infarction (STEMI) and non-STEMI, the study examines the relative strength of association of admission blood glucose and prior diabetes on short- and long-term mortality.

Chapter Five describes the analysis of the same MINAP cohort but looking at the association of SA and WE ethnicity with short- and long-term mortality post AMI. Comparison of SA and WE patients groups with AMI gives an insight into the differing clinical characteristics of the SA patients, and its impact on prognosis has been examined. The finding of high mean blood glucose levels at admission in SA patients without prior diagnosis of diabetes and similar data from other studies (Ramachandran et al. 2005, Salamasi et al. 2006) informed the design and conduction of the Screening White Europeans and Ethnic South Asian for glucose inTolerance following a Heart attack: SWEET-Heart study.

The SWEET-Heart study is a prospective cohort study primarily examining the prevalence of screen-detected T2DM and IGR in SA and WE patients admitted with AMI and previously not known to have glucose abnormalities. The primary
hypothesis is that the rates of newly detected T2DM and IGR will be higher in SA compared with WE people in the high risk cohort of AMI. I also aimed to assess the diagnostic yield and utility of the OGTT and HbA1c tests in identifying chronic hyperglycaemia post AMI. The Chapters Six, Seven and Eight describe the work undertaken in the SWEET-Heart study.

Chapter Six describes the methodology of the SWEET-Heart study.

Chapter Seven reports the main findings of the SWEET-Heart study. For the SA and WE patients admitted with AMI and not known to have diabetes, the various demographic and clinical characteristics are described. The rates of newly diagnosed chronic hyperglycaemia in the SA and WE ethnic groups ascertained using the conventional OGTT as well as the new HbA1c criteria are reported. Univariate and multivariate associations between ethnicity and chronic hyperglycaemia are reported. This sets the scene for chapter eight which discusses how best to screen for chronic hyperglycaemia in AMI.

Chapter Eight focuses on diagnostic yield and utility of HbA1c versus OGTT in identifying T2DM and IGR/high-risk state following presentation with AMI and discusses various approaches for screening for chronic hyperglycaemia in the setting of AMI. At the end, the relevance of findings of the SWEET-Heart study to the screening recommendations given in the NICE guidance ‘Hyperglycaemia in Acute Coronary Syndrome. Clinical guidelines 130’ (NICE 2013) are discussed.
Chapter Nine summarises the main findings in this thesis and provides directions for clinical practice, policy making and future research.

1.3 Primary research aims

The primary aims of this thesis are to:

1. Review literature on the adverse association of T2DM and IGR with CHD in particular AMI in SA population and identify areas needing further research.
2. Conduct a systematic review and meta-analysis examining the association between diabetes and long-term mortality post AMI.
3. To establish the prevalence of previously diagnosed diabetes in SA and WE patients with AMI and its impact on mortality following AMI.
4. Undertake a prospective cohort study examining the prevalence and prognostic significance of previously undiagnosed T2DM and IGR in UK SA and WE patients admitted with AMI.
5. To establish diagnostic yield and usefulness of HbA1c versus OGTT in diagnosing chronic hyperglycaemia in patients admitted with AMI and suggest strategies and care pathways for screening for chronic hyperglycaemia in a multiethnic UK population in the setting of AMI.
Chapter Two: Coronary heart disease and type 2 diabetes, and its significance in the South Asian population: A literature review

2.1 Chapter Overview

Chapter Two provides a broad literature review on T2DM and CHD, in particular AMI, and highlights the ethnic variations in epidemiology, pathophysiology and outcomes of these disorders in the SA population. Furthermore, the review identifies the key research priorities in reducing the larger burden of these disorders in the British SA population. The information on CHD and T2DM in the SA population in this chapter is published as an original research article in a peer-reviewed journal and has been highly cited (Gholap et al. 2011).

2.2 Abstract

Diabetes is a major risk factor for morbidity and mortality from CHD, attributed mainly to the array of athero-thrombogenic abnormalities seen in diabetes. South Asian populations across the globe and in the UK harbour a significantly higher risk of developing CHD and T2DM. This excess risk is largely related to increased adiposity, insulin resistance and related novel atherosclerosis risk factors in SA people, resulting from a complex interplay of gene-environment and socio-cultural factors. This narrative review provides insight into the epidemiology, characteristic pathophysiology and outcomes of CHD in people with T2DM with a particular focus on the SA population.
2.3 Introduction

Diabetes, especially T2DM, is now a major driver behind CHD (Danaei et al. 2006). T2DM is growing at an alarming rate (IDF 2015) and is associated with a parallel rise in CHD-related morbidity and mortality (Rydén et al. 2013). As reported in a recent meta-analysis, a 50-year-old with diabetes has a risk of dying on average 6 years earlier than someone of the same age without diabetes (Seshasai et al. 2011). The excess risk of death in diabetes is attributed to deaths from both vascular and nonvascular causes (Seshasai et al. 2011). With estimated 415 million people worldwide having diabetes in 2015 and predicted to increase to 642 million by 2040, diabetes remains a major health and economic challenge globally (IDF. 2015). The cost of diabetes care can be as high as 12% of the national health budget (IDF 2015). Furthermore, there are significant ethnic variations with the SA populations both on the sub-continent and in diaspora suffering from a much higher incidence and prevalence of T2DM and CHD. South Asian people develop these disorders at an earlier age and suffer from premature and high mortality. Tackling the excess burden of CHD and T2DM and related healthcare inequalities remain the major task for the governments and policy makers worldwide.

The main purpose of this review is:

- To outline epidemiology and pathophysiology of CHD with a particular focus on the impact of rising rates of T2DM on the risk of AMI.
- To review the current knowledge on epidemiology and characteristic pathophysiology of T2DM and CHD in a British SA population.
To draw specific attention to the role of the novel, cultural and socioeconomic factors on occurrence and outcomes of CHD in the SA population.

To identify the research gaps and suggest the way forward in tackling challenges posed by CHD and T2DM in the British SA population.

2.4 Coronary heart disease

2.4.1 Burden of CHD in the UK

Coronary heart disease remains the biggest killer in the UK despite a significant >50% fall in CHD mortality over the last 50 years. Furthermore, CHD is the most common cause of premature (<75 years of age) deaths in the UK and in 2010, accounted for about 25,000 premature deaths (Scarborough et al. 2011). In 2009, CVD cost £8.7 billions to the UK healthcare economy and £19 billions in total to the UK economy. Furthermore significant ethnic, regional and socioeconomic inequalities are seen in the epidemiology of CHD in the UK (Scarborough et al. 2011). Moreover, diabetes and obesity, the major risk factors for CHD and associated mortality are rising rapidly, threatening to reverse the recent trends of improvement in CHD mortality seen over the last few decades (Bottle et al. 2009, Scarborough et al. 2011).

People of SA origin comprise about 5% of the total UK population, and contribute to disproportionately high 25% of all death from CHD in the UK (Scarborough et al. 2011, APHO. 2005). The inequalities surrounding premature and high incidence as well as mortality from CHD and T2DM remain a particular issue for the SA population in the UK.
2.4.2 Classification of Coronary Heart Disease:

Coronary heart disease has a spectrum of presentations including:

- Stable angina;
- Acute coronary syndrome,
  - unstable angina,
  - AMI,
    - STEMI, and
    - NSTEMI; and
  - sudden cardiac death; and
- Heart failure

Myocardial necrosis is usually diagnosed in clinical practice by clinical findings including symptoms and signs, electrocardiographic changes, raised cardiac biomarkers of Troponins or Creatinine kinase; and also by cardiac imaging studies and pathological changes in the heart on post-mortem studies.

2.4.3 Acute myocardial infarction

Acute myocardial infarction which is the focus of this thesis indicates that myocardial cell necrosis due to significant ischaemia has taken place. Acute myocardial infarction can be the first presentation of CHD or occur in patients with established other forms of CHD such as stable angina. Acute myocardial infarction is the most common cause of death from CHD, accounting for almost 50% of the total CHD deaths. Over the last few years, the incidence of AMI in the UK has reduced significantly in all age groups (Scarborough et al. 2011). Conversely the data on the prevalence of AMI show inconsistent and fluctuating
trends with increased prevalence seen in people aged 75 and over between 1971 and 2006 (Scarborough et al. 2011).

2.4.3.1 Changes in the definition of AMI over the years
The definition of AMI has evolved over the past few decades and this needs to be taken into consideration while comparing findings of studies conducted in different periods. The past two decades have seen the development of more sensitive and specific cardiac biomarkers and imaging techniques enabling detection of a very small amount of myocardial necrosis. The presentation and prognosis of episodes of AMI diagnosed on such sensitive tests can be different to the episodes diagnosed using the old criteria. Furthermore, apart from the ‘spontaneous’ AMI, other types of AMI resulting from coronary intervention procedures (such as coronary angiography and angioplasty) are increasingly seen due to the increased use of these procedures in coronary practice. This has led to changes in the definition of AMI over the past few years. The details of current (Thygesen et al. 2012) and past definitions of AMI are provided in Appendix Two. The current classification of AMI is as follows provided in Box 2.1 on the next page.

2.4.3.2 Pathophysiology of coronary atherothrombosis in AMI:
The atherosclerotic plaques evolve through a complicated course of endothelial dysfunction, lipid deposition and vascular inflammation, compounded by adhesion, incorporation and proliferation of inflammatory cells and smooth muscle cells, ultimately forming an advanced plaque with necrotic core and fibrous cap (Figure 2.1) (Falk et al. 2012, Libby et al. 2013).
Box 2.1: Classification of myocardial infarction:
The usual categories of AMI is based on the ECG changes..

- **ST elevation MI (STEMI):** New ST elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V2–V3 where the following cut points apply: ≥ 0.2 mV in men ≥40 years; ≥0.25 mV in men <40 years, or ≥0.15 mV in women.
- **Non-ST elevation MI (NSTEMI):** Those patients with MI without ECG changes of ST elevation.

Furthermore AMI is classified depending on the development of Q waves on the ECG:
- **Q wave MI and**
- **Non-Q wave MI,**

AMI is also classified based on pathological, clinical and prognostic differences, along with different treatment strategies into
- **Type 1 to 5** (see Box S2.1, Appendix 2)

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**Figure 2.1, Stages in pathogenesis of atherosclerotic plaque (Modified with permission from Libby et al, Nature 2011)**

- **a,** normal three layers of arterial wall; **b,** stage of fatty streak formation
- **c,** Fibrous plaque; **d,** Rupture of the advanced plaque with thrombus formation,
With the atherosclerosis process beginning early in life and progressing more rapidly during mid to late stages of adult life, the course is variable and unpredictable in individual cases. Apart from the asymptomatic disease, this progression of coronary atherosclerosis plaque follows two distinct courses:

I. Chronic progressive atherosclerosis causing luminal narrowing usually responsible for the presentation of stable angina, and

II. Acute rapid luminal obstruction from luminal thrombosis and/or plaque haemorrhage causing acute coronary syndrome: unstable angina and acute myocardial infarction.

The New insights into the pathogenesis of AMI (Libby et al. 2013)

The traditional view is that STEMI results from a complete luminal occlusion at the site of a critical atherosclerosis plaque, caused by the formation of a small platelet thrombus. The incomplete or transient occlusion at these sites is considered to cause NSTEMI. Accordingly, the traditional diagnostic approaches aim at detecting such fixed significant/critical obstructive atherosclerotic lesions and treating them with percutaneous intervention or coronary artery bypass grafting (CABG). However, data from recent studies using new imaging techniques such as invasive angiography, intravascular ultrasound scan (USS) and transactional CT angiography, as well as interventional trials have challenged this traditional view.

In these studies, the culprit lesions causing the incident AMI were found to be mostly causing noncritical luminal stenosis. Furthermore, new data suggest that
during much of its life course, the atherosclerotic artery accommodates much of the plaque burden by outward expansion of its wall – vessel remodelling - without causing significant luminal stenosis. The episode of AMI resulting from acute luminal obstruction at such noncritical stenosis therefore may not be preceded by any chronic symptoms of angina, due to the lack of any chronic luminal compromise. Much of this discordance between the lower degree of atherosclerotic coronary stenosis and high propensity for developing an episode of AMI is explained by the culprit plaques being vulnerable ‘thin-cap’ atheromatous plaques with a large (>30%) necrotic lipid core highly prone to acute rupture and subsequent thrombus formation. Such type of plaque rupture is found to be the most common mechanism for acute coronary event. The other less common cause of thrombosis, seen in about 20-25% cases is plaque erosion, identified as missing endothelium overlying the plaque at the site of thrombus formation. Chronic vascular inflammation plays a major role in weakening the collagenous fibrous cap leading to plaque rupture, and the relevance of chronic hyperglycaemia to this process is explained below.

2.5 Diabetes mellitus and IGR/ high-risk state

2.5.1 Diabetes mellitus

Diabetes mellitus is a chronic metabolic disorder of multiple aetiology, characterised by chronic hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism, resulting from the defects in insulin secretion and/or insulin action (WHO 2006). Type 2 diabetes is the commonest form of diabetes affecting about 85-90% people with diabetes. In the UK there are currently 3.2 million (7.5%) people with diabetes and the prevalence is predicted to rise to
4.6 million (9.4%) by 2030 (Diabetes UK 2014). Furthermore, it is estimated that about 633,600 people in the UK have undiagnosed T2DM (Diabetes UK 2014). As per the WHO report, the age-standardised mortality from diabetes in the UK in 2012 was 4.2 per 100,000 people (men, 5.0/100,000 and women 3.6/100,000). Furthermore, there has been a significant rise in T2DM in young people worldwide and in the UK. The higher rates were seen in particular affecting the black and ethnic minority populations (Barret et al, 2009).

2.5.2 Impaired glucose regulation / pre-diabetes / non-diabetes hyperglycaemia / High-risk for diabetes

The terminologies describing hyperglycaemia below the threshold of diabetes diagnosis vary as per the tests used (HbA1c vs glucose measurements). Impaired glucose regulation (IGR) is classified as IFG and IGT as per the WHO 1999 criteria based on the fasting and post-glucose load measurement of plasma glucose levels (Table S2.1, Appendix Two). The new term ‘high-risk state’ indicating a hyperglycaemic state equivalent to IGR is proposed by international (The international expert committee, 2009) and UK expert committees (John et al. 2012) and is based on HbA1c measurements. In a recent position statement from the Diabetes UK, all the terminologies have been accepted (Diabetes UK, 2014). Previous studies suggest that about 15% of world population have IGR. The number of people at high risk of diabetes in the UK is estimated to be 11.5 million (25%) using the criteria of HbA1c levels of 42 to 47 mmol/mol (6.0 to 6.5%) (Diabetes UK, 2014). Impaired glucose regulation or high-risk state is associated with increased risk of developing T2DM (Coutinho et al 1999, Danaei et al. 2006, Selvin et al. 2010).
2.5.3 Methods for diagnosing T2DM and identifying high-risk individuals/IGR

Definitions and classification of diabetes and accordingly the terminologies have evolved over the years since the WHO first published its report on diabetes in 1965 (WHO, 2006) (Appendix Two). The current classification of diabetes recommended by WHO in 1999 is based on the aetiology (WHO, 1999) (Box 2.2).

**Box 2.2: Current classification of diabetes (WHO 1999)**

- **Type 1 DM**, absolute insulin deficiency from immunological/unknown mechanism;
- **Type 2 DM**, variable degree of insulin resistance, impaired insulin secretion, and increased glucose production from heterogeneous mechanisms;
- **Other specific types of DM**, heterogeneous conditions causing defective insulin secretion or action resulting from a variety of etiologies of genetic, metabolic, drugs infection or other origin;
- **Gestational DM**, insulin resistance resulting from metabolic changes in pregnancy.

Diagnosis of diabetes had been traditionally based on plasma glucose measurements (Alberti et al. 1998) and the fasting plasma glucose (FPG) test was in common use on pragmatic grounds. In 2011, the WHO recommended the use of HbA1c as an additional diagnostic test for diagnosing T2DM in non-pregnant adults (WHO, 2011). However, the WHO did not recommend the use of HbA1c for diagnosis of IGR. Using HbA1c for diagnosis of T2DM requires the International Federation of Clinical Chemistry (IFCC) standardised assays for its measurement to ensure the results produced using different assays are equivalent and reliable. There are advantages of using HbA1c over glucose-
based tests for a diagnostic purpose including the convenience of doing the test at any time of the day. However clinicians need to be aware of some of the practical issues such as alteration in HbA1c levels in certain haematological and other diseases, and HbA1c shouldn’t be used for diagnostic purpose in these conditions. The current criteria for diagnosing diabetes using either HbA1c or blood glucose are given in Table 2.1.

Table 2.1: The WHO diagnostic criteria for T2DM, IFG, IGT

<table>
<thead>
<tr>
<th>Test</th>
<th>Diabetes</th>
<th>Impaired glucose tolerance</th>
<th>Impaired fasting glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c* (DCCT aligned)</td>
<td>≥48 mmol/mol (≥6.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fasting plasma glucose**</td>
<td>≥7.0 mmol/l</td>
<td>-</td>
<td>≥6.1 mmol/l and &lt; 7.0 mmol/l</td>
</tr>
<tr>
<td>Random plasma glucose**</td>
<td>≥ 11.1 mmol/l</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oral glucose tolerance test**, #</td>
<td>2-hour plasma glucose ≥11.1 mmol/l</td>
<td>2-hour plasma glucose ≥ 7.8 mmol/l and &lt; 11.1 mmol/l</td>
<td></td>
</tr>
</tbody>
</table>

*Conditions precluding accurate measurement of HbA1c need to be excluded (See Box).
**In the presence of classical symptoms, one abnormal value is diagnostic of diabetes. In the absence of symptoms, two abnormal values are required to confirm the diagnosis of diabetes.
Any of the above criteria are suitable for diagnosis of diabetes.
In the absence of unequivocal hyperglycaemia, repeat testing is required to confirm the diagnosis.
Plasma glucose and HbA1c values are for venous plasma samples.
Fasting is defined as no caloric intake for at least 8 hours
#The oral glucose tolerance test should be conducted using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. A fasting and 2-h post-glucose loading sample is required.
DCCT = Diabetes Control and Complications Trial
2.6 Coronary heart disease in people with T2DM and IGR

Coronary heart disease remains the leading cause of mortality and morbidity in people with T2DM, affecting about three-quarters of them (Davis et al. 2008, Seshsai et al. 2011, Emerging risk collaborator. 2010, Rydén et al. 2013). Furthermore, diabetes is associated with a greater CHD risk in the subgroup with low absolute baseline risk for CVD, for example, women, younger patients and non-smokers, lower thirds of blood pressure and body mass index (Emerging Risk Factor Collaboration. 2010). Furthermore, the diagnosis of T2DM at a young age increases the risk of myocardial infarction by fourfold (Hillier et al. 2003, Khan et al. 2014). Limited evidence indicates that CHD is becoming a leading cause of mortality and morbidity in type 1 diabetes (Schnell et al. 2013). The excess and long-term risk of CHD (and also that of Stroke, PVD and heart failure) in diabetes often remains underappreciated.

In T2DM, the excess CHD risk is apparent before diagnosis in the stage of IGR. A continuous linear relationship is seen between sub-threshold postprandial hyperglycaemia assessed by the OGTT (rather than fasting glucose) or HbA1c levels and CHD risk (Selvin et al. 2010, Sattar N. 2012, Morris et al. 2013). In fact the excess CHD mortality is higher in those with IGT or elevated sub-threshold HbA1c compared with those with established diabetes. (Khaw et al. 2001, Ning et al. 2010, Selvin et al. 2010) The association of ‘Metabolic syndrome’ a constellation of insulin resistance and related cardiovascular risk factors as defined by WHO with excess CHD risk remains controversial. (Simmons et al. 2010, Satter N. 2013).
2.6.1 Mechanisms behind accelerated atherosclerosis and development of AMI in diabetes/IGR

The traditional risk factors of hyperlipidaemia, hypertension and smoking are the major culprits behind increased CHD risk in diabetes, and these risk factors are at least twice more strongly associated with CHD risk in people with, compared to those without diabetes (Stamlar et al. 1993). However, these risk factors fail to entirely explain the heightened CHD risk in diabetes (Stamlar et al. 1993). With the advances in our understanding of atherosclerosis over the past two decades, the novel risk factors related to insulin resistance, endothelial dysfunction, increased adiposity, systemic inflammation, and prothrombotic state are emerging as the key factors explaining some of the excess CHD risk in diabetes. Multiple mechanisms have been proposed working in a complex manner influencing the entire course of atherosclerosis in diabetes (Aronson et al. 2002, Beckman et al. 2002, Orasanu et al. 2009, Laakso M. 2010). The process begins during the stage of IGR (Beckman et al. 2002, Orasanu et al. 2009, Laakso M. 2010) and affects relevant cells including endothelial, vascular smooth muscles, inflammatory cells (monocytes, T lymphocytes) and platelets. Among the various mechanisms, insulin resistance possibly plays a dominant role and also influences all the other mechanisms. Subclinical inflammation and cytokine production resulting from intra-abdominal fat are closely linked to insulin resistance, endothelial dysfunction and atherogenesis through multiple complex pathways (Aronsson et al 2002, Bastard et al. 2006, Libby et al. 2010, Barlovic et al. 2011). The end results of various interactions in the coronary vasculature are the development of premature, accelerated and diffuse atherosclerosis with the resulting plaques
being large, unstable and highly prone to rupture. Furthermore, diabetes is associated with an excess risk of thrombosis and impaired fibrinolysis making thrombus formation more likely upon rupture/erosion of the plaque. Platelets in diabetes are hyperactive causing enhanced platelet adhesion, activation and aggregation (Ferreiro et al. 2011). Levels of coagulants of tissue factor and factor VII are increased while levels of natural anticoagulant of antithrombin III and protein C are reduced. Furthermore levels of the fibrinolytic plasminogen activator inhibitor (PAI) type 1 are increased making the thrombus in diabetes resistant to lysis (Undas et al. 2008).

2.6.2 Prevalence and prognostic importance of glucose abnormalities in AMI

The last few decades have seen aggressive management, and resultant improvement, in the prevalence of traditional cardiovascular risk factors especially of hypercholesterolaemia, hypertension, and smoking in the population (Hardoon et al. 2011, Scarborough et al. 2011). However, over this period there has been a significant and progressive rise in the rates of obesity and T2DM. This has considerably changed the characteristic risk profile of patients presenting with AMI in the recent years with two-thirds of the individuals now having chronic hyperglycaemia (diabetes or IGR) at presentation (Bottle et al. 2009, Rydén et al. 2013). However in almost half of these cases,, glucose abnormalities can remain undetected unless a systematic screening with the OGTT is undertaken (Norhammar et al. 2002, Rydén et al. 2013.).
The Euro Heart study reported data on 4961 people with acute (3247) or chronic CVD (1717) attending hospitals in 25 European countries (Bartnik et al. 2004). Of the 2107 patients with acute CVD, most of them with acute coronary events, 664 (31.5%) were known to have diabetes. Of the remaining, 923 patients underwent an OGTT and this identified a further 534 (58%) with abnormal glucose tolerance: T2DM 201(22%), IGT 294 (34%), IFG 39 (4%). A similar high prevalence of glucose abnormalities was seen in 997/1717 (58.1%) patients with chronic CHD who underwent an OGTT.

In the prospective Glucose metabolism in Acute Myocardial Infarction (GAMI) study, a total of 164 patients with AMI without known T2DM and admission glucose < 11.0 mmol/L underwent a standard OGTT before discharge of which 109(66%) patients had chronic hyperglycaemia comprising of 58(35%) with IGT and 51(31%) with T2DM (Norhammar et al. 2002).

In addition to the chronic hyperglycaemia, acutely elevated blood glucose levels – acute hyperglycaemia irrespective of underlying chronic hyperglycaemia is a very common finding in AMI affecting up to 50% of patients with about 18% people having severe hyperglycaemia (blood glucose >11.0 mmol/L) (Capes et al. 2000, Kosiborod et al. 2008). In some, acute hyperglycaemia may be due to previously undiagnosed T2DM/IGR (Ishihara et al. 2006, deMudler et al. 2012) while in others it represents an epiphenomenon of stress resulting from excess production of stress hormones such as catecholamine and cortisol (Ishihara et al. 2006, de Mudler et al. 2012, Ceriello et al. 2001). In many studies, the correlation between acute and underlying chronic hyperglycaemia is found to
be poor suggesting that the acute hyperglycaemia is not always a surrogate of undiagnosed chronic hyperglycaemia (Ishihara et al. 2006, de Mulder et al. 2012).

**2.6.3 Prognosis following AMI in people with diabetes**

Apart from an increased risk of developing AMI, people with diabetes also suffer from increased risk of complications after AMI including death, nonfatal myocardial infarction, heart failure and stroke. Such heightened risk is observed among those with known (Donahoe et al. 2007, Bauters et al. 2016), as well as newly-diagnosed diabetes (Lenzen et al. 2006, Arnold et al. 2014, Aggarwal et al. 2016, Pararajsingham et al. 2016), detected at presentation of AMI. The diabetes associated excess risk is persistent despite modern treatments for AMI (Donahoe et al. 2007, De Luca et al. 2013).

In an individual-patient meta-analyses of 11 TIMI group of trials involving 62,036 patients with ACS (613 (17.1%) with diabetes), enrolled after 1999, diabetes was independently associated with higher all-cause 30-day mortality, both in patients with STEMI (Odds ratio (OR), 1.40; (1.24-1.57)) and NSTEMI/UA (OR, 1.78; (1.24-2.56)) (Donahoe et al. 2007). Similarly, the all-cause mortality 1-year post ACS was about two-fold higher in patients with, compared with those without diabetes (Donahoe et al. 2007). Furthermore, the diabetes associated excess risk was higher in unstable angina or NSTEMI (adjusted HR 1.65; (1.30 – 2.10) compared with that in STEMI (adjusted HR 1.22: 1.08 – 1.38). In another individual-patient meta-analysis of 11 trials of patients with STEMI treated with stents (n= 6298), the all-cause mortality up to
3.3 years after hospitalisation with STEMI was 76% higher in patients with, compared with those without, diabetes (De Luca et al. 2013). In the Euro Heart survey, diagnosis of known as well as screen-detected diabetes at admission with ACS had a negative influence on 1-year outcomes post ACS (Lenzen et al, 2006).

However many of the studies assessing prognosis post AMI in diabetes have focussed mainly on short-term outcomes and studies on long-term (more than 1 year) prognosis are relatively few and show inconsistent results. In some of these studies, diabetes was not found to be independently associated with long-term mortality and further research in this area is necessary to robustly establish any association between diabetes and long-term survival post AMI.

Furthermore, acute hyperglycaemia at index AMI is associated with adverse prognosis regardless of the underlying diabetes status (Capes et al. 2000, Goyal et al. 2006, Kosiborod et al. 2008). Various cellular mechanisms have been proposed to explain this adverse association including the toxic effects of acutely elevated glucose levels, increased oxidative stress, prothrombotic and proinflammatory milieu and microvascular dysfunction leading to ‘no reflow’ phenomenon after revascularisation (Ceriello A. 2001, Ananatharaman et al. 2009).

People with an admission glucose of >8mmol/L are at a greater risk of mortality compared with those with a level <8mmol/L (Goyal et al. 2006). The outcome of people with acute hyperglycaemia in AMI, is worse in people previously not
known to have diabetes compared with those with prior diabetes (Petursson et al. 2007, Stranders et al. 2007, Wahab et al. 2002).

Additionally, there is debate on the relative importance of acute versus chronic hyperglycaemia. Some studies suggest that only the acutely elevated glucose is important in predicting adverse clinical outcomes following AMI (Cao et al. 2005). Others speculate that the impact of acute and chronic hyperglycaemia on outcomes following AMI may be different and time-dependent i.e. early versus long-term, and only chronic rather than acute hyperglycaemia determines the long-term prognosis (Ishihara et al. 2007, Tenerz et al. 2003).

There is a common perception that acute hyperglycaemia in AMI is important only in those with previously known diabetes. This is reflected by the findings that >65% people with elevated glucose at admission with AMI, but without diabetes, do not receive active blood glucose lowering treatment (Weston et al. 2007). Further studies examining relative strength of association of acute versus chronic hyperglycaemia on outcomes post AMI are therefore required.

2.6.4 Mechanisms of adverse outcomes post AMI in diabetes

In general, the determinants of adverse prognosis post AMI include older age, female gender (<55 years), presence of co-morbidities (for example hypertension, renal dysfunction, prior CHD, prior heart failure), severe coronary atherosclerosis (multi-vessel or left main or proximal LAD lesions), presentation with STEMI vs NSTEMI (short-term prognosis), severe myocardial damage, late presentation due to atypical chest pain and underutilisation of
recommended acute and secondary prevention therapies for AMI (Wilson et al. 2017). In addition lower socioeconomic factors, experience of the treating clinicians and the hospital, out-of-hours presentation and access to ongoing care can all affect survival post AMI. People with diabetes suffering from AMI are more likely to have these adverse prognostic features compared with those without diabetes.

A systematic review identified various mechanisms behind in-hospital and long-term outcomes after AMI in patients with diabetes (Aronson et al, 1997). In this review, the increased short-term mortality in diabetes was found to be due to the greater incidence of congestive cardiac failure resulting from the reduced compensatory ability of non-infarcted myocardium (Aronson et al. 1997). Diabetes-associated severe coronary atherosclerosis, along with vasomotor and other metabolic abnormalities were thought to affect non-infarcted myocardium through a variety of mechanisms such as reduced blood flow, impaired myocardial glucose metabolism and presence of diabetic cardiomyopathy. Conversely, excess long-term mortality was found to be due to recurrent episodes of myocardial infarction and pre-existing left ventricular dysfunction (Aronson et al. 1997). Factors such as multivascular coronary atherosclerosis, excess number of vulnerable non-culprit plaques and hypercoagulable state, were found to be responsible for recurrence of cardiac ischaemic events over the longer course following AMI. This view is further supported by a recent study of patients with ACS treated with PCI. In this study, the number and length of the non-culprit vessel atherosclerotic plaques and necrotic cores, and calcium content of these plaques were significantly higher
among patients with diabetes or metabolic syndrome, and these plaque characteristics were associated with higher rates of future major adverse cardiovascular events in these patients (Marso et al. 2012).

2.6.5 Management of people with diabetes and AMI.

The published guidelines on management on AMI in diabetes are based mainly on the subgroup analysis of major trials (Rydén et al. 2013, Tardif et al. 2013, Vergès et al. 2012, NICE 2011, Deedwania et al. 2008). Available data suggest that most acute and secondary prevention therapies for AMI are equally beneficial among people with and without diabetes, with the absolute benefits being greater among those with diabetes due to their higher baseline risk (Anselmino et al. 2008). Dedicated trials on management of AMI in diabetes are needed to generate strong and reliable evidence on benefits of various therapeutic approaches in this high-risk group.

However, the greater issue is thought to be around underutilization of the available evidence-based therapies in diabetes (Anselmino et al. 2008). People with diabetes often have atypical symptoms and present late after developing AMI. Furthermore, clinicians treating them may not follow the risk-stratification strategies and adopt a risk-averse approach when using reperfusion/revascularisation therapies and antiplatelet agents at index admission (Anselmino et al. 2008, Gale et al. 2011). In the longer term, contributory factors could be those known to compromise effective management of chronic conditions including suboptimal care in the community setting, clinical inertia in the utilisation of evidence-based interventions, and
poor patient compliance (McAlister et al. 2009, Gale et al. 2011). Further research to address these issues is needed.

Regarding the management of acutely elevated glucose levels, trials assessing benefits of intensive glucose lowering using insulin have shown inconsistent results (Malmberg et al. 1995, Malmberg et al, 2005). This is partly due to the shortcomings in some of the trials including significant under-recruitment, no or little difference in the achieved glucose levels between the intervention and control arm and a small number of events (Malmberg et al. 2005, Deedwania 2008). However, the negative results of the trials are misinterpreted by many and the intensive glucose-lowering treatment is considered as being ineffective. The guidelines from professional societies also differ in their recommendations. In the North American guidelines, intensive glucose controlling is recommended in patients with ACS and significant hyperglycaemia (blood glucose levels >10.0 mmol/l) admitted to an intensive care unit (Deedwania et al. 2008). In contrast, the NICE guidance recommends against routine use of intensive insulin therapy to manage hyperglycaemia in ACS (NICE 2011). However, all these guidelines highlight the need for large-scale randomised controlled trials (RCTs) addressing specific knowledge gaps in this area. Recent guidelines from Canada (Tardif et al. 2013) and Europe (Author/Member of Task force. 2013) have provided specific recommendations on management of AMI in people with diabetes.

2.6.6 Case for screening for T2DM/IGR in AMI
There is a strong case for screening for chronic hyperglycaemia in patients presenting with AMI due its high prevalence and potentials to improve the associated adverse outcomes by its early detection and management. Early diagnosis of T2DM in AMI would allow earlier initiation of glucose-lowering agents and aggressive management of cardiovascular risk factors with evidence-based therapies. Furthermore, it would allow a selection of therapeutic approaches appropriate for people with diabetes and CHD, potentially improving the outcomes (Gæde et al. 2008, Holman et al. 2008, Rydén et al. 2013, Expert Committee 2013). For example in ACS, newer antiplatelet agents Ticagrelor or Prasugrel are more effective over Clopidogrel in reducing recurrent events in those with diabetes (Angiolillo et al. 2011, Wiviott et al. 2008, James et al. 2010). Similarly in terms of revascularisation, an early invasive rather than conservative (selective invasive) strategy (Fox et al. 2010) and the use of CABG using internal mammary graft over PCI is beneficial in people with diabetes and non-ST elevation ACS (Farkouh et al. 2012). In the general diabetic population, optimisation of glycaemic control at an early stage in T2DM has a legacy effect of reducing complications of CHD in the longer term (Holman et al. 2008, Ray et al. 2009). Recent reports on cardiovascular benefits of newer drugs bring hopes in improving mortality among people with T2DM who have multiple cardiovascular risk factors or established CVD (Marso et al. 2016, Zinman et al. 2015). Early diagnosis of IGR would allow initiation of lifestyle interventions, including diet and exercise, and in some cases pharmacotherapy to prevent T2DM and associated complications including CHD (Chiasson et al. 2003).
2.6.6.1 Shortfalls in the current recommendations for screening for T2DM/IGR in AMI

The case for screening for chronic hyperglycaemia in AMI is acknowledged in various guidelines but there is a lack of agreement on screening strategies and care pathways. For example, in 2012, NICE suggested selective screening for diabetes in patients with ACS who have hyperglycaemia (blood glucose >11.0 mmol/L) on admission using FPG or HbA1c, and advised against the routine use of the OGTT in those with normal HbA1c or FPG. Conversely, the revised European guidelines published in 2013 recommended universal screening for chronic hyperglycaemia in people with CVD, and furthermore suggested performing an OGTT if HbA1c or FPG are inconclusive (normal) (Rydén et al. 2013). The need for the OGTT is stated to be necessary because people with CHD often have only postprandial hyperglycaemia which can be detected by the OGTT (Rydén et al. 2013). The effectiveness of selective versus universal screening approaches based on the glucose- or HbA1c- based criteria need proper evaluation in order to develop optimum screening strategies in the acute coronary setting.

2.7 Coronary heart disease and T2DM in the SA population

2.7.1 Ethnicity and health (Senior et al, 1994, Bhopal R. 2007)

The term ‘ethnicity’ comes from the Greek word ‘ethnos’ meaning ‘a group of people, nation’. An ethnic group can be a group of people with shared ancestral, social, cultural, religious, lingual, ideological or homeland background which is distinctive and maintained between generations. The concept of ethnicity is rather complex with blurred and changing boundaries.
Ethnicity is not limited to race (which is based on biological features mainly physical appearance) or nationality and accordingly, should be used distinctively.

Consideration of ethnicity in studying population health is useful in many ways. Importantly it can identify aetiology and pattern of a disease originating from the shared biological and/or socio-cultural factors related to the ethnic origin. Furthermore, it helps in assessing health needs, plan strategies for treatments and delivery of health services, make health policies and undertake further research into pathogenesis and management of a disease. This is in contrast to consideration of race which although important in a biological variation of certain disease prevalence, ignores socio-cultural and behavioural factors associated with any disease.

In the UK there has been a strong focus on reducing the observed ethnic health inequalities (APHO 2005). Under the Race Relations (Amendment) Act 2000, public authorities including health authorities have a new statutory duty to promote race equality. As a part of compliance with this act, ethnicity data needs to be collected and monitored, and since 2001 there has been a drive towards improving recording of ethnicity in the health sector in the UK. The policies of recording self-reported ethnicity in hospital episode statistics and secondary care and at the time of new GP registration (as a part of the quality and improvement framework) came in place in 1995 and 2005 respectively and has improved ethnicity recording in the NHS.
2.7.2 South Asians in the UK

South Asians have origins on the Indian sub-continent (India, Pakistan, Bangladesh, Sri Lanka and Nepal) and collectively they form 20% of the world population. Since the Second World War, there has been a progressive migration of people from these countries to many countries in Europe and North America. In the UK they are the largest ethnic minority group comprising about 5% of the total UK population (ONS, 2013) (Figure 2.2)
2.7.2.1 Migration of the SA population to UK

The Moving Here website (Moving Here 2013) and a recent review prepared jointly by Diabetes UK and the South Asian Health Foundation (Hanif et al. 2009) have summarised migration history of the SA population to UK.

A small scale migration from the Indian subcontinent to Britain mainly of professionals such as doctors, lawyers, university graduates was taking place after the mid-19th century. In the early 1950s, the first large-scale migration from the Indian subcontinent to Britain occurred due to the acute shortage of industrial labour during the course of the Second World War. During this migration, people mainly from three distinct geographical areas arrived in the UK: the Gujarat and Punjab province in India (mostly Gujaratis and Sikhs), Mirpur in Pakistan (Muslims), and the Sylhet in Bangladesh (Bangladeshi Muslims). They were mostly unskilled people who mainly worked in the industries in Southhall (London), Birmingham, Sheffield, Manchester and Bradford. They were literate in their own languages of Urdu, Panjabi, Gujarati but did not have a formal qualification and their knowledge of English language was poor.

The further large-scale migration took place in the 1970s due to political instability in East Africa with Britain admitting about 28,000 SA refugees living in Uganda. They were educated businesspeople from Gujarati community (mostly Hindus) who settled mainly in Leicester and Wembley, London. More recently Tamil refuges from the civil war in Sri Lanka migrated to the UK.
In addition, people from other parts of the subcontinent including Kerala, Goa and SA settlers in other regions such as Singapore, Malaysia, Mauritius, Fiji and West Indies have migrated to the UK over the last half century. Many are highly skilled workers and professionals including IT professional, Nurses, and about 30% of doctors working in the NHS.

2.7.2.2 Heterogeneity in UK SA population
South Asians are a heterogeneous group of people with differing national, religious, cultural, and traditional and language backgrounds. Furthermore, there is racial heterogeneity with people from northern part of Indian subcontinent largely being descendants of Aryans who migrated to the subcontinent about 3,500 years back. Those living in the Southern part are mainly Dravidians, the original inhabitants of the subcontinent (Hanif et al. 2009). The various aspects of heterogeneity in SA population are less appreciated especially in the reports of health research studies.

While SA people live in all areas of UK, there is clustering of certain groups in certain geographical areas. This is to do with the reason for migration, for example industrial work and the origin of migration from the regions of Indian subcontinent. For example, the main concentration of SA people is still found around the industrial areas in the past where the migrants originally settled; most Pakistanis living in Bradford and Birmingham are from Mirpur, Sikhs in Southall are from Punjab, and Bangladeshis in Tower hamlet, London are from Sylhet.
2.7.3 Coronary Heart Disease in SA populations:

South Asians not only on the sub-continent but also in diaspora harbour the highest risk of developing CHD and T2DM with a projection illustrating that in 2020 they will contribute 40% of the global CVD burden, and in 2030 to the greatest rise in diabetes prevalence (Goyal et al. 2006, Reddy et al. 2004, Shaw et al. 2010). Furthermore, CHD and T2DM develop at an earlier age in SA and associated complications including mortality are seen more commonly in this ethnic population compared with other common ethnic groups (Mather et al. 1998, Joshi et al. 2007).

The early evidence on the excess CHD risk in migrant SA people comes from a 1959 study reporting seven times higher prevalence of CHD on post-mortem of Indians compared with Chinese living in Singapore (Danaraj et al. 1959). In 1961, another report based on the data from death certificates showed mortality from all types of CVD and arteriosclerotic and degenerative heart diseases being significantly high in Asian (mostly Indians) male and females compared with their South African counterparts (Adelstei et al. 1961). Since then, studies from across the world including the UK (Pedoe et al. 1975, Bhopal et al. 2000, Harding et al. 2008), South Africa (Walker et al. 1980), Canada (Anand et al. 2000), Singapore (Mak et al. 2003) and the North America (Palaniappan et al. 2004) have shown excess CHD risk in the SA in comparison with other common ethnic groups.

2.7.3.1 Epidemiology of CHD in British SA population
The ethnic inequality in incidence and mortality of CHD remains an important health challenge in the UK (Scarborough et al. 2010). Furthermore, despite an overall fall in the absolute rates of CHD, there seems to be a lack of relative decline in CHD rates in the SA compared with the WE populations in the UK (Harding et al. 2008), suggesting that the inequalities gap is not being addressed as successfully as desired.

The evidence on excess CHD risk in the British SA population started to become more evident from the excess cardiovascular deaths seen in the consecutive UK census data since 1971. Over the last four decades, Census data in England and Wales have consistently shown up to 50% higher CHD mortality and a relatively slower decline in the excess mortality rates over this period in people born in SA countries compared with those born in England and Wales (Scarborough et al. 2010, Harding et al. 2008).

In a study based on the census data for England and Wales, standardised mortality rates (SMR) from CHD were highest in 1971 census for men (SMR 128) and women (SMR 129) born in the SA countries and rose by 6% and 13% to SMR of 136 and 146 respectively in 1981 census (Balarajan R. 1991, Balarajan et al. 1984). Of note, the mortality rates in young SA men (age 20 to 49 years) was 65% higher than those from England and Wales. A similar trend of highest mortality from CHD in people born in the SA countries and living in the UK was seen in Census in 1991 (SMR: men, 146; women, 151; young men (age 20 to 44 years), 169) (Wild et al. 1997) and again in 2001.
In a trend analysis of data from censuses of the three decades (1981, 1991, 2001), which compared the standardised rates of CHD for people born in England and Wales, rate ratios increased for men from Pakistan (1981: 1.14 (1.04 to 1.25); 2001: 1.93 (1.81 to 2.06)) and Bangladesh (1981: 1.36, (1.15, 1.60); 2001: 2.11 (1.90, 2.34)); and for women from Pakistan ((1981: 1.14 (0.88, 1.47); 2001: 2.45 (2.19, 2.74)); reflecting a slow decline in death rates in these groups (Harding et al. 2008).

Apart from the census, the evidence on increased CHD mortality in the British SA population also comes from a large prospective longitudinal study – the Southall study in which CHD risk factors and mortality in 1420 SA and 1787 WE men aged between 40 and 69 years at baseline, randomly recruited from GP practices and work places during 1988 to 1991 were compared (Gill et al. 2004). The age-adjusted CHD mortality at a median follow-up of 16.2 years, was 60% greater in SA compared with WE men.

2.7.3.2 Case fatality Vs Incidence as a cause of excess CHD mortality in British and other migrant SA populations

Acute myocardial infarction being the most common and potentially fatal form of CHD, higher case fatalities following AMI (and also following other forms of manifest CHD) had been considered as a potential reason behind the excess CHD deaths seen in the census data. This view was supported by the studies showing higher case-fatality rates following AMI (Wilkinson et al. 1996, Hughes et al. 1989) or chronic CHD (Zaman et al. 2012) in SA, compared with WE patients in the UK. However other studies from the UK and Canada suggested
similar prognosis following AMI (Mukhtar et al. 1995, Raghavan et al. 2008) or chronic CHD (Zaman, et al. 2008, Zaman et al. 2009) for the two ethnic groups. More recent and larger studies from the UK and Canada have shown even better adjusted survival after AMI for migrant SA compared with WE patients in these countries (Khan et al. 2010, Zaman et al. 2013). Furthermore, a recent meta-analysis of 12 studies (14,531 SA patients with 1591 events, 274,977 WE subjects with 63,758 events) including people with either ACS or chronic stable angina have shown a better survival in SA compared with WE people (Zaman et al. 2013).

Conversely, earlier (Mather et al. 1998, UKPDS group. 1998, Khattar et al. 2000) and more recent (Patel et al. 2008, Fischbacher et al. 2007, Zaman et al. 2012, Tillin et al. 2013) studies indicate that SA patients in the UK suffer from a higher incidence of manifest CHD including AMI. In a recently published meta-analysis of nine such studies involving 11 cohorts (111,555 SA subjects with 2527 events, 4,197,923 WE subjects with 65,241 events), SA participants were found to suffer from a higher incidence of CHD compared with their WE counterparts (HR: 1.35 (1.30 to 1.40)) (Zaman et al. 2013). The results were consistent in the subgroups of studies examining either fatal-only CHD or fatal and non-fatal CHD. This has led to the emerging thinking that there is possibly a discordance of high incidence but better prognosis for CHD in the migrant SA population; and that the high overall CHD mortality in SA (as seen in the census data) in the UK is possibly due to the high incidence of CHD including that of AMI rather than high case fatalities following AMI or other manifest CHD (Zaman et al. 2012, Zaman et al. 2013).
2.7.4 Reasons behind excess CHD risk in the SA population

2.7.4.1 Higher prevalence of prior T2DM and IGR

A number of studies indicate that the greater burden of CHD in SA populations across the globe is partly due to increased prevalence of traditional risk factors, in particular T2DM and insulin resistance present from a younger age in this population (Joshi et al. 2007). In England, the SA individuals have been estimated to suffer from at least one and half times higher prevalence of diabetes (both known and undiagnosed) compared with the indigenous WE individuals (Holman et al. 2014). In the 20 years follow-up of the SABRE study, 40 to 50% of British SA men and women developed diabetes by 80 years of age, a proportion significantly higher than in the WE participants in the study (Tillin et al. 2013). Furthermore, SA people in the UK suffer from excess rates of IGR and three times greater risk of progression of IGR to T2DM (Srinivansan et al. 2007, Oldroyd et al. 2007).

More importantly the hazards of developing CHD events including AMI and associated mortality seems to be increased in SA people with T2DM or IGR compared with their WE counterparts (Bellary et al. 2010, Chaturvedi et al. 1996, Mather et al. 1998, Davies et al. 2014, Arabi et al. 2004). In the longitudinal Southall and Brent study, nearly half of the total CHD deaths in the SA participants were seen among those with diabetes compared with 16% in their WE counterparts (Forouhi et al. 2006). In another prospective study of 730 SA and 304 WE people with diabetes living in the UK, mortality from CHD was two-fold higher in the younger SA (30–64 years) participants, and the prevalence of CHD in the survivors was 3.8 times higher in the SA compared
with the WE group (Mather et al. 1998). However in some longitudinal studies, the hazard of higher CHD-related deaths linked to diabetes status of SA people was not observed (Davies et al. 2014), and this area needs further evaluation.

Looking at the association between T2DM and CHD from a different perspective, in those with manifest CHD especially AMI, the prevalence of prior diabetes is more than two-fold in SA compared with WE patients (Zaman et al. 2013). In the INTERHEART study, the largest, global case–control study of risk factors for AMI, diabetes was one of the three risk factors particularly associated with premature myocardial infarction (age below 60 years) in the native SA patients, the other two factors being a high waist-to-hip ratio and dyslipidaemia (Joshi et al. 2007). Aarabi and colleagues conducted a systemic review of longitudinal studies investigating differences in the established risk factors for CHD between SA and WE patients. They found that SA without diabetes had significantly higher levels of FPG and HbA1c levels compared with the WE patients. The authors speculated that a high prevalence of IGR in SA patients could also be contributing to increased CHD risk in this population (Arabi et al, 2004).

Furthermore, studies examining the influence of diabetes on mortality and other outcomes among those with manifest CHD have showed conflicting results. One study showed that the SA patients admitted with AMI have a 50% higher 6-month mortality compared with the WE patients, largely attributed to the higher prevalence of diabetes in the SA patients (Wilkinson et al. 1996). In a recent large UK study, although the overall prognosis following ACS was not
worse in the SA patients, the impact of diabetes on mortality post ACS was stronger in the SA compared with the WE subjects (age-adjusted HR, SA: 1.83 (95% CI 1.59 to 2.11) vs WE:1.53 (95% CI 1.49 to 1.57)) (Zaman et al. 2013). Conversely, in a study from Canada, the association between diabetes and mortality post AMI was similar for WE and SA patients (Nijjar et al. 2010).

2.7.4.2 Undiagnosed T2DM and IGR

The prevalence of previously undiagnosed T2DM and IGR is high in WE patients presenting with AMI (section 2.6.2), adversely affecting their prognosis post AMI (Rydén et al. 2013). However, studies in this area involving SA patients are very limited. It is very likely that a significantly higher proportion of SA patients with CHD have undiagnosed chronic hyperglycaemia. In support of this, in one Indian study, less than 16% of urban Indians admitted with ACS had normal glucose tolerance on screening with an OGTT (Ramchandran et al. 2005). In another study from the UK, an OGTT conducted at 3 months post AMI showed a higher rate of T2DM and IGT in SA (66%) compared with WE (25%) patients (Salmasi et al. 2006).

The findings from the above studies indicate that diabetes is the major driver behind incident CHD, in particular AMI, in the SA population and probably influence outcomes post AMI. However, further studies robustly estimating the prevalence and prognostic influence of known and previously undiagnosed chronic hyperglycaemia in SA patients with CHD are urgently needed.
2.7.4.3 Increased insulin resistance and profile of metabolic syndrome

Emerging evidence shows that the high prevalence of CHD and T2DM in the SA population is stemming from the common underlying problem of insulin resistance and related metabolic abnormalities (McKeigue et al. 1991, Knight et al. 1992, Tillin et al. 2005).

Compared with WE, SA people are more insulin resistant due to increased adiposity, central obesity (abdominal fat) and effects of metabolically active intra-abdominal fat in the SA people (Yajnik et al. 2002, Yajnik et al. 2002, Yajnik et al. 2004, Shelgikar et al. 1991, Hall et al. 2008). Furthermore, for the same level of BMI, compared with WE, SA people have a significantly high body fat percentage (thin–fat phenotype), distributed mainly in upper body part especially in the abdomen area (best measured clinically by waist circumference) (Yajnik et al. 2004). As a result, SA people develop insulin resistance at a much lower level of BMI and waist circumference. This characteristic profile of central obesity and insulin resistance (high FPG, hyperinsulinaemia, hypertriglyceridaemia, low HDL and hypertension) also described as metabolic syndrome is more common in SA individuals with CHD or T2DM (Tillin et al. 2005, Anand et al. 2000). To address the issue of high risk of metabolic syndrome at low BMI in the SA population, some definitions of metabolic syndrome have included lower thresholds for waist circumference for SA people (men >90 cm and female >80 cm) (The IDF 2006). Furthermore, the recommended BMI cut-off levels are lower for SA people – Normal BMI (18–22.9 kg/m2), Overweight (23–24.9 kg/m2) and Obesity (≥25.0 kg/m2) (Kumar et al. 2011, Misra et al. 2009).
Furthermore, there is a worrying trend of a higher percentage of body fat and higher insulin resistance for a given BMI in SA children and adolescents compared with their WE counterparts (Ehtisham et al. 2005, Whincup et al. 2002, Whincup et al. 2005, Shaw et al. 2007). The prevalence of T2DM has been found to be higher in SA compared with WE children (Whincup et al. 2005). Furthermore, it is hypothesised that the origin of central obesity, increased adiposity and insulin resistance is pre-conceptual (Yajnik et al. 2008).

The reasons for the heightened insulin resistance and associated risk of T2DM and CHD in SA people are not clear. Various hypothesis/models have been suggested (Hall et al. 2008), including:

- *Gene–environment interaction* - the ‘*thrifty genotype*’ hypothesis (Neel et al. 1962);
- the ‘*thrifty phenotype*’ hypothesis (Hales et al. 1992, Yajnik et al. 2001);
- the ‘*Developmental Origins of Health and Disease*’ (DOHaD) model (Yajnik et al. 2008); and
- *Adipose tissue overflow mechanism – altered adipose tissue location/functionality* (Sniderman et al. 2007).

Overall, the evidence indicates a strong gene-environment element behind excess insulin resistance in the SA population and further studies are needed to confirm these hypotheses.
2.7.4.4 Novel and emerging risk factors

The role of novel risk factors in the pathogenesis of atherosclerotic vascular diseases and T2DM is an area of active research and is very relevant to the SA population. In the Southall and Brent study, CHD mortality remained significantly high in SA compared with the WE men, despite adjustment for conventional risk factors as well as those related to insulin resistance, and the authors speculated role of unmeasured risk factors related to or distinct from insulin resistance (Gill et al. 2004) behind this excess mortality in SA participants. The metabolically active abdominal fat produces various adipokines including leptin, adiponectin, inflammatory (CRP, TNF-alpha, IL-6) and prothrombotic cytokines (PAI-1, t-PA) which have all been linked to the pathogenesis of atherosclerosis. In the previous sections (2.6.1 and 2.6.2), I discussed the role of insulin resistance, chronic hyperglycaemia, and associated atherogenic risk factors such as endothelial dysfunction, chronic inflammation and dyslipidaemia in the development and progression of atherosclerosis, and furthermore in the destabilisation and rupturing of the atherosclerotic plaque leading to an episode of AMI (Libby et al. 2010, Libby et al. 2013). These metabolic abnormalities and related novel risk factors are thought to be more perturbed in the SA population thereby contributing to their heightened CHD risk (Forouhi et al. 2006).

Microalbuminuria is also known to be an independent predictor of future CHD risk, and SA patients with T2DM have a three fold higher prevalence of microalbuminuria compared with WE patients, even in those who are normotensive (Dixon et al. 2006, Mather et al. 1998).
Another novel risk factor of considerable interest in SA population is lipoprotein (a) which is an LDL particle with additional lipoprotein–apoprotein ‘a’ linked to apo B-100 of LDL by a disulphide bond (Enas et al. 2006). Studies have shown that Lp (a) levels confer a genetic predisposition to CHD in young Asian Indians (Gambhir et al. 2008).

2.7.4.5 Role of conventional CHD risk factors

The common belief is that the conventional risk factors including hypercholesterolemia, hypertension and smoking do not explain the excess CHD risk in SA people. The INTERHEART study has challenged this view showing that nine risk factors can explain over 90% of the risk of developing AMI in different populations across the world including the SA populations (18% of study participants) (Joshi et al. 2007). These risk factors include: apolipoprotein B100/apolipoprotein A1 ratio, current and former smoking, hypertension, diabetes, high waist-to-hip ratio – WHR, psychological factors of stress or depression, moderate or high intensity exercise, alcohol consumption > once/week and consumption of fruit and vegetable > 1/day.

The INTERHEART study also showed that the earlier age of MI in native SA was mostly related to the presence of higher levels of these risk factors at a younger age compared with individuals from other countries. The four risk factors which consistently showed a strong association with CHD at a younger age in the study were smoking, hypertension, dyslipidaemia (high apoprotein B100/apoprotein A1 ratio) and diabetes.
Further analysis of the INTERHEART study also found an association of LDL cholesterol with the risk of MI amongst SA people despite the lower baseline levels found both in cases and controls (Karthikeyan et al. 2009), suggesting that LDL cholesterol may have a causative role in CHD in the SA population even at a lower level. Moreover, total cholesterol often appears lower in SA, (Forouhi et al. 2006), due to the low high-density lipoprotein (HDL) cholesterol values prompting some experts to suggest that the total cholesterol to HDL cholesterol ratio would be a better predictor of CHD risk in the SA population rather than just the total cholesterol level (Patel et al. 2009).

Overall, hypertension is not more prevalent in the SA compared with the WE population. However, there is a subgroup heterogeneity with hypertension being higher in Indians (particularly Sikhs) and lower in Bangladeshis than WE people (Agyemang et al. 2002) and hypertension is also known to be related to the excess CHD mortality in the SA population (Agyemang et al. 2002, Patel et al. 2008, Bhopal et al. 2000, Khattar et al. 2000, Teo et al. 2006).

Use of smokeless tobacco (chewing tobacco and paan) is very common in the rural population in India (Teo et al. 2006) and has been considered to afford an equivalent risk for MI as smoked tobacco and hence the accommodation of smokeless tobacco within the NICE guidelines for smoking cessation (NICE 2008).

The above evidence suggests that conventional risk factors are equally prevalent in SA people but perhaps are more potent and do contribute to their
higher CHD risk. Furthermore, the prevalence of some of these risk factors is increasing (total cholesterol, smoking rates) in the SA population in contrast to the improvements seen in the general population (except for obesity) (Zaman et al. 2010). Despite this, deficiencies are seen in management of conventional risk factors as per the current guidelines in SA populations across the globe. In one study, the Black and SA patients with diabetes were significantly less likely to meet all three national treatment targets (HbA1c ≤7.4%, blood pressure ≤145/85mmHg, total cholesterol ≤5 mmol/L than WE patients (25.3%, 24.8%, and 32.0%, respectively) (Gray et al. 2007). So far the evidence on improvement in this situation and equality of care is inconsistent (Millet et al. 2009, Alshamsan et al. 2010, James et al. 2012).

2.7.4.6 Lifestyle, social and cultural risk factors

South Asians living in the UK are a heterogeneous group of different religious (Sikhs, Muslims, Gujarati and others), educational and socioeconomic backgrounds (factory workers, business people, highly skilled workers like doctors) (Hanif et al. 2009). Despite this, many factors especially related to SA culture are common to all and influence risk of developing CHD and T2DM.

The socio-economic status and educational levels of SA people in general are low with many first-generation migrants still having communication difficulties due to their poor knowledge of English. Furthermore, social gradients for CHD, once absent (Marmot et al. 1984) are now emerging in the SA population and these may be the potent risk factors for CHD in the UK SA population (Tillin et al. 2008, Zaman et al. 2008).
Many SA people believe that their health problems are inevitable due to destiny and accept it with resignation (Webster et al. 2003). Such attitudes make them less proactive towards modifying health behaviour and accessing healthcare. Also, the cultural norms and expectations prevent many SA individuals especially women looking after their health, taking leisure-time physical exercise and eating a healthy diet.

Many studies have shown low levels of physical activity in British SA compared with the indigenous WE people (Fischbacher et. Al. 2004, Khunti et al. 2007). Many traditional SA recipes contain a high proportion of ‘ghee’ which is a saturated fat and is shown to be associated with premature CHD (Ismail et al. 2004). Traditional vegetarian SA diets can also increase post-prandial plasma glucose and insulin levels (Sevak et al. 1994) and the risk of developing T2DM due to its high carbohydrate content (Radhika et al. 2008). Fruit and vegetable intake is protective and was found to be low in SA patients with AMI (Ismail et al. 2004, Iqbal et al. 2008, Dhanjal et al. 2001).

Furthermore, low literacy level, language difficulties, lack of knowledge about health services and poor expectations are all barriers in SA people effectively accessing healthcare and adhering to the medications and self-management in chronic diseases, thereby resulting in poor clinical outcomes (Webster et al. 2003, Tod et al. 2001). The problem can be compounded by healthcare professionals being less aware of these issues and relevant care needs of the migrant SA people.
These data would suggest that the excess risk of CHD in the SA population is due to the complex interaction of gene-environment and socio-cultural factors and all these factors may be equally relevant in affecting the incidence of CHD and associated prognosis. Longitudinal studies are needed to robustly establish the pathogenic mechanisms through which such known and yet unknown factors influence the development of and complications from CHD in the SA population.

2.7.5 Measures to improve risk of CVD and T2DM in SA

2.7.5.1 Raising awareness

Increasing awareness amongst SA people and healthcare professionals about the risk of CHD and T2DM and furthermore about the barriers to the uptake of interventions is important. Wider initiatives at national and international levels involving healthcare professionals, policy makers, non-government and diabetes organisations, and community leaders are needed to tackle the challenge. In the UK, the South Asian Health Foundation (SAHF) in collaboration with Diabetes UK and Department of Health is working in this direction, and in 2009 published recommendations on research priorities for diabetes in the British SA population (Khunti et al, 2009). Additionally, educational resources on this topic are freely available on the SAHF website.

2.7.5.2 Screening, early detection, aggressive management, and prevention of T2DM / CHD

It is evident that reducing risk factors like smoking, blood pressure and cholesterol in the population have significantly reduced the incidence and
mortality from CHD especially AMI (Scarborough et al. 2011, Hardoon et al. 2008). Therefore, screening, early detection and prevention of cardiovascular risk factors should form the cornerstone of any approach to reduce the burden of CHD in the SA population (Khunti et al. 2009, Davies et al. 2009). Under the NHS Health Checks Programme in England, the recommendations on the use of QRISK 2 score for accurate assessment of CHD risk and that of ethnic-specific BMI (>27.5 kg/m² for SAs in contrast to >30 kg/m² for general population) in ascertaining diabetes risk are the right steps in addressing the high risk of these disorders in the British SA population.

The barriers to the uptake of any screening and intervention programmes include fatalistic beliefs, language difficulties and passive approach towards risk or disease modifying behaviour. These challenges need addressing proactively through education and innovative interventions (Mathews et al. 2007, Khunti et al. 2008, Stone et al. 2009).

2.7.5.3 Ethnic-specific interventions:

Any intervention in the SA population needs to be multifaceted and based on ethnic-specific evidence. A recent study demonstrated reduced oxidative capacity and capacity for fatty acid utilisation at the whole body level as the key features of the insulin resistant phenotype in SA people (Hall et al. 2010). Based on these data the authors speculated that innate differences in physiology may be contributing to low cardiorespiratory fitness in SA people (Ghouri et al. 2013). The group highlighted the need for ethnicity-specific recommendations of higher levels of physical activity of 230-250 minutes per
week in SA than the recommended 150 minutes per week in WE people to achieve favourable cardio-metabolic profile similar to WE people (Ghouri et al. 2013, Celis-Morales et al, 2013, Iliodromiti et al. 2016). Similar issue remains with the appropriateness of current treatment thresholds for the conventional risk factors such as cholesterol, as the thresholds are mainly derived from Western populations. It is clear that the risk is continuous and therefore thresholds for intervention should not be uniform for all individuals, and in order to establish equity in terms of primary prevention of CHD in the SA population, thresholds for intervention may well need to be lower. More research in this area is required (Patel et al. 2009).

2.7.5.4 Need for further research

The Diabetes UK and SAHF and have jointly published recommendations on diabetes research for the British SA population in which the following research priorities for CHD have also been reviewed (Gholap et al. 2009).

- Large epidemiological studies to determine the role of traditional and novel risk factors on the development and outcomes of T2DM and CHD.
- Longitudinal studies assessing the association between admission hyperglycaemia and outcomes in AMI and furthermore evaluating the effects of glucose-lowering interventions on improving outcomes post AMI.
- Studies of inflammatory markers such hs-CRP in SA patients with AMI
- Large-scale longitudinal studies to establish the prevalence and prognostic significance of IGR on ventricular structural abnormalities and abnormalities of various biomarkers such as brain natriuretic peptides.
• Investigations to determine the impact of using non-invasive techniques on earlier detection of asymptomatic CHD in people with T2DM.
• Studies to assess revascularisation strategies in SA people with diabetes and CHD, including the benefits of revascularisation in patients with silent ischaemia but prognostically significant anatomical disease.
• Prospective trials assessing the effect of pharmacological interventions aimed at achieving lower than current targets for lipids and blood pressure and modifying the novel risk factors on CHD and stroke outcomes in SA patients with T2DM.

Other areas which need attention are the ethnic-specific structured educational programmes to change health-related behaviour and attitudes and targeted public health interventions in reducing specific risk factors in SA populations. Furthermore, focus should be on improving ethnicity recording to generate good quality national data on trends in inequalities in incidence and prevalence of risk factors and associated diseases, their treatment and outcome. These data should then inform policies and measures to reduce any inequalities.

2.8 Conclusions
The world is facing a challenge of the exponential rise in T2DM and CHD. However, SA populations worldwide, and in the UK in particular, suffer from a disproportionately high burden of CHD and T2DM. The understanding of the interplay of gene-environmental, socio-cultural, conventional and novel risk factors in the pathogenesis of these conditions is evolving. There is greater need to further the knowledge in epidemiology and pathogenesis of these
disorders in SA populations across the globe, paving the way for development of specific interventions to tackle these disorders. Until such research is awaited, greater emphasis should be on screening, early detection, aggressive management and prevention of these disorders and their risk factors. Furthermore, efforts must be taken to increase uptake of these interventions among SA communities through health education, awareness-raising campaigns and other novel approaches.
Chapter Three: Long-term mortality following acute myocardial infarction among those with and without diabetes: A systematic review and meta-analysis of studies in the post-reperfusion era.

3.1 Chapter overview

As discussed in chapter Two, diabetes is associated with increased incidence of AMI and higher rates of complications post AMI. However, most studies examining survival after AMI among people with diabetes have focused on short-term mortality and the reports on long-term survival are limited and show inconsistent results. In diabetes, an episode of AMI may mark the beginning of upcoming recurrent non-fatal or fatal ischaemic events in a chronic and accelerated process of atherosclerosis. With the rates of diabetes rising at an alarming rate and increasingly affecting younger people, the reduced life expectancy following AMI among these individuals could be a significant public health problem. Therefore to robustly establish and quantify the association between diabetes and long-term mortality post AMI, I conducted a systematic review and meta-analysis of studies in this area. For this review I formulated the research question, devised the search strategy, conducted the search, extracted the data, inferred the results and led the overall conduct of this research project. The advanced level statistical analysis was performed by a team of statistical experts with the help of my clinical input. As the first author, I led the work on publishing this study in Diabetes Obesity and Metabolism. I
wrote the whole manuscript, conducted basic statistical analysis and produced the tables in this article.

3.2 Abstract

Aims/Objectives: Considerable medical advances have seen an improved survival following an acute myocardial infarction (AMI), whether these benefits extend to those with diabetes remains less clear. This systematic review and meta-analysis aim to provide robust estimates of the association between diabetes and long-term mortality (≥one year) following AMI.

Methods: Medline, Embase and Web of Science databases were searched (January 1985 - July 2016) for terms related to long-term mortality, diabetes and AMI. Both cohort studies and RCTs were included. Hazard ratios (HR) comparing mortality in people with and without diabetes were pooled across studies using Bayesian random effects meta-analysis.

Results: Ten randomised controlled trials and 56 cohort studies, including 714,780 patients, reported an estimated total of 202,411 deaths over the median follow-up of 2.0 years (range 1 to 20). The risk of death over time was significantly higher among those with diabetes than those without (unadjusted Hazard Ratio (HR) 1.82; 95% Credible Interval (CrI) 1.73 to 1.91). Mortality remained higher in the analysis restricted to 23/64 cohorts which had adjusted for confounders (adjusted HR 1.48 (1.43 to 1.53)). The excess long-term mortality in diabetes was evident irrespective of the phenotype and modern treatment of AMI and persisted in early survivors (unadjusted HR 1.82 (1.70 to 1.95)).
Conclusions: Despite medical advances, individuals with diabetes have a 50% increased long-term mortality than those without. Further research to understand the determinants of this excess risk are important for public health, given the predicted rise in global diabetes prevalence.

3.3 Introduction

Diabetes is a major risk factor for cardiovascular disease, conferring approximately a two-fold increase in the risk of AMI (The Emerging risk factor collaborators. 2010). Diabetes and impaired glucose tolerance are very common among people with AMI - seen in almost two-thirds of the patients at presentation - and are associated with an approximately two-fold increase in mortality rate compared to those with normoglycaemia (Bartnik et al. 2004, Lenzen et al. 2006). Furthermore, the recent trends in improved survival following AMI (Yeh et al. 2010) attributed to improved acute care and better use of preventative strategies, are less obvious among those with diabetes compared to those without (Eliasson et al. 2011, Cubbon et al. 2007).

While many studies have examined survival following AMI among individuals with diabetes, the focus has been on short-term rather than long-term mortality. This is also reflected in the scores used for risk stratification at index admission with AMI which are derived to predict inpatient and six-month mortality (Granger el al. 2003, Eagle et al. 2004). Furthermore, those studies which have assessed long-term mortality post-AMI have reported inconsistent findings. In some studies, long-term mortality is found to be high in people with compared to without diabetes, with some studies even suggesting that diabetes has a
greater impact on long-term rather than short-term mortality (Ishihara et al. 2007, Koek at al. 2007). On the contrary, in other studies, diabetes was not independently associated with long-term survival post AMI (Hoebers et al. 2012, Gowda et al. 1998). Two meta-analyses have been performed to date and whilst informative, their findings may not provide reliable risk estimates in broader populations (Donahoe et al. 2007, De Luca et al. 2013). The first study included only RCTs and reported information on 11 trials including 62,036 individuals from the Thrombolysis in Myocardial Infarction (TIMI) database and therefore excluded a large number of global trials whilst assessing mortality only as far as one-year post ACS (Donahoe et al. 2007). The other major meta-analysis included a select group of patients with STEMI treated with PCI and stent insertion from 11 studies and reported on 6298 patients (De Luca et al. 2013). In order to provide more reliable evidence than hitherto possible on the impact of diabetes on long-term mortality following AMI, I conducted a systematic review and meta-analysis of all available data in the post-reperfusion era and compared the long-term mortality (one year and longer) among those with and without diabetes, following hospitalisation with AMI.

3.4 Materials and Methods

3.4.1 Data Sources and Searches

I searched the Medline, EMBASE, and Web of Science (WOS) databases for articles in English. The definitions of diabetes as well as AMI have evolved over the years. For instance, with the advent of troponin and high sensitivity troponin assays, patients previously classified as unstable angina would now be labelled as AMI or non-ST elevation MI (NSTEMI) (Appendix Two). Similarly,
terminologies used in the literature for describing disorders of glucose metabolism have evolved over time (Appendix Two). I therefore adopted an approach using broader search terms (described below) than simply AMI and diabetes and then sifting through the results. My search strategy comprised of three categories of search terms related to diabetes and/or glucose abnormalities, acute myocardial infarction and/or ACS and mortality or survival. I used the following medical subject headings (MeSH) and the key words:

3.4.1.1 MeSH and the key words for diabetes and abnormalities of glucose metabolism
diabetes mellitus/ or exp diabetes mellitus, type 2/ or prediabetic state/ or exp hyperglycemia/ or (diabetes mellitus or type 2 diabetes or type II diabetes or hyperglycaemia or hyperglycemia or glucose intolerance or NIDDM or non-insulin dependent diabetes mellitus or prediabetic state).ti,ab. or (impaired glucose tolerance or abnormal glucose regulation or impaired glucose regulation or dysglycaemia or dysglycemia or impaired fasting glucose).ti,ab. OR exp Blood Glucose/ OR (admission hyperglycaemia or admission blood glucose or euglycaemia or elevated blood glucose or stress hyperglycaemia).ti,ab.

3.4.1.2 MeSH and the key words for myocardial infarction
acute coronary syndrome/ or exp myocardial infarction/ OR (acute coronary syndrome or myocardial infarction or MI).ti,ab.

3.4.1.3 MeSH and the key words for long term mortality
exp morbidity/ or incidence/ or exp mortality/ OR follow up studies.sh. or (prognos$ or predict$ or course$).tw. or outcome$.ti

The search strategy used in MEDLINE is available in Appendix Three. The same strategy was used for other databases. Search strategies were tailored to the relevant databases and furthermore, reference lists from the selected articles for other relevant studies were searched.

3.4.2 Study selection

Each title and abstract were independently scrutinised by me and another author for suitability. Identified papers were independently assessed by me and the other author to assess suitability for inclusion. Thrombolysis came into use as the preferred treatment option for Q wave myocardial infarction (STEMI) after the publication of the GISSI trial in 1986 (GISSI 1986) and became well established by early 1990, and was subsequently superseded by primary PCI in most parts of the world. Furthermore, the mid-1980s saw the emergence of the current invasive approach to the management of Non-Q wave myocardial infarction (the equivalent of NSTEMI in contemporary practice), albeit restricted initially in the high-risk patients with persistent ischaemia (Rahimtoola SH. 1988). Therefore, in order to include AMI patients likely to have been treated by modern reperfusion or early invasive strategies, I rationalised the inclusion criteria as follows:

i) articles published after January 1985 until July 2016;

ii) reporting studies had to have commenced recruitment after January 1985;
iii) studies where recruitment commenced before 1985 but continued after 1985 would only be included if 50% of the recruitment period occurred after January 1985.

I excluded studies where:

i) there was < one year of follow-up;

ii) there were <100 total participants;

iii) the design was case control;

iv) individuals were systematically screened during the index AMI admission for identifying newly diagnosed diabetes;

v) individuals were diagnosed to have diabetes based solely on elevated glucose levels > 11.0 mmol/mol at index admission;

vi) the report focused on mortality in relation to blood glucose levels without reporting mortality for those with and without diabetes; reporting was only on subgroups which could not be generalised e.g. reports restricted to those with left ventricular failure or cardiogenic shock.

Where studies had a mixed cohort of patients with AMI and unstable angina, data related to only AMI (STEMI and non-STEMI) were extracted. Since this was an analysis of hospitalised AMI, out-of-hospital deaths as a presentation of index AMI were excluded. In articles reporting more than one cohort, information on each study was extracted separately and in the case of multiple reports of the same study, the data from the most informative article was used.
3.4.3 Data extraction

I performed data extraction using a standardised data extraction form. Both cohort studies and RCTs were included. I independently extracted data, stratified by diabetes status on important prognostic variables including age, sex, prior medical history, prior medications, phenotype, presentation and severity of AMI, acute treatments and medications at discharge. Information on duration of follow-up, the absolute number of deaths over the whole follow-up period and measures of risk (hazard ratio, relative risk, odds ratio) together with confidence intervals were extracted. In addition, information on variables used in the adjusted analysis was obtained. Furthermore, when reported, I obtained data on long-term mortality in early survivors – those who survived to discharge or the first 30 days following the index AMI. For the studies not reporting actual death numbers, authors were contacted. When such information was not available from the authors, the death numbers were derived from survival graphs (Guyot et al. 2012), and percentages. This new method of using data derived from digitized KM curves has been reported not to generally bias the estimates (Guyot et al. 2012).

3.4.4 Quality assessment

The quality of studies was assessed by me and the other author using the US Preventive service task force (USPSTF) Quality criteria and studies were categorised into good, fair and poor quality groups (Appendix Three) (Harris et al. 2001). Disagreements related to any aspects of the review, selection, data extraction or quality assessment were resolved through discussion.
3.4.5 Data extraction and quality assessment

I included both non-interventional cohort studies and the RCTs of various interventions if they fulfilled our inclusion/exclusion criteria. The Bayesian random effects meta-analysis was conducted by a team of statisticians (Dr Laura Gray and Dr Felix Achana) with expertise in this area. Further information provided in this methodology section is based on their analysis approach.

The analysis was performed in two different ways, producing two sets of outcome data.

Firstly, for all the selected studies, risk ratios were derived from the reported number of patients and the number of deaths in diabetes and non-diabetes groups. It was assumed that the number of deaths in the two groups follow a binomial distribution and that the probability of death is dependent on the mean (or median) length of follow-up, under the assumption that the risk of death remains constant over the entire follow-up period (Dias et al. 2011). The time-dependent risk ratios were then log-transformed and pooled across all the studies using Bayesian random effects meta-analysis to produce a summary hazard ratio and 95% Credible Intervals (Crl, the Bayesian equivalent of confidence intervals).

The second analysis involved only those studies in which adjusted hazard or odd ratios and 95% confidence intervals were reported. For these studies, additional information on covariates included in the maximally adjusted multivariable models was obtained. The subsequent maximally adjusted
hazard/odds ratios and standard error (derived from the corresponding confidence intervals) were log-transformed and pooled across these studies using Bayesian random effects meta-analysis to produce a summary hazard ratio and 95% Credible Intervals.

The model accounts for the heterogeneity in the hazard ratios across different study populations by assuming that the association between long-term mortality and diabetes varies from study to study. The full extent of heterogeneity in hazard ratio was quantified using a between-study variance parameter $\tau$ (tau). Note that the pooled mean effect in a random effects meta-analysis only represents the average of effect sizes across individual studies and may not accurately represent the effect sizes across the different study populations. Therefore, to comply with the best practice (Higgins et al. 2009), we also obtained the estimate of predictive mean effect and interval, which incorporates the full extent of heterogeneity in meta-analysis. The predictive interval typically widens the uncertainty around the mean effect and thus provides a conservative but robust estimate of the true effect. Such a predictive effect and its interval can be seen as the equivalent of expected mean effect size and its variance in the outcomes if new studies are undertaken in the future (Higgins et al. 2009). The sources of heterogeneity were assessed through subgroup analysis. To eliminate any bias related to the difference in early case fatalities between the diabetes subgroups, we conducted a separate meta-analysis of selective studies reporting long-term mortality in early survivors – those who survived to discharge or the first 30 days post AMI. For this analysis, we pooled data on mortality after 30 days (or after hospital discharge) until the end of
follow-up from the studies reporting such event data and conducted Bayesian random effects meta-analysis.

Publication bias was assessed by visual inspection of funnel plots and Egger's test (Egger et al. 1997). Where significant publication bias was found, the Duval and Tweedie (Duval et al. 2000) nonparametric trim-and-fill method was used to provide an estimate of the number of unpublished studies and an estimate of predicted effect, if all studies were available. The meta-analyses were carried out using WinBUGS (Lunn et al. 2000). The WinBUGS codes used to fit the analysis are given in Appendix Three. Publication bias assessment was carried out using Stata. Statistical significance relates to p<0.05 and 95% Credibility Intervals are quoted throughout. The meta-analysis was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses - PRISMA statement (Moher at el. 2009).

3.5 Results

A total of 65 articles, reporting data on 66 cohorts (10 RCTs and 56 non-RCT) were eligible for the meta-analysis (Figure 3.1). Details of the studies included in the meta-analysis are provided in Table S3.2 in Appendix Three. Data on estimated 202,411 deaths in 714,780 individuals, over the median follow-up of 2.0 years (range 1 to 20) were reported.

3.5.1 Studies included and patient characteristics

Detail characteristics of the selected studies including: type and sampling structure of each study, recruitment period, number of participants, mean age,
gender, acute intervention for AMI (RCT), absolute number of deaths, measures of risk (hazard ratio, relative risk, odds ratio), and information on variables used in the adjusted analysis, are presented in Table S3.2 in Appendix Three. The studies covered the globe with 14.0% multinational studies (mostly from Western and developed countries), 13.5% from North America, 48.5% from Western Europe, 10.6% multinational and the remainder from other regions. All studies were incepted between 1985 and 2011 except two, which commenced recruitment prior to 1985 (1979 and 1981) and continued after 1985 (Ishihara et al. 2001, Gandhi et al. 2006). In 26/66 studies the recruitment commenced in the year 2000 onwards. In 15/66 studies (Table S3.2 in Appendix Three), outcome data were not reported in a suitable format and were derived from survival graphs or other sources as described in Supplementary Results 1. Adjusted analysis for the outcome of long-term mortality was reported in 23/66 studies (Table S3.2 in Appendix Three). Ascertainment of diagnosis of diabetes varied across the studies and was based on: self-reporting/admission records/physician-ascertainment (52/66) plus new diagnosis during the admission established using routine glucose measurement (13/66); and information in the discharge records (1/66). The definition of AMI in the 66 cohorts varied. In general, prior to the year 2000, the diagnosis of AMI was based on symptoms, raised cardiac enzymes and characteristic electrographic (ECG) changes (WHO 1979, Tunstall-Pedoe et at. 1994), while after the year 2000, studies used the European Society of Cardiology/American College of Cardiology criteria of changes in troponin levels plus typical symptoms and/or ECG changes (The Joint ESC/ACCC 2000, Thygesen et al. 2007). In 10/66 studies no such method was explicitly provided.
The cohort size varied from 198 to 141,680 (median 2250, interquartile range (IQR) 5401) with the diabetes prevalence ranging from 7.2% to 43.6 % (median 18.0%, IQR 10.0%). The follow-up varied, ranging from 1 year to 20 years (median 2.0 years, IQR 4.0 years). The majority of the studies assessed longer-term mortality – up to five years after index AMI – while in eight studies long-term mortality – up to 20 years – was assessed. In most of the 23/66 cohorts reporting adjusted data, the adjusted analysis included important confounders including age, gender, co-morbidities, severity of AMI and acute reperfusion therapies (Table S3.2, Appendix Three). There were 57,034 deaths in 155,526 participants with diabetes (36.7%) compared with 145,377 deaths in 559,254 patients (26.0%) without diabetes, p<0.00001.

Most studies did not differentiate between types of diabetes, and therefore ‘diabetes’ was considered as one diagnosis with no differentiation between type 1 and T2DM. Compared to people without diabetes, those with diabetes were older (median age, 65.0 years (IQR 4.0) vs 63.0 years (IQR 5.0)) and less frequently male (median proportion, 64.0% (IQR 7.8) vs 73.1% (IQR 8.6)) (Table S3.2, Appendix Three). Reporting of cardiovascular risk factors varied widely across the studies. Those with diabetes had higher prevalence of hypertension (median prevalence, 54.0% (IQR 16.5) vs 36.5% (IQR 14.6)) and prior myocardial infarction (median prevalence, 22.5% (IQR 16.3) vs 17.0% (IQR 11.0)) and lower prevalence of smoking (median prevalence, 32% (IQR 22) vs 47.0% (IQR 18.5)).
3.5.2 Quality Assessment

Based on the USPSTF Quality Rating Criteria (Box S3.1, Appendix Three) (Harris et al. 2001) 43/66 studies not reporting any adjusted data for mortality risk among patients with compared to without diabetes were rated as ‘poor’ (Table S3.2, Appendix Three). In a majority of these studies, people with diabetes were older and had a higher prevalence of cardiovascular risk factors at baseline which could have contributed to their higher mortality rates. Among the 23/66 studies reporting adjusted data, three studies adjusting analyses for key confounders (baseline differences in clinical characteristics and risk factors, acute therapies for AMI and secondary prevention therapies post AMI) and also achieving >80% follow-up as per the requirement of the USPSTF criteria were graded as ‘good’ (Table S3.2, Appendix Three). The rest 20/23 adjusted studies were graded as ‘fair’.

3.5.3 Outcomes

3.5.3.1 Diabetes and long-term mortality

From the meta-analysis of all 66 cohorts, there was evidence that long-term mortality was significantly higher among those with diabetes compared to without (unadjusted HR 1.82; 95% CrI 1.73, 1.91) (Figure 3.2). In the meta-analysis of 23/66 cohorts reporting adjusted analysis, the adverse association between diabetes and excess long-term mortality was still seen after adjusting for various confounders (adjusted HR 1.48 (95% CrI 1.43,1.53)) (Figure 3.3). The Bayesian predictive effect was HR 1.81 (95% CrI 1.31, 2.49) for analysis based on the actual event data (66/66 cohorts) and HR 1.48 (95% CrI 1.31, 1.68) for the analysis using the reported adjusted HRs/ORs (23/66 cohorts).
In the subgroup analysis, diabetes remained associated with excess mortality with no evidence of interaction across phenotypes of AMI, first or recurrent AMI, recruitment period before or after the year 2000, cohort studies or RCTs, and different lengths of follow-up (Figure 3.4). Statistically, an interaction was found (p=0.032) when the cohorts of patients with STEMI treated with PCI were compared with rest of the cohorts of AMI, although diabetes was associated with a significant excess mortality in both. To account for the advances in the acute management of AMI over recent years, we did a subgroup analysis of studies with the recruitment taking place before and after the year 2000. For this analysis we excluded 12 studies in which the recruitment commenced before and continued after the year 2000 with the total recruitment period exceeding five years (Table S3.2, Appendix Three). The adverse impact of diabetes on mortality was not significantly higher in studies with recruitment taking place before (HR 1.88 (95% CrI 1.75, 2.02) compared to after the year 2000 (HR 1.74 (95% CrI 1.60, 1.91), p=0.178. Additionally, on analysing mortality as per time since index AMI, the adverse impact of diabetes was not significantly different in subgroups of studies with different lengths of follow-up (up to 1 year, >1 to 5 years, >5 to 10 years and >10 years) (Figure 3.4).

To assess for any differential effect of age or gender on mortality among those with and without diabetes, I conducted analyses using the between-group difference in mean age and mean percentage of men reported in each study as a covariate in the meta-regression. While the risk of excess long-term mortality in the diabetes group was significantly higher in studies with older patients (interaction term 1.054 per year; 95% CrI 1.016, 1.092; p = 0.007) no such
effect was seen in the studies with a higher proportion of men (interaction term 1.002 per percentage point; 95% CI 0.996, 1.008; p = 0.487).

3.5.4 Assessment of publication bias and heterogeneity

There was evidence of funnel plot asymmetry (indicating possible publication bias) on visual inspection of the funnel plot for long-term mortality outcome (Figure 3.5), which was confirmed by formal testing (Egger's test t=11.67, p ≤0.000) (14), and suggested a tendency for negative findings from small studies to remain unpublished. Adjusting for publication bias using the trim and fill method (Duval et al. 2000) reduced the HR to 1.38 (95% CI 1.32, 1.46) for the unadjusted analysis (66/66 cohorts), however the HR remained the same at 1.46 (1.37 to 1.55) for the analysis based on the adjusted data (23/66 cohorts).

Estimates of the between-study standard deviation parameter, τ on the log hazard-ratio scale was 0.16 (95% CI 0.13, 0.21) for cohorts with unadjusted data, and 0.17 (95% CI 0.12, 0.24) for cohorts with adjusted analyses, indicating a minimal to moderate degree of variance in the HRs across the two analyses.

3.5.5 Sensitivity analysis

In the sensitivity analysis – excluding the studies (15/66) that did not report outcome data in the suitable format – no difference to the findings of an association between diabetes and long-term mortality was seen (Table S3.3, Appendix Three). Furthermore when the entire analyses were restricted to the subgroup of early survivors (42/64 studies), the association between diabetes and excess mortality was still evident (unadjusted HR1.82, 95% CrI 1.70, 1.95;
Bayesian predictive effect HR 1.82, 95% CrI 1.28, 2.59) (Figure S3.1, Appendix Three). Further details on analyses of early survivors are provided in Appendix Three, Results S2, Figures S3.1, S3.2 and Table S3.4.

3.6 Discussion

I examined the association between diabetes and long-term mortality following AMI using a meta-analysis of all the data in the post-reperfusion era. My results based on the findings of 66 studies conducted over the last three decades and including information on the estimated 202,411 deaths in 714,780 individuals over the median follow-up of 2.0 years (range 1 to 20) clearly show an adverse association between diabetes and long-term mortality post-AMI. Compared to people without diabetes, those with diabetes had about 80% excess risk of long-term mortality on univariate analysis, and about 50% on multivariate analysis adjusted for important confounders including demographic characteristics, co-morbidities, the severity of AMI, and management at index admission. Furthermore, this association between diabetes and risk of mortality remained consistent (40 to 50% excess risk) after adjusting for publication bias. These findings robustly show that diabetes is strongly and independently associated with poor long-term survival following AMI.

The findings were consistent across major subgroups, including cohorts of STEMI or first AMI. The findings persisted in early survivors - those who survived to discharge or the first 30 days after index AMI and remained relevant in the long-term up to 20 years after index AMI (Figure 3.4). Furthermore, the excess risk of mortality associated with diabetes was similar in cohorts with
different proportions of men and was greater in cohorts whose patients were older. Importantly, in contrast to some of the reports (Gowda et al. 1998, Hasdai et al. 2000, Squire et al. 2010, de Mulder et al. 2010, Chen et al. 2014), increased mortality in diabetes was persistent despite modern background management of diabetes and AMI, as reflected in the subgroup analysis of studies with recruitment taking place before and after the year 2000 and additionally of patients with STEMI treated with primary PCI.

My findings are consistent with previous meta-analyses. In the meta-analysis of 11 trials from the TIMI group involving 62,036 patients with ACS (STEMI 46577, non-STEMI/unstable angina 15459), all-cause mortality at 1 year was two-folds higher in patients with diabetes than those without (Donahoe et al. 2007). Another meta-analysis of 11 trials involving 6298 patients with STEMI treated with stents showed all-cause mortality at mean 3.3 years being 76% higher in patients with diabetes compared to those without (De Luca et al. 2013). In a more recent meta-analysis of 61 studies, assessing mortality at 6 to 12 months after index AMI or ACS, people with diabetes had 86% higher mortality on univariate analysis compared to those without (Bauters et al. 2016). Unlike these previous meta-analyses, my findings are based on a much larger sample size and event numbers and involve both unselected patients managed in real-world practice from the cohort studies, as well as selected patients managed in the highly controlled environment of RCTs. My report confirms the findings of these previous meta-analyses and extends it to a broader group of patients with AMI followed up for a much longer period of up to 20 years.
In contemporary practice, compared to STEMI, presentation of non-STEMI is more common, especially in those with co-morbidities such as diabetes and is associated with a similar or higher mortality rate in the longer term (Kostis et al. 2010). In the meta-analysis of TIMI trials (Donahoe et al. 2007), the risk of diabetes-associated mortality at 1 year was stronger amongst those with unstable angina or non-STEMI (adjusted RR 1.65; (95% CI 1.30, 2.10) compared to those with STEMI (adjusted RR 1.22 (95% CI 1.08, 1.38). In our subgroup analysis, no such difference in the adverse impact of diabetes across STEMI, non-STEMI/non-Q-wave AMI and mixed phenotypes of AMI was observed. Conversely, I found the adverse impact of diabetes on mortality being greater in cohorts with older patients. While this finding could indicate risk of excess mortality increasing with age in diabetes, I could not explore this finding in detail due to the limitation of using summary data of mean age in each cohort for this analysis. It is possible that in older patients, factors related to both longer duration and severity of diabetes independently contributed to the increased risk of cardiovascular events and consequent long-term mortality (Yeap et al. 2015). In line with the previous reports, my findings of subgroup analyses support the notion that the gap in survival after AMI between patients with and without diabetes still persists in the modern treatment era [Cubbon et al. 2007, Donahoe et al. 2007, Bauters et al. 2016]. That I found no difference in the adverse impact of diabetes among cohorts with different proportions of men perhaps supports the growing body of evidence that diabetes attenuates any gender-related survival benefits in women (Huxley et al. 2006).
There could be several factors specific to diabetes operational both at presentation of AMI and over a longer period thereafter, affecting survival post-AMI (Gale et al. 2011). These include diffuse multi-vessel coronary disease; distinct pathophysiology of coronary atherothrombosis with associated increased risk of recurrent ischaemic events; a characteristic patient profile of older age and multiple co-morbidities; and as yet unknown novel pathological risk factors. Additional contributory factors could be those known to compromise long-term management of chronic conditions including suboptimal care in the community setting, clinical inertia in the utilisation of evidence-based interventions, and patient compliance (Gale et al. 2011).

Diabetes is a major driver behind incident CHD, especially AMI; almost two-thirds of those presenting with CHD now have either diabetes or impaired glucose regulation (Rydén et al. 2013). My findings highlight the challenges faced by healthcare professionals and policy makers from the rising prevalence and fatal impact of diabetes among people with CHD. My study provides both patients and healthcare professionals with a robust estimate of excess mortality risk associated with diabetes, which they should consider while making treatment decisions. I believe that, to improve long-term survival after AMI in people with diabetes, a broader approach to the care after the event is needed, incorporating intensification of care at various levels, aggressive management of multiple cardiovascular risk factors, and importantly, patient education and support. Recent guidelines from professional societies incorporate several new recommendations for effective management of CHD in diabetes, including coronary bypass grafting surgery instead of PCI for multi-vessel or complex
coronary lesions and the use of newer, more potent antiplatelet agents (Rydén et al., 2013, Tardif et al. 2013, Vergès et al. 2012). The latest reports on cardioprotective benefits of glucose lowering agents Empagliflozin and Liraglutide bring new hopes in improving outcomes in people with type 2 diabetes at high risk for cardiovascular events (Zinman et al. 2015, Marso et al. 2016, Saraiva et al. 2014). Structured education programmes improve heath behaviour and self-management in patients with diabetes (Rydén et al., 2013, Davies et al. 2008) and need to be offered more widely, perhaps as an integral part of the patient’s cardiac rehabilitation programme. Integration of specialist and community care is a novel way to optimise care of chronic conditions, and would help provide comprehensive assessment and management of both CHD and diabetes in the long-term after AMI (Worskwick et al. 2013, Tricco et al. 2012). This is especially important in the UK since there is a drive towards moving diabetes care from specialist setting into the primary care. Up-skilling primary care teams in providing high-quality diabetes care, therefore, will need greater attention. It is equally important that attention is paid to the primary prevention of CHD in people with diabetes by intensive management of multiple risk factors to reduce their risk of developing AMI (Gæde et al. 2008). Finally, research is essential for greater understanding and explanation of novel risk factors and drivers of excess CHD risk in diabetes. Future research programmes need to drive the development of novel interventions addressing both pathophysiological and care process-related factors behind poor survival in diabetes.
3.7 Limitations

The type, duration and therapies (insulin versus non-insulin) for diabetes, adequacy of long-term glycaemic control, and prevalence and management of acute hyperglycaemia at admission with AMI were not universally reported and therefore not considered in the analysis. The outcome in diabetes may differ in the subgroups defined by these characteristics. I excluded studies reporting long-term mortality in patients with screen-detected diabetes. Such patients newly diagnosed with diabetes during index admission are likely to have differential and possibly worse prognoses compared to those known to have diabetes and who were treated adequately prior to the index AMI.

Management of diabetes has revolutionised in recent years, with the cardiovascular risk of contemporary cohorts being better than those in the past. On the other hand, the definition of AMI changed after the year 2000, and since then a widespread use of more sensitive cardiac biomarker of troponin since has lowered the diagnostic threshold. As a result, the contemporary cohort of AMI has a higher proportion of people with non-STEMI who often have a higher burden of co-morbidities and are over-represented in the diabetes cohort. Confounders related to lower diagnostic thresholds and modern management of both diabetes and CHD affecting our findings cannot be excluded. Furthermore, I could not find studies from the developing world fulfilling the selection criteria, and the proportion of ethnic minority participants in the included studies such as those from the SA population were very minimal. Therefore the findings of this study may not be entirely applicable to patients presenting with AMI from the developing world. My analysis is based on
summary data rather than patient-level data and does not include cause-specific mortality. Despite these limitations, the key strength of our analysis is the inclusion of a very large number of participants from across the globe from cohort studies and RCTs who were followed up for up to 20 years, providing enough power for robust assessment of the association between diabetes and long-term mortality post-AMI.

3.8 Conclusions

My review found that diabetes is associated with at least a 50% increase in long-term mortality following AMI, even after adjusting for confounders including demographic characteristics, comorbidities, the severity of AMI and management at index admission. Furthermore, the excess mortality in diabetes was consistent irrespective of presentation and modern treatment of AMI, persisted in the longer-term following AMI, and was evident in those who survived to discharge or first 30 days after index AMI. More research to understand mechanisms behind this excess risk and develop novel intervention is needed.

This meta-analysis identified two other important issues: i) most studies reporting adjusted estimates of association of diabetes with long-term mortality did not consider admission glucose levels in the adjusted model and therefore failed to assess relative impact of diabetes and admission hyperglycaemia on long-term mortality; ii) suitable studies, comparing long-term mortality post AMI in migrant SA patients with and without diabetes were almost non-existent on
the systematic literature search and therefore not included in the meta-analysis. These issues are addressed in the next two chapters.

In the next Chapter Four, I present findings of a large observational study in which I have examined the relative strength of association of acute versus chronic hyperglycaemia on survival post AMI. At the time of publishing the above-mentioned meta-analysis, searches were updated and the findings of the study presented in Chapter Four were included in the meta-analysis.

In Chapter Five, I report findings from the same observational study, on the association of diabetes and ethnicity with short and long-term mortality in SA and WE patients admitted with AMI. I hypothesised that the high prevalence of diabetes in SA patients with AMI, as compared with the WE patients will be associated with higher mortality following AMI.
Figure 3.1 Flow Diagram – Study Identification, Selection and Exclusion

No of potentially relevant articles identified and screened (n= 32,917)

No of articles excluded on the basis of title and abstract (n= 32,632)

No of full text articles retrieved for detail assessment (n=285)

No of full-text articles excluded based on various criteria (n= 220)
- Duplicate articles and multiple articles from the same cohort = 57
- Reporting on post AMI mortality less than one year = 27
- Reporting on mixed cohorts of: acute coronary syndrome including unstable angina or; AMI plus stable coronary heart disease = 49
- Reporting on selective group of patients with AMI = 6
- Reporting on mixed cohort of known and screen detected diabetes = 12
- Reporting on mortality associated with admission blood glucose without providing number of deaths in those with and without diabetes = 19
- Reporting cardiovascular rather than all-cause deaths = 3
- Reporting number of deaths in only one cohort of patients either with or without diabetes = 13
- Other miscellaneous reasons = 34

No of article included in the meta-analysis. (n= 65 articles reporting 66 studies)
Figure 3.2 The unadjusted hazard ratio (HR) for long-term mortality in people with diabetes compared to those without. HR greater than 1 indicates increased risk of death in people with diabetes compared to those without. Follow-up time refers to mean, median or maximum duration of follow-up. The figures on the left-hand side of the forest plot under the ‘No diabetes’ and ‘Diabetes’ columns refer to number of deaths (numerator) and the total number of participants (denominator) respectively in each study.
Figure 3.3: Adjusted hazard ratio (HR) for long-term mortality in people with diabetes compared to those without. Follow-up time refers to mean, median or maximum duration of follow-up. The figures on the left-hand side of the forest plot under the ‘No diabetes’ and ‘Diabetes’ columns refer to number of deaths (numerator) and the total number of participants (denominator) respectively in each study.
Figure 3.4 The risk of long-term mortality in people with diabetes compared to those without across various subgroups. Hazard ratios greater than 1 indicate increased the risk of death in people with diabetes compared to those without.

*studies with a mixed population of patients with STEMI/NSTEMI/AMI.
Figure 3.5 Funnel plot of the standard error of risk ratio versus risk ratio on a logarithmic scale assessing publication bias in the evidence on the risk of long-term mortality in people with diabetes compared to those without.
Chapter Four: Is admission blood glucose concentration a more powerful predictor of mortality after acute myocardial infarction than diabetes diagnosis? A retrospective cohort study

4.1 Chapter Overview

In Chapter Two, I discussed the controversy around the importance of acute versus chronic hyperglycaemia on prognosis post AMI. As a result, two-thirds of people with acute hyperglycaemia at admission with AMI and previously not known to have diabetes are not actively treated with glucose-lowering interventions. In many studies, acute hyperglycaemia is found to adversely impact survival post AMI, independent of diabetes status. However, these studies examined individual rather than a relative association of these two measures of glucose abnormalities with prognosis after AMI. I therefore undertook a retrospective analysis of a large cohort of AMI assessing the relative association of admission blood glucose levels and antecedent diabetes with mortality post AMI. I jointly formulated the research aims and methodology of the study with Professors Khunti and Squire. I cleaned the dataset, extracted the relevant information and undertook all the analysis including the survival analysis under the supervision of a statistician Rajanikant Mehta. I am the first author on the research paper resulting from this work. I led the work on this publication including writing the manuscript, creating the tables; and addressing the comments (available online) from three national experts in this field who were the peer reviewers of the article.
4.2 Abstract

**Aims/Objectives:** To explore the relative impact of admission blood glucose levels and antecedent diabetes on survival in patients with STEMI and NSTEMI.

**Methods:** Retrospective cohort study based on the MINAP dataset involving 4111 (N=835, 20.3% known diabetes) consecutive patients with AMI (58.3% with STEMI) admitted to a tertiary centre Coronary Care Unit in the UK, between October 2002 – September 2008. The relative strength of association of admission blood glucose and antecedent diabetes with all-cause mortality at 30-days and at 1-year post AMI was assessed using Cox regression analysis.

**Results:** By 30 days and 1 year, 409 (9.9%) and 677 (16.5%) patients had died. After adjusting for covariates, diabetes did not show an independent association with mortality at any time point in the entire cohort (HR 30 days 0.93 (CI 0.63, 1.38); 1-year 1.00 (0.77, 1.30)) or in subgroups of STEMI (HR 30days 1.03 (CI 0.65, 1.64); 1 year 1.08 (0.77, 1.51)) and non-STEMI (HR 30-days 0.62 (0.26, 1.50); 1-year 0.87(0.56, 1.36)). In contrast, after adjusting for covariates, admission glucose showed a robust and independent association with mortality in the entire cohort (HR per mmol/L increase; 30 days 1.07 (1.04, 1.10); 1-year 1.05 (1.03, 1.08)), and in the subgroup of STEMI (30-days 1.07 (1.03, 1.10); 1-year1.07 (1.04, 1.10)), and NSTEMI (HR 30 days 1.07 (1.00, 1.14); 1-year 1.02 (0.97, 1.06)).

**Conclusion:** Admission glucose is strongly associated with mortality in all presentations of AMI, irrespective of established diabetes diagnosis. The increased risk is maintained up to 1 year. Future studies are required to assess the impact of active management of elevated blood glucose in improving mortality in individuals admitted with AMI.
4.3 Introduction


In some studies (Capes et al. 2000, Squire et al. 2010), the association between admission blood glucose concentration and adverse outcome was more powerful in patients without compared to those with prior diabetes. Indeed in one study from our centre, we reported a more powerful association with 30-day and 1-year mortality after STEMI, for admission blood glucose concentration compared to the diagnosis of diabetes (Squire et al. 2010). On the contrary, others have reported that the impact of acute and chronic hyperglycaemia on outcome post AMI may be different and time dependent (early versus long term), and only chronic rather than acute hyperglycaemia determines long-term prognosis (Ishihara et al. 2007, Tenerz et al. 2003). In my recent meta-analysis (Chapter Three), I found that most studies reporting adjusted analysis of the association of diabetes with long-term mortality have failed to consider admission blood glucose as a covariate in the adjusted models.
While a causal relationship is unproven, there are numerous potential pathophysiological mechanisms by which acute hyperglycaemia may impart toxicity during myocardial ischaemia (Ceriello et al. 2001, DeCaterina et al. 2010). Indeed, observational data suggest that an elevated blood glucose may contribute directly to adverse outcome after an AMI. Prognosis is worse for patients in whom hyperglycaemia persists in the 24-48 hours after AMI compared to those in whom blood glucose normalises (Goyal et al. 2006, Norhammer et al. 1999). In patients without prior diabetes, insulin-based treatment of hyperglycaemia after AMI is associated with an improved prognosis (Weston et al. 2007, Schnell et al. 2004). Furthermore, in RCTs of intensive insulin-based blood glucose management during admission with AMI, a survival benefit was evident only when the intervention effectively lowered blood glucose concentration (Malmberg et al. 1995, Malmberg et al. 2005).

While the relationship between blood glucose concentration and outcome after AMI has largely been described in patients with STEMI, the majority of ACS in contemporary practice are NSTEMI. While one study reported a similar association between the degree of dysglycaemia and outcome at 6 months in STEMI and NSTEMI (Sinnaeve et al. 2009), this report suggested that after adjusting for covariates, admission blood glucose did not show an association with post-discharge mortality (Sinnaeve et al. 2009).

The aim of the current analysis was to compare the relative strength of association with 30-day, 1-year and longer term mortality of antecedent diabetes diagnosis and admission blood glucose concentration in patients with
STEMI and with NSTEMI, and in those with and without a history of diabetes in a multi-ethnic population. I also assessed the relevance of blood glucose concentration, recorded soon after admission to hospital with AMI, to mortality in patients surviving to discharge.

4.4 Methods

Data were collected from consecutive admissions between 1st October 2002 and 30th September 2008 to the two coronary care units (CCU) of a large teaching hospital serving the population of Leicestershire, UK (approximately 946,000 residents in 2004). Data were gathered as part of the hospital’s mandatory participation in the Myocardial Ischaemia National Audit Programme (MINAP). Established in 1998, MINAP is a national registry of patients admitted with acute coronary syndrome (ACS) and since 2002 all acute NHS hospitals in England and Wales have participated (Herrett et al. 2010). Data collection for MINAP has approval from the Patient Information Advisory Group, a committee appointed by the English Secretary of State for Health under Section 60 of the English Health and Social Care Act 2001 (re-enacted under Section 251 of the NHS act 2006), to use patient and physician identifiable information essential to the project, specifically the unique NHS number, without individual patient consent (Health research authority). The study was approved by the local research ethics committee.

In the MINAP, for all patients we record clinical and demographic data including information on diagnosis (STEMI/NSTEMI), electrocardiographic (ECG) site of infarct, medical history, coronary heart disease risk-factors, and prescribed
medication. Data are record-linked to mortality information (Blackledge et al. 2003), and include self-reported coding for ethnicity, for which local coverage is thorough. Approximately 14% of the local Leicestershire population are of SA ethnic origin, over twice the UK national average.

During the period of study, primary percutaneous coronary intervention (PCI) gradually replaced thrombolysis as the preferred mode of reperfusion for STEMI. Accordingly we defined reperfusion therapy for STEMI as receipt of thrombolysis and/or primary PCI. Patients with NSTEMI were initially stabilised with medical therapies, and coronary angiography considered thereafter. Revascularisation for STEMI or NSTEMI at index admission was defined as treatment with PCI or coronary artery bypass graft surgery during the index admission. Patients with persistently elevated blood glucose levels >11.0 mmol/l on admission were administered intravenous sliding scale insulin for the first 24-48 hours.

Patients were categorised as having a diagnosis of diabetes if this was self-reported by the patient or on the basis of medication prescribed prior to admission. All patients with AMI routinely underwent blood glucose measurement, in most cases within first 12 hours after admission with blood samples assayed in the hospital laboratory. We used such first recorded admission glucose levels for this analysis. All diagnoses of AMI (STEMI and NSTEMI) were verified prior to submission to the national MINAP database; the diagnosis of AMI was made according to the joint ESC/ACCF/AHA/WHF definition (Thygessen et al. 2007). For patients with multiple AMI admissions
(n=412) during the study period, we considered only the first event. The number of cases admitted with AMI during the study period determined the sample size.

Survival was measured from the date of the first admission for AMI (between 1st October 2002 and 30th September 2008) until the date of death or the end of follow-up (censored at 30th September 2009), whichever was earlier, providing a minimum of one-year follow-up for survivors. Follow-up data on mortality was available for all the patients. Mortality data are supplied to the hospital on a monthly basis on an ongoing basis via record linkage to the UK Office for National Statistics.

The pre-defined primary outcome measure was all-cause mortality at 30 days and 1-year. I also considered all-cause mortality during in-patient stay and over the entire period of follow-up. I assessed the relative strength of association with mortality for diabetes diagnosis and for admission blood glucose concentration in the entire cohort and in the subgroups of STEMI and NSTEMI.

4.4.1 Statistical analysis

Prior to undertaking the analysis, I had undergone training in basic and intermediate level statistics using the SPSS software. For this study I initially conducted the analysis under the supervision of a statistician with expertise in survival analysis (Raj Mehta). This initial experience and further training in survival analysis by attending a conference enabled me to conduct rest of the analysis independently.
Baseline characteristics were compared between groups using independent two-sample t-tests for continuous variables and chi-squared tests for categorical variables. Mortality during the in-patient stay, at 30 days, 1 year and the end of follow-up, in the entire cohort and in those patients surviving to discharge were calculated.

I calculated mortality proportions for patients admitted from 1\textsuperscript{st} October 2002 to 30\textsuperscript{th} September 2008 with follow-up censored at 30\textsuperscript{th} September 2009. Survival probabilities were calculated using Kaplan-Meier [KM] analyses and patient groups compared using survival analysis log-rank test. The relative risk of mortality, as a function of explanatory variables, was examined using Cox proportional hazards techniques. I initially assessed the unadjusted, univariate association with outcome for admission blood glucose and for diabetes, and for other potentially relevant clinical and demographic variables (age, sex, ethnicity, smoking, type of AMI (STEMI, NSTEMI), prior history (hypertension, any coronary artery disease, cerebrovascular or peripheral vascular disease), admission systolic blood pressure and heart rate, estimated glomerular filtration rate (eGFR), coronary reperfusion and/or revascularisation during the index admission, pre-admission and discharge drug therapy (anti-platelet, beta-blocker, statin, angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker), and index loop diuretic use. An interaction term representing calendar year of admission was included to adjust for potential temporal changes in the management of acute coronary artery disease.
Demographic and clinical covariates with the univariate association (p<0.10) with mortality were entered into multivariate models (Cox proportional hazards). All quantitative variables were entered as continues variables into the model. Patients with missing data (Table 1) were not excluded but there values were set as missing. Statistical significance for all comparisons was set at p<0.05 (2 sided). Data are presented as hazard ratio (HR) and 95% confidence intervals (CI). I used fractional polynomials to model admission glucose to account for any non-linearity and assessed its independent association with mortality in subgroups with and without diabetes. Analyses were carried out using SPSS version 18.

4.5 Results

The study population comprised of 4111 patients admitted between 1st October 2002 – 30th September 2008 with a discharge diagnosis of AMI (STEMI 2397, 58.3%) and for whom a minimum of 365 days follow-up was available from the date of admission. For this cohort, median follow-up was 912 days (range 1 to 2556) days; for 3792 (92.2%) patients surviving to discharge from the index admission, median follow-up was 1031 (range 1 to 2556) days.

Demographic details of the study population are presented in Table 4.1. Prior diabetes was recorded in 835 (20.3%) patients. Compared to those without, patients with antecedent diabetes were on average older (68.6 vs 65.8 years, p<0.005), more likely to be female (33.9% vs 28.9%, p = 0.022) and had prior cardiovascular co-morbidities (hypertension 70% vs 45%, p<0.005; CHD 17.9% vs 10.6%, p<0.005); CVA 10.3% vs 5.2%, p<0.005; PVD 5% vs 3.5%, p=0.041).
Presentation with NSTEMI was more prevalent in cases with (50.1%), compared to those without (39.6%) prior diabetes (p <0.005). Mean plasma glucose was higher in patients with diabetes (12.0 ± 5.5 mmol/L) compared to those without (7.9 ± 3.3 mmol/L) (p <0.005). Mean peak CK was lower in patients with diabetes.

During the index admission, administration of loop diuretic was more frequent (52.7% vs 33.4%, p<0.005) and coronary reperfusion/revascularisation therapies less frequent (50.2% vs 60.9%, <0.005), in patients with diabetes. Other than for slightly lower use of beta-blockers and aspirin in patients with diabetes, patterns of prescription of secondary prevention therapies at discharge were similar in the two groups.

4.5.1 Mortality – Univariate analysis

The number of people who died during hospitalisation and over 30-days, 1 year and the entire period of follow-up were 319 (7.8%), 409 (9.9%), 677 (16.5%) and 1041 (25.3%) respectively. Age, female sex, higher admission heart rate, higher eGFR, lower systolic blood pressure and presentation with STEMI (compared to NSTEMI), as well as prior smoking and hypertension, each showed univariate association with mortality risk over all time periods (Table 4.2). Loop diuretic was associated with a 3-4 fold increase in mortality during follow-up: HR 30 days 3.46 (2.81 - 4.26); 1 year 4.35 (3.68 - 5.14); all follow-up 4.05 (3.56 - 4.62). Survival improved over the period of observation.
Prior diabetes showed strong univariate association with mortality risk over all time periods: HR 30 days 1.40 (1.12 - 1.75); 1 year 1.58 (1.33 - 1.86); all follow-up 1.66 (1.44, 1.90)) (Table 4.2). The strength of association between glucose and mortality was consistent at 30-days and at 1-year, each mmol/L increase in admission glucose concentration being associated with a 6-7% increase in the hazard of mortality over all time periods.

4.5.2 Post-discharge mortality

In those surviving to discharge (N=3792), 106 (2.8%), 363 (9.6%) and 726 (19.1%) had died by 30-days, 1-year and over the entire follow-up period respectively. Univariate associations with mortality were similar to those in the entire population. Prior diabetes showed univariate association with increased risk of death at all times, although this was not statistically significant at 30 days (HR 1.36, (0.87 - 2.12)). For admission glucose, the strength of association with post-discharge mortality was very similar to that in the entire cohort, with a 5-7% increase risk per mmol/L increase in glucose.

4.5.3 Mortality – Multivariate analysis

Table 4.3 shows the results of the multivariate analysis. Age, lower admission systolic blood pressure and higher heart rate, lower eGFR, prescription of a loop diuretic, and STEMI (compared to NSTEMI) each retained an independent association with mortality, as did prescription of individual discharge medications. After covariate adjustment, diabetes did not retain an independent association with mortality at any time. In contrast, adjustment for covariates had
little impact on the risk of mortality associated with admission glucose concentration.

4.5.4 Post-discharge mortality
For patients surviving to discharge, associations between clinical variables and the risk of mortality were similar to those seen in the entire cohort. While there was no association between prior diabetes and risk of mortality at any time (HR 30 days 0.64 (0.31 – 1.300); 1 year 0.91 (0.66 – 1.26); all follow-up 1.08 (0.86 – 1.36)), blood glucose retained a powerful association with the primary endpoint. This was evident at 30 days (HR per mmol/L 1.10, 95% CI 1.05 – 1.15), 1 year (1.05, 1.02 – 1.08), and overall follow-up (1.04, 1.02 – 1.06)).

4.5.5 Admission glucose – influence on mortality in patients with or without diabetes
I repeated multivariate analysis including a term for interaction between diabetes diagnosis and admission glucose concentration. While numerically greater in individuals without diabetes (Figure 4.1), there was no conventional statistically significant difference in the association between mortality and admission blood glucose for patients with and without diabetes (30 days HR 1.00, (CI 0.97 – 1.03, p=0.95; 1 year 0.99, (0.97 – 1.02), p=0.66; entire follow-up 0.99, (0.97 – 1.01, p=0.42)).
4.5.6 Diabetes and glucose after AMI – influence on mortality in STEMI and NSTEMI

After adjustment for covariates, diabetes showed no statistically significant association with mortality at any time period either for STEMI or NSTEMI (Table 4.4). The strength of association between blood glucose and mortality was very similar in the first 30 days after STEMI or NSTEMI. The strength of this relationship declined with time only for NSTEMI.

4.6 Discussion

It is well known that both prior diabetes diagnosis and admission blood glucose concentration, are associated with adverse outcomes after AMI. In this study I compared the relative association of these two measures of dysglycaemia with survival after STEMI as well as NSTEMI. Irrespective of the type of AMI, the univariate association with mortality risk for antecedent diabetes (40% excess at 30 days, 55-65% thereafter) was no longer apparent after adjustment for relevant covariates including admission glucose concentration. In contrast, the excess risk associated with increasing glucose was not reduced after adjustment, was similar in those with and without known diabetes, and remained relevant in patients discharged alive from the index event.

In a previous report from our group of over 4000 patients with STEMI admitted in 1993-2004 (Squire et al. 2010), the 50% increase in 30-day and 1-year mortality risk associated with known diabetes was attenuated by half on covariate adjustment and removed completely when admission blood glucose concentration was included in the analysis. The current report confirms these
observations and extends them to a contemporary period, and to patients with NSTEMI as well as STEMI. In both of these subgroups, the strength of association between admission blood glucose concentration and 30-day mortality risk was similar and concentration dependent. Importantly, the excess risk, around 7% for each 1mmol/L increase in admission glucose concentration, was maintained up to and beyond 1 year from the index infarction. Furthermore, this phenomenon persisted with time, albeit to a lesser extent in those with NSTEMI, and was evident even in those patients who survived to discharge from the hospital, two potentially important clinical observations. These findings are in contrast to one previous report which reported the association between admission glucose and mortality to be confined to in-hospital deaths following either STEMI or NSTEMI (Sinnaeve et al. 2009). They are however in keeping with the vast majority of reports in this area (Malmberg et al. 2000, McGuire et al. 2002, Svensson et al. 2005, Capes et al. 2000, Wahab et al. 2002, Kosiborod et al. 2005, Cao et al. 2005, Squire et al. 2010, De Caterina et al. 2010).

Previous studies and my meta-analysis reported in Chapter 3 have shown an independent association between diabetes and mortality risk with some studies further showing the highest risk in the subgroup of diabetes patients on insulin therapy. No such independent association was seen in this study. However, to my knowledge and unlike the present report, most of these studies did not adjust for admission blood glucose, and each reported individual relationships between mortality after AMI and either diabetes diagnosis (Malmberg et al. 2000, McGuire et al. 2002, Capes et al. 2000, Sinnaeve et al. 2009) or blood

The current analysis and a previous study (Squire et al. 2010) are the only reports to compare the relative association with the outcome of both diabetes and blood glucose concentration. Both studies demonstrate a much stronger relationship between survival and blood glucose and the loss of the association between mortality and diabetes, when blood glucose is considered.

The strength of the association between diabetes and mortality risk after AMI has been seen to at least remain constant over the longer follow-up period as seen in our meta-analysis, and in some studies has been found to even increase with time from the event (Melchior et al. 1999). While I observed such a trend on univariate analysis, this was attenuated in multivariate analysis, an observation which may relate to my inclusion of blood glucose as a covariate. Furthermore, a previous meta-analysis suggested a stronger association between admission blood glucose and adverse outcomes in people without diabetes. (Capes et al. 2000) While I could not demonstrate formal statistical evidence of such a phenomenon, my data convincingly show that the relationship between glucose and outcome is at least as powerful in patients without known diabetes.

An important observation from this study is the continued association between admission blood glucose concentration and mortality risk in patients surviving to discharge, in both NSTEMI and STEMI. It is possible that blood glucose
concentration at admission reflects the degree of individual physiological stress or the extent of infarction. However my findings could also suggest a direct adverse influence of acute hyperglycaemia on prognosis. The possible mechanisms by which elevated glucose may be directly cardiotoxic include attenuation of ischaemic preconditioning, QT prolongation, increased thrombophilia, and endothelial dysfunction (Ceriello et al. 2001). Furthermore, clinical studies overwhelmingly support a possible causal link between hyperglycaemia and adverse prognosis after AMI. Hyperglycaemia persisting at 24 hours after admission is associated with adverse outcome (Goyal et al. 2006, Norhammer et al. 1999, Malmberg et al. 2005).

While observational studies consistently show the adverse association between hyperglycaemia and outcomes post AMI, results of the RCTs of active management of blood glucose have been inconsistent (Malmberg et al. 1995; Malmberg et al. 2005) However in such trials, effective reduction in blood glucose with an intervention after AMI was associated with improved prognosis (Malmberg et al. 1995). The guidelines from professional societies in this area differ in their recommendations. In the North American, Canadian and European guidelines, intensive glucose control is recommended in patients with AMI and significant hyperglycaemia (blood glucose levels >10.0 mmol/L (>11.0 mmol/L in the Canadian guideline) admitted in an intensive care unit, aiming to maintain blood glucose between 7.0 to 10.0 mmol/L (Deedwania et al. 2008, Rydén et al. 2013, Expert committee. 2013). In contrast, the NICE guidance recommends against routine use of intensive insulin therapy to manage hyperglycaemia (blood glucose levels > 11.0 mmol/L) in patients with ACS (NICE. 2011). The
latter guidelines highlighted a need for RCTs addressing specific gaps in knowledge in this area.

My findings are subject to the limitations inherent in all observational cohort studies.

- The dataset lacked complete data on acute inpatient glucose-lowering therapies for raised glucose on admission. There is a possibility that the elevated glucose levels were aggressively managed selectively in patients with known diabetes and it would have improved their survival compared to those with elevated glucose but without known diabetes. This may in turn contribute to the finding in my analysis that diabetes status is a less significant predictor of mortality compared to admission glucose levels. However, if this is true, it further strengthens the message that if elevated glucose contributes to the prognosis, active management as early as possible irrespective of diabetes status is likely to be beneficial.

- I had no information regarding the number of patients who were given a diagnosis of diabetes during, or subsequent to the index admission. It is likely that a proportion of our cohort had previously undiagnosed diabetes which may contribute to the association between admission glucose and subsequent mortality risk. However if elevated glucose contributes directly to prognosis, active management is likely to confer a greater benefit when delivered as early as possible, irrespective of subsequent diabetes status.
Outcomes of mortality could vary in subgroup of patients categorised by either type of diabetes (type 2 vs. type 1) or different glucose-lowering therapies (Insulin vs. Non-insulin therapies). However my dataset lacked information on types of diabetes and long-term glucose-lowering therapies and furthermore the study does not have enough power to come to any meaningful conclusion on relationship between types of diabetes/medical therapies and outcomes.

During early years of MINAP project, data were only collected for STEMI. Furthermore data collected for MINAP are gathered mainly in the setting of coronary care unit. All these factors are likely to have caused selection bias resulting in a relative high proportion of patients with STEMI (58.4%) compared to NSTEMI in our cohort. The proportion of NSTEMI was low in people with diabetes and that could have resulted in the better survival observed in this group.

The database lacks information on left ventricular (LV) ejection fraction, evidence of heart failure and a number of other potentially relevant variables. Furthermore, I had no information on interventions or changes to therapy after discharge. However it is unlikely that these impacted on outcome in a major way, as the strongest association between mortality and glucose was in the first 30 days.

In summary, admission blood glucose concentration is a powerful, routinely available marker of mortality risk after AMI. The association between blood glucose concentration and mortality risk is of similar magnitude in patients with and without known diabetes, is evident for NSTEMI as well as STEMI, and
persists beyond 1 year from the index event, including in patients surviving to discharge. If an elevated glucose contributes directly to prognosis, active management is likely to confer a greater benefit when delivered as early as possible irrespective of underlying diabetes status. Future well-designed RCTs are needed on the impact of active management of blood glucose in patients with all presentations of ACS, irrespective of diabetes diagnosis. Until then it is prudent to treat significant hyperglycaemia (blood glucose >11.0 mmol) to target levels between 7.0 to 10.0 mmol/l; monitoring carefully for hypoglycaemia.

Further studies are also needed in SA populations to understand the impact of acute hyperglycaemia on prognosis as SA people have a higher prevalence of glucose abnormalities (Chapter 2). To our knowledge, no such studies have been reported. In the next Chapter Five, I report further analysis of this study cohort, examining the prevalence and prognostic significance of both acute and chronic hyperglycaemia in SA and WE patients with AMI.
Table 4.1: Baseline characteristics at admission stratified by diabetes status

<table>
<thead>
<tr>
<th>Demography</th>
<th>All n=4111</th>
<th>Known DM n=835 (20.3%)</th>
<th>Not Known DM n=3276 (79.7%)</th>
<th>( P ) Value</th>
<th>Missing Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.4 (13.3)</td>
<td>68.6 (11.8)</td>
<td>65.8 (13.6)</td>
<td>&lt;0.005</td>
<td>0.0</td>
</tr>
<tr>
<td>Women (%)</td>
<td>1224 (29.8)</td>
<td>276 (33.1)</td>
<td>948 (28.9)</td>
<td>0.022</td>
<td>0.0</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White European</td>
<td>3381 (82.2%)</td>
<td>545 (16.1)</td>
<td>2836 (86.6)</td>
<td>&lt;0.005</td>
<td>0.0</td>
</tr>
<tr>
<td>South Asian</td>
<td>730 (17.8%)</td>
<td>290 (39.7)</td>
<td>440 (60.3%)</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Medical History (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2048 (50.3)</td>
<td>584 (70.0)</td>
<td>1464 (45.0)</td>
<td>&lt;0.005</td>
<td>1.0</td>
</tr>
<tr>
<td>Current/Ex Smoker</td>
<td>1366 (35.7)</td>
<td>149 (17.9)</td>
<td>342 (10.6)</td>
<td>&lt;0.005</td>
<td>0.9</td>
</tr>
<tr>
<td>Coronary Heart Disease§</td>
<td>491 (12.1)</td>
<td>149 (17.9)</td>
<td>342 (10.6)</td>
<td>&lt;0.005</td>
<td>0.9</td>
</tr>
<tr>
<td>CVA</td>
<td>254 (6.3)</td>
<td>86 (10.3)</td>
<td>168 (5.2)</td>
<td>&lt;0.005</td>
<td>1.2</td>
</tr>
<tr>
<td>PVD</td>
<td>154 (3.8)</td>
<td>42 (5.0)</td>
<td>112 (3.5)</td>
<td>0.041</td>
<td>1.2</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>190 (4.7)</td>
<td>76 (9.1)</td>
<td>114 (3.5)</td>
<td>&lt;0.005</td>
<td>1.2</td>
</tr>
<tr>
<td>Type of Infarction (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>2397 (58.3)</td>
<td>417 (49.9)</td>
<td>1980 (60.4)</td>
<td>&lt;0.005</td>
<td>0.0</td>
</tr>
<tr>
<td>nSTEMI</td>
<td>1714 (41.7)</td>
<td>418 (50.1)</td>
<td>1296 (39.6)</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>81.1 (24.3)</td>
<td>85.5 (25.3)</td>
<td>80.0 (24.0)</td>
<td>&lt;0.005</td>
<td>1.5</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>136.5 (28.4)</td>
<td>137.7 (30.7)</td>
<td>136.2 (27.8)</td>
<td>0.202</td>
<td>1.0</td>
</tr>
<tr>
<td>Biochemical Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak CK (IU/L, Normal range &lt; 200)</td>
<td>1113.5</td>
<td>939.9</td>
<td>1156.4</td>
<td>&lt;0.005</td>
<td>7.6</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>116.4 (63.8)</td>
<td>128.8 (76.1)</td>
<td>113.1 (59.8)</td>
<td>&lt;0.005</td>
<td>16.8</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>63.0 (22.2)</td>
<td>57.7 (23.6)</td>
<td>64.4 (21.7)</td>
<td>&lt;0.005</td>
<td>16.6</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.1 (1.3)</td>
<td>4.4 (1.2)</td>
<td>5.2 (1.3)</td>
<td>&lt;0.005</td>
<td>16.6</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>13.7 (1.9)</td>
<td>13.0 (1.9)</td>
<td>13.9 (1.8)</td>
<td>&lt;0.005</td>
<td>66.6</td>
</tr>
<tr>
<td>Plasma glucose (mmol/L)</td>
<td>8.8 (4.2)</td>
<td>12.0 (5.5)</td>
<td>7.9 (3.3)</td>
<td>&lt;0.005</td>
<td>14.9</td>
</tr>
<tr>
<td>Therapies (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to index admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>2671 (65.0)</td>
<td>622 (74.5)</td>
<td>2049 (62.5)</td>
<td>&lt;0.005</td>
<td>0.0</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>990 (25.6)</td>
<td>265 (33.2)</td>
<td>725 (23.6)</td>
<td>&lt;0.005</td>
<td>6.0</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>1097 (28.3)</td>
<td>407 (51.0)</td>
<td>690 (22.5)</td>
<td>&lt;0.005</td>
<td>5.8</td>
</tr>
<tr>
<td>Statins</td>
<td>1083 (28.0)</td>
<td>389 (48.7)</td>
<td>694 (22.6)</td>
<td>&lt;0.005</td>
<td>5.8</td>
</tr>
<tr>
<td>In-hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reperfusion/Revascularisation therapies #</td>
<td>2414 (58.7)</td>
<td>419 (50.2)</td>
<td>1995 (60.9)</td>
<td>&lt;0.005</td>
<td>0.0</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>1502 (37.4)</td>
<td>436 (52.7)</td>
<td>1066 (33.4)</td>
<td>&lt;0.005</td>
<td>2.3</td>
</tr>
<tr>
<td>At discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>2701 (68.1)</td>
<td>529 (65.3)</td>
<td>2172 (68.8)</td>
<td>0.057</td>
<td>3.5</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>2513 (63.3)</td>
<td>483 (59.6)</td>
<td>2030 (64.3)</td>
<td>0.013</td>
<td>3.5</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>2493 (62.9)</td>
<td>495 (61.0)</td>
<td>1998 (63.4)</td>
<td>0.222</td>
<td>3.6</td>
</tr>
<tr>
<td>Statins</td>
<td>2704 (67.7)</td>
<td>537 (65.6)</td>
<td>2167 (68.2)</td>
<td>0.167</td>
<td>2.8</td>
</tr>
</tbody>
</table>

All values are mean (SD) or number (%). * known diabetes vs not known diabetes.
DM, Diabetes Mellitus; CVA, Cerebrovascular accidents; PVD, Peripheral Vascular Disease; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; SBP, Systolic blood pressure; CK, Creatinine Kinase; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

# thrombolysis and/or coronary intervention (PCI or CABG) in STEMI and emergency coronary angiography ± coronary intervention in NSTEMI
Table 4.2: Univariate association of clinical variables with 30-day, 1-year, and total mortality in the entire cohort. Data are hazard ratio (95% confidence intervals)

<table>
<thead>
<tr>
<th>Demographic Variable</th>
<th>Mortality, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 days</td>
</tr>
<tr>
<td>N=4111</td>
<td>409 (9.95)</td>
</tr>
<tr>
<td>Demographic Variable</td>
<td></td>
</tr>
<tr>
<td>Gender (Female vs Male)</td>
<td>0.535 (0.439 , 0.650)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>1.068 (1.059 , 1.078)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.979 (0.976 , 0.983)</td>
</tr>
<tr>
<td>Heart Rate (beat/min)</td>
<td>1.010 (1.006 , 1.013)</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>0.732 (0.666 , 0.806)</td>
</tr>
<tr>
<td>Admission glucose (mmol/L)</td>
<td>1.072 (1.052 , 1.084)</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>0.956 (0.951 , 0.961)</td>
</tr>
<tr>
<td>NSTEMI vs STEMI</td>
<td>0.504 (0.405 , 0.627)</td>
</tr>
<tr>
<td>Year of Admission</td>
<td></td>
</tr>
<tr>
<td>Oct 2002-Dec 2003</td>
<td>1</td>
</tr>
<tr>
<td>2004</td>
<td>0.909 (0.688 , 1.200)</td>
</tr>
<tr>
<td>2005</td>
<td>0.591 (0.402 , 0.870)</td>
</tr>
<tr>
<td>2006</td>
<td>0.830 (0.592 , 1.164)</td>
</tr>
<tr>
<td>2007</td>
<td>0.759 (0.570 , 1.010)</td>
</tr>
<tr>
<td>2008</td>
<td>0.485 (0.338 , 0.696)</td>
</tr>
<tr>
<td>Test for Linear Trend (p-value)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ethnicity (SA vs. WE)</td>
<td>1.013 (0.786 , 1.304)</td>
</tr>
<tr>
<td>Medical History (Yes vs No)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.016 (0.819 , 1.259)</td>
</tr>
<tr>
<td>Prior Diabetes</td>
<td>1.400 (1.121 , 1.750)</td>
</tr>
<tr>
<td>Prior Coronary Heart Disease §</td>
<td>0.862 (0.628 , 1.182)</td>
</tr>
<tr>
<td>Prior Hypertension§</td>
<td>1.286 (1.056 , 1.567)</td>
</tr>
<tr>
<td>Pre - Admission Medication (Yes vs. No)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.746 (0.613 , 0.909)</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>1.385 (1.116 , 1.719)</td>
</tr>
<tr>
<td>Statin</td>
<td>0.994 (0.795 , 1.245)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>1.242 (1.002 , 1.540)</td>
</tr>
<tr>
<td>Admission treatment (Yes vs No)</td>
<td></td>
</tr>
<tr>
<td>Reperfusion/Revascularisation#</td>
<td>0.616 (0.507 , 0.749)</td>
</tr>
<tr>
<td>Loop Diuretic</td>
<td>3.457 (2.807 , 4.256)</td>
</tr>
<tr>
<td>Discharge Medication (Yes vs No)</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.043 (0.029 , 0.062)</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>0.038 (0.025 , 0.058)</td>
</tr>
<tr>
<td>Statin</td>
<td>0.043 (0.029 , 0.062)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>0.047 (0.031 , 0.070)</td>
</tr>
</tbody>
</table>

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction/ percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)

# thrombolysis and/or coronary intervention (PCI or CABG) in STEMI and emergency coronary angiography ± coronary intervention in NSTEMI.

123
Table 4.3: Multivariate association of clinical variables with 30-day, 1-year, and total mortality in the entire cohort. Data are hazard ratio (95% confidence intervals).

<table>
<thead>
<tr>
<th></th>
<th>Mortality, N (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 days</td>
<td>1 Year</td>
<td>Entire follow-up period (Median 912 days)</td>
</tr>
<tr>
<td></td>
<td>409 (9.95)</td>
<td>677 (16.5)</td>
<td>1041 (25.3)</td>
</tr>
</tbody>
</table>

### Admission Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>30 days</th>
<th>1 Year</th>
<th>Entire follow-up period (Median 912 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Female vs Male)</td>
<td>1.268 (0.885, 1.819)</td>
<td>1.094 (0.865, 1.383)</td>
<td>1.114 (0.931, 1.332)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>1.059 (1.040, 1.078)</td>
<td>1.062 (1.048, 1.075)</td>
<td>1.073 (1.062, 1.083)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.987 (0.981, 0.992)</td>
<td>0.991 (0.987, 0.995)</td>
<td>0.993 (0.990, 0.996)</td>
</tr>
<tr>
<td>Heart Rate (beat/min)</td>
<td>1.007 (1.001, 1.013)</td>
<td>1.006 (1.002, 1.010)</td>
<td>1.007 (1.005, 1.010)</td>
</tr>
<tr>
<td>Admission plasma glucose (mmol/L)</td>
<td>1.072 (1.042, 1.104)</td>
<td>1.059 (1.037, 1.081)</td>
<td>1.053 (1.036, 1.071)</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>0.987 (0.978, 0.996)</td>
<td>0.983 (0.977, 0.990)</td>
<td>0.988 (0.983, 0.993)</td>
</tr>
<tr>
<td>NSTEMI vs STEMI</td>
<td>0.411 (0.282, 0.597)</td>
<td>0.558 (0.443, 0.704)</td>
<td>0.700 (0.587, 0.834)</td>
</tr>
<tr>
<td>Ethnicity (South Asian vs White European)</td>
<td>1.355 (0.893, 2.057)</td>
<td>1.155 (0.851, 1.568)</td>
<td>0.996 (0.779, 1.273)</td>
</tr>
</tbody>
</table>

### Medical History (Yes vs No)

<table>
<thead>
<tr>
<th>Variable</th>
<th>30 days</th>
<th>1 Year</th>
<th>Entire follow-up period (Median 912 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>1.125 (0.788, 1.607)</td>
<td>0.953 (0.749, 1.213)</td>
<td>0.942 (0.786, 1.130)</td>
</tr>
<tr>
<td>Prior Diabetes</td>
<td>0.934 (0.631, 1.382)</td>
<td>1.001 (0.770, 1.300)</td>
<td>1.134 (0.927, 1.386)</td>
</tr>
<tr>
<td>Prior Coronary Heart Disease§</td>
<td>0.717 (0.402, 1.278)</td>
<td>0.898 (0.632, 1.277)</td>
<td>1.111 (0.864, 1.428)</td>
</tr>
<tr>
<td>Prior Hypertension</td>
<td>1.291 (0.903, 1.846)</td>
<td>1.155 (0.913, 1.461)</td>
<td>1.133 (0.949, 1.353)</td>
</tr>
</tbody>
</table>

### Pre -Admission Medication (Yes vs No)

<table>
<thead>
<tr>
<th>Variable</th>
<th>30 days</th>
<th>1 Year</th>
<th>Entire follow-up period (Median 912 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>0.944 (0.667, 1.335)</td>
<td>0.989 (0.781, 1.252)</td>
<td>1.010 (0.842, 1.213)</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>1.288 (0.898, 1.849)</td>
<td>1.363 (1.067, 1.742)</td>
<td>1.173 (0.970, 1.418)</td>
</tr>
<tr>
<td>Statin</td>
<td>0.863 (0.579, 1.286)</td>
<td>0.877 (0.668, 1.150)</td>
<td>0.918 (0.743, 1.135)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>0.719 (0.497, 1.042)</td>
<td>0.932 (0.728, 1.194)</td>
<td>1.017 (0.840, 1.232)</td>
</tr>
</tbody>
</table>

### Admission treatment (Yes vs No)

<table>
<thead>
<tr>
<th>Variable</th>
<th>30 days</th>
<th>1 Year</th>
<th>Entire follow-up period (Median 912 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop Diuretic</td>
<td>1.416 (0.993, 2.019)</td>
<td>1.703 (1.322, 2.195)</td>
<td>1.532 (1.268, 1.851)</td>
</tr>
</tbody>
</table>

### Discharge Medication (Yes vs No)

<table>
<thead>
<tr>
<th>Variable</th>
<th>30 days</th>
<th>1 Year</th>
<th>Entire follow-up period (Median 912 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>0.297 (0.157, 0.562)</td>
<td>0.656 (0.479, 0.897)</td>
<td>0.861 (0.676, 1.097)</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>0.257 (0.133, 0.494)</td>
<td>0.564 (0.423, 0.753)</td>
<td>0.671 (0.544, 0.828)</td>
</tr>
<tr>
<td>Statin</td>
<td>0.628 (0.295, 1.339)</td>
<td>0.683 (0.484, 0.963)</td>
<td>0.629 (0.490, 0.808)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>0.470 (0.229, 0.968)</td>
<td>0.610 (0.443, 0.839)</td>
<td>0.850 (0.668, 1.081)</td>
</tr>
</tbody>
</table>

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)
Table 4.4: Multivariate association of clinical variables with 30-day, 1-year, and total mortality in the subgroups of patients with STEMI and NSTEMI. Data are hazard ratio (95% confidence intervals)

<table>
<thead>
<tr>
<th>N=4111 (STEMI (2397), NSTEMI (1714))</th>
<th>Mortality</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 days</td>
<td>1 Year</td>
<td>Entire follow-up period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>STEMI</td>
<td>NSTEMI</td>
<td>STEMI</td>
<td>NSTEMI</td>
<td>STEMI</td>
<td>NSTEMI</td>
<td></td>
</tr>
<tr>
<td>Admission Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>1.055 (1.033 - 1.077)</td>
<td>1.073 (1.031 - 1.116)</td>
<td>1.061 (1.044 - 1.078)</td>
<td>1.056 (1.035 - 1.079)</td>
<td>1.077 (1.062 - 1.091)</td>
<td>1.061 (1.046 - 1.077)</td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.988 (0.982 - 0.994)</td>
<td>0.983 (0.970 - 0.995)</td>
<td>0.992 (0.987 - 0.997)</td>
<td>0.988 (0.982 - 0.995)</td>
<td>0.993 (0.989 - 0.997)</td>
<td>0.994 (0.990 - 0.998)</td>
<td></td>
</tr>
<tr>
<td>Heart Rate (beat/min)</td>
<td>1.008 (1.001 - 1.015)</td>
<td>1.008 (0.997 - 1.02)</td>
<td>1.008 (1.002 - 1.013)</td>
<td>1.007 (1.001 - 1.013)</td>
<td>1.008 (1.004 - 1.012)</td>
<td>1.007 (1.002 - 1.011)</td>
<td></td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>0.986 (0.975 - 0.997)</td>
<td>0.987 (0.969 - 1.005)</td>
<td>0.982 (0.974 - 0.991)</td>
<td>0.978 (0.968 - 0.989)</td>
<td>0.986 (0.979 - 0.993)</td>
<td>0.987 (0.979 - 0.995)</td>
<td></td>
</tr>
<tr>
<td>Admission plasma glucose (mmol/L)</td>
<td>1.070 (1.034 – 1.107)</td>
<td>1.074 (1.005 - 1.148)</td>
<td>1.071 (1.042 - 1.10)</td>
<td>1.021 (0.979 - 1.066)</td>
<td>1.076 (1.051 - 1.10)</td>
<td>1.014 (0.983 – 1.047)</td>
<td></td>
</tr>
<tr>
<td>Prior Diabetes</td>
<td>1.035 (0.652 - 1.641)</td>
<td>0.629 (0.264 - 1.502)</td>
<td>1.083 (0.772 - 1.518)</td>
<td>0.878 (0.566 – 1.36)</td>
<td>1.189 (0.907 - 1.559)</td>
<td>1.055 (0.773 – 1.44)</td>
<td></td>
</tr>
<tr>
<td>Admission treatment (Yes vs No)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop Diuretic</td>
<td>1.330 (0.890 - 1.989)</td>
<td>1.66 (0.759 - 3.629)</td>
<td>1.706 (1.248 (2.33)</td>
<td>1.988 (1.283 - 3.081)</td>
<td>1.365 (1.068 - 1.745)</td>
<td>2.03 (1.496 - 2.756)</td>
<td></td>
</tr>
<tr>
<td>Discharge Medication (Yes vs No)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.301 (0.135 - 0.672)</td>
<td>0.308 (0.088 - 1.076)</td>
<td>0.499 (0.322 - 0.773)</td>
<td>0.869 (0.523 - 1.433)</td>
<td>0.697 (0.501 - 0.970)</td>
<td>1.052 (0.711 - 1.557)</td>
<td></td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>0.208 (0.095 - 0.455)</td>
<td>0.337 (0.094 - 1.207)</td>
<td>0.469 (0.320 - 0.687)</td>
<td>0.77(0.485 - 1.222)</td>
<td>0.520 (0.393 - 0.698)</td>
<td>0.939 (0.674 - 1.308)</td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>1.046 (0.375 - 2.918)</td>
<td>0.255 (0.066 - 0.992)</td>
<td>0.551 (0.334 - 0.908)</td>
<td>0.745 (0.449 - 1.237)</td>
<td>0.615 (0.429 - 0.880)</td>
<td>0.65 (0.444 - 0.951)</td>
<td></td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>0.392 (0.153 - 1.006)</td>
<td>0.451 (0.121 - 1.673)</td>
<td>0.903 (0.545 - 1.496)</td>
<td>0.541 (0.348 - 0.841)</td>
<td>1.041 (0.712 - 1.523)</td>
<td>0.857 (0.616 - 1.194)</td>
<td></td>
</tr>
</tbody>
</table>

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers.
Figure 4.1: Unadjusted odds of 30-day mortality according to admission blood glucose concentration in people with and without diabetes. **Solid bars and black lines** indicate patients with diabetes. **Clear bars and red lines** indicate patients without Diabetes. **Solid lines** indicate odds ratios while **dotted lines** indicate 95% confidence intervals.
Chapter Five: Survival in South Asian and White European patients after acute myocardial infarction.

5.1 Chapter overview

In the previous chapters I highlighted that studies investigating glucose abnormalities in SA patients presenting with AMI or other forms of CHD are very limited and show inconsistent results. As discussed in Chapter Two, section 2.7.3, some studies have shown that compared to WE, SA people with diabetes suffer from higher CHD-related deaths. Further analysis of the data reported in Chapter Four showed that SA patients with AMI had a significantly high prevalence of prior diabetes (40%) compared to their WE counterparts (16%). In this chapter I am extending the analysis of the cohort reported in Chapter Four to understand how ethnicity and related differences in glucose abnormalities impacts survival in SA and WE patients post AMI. For this study I formulated the research hypothesis, designed the analysis approach, and independently conducted all the analysis. I presented the study findings as audio posters in national cardiology and international diabetes conferences (North America). I am also the first author on the research paper resulting from this study published in the Heart. For this article I wrote the manuscript, conducted all the analysis including extensive subgroup analysis suggested by the reviewers, and produced all the tables.
5.2 Abstract

**Aims/Objective:** To examine the association between ethnicity and survival following AMI in WE and SA patients from a multiethnic UK population.

**Methods:** A retrospective cohort study of 4111 (N=730, 17.8% of SA ethnicity) hospitalised patients with AMI, from a tertiary coronary care centre in the UK, admitted between October 2002 and September 2008. The primary end point was all-cause mortality. The association between ethnicity and survival following AMI was assessed using the Cox regression analysis.

**Results:** Compared with WE patients, SA patients were on average younger (62.0 years vs 67.3 years) and had higher prevalence of cardiovascular risk factors including diabetes (39.7% vs 16.1%). During follow-up (median 912, range 1–2556, days), crude mortality rate was 22.6% in SA patients and 26.0% in WE patients (p=0.061). SA ethnicity did not show univariate (HR 0.85 (0.72 to 1.01)) or multivariate (HR, 1.12 (0.94 to 1.34)) association with mortality. Findings were similar for mortality during 0–30 days (1.30 (0.99 to 1.70)), >30 days–1 year (0.97 (0.67 to 1.40)), >1 year–3 years (1.21 (0.83 to 1.76)), >3 years (0.82 (0.47 to 1.41)), and for long-term mortality in survivors from 30 days (1.02 (0.81 to 1.29)).

**Conclusions:** When adjusted for the differing prevalence of cardiovascular risk factors in the two ethnic groups, survival following AMI was similar for SA and WE patients in the UK.
5.3 Introduction

People of SA origin (countries of the Indian subcontinent, India, Pakistan, Sri Lanka, Bangladesh and Nepal) constitute important ethnic minority groups in many parts of the world outside South Asia. In the UK, the SA population is the largest ethnic minority group, comprising about 5% of the total population (ONS. 2013). As discussed in Chapter 2, section 2.7.3, many migrant SA populations show higher CHD prevalence and mortality rates compared with native populations, a phenomenon demonstrated in several countries including Canada (Anand et al. 2000), South Africa (Walker et al. A. 1980) and the UK (Bhopal et al. 2000, Fischbacher et al. 2007, Harding et al. 2008). Furthermore, studies from Canada (Gupta et al. 2002, Khan et al. 2010), and the UK (Bhopal et al. 2000, Fischbacher et al. 2007) show that CHD presents at a younger mean age in the migrant SA populations compared with the indigenous populations.

As highlighted in Chapter 2, section 2.7.3, although CHD is more prevalent in SA populations, the influence of ethnicity on the prognosis for patients with CHD is less clear. While some studies have suggested higher case-fatality rates following acute myocardial infarction (AMI) in migrant SA patients compared with White European (WE) patients in the UK (Wilkinson et al. 1996, Hughes et al. 1989), others from the UK and Canada have suggested similar (Mukhtar et al. 1995, Jones et al. 2012, Raghavan et al. 2008, Liew et al. 2006) or better (Fischbacher et al. 2007, Zaman et al. 2013, Khan et al. 2010) adjusted survival for these ethnic groups in this setting.
I have shown in previous Chapters that various abnormalities of glucose metabolism have strong associations with a high prevalence of CHD and are associated with an adverse prognosis. Several studies have suggested that the high prevalence of CHD, in particular AMI, in the SA population is due to the greater prevalence of traditional CHD risk factors, in particular, diabetes (Joshi et al. 2007, Wilkinson et al. 1996). However, further research is needed to understand the impact of high prevalence of diabetes on CHD outcomes in the SA population.

In this study, I aimed to compare survival following AMI in a large cohort of WE and SA patients drawn from a multiethnic UK population in the contemporary treatment era. I also examined the significance of high prevalence of diabetes in SA patients on survival post AMI. I hypothesised that, in the context of higher overall coronary mortality in the SA population, case-fatality following AMI would be higher in SA patients compared with WE patients even after adjusting for the prevalence of classical cardiovascular risk factors, in particular, abnormalities of glucose metabolism.

5.4 Methods

I conducted a retrospective cohort study of the same cohort described in Chapter Four comprising of consecutive patients with AMI admitted between 1 October 2002 and 30 September 2008 at the two coronary care units (CCUs) of the University Hospitals of Leicester. These CCUs serve the population of Leicestershire, where individuals of SA ethnic origin constitute a large ethnic
minority group: 31.8% of the population living in the city of Leicester and 14% of the total Leicestershire population of approximately 1 million (ONS. 2011).

The study is based on the routine care MINAP dataset, details of which are described in Chapter Four. The diagnosis and classification of AMI (STEMI and NSTEMI) were made according to the joint ESC/ACCF/AHA/WHF criteria (Thygesen et al. 2007). Patients were categorised as having diabetes if self-reported or based on prescribed medications prior to the index event. Admission glucose was taken as the first recorded measurement after admission. The coding of SA and WE ethnicity was based on self-reporting. Information on mortality is obtained by record-linkage.

The predefined primary outcome measure was all-cause mortality over the entire follow-up period. I also considered all-cause mortality in landmark analyses at 0–30 days, >30 days–1 year, >1–3 years, >3 years–end of follow-up, and long-term mortality in survivors from 30 days. I compared mortality stratified by SA and WE ethnicity, and by AMI phenotypes. Survival was measured from the date of first admission for AMI (between 1 October 2002 and 30 September 2008) until the date of death or the end of follow-up (censored at 30 September 2009), whichever was earlier, providing a minimum of 1-year follow-up for survivors. The project was approved by the local research ethics committee.
5.4.1 Statistical analysis

I gained considerable experience in statistical analysis under the supervision of the statistician (RM) while conducting the analysis for the previous study (Chapter Four). This enabled me to independently conduct all the statistical analysis in this study, with advice on analysis approach taken when needed from another statistician Dr Danielle Bodicoat. As described below, I performed the analysis in two different ways, producing different sets of outcome data.

5.4.1.1 Analysis 1

This primarily involved assessing the association between ethnicity and mortality in the entire cohort. Baseline characteristics between ethnic groups were examined using independent two-sample t-tests and χ² tests. The association of ethnicity with mortality was determined using Cox proportional hazards regression models. Missing data were imputed in the Cox analyses (Cattle et al. 2011). Missing medical history and medication variables were assumed to be ‘no’ and default imputed. All other variables were subject to multiple imputations with continuous variables imputed using predictive mean matching and binary variables using logistic regression. The predictive variables for the imputation of missing data were age, gender, year of admission, past medical history, AMI phenotypes, inpatient therapies of reperfusion and diuretics, mortality status, survival time and ethnicity; 25 imputation data sets were created and estimates generated using Rubin’s rules (Rubin et al. 2004).

I initially assessed the univariate strength of association of ethnicity and other potentially relevant clinical and demographic variables with mortality in our
cohort. Year of admission was included in the analysis to adjust for temporal changes in the management of ACS (Gale et al. 2012, Gale et al. 2014).

I then conducted multivariate analysis examining the association between ethnicity and mortality. Variables known to have an association with ethnicity and survival post AMI (age, gender, antecedent diabetes, prior hypertension, prior CHD, smoking history and AMI phenotype) were preselected as potential confounders in the multivariate models. I further adjusted for the following variables known to influence prognosis after AMI: admission plasma glucose, estimated glomerular filtration rate (eGFR), severity of AMI as indicated by systolic blood pressure (SBP) and heart rate at admission, inpatient use of diuretics (as a surrogate for LV dysfunction), acute reperfusion/revascularisation therapies, and secondary prevention therapies at discharge.

5.4.1.2 Analysis 2

I assessed the relevance of high prevalence of diabetes to survival in SA patients by conducting analysis stratified both by both diabetes status and by ethnicity. In the analysis stratified by diabetes status, differences in baseline characteristics between the SA and WE patient within the subgroup of those with and without diabetes were compared using the independent two-sample t-tests and chi-squared tests. Furthermore, multivariate Cox proportional hazards regression models were created to determine the association between ethnicity and mortality in each of the two diabetes subgroups. The multivariate analysis was adjusted for age, gender, prior hypertension, prior CHD, AMI phenotype, and further for admission glucose, eGFR, SBP and heart rate, diuretic use,
acute reperfusion/revascularisation therapies, and secondary prevention therapies. In a separate Cox proportional hazards regression analysis, univariate and multivariate associations between diabetes and mortality were evaluated in SA and WE subgroups.

For computational reasons, multivariate analyses were performed on the complete data but effect estimates are based on the multiply imputed data. A p value of <0.05 (two-sided) was considered to indicate statistical significance in all analyses. The assumption of proportional hazards for the Cox analyses was checked by hazard and log-minus-log graphs. Data are presented as HR and 95% CIs. All analyses were carried out using SPSS V.20.

5.5 Results

Between 1 October 2002 and 30 September 2008, 4188 admissions with a discharge diagnosis of AMI were recorded. After exclusion from analysis of 77 (1.9%) patients with a recorded ethnicity other than SA or WE, the final cohort comprised 4111 individuals: 730 (17.8%) SA and 3381 (82.2%) WE (Figure 5.1). Median follow-up time was 912 (range 1–2556) days. Of the 32 preselected variables, 22 had at least one value missing at random. Of the total 131,552 values, 5729 (4.4%) values were missing and were imputed as described above.

5.5.1 Analysis 1

Table 5.1 shows baseline characteristics stratified by ethnicity. Presentation with STEMI (58.3%) was more common than NSTEMI (41.7%), with no ethnic
difference in this regard. Compared with WE patients, SA patients were on average 5 years younger (62.0 years vs 67.3 years), and slightly more frequently male (73.2% vs 69.6%). Compared with WE patients, SA patients had a higher prevalence of prior diabetes, prior hypertension and heart failure, a lower prevalence of smoking and prior peripheral vascular disease, lower total cholesterol and eGFR, and were more often prescribed cardiovascular medications prior to admission (Table 5.1). Rates of coronary reperfusion and revascularisation therapies during index admission and prescription of secondary prevention treatments at discharge were similar between the ethnic groups.

5.5.1.1 Ethnic differences in antecedent diabetes and admission hyperglycaemia

Antecedent diabetes was approximately 2.5 times more prevalent in SA compared with WE patients (39.7% vs 16.1 %, p<0.005). Similarly, compared with WE, the mean random plasma glucose was higher in SA patients (8.5 ± 3.8 mmol/L vs. 10.1 ± 5.6 mmol/L, p<0.005) (Table 5.1). Furthermore, compared with WE, SA patients had higher rates (20.5% vs 37.5%, p<0.005) of ‘significant hyperglycaemia’ (blood glucose > 10.0mmol/l), the glucose category for which some international guidelines recommend glucose-lowering interventions at admission with AMI (Deedwania et al. 2008, Rydén et al. 2013).

5.5.1.2 Ethnicity and mortality

Table 5.2 compares crude mortality rates for SA patients and WE patients. A total of 1043 (25.3%) patients died during follow-up (SA=165/730, 22.6%;
WE=878/3381, 26.0%). In general, mortality was numerically greater in WE patients compared with SA patients and of borderline statistical significance over the entire follow-up period. This pattern of better survival in SA patients was statistically more evident in patients with STEMI (WE=527/1976, 26.7%; SA=92/421, 21.8%, p=0.043) and in patients who survived to 30 days (WE=541/3054, 17.8%; SA=91/657, 13.9; p=0.016) (table 5.2).

5.5.1.3 Mortality over the entire follow-up period

On univariate analysis, SA ethnicity did not show an association with mortality (0.85 (0.72, 1.01)). This did not change on multivariate analyses, adjusted initially in model 1 for age, gender, prior diabetes, prior hypertension, smoking history and AMI phenotype (HR 1.12 (0.94 to 1.34), and further in model 2 for admission glucose, eGFR, heart rate, SBP, diuretic therapy, acute reperfusion/revascularisation and secondary prevention therapies (HR, 1.08 (0.91 to 1.30), Table 5.3). This lack of association of SA ethnicity with risk of mortality was consistent in subgroups of patients with STEMI (adjusted HR: model 1A, 1.05 (0.83 to 1.32); model 2A, 1.01 (0.80 to 1.29)) and NSTEMI (adjusted HR: model 1B, 1.22 (0.93 to 1.61); model 2B, 1.16 (0.88 to 1.53)) (Table S5.2, Appendix Five).

5.5.1.4 Landmark analysis

In patients surviving to 30 days, subsequent crude overall mortality was lower in SA patients compared with WE patients in the total cohort (13.9% vs 17.9%, p=0.016) and in patients with STEMI (10.6% vs 16.3%, p=0.007) (Table 5.2). Following covariate adjustment, SA ethnicity was not associated with an
increased mortality risk over early (HR, 0–30 days: model 1, 1.30 (0.99 to 1.70); model 2, 1.25 (0.95 to 1.64)), long-term (HR, >30 days–end of follow-up: model 1, 1.02 (0.81 to 1.29); model 2, 0.98 (0.77 to 1.24)) or any other landmark time periods (Table 5.3). These observations were generally consistent in patients with STEMI and NSTEMI (Table S5.2A, Appendix Five).

5.5.2 Analysis 2

In this analysis, I examined the significance of the high prevalence of diabetes in SA patients on survival post AMI. Table 5.4 shows a comparison of baseline characteristics between SA and WE patients in the subgroups of those with and without diabetes. Individuals with diabetes were generally older than those without it, and the age gap between WE and SA patients was consistent across the diabetes subgroups. In those with diabetes, the proportion of men was similar among WE and SA people. In contrast, in those without diabetes, the proportion of men was significantly higher in the SA group.

In people with diabetes, compared with WE, SA patients had higher mean plasma glucose levels (11.6 ± 5.2 mmol/L vs. 13.0 ± 6.0 mmol/L, p=0.003); no such ethnic difference was seen in those without diabetes. Furthermore, compared with WE, the SA cohort had a higher prevalence of admission hyperglycaemia (13.8% vs 19.6%, p 0.001) (Table 5.4), across the diabetes subgroups. Furthermore, compared with WE, SA patients had higher rates (20.5% vs 37.5 %, p <0.005) of ‘significant hyperglycaemia’ (blood glucose at admission > 10.0mmol/l).
In those with diabetes, no ethnic difference in prevalence of cardiovascular co-morbidities (except for PVD) or levels of cholesterol and eGFR was seen. On the contrary, in those without diabetes, compared with WE, SA had a significantly lower prevalence of prior CHD or cerebrovascular disease, lower mean cholesterol and higher mean eGFR levels. Furthermore, in those without diabetes, compared with WE, SA had lower in-patient use of diuretic therapy - a possible surrogate of the presence of cardiac failure and thereby severity of AMI. Across the diabetes subgroups, no ethnic difference in the rates of coronary reperfusion/revascularisation therapies during the index admission and prescription of discharge therapies at discharge were seen.

5.5.2.1 Diabetes, ethnicity and mortality

During the follow-up, a total of 293/835 (35.0%) patients with diabetes died compared with 750/3276 (22.9%) patients without diabetes. In patients with diabetes (SA=88/290, 33.0%; WE=205/545, 37.6%, p=0.040) and those without diabetes (SA=77/440, 17.5%; WE=673/2836, 23.7%, p=0.003), crude mortality rates were numerically greater for WE patients compared with SA patients. On multivariate analyses adjusted for relevant confounders, ethnicity did not show association with mortality within diabetes or nondiabetes subgroups (Table 5.5). This was consistent for mortality at early (30 days), long-term (>30 days) and other landmark time periods (Table 5.5). Furthermore, there was no interaction between diabetes and the relationship between ethnicity and mortality (p=0.841) in the whole cohort.
In the analysis stratified by ethnicity, the univariate strength of the association between diabetes and mortality appeared statistically similar in SA patients (HR 1.90 (1.40 to 2.58)) compared with WE patients (HR 1.72 (1.47 to 2.01)). After adjustment for covariates, the association between diabetes and mortality remained similar (model 1 E/F: age, gender, prior hypertension, prior CHD, smoking history and AMI phenotype (HR, SA 1.67 (1.21 to 2.32); WE 1.52 (1.29 to 1.78)) (Table S5.3A, Appendix Five) Further adjustments in model 2E/F for admission glucose, eGFR, diuretic use, acute reperfusion/revascularisation and secondary prevention therapies, did not reveal a difference in the association of diabetes with mortality in SA (HR 1.27 (0.88 to 1.84)) or WE (HR 1.10 (0.92 to 1.31)) subgroups (Table S5.3A, Appendix Five).

5.6 Discussion

The current report is one of the largest contemporary studies of prognosis after AMI in SA patients and WE patients in the UK. It shows that following hospitalisation with AMI, adjusted short-term and long-term survival is similar for SA patients and WE patients in the UK. This was evident over the entire follow-up period, and in patients surviving to 30 days, and was consistent in subgroups of patients with STEMI and NSTEMI. The study also shows that in both the ethnic groups, after covariate adjustment, prior diabetes does not show an independent association with mortality risk up to 3 years after AMI. Furthermore, when analysed separately, SA ethnicity was not associated with mortality in the subgroups of those with or without diabetes.
Previous studies in this area have provided conflicting results. While early studies showed worse (Hughes et al. 1989, Wilkinson et al. 1996) prognosis in SA patients, more recent studies suggested similar (Mukhtar et al. 1995, Liew et al. 2006, Jones et al. 2012) or better (Fischbacher et al. 2007, Khan et al. 2010, Zaman et al. 2013) prognosis in SA patients compared with WE patients. Many of the earlier studies have one or more important limitations, including small sample size, short follow-up or statistical analysis failing to consider potential confounders. My analysis addresses these issues and suggests that following AMI, survival is similar for SA and WE patients in the UK.

My finding of the lack of ethnic difference in survival post AMI are generally in line with those of recently published large-scale studies from Canada (Khan et al. 2010) and the UK (Zaman et al. 2013). The Canadian study involved 2190 SA and 38,479 WE patients hospitalised with AMI in the period 1994–2003 (Khan et al. 2010). After adjusting for important confounders, mortality at 30 days was similar for the SA (170/2190, 7.8%) and WE (3321/38479, 8.6%) patients (Odds ratio 0.88 (0.75, 1.03), p=0.1). Furthermore, in patients who survived to 30 days, the relative risk of longer term mortality over a median of 3.2 years was 35% lower in SA (39 deaths/1000 patient year) compared with WE (61 deaths/1000 patient year) patients (HR 0.65 (0.57, 0.72), p <0.001) (Khan et al. 2010). My study findings are generally in line with this Canadian study and suggest that mortality following AMI is not higher in SA compared with WE patients in the UK on the background of a higher CHD incidence in SA patients. Furthermore, my observation is in keeping with the findings of another recent study from the UK involving a multiethnic cohort of ACS (SA 8251, WE
This study based on the MINAP database involved all consecutive patients admitted with ACS between 2004 and 2008 from all 230 hospitals in England and Wales. At presentation with ACS, SA patients were younger than WE patients and were more likely to reside in the deprived areas. Furthermore, they had higher prevalence of diabetes (42.4% vs 16.9%). However, their adjusted mortality after ACS was in comparison with WE patients at 30 days (HR 0.85 (0.77 to 0.94)) and one year (HR 0.83 (0.78 to 0.89)) of follow-up.

My findings are also consistent with the results in other presentations of CHD including out-of-hospital cardiac arrest (Shah et al. 2010), angina pectoris (Zaman et al. 2009), heart failure (Blackledge et al. 2003), and a mixed cohort of patients undergoing PCI (Jones et al. 2012) where no ethnic differences in mortality were seen for SA and WE groups. I observed similar patterns of management of AMI in SA and WE patients, in keeping with those from other cohorts of ACS from the UK (Jones et al. 2012, Zaman et al. 2013).

My finding of the lack of any adverse impact of higher prevalence of diabetes on mortality following AMI in SA patients needs further attention. In Chapter Three and Four, I have demonstrated that, antecedent diabetes as well as acutely elevated glucose levels at index admission is associated with excess all-cause mortality post AMI. In my study, compared with WE, SA patients had a 2.5 fold higher prevalence of diabetes and worse level of glycaemic control as reflected by higher mean blood glucose levels. On this basis, one would expect SA patients in my study to have a worse prognosis compared with their WE
counterparts. However after adjusting for various confounders, SA and WE patients in my study were found to have similar prognosis, with no interaction seen between ethnicity and diabetes in its influence on all-cause mortality. Furthermore, SA ethnicity was not associated with mortality at any time point in the subgroups of those with or without diabetes. Additionally, diabetes was not associated with mortality in the subgroup analysis of SA and WE patients. These findings suggest that diabetes did not have a differential impact or confer excessive mortality risk in SA patients with AMI compared with their WE counterparts. These findings are broadly in line with the above-mentioned studies from Canada (Khan et al. 2010, Nijjar et al. 2010) and UK (Zaman et al. 2013) in which despite 1.5 to 2.5 fold higher prevalence of diabetes in SA patients, their risk of all-cause mortality post AMI was not higher than WE patients. The UK study, the largest (n= 203 092, SA 8251) in this area, unlike mine and Canadian study (Nijjar et al. 2010) did indicate some adverse association between diabetes and survival in SA patients compared with WE patients after adjustment for age (age-adjusted HR 1.83 (95% CI 1.59 to 2.11) vs 1.53 (95% CI 1.49 to 1.57)) (Zaman et al. 2013). Differences in sample size, adjustments for several covariates including admission glucose in my study and several other factors could be behind this difference in the findings of the two studies. However the observed adverse association between diabetes and survival seen in the SA patients in the UK study did not affect their survival and all-cause mortality at 30-day and one year in the SA cohort was similar to the WE cohort.
The discrepancy between the high prevalence of glucometabolic abnormalities and the lack of associated increase in mortality in SA patients described above is rather unexplained and more information on the interaction of diabetes and other factors such as age and comorbidities on cause-specific deaths post AMI is required. Age is an important factor determining prognosis post AMI. For example, in the studies included in my meta-analysis (Chapter Three), compared to people without those with diabetes were older at admission with AMI. In the subgroup analysis of the meta-analysis, the risk of excess long-term mortality post AMI in the diabetes group was significantly higher in studies with older patients (interaction term 1.054 per year; 95% CrI 1.016, 1.092; p = 0.007) (Chapter Three, section 3.5.3). There I discussed that in older patients; factors related to both longer duration and severity of diabetes could independently contribute to the increased risk of cardiovascular events and consequent long-term cardiovascular mortality (Yeap et al. 2015). In a recently published trend analysis from New Jersey involving 285,397 patients hospitalised with first AMI, a reduction in the in-hospital deaths but a notable increase in 30-day and 1-year postdischarge mortality was seen from 1986 to 2007 (Kostis et al. 2010). This increase in postdischarge mortality was seen predominantly in the older age group and resulted mainly from noncardiovascular diseases (NCVD) such as respiratory and renal diseases, cancer and septicaemia. Thus, older age is likely to contribute to increase in deaths from both cardiovascular and NCVD post AMI.

In various studies, SA patients regardless of diabetes diagnosis are significantly younger than WE patients at admission with AMI and it is highly likely that
various confounders, measured and unmeasured, related to younger age have an impact on their cause-specific mortality after AMI. While the risk of cardiovascular events and mortality following AMI could be high in SA patients related to excess prevalence of diabetes, due to younger age at they are less likely to die of NCVD such as cancers, respiratory or renal disease thereby reducing their overall mortality risk following AMI. This possibly explains the observed discrepancy between the high prevalence of diabetes and the lack of associated adverse prognosis in SA patients presenting with AMI. Some authors (Khan et al. 2010) have speculated that the lower long-term mortality after AMI observed in SA patients in their study could be due to factors such as better family support available in the SA community, and the aggressive use of acute and secondary prevention therapies in this population, resulting from a greater awareness among clinicians of the heightned CHD risk in this population.

Similar discrepancies in the association of diabetes with risk of CVD and associated mortality in SA and WE have been seen in studies involving the general diabetes population. In the United Kingdom Asian Diabetes Study (UKADS), SA individuals with diabetes have been reported to suffer from higher rates of fatal and non-fatal cardiovascular events on longitudinal follow-up (Bellary et al. 2010). In other studies, SA individuals with diabetes were three times more likely to die from cardiovascular disease than their WE counterparts (Mather et al. 1998, Foroughi et al. 2006). Conversely, a report from the United Kingdom Prospective Diabetes Study (UKPDS) cohort found SA individuals with
diabetes being at a lower risk of fatal or non-fatal myocardial infarction events (Davies et al. 2014) compared with WE patients in the study.

It has been debated whether the high overall CHD mortality in the SA ethnic group is due to high incidence or high case fatality following presentation with CHD (Wilkinson et al. 1996, Zaman et al. 2013). My study along with the other recent reports (Khan et al. 2010, Jones et al. 2012, Zaman et al. 2013), strengthens the evidence suggesting that prognosis following AMI is not worse in SA groups compared with WE groups, even after adjustment for important covariates, including young age and high prevalence of metabolic risk factors in SA patients. Taken together with these prior analyses, my findings suggest that the overall high CHD mortality in SA patients is most likely due to the high prevalence of the disease rather than greater case fatality (Zaman et al. 2013, Zaman et al. 2013). Moreover in-hospital management of AMI in the UK for patients with STEMI may have reached a performance plateau, as evidenced by low in-hospital mortality rates (Gale et al. 2012). We suggest that the focus of the debate should shift towards how best to control the premature and high incidence of CHD in the SA and WE ethnic populations.

As discussed in Chapter Two (section 2.7.4), the heightened CHD risk in SA populations is mainly due to the higher burden of metabolic risk factors present at a younger age, resulting from a complex interplay of factors including gene-environment interaction and sociocultural influence. Therefore early detection and prevention (primary and secondary) of CHD and its risk factors should form the cornerstone of any approach seeking to improve the situation. Equally,
emphasis should also be placed on educating SA populations about their heightened CHD risk and empowering them to improve risk modifying behaviour.

My study is subject to the limitations inherent in all observational cohort studies. My results are from a single centre study. A relatively high proportion of STEMI (58.4%) in my study suggest a possible selection bias as the study population is of patients admitted to a tertiary centre CCU. This is not directly relevant to my observations as proportions of STEMI and NSTEMI were similar in SA and WE subgroups. The data set lacks complete information on hypercholesterolaemia, body mass index, types of diabetes, previously undiagnosed diabetes and glucose-lowering therapies. Furthermore the information on evidence of heart failure, angiographic findings and events other than mortality after the index admission, was not available. The data set also lacks information on socioeconomic status, which may be relevant to outcome after AMI. As this registry-based study included consecutive patients, case ascertainment was not biased by ethnicity. This is an analysis of hospitalised patients with AMI and the findings may not be applicable to those not admitted to the hospital, although such numbers are likely to be small. However bias due to differences between ethnic groups in health-seeking behaviour cannot be completely excluded. Finally, SA populations are heterogeneous including subpopulations with varying demographic characteristics. My study findings are based predominantly on Indian Gujaratis living in Leicester city and may not be entirely applicable to other SA subgroups.
In summary, adjusted survival following hospitalisation with AMI was similar for SA and WE patients in the UK, when adjusted for differing background cardiovascular risk factor profiles. Therefore, the high overall CHD mortality in SA patients in the UK seen in the census data does not appear to be related to increased case fatality after AMI. There was no difference in the influence of prior diabetes on all-cause mortality between SA and WE groups after adjustment for relevant covariates. However, the association between high prevalence of various glucometabolic abnormalities and cause-specific mortality in SA patients presenting with AMI needs further research.

The other notable finding in my study was the high prevalence of ‘significant hyperglycaemia’ (admission blood glucose >10.0 mol/L) among SA patients without prior diagnosis of diabetes. As discussed in Chapter Two, raised blood glucose at admission with AMI could represent undiagnosed T2DM or IGR. No studies so far have systematically looked at prevalence, the optimum method of detection, and prognostic impact of previously undiagnosed T2DM and IGR in migrant SA patient presenting with AMI. This prompted me to undertake the SWEET-Heart (Screening White Europeans and Ethnic South Asians for glucose in Tolerance following Heart attack) study, the methodology, results and clinical practice implications of which are described in Chapter Six, Seven and Eight.
Figure 5.1: Flowchart of acute myocardial infarction patients in the study

Number of hospital episodes of acute coronary syndrome (ACS) recorded in the dataset between 1st Oct 2002 and 30th Sept 2008
N=6636

Number of episodes excluded: n=2448
- Recurrent ACS (N= 412)
- Troponin negative ACS (N=288)
- Other cardiac diagnosis (n=1748)

Number of patients with recorded first episode of acute myocardial infarction (AMI) between 1st Oct 2002 and 30th Sept 2008
N=4188

Number of patients of ethnicity other than White European and South Asian excluded: n=77
- Afro-Caribbeans (N= 63)
- Other ethnicity (N=14)

Number of patients with index AMI between 1st Oct 2002 and 30th Sept 2008
N=4111

White Europeans
N=3381

South Asians
N=730
### Table 5.1: Baseline characteristics stratified by ethnic origin

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=4111)</th>
<th>White European n=3381 (82.2%)</th>
<th>South Asian n=730 (17.8%)</th>
<th>Missing values (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Admission Demography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.4 (13.3)</td>
<td>67.3 (13.1)</td>
<td>62.0 (13.3)</td>
<td>0.0</td>
</tr>
<tr>
<td>Male (%)</td>
<td>1224 (70.2)</td>
<td>1028 (69.6)</td>
<td>196 (73.2)</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Prior disease &amp; Risk factors (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior diabetes diagnosis</td>
<td>835 (20.3)</td>
<td>545 (16.1)</td>
<td>290 (39.7)</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2048 (50.3)</td>
<td>1649 (49.3)</td>
<td>399 (55.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Coronary Heart Disease§</td>
<td>491 (12.1)</td>
<td>406 (12.1)</td>
<td>85 (11.7)</td>
<td>0.9</td>
</tr>
<tr>
<td>CVA</td>
<td>254 (6.3)</td>
<td>215 (6.4)</td>
<td>39 (5.4)</td>
<td>1.2</td>
</tr>
<tr>
<td>PVD</td>
<td>154 (3.8)</td>
<td>144 (4.3)</td>
<td>10 (1.4)</td>
<td>1.2</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>190 (4.7)</td>
<td>145 (4.3)</td>
<td>45 (6.2)</td>
<td>1.2</td>
</tr>
<tr>
<td>Current/Ex Smoker</td>
<td>1366 (35.7)</td>
<td>1259 (39.9)</td>
<td>107 (16.0)</td>
<td>7.1</td>
</tr>
<tr>
<td><strong>Prior therapies (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>2671 (65)</td>
<td>2176 (64.4)</td>
<td>495 (67.8)</td>
<td>0.0</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>990 (25.6)</td>
<td>796 (25.1)</td>
<td>194 (28.0)</td>
<td>6.0</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>1097 (28.3)</td>
<td>866 (27.2)</td>
<td>231 (33.3)</td>
<td>5.8</td>
</tr>
<tr>
<td>Statins</td>
<td>1083 (28.0)</td>
<td>859 (27.0)</td>
<td>224 (32.3)</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>Type of Infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>2397 (58.3)</td>
<td>1976 (58.4)</td>
<td>421 (57.7)</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Physical Examination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate, beats/min (SD)</td>
<td>81.1 (24.3)</td>
<td>80.9 (24.4)</td>
<td>82.8 (23.9)</td>
<td>1.5</td>
</tr>
<tr>
<td>SBP, mmHg (SD)</td>
<td>136.5 (28.4)</td>
<td>136.5 (28.2)</td>
<td>136.5 (29.6)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Biochemical Data (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CK (IU/L) Normal range &lt;200</td>
<td>1113 (1810)</td>
<td>1091.7 (1857)</td>
<td>1176.5 (1570)</td>
<td>7.6</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>116.4 (63.8)</td>
<td>116.3 (61.5)</td>
<td>117 (73.9)</td>
<td>16.8</td>
</tr>
<tr>
<td>eGFR mL/min</td>
<td>63.0 (22.2)</td>
<td>62.5 (22)</td>
<td>65.3 (23.5)</td>
<td>16.6</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>5.1 (1.3)</td>
<td>5.2 (1.3)</td>
<td>4.9 (1.2)</td>
<td>16.6</td>
</tr>
<tr>
<td>Admission plasma glucose (mmol/L)</td>
<td>8.8 (4.2)</td>
<td>8.5 (3.8)</td>
<td>10.1 (5.6)</td>
<td>14.9</td>
</tr>
<tr>
<td><strong>In-Hospital therapies (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reperfusion/Revascularisation#</td>
<td>2420 (58.7)</td>
<td>1979 (58.4)</td>
<td>441 (60.4)</td>
<td>0.0</td>
</tr>
<tr>
<td>Reperfusion/Revascularisation in STEMI</td>
<td>1818 (75.8)</td>
<td>1483 (75.1)</td>
<td>335 (79.6)</td>
<td>0.0</td>
</tr>
<tr>
<td>Emergency coronary angiography** in NSTEMI</td>
<td>602 (35.1)</td>
<td>496 (35.3)</td>
<td>106 (34.3)</td>
<td>0.0</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>1502 (37.4)</td>
<td>1239 (37.5)</td>
<td>263 (36.8)</td>
<td>2.3</td>
</tr>
<tr>
<td><strong>Discharge therapies (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>2701 (68.0)</td>
<td>2233 (68.6)</td>
<td>468 (66.0)</td>
<td>3.5</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>2513 (63.3)</td>
<td>2072 (63.6)</td>
<td>441 (62.2)</td>
<td>3.5</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>2493 (62.9)</td>
<td>2076 (63.8)</td>
<td>417 (59.8)</td>
<td>3.6</td>
</tr>
<tr>
<td>Statin</td>
<td>2704 (67.7)</td>
<td>2230 (68.0)</td>
<td>474 (66.2)</td>
<td>2.8</td>
</tr>
</tbody>
</table>

* South Asian vs. White European. § any of angina/ myocardial infarction / percutaneous intervention (PCI)/ coronary artery bypass grafting (CABG). # thrombolysis and/or coronary intervention (PCI or CABG) in STEMI and emergency coronary angiography ± coronary intervention in NSTEMI. **emergency coronary angiography ± coronary intervention ((PCI or CABG)) in NSTEMI. CVA, Cerebrovascular accident; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; STEMI, NSTEMI, non- ST-elevation myocardial infarction; CK, Creatinine Kinase; eGFR, estimated Glomerular filtration rate calculated by the Modification of Diet in Renal Disease (MDRD) equation; PVD, Peripheral Vascular Disease; SBP, Systolic blood pressure.
Table 5.2: Crude mortality rates following acute myocardial infarction stratified by ethnicity

<table>
<thead>
<tr>
<th>Mortality time periods</th>
<th>Total cohort N=4111</th>
<th>STEMI N=2397</th>
<th>NSTEMI N=1714</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White European N=3381</td>
<td>South Asian N=730</td>
<td>p-value*</td>
</tr>
<tr>
<td>Over entire follow-up (median 912 days)</td>
<td>878 (26.0)</td>
<td>165 (22.6)</td>
<td>0.061</td>
</tr>
<tr>
<td>Early mortality 0 - 30 days</td>
<td>337 (10.0)</td>
<td>74 (10.1)</td>
<td>0.892</td>
</tr>
<tr>
<td>Long term mortality in 30-day survivors</td>
<td>542 (17.8)</td>
<td>91 (13.9)</td>
<td>0.016</td>
</tr>
<tr>
<td>&gt;30 days - 1 year</td>
<td>231 (7.6)</td>
<td>38 (5.8)</td>
<td>0.115</td>
</tr>
<tr>
<td>&gt;1 year - 3 years</td>
<td>196 (7.0)</td>
<td>37 (6.0)</td>
<td>0.427</td>
</tr>
<tr>
<td>&gt; 3 years - end of follow-up</td>
<td>115 (4.4)</td>
<td>16 (2.8)</td>
<td>0.082</td>
</tr>
</tbody>
</table>

* South Asian vs. White European
All values are number (percentage)
STEMI = NSTEMI = non-ST elevation myocardial infarction
Table 5.3: Association between ethnicity ((South Asian versus White Europeans) and mortality following acute myocardial infarction (AMI), in the whole cohort: Cox proportionate hazard multivariate analysis*

<table>
<thead>
<tr>
<th>Mortality time periods</th>
<th>Multivariate analysis</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Over entire follow-up, median 912 days</td>
<td>1.12 (0.94, 1.34)</td>
<td>0.206</td>
<td>1.08 (0.91, 1.30)</td>
<td>0.380</td>
</tr>
<tr>
<td>N=1043/4111</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early mortality 0 - 30 days</td>
<td>1.30 (0.99, 1.70)</td>
<td>0.060</td>
<td>1.25 (0.95, 1.64)</td>
<td>0.114</td>
</tr>
<tr>
<td>N=411/4111</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long term mortality in 30-day survivors</td>
<td>1.02 (0.81, 1.29)</td>
<td>0.877</td>
<td>0.98 (0.77, 1.24)</td>
<td>0.838</td>
</tr>
<tr>
<td>N=633/3700</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality &gt;30 days - 1 year</td>
<td>0.97 (0.67, 1.40)</td>
<td>0.861</td>
<td>0.91 (0.63, 1.32)</td>
<td>0.631</td>
</tr>
<tr>
<td>N=269/3701</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality &gt;1 year - 3 years</td>
<td>1.21 (0.83, 1.76)</td>
<td>0.318</td>
<td>1.16 (0.80, 1.70)</td>
<td>0.433</td>
</tr>
<tr>
<td>N=233/3424</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality &gt; 3 years - end of follow-up</td>
<td>0.82 (0.47, 1.41)</td>
<td>0.969</td>
<td>0.80 (0.46, 1.40)</td>
<td>0.432</td>
</tr>
<tr>
<td>N=131/3293</td>
<td></td>
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</tr>
</tbody>
</table>

*Missing data were imputed. Variables included in the multivariate Cox regression models:
Model 1: age, gender, prior diabetes, prior hypertension, prior coronary heart disease, smoking history, AMI phenotype
Model 2: Model 1 plus admission glucose, estimated glomerular filtration rate (eGFR), in-patient diuretic use, acute reperfusion/revascularisation, prescription of secondary prevention therapies at discharge.
Table 5.4: Baseline characteristics stratified by diabetes status and ethnicity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Known diabetes n=835</th>
<th>Not known diabetes n=3276</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White European n=534 (65.3%)</td>
<td>South Asian n=296 (34.7%)</td>
<td></td>
</tr>
<tr>
<td>Admission Demography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.4 (11.8)</td>
<td>65.3 (11.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>367 (67.3)</td>
<td>192 (66.2)</td>
<td>0.758</td>
</tr>
<tr>
<td>Prior disease (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>370 (68.0)</td>
<td>214 (73.8)</td>
<td>0.096</td>
</tr>
<tr>
<td>Coronary Heart Disease§</td>
<td>96 (17.6)</td>
<td>53 (18.3)</td>
<td>0.850</td>
</tr>
<tr>
<td>CVA</td>
<td>57 (10.5)</td>
<td>29 (10.0)</td>
<td>0.905</td>
</tr>
<tr>
<td>PVD</td>
<td>37 (6.8)</td>
<td>5 (1.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>47 (8.7)</td>
<td>29 (10.0)</td>
<td>0.529</td>
</tr>
<tr>
<td>Current/Ex Smoker</td>
<td>240 (47.2)</td>
<td>42 (16.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior therapies (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>399 (73.2)</td>
<td>223 (76.9)</td>
<td>0.278</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>165 (31.7)</td>
<td>100 (36.1)</td>
<td>0.208</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>265 (50.8)</td>
<td>142 (51.4)</td>
<td>0.882</td>
</tr>
<tr>
<td>Statins</td>
<td>253 (48.6)</td>
<td>136 (48.9)</td>
<td>0.941</td>
</tr>
<tr>
<td>Phenotype of AMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>274 (49.7)</td>
<td>146 (50.3)</td>
<td>0.885</td>
</tr>
<tr>
<td>Physical Examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate, beats/min (SD)</td>
<td>85.6 (25.8)</td>
<td>85.3 (24.6)</td>
<td>0.831</td>
</tr>
<tr>
<td>SBP, mmHg (SD)</td>
<td>137.8 (31.0)</td>
<td>137.5 (30.3)</td>
<td>0.861</td>
</tr>
</tbody>
</table>
Table 5.4: Baseline characteristics stratified by diabetes status and ethnicity (continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Known diabetes n=835</th>
<th>Not known diabetes n=3276</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White European n=534 (65.3%)</td>
<td>South Asian n=296 (34.7%)</td>
</tr>
<tr>
<td><strong>Biochemical Data (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total CK (IU/L) Normal &lt;200</td>
<td>869.7 (1101.9)</td>
<td>1076.4 (1561.0)</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>130.1 (76.5)</td>
<td>126.4 (75.4)</td>
</tr>
<tr>
<td>eGFR mL/min</td>
<td>56.7 (23.0)</td>
<td>59.8 (24.7)</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>4.4 (1.2)</td>
<td>4.6 (1.3)</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>13.2 (2.01)</td>
<td>12.8 (1.9)</td>
</tr>
<tr>
<td>Admission plasma glucose (mmol/L)</td>
<td>11.6 (5.2)</td>
<td>13.0 (6.0)</td>
</tr>
<tr>
<td>Admission glucose &gt; 10.0 mmol/L</td>
<td>256 (54.6)</td>
<td>159 (63.6)</td>
</tr>
<tr>
<td><strong>In-Hospital therapies (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reperfusion/Revascularisation#</td>
<td>265 (48.6)</td>
<td>154 (53.1)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>292 (54.2)</td>
<td>144 (50.0)</td>
</tr>
<tr>
<td><strong>Discharge therapies (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>348 (65.9)</td>
<td>181 (64.2)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>316 (59.7)</td>
<td>167 (59.2)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>332 (62.8)</td>
<td>163 (57.8)</td>
</tr>
<tr>
<td>Statin</td>
<td>351 (65.9)</td>
<td>186 (65.3)</td>
</tr>
</tbody>
</table>

* South Asian vs. White European
§ any of angina/ myocardial infarction / percutaneous intervention (PCI)/ coronary artery bypass grafting (CABG)
# thrombolysis and/or coronary intervention (PCI or CABG) in STEMI and emergency coronary angiography ± coronary intervention in NSTEMI
**emergency coronary angiography ± coronary intervention ((PCI or CABG)) in NSTEMI.
CVA, Cerebrovascular accident; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; STEMI, NSTEMI, non-ST elevation myocardial infarction; CK, Creatinine Kinase; eGFR, estimated Glomerular filtration rate calculated by the Modification of Diet in Renal Disease (MDRD) equation; PVD, Peripheral Vascular Disease; SBP, Systolic blood pressure.
Table 5.5: Association between ethnicity (South Asian versus White Europeans) and mortality following acute myocardial infarction, in subgroups of patients with and without diabetes: Cox proportionate hazard multivariate analysis*

<table>
<thead>
<tr>
<th>Mortality time periods (Number of deaths /total number of survivors in DM and No DM subgroups)</th>
<th>Diabetes (N=835, SA 34.7%)</th>
<th>No diabetes (N=3276, SA 13.4%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1C</td>
<td>Model 2C</td>
<td>Model 1D</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>p-value</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>Over entire follow-up, median 912 days (DM 293/835, No DM 750/3276)</td>
<td>1.05 (0.80, 1.38)</td>
<td>0.704</td>
</tr>
<tr>
<td>Early mortality 0 - 30 days (DM 108/835, No DM 303/3276)</td>
<td>1.30 (0.84, 2.00)</td>
<td>0.237</td>
</tr>
<tr>
<td>Long term mortality in 30-day survivors (DM 185/727, No DM 448/2526)</td>
<td>0.94 (0.66, 1.34)</td>
<td>0.732</td>
</tr>
<tr>
<td>Mortality &gt;30 days - 1 year (DM 83/727, No DM 186/2974)</td>
<td>0.84 (0.50, 1.40)</td>
<td>0.495</td>
</tr>
<tr>
<td>Mortality &gt;1 year - 3 years (DM 64/642, No DM 169/2782)</td>
<td>1.15 (0.64, 2.09)</td>
<td>0.638</td>
</tr>
<tr>
<td>Mortality &gt; 3 years - end of follow-up (DM 38/302, No DM 93/1502)</td>
<td>0.86 (0.39, 1.93)</td>
<td>0.721</td>
</tr>
</tbody>
</table>

*Missing data were imputed. DM, Diabetes mellitus; SA, South Asian.

Variables included in the multivariate Cox regression models: Model 1C, 1D: age, gender, prior hypertension, prior coronary heart disease, smoking history, AMI phenotype. Model 2C, 2D: Model 1C/D plus admission plasma glucose, estimated glomerular filtration rate (eGFR), in-patient diuretic use, acute reperfusion/revascularisation, prescription of secondary prevention therapies at discharge.
Chapter Six: The SWEET-Heart prospective cohort study - methods and design

6.1 Chapter overview

As discussed in Chapter Two, the knowledge about undiagnosed T2DM and IGR at admission with AMI in patients from the high-risk SA population is very limited. To research this subject further, I embarked on the SWEET-Heart (Screening White Europeans and Ethnic South Asians for glucose inTolerance following Heart attack) study. This Chapter describes the rationale, aims, design and methodology of the SWEET-Heart study. The results of the study are reported in Chapter Seven and Eight.

For this study I studied the background literature, formulated the hypothesis and designed and planned the study. I developed the protocol and all other study documents and sought approval of the regional ethnic committee and the local research and development department (Appendix Six). The recruitment took place on the CCU and acute cardiac wards, and the study also involved collecting, processing and storing blood samples for future biomarker analysis. I liaised with our cardiology - clinical and biomedical research unit staff, seeking their cooperation throughout the study period. Furthermore, I was the project lead and manager of this study. Apart from overseeing the running of this prospective study, I was working on the ground identifying suitable patients admitted with AMI, obtaining their consent and carrying out the study procedures including the OGTT and the processing/storage of the biomarker samples. As this was a complex project and involved two visits running in
parallel, I was helped by a team of two research nurses in conducting the study procedures. I was responsible for training and supervising the research nurses and administrators working for the study. The study in its later phase was extended to a hospital in Lincolnshire and I oversaw the whole process of this extension. I was responsible for data collection and data analysis in the study.

6.2 Abstract

Aims/Objectives: The main aim of the study was to determine the rates of undiagnosed T2DM and IGR in British SA and WE individuals admitted with AMI. A further aim was to compare diagnostic yield and utility of the OGTT versus HbA1c and suggest optimum strategies for screening for chronic hyperglycaemia in the setting of AMI.

Methods: In this prospective study, I planned to screen 441 WE and 111 SA adults admitted with AMI for undiagnosed T2DM and IGR. The recruitment took place on the CCU and cardiology wards of two different UK hospitals over an 18 month period. The participants underwent a 75g-OGTT, HbA1c and other study procedures on day 2 onwards of their hospital stay and again after six weeks (two weeks if the initial OGTT was suggestive of T2DM) following hospital discharge. The confirmation of T2DM and IGR was based on the WHO 1999 OGTT criteria. Furthermore, I established the prevalence of chronic hyperglycaemia using the new HbA1c criteria. The WE and SA groups were compared for the primary outcome of prevalence of screen-detected T2DM, IFG, IGT and multivariate association of ethnicity with these abnormalities were established. Furthermore, the sensitivity, specificity, and positive/negative
predictive values for diagnosis of T2DM assigned on screening approach based on OGTT or HbA1c or both combined were calculated.

**Results:** The results are reported in Chapters Seven and Eight.

**Conclusion:** The SWEET-Heart study is a prospective multi-ethnic study examining the prevalence of undiagnosed T2DM and IGR in British SA and WE patients admitted with AMI. Furthermore, the study will help establish methods of screening for chronic hyperglycaemia in the setting of AMI. Overall, this programme of work will significantly help optimising screening, early detection and management of T2DM and IGR in patients with AMI from the multi-ethnic UK population, thereby improving their outcomes post AMI.

### 6.3 Background and Rationale

As outlined in Chapter Two, there has been a significant shift in the risk profile of patients presenting with AMI over the recent years, and two-thirds of the contemporary cohort have T2DM or IGR at presentation (Rydén et al. 2013, Bauters et al. 2016). However, in almost half of them, systematic screening with an OGTT is required to detect undiagnosed glucose abnormalities (Norhammer et al. 2000, Rydén et al. 2013). As highlighted in Chapter Two, section 2.6.3, newly detected chronic hyperglycaemia especially T2DM is associated with an excess risk of mortality and morbidity post AMI (Lenzen et al. 2006). Early detection of these glucose abnormalities during admission facilitated by a simple and effective screening strategy and followed by early initiation of diabetes-specific coronary therapies and multifactorial secondary prevention measures may have the potential to improve prognosis post AMI. However, the optimum screening approach for chronic hyperglycaemia following AMI remains
debated, potentially leaving many undiagnosed and untreated. Recently the NICE guidelines (NICE 2011), in contrast to other international guidelines (Rydén et al. 2013, Expert Committee 2013), recommended the use of FPG or HbA1c for screening purpose in patients with AMI, and further advised to restrict such screening only to those with a raised plasma glucose on admission. The NICE guidelines recommends against the routine use of OGTT for screening purpose in the setting of AMI. The diagnostic yield of such selective screening approach based on FPG/HbA1c (rather than an OGTT) in the setting of AMI is unknown. It has been reported that even the lower cut-off levels of FPG (5.3mmol/L) and HbA1c (> 4.9%) have limited sensitivity in comparison with the OGTT in informing the underlying state of chronic hyperglycaemia in AMI (Wallander et al. 2008). On the contrary the OGTT, although considered as a gold standard test, involves time and resources making it rather an inconvenient test in the acute coronary setting. There is a need for further research in this area to help develop an optimum screening approach for chronic hyperglycaemia in the setting of AMI.

As described in Chapter Two (section 2.7.4.2), despite a higher prevalence of T2DM and CHD, studies investigating the prevalence and impact of undiagnosed chronic hyperglycaemia in migrant SA patients with established CHD are almost non-existent. In one study from India, the majority (102/146, 84%) of patients admitted with ACS and previously not known to have T2DM had either T2DM or IGT when screened with an OGTT (Ramchandran et al. 2005) during the index admission. In another study from the UK, an OGTT conducted at 2 months post AMI showed a significantly higher rate of T2DM
and IGT in SA (21/42, 50%) compared with WE (32/132, 24.2%) patients (Salmasi et al 2006). Arabi and colleagues conducted a systemic review of longitudinal studies investigating differences in established risk factors for CHD between WE and SA. They found that, after adjustment for conventional CHD risk factors, SA people without diabetes had significantly higher FPG and HbA1c values. Furthermore, they observed that in this group without diabetes, SA people had an excess risk of CHD compared with their WE counterparts not accounted for by differences in the traditional risk factors. They postulated that the observed excess CHD risk in SA patients without diabetes could be due to their excess prevalence of sub-threshold hyperglycaemia.

Patients presenting with AMI and new-onset hyperglycaemia during the index admission are found to have differential and worse prognoses post AMI, compared to those with known diabetes (Wahab et al. 2002, Stranders et al. 2004, Kosiborod et al. 2008). Authors of these studies believe that many with such new-onset hyperglycaemia at index admission have undiagnosed and untreated diabetes and related metabolic abnormalities, potentially for many years compared with those known to have diabetes and treated adequately before the index AMI. Therefore the former group is likely to have a greater endothelial damage and micro- and macrovascular morbidities, in turn accounting for their poorer prognosis post AMI. In the retrospective study reported in Chapter Five, a higher proportion of SA than WE patients admitted with AMI and previously not known to have diabetes had blood glucose >10.0 mmol/L (significant hyperglycaemia). Information is therefore needed on the prevalence of previously undiagnosed chronic hyperglycaemia in SA patients.
with AMI in the UK and its impact on adverse clinical outcomes after AMI. It is likely that SA patients with AMI have higher rates of undiagnosed chronic hyperglycaemia than WE patients and this could be a key factor driving the premature and excess rates of AMI in SA populations.

The association between chronic hyperglycaemia and CHD is not entirely explained by the traditional risk factors such as obesity, hypertension and hyperlipidaemia and the role of novel risk factors is thought to be equally important in this adverse relationship. In some studies, such novel risk factors including biomarkers related to adipose tissue metabolism are found to be significantly perturbed in SA compared with WE individuals (Kain et al. 2001, Aijan et al. 2007, Forouhi et al. 2003, Wasim et al. 2005, Forouhi et al. 2007, Nazmi et al. 2007, Goel et al. 2010). Such novel and some additional risk factors such as dietary habits, low levels of physical activities and psychosocial stress are thought to be independently conferring excess CHD risk in SA individuals. However studies comparing the prevalence and prognostic impact of non-traditional risk factors in SA and WE people with AMI are also very scarce and further research in this area is required.

**Primary Hypothesis**

The rates of previously undiagnosed chronic hyperglycaemia including T2DM, IGT and IFG are significantly higher in SA compared with WE patients admitted with an AMI.
6.3.1 Aims and Objectives

- To determine the prevalence of screen-detected T2DM and IGR using an OGTT in SA and WE people post AMI. A further aim was to assess the utility and validity of different methods (OGTT, FPG, admission plasma glucose and HbA1c) of identifying chronic hyperglycaemia in the setting of an AMI in a multiethnic UK population.

- To establish insulin sensitivity and secretion and assess the pattern of novel risk factors including markers of inflammation - hsCRP, IL-6, adipokines - Leptins and Adiponectin, markers of ventricular stress - plasma BNP/ N-BNP, microalbuminuria, physical activity levels, dietary habits, psychological distress (anxiety and depression) and Health-Related Quality of Life (HRQL) across the spectrum of chronic hyperglycaemia in SA and WE patients post MI. (This is out of the scope of my PhD)

- To assess the differences in various post-MI adverse outcomes including mortality, cardiovascular (CV) morbidity (myocardial infarction, unstable angina, heart failure, stroke), revascularisation procedures and incidental cases of T2DM diagnosed through routine care over an initial 12 month period and then in the longer term at two, five and ten years, across the spectrum of glucose intolerance and in relation to the above-mentioned novel risk factors in SA and WE populations. (This is out of the scope of my PhD)
6.3.2 Outcome Measures

6.3.2.1 Primary outcome

- The prevalence of screen-detected T2DM, IGT and IFG post myocardial infarction in WE and SA patients using OGTT with results interpreted as per the current WHO glucose criteria for the diagnosis of T2DM.

6.3.2.2 Secondary outcomes

To compare across the spectrum of glucose intolerance, WE and SA ethnic study groups in terms of:

- The utility of the OGTT and other pragmatic methods (admission plasma glucose, FPG, HbA1c) in identifying chronic hyperglycaemia post MI.
- Insulin sensitivity and insulin secretion determined by the method of Homeostasis Model Assessment (HOMA) (HOMA-B for β cell function and HOMA-IR for Insulin resistance).
- Levels of novel biomarkers including BNP/N-BNP, hs-CRP, IL-6, Adiponectin, Leptin, Microalbuminuria and Vitamin D levels. (Sample also stored for measurement of any other biomarkers to emerge in the future).
- Health-Related Quality of Life (HRQL) at admission using the SF-8 instrument.
- The adverse clinical outcomes including mortality, cardiovascular morbidity (myocardial infarction, unstable angina, heart failure, stroke), need for revascularisation procedures and incidental cases of T2DM diagnosed through routine care during one year follow up and then in the longer term at 2 years, 5 years and 10 years time.
6.4 Methods

6.4.1 Recruitment

For this study, patients were recruited between 1\textsuperscript{st} November 2010 and 31\textsuperscript{st} August 2012. I initially recruited patients from the Glenfield General Hospital (GGH) site of the University Hospitals of Leicester (UHL) NHS Trust. However as the recruitment was slow, I submitted a substantial amendment application and saught approval (Appendix Six) to recruit from an additional site, the Lincoln County Hospital (LCH) of the United Lincolnshire Hospitals. The UHL covers a Leicestershire population of over 950,000, one-third of whom are residents in the City of Leicester. In the 2011 census, in the city of Leicester, 30\% people classed themselves as belonging to Indian, Pakistani or Bangladeshi ethnic groups (the national average is 4.4\%). A previous audit of the UHL hospital data showed that approximately 1100 patients with ACS are admitted every year, one-fifth of whom are of SA (Indian, Pakistani, Bangladeshi or ShriLankan) ethnic origin. LCH is a district general hospital serving the city of Lincoln (population about 94600) and the North Lincolnshire area (population about 168,400). In 2011 census, about 1.8\% people in the City of Lincoln were born in the Middle East and Asia, a proportion well below the national average. Prior to the commencement of the recruitment, an agreement was reached with the cardiovascular clinicians at the UHL, who are co-investigators, to collaborate on this project. Similarly an agreement with the diabetologist and cardiologists at the LCH was made. Both the sites received a Study Pack giving them general information and contact numbers, and Standard Operating Procedures (SOP) for the study.
6.4.2 Participants

Patients admitted with a confirmed AMI (STEMI and NSTEMI) to the CCU or the cardiology wards at the GGH or the LCH and fulfilling the inclusion criteria were invited to participate. Information on ethnicity was self-reported by the patients. Patients with a prior diagnosis of diabetes were identified if the diagnosis was self-reported by the patient or recorded in the medical notes or if they were on a glucose lowering medication prior to admission. At the GGH, in my capacity as a research specialist registrar (SpR) employed by the UHL, I had access to patient records for identification purpose. At the GGH, I and a research nurse on the study visited the admission wards daily during the weekdays and liaised with the clinical teams to identify the eligible participants by checking the requirements of the inclusion and exclusion criteria. Similarly at the LCH, an experienced research nurse visited the CCU twice a week and liaised with the cardiologist on the CCU to identify the eligible participants.

If the participants agreed to take part in the study, I (GGH site) or the research nurse (GGH and LCH site) obtained the informed consent using a standard procedure, after fully explaining the nature of the study. Patient information leaflets and informed consent forms were provided prior to this discussion. When necessary the information was provided in different languages. The arrangements were in place to seek such help from professional translators if available or else from staff or relatives with bilingual skills providing the written and oral information in a specific language. Any such staff providing support with translation needed to be independent of the SWEET-Heart research study. In most cases we had only a limited window of time to recruit patients prior to
their discharge from the hospital, and arranging a professional translator at a short notice was very challenging. Therefore in most cases we relied on the independent healthcare staff for translation. Participants were reminded that non-participation in the study would not have any negative consequence on their medical care. We aimed to recruit 552 eligible patients including 441 WEs and 111 SAs without established T2DM at the time of admission and screen them to detect T2DM and IGR. The justification for this sample size is described later in this chapter in section 6.4.6.

On discharge, patients who had participated or agreed to participate in the study received a letter which informed their GP that they had been enrolled in the study.

6.4.3 Eligibility

6.4.3.1 Inclusion Criteria

- Adults aged ≥ 18 years
- confirmed AMI (STEMI and NSTEMI)

Acute myocardial infarction was defined as per the definition by the joint European Society of Cardiology/American College of Cardiology committee – ESC/ACCC definition of myocardial infarction published in the year 2007 (Thygessen et al. 2007, Appendix Two)). This included significant myocardial necrosis as indicated by raised Troponin I levels above 99th centile of the normal range for the respective laboratory at the UHL or LCH hospitals, confirmed on two occasions plus either appropriate symptoms; or dynamic ECG changes (ST elevation or ST depression) or both.
6.4.3.2 Exclusion criteria

- Unable to give informed consent
- Severe co-morbidity (such as malignancy) leading to likely death within six months time
- Known to have diabetes mellitus

6.4.4 Invitation to participate

I (GGH site) or the research nurse or a cardiology ward nurse looking after the patients, all employed by the appropriate NHS trust, approached the participants, briefly explained the study and handed over the invitation letters on behalf of the principal investigator. Along with the invitation letter potential participants were also given (Appendix Six):

- An information sheet about the study
- A consent form
- A reply slip

All the standard procedures for invitation and consenting were followed. Initially, we gave minimum 24 hours to reply. However, as many patients were only admitted for 48 hours and the protocol required 12 hours of fasting, it was not feasible to give participants the standard minimum 24 hours time to reply. I then submitted a substantial amendment and sought approval for reducing the reply time to 6 hours when necessary (Appendix Six).

At the time of initial approach, I went through the study information in detail to ensure that the participants had understood the study and the procedures
involved in it. I also ensured that their in-patient stay was not unnecessarily prolonged due to their participation in the study. Patients were also given the number of a dedicated phone line to contact if they were interested and/or required further information. I (GGH site) or the healthcare team (the GGH, LCH sites) then approached the patients after they had been given the study information and asked if they wanted to participate. They were approached in a sensitive manner and there was absolutely no pressure to participate. Additionally, the individuals taking part in the study also had an option of returning the reply slip.

6.4.5 Study visits and procedures
The study flow chart is provided in Figure 6.1. Additionally, the study procedures carried out during screening and follow-up visits are provided in Table 6.1.

6.4.5.1 Screening visit
At the GGH and LCH many patients with NSTEMI were being discharged on 2\textsuperscript{nd} or 3\textsuperscript{rd} day of admission, if they were stable and had undergone coronary intervention if necessary. Patients with STEMI stayed longer than those with NSTEMI. I adopted a pragmatic approach to the timing of screening visit during the admission with AMI, working around the routines of inpatient coronary practice in the real-world setting. Patients who agreed to participate in the study underwent screening on the admission ward in their steady state, on day 2 onwards of their hospital stay prior to being discharged. In those patients with elevated blood glucose >11.0 mmol/L and without prior diabetes and who were
treated with intravenous insulin therapy, an OGTT was done after 24 hours of coming off the insulin infusion. There were situations where patients were interested in participating in the study but were due to be discharged and therefore unable to undergo the screening procedures on the ward before being discharged. Such participants were then invited to return to the screening visit within 10 days following their discharge from the hospital. This approach to the timing of the first OGTT was based on the large, multicentre (25 European countries) Euro Heart Survey on diabetes and heart (Bartnik et al. 2004). In this study, to establish the glucometabolic state of those with AMI without previously known diabetes, an OGTT was performed as soon as they were in a stable condition prior to hospital discharge, or within two months following the index consultation (Bartnik et al. 2004). In the landmark GAMI study published in 2002, the OGTT was done on day 4 or 5 of admission with AMI. However such timing to perform the first OGTT is not feasible in the contemporary acute coronary practice as many patients with NSTEMI are discharged on day 2 or 3 of the admission. Screening involved the following procedures:

### 6.4.5.2 Biochemical Investigations

After at least an eight-hour overnight fast, the participants underwent the following blood tests on the day of the screening:

- Fasting venous blood sample for
  - Glucose (2.7ml Fluoride )
  - HbA1c (2.7ml EDTA)
  - Urea & Electrolytes (Sodium, Potassium, Urea, Creatinine) (4.7ml Serum Gel)
Biomarkers including Insulin, Proinsulin, BNP/N-BNP, hs-CRP, IL-6, Adiponectin, Leptin, 25 , (2 × 9ml EDTA & 1 × 9 ml Serum Gel)

- Standard OGTT: After taking a fasting venous sample, a 75 g oral glucose load (410 ml Lucozade) was given and a venous sample was taken after 120 minutes for plasma glucose measurement (2.7ml Fluoride). Additional venous blood samples were collected during the OGTT for measurements of Insulin (4.7ml EDTA) and glucose (2.7 ml Fluoride) 120 minutes post glucose load for determination of HOMA indices of insulin sensitivity and insulin secretion.

Early morning urinary albumin and creatinine levels were measured and the albumin: creatinine ratio (ACR) calculated.

All the samples were analysed in the same laboratory (UHL or LCH site) using stable methodology standardised to external quality assurance reference values. All these tests were carried out over and above routine clinical practice.

It is a routine practice at the UHL and LCH to send blood samples for measurements of plasma blood glucose and other routine bloods including full blood count (FBC), urea and electrolytes, liver functions tests (LFTs:total bilirubin, ALT, ALP, Gamma-GT) and lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (TG)) soon after admission, usually within the first 12 to 24 hours. Data on these routine laboratory tests were collected from patient’s in-patient records.
6.4.5.3 Anthropometry

The following anthropometric measurements were performed

- Height, weight measured to nearest 0.5 cm and 0.1 kg respectively and body mass index (BMI) calculated.
- Waist circumference (WC) - measured with a soft tape on standing, midway between the lowest rib and iliac crest.
- Blood pressure (BP) (Omron, Healthcare, Henfield, UK) - three BP recordings were obtained from the right arm of the patient in the sitting position after 3 minutes of rest, at 1-minute intervals, and then the mean value was calculated of the second and third reading discounting the first.

The participants were interviewed to collect information on the presence of any classical symptoms of diabetes, cardiovascular risk factors, past medical history, family history of CVD or diabetes, social history and prior medication history. Self-reported information on past medical history was supplemented by information recorded in the admission notes. Smoking was reported as never, former (if quitted <1 month) or current. Diagnosis of hyperlipidaemia at index admission was ascertained by either prior prescription of lipid-lowering medications or admission lipid profile showing total cholesterol > 5.0 mmol/L, HDL-cholesterol <1.0 mmol/L in men, or <1.1 mmol/L in women, triglycerides >2.0 mmol/l.
6.4.5.4 Questionnaire-based assessment

The participants were approached for various questionnaire-based assessments. The questionnaires were completed by the participants and assistance was offered by the study team if requested. The questionnaire covered various areas as follows:

- Demographic characteristics including gender, age, socio-economic status, ethnic background, nationality, country of birth and in the case of immigrants the total length of time they have lived in the UK and the generation they belong to.
- Health-related quality of life - HRQL using the Short-Form health status measures- SF-8 tool (Ware et al. 2001).
- Emotional state using the Hospital Anxiety and Depression Scales (HADS) tool (Zigmoid et al. 2006),
- Physical activity levels using the International Physical Activity Questionnaire (IPAQ) -short last seven days format (SF) (Craig et al. 2003).
- Dietary habits using the Dietary Instrument for Nutrition Education or DINE questionnaire (Roe et al. 1994)

As mentioned before, when necessary the information in the questionnaire was provided in different languages (Gujrati, Hindi, Punjabi) with the help of translators.

Furthermore relevant information on the clinical characteristics of patients at admission required for calculating the Global Registry of Acute Coronary
Events (GRACE) score (Granger et al. 2003, Eagle et al. 2004) and details of inpatient medications, procedures and complications were noted from their in-patients records.

6.4.5.5 Follow up visit:

All participants underwent a repeat OGTT irrespective of the results of the first OGTT. An exception was those who had classical symptoms of diabetes and diabetes-range blood sugar levels on the first OGTT and therefore were confirmed to have T2DM as per the WHO 1999 criteria.

The research team contacted all the patients who underwent an OGTT during their hospital stay and invited them to attend a clinic session for repeat OGTT at the UHL research unit. Those showing a diabetes-range high blood sugar levels on the first OGTT were recalled for a repeat OGTT in approximately two weeks time with a third OGTT arranged if the second OGTT showed equivocal results. The rest were recalled in six to eight weeks time. During the study, we experienced that participants were finding it difficult to attend the second visit in the six to eight weeks window due to various reasons such as cardiology appointments, re-admission and travel from a distance. In such situations, a flexible approach was taken and participants were allowed to attend the follow-up visit beyond the eight weeks window. Travel expenses were reimbursed up to £15 per person per visit.

During this follow-up visit a trained member of the research team carried out the following tests:
- Repeat OGTT
- Glycated haemoglobin (HbA1c)
- Urea & Electrolytes (Sodium, Potassium, Urea, Creatinine)
- Repeat Biomarker studies for Insulin, Proinsulin, BNP/N-BNP, hsCRP, IL-6, Adiponectin, Leptin, as before.
- Urine Microalbuminuria.

All the participants, their GPs and consultant cardiologists were informed about the results in writing within two weeks of the second OGTT. Those confirmed to have diabetes were informed by telephone within two days of their OGTT. All the participants newly diagnosed to have T2DM in the study were referred to the hospital diabetes team. Patients with IGR were referred to their GP for standard care.

The diagnosis of T2DM or IGR (IGT, IFG or both) in this study was confirmed using the WHO 1999 OGTT criteria only (Alberti et al. 1998). An algorithm used for interpretation of plasma glucose results, repeating the tests and diagnosing T2DM and IGR is provided in the Appendix Six. We also analysed the results of the HbA1c test to establish the prevalence of diabetes as per 2011 WHO criteria (WHO, 2011), and the prevalence of high-risk state, an equivalent of IGR. Diagnosis of diabetes was indicated if HbA1c ≥ 6.5% (48mmol/mol) while the HbA1c levels between 6.0 and 6.4% (42.0 and 47 mmol/mol) were considered as high-risk state (John et al. 2012, NICE. 2012).
The rationale behind repeating various tests, including the OGTT and biomarkers, in all the participants irrespective of the results of the tests performed at the visit was to assess the trend in these biochemical parameters between immediate post MI period and a steady state after the AMI event. In the GAMI study, a repeat OGTT was done at 3 months and 12 months post MI (Norhammer et al. 2002). Although the intra-group tracking of the OGTT from discharge to follow-up was poor, the overall prevalence of T2DM and IGR remained the same at 3 and 12 months in this GAMI study. I wanted to establish whether the same holds true in a multiethnic UK population. This is important because if confirmed, the early detection of these abnormalities of chronic hyperglycaemia during the course of hospitalisation for AMI can potentially open the doors for early initiation of novel therapies for secondary prevention in such patients. Regarding the biomarkers, studies have shown a significant correlation between a pattern of change in biomarkers levels between admission and few weeks at follow up with adverse outcomes and such information in a mixed ethnic population is needed.

A plan has been put in place to follow up the participants initially up for 12 months to determine the mortality (cardiovascular and non-cardiovascular), CV morbidity, revascularisation procedures and incidental cases of new T2DM diagnosed through routine clinical care, in those people who did not have this at screening. Furthermore, it has been planned to tag them for long term follow-up at 2 years, 5 year and 10 years time. The details of definitions of various post AMI outcomes and the procedures to collect information on these outcomes are provided in the study protocol. The participants were consented at the time of
enrolment for obtaining any such information on their outcomes from any sources.

### 6.4.6 Power calculations and sample size

The primary aim of the study was to compare the prevalence of chronic hyperglycaemia (T2DM + IGR (IGT +IFG)) post MI in WE and SA people without an established diagnosis of T2DM. In the GAMI study involving mainly Caucasians, 66% patients admitted with AMI and no previous diagnosis of T2DM had either IGR (35%) or newly detected T2DM (31%) (Norhammer et al. 2002). A similar finding was reported in the 25-country Euro Heart Study again involving mainly Caucasians with acute and stable CHD (Bartnik et al. 2004). In 1920 people without known T2DM undergoing an OGTT, 55% patients had either IGR (37%) or newly detected T2DM (18%). In an Indian study involving 142 urban Indians without known T2DM at admission with ACS and subjected to an OGTT before hospital discharge, nearly 84% had either IGR (IFG + IGT) (45.9%) or newly detected T2DM (37.7%) (Ramchandran et al. 2005). Based on this information we assumed that 84% of SA patients would have T2DM or IGR compared with 66% in WE patients. On average, 1100 patients with AMI are admitted per year in UHL and 20% them are of SA origin. Based on alpha 0.5 and 90% power, to detect an 18% difference, 552 patients needed to be recruited to the study. This assumed a ratio of 4:1 for WE (441) to SA (111) patients and a 25 % drop-out rate.

An estimated intake of patients with AMI over the anticipated 18 month study period was 1650, of which our audit data indicated that about 18% (300) would
be identified as having established diabetes and therefore would be unsuitable for the main study. Of the remaining 1350 patients, assuming a 50% response rate, we expected at least 675 to be potentially available for the recruitment. The required sample size of our study of 552 patients was less than the estimated 50% of the total number of recruitable patients and hence was thought to be feasible.

This being a unique and a larger study compared with other studies in this area, we decided to thoroughly phenotype the participants using the secondary outcomes.

6.4.7 Data collection and analysis

6.4.7.1 Blood tests

Robust arrangements were in place for the storage of data and blood samples. The EDTA samples which were collected for storage of plasma were spun within two hours at 3000 RPM and plasma saved into 4 separate aliquots of 0.5mls using well-labelled epindorphs. The serum gel samples for storage were centrifuged after 30 minutes, pipetted and then frozen. Samples were initially stored in a –20 freezer and then transferred to a –80 freezer within 3 months. Blood samples for biomarkers were stored in a locked freezer in an access-controlled room for future analysis. The patients have the right to have their samples destroyed if they withdrew consent.
6.4.7.2 Laboratory analysis

The samples for plasma glucose, HbA1c and Urea & Electrolytes were sent to the lab within 60 minutes of collection. Plasma glucose and Urea and Electrolyte were measured using standard enzymatic endpoint methods on an ADVIA Chemistry System (Bayer Healthcare, NY, USA). HbA1c was measured by ion-exchange liquid chromatography (G7; Tosoh, Tokyo, Japan). The samples for biomarkers would be analysed using the commercially available kits.

6.4.7.3 Statistical analysis

Baseline characteristics of the SA and WE participants are expressed as means with standard deviations for continuous variables and counts and percentages for categorical variables. Ethnic differences in the baseline characteristics between the ethnic groups were examined using independent two-sample t-tests (continuous variables) and (Chi-squared) tests (categorical variables). The association ethnicity with newly diagnosed chronic hyperglycaemia was examined using logistic regression analysis. Initially univariate association of ethnicity with newly diagnosed chronic hyperglycaemia was assessed. The multivariate association of ethnicity with newly diagnosed chronic hyperglycaemia adjusting for important confounders was then examined. The confounders of age, gender, BMI, waist circumference and smoking status were preselected based on their known association with both ethnicity and chronic hyperglycaemia. Furthermore, the sensitivity and specificity for diagnosis of T2DM based either on OGTT or HbA1c or both combined were calculated. Statistical analyses were performed using SPSS
20.0 software (Statistical Package for the Social Sciences, Chicago, IL). All analyses are two-sided and p<0.05 relate to a statistically significant difference.

6.5 Ethical issues

The study was approved by the local Research Ethics Committee, University Hospitals of Leicester NHS Trust, and University Hospitals of Lincolnshire NHS trust (see Appendix Six for the details).

An internal Data Safety Monitoring Committee was in place to oversee all activities performed and to determine the safe and effective conduct of the study. The committee met regularly to review data collection. Any issues raised were addressed with the Principal Investigators and reports and recommendations provided.

6.6 Conclusion

This chapter described in detail the rationale and design of the SWEET-Heart study. Chapter Seven and Eight describes the results related to primary outcomes and selected secondary outcomes of the study.
Figure 6.1: Study flowchart

Consecutive eligible participants recruited from hospitals following an acute MI.

Patient not known T2DM

Following tests done before discharge from hospital:
- Standard OGTT plasma Insulin, proinsulin levels fasting and at 120 minute of the OGTT
- Glycated haemoglobin (HbA1c),
- Urea & Electrolytes
- Urine for Microalbuminuria ,
- Bloods for biomarkers collected and frozen
- Assessment with SF-8, IPAQ, DINE, HADS
- General information and Anthropometry

6 to 8 weeks after recruitment, participants underwent the following tests at the UHL/LCH clinics:
- Repeat OGTT with additional plasma insulin/proinsulin tests
- Glycated haemoglobin (HbA1c), Urea & Electrolytes
- Urine Microalbuminuria
- Biomarkers (fasting) sample collected and frozen

Patients classified into
- Type 2 DM
- IGT and IFG
- Normal Glucose tolerance

Determined in SA and WE participants, the prevalence of screen detected T2DM and IGR. Determined across the spectrum of glucose intolerance in SA and WE participants:
- The utility of OGTT and other methods (FPG, Admission plasma glucose, HbA1c) in identifying T2DM and IGT, IFG post MI.
- Insulin secretion and Insulin resistance (HOMA indices)
- Trends in biomarkers
- Physical activity levels (IPAQ - SF)
- Dietary Habits (DINE)
- Anxiety and Depression (HADS)
- Health Related Quality of Life (SF-8)

Follow-up of participants for 12 months to determine across the spectrum of glucose tolerance and novel risk factors in SA and WE participants:
- Mortality
- Cardiovascular morbidity
- Revascularisation procedures
- Incidental new cases of T2DM not diagnosed at screening
- Develop a risk score model and compare its utility with the GRACE score in predicting long term mortality.

Participants to be tagged for follow up at 2, 5 and 10 years.
Table 6.1: Laboratory and anthropometric measures and questionnaires

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Patients not known</th>
<th>T2DM</th>
<th>Baseline</th>
<th>6-8 weeks</th>
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<td>Oral Glucose Tolerance Test</td>
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<td>Plasma Glucose and Insulin both at 30 and minutes</td>
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<td>post glucose load during the OGTT</td>
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<td>Fasting plasma glucose</td>
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<tr>
<td>HbA1c</td>
<td>x</td>
<td>x</td>
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<tr>
<td>U &amp; E (Na, K, Urea, Creatinine,)</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Biomarkers</td>
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<tr>
<td>Urine for albumin creatinine ratio</td>
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<tr>
<td><strong>Anthropometry</strong></td>
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<tr>
<td>Height</td>
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<td>Weight</td>
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<td>BMI</td>
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<tr>
<td>Blood Pressure (x 3 measurements)</td>
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<td><strong>Questionnaires</strong></td>
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<td>Family history of cardiovascular diseases and T2DM</td>
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<td>IPAQ - SF</td>
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<td>DINE</td>
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<td><strong>Information from Inpatient records</strong></td>
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<td>GRACE At Discharge score</td>
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<td>Liver Function tests</td>
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<td>In-patient procedures/treatment of MI</td>
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<td>Medications on admission and at discharge</td>
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<td>Diagnosis at discharge</td>
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<td>In-patient adverse outcomes.</td>
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</table>
Chapter Seven: Prevalence of undiagnosed chronic hyperglycaemia in South Asian and White European patients admitted with acute myocardial infarction

7.1 Chapter Overview

In Chapter Two, I reviewed the literature and demonstrated that very little is known about undiagnosed chronic hyperglycaemia in patients presenting with AMI from a mixed ethnic UK population. In the retrospective cohort study described in Chapter Five, the prevalence of significant acute hyperglycaemia (blood glucose levels >10.0 mmol/l) in those admitted with AMI and without known diabetes was higher (20%) in SA compared with WE patients (14%). It is possible that many of these SA patients had undiagnosed chronic hyperglycaemia, which presented during the physiological stress of AMI as acute hyperglycaemia. In the SWEET-Heart study, I aimed to explore this further and robustly establish the ethnic differences in the rates of undiagnosed T2DM and IGR in patients presenting with AMI. To my great disappointment a smaller number of participants were recruited to the SWEET-Heart study, precluding any robust conclusions; nonetheless, the analysis of the SA and WE groups reported in this Chapter show some important trends, providing direction for future studies in this area.
7.2 Abstract

Aims/Objectives: To compare rates of undiagnosed T2DM and IGR in British SA and WE patients admitted with AMI.

Methods: In a prospective study, a total of 210 (10% of SA origin) patients with AMI and without antecedent diabetes underwent an OGTT, HbA1c and other study procedures during their index admission to the two UK hospitals, between November 2010 and August 2012. Of them, 163 (10.4% of SA origin) underwent a repeat OGTT, HbA1c at median 22 days (range 11 to 114) following discharge from hospital.

Results: Compared with WE patients, SA patients were on average 4.4 years younger (58.8 vs. 63.3 years, p=0.096), had a lower BMI (BMI 26.9 vs. 29.0 kg/m², p=0.079) and were less likely to have central obesity (WC 96.6 vs. 102.7 cm, p=0.054). At both visits, compared with WE patients, rates of undiagnosed diabetes-range hyperglycaemia (FPG ≥7.0 mmol/l and/or 2hPG ≥11.1 mmol/l) on OGTT were higher in SA patients (admission: 23.8% vs. 9.5%, p=0.062; follow-up: 17.6% vs. 4.9%, p=0.073), driven solely by a higher prevalence of post–glucose challenge hyperglycaemia in SA patients. SA ethnicity showed an association with a confirmed diagnosis of T2DM (OGTT) on univariate (HR 5.0, CI 1.13, 22.2) and multivariate (HR 6.01, 95 CI 1.11, 32.6, p=0.038) logistic regression analysis. Findings were generally similar for diagnosis of T2DM confirmed by the HbA1c criteria (multivariate HR 5.06, 95 CI 1.06, 24.26).

Conclusions: Compared with WE patients, SA patients presenting with AMI are at five- to six-fold increased risk of having previously undiagnosed T2DM. If confirmed in a larger cohort, the current UK recommendations for screening for T2DM in the setting of AMI will need reviewing.
7.3 Background

The rationale and background of the SWEET-Heart study have been outlined in Chapter Six. The main aim of the SWEET-Heart study was to compare the rates of undiagnosed T2DM and IGR following admission with an AMI in SA and WE individuals drawn from a contemporary UK multi-ethnic population. Such information would help determine the need for ethnic-specific strategies for screening, early detection and management of T2DM and IGR in the SA population post AMI. In the context of higher rates of known T2DM/IGR and also CHD in the general SA population, I hypothesised that the ethnic gap in the rates of previously undiagnosed T2DM or IGR would be even wider in the high-risk cohort of AMI.

7.4 Methods:

The detailed methodology of the study including eligibility criteria, invitation, and approach and consenting of the participants, recruitment process, study visits and procedures and statistical approach to the analysis are described in details in Chapter Six.

7.5 Results:

Figure 7. 1 shows the study flow chart.

7.5.1 Screening visit before discharge:

A total of 215 patients were consented between November 2010 and July 2012 including 22 SA and 193 WE participants. Among them, 209 were recruited from the GGH and 6 from the LCH. Of the 215 participants, five were excluded due to either protocol violation (n=2) or withdrawal of the consent (n=3),
resulting in a final cohort of 210 (SA= 21) participants undergoing the study procedures including an OGTT at baseline. Among those who attended the screening visit, 2-hour glucose (2hPG) and HbA1c values were not available in four and one participants respectively due to post sampling errors.

The achieved sample size of 210 was smaller than the expected 552 patients with even a smaller 10% of SA patients recruited against the predicted 25% of the total cohort. This reduced the power of the study. The under-recruitment was mainly due to two factors. Firstly, due to multiple other cardiology studies running recruitment in parallel, the available pool of potential participants was significantly reduced by about 50 - 60%. Secondly, the response rate was lower especially in the SA group at about 25%. Additionally, some issues with recruitment strategies contributed to the initial slow recruitment including method of identifying participants, the time given to patients to respond, and the timing of screening visit as in-patient only.

7.5.2 Follow- up visit after discharge:
T2DM was confirmed on the first OGTT in one patient on the basis of unequivocal symptoms and abnormal OGTT and did not need a follow-up OGTT. Among the remaining 209 patients, 163 (77.6%) (WE 146, SA 17) patients attended a follow-up visit and underwent an OGTT and other procedures. Among them were 18/163 (11.0%) participants who had early follow-up at about two weeks since they had diabetes-range hyperglycaemia (FPG ≥7.0 mmol/l and/or 2hPG ≥11.1 mmol/l) on the first OGTT. The remaining 146/163 (66.6%) attended the follow-up at six weeks or later following hospital
discharge. In addition, one participant attended a third visit to undergo a repeat OGTT to confirm/refute the new finding of asymptomatic diabetes-range hyperglycaemia on the second OGTT.

Among the 46/209 (22%) participants who did not attend follow-up, four had diabetes-range hyperglycaemia on the first OGTT – one participant died while the other three declined to attend the appointment. The reasons behind non-attendance in the remaining 42/209 (20.1%) participants were mainly unwillingness (39) or death (3).

In the follow-up group, FPG, 2-hPG and HbA1c values were missing in one, one and five participants respectively, all in WE patients, due to post sampling errors.

7.5.3 Index admission to screening time:
The median time from admission to screening was 3 days (range 1 to 36 days, interquartile range 5) with 118 (56.2%) patients undergoing screening between 2 to 3 days, 50 (23.8%) between 4 to 7 days, 19 (9.0%) between 8 and 10 days and the remaining 23 (11.0 %) after 10 days of admission. Almost half (19/42) of those screened beyond seven days from the admission date were the ones transferred from another hospital to GGH for the tertiary management of AMI few days after the index event.

7.5.4 Screening to follow-up time:
The median time from screening to follow-up visit in 17 patients with diabetes-range hyperglycaemia (and therefore undergoing early follow-up) was 22 days (range 11 to 114) with 2/17 participants attending their follow-up later than planned date at 56 and 114 days as per their convenience. While we planned to conduct the follow-up visit between 6 to 8 weeks in the remaining 146 patients, we needed to take a pragmatic approach to the timing of the follow-up visit and work around patient availability. Therefore, the median time from screening to follow-up visit in these 146 patients was 62 days (range 13 to 237). Five participants underwent the follow-up OGTT earlier than 6 weeks at a range of 13 to 41 days as their blood glucose levels on the screening OGTT were significantly raised approaching the diagnostic cut-off points for diabetes. Of the remaining 141/146 participants, 48 (25.5%) had follow-up between six to eight weeks, 54 (28.7%) between nine to 12 weeks, 35 (18.6%) between 13 to 24 weeks. Any delay in follow-up was due to the patients requesting to reschedule their appointments because of hospital readmissions, cardiology out-patient appointments, or other health problems.

7.5.5 Patient population and characteristics:

Tables 7.1 and 7.2 show baseline characteristics of the participants stratified by ethnicity. Of the total 210 patients, 85 (40.5%) presented with STEMI and 125 (59.6%) with NSTEMI, with about 10% having Killips score >1. Compared with WE patients, SA patients were on average 4.4 years younger (63.3 years vs. 58.8 years, p=0.096), had a lower BMI (BMI 29.0 kg/m² vs. 26.9 kg/m², p=0.079) and were less likely to have central obesity (WC 102.7 cm vs. 96.6 cm, p=0.054). A quarter had a prior history of CHD and more than a third were
known to have hypertension with no ethnic difference in this regard. About two-thirds were smokers at some stage in their life, a third being current smokers. South Asians were less likely to be smokers compared with WE patients (19.0 vs. 39.6, p=0.078). About a third from each ethnic group were receiving cardio protective medications including antiplatelet agents, statins or angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB). A total of five patients were on long-term prednisone therapy. A significant proportion of SA patients with screen-detected T2DM had first-degree relatives with diabetes. South Asian patients had higher mean admission glucose and higher mean triglycerides (Table 7.2). The use of coronary reperfusion and revascularisation therapies during index admission and the prescription of secondary prevention therapies at discharge were similar in the two groups.

Tables 7.2 and 7.3 show the levels of mean glucose (OGTT) and HbA1c measured at screening and follow-up, stratified by ethnicity. At both screening and follow-up, compared with WE patients, SA patients had higher mean HbA1c and 2hPG levels.

7.5.6 Chronic hyperglycaemia (T2DM or IGR) - the WHO 1998 glucose criteria

Table 7.4 shows the results of categorisation of glycaemic status at screening and follow-up, based on the WHO 1998 glucose criteria.

Of the 210 patients, 40% (85/210) had newly detected chronic hyperglycaemia (T2DM or IGR) on first OGTT including 11% (23/210) with T2DM. One patient
with T2DM on the first OGTT had unequivocal symptoms and therefore was confirmed to have T2DM and commenced on treatment. On repeating the OGTT in 163 participants who attended follow-up, it was found that the prevalence of chronic hyperglycaemia reduced to 23% (37/163) while that of T2DM reduced to 6.2% (10/163). A large proportion of the glucose abnormalities on the first and repeat OGTT were diagnosed on the 2hPG measurements and would have been missed if only FPG criteria were applied (Table 7.4). A total of 10 patients (4.8%, SA 3) fulfilled the WHO criteria and were confirmed to have T2DM (two abnormal OGTTs or one abnormal OGTT in presence of unequivocal symptoms) and commenced on treatment.

At both the visits, the prevalence of previously undiagnosed T2DM was higher in SA compared to their WE counterparts (screening: 23.8% vs. 9.5%, p=0.062; follow-up: 17.6% vs. 4.9%, p=0.073), driven solely by a higher prevalence of post–glucose challenge hyperglycaemia in SA patients (Table 7.4). At screening, none of the 5/21 SA patients with T2DM had a FPG in diabetes range (≥ 7.0 mmol/L). On final classification more SA than WE patients were confirmed to have T2DM and commenced on treatment for T2DM (17.3% vs. 3.7%, p=0.066). Conversely, no ethnic difference in the rates of IGR was observed at screening (SA, 28.6% vs. WE, 29.6%, p=1.00) or at follow-up (SA, 17.6% vs. WE 16.4%, p=1.00) (Table 7.4).

On univariate logistic regression analysis, SA ethnicity was associated with higher rates of newly diagnosed chronic hyperglycaemia (HR 2.36, 95% CI 0.85, 6.57; p=0.099) and confirmed diabetes (HR 5.0, 95% CI 1.13, 22.2).
multivariate logistic regression analysis adjusted for age, gender, BMI, waist circumference and smoking status, this adverse association between SA ethnicity and newly diagnosed chronic hyperglycaemia (HR 3.53, 95% CI 1.14, 10.92; p=0.029) or confirmed diabetes (HR 6.01, 95% CI 1.11, 32.6; p=0.038) was persistent. Conversely, SA ethnicity was not associated with IGR on its own at any time point.

Table 7.5 shows differences in baseline characteristics and biochemical parameters in those with and without confirmed diabetes, stratified by ethnicity. Among the WE patients, characteristics of metabolic syndrome such as waist circumference, triglycerides levels and fasting plasma glucose levels were significantly perturbed in those diagnosed with diabetes compared with those without. No such differences in waist circumference or triglyceride levels were found among SA patients with or without diabetes.

7.5.7 Chronic hyperglycaemia - the WHO 2011 HbA1c criteria for T2DM and the UK Expert Group HbA1c criteria for the high-risk state

Table 7.6 shows the prevalence of T2DM (HbA1c ≥48.0 mmol/mol), high-risk state (HbA1c 42.0 - 47.0 mmol/mol, considered as the equivalent of IGR) and chronic hyperglycaemia (HbA1c ≥42.0 mmol/mol) if the new HbA1c criteria (WHO 2011, John et al 2012) were to be applied. At screening, a total of 43.5% patients had chronic hyperglycaemia including 8.6% with T2DM. At follow-up, the prevalence of chronic hyperglycaemia was 46.5%, with 12.4% having T2DM. Applying the WHO 2011 HbA1c criteria and considering the results of the two successive HbA1c tests (except in those with unequivocal symptoms),
a total of 8.2% (13/160) cases of T2DM were identified. Additionally, 4.3% (7/163) patients had HbA1c ≥48.0 mmol/mol at follow-up only, thereby requiring a further HbA1c test to confirm/refute the diagnosis of T2DM in these patients.

At screening, the prevalence of chronic hyperglycaemia was significantly higher in the SA compared with the WE group (71.4% vs. 40.4%, p=0.010), driven mainly by a higher prevalence of high-risk state in the SA group (57.1% vs. 32.4%, p=0.031). At follow-up, while the crude rate of chronic hyperglycaemia was still numerically higher in SA compared with WE patients (58.8% vs. 45.1%, p=0.313) the difference was not statistically significant. However, the prevalence of T2DM (29.4% vs. 10.6%, p=0.043) at follow-up was higher in SA compared with WE group. When the results of two successive HbA1c tests were considered (except for those with symptoms), the prevalence of T2DM was numerically higher in SA compared with WE, however this difference didn’t reach statistical significance (17.6% (3/17) vs. 7.0% (10/146), p=0.147).

On univariate analysis SA ethnicity was not associated with chronic hyperglycaemia (HR 1.74, 95% CI 0.63, 4.83; p=0.287) or confirmed cases of T2DM (HR 3.14, 95% CI 0.76, 12.98). On multivariate analysis, adjusted for age, gender, BMI, waist circumference, and smoking status, SA ethnicity was associated with significantly increased risk of T2DM (HR 5.06, (1.06, 24.26) but not with risk of chronic hyperglycaemia (HR 2.13, (0.73, 6.17). On multivariate analysis, SA ethnicity was not associated with the high-risk state on its own at follow-up.
7.6 Discussion:

I intended to conduct a large-scale study examining ethnic differences in the prevalence of undiagnosed chronic hyperglycaemia in patients admitted with AMI. While the smaller than expected sample size precludes robust conclusions, the ethnicity analysis from the SWEET-Heart study certainly shows important trends, providing direction for future studies in this area. Apart from the OGTT, the study uniquely provides data on consecutive HbA1c tests performed during admission with AMI and following hospital discharge. This gives an insight into the prevalence of screen-detected diabetes and IGR/high-risk state using the new WHO 2011 criteria in patients with AMI and further in the ethnic subgroups.

Firstly, in line with the previous studies, the SWEET-Heart study confirmed the high prevalence of previously undiagnosed diabetes and IGR/high-risk state in patients admitted with AMI when systematically screened with an OGTT or HbA1c test. This supports the recommendations from various organisations that systemic screening for chronic hyperglycaemia should be undertaken in people admitted with AMI (Rydén et al. 2013, NICE 2011, Tardif et al. 2013, Vergès et al. 2012). A large proportion of previously undiagnosed glucose abnormalities in the study would have been missed if only the FPG test was used, highlighting post-glucose challenge hyperglycaemia as the predominant glucose abnormality in this cohort. Similarly, a large proportion of people with chronic hyperglycaemia on HbA1c had normal FPG tests, further highlighting the limitation of reliance on the FPG test as a preferred screening test. However the prevalence of chronic hyperglycaemia based on the OGTT both at
screening (40%, diabetes 11%) and follow-up (23%, diabetes 6.2%) in the SWEET-Heart were lower than that of 60-70% reported in various studies from the UK (Evan et al, 2008) and other parts of the world (Norhammer et al, 2002; Bartnik et al, 2004). The prevalence of chronic hyperglycaemia using the new HbA1c criteria was similarly low (screening visit 43% and follow-up visit 46.5%) compared with the 70% prevalence reported in a recent large multicentre European study (Gyberg et al, 2015). This could be due to the widespread availability of diabetes screening activities in primary care setting in the UK, leaving a proportion of those yet undiagnosed with chronic hyperglycaemia in the population much smaller than in other parts of the world.

The main finding of the study is the two and half times higher crude prevalence of undiagnosed T2DM, identified mainly on the post-glucose challenge glucose measurement, in the SA than WE patients. This finding was seen at screening, and when the results of two successive OGTTs and symptoms according to the WHO 1998 glucose criteria were taken into consideration. Furthermore, a similar finding was seen using WHO 2011 HbA1c criteria and on a pooled prevalence after combining results of HbA1c and the OGTT at follow-up. When important confounders such as differences in age, gender, BMI and waist circumference between the two ethnic groups were taken into consideration, SA patients were up to six times more likely to have undiagnosed diabetes compared with their WE counterparts, on both the OGTT and HbA1 criteria.

These findings from the SWEET-Heart study are broadly in line with the observed higher prevalence of undiagnosed diabetes seen in general SA
population living in the UK. In the largest population-based diabetes screening study involving SA patients, the ADDITION-Leicester study (n=WE 4,688, SA 1,353), 5.1% SA had diabetes compared with 2.7% of WE patients and on adjusted analysis SA were at two times higher risk of having undiagnosed diabetes compared with the WE participants (OR 2.18, 95% CI 1.56–3.06), P<0.05)) (Webb et al 2011). The SWEET-Heart study extends these findings to the high-risk cohort of established CHD and for the first time provides crude and adjusted risk estimates of undiagnosed diabetes identified using both the OGTT and HbA1c criteria in SA and WE individuals admitted with AMI. As hypothesised, the gap in the prevalence and risk of diabetes between SA and WE population seems to be even wider in the high-risk cohort with AMI.

Interestingly, the prevalence of IGR at screening and follow-up visits and that of high-risk state (HbA1c 42-47 mmol/mol) at follow-up in the SWEET-Heart study were similar for the two ethnic groups in this cohort of AMI. Furthermore, on adjusted analysis, ethnicity was not independently associated with the risk of undiagnosed IGR or the high-risk state. In the ADDITION-Leicester study, undiagnosed IGT or IFG occurred more frequently in SA compared with WE in the general population with an odds ratio (adjusted for age, sex, central obesity and deprivation) being 1.53 (95% CI 1.26–1.87) (Webb et al 2011). A smaller sample size of the SWEET-Heart study or the rapid conversion of IGR state to T2DM seen in the SA population (Srinivasan et al. 2007, Oldroyd et al. 2007) could explain the apparent lack of ethnic difference in the rates of IGR in the study. However, it is also possible that unlike diabetes, CHD risk associated with IGR/high-risk state is not different in SA and WE people. In support of this,
a recent study involving 682 WE and 520 SA men and women, aged 58–85 years showed that pre-diabetes identified by either an OGTT or HbA1c is less associated with cardiovascular disease in the SA than in the WE group (Eastwood et al. 2016). The finding from the SWEET-Heart study, therefore needs further evaluation in the larger sample as it will have implication on screening, early detection and management of IGR state in the SA population.

Published studies examining the prevalence of undiagnosed diabetes and IGR in SA patients admitted with AMI are very limited (Ramachandran et al. 2005, Salamasi et al. 2006). In an Indian study from Chennai, a total of 34% (55/146) patients had diabetes on OGTT performed during their admission with ACS (Ramachandran et al. 2005). Among those attending the follow-up one to two months after discharge, the prevalence of diabetes was 19.6%. The rates of IGR were 68.5% (63/146) and 38.0% (35/92) at screening and follow-up respectively. The rates of diabetes (screening 23.8%, follow-up 17.6%) and IGR (screening 28.6%, follow-up 17.6%) in SA patients in the SWEET-Heart study are lower than in the Indian study, and as explained earlier could be due to wider availability of screening programmes in the general UK population over the recent years.

The findings of the SWEET-Heart study need to be interpreted in a broader context of an adverse association between diabetes and CHD. In Chapter Five, I have shown that the crude prevalence of known diabetes in SA patients admitted with AMI was 39.7%, compared with 16.1% in WE patients. Combining these rates of known diabetes with that of screen-detected diabetes
(SA 17.3%, WE. 3.7%) from the SWEET-Heart study, a total crude prevalence of diabetes (diagnosed and undiagnosed) in SA patients with AMI is about 57% compared with 19.8% in their WE counterparts. This strongly supports the belief that among the conventional risk factors, diabetes is a major driver behind incident CHD in SA compared with WE population (McKeigue et al. 1991, Joshi et al. 2007, Tillin et al. 2013, Tillin et al 2013, Zaman et al. 2012). As outlined in Chapter Two, section 2.8, insulin resistance and central obesity are widely thought to be the main determinants of excess diabetes risk in SA people (McKeigue et al. 1991, McKeigue et al. 1992, Tillin et al. 2013).

The important question is whether the overall excess CHD mortality seen in the British and other migrant SA populations is due to such high prevalence of diabetes in those with manifest CHD including AMI, thus leading to worse prognosis. Findings from my meta-analysis (Chapter Three) suggest that people with diabetes have 50% excess mortality post AMI. A similar finding has been reported in people diagnosed with screen-detected diabetes during admission with AMI (Lenzen et al. 2006, Arnold et al. 2014, Pararajasingam et al. 2016, Aggarwal et al. 2016). However, the MINAP study reported in Chapter Five and recent other reports (Zaman et al. 2013, Nijjar et al. 2010) surprisingly show similar or better survival post AMI in SA than WE patients, despite the much higher prevalence of diabetes in the SA patients. While the younger mean age of SA participants could be a confounding factor, equitable access to care and advances in therapies for both diabetes and CHD are pertinent to this finding. Although further longitudinal studies involving diverse SA populations with manifest CHD are certainly needed, the emerging belief is that the higher
rates of diabetes accounts for higher incidence of CHD (rather than worse prognosis following manifest CHD), in turn accounting for the observed overall excess CHD mortality in these populations (Zaman et al. 2012).

The findings of the SWEET-Heart study therefore have major implications for clinical practice and future research. Firstly, the higher prevalence of diabetes among SA patients strongly supports that screening, early detection and aggressive management of diabetes in general SA population is important to curb the higher incidence of associated CHD in this population. Efforts will be needed to increase uptake of such interventions among SA communities using innovative approaches. In the ADDITION–Leicester study, intensive multifactorial intervention significantly reduced modelled coronary risk in those with screen-detected diabetes, achieved mainly by lipid-lowering and antihypertensive therapies (Webb et al, 2012). Secondly, in SA people with established CHD such as AMI, screening for diabetes needs to be conducted universally and more proactively to allow initiation of early and aggressive interventions to reduce the burden of diabetes associated adverse outcomes in the longer term. In the retrospective study presented in Chapter Four and Five, antecedent diabetes was associated with increased univariate and multivariate short- and long-term mortality after AMI in the whole cohort and in the SA and WE groups, and this association was attenuated after inclusion of another measure of glucose metabolism – admission glucose levels as a covariate in the adjusted models. Moreover, admission glucose was independently associated with excess risk of mortality in those with as well as without known diabetes in this study cohort. It is possible that many patients in the latter group
had undiagnosed diabetes or IGR, and untreated hyperglycaemia and related metabolic abnormalities contribute to their excess mortality post AMI. Previous 

In the UK, while the current NICE guidelines (NICE 2011) recommend conducting FPG or HbA1c tests to identify ACS patients at risk of developing diabetes, it is advocated only in those with hyperglycaemia (blood glucose > 11.0 mmol/l) on admission. In light of the findings of the SWEET-Heart study including much higher prevalence of diabetes in SA patients, the current NICE recommendations need changing to adopt a policy of universal screening for diabetes and IGR in ACS. This will optimise early detection of diabetes and IGR in SA patients. Furthermore, studies looking at the prognosis of SA and WE patients found to have screen-detected diabetes at presentation, with AMI are needed to advance knowledge in this area.

Finally, the under-recruitment in the SWEET-Heart study needs further attention. Throughout the study period, I took efforts to mitigate any issues around low recruitment. Potential participants and their healthcare professionals were made aware of the SWEET-Heart study using posters, leaflets, personal communication and other valid means. The study team was made aware of the potential challenges of recruiting SA participants to any research study (Gill et al. 2009) and was advised to approach them in a
culturally sensitive manner to improve response rate. Soon after the study was commenced, a meeting with the principal investigators of various cardiology studies recruiting on the CCU (UHL) was arranged and ways to increase uptake to the SWEET-Heart study amidst parallel recruitment to other cardiology studies were discussed.

To resolve some of the issues around recruitment strategies described in section 7.5.1, decision to make substantial amendment to the protocol was made four months after the study was commenced. It took about six weeks to seek the final approval of the amendment from various regulatory authorities. This substantive amendment allowed the following important changes to the recruitment process:

i) A nurse from CCU/cardiology ward or the SWEET-Heart study team could identify and recruit patients. In the original protocol only a research doctor of registrar grade was allowed to undertake these tasks.

ii) The time allowed from invitation to consider participation in the study was reduced from 24 hours (original protocol) to six hours. This provided a greater flexibility to approach and consent patients and conduct the screening procedures within the available in-patient time window and prevented any non-participation due to an early discharge from the hospital.

iii) Interested patients who had given consent could return for the screening visit within 10 days after their discharge from the hospital if the screening was not carried out prior to discharge due to any reason. In the original protocol screening needed to be undertaken during the index admission only.
While the above measures did improve the uptake to the study, in an attempt to boost the recruitment further a decision was taken to extend the study to other centres. Almost one year after the study was commenced, two centres, the Kettering General Hospitals (KGH) and the LCH were approached. However due to the staffing issues at the KGH, the study could be extended only to the LCH. Furthermore, it took about eight months from the original decision to complete all the procedures required for extending the study and commence the recruitment at the LCH. As a result, only six weeks of the total 18 months study period was available to conduct the study at the LCH, resulting in recruitment of only six patients.

Obtaining informed consent is challenging in any research study. Consenting to a research study during life changing event of AMI (Williams et al. 2003) can be even more difficult and can affect uptake to the study. Furthermore, recruiting SA participants to a research study is known to be problematic due to various factors including cultural and communication difficulties, motivation deficiency, fatalistic attitude towards health and fear about participation in research processes (Gill et al, Douglas et al). Such problems have caused recruitment delays in other trials in the past. (Douglas et al. 2011, Hure et al). In hindsight, I feel I should have anticipated the potential recruitment issues at a much earlier stage and considered extending the study to multiple other centres in nearby areas such as Birmingham and Coventry with a high percentage of SA ethnic population. However, I also feel that the study had limited resources and monitoring parallel recruitment in multiple other centres could have been very demanding.
While my efforts to boost the recruitment were only partly successful, lessons learnt from the entire experience would be very useful for future studies in this area. In one recent study, strategies of working in partnership with SA community leaders and organisations and adopting a personalised approach to recruitment helped increase the uptake of SA participants to this community-based study (Douglas et al. 2011). Further research on identifying strategies to improve participation of SA in-patients to hospital-based studies are needed.

**7.7 Conclusions:**

Screening SA and WE patients admitted with AMI showed a much higher prevalence of undiagnosed diabetes in SA compared with WE patients. This difference was seen irrespective of the OGTT and HbA1c criteria used for the diagnosis. Rates of screen-detected IGR/high-risk state were similar for the two ethnic groups. Further large studies are needed to confirm these findings.

While I desired to examine ethnic differences in yield, concordance and reproducibility of the OGTT in comparison with HbA1c, a small number of participants in each subgroup precluded such in-depth analysis. However, I have reported such analysis involving the whole cohort in next Chapter Eight.
Figure 7.1: Patient flowchart

Patient recruited
213 (WE 191, SA 22)

Patient excluded = 3
Protocol violation 2
Withdrawal of consent 1

Patient attending screening visit
210 (WE 189, SA 21)

Reasons for non-attendance
Death 4
Refusal 47
Not required 1

Patient attending follow-up visit
163 (WE 146, SA 17)
Table 7.1: Baseline characteristics stratified by ethnicity

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All (n=210)</th>
<th>White European n=189 (90.0%)</th>
<th>South Asian n=21 (10.0%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic demography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.7 (11.5)</td>
<td>63.2 (11.5)</td>
<td>58.8 (11.1)</td>
<td>0.096</td>
</tr>
<tr>
<td>Male (%)</td>
<td>175 (83.3)</td>
<td>158 (83.6)</td>
<td>17 (81.0)</td>
<td>0.759</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.6 (17.6)</td>
<td>84.7 (17.4)</td>
<td>74.2 (16.4)</td>
<td>0.011</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.8 (5.8 )</td>
<td>29.0 (5.9)</td>
<td>26.9 (5.0)</td>
<td>0.079</td>
</tr>
<tr>
<td>Overweight#</td>
<td>96 (45.7)</td>
<td>32.0 (43.2)</td>
<td>10 (47.6)</td>
<td>0.684</td>
</tr>
<tr>
<td>Obesity##</td>
<td>78 (37.1)</td>
<td>69 (36.5)</td>
<td>9 (42.9)</td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>102 (15.0)</td>
<td>102.7 (15.1)</td>
<td>96.6 (12.8)</td>
<td>0.054</td>
</tr>
<tr>
<td>Central Obesity§</td>
<td>173 (82.8)</td>
<td>155 (82.4)</td>
<td>18 (85.7)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Prior disease &amp; risk factors (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>30 (14.3)</td>
<td>29 (15.3)</td>
<td>1 (4.8)</td>
<td>0.390</td>
</tr>
<tr>
<td>Coronary Heart Disease§§</td>
<td>52 (24.8)</td>
<td>47 (24.9)</td>
<td>5 (23.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>CVA</td>
<td>16 (7.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>90 (42.9)</td>
<td>81 (42.9)</td>
<td>9 (42.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>PVD</td>
<td>6 (2.9)</td>
<td>6 (3.2)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Current smoker</td>
<td>64 (30.5)</td>
<td>58 (31)</td>
<td>6 (28.6)</td>
<td>0.078</td>
</tr>
<tr>
<td>Ex Smoker</td>
<td>78 (37.1)</td>
<td>74 (39.6)</td>
<td>4 (19.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Prior therapies (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin/Clopidogrel</td>
<td>63 (30)</td>
<td>55 (30.1)</td>
<td>8 (39.1)</td>
<td>0.790</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>42 (20.0)</td>
<td>28 (30.1)</td>
<td>4 (19)</td>
<td>1.000</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>65 (30.7)</td>
<td>60 (31.8)</td>
<td>5 (25.8)</td>
<td>0.111</td>
</tr>
<tr>
<td>Statins</td>
<td>67 (31.9)</td>
<td>59 (31.2)</td>
<td>8 (38.1)</td>
<td>0.622</td>
</tr>
<tr>
<td>Diuretics (Loop or thiazide)</td>
<td>25 (11.9)</td>
<td>23 (12.2)</td>
<td>2 (9.5)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First degree relative with diabetes</td>
<td>46 (21.9)</td>
<td>37 (19.6)</td>
<td>9 (42.9)</td>
<td>0.055</td>
</tr>
<tr>
<td>First degree relative with CHD</td>
<td>108 (51.4)</td>
<td>96 (50.8)</td>
<td>12 (57.1)</td>
<td>-</td>
</tr>
<tr>
<td>First degree relative with CVA</td>
<td>46 (21.9)</td>
<td>44 (23.3)</td>
<td>2 (9.5)</td>
<td>0.296</td>
</tr>
<tr>
<td>First degree relative with Hypertension</td>
<td>57 (27.1)</td>
<td>48 (25.4)</td>
<td>9 (42.9)</td>
<td>-</td>
</tr>
</tbody>
</table>

All figures are mean ± SD or %

* South Asian vs. White European

# White European, BMI > 25.0 – 30 kg/m²; South Asian BMI >23.0 – 27.5 kg/m²

## White European, BMI > 30.0 kg/m²; South Asian BMI >27.5 kg/m²

§ White European, male WC ≥ 94, ≥ female, WC ≥ 80; South Asian male WC ≥ 90, female WC ≥ 80

§ § Any of angina/ myocardial infarction / percutaneous intervention (PCI)/ coronary artery bypass grafting (CABG)

CVA, Cerebrovascular accident; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PVD, Peripheral Vascular Disease; SBP, Systolic blood pressure.
Table 7.2: Characteristics of and therapies for AMI

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=210)</th>
<th>White European (n=189)</th>
<th>South Asian (n=21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics of AMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>85 (40.5)</td>
<td>74 (39.2)</td>
<td>11 (52.4)</td>
<td>0.251</td>
</tr>
<tr>
<td>Killip Class &gt;1</td>
<td>24 (11.5)</td>
<td>18 (9.6)</td>
<td>6 (28.6)</td>
<td></td>
</tr>
<tr>
<td>GRACE score at admission</td>
<td>134 (34.5)</td>
<td>133.6 (34.9)</td>
<td>138 (32.0)</td>
<td>0.562</td>
</tr>
<tr>
<td><strong>Biochemistry at admission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>14.2 (1.6)</td>
<td>14.2 (1.6)</td>
<td>14.2 (1.3)</td>
<td>0.989</td>
</tr>
<tr>
<td>White blood cells</td>
<td>10.4 (3.6)</td>
<td>10.3 (3.6)</td>
<td>11.2 (3.1)</td>
<td>0.255</td>
</tr>
<tr>
<td>Peak troponin (ng/l)</td>
<td>27274.9</td>
<td>27881.5</td>
<td>22103.1</td>
<td>0.634</td>
</tr>
<tr>
<td>(99658.8)</td>
<td>(104568)</td>
<td>(38530.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission creatinine (µmol/l)</td>
<td>85.3 (28.5)</td>
<td>85.4 (27.5)</td>
<td>84.8 (37.8)</td>
<td>0.940</td>
</tr>
<tr>
<td>Admission glucose (mmol/l)</td>
<td>6.6 (1.6)</td>
<td>6.5 (1.6)</td>
<td>7.2 (1.3)</td>
<td>0.052</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.0 (1.2)</td>
<td>4.9 (1.2)</td>
<td>5.3 (1.4)</td>
<td>0.224</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.0 (1.7)</td>
<td>1.6 (1.1)</td>
<td>3.5 (3.8)</td>
<td>0.059</td>
</tr>
<tr>
<td><strong>In-Hospital therapies (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reperfusion/Revascularisation in STEMI</td>
<td>73 (85.9)</td>
<td>62 (32.8)</td>
<td>11 (52.4)</td>
<td>0.092</td>
</tr>
<tr>
<td>Emergency coronary angiography** in NSTEMI</td>
<td>104 (83.2)</td>
<td>95 (82.6)</td>
<td>9 (90.0)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Discharge therapies (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin/ Clopidogrel/Other antiplatelet</td>
<td>200(95.2)</td>
<td>181 (96.3)</td>
<td>18 (85.7)</td>
<td>0.210</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>188 (89.5)</td>
<td>170 (90.0)</td>
<td>18 (85.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>177 (84.3)</td>
<td>161 (85.2)</td>
<td>16 (76.2)</td>
<td>0.510</td>
</tr>
<tr>
<td>Statin</td>
<td>198 (94.3)</td>
<td>178 (94.2)</td>
<td>20 (95.2)</td>
<td>0.603</td>
</tr>
</tbody>
</table>

* South Asian vs. White European
**emergency coronary angiography ± coronary intervention ((PCI or CABG)) in NSTEMI

STEMI, NSTEMI, non- ST-elevation myocardial infarction; CK, Creatinine Kinase; eGFR, estimated Glomerular filtration rate calculated by the Modification of Diet in Renal Disease (MDRD) equation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; STEMI, NSTEMI, non-ST-elevation myocardial infarction; CK, Creatinine Kinase; eGFR, estimated Glomerular filtration rate calculated by the Modification of Diet in Renal Disease (MDRD) equation; PVD, Peripheral Vascular Disease; SBP, Systolic blood pressure.
Table 7.3: Glucose (OGTT), HbA1c levels at the screening and follow-up stratified by ethnicity

<table>
<thead>
<tr>
<th>Test</th>
<th>Screening visit</th>
<th>Follow – up visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total cohort n=210</td>
<td>White European n=189 (90%)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>5.3 (0.8)</td>
<td>5.3 (0.8)</td>
</tr>
<tr>
<td>2-hour plasma glucose (mmol/l)</td>
<td>7.4 (2.6)</td>
<td>7.2 (2.4)</td>
</tr>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>40.8 (5.3)</td>
<td>40.5 (5.3)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.9 (0.4)</td>
<td>5.9 (0.4)</td>
</tr>
</tbody>
</table>

Data are mean (SD)

*South Asian versus White European.
### Table 7.4: Glycaemic categorisation using OGTT performed during admission and at follow-up post-discharge.

<table>
<thead>
<tr>
<th>Glycaemic categories</th>
<th>Screening visit</th>
<th></th>
<th></th>
<th></th>
<th>Follow-up visit</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total cohort n=210</td>
<td>White European n=189 (90%)</td>
<td>South Asian n=21 (10%)</td>
<td>p* Value</td>
<td>Total cohort n=163</td>
<td>White European n=146 (89.6%)</td>
<td>South Asian n=17 (10.4%)</td>
<td>p* Value</td>
</tr>
<tr>
<td>Normal glucose tolerance</td>
<td>125 (59.5)</td>
<td>115 (60.8)</td>
<td>10 (47.6)</td>
<td>0.251</td>
<td>126 (77.3)</td>
<td>115 (78.8)</td>
<td>11 (64.7)</td>
<td>0.222</td>
</tr>
<tr>
<td>Impaired glucose regulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired fasting glucose - IFG</td>
<td>20 (9.5)</td>
<td>18 (9.5)</td>
<td>2 (9.5)</td>
<td>1.000</td>
<td>18 (11.1)</td>
<td>16 (11.0)</td>
<td>2 (11.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Impaired glucose tolerance - IGT</td>
<td>55 (26.2)</td>
<td>51 (27.0)</td>
<td>4 (19.0)</td>
<td>0.602</td>
<td>20 (12.4)</td>
<td>17 (11.8)</td>
<td>3 (17.6)</td>
<td>0.447</td>
</tr>
<tr>
<td>IGF plus IGT</td>
<td>12 (5.7)</td>
<td>12 (6.3)</td>
<td>0 (0.0)</td>
<td>0.614</td>
<td>7 (4.4)</td>
<td>5 (.5)</td>
<td>2 (11.8)</td>
<td>0.162</td>
</tr>
<tr>
<td>Impaired glucose regulation - IGR (IFG/IGT/IFG+IGT)</td>
<td>62 (29.5)</td>
<td>56 (29.6)</td>
<td>6 (28.6)</td>
<td>1.000</td>
<td>27 (16.6)</td>
<td>24 (16.4)</td>
<td>3 (17.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes-range FPG (≥7.0 mmol/l)</td>
<td>7 (3.3)</td>
<td>7 (3.7)</td>
<td>0 (0.0)</td>
<td>1.000</td>
<td>3 (1.9)</td>
<td>2 (1.4)</td>
<td>1 (5.9)</td>
<td>0.284</td>
</tr>
<tr>
<td>Diabetes range 2hPG (≥11.1 mmol/l)</td>
<td>20 (9.5)</td>
<td>15 (7.9)</td>
<td>5 (23.8)</td>
<td>0.035</td>
<td>10 (6.2)</td>
<td>7 (4.9)</td>
<td>3 (17.6)</td>
<td>0.074</td>
</tr>
<tr>
<td>Diabetes-range FPG and 2hPG</td>
<td>4 (1.9)</td>
<td>4 (2.1)</td>
<td>0</td>
<td>1.000</td>
<td>3 (1.9)</td>
<td>2 (1.4)</td>
<td>1 (5.9)</td>
<td>0.284</td>
</tr>
<tr>
<td>Diabetes-range FPG/2hPG/FPG+2hPG</td>
<td>23 (11.0)</td>
<td>18 (9.5)</td>
<td>5 (23.8)</td>
<td>0.062</td>
<td>10 (6.2)</td>
<td>7 (4.9)</td>
<td>3 (17.6)</td>
<td>0.074</td>
</tr>
<tr>
<td>Diabetes or IGR (chronic hyperglycaemia)</td>
<td>85 (40.5)</td>
<td>74 (39.2)</td>
<td>11 (52.4)</td>
<td>0.251</td>
<td>37 (22.7)</td>
<td>31 (21.2)</td>
<td>6 (35.3)</td>
<td>0.222</td>
</tr>
</tbody>
</table>

All values are numbers (percentages). *South Asian versus White European.
Among those who attended the screening, 2-hour glucose (2hPG) values were not available in four participants.
In the follow-up group, FPG level was missing in one participant while 2hPG in another participant.
Table 7.5: Comparison of baseline characteristics of those with and without screen-detected T2DM on the OGTT, stratified by ethnicity.

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>White European n=147</th>
<th></th>
<th>South Asian n=17</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diabetes n=7</td>
<td>No Diabetes n=140</td>
<td>p* Value</td>
<td>Diabetes n=3</td>
</tr>
<tr>
<td><strong>Basic demography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.4 (13.6)</td>
<td>63.2 (10.9)</td>
<td>0.369</td>
<td>60.3 (5.2)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>6 (85.7)</td>
<td>120 (85.7)</td>
<td>1.000</td>
<td>3 (100.0)</td>
</tr>
<tr>
<td>BMI</td>
<td>37.4 (14.1)</td>
<td>28.9 (5.3)</td>
<td>0.164</td>
<td>28.5 (3.1)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>97.2 (28.8)</td>
<td>85.5 (16.8)</td>
<td>0.326</td>
<td>79.5 (12.3)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>115.0 (19.3)</td>
<td>102.5 (13.3)</td>
<td>0.019</td>
<td>100.3 (11.0)</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>121.0 (13.6)</td>
<td>120.7 (16.3)</td>
<td>0.855</td>
<td>117.0 (2.5)</td>
</tr>
<tr>
<td><strong>Prior disease and risk factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prior CHD</td>
<td>1 (14.3)</td>
<td>32 (22.9)</td>
<td>1.000</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Prior hypertension</td>
<td>3 (42.9)</td>
<td>56 (40.0)</td>
<td>1.000</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>prior CVA</td>
<td>0 (0.0)</td>
<td>10 (7.1)</td>
<td>1.000</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>current/ex-smokers</td>
<td>4 (57.1)</td>
<td>44 (31.9)</td>
<td>0.220</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td><strong>Family history in first-degree relatives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (57.1)</td>
<td>29 (20.7)</td>
<td>0.045</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>CHD</td>
<td>4 (57.1)</td>
<td>69 (49.3)</td>
<td>0.719</td>
<td>2 (66.7)</td>
</tr>
<tr>
<td>CVA</td>
<td>1 (14.3)</td>
<td>32 (22.9)</td>
<td>1.000</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (28.6%)</td>
<td>36 (25.7)</td>
<td>1.000</td>
<td>1 (33.3)</td>
</tr>
<tr>
<td><strong>Metabolic parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.9 (1.8)</td>
<td>4.9 (1.2)</td>
<td>0.087</td>
<td>5.6 (1.9)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>4.2 (0.8)</td>
<td>1.7 (1.1)</td>
<td>&lt;0.001</td>
<td>6.0 (9.0)</td>
</tr>
<tr>
<td>HDL</td>
<td>1.7 (1.1)</td>
<td>1.3 (0.5)</td>
<td>0.495</td>
<td>1.2 (0.1)</td>
</tr>
<tr>
<td>eGFR</td>
<td>72.9 (17.3)</td>
<td>77.9 (10.9)</td>
<td>0.475</td>
<td>77.7 (13.1)</td>
</tr>
<tr>
<td>Admission glucose</td>
<td>7.9 (2.0)</td>
<td>6.5 (1.6)</td>
<td>0.038</td>
<td>7.1 (1.0)</td>
</tr>
<tr>
<td>HbA1c at screening</td>
<td>50.3 (9.0)</td>
<td>40.2 (4.4)</td>
<td>0.025</td>
<td>48.7 (6.0)</td>
</tr>
<tr>
<td>FPG at screening</td>
<td>7.1 (1.0)</td>
<td>5.2 (0.6)</td>
<td>&lt;0.001</td>
<td>6.0 (0.7)</td>
</tr>
<tr>
<td>2hPG at screening</td>
<td>12.4 (2.2)</td>
<td>6.9 (2.2)</td>
<td>&lt;0.001</td>
<td>15.1 (2.5)</td>
</tr>
<tr>
<td>HbA1c at follow-up</td>
<td>52.0 (10.9)</td>
<td>38.0 (5.5)</td>
<td>0.049</td>
<td>49.3 (5.1)</td>
</tr>
<tr>
<td>FPG at follow-up</td>
<td>6.9 (0.3)</td>
<td>5.2 (0.5)</td>
<td>&lt;0.001</td>
<td>5.9 (1.2)</td>
</tr>
<tr>
<td>2hPG at follow-up</td>
<td>12.4 (1.0)</td>
<td>5.9 (1.8)</td>
<td>&lt;0.001</td>
<td>12.2 (0.5)</td>
</tr>
</tbody>
</table>

* For difference between diabetes and non-diabetes groups
Data are mean (SD) or number (percentage)
Units of various biochemistry values are as follows: Cholesterol mmol/l; Triglycerides mmol/l; HDL mmol/l; eGFR ml/mim; glucose mmol/l; HbA1c mmol/mol
Table 7.6: Glycaemic categorisation using HbA1c tests performed during admission and at follow-up post-discharge

<table>
<thead>
<tr>
<th>Glycaemic categories</th>
<th>During admission</th>
<th>Follow-up after discharge</th>
<th>p Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total cohort</td>
<td>White European</td>
<td>South Asian</td>
<td>n=189 (90%)</td>
</tr>
<tr>
<td>Normal glucose tolerance</td>
<td>118 (56.5)</td>
<td>112 (59.6)</td>
<td>6 (28.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>High risk state</td>
<td>73 (34.9)</td>
<td>61 (32.4)</td>
<td>12 (57.1)</td>
<td>0.031</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18 (8.6)</td>
<td>15 (8.0)</td>
<td>3 (14.3)</td>
<td>0.401</td>
</tr>
<tr>
<td>Diabetes or High-risk state†</td>
<td>91 (43.5)**</td>
<td>76 (40.4)</td>
<td>15 (71.4)</td>
<td>0.010</td>
</tr>
</tbody>
</table>

(HbA1c values missing in 1 and 4 participants at screening and follow-up respectively)
** HbA1c values missing in 1/210 participants; # HbA1c values missing in 4/163 participants
† High-risk state is defined as HbA1c levels between 42-47 mmol/mol (6.0 -6.4%) as per the UK Expert Committee criteria (John et al. 2012).
Chapter Eight: Potential implications of using HbA1c over the OGTT in screening for chronic hyperglycaemia in patients admitted with AMI

8.1 Chapter Overview

Chapter eight focuses on the secondary aims of the SWEET-Heart study. I oversaw the whole diabetes screening programme in this study and was in the forefront of performing the screening procedures. I interpreted the blood test results to confirm the T2DM or IGR status. I analysed the data comparing the diagnostic yield, concordance and reproducibility of the OGTT and HbA1c. I informally collected feedback from the staff and patients on the barriers to the uptake of screening for chronic hyperglycaemia in the setting of AMI. The entire process provided me with a good insight into the approach to screening for chronic hyperglycaemia and subsequent care pathway in patients admitted with AMI. Furthermore, based on my initial experience of running the SWEET-Heart study and review of the literature, I devised and published a simple strategy for screening for chronic hyperglycaemia in patients admitted with AMI. The strategy advocated the use of HbA1c as the preferred diagnostic test and restricted the use of OGTT to a small proportion of patients. In this chapter, I describe the potential impact of the use of HbA1c over OGTT in screening for diabetes and IGR in patients admitted with AMI. Furthermore, I explore various diabetes screening strategies to optimise diagnostic yield and screening uptake in the acute coronary setting.
8.2 Abstract

**Aims/Objectives:** To compare the diagnostic yield and utility of the OGTT versus HbA1c in screening for diabetes and high-risk state in patients with AMI, and suggest optimum screening strategies in the setting of AMI.

**Methods:** Analysis of 164/210 patients from the SWEET-Heart study who attended consecutive OGTT and HbA1c tests. The prevalence of confirmed cases of T2DM was established, and the concordance of cases of diabetes or IGR/high-risk detected using the OGTT and HbA1c criteria were determined. Furthermore, the sensitivity and specificity of the two different screening approaches in diagnosing diabetes were established.

**Results:** Compared with the OGTT, the HbA1c criteria identified higher proportion of people with diabetes (8.5% vs 6.0%) or IGR/high-risk state (42.1% vs 34.5%). However, the two criteria identified different groups of people as having diabetes or IGR/high-risk state with limited overlap between the groups. HbA1c misclassified about 30% cases of diabetes and 17.7% cases of IGR detected on OGTT, as having normal glucose tolerance. On universal screening, the approaches using either ‘HbA1c and limited OGTT’ or ‘HbA1c plus FPG’ correctly identified 94.4% and 83.3% of confirmed cases of T2DM respectively.

**Conclusions:** In this multi-ethnic UK cohort of patients presenting with AMI, compared with an OGTT, the use of HbA1c identified a different and higher proportion of cases with diabetes or high-risk state. I demonstrated the utility and validity of the two alternative but simple screening strategies to effectively identify people with diabetes detected on either HbA1c or the OGTT or both in this population.
8.3 Introduction and background:

In Chapter Two, section 2.6.6, and Chapter Six, section 6.3, I outlined the significance for systematically screening patients admitted with AMI for T2DM /IGR and briefly highlighted the limitations of the current screening recommendations from various organisations. In 2013, the revised European guidelines recommended universally screening everyone with CVD and using OGTT for such screening if the initial HbA1c or FPG are inconclusive (Rydén et al. 2013). However, no specific information on the timing of such screening activity following an acute CVD event such as AMI is provided. Recent Canadian guidelines recommend that patients with ACS should be screened with FPG, HbA1C or OGTT methods prior to their discharge from hospital (Tardif et al. 2013). Current French guidelines recommend performing HbA1c during admission with ACS and performing an OGTT between 7 to 28 days in those with HbA1c < 48 mmol/mol (6.5%) (Vergès et al. 2013). Of note, all the three guidelines have suggested universal screening in the population of AMI and have recommended the use of OGTT if initial HbA1c or FPG tests are inconclusive. In contrast, the NICE guidelines on the management of hyperglycaemia in ACS have advocated screening using HbA1c before discharge and FPG four days after the onset of ACS selectively in those with hyperglycaemia (blood glucose > 11.0 mmol/l) on admission with an aim to identify those at risk of progression to diabetes (NICE 2011). The NICE guidelines recommend against the routine use of OGTT in patients with ACS when FPG and HbA1c are in the normal range (NICE 2011). During the consultation stage, the NICE committee in their rebuttal argued that formal testing and diagnosis of diabetes and IGR should take place in the
community setting after an acute episode. However, clear guidance and pathway on performing subsequent testing in those with abnormal HbA1c/FPG on initial testing during admission with AMI are lacking from the NICE guidance (NICE 2011). Similarly, there are no recommendations regarding screening those without hyperglycaemia following admission with ACS. The diagnostic yield of such selective screening approach based on FPG plus HbA1c and excluding the use of an OGTT in the setting of AMI is unknown.

These differences in the screening recommendations are mainly resulting from the arguments around efficacy and practicality of using HbA1c or an OGTT on its own (Mostafa et al. 2010, Bonara et al. 2011). The proponents of the OGTT cite its superior sensitivity and greater prognostic value in predicting the outcomes post ACS (Bonora et al. 2011, Hage et al. 2013, Gyberg et al. 2015). Conversely, the OGTT is perceived as an inconvenient and unreliable test to perform during an acute admission (Knudsen et al. 2009, Eborall et al. 2012). The difficulty in complying with the requirements of optimum carbohydrate diet and physical activity levels prior to the test and physiological stress related to AMI can all affect reproducibility of the results (Hage et al 2010). An OGTT performed within 4–5 days of ACS may be less reliable, especially if there has been an extensive myocardial damage (Hage et al. 2010). In the Euro Heart Survey, the recommended OGTT was performed in only 56% of the patients with ACS or CHD, reflecting these various issues with an OGTT (Bartnik et al. 2007). The alternative test used by many clinicians on the pragmatic grounds until recently has been FPG,
and now increasingly being replaced by HbA1c alone or in combination with FPG (Arnold et al. 2014). However, FPG alone lacks sensitivity even when lower diagnostic thresholds are used, and may not detect glucose intolerance in over 40% of ACS cases (Bartnik et al. 2007). Furthermore, FPG can be affected by an epiphenomenon of stress hyperglycaemia and additionally involve inconvenience of having to fast overnight. In comparison, HbA1c has the advantage of being a simple and convenient test that can be done in the non-fasting state. HbA1c is less affected by stress-related acute changes in blood glucose levels, making it a reliable test in the acute setting. HbA1c has been shown to be a strong and independent predictor of incident T2DM, cardiovascular disease and mortality in people without diabetes and evidence is also emerging on its prognostic value in people with ACS (Norhammar et al. 2002, Selvin et al. 2010, Timmer et al. 2011, Arnold et al. 2014, Pararajasingam et al. 2016).

Therefore, an approach to screening for T2DM and IGR/high-risk state in AMI, using HbA1c as the preferred initial diagnostic test may be more appealing on pragmatic grounds (Gholap et al. 2012). In the wake of some conflicting data on diagnostic yield (Gyberg et al. 2015), and prognostic value of HbA1c (Tian et al. 2013, Lazzeri et al. 2012, Arnold et al. 2014, Pararajasingam et al. 2016, Aggarwal et al. 2016, Timmer et al. 2011) in patients with ACS, it may be prudent to use the OGTT in equivocal cases until robust evidence on the efficacy of HbA1c is available. The post-challenge hyperglycaemia may be the predominant abnormality in AMI and has a strong association with prognosis (Bartnik et al. 2007, Henareh et al. 2012). However, since the OGTT is performed infrequently in the acute
setting (Bartnik et al. 2004), an undue insistence on its use as the preferred screening test could result in poor screening uptake, offsetting any benefits gained from its superior prognostic value (Eborall et al. 2012).

The preliminary evidence suggests that using a combination of OGTT and HbA1c for screening purpose in patients presenting with AMI may have an added prognostic benefit than the use of either of these tests on their own, making a case for using such a combination in a judicious way in routine coronary practice (Pararajasingam et al. 2016). The use of an OGTT in equivocal cases is also supported by various international organisations as described earlier. On these grounds, I suggested in a published commentary, a novel algorithm which uses HbA1c as the initial test performed during admission with AMI, and limits the use of the OGTT after discharge in indeterminate cases (HbA1c between 42 and 47 mmol/mol (6.0 and 6.4%)), (Gholap 2012) (Figure 8.1).

There is now a need to gather more data on the true prevalence of chronic hyperglycaemia using the OGTT and HbA1c methods to inform development and validation of any such novel screening strategies in the setting of AMI. As per the WHO diagnostic criteria (WHO 1999 or WHO 2011) most people need to have two consecutive abnormal tests to confirm the presence of diabetes. However in majority of the studies, the reported prevalence of T2DM in AMI is based on a single test (OGTT or HbA1c) performed during index admission (Bartnik et al. 2004, Arnold et al. 2014, Gyberg et al. 2015).
The aim of this analysis was to establish the prevalence of confirmed cases of T2DM and IGR in patients admitted with AMI using either the HbA1c (WHO 2011) or OGTT (WHO 1999) or both the criteria combined and to assess the impact of using different diagnostic methods on the differential prevalence of these glycaemic disorders in a multiethnic UK population. Additionally, I aimed to compare the performance of two diabetes screening strategies in a cohort of AMI, each involving HbA1c as the initial test. The first strategy is the one described earlier in my published commentary (Gholap et al. 2012), incurring initial HbA1c test conducted during admission with AMI followed by an OGTT conducted in a selective group after discharge. The second strategy is based on the combination HbA1c plus FPG tests as suggested in the NICE guidelines (NICE 2011) but with these tests done universally in all patients rather than selectively in those with admission hyperglycaemia.

8.4 Methods:

The detailed methodology of the SWEET-Heart study including statistical methods is described in Chapter Six. The analysis presented in this Chapter is based on a total of 164/210 patients who either attended both the visits or did not need the second visit (one patient). At the first visit, the results of 2hrPG in two patients and that of HbA1c (1/164) in one patient were missing and their final glycaemic categorisation was based on the results of their follow-up tests. At the follow-up visit, test results were missing in four patients: FPG (1), 2hrPG (1) Hb1c (3); and their glycaemic categorisation
were based on the results of glucose test available from their first or the follow-up visits.

The final glucose categorisation in the study was based on the WHO 1999 OGTT criteria as detailed in Chapter Six. Cases were assigned to have IGR if the glucose abnormalities on the OGTT were present at first, follow-up or both the visits. For this analysis, the categorisation of diabetes as per the HbA1c levels is based on the WHO 2011 criteria (WHO 2011) and that of the high-risk state is based on the recommendations from a UK expert committee (John et al. 2012). Patients were considered to have a high-risk state if their HbA1c levels were between 42-47 mmol/mol (6.0 and 6.4 %) at first, follow-up or both the visits. Furthermore, patients who had HbA1c ≥48mmol/mol (≥6.5%) on the first tests but <42.0 mmol/mol (6.0%) on the second test were considered to have a high-risk state.

8.4.1 Statistical analysis.

The proportion of people found to have diabetes or IGR/high-risk state is expressed as a percentage of the total cohort. The concordance of the OGTT and the HbA1c criteria in detecting diabetes or IGR status is demonstrated using the Venn diagrams. The correlation of the results of different tests between the screening and follow-up visits is analysed using the Pearson’s correlation coefficient (r). For each screening strategy, the sensitivity, specificity values for the diagnosis of T2DM assigned by either an OGTT or HbA1c or both the methods combined were calculated. Additionally the impact of using each of the two approaches on the total volume of
subsequent tests (OGTT, HbA1c or FPG) required to identify/confirm diagnosis of T2DM was assessed.

8.5 Results:

In the total cohort of 164, the mean age of participants was 62.9 years, 85.4% were men and 10.4% were of SA ethnicity. Presentation with STEMI was seen in 38.4% patients. Prior history of AMI, any form of CHD and hypertension, was seen in 12.2%, 23.2% & 41.5% cases respectively. A total of 36% were current or ex-smokers. Family history of diabetes, CHD and hypertension were present in 25.0%, 50.0% and 26.2% of patients respectively. Mean BMI was 29.1 kg/m², and mean waist circumference 84.9 cm.

Random plasma glucose (RPG) level on admission, measured as a part of routine care was available in 135/164 (82.0%) patients. These included 9/10 with confirmed diagnosis of T2DM on the OGTT and 11/14 confirmed on HbA1c. The mean admission RPG level was 6.6 (±1.6) mmol/L, and 1/164 (0.6%) had admission blood glucose levels ≥11.0 mmol/L, 31/164 (18.9%) had levels between 7.8 And 11.0 mmol/L and 103/164 (62.8%) had levels <7.8 mmol/L. Among those with confirmed T2DM on the OGTT, one patient (10%) had RPG ≥11.0 mmol/L, 6/10 (60%) had levels between 7.0 to 8.1 mmol/L, and 2/10 (20%) had it below 6.0 mmol/L.
The median time from admission to screening was 3.0 days (range 1 to 36 days, interquartile range 4.0 days). At screening, the mean FPG was 5.3 mmol/L, mean 2 hrPG 7.4 mmol/L and mean HbA1c 40.0 mmol/mol (5.9%).

8.5.1 Diagnostic implication of using HbA1c over OGTT on the prevalence of T2DM

Table 8.1 shows the number of ‘confirmed’, ‘potentially confirmed’ and ‘maximum total’ cases of T2DM detected on either the OGTT or HbA1c or both the tests. The OGTT criteria identified 10/164 (6.1%) patients with confirmed T2DM. Two patients were found to have diabetes-range hyperglycaemia at follow-up testing only; one among them had symptoms and was confirmed to have diabetes; the other patient underwent a third OGTT which did not confirm the diagnosis of T2DM. If the WHO HbA1c criteria were applied, 14/164 (8.5%) patients would have been detected as confirmed T2DM. The total number of confirmed cases of T2DM detected using either the OGTT or the HbA1c or both the methods would have been 18/164 (11.0%).

Additionally, eight more patients were found to have HbA1c ≥48 mmol/mol on the second test only and did not have symptoms, thus requiring a third HbA1c test to confirm or reject the presence of T2DM. Overall, compared with the OGTT, the HbA1c criteria identified additional 2.5% (4/164) confirmed cases of T2DM; and the proportion of such confirmed cases of T2DM would have reached a maximum of 8.6% (12/164), if all the above-mentioned eight patients were to have HbA1c ≥48.0 mmol/mol on the third
test as well. For all practical purposes, in this analysis I assumed the total number of people potentially confirmed to have T2DM on HbA1c alone to be 22/164 (13.4%) (Table 8.1). Taking into account the possible number of T2DM cases diagnosed using either of the criteria, the maximum total number of cases of T2DM detected on the OGTT or HbA1c or both the tests would be 26/164 (15.9%) (Table 8.1).

While HbA1c detected up to 12 additional cases (120% more compared with the OGTT criteria) of T2DM, as described earlier, there was a discordance in the diagnostic results of the two tests (Figure 8.2, panel A). As seen in Figure 8.2, panel A, of the maximum 26 (15.9% of the total cohort) patients with T2DM diagnosed using either the OGTT, HbA1c or both the methods combined, only 23% (6/26, 3.7% of the total cohort) had T2DM on both the tests. Of the ten participants (6.0% of the total cohort) confirmed to have T2DM on the OGTT, 60% (6/10, 3.7% of the total cohort) had HbA1c ≥48mmol/mol. Conversely, of the 22 (13.4% of the total cohort) participants potentially confirmed to have diagnosis of T2DM on HbA1c alone, 27% (6/22, 3.7% of the total cohort) had the corresponding abnormalities on the OGTT. Thus if the HbA1c criteria alone were used for the screening purpose, 40% (4/10, 2.4% of the total cohort) patients who had T2DM on the OGTT criteria would be incorrectly classified as not having T2DM in this cohort.

8.5.2 Implications of using HbA1c versus OGTT on the prevalence of IGR/high-risk state
Using the OGTT criteria, 57/164 (34.8% of the total cohort) participants were considered as having IGR (first visit 30/164, second visit 13/164, both visits 14/164). On applying the HbA1c criteria, 69/164 (42.1% of the total cohort) participants were classed as having a high-risk state (first visit, 15/164; second visit, 24/164; and both the visits, 30/164).

Thus, compared with the OGTT, the use of HbA1c increased the absolute prevalence of IGR/high-risk state by 7.3%. Furthermore, the OGTT and HbA1c test identified different groups of people as having IGR/high-risk state with a limited overlap between the groups (Figure 8.2, panel B). As seen in Figure 8.2, panel B, of the maximum 98/164 (59.8% of the total cohort) patients with IGR/high-risk state, diagnosed using either the OGTT, HbA1c or both, only 28.6% (28/98, 17.1% of total cohort) had these glycaemic abnormalities on both the tests. Of those detected with IGR on the OGTT, only 50% (28/57, 17.1% of the total cohort) had HbA1c levels between 42 and 47 mmol/mol. Conversely, of those with the high-risk state, about 40% (28/69, 17.1% of the total cohort) had abnormal OGTT results showing IGR (Figure 8.2, panel B). The use of HbA1c only would have led to 50.9% (29/57, 17.7% of the total cohort) cases of IGR diagnosed on the OGTT being wrongly categorised as having normal glycaemic status.

8.5.3 Comparison of the reproducibility of the OGTT and HbA1c results:
On reclassifying the glycaemic status using the OGTT at follow-up, there was a significant reduction in the prevalence of chronic hyperglycaemia (T2DM and IGR). Among those (62/163, 38%) who had chronic hyperglycaemia on
the initial OGTT, less than half (27/62, 16.6% of the total cohort) were confirmed to have persistent abnormalities at follow-up. In total, 9/163 (6.1%) new cases of chronic hyperglycaemia were detected on the follow-up OGTT. There was a moderate correlation between FPG at screening and follow-up (r=0.49, p<0.001) and a strong correlation between 2hPG at screening and follow-up (r=0.65, p<0.001).

Conversely, among the 66/163 (40.5%) participants with chronic hyperglycaemia on the initial HbA1c test, more than three-quarters (51/66, 31.3% of the total cohort) had persistent abnormalities at follow-up. Furthermore, 24/163 (14.7%) new cases of high-risk state were identified at follow-up who had normal HbA1c on the initial test, suggesting a likely progression from normal to abnormal glycaemic status rather than the issues of reproducibility of the HbA1c test.

The significant reduction in the prevalence of chronic hyperglycaemia on the follow-up OGTT was however notable. The results of the OGTT performed during an acute illness such as AMI can be spurious due to factors such as altered diet, reduced physical activity levels and release of stress hormones. Similarly, prolonged interval between two OGTTs can affect the results of the second test if the person changes his/her diet, physical activity levels between the tests, thereby altering the glucose metabolism. I therefore conducted further analysis looking at the persistence of glycaemic abnormalities in relation to time to screening from the index event and time to follow-up OGTT from the screening OGTT. I mainly examined if an early
OGTT within 4 days of the index event and separately a repeat OGTT within eight weeks of the first OGTT had an effect on reproducibility of the test. Among those with chronic hyperglycaemia detected at screening (n=62), the screening OGTT was conducted within 4 days of the index event in 39/62 (63%) patients and 17/39 (43.6%) of them showed persistent hyperglycaemia at follow up. In the remaining 23/62 (37%), the screening OGTT was performed after 4 days of the index event. In this group as well, a similar 43.5% (10/23) showed persistent hyperglycaemia at follow up. Furthermore, the mean time to screening was about the same 5.04 and 5.17 days (p=0.954) in those with and without persistent chronic hyperglycaemia respectively. This indicates that the persistence of chronic hyperglycaemia at follow up may not depend upon the timing of the first OGTT after the index AMI.

A total of 39/62 (63%) patients with chronic hyperglycaemia at screening had their repeat OGTT conducted within 8 weeks of the initial OGTT and 19/39 (48.7%) of them showed persistent glycaemic abnormality on the repeat test. In comparison, in the remaining 23/62 (37%) undergoing the repeat test after eight weeks of the initial OGTT, 8/23 (34.8%) had the persistent hyperglycaemia abnormality. Furthermore, the mean time to follow-up from screening was significantly less 26.6 days in those with persistent chronic hyperglycaemia compared with 35.13 days in those without (p=0.015). This indicates that any delay in conducting the repeat OGTT might have accounted for some reduction in the prevalence of chronic hyperglycaemia at
follow-up seen in the study. However, the small sample size precludes any firm conclusions in this regard.

Furthermore, I found that among the 35/163 patients whose initial glycaemic status changed from chronic hyperglycaemia to normal glucose tolerance on the repeat OGTT, two thirds (21/35) had HbA1c ≥42 mmol/mol (at follow-up) indicating that they perhaps still had persistent chronic hyperglycaemia at follow-up (as reflected by high HbA1c) but it was not detected on the OGTT possibly due to the issue of poor reproducibility of the test. In support of this speculation, I also found that among the 10 new cases of chronic hyperglycaemia identified on OGTT at follow-up, six had HbA1c levels ≥42 mmol/mol at screening indicating they also had chronic hyperglycaemia at screening which was not detected on the first OGTT.

Additionally, among 47/210 participants who did not attend the follow-up, 23/47 (50%) had chronic hyperglycaemia, 5/23 (21.7%) had diabetes-range hyperglycaemia; 18/23 (28.3%) had IGR on the first OGTT. Thus a large number of those with chronic hyperglycaemia on the initial OGTT not attending the follow-up might have contributed to the reduction in the overall prevalence of chronic hyperglycaemia detected on the OGTT at follow-up.

8.5.4 Validity of the two different approaches to screening for chronic hyperglycaemia in patients with AMI:

8.5.4.1 The approach involving initial HbA1c plus limited OGTT

This first approach involves using HbA1c alone as an initial test and performing repeat HbA1c in those with initial HbA1c ≥48 mmol/mol (≥6.5%)
(if asymptomatic), and conducting an OGTT in those with HbA1c 42-27 mmol/mol (6 to 6.4%) as per my published algorithm (Figure 8.1). Figure 8.3 shows the spread of total ten patients confirmed to have T2DM on the OGTT across the three admission HbA1c categories: <42 mmol/mol; 42-47 mmol/mol; and ≥48. Among the 94/164 patients with HbA1c <42 mmol/mol (<6.0%), only one had T2DM confirmed as per the OGTT criteria (Figure 3), thereby indicating that the HbA1c cut-point of <42 mmol/mol (<6.0%) correctly eliminated the need for the OGTT in most patients in this category. The HbA1c cut-point of ≥48 mmol/mol (≥6.0%) precisely identified 60% (6/10) of total cases of T2DM diagnosed on OGTT in the study (Figure 8.3). If HbA1c is solely used as an initial test, 60% (6/10) of these cases of T2DM would have been still identified as T2DM on the repeat HbA1c test, further eliminating the need for an OGTT in this category. The remaining 30% (3/10) of T2DM cases would have only been detected if an OGTT was done on a third (53/164) of the total cohort who had HbA1c levels 42-48 mmol/mol (Figure 8.3).

The strategy of performing HbA1c during hospitalisation and using the cut-off of HbA1c ≥42 mmol/mol for selecting patients for further tests had 96.4% sensitivity and 67.4% specificity in correctly selecting the cases who possibly have T2DM on an OGTT and/or HbA1c combined. Furthermore, this approach (initial HbA1c and limited OGTT) captured majority (17/18, 94.4%) of the ‘confirmed’ cases of T2DM detected by an OGTT or HbA1c or both the tests, thereby having 94.4% sensitivity and 67.7% specificity in identifying confirmed cases of T2DM. This approach however missed the new eight
patients of T2DM with HbA1c ≥48.0 mmol/mol on the follow-up test only, and therefore showed a reduced sensitivity of 68% for detecting maximum total number (26/164, Table 8.1) of T2DM in the study (Figure 8.3).

On the whole, using HbA1c as an initial screening test during hospitalisation would eliminate the need for an OGTT in a significant two-thirds of the total cohort. If the remaining third of the cohort undergoes repeat testing either with an OGTT or HbA1c following discharge (Figure 8.3), it would accurately detect 90% (9/10) of the confirmed cases of T2DM as per an OGTT, and 94.4% (17/18) of the confirmed cases identified by either an OGTT or HbA1c or both.

8.5.5 The approach involving HbA1c plus FPG

This second approach partly based on the NICE recommendation involves performing HbA1c and FPG tests in all patients before discharge and then repeating the tests after discharge in only those with abnormal results (Figure 8.4). Of note, if the NICE recommendations were strictly applied, only 1/164 with hyperglycaemia on admission (RPG >11.0 mmol/L) would have qualified to undergo FPG or HbA1c test in the first instance, thereby missing T2DM diagnosis in most (90%) cases identified as having the condition. Figure 8.4 shows the spread of total ten patients confirmed to have T2DM on the OGTT across the three categories, assigned according to their HbA1c/FPG levels. Furthermore, the figure shows the proportion of people who would have been diagnosed to have T2DM under each category if HbA1c and FPG criteria were used. Firstly, on universal screening performed during hospitalisation, a
half (76/164, 46.3%) of the total study cohort had abnormal HbA1c (≥42 mmol/mol) and/or FPG (≥6.0 mmol/L) results (Figure 8.4). One of them was confirmed to have T2DM based on the symptoms (Figure 8.4) and HbA1c ≥48.0 mmol/mol. Among the 20 (12.2% of the total cohort) patients with abnormal HbA1c plus FPG results (and therefore requiring both the tests repeated), seven (4.3% of total cohort) patients were confirmed to have T2DM on the repeat tests (all on repeat HbA1c) (Table 8.4). Among the remaining 55 (33.5% of the total cohort) patients with abnormal HbA1c or FPG (and therefore requiring only one of the two tests repeated), six (3.7% of total cohort) were confirmed to have T2DM on the repeat tests (all on HbA1c) (Table 8.4). Thus a total of 14 (8.5% of total cohort) patients had confirmed T2DM using this approach combining FPG and HbA1c tests but excluding OGTT. Among these 14 patients, one had HbA1c ≥48 mmol/mol on the repeat test only and also had symptoms and was confirmed to have T2DM. Furthermore, one patient had FPG >7.0 mmol/L and eight patients had HbA1c ≥48 mmol/mol on the repeat test only, suggesting additional cases of diabetes (if as per the criteria a repeat test on a third occasion is abnormal).

Now taking into account those confirmed to have T2DM on the OGTT in the study, this approach captured 70% (7/10) and missed 30% (3/10) of cases of OGTT-confirmed T2DM from this group. However, these 30% (3/10) cases would have been still detected to have high-risk state/IGR on HbA1c/FPG tests using this approach. Furthermore, two of these three missed cases had raised FPG >7.0 mmol/L or HbA1c ≥48 mmol/mol on the initial tests.
The strategy of performing both HbA1c and FPG during hospitalisation and using the cut-off of HbA1c ≥42 mmol/mol and FPG ≥6.0 mmol/L for selecting patients for further tests had 100% sensitivity and 63% specificity in correctly selecting all the cases who possibly had T2DM on an OGTT and/or HbA1c. Furthermore, this approach (initial HbA1c plus FPG) captured 83.3% (15/18), of the ‘confirmed’ cases of T2DM and 88.5% (23/26) of the maximum number of cases of T2DM detected by an OGTT or HbA1c or both. As the subsequent tests in this approach excluded an OGTT, and used HbA1c and/or FPG, it missed 16.7% (3/18) of the confirmed cases and 11.5% (3/26) of the maximum total cases of T2DM, reducing the sensitivity of this approach in identifying all possible cases of T2DM to 88.5%.

8.6 Discussion:
The use of HbA1c in screening for T2DM and high-risk state is becoming widespread. To my knowledge, the SWEET-Heart is the first published study to demonstrate the prevalence of confirmed cases of T2DM based on the WHO requirement of two consecutive tests (OGTT or HbA1c) in a multiethnic UK cohort of AMI. I showed that applying the HbA1c criteria can increase the prevalence of confirmed cases of T2DM by over 1.5 fold, as seen in the study, from 6.0% (OGTT) to 8.5% (HbA1c). Similarly, the prevalence of high-risk state (HbA1c 42 – 47 mmol/mol) was marginally higher (42.1%) compared with the equivalent state of IGR (34.8%).

In the studies involving contemporary cohorts of AMI, the prevalence of screen-detected diabetes based on a single measurement of HbA1c has
varied from 7.0 to 17.5 %, the corresponding figures using the OGTT ranging between 14.0% and 28.0% (Arnold et al. 2014, Pararajsingam et al. 2016, Aggarwal et al. 2016, Gyberg et al. 2015). On the background of the overall low prevalence of screen-detected T2DM in the SWEET-Heart study, the findings of the SWEET-Heart study are in contrast with some of these contemporary studies. For example in the EUROASPIRE study (n= 4004), the total prevalence of screen-detected T2DM using an OGTT and HbA1c together was 28.9% (n=1158), and the OGTT identified far more 96% (n=1153) of these cases compared with 17% (n=193) using the HbA1c criteria (Gyberg et al. 2015). Similarly, in another study (n=548), the OGTT identified 27% patients with undiagnosed T2DM compared with 7% by HbA1c (Pararajsingam et al. 2016). In yet another study involving patients undergoing acute or elective angiography (n=1015), the prevalence of T2DM using a single measurement of OGTT was far higher at 14% compared with 4% using HbA1c (Doerr et al. 2011). However, an OGTT performed in the acute setting of AMI can be abnormal due to the effect of change in diet and physical activity levels and the phenomenon of stress hyperglycaemia (Hage et al. 2011) during the illness. Therefore, unless a repeat test is performed after discharge that too at the correct interval, prevalence figures based on the admission OGTT can be less reliable. In the SWEET-Heart study, the proportion of patients with an abnormal OGTT suggestive of T2DM or IGR was reduced by almost 50% following discharge with the likelihood of diagnostic OGTT being normal increasing with time taken to conduct the second test since discharge. These findings of the SWEET-Heart study, partly reflecting the effect of various factors on the reproducibility of the
OGTT highlight the need to undertake a repeat OGTT in the optimum condition before correctly making a new diagnosis of diabetes following AMI.

The conflicting results of the sensitivity of the OGTT versus HbA1c were also found in population-based studies (Mostafa et al. 2010, Christensen et al. 2010, Bonora et al. 2011). Factors such as higher mean age and a higher ethnic mix of the populations studied could explain the observed higher prevalence of chronic hyperglycaemia detected by HbA1c in these studies (Bonora et al. 2011, Herman et al. 2007, Christensen et al. 2010). Increased awareness and the widespread availability of diabetes screening programmes in Leicestershire may have also reduced the pool of people with undiagnosed diabetes identified by the OGTT method in the local population and thereby in those with incident AMI. The prevalence of T2DM and IGR/high-risk state diagnosed by the HbA1c and OGTT methods thus may vary across populations driven by the above-mentioned and yet unknown factors. These uncertainties need to be considered while choosing local diabetes screening strategies in AMI.

The other key finding is the discrepancy in the cases of T2DM and IGR identified using the two criteria. Only about a fourth of the potential total 26 (15.9%) cases of T2DM detected by the HbA1c and OGTT criteria combined had the glycaemic abnormality on both the tests and similar findings were seen with regard to IGR/high-risk state. The HbA1c cut-off ≥48mmol/mol (6.5%) misclassified 30% cases of diabetes diagnosed on the OGTT as a high-risk state in the study and further 10% were classified as having normal
glucose tolerance. Such findings have been seen universally in other studies involving patients with AMI (Gyberg et al. 2015, Pararajasingam et al. 2016) or the general population (Mostafa et al. 2010, Mohan et al 2010, Bonora et al 2011) and the reasons are unclear. According to some experts, in those with T2DM detected using the HbA1c criteria only, the HbA1c test perhaps has detected the underlying T2DM status at an earlier stage (Sattar et al. 2012). The data on the phenotype and prognosis of such patients with diabetes-range HbA1c but normal OGTT are very limited. Population-based studies suggest that people with HbA1c ≥48 mmol/mol (6.5%) were found to have a lower cardiovascular risk compared to those with T2DM detected on an OGTT (Mostafa et al. 2010), no such difference was seen in the cohort of AMI in a recent study (Pararajasingam et al. 2016). Studies robustly comparing the long-term prognosis among individuals presenting with AMI and found to have T2DM using different diagnostic methods are currently lacking. Another group of authors (Bonara et al. 2011) reported that the rise in HbA1c levels secondary to glycation of haemoglobin from chronic hyperglycaemia occurs at a later stage of T2DM, and that it could explain the findings of normal or borderline elevated HbA1c in those with T2DM detected solely by an OGTT. Furthermore, it is hypothesised that over time the different measures of glycaemia would rise together in most individuals resulting in the coalescence of the groups diagnosed with T2DM using the different measures (Sattar N. 2012).

I believe the use of HbA1c as a preferred screening test for diabetes is likely to capture a significant proportion of those with diabetes-range OGTT as
having either T2DM or a high-risk state, but a minority will be misclassified as having normal glycaemic status. If so, studies (which are currently limited) on the long-term prognosis of such patients with normal HbA1c but abnormal OGTT become pertinent. In one such recent study, those with T2DM on an OGTT but HbA1c < 48 mmol/mol (6.5%) had significantly high mortality risk during a long 9.8 years period following AMI compared with those categorised as normal/IFG/IGT on an OGTT and also having HbA1c < 48 mmol/mol (6.5%) (Pararajasingam et al. 2016). If this finding is true and replicated in future studies, it will be imperative to capture T2DM diagnosed by both the HbA1c and OGTT methods and novel and cost-effective strategies will be required to undertake the screening.

In this cohort, I therefore assessed the use of two pragmatic screening strategies in identifying patients with T2DM diagnosed using different methods. The first approach using a combination of HbA1c and limited OGTT accurately excluded 99% patients with normal glucose tolerance, identified 17/18 (94.4%) confirmed cases of previously undiagnosed T2DM (defined as per either HbA1c or OGTT criteria) and reduced the number of OGTT to a third. The other approach, avoiding the use of OGTT partly in line with the NICE recommendations, also correctly excluded all patients with normal glucose tolerance and identified 15/18 (83.3%) confirmed cases of previously undiagnosed T2DM (detected on either HbA1c or the OGTT in the study); the other three cases (16.7%) being detected as having high-risk state. The sensitivity and specificity of the first approach were not very different to the second approach mainly because the HbA1c and FPG tests were performed.
universally in all patients in the second approach. More than 80% patients diagnosed with T2DM either on HbA1c or OGTT in the study did not have significant hyperglycaemia (RPG >11.0 mmol/L) on admission, and restricting the screening tests only to those with admission hyperglycaemia as per the NICE recommendations would have missed the diagnosis of diabetes in 90% of such cases. In a recent American study, two cost-saving screening approaches based on admission RPG cut-points of either >7.8 or >10.0 mmol/L in patients admitted with AMI were assessed (Arnold et al. 2014). Those with RPG below these cut-points underwent FPG. Only those with RPG above these cut-points or FPG >7.0 mmol/L underwent further testing with Hba1c. This resulted in performing costlier HbA1c test in a limited 40 to 50% of the total study cohort, and still identified 82-86% of the total cases of T2DM (detected as per the ADA HbA1c criteria). However, the implications of these approaches (based on initial RPG levels plus limited FPG) on correctly identifying patients with T2DM diagnosed by the OGTT criteria, were not assessed in this study. Notably, half of those with Hba1c ≥48.0 mmol/mol in this study had admission RPG levels <10.0 mmol/L, a finding further highlighting the limitations of the NICE recommendations of restricting diabetes screening in AMI to only those with admission hyperglycaemia.

Emerging data suggest that the individuals with screen-detected T2DM identified using either HbA1c (Arnold 2014, Pararajasingam 2016) or OGTT (Aggarwal 2016, Pararajasingam 2016) have an adverse prognosis post AMI similar to those previously known to have diabetes, and both the groups have almost 50% higher mortality than those without diabetes. Screening and
early detection of chronic hyperglycaemia following AMI and initiation of appropriate therapies for hyperglycaemia and cardiovascular disease in those newly diagnosed with these abnormalities have the potential to improve their prognosis (Ryden et al. 2013). In order to achieve this, diabetes screening needs to be simplified to increase its uptake, and the use of either of the strategies explored in this chapter can be of benefit.

My suggestion of the specific HbA1c cut off points to limit the use of HbA1c in the first strategy (Figure 8.1) is based on pragmatic grounds, as studies in this area involving a population of AMI are limited. An international expert committee and later a UK Expert committee described the HbA1c levels between 42 and 47 mmol/mol (6.0 and 6.4%) as 'high-risk' category and the equivalent of IGR (International Expert Committee 2009). HbA1c is a continuous risk factor for mortality, as demonstrated in an epidemiological study where the majority of deaths (75%) over 6 years follow-up occurred in people without diabetes and moderately elevated HbA1c levels between 37 and 52 mmol/mol (5.5 and 6.9%) (Khaw et al. 2004). Similarly, in patients with AMI without diabetes, HbA1c levels below the diagnostic threshold of 48 mmol/mol (6.5%) demonstrate an incremental association with increased mortality (Timmer et al. 2011). However, the WHO has not recommended the use of HbA1c for diagnosis of impaired glucose regulation and an OGTT may still be required for the diagnosis of IGR (WHO 2011). Considering this background and the conflicting reports of superior prognostic value of the OGTT over HbA1c in AMI, described earlier in section 8.3, I recommended performing an OGTT post-discharge in those with HbA1c between 42 and 47
mmol/\text{mol} (6.0 and 6.4\%) for accurate categorization of glucose intolerance (Figure 8.1). Furthermore, as discussed earlier in section 8.3, my suggestion for performing the OGTT in equivocal cases is also in line with recommendations from some of the international organisations. In the first approach, in contrast to the NICE recommendations, I did not consider performing FPG in addition to HbA1c for initial screening. HbA1c alone (without FPG) is a strong predictor of undiagnosed glucose intolerance in people with ACS (Norhammar et al. 2002). Furthermore, higher HbA1c levels are associated with increased risk of developing diabetes, cardiovascular disease and mortality, independent of baseline FPG (Selvin 2010). In addition, FPG can be acutely elevated and therefore unreliable in the first 2 days of an acute event and in a large myocardial infarction (Hage et al. 2010). In the SWEET-Heart study, none of those with FPG >7.0 mmol/L on the first test had the persistent abnormality on repeat testing. The NICE guidelines have suggested that FPG testing should not be conducted within the first 4 days of the acute event. (NICE 2011). However, in the current era of early reperfusion therapies, many patients with ACS are discharged earlier than day four of admission. Moreover, the logistical benefits of using a non-fasting HbA1c test can be offset by the inconvenience of an additional fasting test, consequently affecting the screening uptake. Nevertheless, I explored the use of FPG along with HbA1c in the second algorithm. The addition of FPG to HbA1c does not significantly change the proportion of people confirmed to have T2DM mainly because of the poor reproducibility of the FPG test. My algorithm suggested in the first approach (Figure 8.1) and associated recommendations have been cited in the Canadian Diabetes
Association Clinical Practice guidelines on the management of ACS (Tardif et al. 2013).

8.7 Conclusions

Despite its high prevalence, recommendations on screening for undiagnosed chronic hyperglycaemia in people with AMI differ globally. I established that compared with the OGTT, the HbA1c criteria detected a greater number of cases of T2DM in patients with AMI drawn from a contemporary multiethnic UK population. However, relying solely on HbA1c can misclassify about 30% of T2DM cases detected on OGTT as having normal glucose tolerance. I highlighted the limitations of selective screening approach based on initial RPG recommended in the NICE guidelines and demonstrated the utility and validity of the two alternative but simple screening strategies to effectively identify most people with T2DM in this population. The main limitation of the SWEET-Heart study is its small sample size, and the findings need confirmation in a larger study and in diverse populations.
Table 8.1: Number of cases of type 2 diabetes (T2DM) detected using the OGTT and HbA1c methods

<table>
<thead>
<tr>
<th>Categories of T2DM cases</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed* cases based on the OGTT only</td>
<td>10 (6.1%)</td>
</tr>
<tr>
<td>Confirmed* cases based on HbA1c only</td>
<td>14 (8.5%)</td>
</tr>
<tr>
<td>Confirmed cases based on the OGTT or HbA1c or both</td>
<td>18 (11.0%)</td>
</tr>
<tr>
<td>Potentially confirmed** cases based on HbA1c only</td>
<td>22 (13.4%)</td>
</tr>
<tr>
<td>Maximum total number of cases based on the OGTT or HbA1c or</td>
<td>26 (15.9%)</td>
</tr>
<tr>
<td>both</td>
<td></td>
</tr>
</tbody>
</table>

*In the absence of unequivocal symptoms, two consecutive tests were performed and were abnormal

**Confirmed cases plus cases with HbA1c >48 mmol/mol (6.5%) at follow-up only requiring another test on a third occasion to confirm or reject diagnosis of diabetes
Figure 8.1: Algorithm for screening for Type 2 diabetes and impaired glucose regulation or high-risk state in patients admitted with acute myocardial infarction. (Adapted from Gholap et al. 2012)
Figure 8.2: The prevalence of maximum total number of cases of T2DM (panel A) and IGR/high-risk state (panel B) in 164 patients detected by the OGTT (1999 WHO criteria) and HbA1c (2011 WHO criteria and the UK Expert Committee criteria (high-risk state = 42-47 mmol/mol (6-6.4%)).

A: T2DM

T2DM on OGTT and HbA1c
N=6 (3.7%)

T2DM on OGTT
N=10 (6.0%)

N=4
2.4%

N=16
9.8%

N=26 (15.9%)

Total prevalence of T2DM on combined OGTT & HbA1c
B: IGR or high-risk state

IGR/high-risk state on both OGTT & HbA1c
n=28 (17.1%)

IGR/high-risk state on OGTT
N=57 (34.8%)

N=29
17.7%

N=41
25%

IGR/high-risk state on HbA1c
N=69 (42.1%)

IGR/high-risk state on combined OGTT & HbA1c
N=98 (59.8%)
Figure 8.3: The implications of using a screening approach using an initial HbA1c test performed before discharge and an HbA1c (if initial HbA1c ≥48 mmol/mol (6.5%)) or OGTT (if initial HbA1c 42-47 mmol/mol (6-6.4%)) conducted after discharge on identifying maximum total number of cases of undiagnosed T2DM.

*NbA1c at screening was missing in one patient whose follow-up HbA1c was 50 mmol/mol (6.6%).
Figure 8.4: The implications of using a screening approach using HbA1c plus fasting plasma glucose (FPG) performed prior to discharge and repeating the tests after discharge if the initials results were abnormal on identifying maximum total number of cases of undiagnosed T2DM.

*HbA1c≥42mmol/mol(6.0%), FPG≥6.0mmol/L,
# screening HbA1c not available in one patient whose follow-up HbA1c was in the diabetes range.
**Follow-up HbA1c was not available in two patients. Their screening and follow-up FPG and screening HbA1c were normal and therefore they were considered in the 'Normal' category.
~Follow-up HbA1c was missing in two patients. Of these, one had HbA1c level at screening of 52 mmol/mol (6.9%) and therefore was considered to have T2DM while the other had HbA1c 42 mmol/mol (6.0%) and was considered to have a high-risk state.
Chapter Nine: Overall summary and future directions

9.1 Chapter Overview

In this thesis, I have presented work pertinent to the prevalence and prognostic significance of glycaemic abnormalities in patients presenting with AMI with a focus on patients from a UK multiethnic community. This chapter summarises the findings and implications of studies undertaken for this thesis and describes how this work can shape future research in this area.

9.2 Introduction:

In the late 90s, as a junior doctor in internal medicine in India, I was stunned after reading reports after reports on premature and excess CHD deaths in the migrant SA population residing in Western and other countries. I also started to notice the emergence of this phenomenon among native Indians especially those living in urban India. I further witnessed several of my family members, friends, teachers and many others getting affected with premature CHD and T2DM over the years. This generated an intense desire in me to undertake research in this area and get an insight into the pathogenic connection between AMI and its risk factors including chronic hyperglycaemia in SA population.

After coming to the UK, I chose to specialise in Diabetes and Endocrinology, and during this period had a golden opportunity to undertake this PhD which led to various research projects in the subject area so close to my heart.
While significant advances have been made since 1990 in this subject, much more work is needed before a real difference could be made to the lives of millions who are at risk of CHD and chronic hyperglycaemia or who are already suffering from these conditions. The original work undertaken for this thesis and summarised below is a step in this direction.

9.3 Thesis summary and implications of its findings

Chapter Two provides a broad literature review on chronic hyperglycaemia and CHD, in particular AMI, and highlights ethnic variation in epidemiology, pathophysiology and outcomes of these disorders in the SA ethnic population. T2DM and associated complications mainly of CVD are growing at an alarming scale. The review identified SA people having a much higher prevalence of T2DM and CHD, occurring at an earlier age and being associated with premature and higher mortality. Conventional and novel risk factors related to central obesity, insulin resistance and yet unknown pathogenic mechanisms, and the risk factors associated with urban lifestyle are central to this heightened risk of CHD and T2DM in this population. AMI is a common and potentially fatal presentation of CHD. However, studies evaluating short- and long- term outcomes after AMI and its determinants in migrant SA populations are limited and show conflicting results. It is unclear whether the overall premature and high CHD mortality in SA population is due to the high prevalence of CHD or excess fatality after manifest CHD especially AMI, or both; and whether the high prevalence of diabetes in SA population plays any role in this regard. Diabetes is a major driver behind incident CHD especially AMI and acute as well chronic hyperglycaemia are
very common in patients admitted with AMI and furthermore adversely impact outcomes post AMI. However, the review highlighted that studies examining the prevalence and prognostic impact of various glucose abnormalities, both known and undiagnosed, in SA patients presenting with AMI are very limited. These data are urgently needed to help plan strategies to tackle the excess burden of CHD in the SA population.

The Chapter also discussed the current uncertainties around approach to screening for T2DM and IGR in the setting of AMI - a reflection of debate on pros and cons of using HbA1c versus glucose –based tests especially OGTT for the screening purpose in AMI. In the UK, the NICE guidelines advocates against universal screening and the routine use of the OGTT in the setting of AMI (NICE. 2011), however the effectiveness of such screening approach is less known (Gholap et al. 2012). The chapter underscored the need for simplifying screening approach in the setting of AMI, guided by data from studies involving local multiethnic UK population. The research gaps identified in this literature review formed the basis of studies undertaken for this thesis and are described in the subsequent chapters.

Chapter Three presented a large systematic review and meta-analysis of 66 cohorts of studies, robustly establishing an association between prior diabetes and long-term mortality following hospitalisation with AMI (Gholap 2016). Based on an estimated total of 202,411 deaths occurring in 714,780 patients over a median follow-up of 2.0 years (range 1 to 20) post AMI, the analysis found that compared with people without diabetes, those with
diabetes had 80% higher unadjusted risk of long-term mortality after AMI. On analysis of 23/64 trial reporting adjusted data, this mortality risk was still 50% higher in those with diabetes. The excess mortality risk was persistent at various time points up to 20 years post AMI and was seen across the subgroups of STEMI/ NSTEMI or first/recurrent AMI. The analysis of studies with recruitment before and after the year 2000 and a separate analysis of studies on patients with STEMI treated with PCI suggested that the diabetes-associated higher mortality risk was persistent despite modern therapies for AMI. These findings are very stark. Apart from the rising rates of diabetes, we are now seeing diabetes becoming more prevalent in the middle-aged and younger people especially from the SA population who as a result are suffering from associated complications of AMI at an earlier age. To mitigate the excess risk, raising awareness among clinicians and patients about the risk and effective management of both CHD and diabetes in the long-term is of paramount importance. The pathophysiology of coronary atherothrombosis leading up to an acute coronary event is different in people with diabetes and any planned acute and ongoing management need to incorporate interventions accordingly. Equally, the emphasis is needed on aggressive primary prevention of CHD in people with diabetes. Finally, research is needed to get insight into the underlying pathophysiological and care process-related mechanisms so that effective interventions could be developed to improve the prognosis after AMI. Only 2 out of 66 studies included in the meta-analysis included SA patients, highlighting the need of further studies in this population. The main limitations were inadequate consideration of confounders in the adjusted analysis reported in individual
studies, related to type, duration and therapies (insulin versus non-insulin) for diabetes; adequacy of long-term glycaemic control; and prevalence and management of admission hyperglycaemia.

Chapter Four and Five described analyses of a retrospective cohort study based on the local MINAP database (Gholap et al. 2012, Gholap et al. 2015). The analyses involved 4111 consecutive patients from WE and SA ethnic populations admitted with AMI between 1st October 2002 and 30th September 2008 at the University Hospitals of Leicestershire NHS Trust, and followed up until 30th September 2009. The aim was to examine associations of various measures of glycaemia as well as ethnicity with short- and long-term all-cause mortality following hospitalisation with AMI. Chapter Four firstly confirmed the findings previously seen in other Western population and showed that in patients with AMI drawn from a UK multiethnic population, both admission plasma glucose as well as antecedent diabetes are associated with excess mortality during in-patient stay, at 30 days and 1 year and in the longer-term beyond 1 year after index AMI (Gholap et al. 2012). Furthermore, for the first time the study demonstrated that the relative association with mortality after AMI was stronger for admission blood glucose levels, compared with prior diabetes status. The findings were consistent for subgroups of STEMI and NSTEMI and were seen in those who survived at discharge. Effective lowering of elevated glucose with an intervention in AMI has been shown to improve prognosis following AMI. The findings of the study have significant implications for management of admission hyperglycaemia in the setting of AMI, especially in those previously not
known to have diabetes, since studies report that such patients do not receive active management for high blood glucose. Raised glucose in AMI is likely to have a direct adverse influence on prognosis through various mechanisms including glucotoxicity (Ceirillo et al. 2001) and patients without known diabetes may be particularly disadvantaged (Capes et al. 2000) if their hyperglycaemia is not managed effectively. My study will help raise awareness among front-line clinicians about this issue and prompt them to proactively use interventions based on current guidelines to safely reduce elevated glucose levels in these patients. Further studies are necessary to robustly establish the benefits of active management of blood glucose in patients with all presentations of acute coronary syndrome, irrespective of diabetes diagnosis. Such studies need to address the uncertainties about glucose threshold that triggers intervention to actively lower glucose levels, the method, timing, duration, safety and feasibility of such intervention, and further the target glucose level that needs achieving (Deedwania et al. 2008, NICE. 2011). The main limitations of the study apart from those inherent in all observational retrospective cohort studies include unavailability of data on glucose-lowering therapies, the proportion of patients with undiagnosed diabetes and other potentially relevant variables which were not considered in the analysis.

Chapter Five described an additional retrospective analysis of the cohort presented in Chapter Four. This compared early and long-term prognosis after AMI in British SA and WE patients hospitalised with AMI, and furthermore investigated the differential impact of a prior diagnosis of
diabetes on their prognosis (Gholap et al. 2015). The study found that compared with WE patients, SA patients were on average five years younger (62.0 years vs. 67.3 years) and had a higher prevalence of cardiovascular risk factors including prior diabetes (39.7% vs. 16.1%). However, adjusted short- and long-term survival was similar for SA and WE patients in this multiethnic UK cohort. This was evident over the entire follow-up period and in patients surviving to 30 days, and was consistent in subgroups of patients with STEMI and NSTEMI. Previous studies have provided conflicting results with early studies (Hughes et al. 1989, Wilkinson et al. 1996) showing worse prognosis, and recent studies suggesting similar (Jones et al. 2013, Liew et al. 2006) or better (Fischbacher et al. 2007, Khan et al. 2010, Zaman et al. 2013) prognosis in SA compared with WE patients. Many of the earlier studies have important limitations including small sample size, short follow-up or inadequate adjustment for potential confounders. The analysis in my study addressed these issues and suggested that following AMI, survival is similar for SA and WE patients in the UK.

Importantly the study found no difference in the influence of prior diabetes on mortality between the SA and WE groups after adjustment for relevant covariates. Furthermore, the 2.5 fold higher prevalence of antecedent diabetes in SA patients did not adversely affect their all-cause mortality which was similar to WE patients in the study. This finding was generally in line with recent other large-scale studies (Khan et al. 2010, Zaman et al. 2013). This discrepancy between the high prevalence of diabetes and the lack of associated adverse impact on prognosis in SA patients presenting with AMI
is rather unexplained. It is likely that any mortality risk associated with the higher rates of diabetes in SA patients is mitigated by their significantly younger age at presentation with AMI. This area certainly needs further research. Overall, the findings of the study indicated that high CHD mortality in SA patients in the UK is not due to high case fatality following AMI, and therefore is likely to be due to the high incidence of CHD as seen in some of the reports (Bellary et al. 2010, Zaman et al. 2013). My study suggested that the hospital management of AMI was equally good for SA and WE patients, and implied that addressing the high prevalence of risk factors, especially diabetes through prevention, early detection and aggressive management is required to tackle premature CHD in the SA population in the UK. Migrant SA people especially those living in deprived areas show poor participation in programmes involving early detection and prevention of diabetes and CVD (Sergeant et al. 2010); the reasons could be many including health beliefs with health problems being seen as something inevitable, mismatch between actual and perceived risk, and cultural, communication, or literacy problems (Gholap et al. 2011). Research is therefore needed to identify methods of effective and cost-effective engagement of ethnic minority populations in screening and prevention and self-management programme.

Apart from the observational nature of the study and the lack of complete information on certain variables, other important limitation includes the data being from a single centre and including SA people predominantly from an Indian Gujarati community. Therefore the findings may not be entirely applicable to other SA subgroups.
Chapter Six describes the methodology of the SWEET-Heart study, a prospective cohort study in which I planned to compare the prevalence of previously undiagnosed T2DM and IGR in 441 WE and 111 SA patients hospitalised with AMI. In this study, T2DM and IGR were diagnosed using the WHO 1999 criteria and an OGTT was conducted during index admission with AMI and a repeat OGTT performed following hospital discharge. Additionally, consecutive HbA1c tests were performed to compare diagnostic validity and utility of the OGTT- and HbA1c-based criteria. Availability of consecutive OGTT as well as HbA1c results provided unique opportunities, to establish the true prevalence of T2DM as per the WHO criteria (WHO 1999, WHO 2011) and explore the validity of novel screening strategies based on HbA1c as the preferred screening test.

Chapter Seven described the clinical characteristics and rates of T2DM and IGR in 21 SA and 189 WE patients admitted with AMI. A total of 164/210 patients attended the follow-up visit after discharge to undergo a repeat OGTT, HbA1c and other procedures. While this smaller than expected sample size reduced the power of the study, the analyses of SWEET-Heart study showed some important trends helpful in planning future studies in this area. The main finding of this study was the two and half fold higher crude prevalence of undiagnosed diabetes identified mainly on the post-glucose challenge in SA patients compared with their WE counterparts (17.3% vs. 3.7%). A similar finding was seen using the WHO 2011 HbA1c criteria and on a pooled prevalence combining results of HbA1c and OGTT tests at follow-up. On adjusting for confounders such as differences in age, gender, BMI
and waist circumference between the two ethnic groups, SA patients were up to six times more likely to have undiagnosed diabetes compared with their WE counterparts, on both the OGTT and HbA1 tests. Interestingly, the prevalence of IGR and that of high-risk state (at follow-up) in the SWEET-Heart study were similar between the two ethnic groups.

If confirmed in larger studies, these findings have significant implications for clinical practice. The findings of significantly high prevalence of both known (39.7%, Chapter Five) and newly diagnosed (17.3%) diabetes in SA patients with AMI strongly support the emerging belief that undiagnosed glycaemic abnormalities are a major driver behind incident CHD in the migrant SA population, and that the resultant high incidence of CHD could be contributing to overall high CHD mortality seen in this population (Zaman et al. 2012, Zaman et al. 2013). The study findings warrant that screening, early detection and aggressive management of diabetes and prevention of those at risk in the general SA population is extremely important to curb premature and higher incidence of CHD and associated mortality in this population. Efforts need to be intensified to increase the uptake of early detection and prevention programmes among the hard-to-reach SA communities using innovation approaches.

Chapter Eight focussed on establishing the prevalence of confirmed cases of T2DM in the entire SWEET-Heart cohort based on the requirement of two consecutive tests (OGTT or HbA1c) as per the WHO criteria. Furthermore, I compared the diagnostic yield, reproducibility and utility of the OGTT versus
HbA1c in screening for T2DM and IGR/high-risk state in a local multiethnic population post AMI and suggested optimum strategies for screening for chronic hyperglycaemia in the setting of AMI.

For the first time, the SWEET-Heart study demonstrated that the prevalence of confirmed cases of T2DM, detected on systemic screening in patients presenting with AMI in the UK is much lower compared with the prevalence based on a single OGTT performed at index admission, reported in previous studies conducted elsewhere (Okosieme et al, 2008, Norhammer et al, 2002; Bartnik et al, 2004, Gyberg et al. 2015). In the SWEET-Heart study the prevalence of diabetes-range OGTT was much higher on initial test performed before discharge but then it dropped by 50% at follow-up. Thus it highlighted that an OGTT performed during the acute phase of AMI can be falsely abnormal due to various factors including the phenomenon of stress hyperglycaemia and the prevalence figures of T2DM based on such single measurements could be inaccurate and high. It further highlighted the need to repeat an OGTT in the optimum conditions and at correct interval following discharge from the hospital before confirming a new diagnosis of diabetes after AMI. Another reason behind the lower prevalence of chronic hyperglycaemia in the SWEET-Heart study compared with other studies from the Europe could be the widespread availability of diabetes screening programmes in the UK possibly reducing the pool of people with undiagnosed T2DM or IGR at the population level and thereby in those presenting with AMI.
Furthermore, the chapter showed that applying the HBA1c criteria increased the prevalence of confirmed cases of T2DM in the multiethnic study cohort by over 1.5 fold, from 6.0% (OGTT) to 8.5% (HbA1c). Furthermore, the reproducibility of HbA1c was found to be much superior to the OGTT in the SWEET-Heart study. These findings are of particular relevance since the NICE guidelines (NICE 2011) recommend use of HbA1c as the preferred screening test in the setting of AMI.

The Chapter also assessed two different pragmatic screening strategies to identify undiagnosed diabetes in patients with AMI. If one would want to use OGTT especially in SA patients who have post glucose-challenge hyperglycaemia as the main abnormality (as seen in the SWEET-Heart study), the approach using HbA1c as the preferred test and limiting the use of the OGTT after discharge to those with HbA1c between 42-47 mmol/mol seems effective and pragmatic. The other approach (which excludes the use of the OGTT) relies on using HbA1c and FPG as initial tests and repeating the tests in those with abnormal results on the first occasion. This approach also showed a reasonable sensitivity and specificity in identifying chronic hyperglycaemia. However I demonstrated that adopting the approach suggested in the NICE guidelines (NICE 2011) of restricting diabetes screening to only those with admission hyperglycaemia would miss very significant cases of previously undiagnosed T2DM. In the light of these findings, I suggested that the NICE recommendations need reviewing. Overall the study provided insights into the prevalence of T2DM and IGR/high-risk state in patients presenting with AMI in the UK and highlighted
the benefits and pitfalls of using various screening tests and strategies in identifying these glycaemic abnormalities.

9.4 Recommendations for future research

- The discrepancy between high prevalence of diabetes and the lack of its adverse impact on mortality in SA patients seen in my study described in Chapter Five warrants further research. The study involved SA people predominantly from Indian Gujarathi community. Similar studies on patients from other SA communities especially Pakistani and Bangladeshi are needed since overall CHD mortality is much higher in these communities (Anonymous 2004, Harding et al. 2008). Furthermore, such studies need to examine the influence of ethnicity, age, diabetes (including its type, duration, degree of glycaemic control and treatment) and other comorbidities on cause-specific mortality and major cardiovascular outcomes post AMI. The availability of the MINAP dataset in the UK makes it convenient to undertake such research and I look forward to collaborating with other groups in this regard.

- While the SWEET-Heart study (Chapter Seven) showed much higher prevalence of screen detected T2DM in SA patients presenting with AMI, the smaller sample size precluded any firm conclusion in this regard. There is now a need to confirm the study finding and its relevance to prognosis after AMI in much larger and multicentre studies. A meta-analysis of published and unpublished data already
existing in this area should be initially conducted and its findings should inform the design of any new study.

- The simplicity of diabetes screening using the non-fasting test of HbA1c is very appealing in the acute setting of AMI. However, further large studies are required to robustly examine the difference in the prevalence of T2DM and IGR using the OGTT and HbA1c in the high risk cohort of AMI. Importantly, the implications of identifying differing cohorts of newly diagnosed chronic hyperglycaemia using the two diagnostic methods on the outcomes following AMI need to be carefully considered, and this should inform the development any diabetes screening strategy in the setting of AMI. The long-term follow up of the SWEET-Heart cohort will provide some insight in this regard. I have already suggested two pragmatic screening approaches in Chapter Eight and assessment and validation of these approaches in larger cohorts should form part of any future studies in this area.

- Admission hyperglycaemia is a common finding in AMI and in those without chronic hyperglycaemia it could reflect underlying subtle abnormalities of glucose metabolism. Future longitudinal studies need to examine the incidence of diabetes in those with elevated glucose levels at index admission but normal glucose tolerance on formal testing. Again the follow-up of the SWEET-Heart study cohort should provide useful information in this area.

- The association between the novel risk factors related to insulin resistance, adiposity, chronic inflammation and haemostatic abnormalities and the excess CHD risk in the SA population has been
examined only in a handful of studies (Forouhi et al. 2006). The analysis of biomarker samples collected in the SWEET-Heart study will provide a unique opportunity to examine such association in presentation of AMI.

- It is now acknowledged that while intensive glycaemic control is beneficial in younger adults with newly diagnosed diabetes, it could be more harmful in frail, elderly individuals with established diabetes especially if they also have multiple comorbidities. However, knowledge about the best approach to manage newly diagnosed diabetes in patients with AMI is very limited. There is a need for RCTs to assess the benefits of intensive management of newly diagnosed diabetes in AMI on reducing adverse outcomes post AMI. The intensive arm of the RCT should assess the benefits of newer glucose-lowering agents shown to improve cardiovascular outcomes (Zinman et al. 2015, Marso et al. 2016, Saraiva et al. 2014).

- Clinical inertia in the long-term management affects patients with diabetes and CHD potentially leading to poorer outcomes (Gale et al. 2011, Norhammar et al. 2007). There is a need for RCTs assessing the benefits of integrated care models incorporating joint working between diabetes specialists and general practitioners in improving management of complex cases of diabetes and CHD.

- Primary prevention of diabetes and CHD in the SA population is of paramount importance. Poor uptake of the prevention, early detection and intervention programmes is one of the barriers to optimising diabetes and CVD risk management in this population. Studies are
required to assess the usefulness of effective inter-agency work in addressing such barriers and delivering flexible and culturally appropriate preventive care in the hard-to-reach SA communities living in the deprived areas.

I have extensively disseminated the findings in this thesis through publications in peer-reviewed journals and presentations at local, national and international meetings and conferences. A summary of the publications and conference presentations and the full text of published articles are available in Appendix Seven. The work undertaken for the SWEET-heart study has informed the design of a randomised controlled trial aimed at delivering educational intervention for people admitted with AMI and identified to have IGR on screening. I contributed to the process of developing the protocol for this study. While working for this thesis, I gained considerable expertise in the area of T2DM and CHD. This enabled me to be a member of the writing committee, updating the UK National Vascular Screening committee’s handbook on ‘Vascular risk assessment, risk reduction and risk management (UK NSC 2012). I developed and published algorithms and accompanying recommendations for screening for chronic hyperglycaemia in the general population (Gholap et al. 2013, Gholap et al. 2012) and separately in those admitted with AMI. I have reviewed a number of original articles in the subject area of glucose metabolism in AMI for major high impact journals including Circulation, Diabetologia, Diabetes Care, International Journal of Cardiology and BMJ. Furthermore, I was a co-investigator on a large cohort study examining the association of HbA1c on
mortality in people with T2DM and with or without CHD, and I co-authored an original research article resulting from this work (Khunti et al. 2012).
Appendix One: Contributions

I led all the work undertaken for the studies in the thesis, under the supervision of professors Khunti and Davies. As the first author, I led the work related to academic publications resulting from this work. This included performing the statistical analysis, writing manuscripts of all the articles, and creating tables and figures. I have already detailed my roles and responsibilities and activities performed for each study in the relevant chapters; the following section provides its summary.

Review of literature on T2DM and CHD (Chapter Two)
- Conducted focussed literature search, read abstract and full-text articles and interpreted the data.
- Wrote the Chapter and the published article.

Systematic review and meta-analysis (Chapter Three)
- Developed search terms and performed the searches
- Read abstracts and full-text articles and extracted the data
- Assembled the data in a suitable format for the meta-analysis
- Conducted basic statistical analysis related to the characteristics of the studies included in the meta-analysis.
- Wrote the Chapter and the published article

The study based on the MINAP database (Chapter Four and Five)
- Cleaned and synthesised the data in a format suitable for the survival analysis
- Learned advanced statistical methods of the imputation of missing data and survival analysis by attending lectures and courses, reading literature, and working under an expert statistician (Rajanikant L Mehta (RLM)).
- Developed the understanding of analysing mortality following AMI by studying the literature and discussion with PhD supervisors, statisticians (RLM) and cardiologist (Prof Iain Squire).
- Undertook the statistical analysis initially under supervision (RLM) (Chapter Four) and then independently with an input from a statistician (Danielle Bodicoat) (Chapter Five).
- Wrote the Chapters and the published two articles

The SWEET-Heart study (Chapter Six, Seven, Eight)
- Formulated research hypotheses, aims and objectives and study methodology
- Developed and wrote study protocol, and all other study documents
- Wrote a small grant application to obtain the support of research nurses, healthcare assistants and other recourses from the Cardiovascular Biomedical Research Unit, Leicester.
- Sought ethics and research and development approval
- Identified, approached, consented and recruited participants
- Performed various study procedures including an OGTT during the first visit.
- Led and managed the whole recruitment and the study logistics
- Communicated all the biomedical results including new diagnosis of diabetes to the participants and their GPs
- Analysed the entire data independently, interpreted the results, and wrote Chapters Six, Seven and Eight and the published ‘commentary’ article.
The details of contributions made by other key people/ collaborators are as follows:

**Key contributors:**

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<tr>
<th>Initials</th>
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<th>Role</th>
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<td>Alpa Pancholi</td>
<td>Administration</td>
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<td>BW</td>
<td>Balu Webb</td>
<td>Laboratory co-ordinator</td>
</tr>
<tr>
<td>BP</td>
<td>Bharti Patel</td>
<td>The SWEET-Heart study Nurse</td>
</tr>
<tr>
<td>CI</td>
<td>Carol Ighofose</td>
<td>Doctor</td>
</tr>
<tr>
<td>CJ</td>
<td>Cath Jones</td>
<td>Cardiology Research Health care Assistant</td>
</tr>
<tr>
<td>CW</td>
<td>Carrie Wilson</td>
<td>Research Nurse</td>
</tr>
<tr>
<td>DB</td>
<td>Danielle Bodicoat</td>
<td>Statistician</td>
</tr>
<tr>
<td>FA</td>
<td>Felix Achana</td>
<td>Statistician</td>
</tr>
<tr>
<td>GPMcC</td>
<td>Gerry McCann</td>
<td>Cardiology senior lecturer</td>
</tr>
<tr>
<td>JH</td>
<td>Joe Howe</td>
<td>Research Nurse</td>
</tr>
<tr>
<td>JH</td>
<td>Jayne Hill</td>
<td>Ethics coordinator</td>
</tr>
<tr>
<td>JW</td>
<td>Jacqueline Wayte</td>
<td>Research Nurse</td>
</tr>
<tr>
<td>IS</td>
<td>Iain Squire</td>
<td>Cardiology Professor</td>
</tr>
<tr>
<td>KK</td>
<td>Kamlesh Khunti</td>
<td>PhD supervisor</td>
</tr>
<tr>
<td>KM</td>
<td>Katrina Maxfield</td>
<td>Cardiology Research Health care Assistant</td>
</tr>
<tr>
<td>KR</td>
<td>Kausik Ray</td>
<td>Cardiologist, Imperial College, London</td>
</tr>
<tr>
<td>KP</td>
<td>Kiran Patel</td>
<td>Cardiology senior lecturer</td>
</tr>
<tr>
<td>LG</td>
<td>Laura Gray</td>
<td>Statistician</td>
</tr>
<tr>
<td>LM</td>
<td>Lynne Matthews</td>
<td>Project Nurse</td>
</tr>
<tr>
<td>LJS</td>
<td>Lee J Simmons</td>
<td>The SWEET-Heart study Nurse</td>
</tr>
<tr>
<td>LN</td>
<td>Leong Ng</td>
<td>Cardiology Professor</td>
</tr>
<tr>
<td>MLEO</td>
<td>Mary L Edmunds Otter</td>
<td>Librarian</td>
</tr>
<tr>
<td>MJD</td>
<td>Melanie Davies</td>
<td>PhD supervisor</td>
</tr>
<tr>
<td>MH</td>
<td>Mary Harrison</td>
<td>Cardiology Research Nurse</td>
</tr>
<tr>
<td>Ms</td>
<td>Marie Snell</td>
<td>Research Nurse, Lincoln County Hospital</td>
</tr>
<tr>
<td>PB</td>
<td>Paul Bray</td>
<td>Administration</td>
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<tr>
<td>RC</td>
<td>Ravikumar Chinnasamy</td>
<td>Diabetologist, Lincoln County Hospital</td>
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<tr>
<td>RL</td>
<td>Robyn Lotto</td>
<td>Cardiology Research Nurse</td>
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<tr>
<td>RLM</td>
<td>Rajnikant L Mehta</td>
<td>Statistician</td>
</tr>
<tr>
<td>RR</td>
<td>Rita Rathod</td>
<td>Administration</td>
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<tr>
<td>SM</td>
<td>Samiul Mostafa</td>
<td>Doctor</td>
</tr>
<tr>
<td>SN</td>
<td>Sineke Ndhlovu</td>
<td>Administration</td>
</tr>
<tr>
<td>NS</td>
<td>Naveed Sattar</td>
<td>Professor of Metabolic Medicine</td>
</tr>
</tbody>
</table>
Published review of literature on T2DM and CHD in the SA population: a part of Chapter Two
I, KK, MJD conceived the idea of undertaking this focused narrative review. KK, MJD, KP and NS critically reviewed the content of the first draft of the manuscript that I wrote and made valuable suggestions.

Systematic review and meta-analysis: Chapter Three
I, KK and MJD conceived the design of the study, and LG, FA and KR helped refine the methodology. MLEO helped me formulating the search terms using the keywords and MeSH. FA, CI and KK helped in independently scrutinising the abstracts and full-text articles and abstracting the data. I performed the basic statistical analysis. FA and LG performed the advanced statistical analysis with my clinical input. FA produced the Forest plots and Funnel diagram. KK, MJD, KR, FA and LG helped in interpreting the data.

The MINAP study: Chapter Four and Five
I, IS and KK conceived the idea of the study and we were responsible for the design of the study. RLM supervised me in undertaking statistical analysis presented in Chapter Four and also produced the Figure 4.2. DB provided input into an approach to the statistical analysis presented in Chapter Five. I, IBS, KK, MJD, LN, RLM and DHB contributed to the interpretation of the results.

The SWEET-Heart study: Chapter Six, Seven, Eight
KK and MJD originally conceived the idea of the study. KK, MJD, IS, GMcC reviewed the protocol and other study documents that I developed and suggested amendments where necessary. KK, MJD and JH reviewed the ethics application that I prepared and JH helped me in organising the submission of the ethics and research and development applications. Research nurses LS, JW, BP, LM, CW, JH helped me in identification, consent and recruitment of the participants and in conducting study related procedures. LS, JW, BP, LM, CW, MH, RL conducted the study procedures during the follow-up visits and were supported by the healthcare assistants KM and KJ. RC was the principle investigator and MS was the research nurse for the study at the LCH site and managed the recruitment and study visits. AP and SN provided administrative support for the study. RR and PB entered the data on spreadsheets which I analysed. I, KK and MJD contributed to the interpretation of the results.
Appendix Two: Supplementary material for Chapter Two

List of contents in this appendix:

Current criteria for diagnosing acute myocardial infarction

Previous criteria for diagnosing acute myocardial infarction

Previous definitions and classification of diabetes and IGR
<table>
<thead>
<tr>
<th>Box S2.1: Current criteria for diagnosing acute myocardial infarction (Thygesen et al. 2012)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In 2012 the Third Global MI Task Force presented the third universal definition of MI which is currently in use. This definition addresses issues related to non-specific rise in troponins from causes other than ischaemia, for example heart failure, renal failure, arrhythmia, pulmonary embolism or following cardiac intervention procedures, and can pose difficulties in diagnosing AMI.</td>
</tr>
<tr>
<td>The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:</td>
</tr>
<tr>
<td>i) Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:</td>
</tr>
<tr>
<td>o Symptoms of ischemia*.</td>
</tr>
<tr>
<td>o New/presumed new significant ST–T changes or new LBBB</td>
</tr>
<tr>
<td>o Development of pathological Q waves in the ECG.</td>
</tr>
<tr>
<td>o Imaging evidence** of new loss of viable myocardium or new regional wall motion abnormality.</td>
</tr>
<tr>
<td>o Identification of an intracoronary thrombus by angiography or autopsy.</td>
</tr>
<tr>
<td>ii) Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.</td>
</tr>
<tr>
<td>iii) Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (_5 _ 99th percentile URL) in patients with normal baseline values (&gt; 99th percentile URL) or a rise of cTn values &gt; 20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.</td>
</tr>
<tr>
<td>iv) Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.</td>
</tr>
<tr>
<td>v) Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (_10 _ 99th percentile URL) in patients with normal baseline cTn values (_99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.</td>
</tr>
</tbody>
</table>
The criteria for diagnosing prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with/without symptoms in the absence of non-ischemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause.
- Pathological findings of a prior MI.

While the above-mentioned definition of MI should be used in routine practice in developed countries, a more flexible approach in defining MI is suggested in resource-constrained developing countries where the new cardiac biomarkers or imaging techniques or even the ECG are not readily available.

* The symptoms of ischaemia mentioned in the diagnostic criteria include pain or discomfort in various areas of chest, upper extremity, mandibular or epigastric occurring on exertion or at rest. Some patients might suffer from ischemic equivalent symptoms such as dyspnea or fatigue. The symptoms of ischaemic discomfort associated with acute MI usually lasts > 20 min, diffuse in nature and can be associated with diaphoresis, nausea or syncope. The symptoms of myocardial ischaemia can be mistaken for other conditions commonly gastrointestinal, pulmonary or musculoskeletal disorders. Sometimes atypical symptoms of palpitations or even cardiac arrest can be the presenting feature of MI. In certain group of patients for example, elderly, diabetics, women, MI can present without any obvious symptoms.

**The commonly used imaging techniques for diagnosing MI based on detecting loss of viable myocardium or new regional wall abnormalities in acute and chronic infarction include: echocardiography, radionuclide ventriculography, myocardial perfusion scintigraphy (MPS) using single photon emission computed tomography (SPECT), and magnetic resonance imaging (MRI) with the positron emission tomography (PET) and X-ray computed tomography (CT) being other less commonly used modalities.

Previous definitions of acute myocardial infarction

1959, World health organisation (WHO) criteria for diagnosis of AMI: typical symptoms of ischaemic cardiac chest pain and serial ECG changes of myocardial infarction.

1970, the case definition of AMI used in international collaborative projects: typical clinical history, ECG changes, cardiac enzymes elevation and post-mortem findings where relevant.

1979, the above definition further revised in a joint report with the International Society and Federation of Cardiology. Development of Minnesota coding to evaluate the ECG changes and explicit coding rules for evaluation of symptoms and cardiac enzymes in defining an episode of AMI.

2000, the First Global MI Task Force presented a new definition of MI.

2007 the above definition revised by the Second Global Task Force, forming the Universal Definition of Myocardial Infarction Consensus Document. The new definition considered any necrosis resulting from myocardial ischaemia as MI and pointed out the conditions causing MI. This document is endorsed by the European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the World Heart Federation (WHF), and adopted by the WHO.
Table S2.1: Previous WHO Classifications and diagnostic criteria for diabetes and intermediate hyperglycaemia

<table>
<thead>
<tr>
<th>Year</th>
<th>Classification</th>
<th>Diagnostic Tests</th>
<th>Diagnostic Criteria: Diabetes</th>
<th>Diagnostic Criteria: Impaired glucose tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td><strong>Diabetes mellitus</strong>&lt;br&gt;Insulin dependent type – Type 1&lt;br&gt;Non Insulin dependent type – Type 2&lt;br&gt;(a) Non-Obese&lt;br&gt;(b) Obese&lt;br&gt;Other types including diabetes associated with certain conditions and syndromes&lt;br&gt;&lt;br&gt;<strong>Impaired glucose tolerance</strong>&lt;br&gt;(a) Non-Obese&lt;br&gt;(b) Obese&lt;br&gt;(c) IGT associated with certain conditions and syndromes&lt;br&gt;&lt;br&gt;<strong>Gestational diabetes mellitus</strong></td>
<td>Random plasma glucose</td>
<td>≥ 11.1 mmol/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fasting plasma glucose**</td>
<td>≥8.0 mmol/l</td>
<td>≥6.0 to &lt;8.0 mmol/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral glucose tolerance test</td>
<td>2-hour plasma glucose ≥11.1 mmol/l</td>
<td>≥8.0 mmol/l to &lt;11.0 mmol/l</td>
</tr>
<tr>
<td>1985</td>
<td><strong>Diabetes mellitus</strong>&lt;br&gt;Insulin-dependent diabetes mellitus – IDDM&lt;br&gt;Non-Insulin dependent diabetes mellitus – NIDDM&lt;br&gt;(a) Non-Obese&lt;br&gt;(b) Obese&lt;br&gt;Malnutrition-related diabetes mellitus - MRDM&lt;br&gt;Other type of diabetes associated with certain conditions and syndromes&lt;br&gt;&lt;br&gt;<strong>Impaired glucose tolerance</strong>&lt;br&gt;(a) Non-Obese&lt;br&gt;(b) Obese&lt;br&gt;(c) associated with certain conditions and syndromes&lt;br&gt;&lt;br&gt;<strong>Gestational diabetes mellitus</strong></td>
<td>Random plasma glucose</td>
<td>≥ 11.1 mmol/l</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fasting plasma glucose</td>
<td>≥7.8 mmol/l</td>
<td>≥6.0 to &lt;7.8 mmol/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral glucose tolerance test</td>
<td>2-hour plasma glucose ≥11.1 mmol/l</td>
<td>2-hour plasma glucose ≥ 7.8 mmol/l and &lt; 11.1 mmol/l</td>
</tr>
</tbody>
</table>
Appendix Three: Supplementary material for Chapter Three

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Box S3.1: The USPSTF Quality Rating Criteria for the RCTs and cohort studies

Figure S3.1 Early survivors, unadjusted analysis

Figure S3.2 Early survivors, subgroup analysis
Supplementary Methods 3.1:

The WinBUGS code used to fit the analysis

```wren
model{

for(i in 1:64){
  tmp1[i] <- id[i]
  tmp2[i] <- ami_type[i]
  tmp3[i] <- f_am[i]
  tmp4[i] <- stem[i]
  tmp5[i] <- recruit[i]
  tmp6[i] <- study_type[i]
  cov[i] <- ami_type[i] # define covariate for meta-regression and sub-group analysis
  delta[i,1] <- 0 # treatment effect is zero for non-diabetes group set to zero
  mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines

  for(k in 1:2){
    r[i,k] ~ dbin(p[i,k],n[i,k]) # Binomial likelihood
    cloglog(p[i,k]) <- log(fup[i])+ mu[i] + delta[i,k] # model
  }
}

# RE MA Model
for(k in 2:2){
  delta[i,k] ~ dnorm(md[i,k],tau)
  md[i,k] <- d[t[i,k]] - d[t[i,1]] + beta[cov[i]]
}
}

d.new ~ dnorm(d[2],tau) # predicted effect in new study

totresdev <- sum(resdev[]) # total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
beta[1]<-0
d[2] ~ dnorm(0,.0001)
rr[1] <- exp(d[2]) # pooled risk ratio for group 1
for(i in 2:3) {
  beta[i] ~ dnorm(0,0.0001)
  rr[i] <- exp(d[2]+beta[i]) # pooled risk ratio for group 2 and 3
  exp.beta[i] <- exp(beta[i]) # interaction term/ratio of rr
  pvalue[i] <- step(beta[i])-1 # 1-sided Bayesian pvalue
}

sd ~ dunif(0,2) # vague prior for between-trial SD

tau <- pow(sd,.2) # between-trial precision
}
```
Supplementary Results

Supplementary Results 3.1:
Fifteen studies did not report outcome data in a format suitable for inclusion in the meta-analysis. These studies did not report the actual event data such as the number of deaths in those with and without diabetes, or the risk estimates such as hazard ratios. In 12/15 studies (Ishihara et al. 2007, De Luca et al. 2013, Granger et al. 1993, Orlander et al. 1994, Ishihara et al. 2001, Kvan et al. 2007, Ouhoummane et al. 2009, De Luca et al. 2010, Claessen et al. 2010, Kahn et al. 2012, Nauta et al. 2012, Patel et al. 2016), Kaplan-Meier survival curves were published and we derived the event data from these curves using a digitization strategy reported by Guyot and colleagues (Guyot et al. 2012). For the remaining three studies, data were derived either from the percentages reported in the bar charts (Wahab et al. 2002), or from age-adjusted mortality rates (Svensson et al. 2007), or by combining percentages reported for multiple groups (Hsu et al. 2007).

Supplementary Results 3.2:
Diabetes and Long-term mortality in early survivors
To eliminate any bias related to the difference in early case fatalities between the diabetes subgroups, we analysed long-term mortality in those who survived to discharge or the first 30 days post AMI. In 42/64 studies (Table S3.2) the actual event data on long-term mortality in such early survivors were available. For the meta-analysis of these 42/64 studies reporting the outcome of long-term mortality in early survivors, risk ratios were calculated using the reported event data. The time-dependent risk ratios were then log transformed and pooled across the 42 studies using the Bayesian random effects meta-analysis to generate summary hazard ratios (HR) and credible intervals (CrI). There was evidence from the meta-analysis of these 42/64 studies that long-term mortality was significantly higher in people with diabetes compared with those without (unadjusted HR 1.82, (95% CrI 1.70, 1.95)) (Figure S3.1). The Bayesian predictive effect in a new study was HR 1.82 (95% CrI 1.28, 2.59), suggesting that mortality remained significantly higher in those with diabetes than those without even after taking into count the heterogeneity in effect sizes across the studies.

Figure S3.2 displays the results of the subgroup analysis. Since none of the 42/64 studies had reported outcome data for NSTEMI, people with STEMI were compared with those with both STEMI/NSTEMI. Within the cohort of early survivors, the adverse effect of diabetes was seen to be generally similar across the phenotypes of AMI, first AMI, cohort or RCTs and different era (all p for interactions >0.1). Furthermore, the estimates of between study standard deviation parameter, τ on the log hazard ratio scale were 0.22 (95 CI 0.15 to 0.31) (unadjusted data) indicating minimal to moderate degree of variance in the hazard ratio. In further analysis of this cohort, excluding 12/41 studies that did not report outcome data in the suitable format (Ishihara et al. 2007, Granger et al. 1993, Orlander et al. 1994, Ishihara et al. 2001, Kvan et al. 2007, Ouhoummane et al. 2009, Kahn et al. 2012, Nauta et al. 2012, Patel et al. 2016, Wahab et al. 2002, Svensson et al. 2007, and Hsu et al. 2007) there was no difference in the findings of association between diabetes and long-term mortality (unadjusted HR 1.78 (1.66, 1.91)) (Table S3.4).
Table S3.1: MEDLINE search strategy

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>diabetes mellitus/ or exp diabetes mellitus, type 2/ or prediabetic state/ or exp hyperglycemia/</td>
<td>202286</td>
</tr>
<tr>
<td></td>
<td>(diabetes mellitus or type 2 diabetes or type II diabetes or hyperglycaemia or hyperglycemia or glucose intolerance or NIDDM or non-insulin dependent diabetes mellitus or prediabetic state).ti,ab.</td>
<td>208655</td>
</tr>
<tr>
<td>2</td>
<td>(impaired glucose tolerance or abnormal glucose regulation or impaired glucose regulation or dysglycaemia or dysglycemia or impaired fasting glucose).ti,ab.</td>
<td>3665</td>
</tr>
<tr>
<td>3</td>
<td>1 OR 2 OR 3 diabetes mellitus/ or exp diabetes mellitus, type 2/ or prediabetic state/ or exp hyperglycemia/ or (diabetes mellitus or type 2 diabetes or type II diabetes or hyperglycaemia or hyperglycemia or glucose intolerance or NIDDM or non-insulin dependent diabetes mellitus or prediabetic state).ti,ab.or (impaired glucose tolerance or abnormal glucose regulation or impaired glucose regulation or dysglycaemia or dysglycemia or impaired fasting glucose).ti, ab.</td>
<td>307875</td>
</tr>
<tr>
<td>4</td>
<td>acute coronary syndrome/ or exp myocardial infarction/</td>
<td>159077</td>
</tr>
<tr>
<td></td>
<td>(acute coronary syndrome or myocardial infarction or MI).ti,ab.</td>
<td>43028</td>
</tr>
<tr>
<td>5</td>
<td>5 OR 6 acute coronary syndrome/ or exp myocardial infarction/ OR (acute coronary syndrome or myocardial infarction or MI).ti,ab.</td>
<td>180459</td>
</tr>
<tr>
<td>6</td>
<td>4 AND 7 diabetes mellitus/ or exp diabetes mellitus, type 2/ or prediabetic state/ or exp hyperglycemia/ or (diabetes mellitus or type 2 diabetes or type II diabetes or hyperglycaemia or hyperglycemia or glucose intolerance or NIDDM or non-insulin dependent diabetes mellitus or prediabetic state).ti,ab.or (impaired glucose tolerance or abnormal glucose regulation or impaired glucose regulation or dysglycaemia or dysglycemia or impaired fasting glucose).ti, ab. AND acute coronary syndrome/ or exp myocardial infarction/ or (acute coronary syndrome or myocardial infarction or MI).ti,ab.</td>
<td>6647</td>
</tr>
<tr>
<td>7</td>
<td>exp morbidity/ or incidence/ or exp mortality/</td>
<td>659966</td>
</tr>
<tr>
<td>8</td>
<td>follow up studies.sh. or (prognos$ or predict$ or course$).tw. or outcome$.ti.</td>
<td>2270871</td>
</tr>
<tr>
<td>9</td>
<td>9 OR 10 exp morbidity/ or incidence/ or exp mortality/ OR follow up studies.sh. or (prognos$ or predict$ or course$).tw. or outcome$.ti.</td>
<td>2746020</td>
</tr>
</tbody>
</table>
Table S3.1: MEDLINE search strategy (continued)

<table>
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<th>#</th>
<th>Searches</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>AND 11 diabetes mellitus/ or exp diabetes mellitus, type 2/ or prediabetic state/ or exp hyperglycemia/ or (diabetes mellitus or type 2 diabetes or type II diabetes or hyperglycaemia or hyperglycemia or glucose intolerance or NIDDM or non-insulin dependent diabetes mellitus or prediabetic state).ti, ab.or (impaired glucose tolerance or abnormal glucose regulation or impaired glucose regulation or dysglycaemia or dysglycemia or impaired fasting glucose).ti, ab. AND acute coronary syndrome/ or exp myocardial infarction/ or (acute coronary syndrome or myocardial infarction or MI).ti,ab. AND exp morbidity/ or incidence/ or exp mortality/ OR follow-up studies.sh. or (prognos$ or predict$ or course$).tw. or outcome$.ti.</td>
<td>3380</td>
</tr>
<tr>
<td>12</td>
<td>exp Blood Glucose/</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>(admission hyperglycaemia or admission blood glucose or euglycaemia or elevated blood glucose or stress hyperglycaemia).ti,ab.</td>
<td>134622</td>
</tr>
<tr>
<td>14</td>
<td>13 OR 14</td>
<td>1428</td>
</tr>
<tr>
<td>15</td>
<td>exp Blood Glucose/ OR (admission hyperglycaemia or admission blood glucose or euglycaemia or elevated blood glucose or stress hyperglycaemia).ti, ab.</td>
<td>135304</td>
</tr>
<tr>
<td>11 AND 17</td>
<td>exp morbidity/ or incidence/ or exp mortality/ OR follow-up studies.sh. or (prognos$ or predict$ or course$).tw. or outcome$.ti. AND acute coronary syndrome/ or exp myocardial infarction/ OR (acute coronary syndrome or myocardial infarction or MI).ti,ab AND diabetes mellitus/ or exp diabetes mellitus, type 2/ or prediabetic state/ or exp hyperglycemia/ or (diabetes mellitus or type 2 diabetes or type II diabetes or hyperglycaemia or hyperglycemia or glucose intolerance or NIDDM or non-insulin dependent diabetes mellitus or prediabetic state).ti,ab.or (impaired glucose tolerance or abnormal glucose regulation or impaired glucose regulation or dysglycaemia or dysglycemia or impaired fasting glucose).ti, ab. OR exp Blood Glucose/ OR (admission hyperglycaemia or admission blood glucose or euglycaemia or elevated blood glucose or stress hyperglycaemia).ti, ab.</td>
<td>3581</td>
</tr>
<tr>
<td>18</td>
<td>limit 18 to (humans and &quot;all adult (19 plus years)&quot;)</td>
<td>3039</td>
</tr>
</tbody>
</table>
Table S3.2: Baseline characteristics of the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study design/year of baseline data collection/Location</th>
<th>Setting including AMI phenotype (%)<em>; and reperfusion (% in the whole cohort or in DM/No DM)</em></th>
<th>No of patients</th>
<th>Mean age (y)</th>
<th>Female (%)</th>
<th>Follow-up (y)</th>
<th>Number of deaths</th>
<th>Hazard ratio/Odds ratio (95% CI) †</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granger et al. 1993 ‡</td>
<td>RCT (TAMI) 1985 – 1989 USA</td>
<td>AMI in &lt;75 y old; randomised to thrombolysis or angioplasty</td>
<td>148/ 923</td>
<td>59/56.</td>
<td>26/19</td>
<td>5</td>
<td>31/138</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Orlander et al. 1994 ‡</td>
<td>Retrospective (CCHP) 1988-1990 USA</td>
<td>AMI in 25-74 y old; cardiac catheterisation at admission 45/56</td>
<td>523/676</td>
<td>62/60</td>
<td>NA</td>
<td>3.6</td>
<td>196/158</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Abbud et al. 1995 ‡</td>
<td>Retrospective (MIDAS) 1986-1987 USA</td>
<td>AMI in 11 – 99 y old</td>
<td>9695/32900</td>
<td>NA</td>
<td>49/41</td>
<td>3</td>
<td>4572/12446</td>
<td>1.24 (1.20, 1.27)</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Herliz et al. 1996 ‡</td>
<td>Retrospective 1986-1987 Sweden</td>
<td>AMI; Thrombolysis in 4% of the whole cohort</td>
<td>97/761</td>
<td>NA</td>
<td>39/32</td>
<td>5</td>
<td>69/369</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Mak et al. 1997 ‡</td>
<td>RCT (GUSTO-I) 1990-1993 UK</td>
<td>STEMI; randomised to streptokinase ± heparin and/or t-PA</td>
<td>5944/34888</td>
<td>64/61</td>
<td>35/23</td>
<td>1</td>
<td>861/3105</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
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<tr>
<td>Miettinen et al. 1998 ‡</td>
<td>Prospective 1988-1992 Finland</td>
<td>First AMI in 25-64 y old; thrombolysis</td>
<td>475/2760</td>
<td>57/56</td>
<td>34/24</td>
<td>1</td>
<td>123/357</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
</tbody>
</table>
Table S3.2: Baseline characteristics of the studies included in the meta-analysis (continued)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study design/year of baseline data collection/Location</th>
<th>Setting including AMI phenotype (%)<em>; and reperfusion (%)</em> in the whole cohort Or in DM/No DM*</th>
<th>No of patients DM/No DM</th>
<th>Mean age (y) DM/No DM</th>
<th>Female (%) DM/No DM</th>
<th>Follow-up (y)</th>
<th>Number of deaths DM/No DM</th>
<th>Hazard ratio/ Odds ratio (95% CI)†</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gowda et al. 1998</td>
<td>Prospective 1992-1996 USA</td>
<td>Non-Q wave AMI treated with PCI without stent</td>
<td>77/299</td>
<td>64/61</td>
<td>40/23</td>
<td>1</td>
<td>7/19</td>
<td>1.4 (0.58,3.43)</td>
<td>Age, gender, DM, hypertension, smoking, hypercholesterolemia, DM therapies, FH of CHD, poor LV function, AMI location, number of diseased vessels, PCI, CABG</td>
<td>Fair</td>
</tr>
<tr>
<td>Waldecker et al. 1999 ‡</td>
<td>Prospective 1990-1996 Germany</td>
<td>STEMI treated with primary PCI</td>
<td>54/358</td>
<td>66/61</td>
<td>54/28</td>
<td>3</td>
<td>18/43</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Löwel et al. 2000 ‡</td>
<td>Prospective 1985 – 1992 Germany</td>
<td>Q wave AMI in 25-74 y old; thrombolysis 21/31</td>
<td>468/1742</td>
<td>64/61</td>
<td>39/22</td>
<td>5</td>
<td>202/396</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Hasdai et al. 2000 ‡</td>
<td>RCT (GUSTO-IIb) 1994-1996 Europe, USA, Australia</td>
<td>STEMI randomised to primary PCI or accelerated alteplase.</td>
<td>177/961</td>
<td>65/62</td>
<td>23/21</td>
<td>1</td>
<td>23/86</td>
<td>1.34 § (0.78,2.31)</td>
<td>Age, sex, Wt, Ht, systolic BP, HR, Hypertension, PVD, time from symptom onset to arrival/randomization/treatment, time from symptom onset to treatment</td>
<td>Fair</td>
</tr>
<tr>
<td>Ishihara et al. 2001 ‡</td>
<td>Retrospective 1981-1999 Japan</td>
<td>AMI, coronary angiography undertaken within 24 hrs of admission; reperfusion 93/93</td>
<td>378/1282</td>
<td>61/61</td>
<td>23/19</td>
<td>10</td>
<td>173/449</td>
<td>1.43 (1.12,1.78)</td>
<td>Age, gender, hypertension, hypercholesterolemia, smoking, prior AMI, Killip class, time to PCI, initial vessel patency, collateral circulation, final coronary reperfusion.</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Table S3.2: Baseline characteristics of the studies included in the meta-analysis (continued)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study design/Year of baseline data collection/Loc</th>
<th>Setting including AMI phenotype (%)<em>; and reperfusion (%) in the whole cohort or in DM/No DM</em></th>
<th>No of patients DM/No DM</th>
<th>Mean age (y) DM/No DM</th>
<th>Female (%) DM/No DM</th>
<th>Follow-up (y)</th>
<th>Number of deaths DM/No DM</th>
<th>Hazard ratio/Odds ratio (95% CI) †</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mukamal et al. 2001</td>
<td>Prospective 1989-1994 USA</td>
<td>AMI; thrombolysis 28/38</td>
<td>399/1536</td>
<td>65/61</td>
<td>41/28</td>
<td>3.7</td>
<td>116/204</td>
<td>1.7 (1.3,3.1)</td>
<td>Age, gender, previous disease (AMI, angina, hypertension), prior medications, smoking, thrombolysis, educational status, CCF, household income, the frequency of exertion</td>
<td>Fair</td>
</tr>
<tr>
<td>Mattos et al. 2001</td>
<td>RCT (STENT-PAMI) Multinational</td>
<td>STEMI, randomised to primary PCI with or without stent</td>
<td>135/758</td>
<td>64/59</td>
<td>37/23</td>
<td>1</td>
<td>6/33</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>De Gevigney et al. 2002‡</td>
<td>Prospective 1993-1995 France</td>
<td>AMI; thrombolysis 31/36</td>
<td>410/1887</td>
<td>70/68</td>
<td>40/30</td>
<td>1.0</td>
<td>127/415</td>
<td>1.4 (1.1,1.8)</td>
<td>Age, gender, SE status, prior disease (AMI or angina, hypertension), smoking, Killip class, Q-wave anterior MI, non-Q wave MI, maximum CK level, re-infarction during the first 3 months</td>
<td>Fair</td>
</tr>
<tr>
<td>Wahab et al. 2002‡</td>
<td>Prospective 1997-1998 Canada</td>
<td>AMI; thrombolysis 27/36, PCI 6/12</td>
<td>451/1213</td>
<td>68/67</td>
<td>41/35</td>
<td>1</td>
<td>106/159</td>
<td>NA</td>
<td>NA</td>
<td></td>
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<tr>
<td>Jonas et al. 2003‡</td>
<td>Prospective 1992-1994 Israel</td>
<td>AMI; thrombolysis 67/68, primary PCI 4/4</td>
<td>1093/3224</td>
<td>65/63</td>
<td>35/23</td>
<td>1</td>
<td>267/432</td>
<td>NA</td>
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</tr>
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</table>
Table S3.2: Baseline characteristics of the studies included in the meta-analysis (continued)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study design/year of baseline data collection/Location</th>
<th>Setting including AMI phenotype (%)<em>; and reperfusion (%) in the whole cohort Or in DM/No DM</em></th>
<th>No of patients DM/No DM</th>
<th>Mean age (y) DM/No DM</th>
<th>Female (%) DM / No DM</th>
<th>Follow-up (y)</th>
<th>Number of deaths DM/No DM</th>
<th>Hazard ratio/ Odds ratio (95% CI) †</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alter et al. 2003 ‡</td>
<td>Retrospective 1992-1993 Canada</td>
<td>AMI</td>
<td>6052/19645</td>
<td>68/66</td>
<td>41/33</td>
<td>5</td>
<td>3340/7131</td>
<td>1.57 (1.50,1.63)</td>
<td>Age, gender, SE status, illness severity, attending physician and hospital characteristics. Secondary analysis in age &gt; 65, additional adjustments for evidence-based therapies, revascularization procedures and outpatient follow-up</td>
<td>Fair</td>
</tr>
<tr>
<td>Stranders et al. 2004 ‡</td>
<td>Retrospective 1989-1996 Netherlands</td>
<td>AMI; thrombolysis 48/57, primary PCI 3/2</td>
<td>109/737</td>
<td>68/64</td>
<td>38/29</td>
<td>4.1</td>
<td>47/208</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Gurm et al. 2004 ‡</td>
<td>RCT (GUSTO-V) 1999-2001 Multinational</td>
<td>STEMI, randomised to fibrinolytic or combination of reduced fibrinolytic plus platelet GPIIb/IIIa inhibition</td>
<td>2633/13782</td>
<td>64/61</td>
<td>33/23</td>
<td>1</td>
<td>334/1027</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Madsen et al. 2005</td>
<td>RCT 1997 – 2001 Denmark</td>
<td>STEMI randomised to primary PCI or thrombolysis</td>
<td>113/1455</td>
<td>64/63</td>
<td>29/26</td>
<td>3.8</td>
<td>27/194</td>
<td>NA</td>
<td>NA</td>
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Table S3.2: Baseline characteristics of the studies included in the meta-analysis (continued)

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<tr>
<th>Author/Year</th>
<th>Study design/Year of baseline data collection/Location</th>
<th>Setting including AMI phenotype (%)<em>; and reperfusion (%) in the whole cohort Or in DM/No DM</em></th>
<th>No of patients DM/No DM</th>
<th>Mean age (y) DM/No DM</th>
<th>Female (%) DM/No DM</th>
<th>Follow-up (y)</th>
<th>Number of deaths DM/No DM</th>
<th>Hazard ratio/Odds ratio (95% CI)†</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kosiborod et al. 2005 ‡</td>
<td>Retrospective 1994-1996 USA</td>
<td>AMI in &gt;65 y old; STEMI 29; thrombolysis 18, PCI 10</td>
<td>43070/98610</td>
<td>NA</td>
<td>NA</td>
<td>1</td>
<td>15998/30837</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
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<tr>
<td>Stuckey et al. 2005 ‡</td>
<td>RCT (CADILLAC) 1997 – 1999 USA</td>
<td>STEMI randomised to primary PCI with or without abciximab</td>
<td>346/1736</td>
<td>59</td>
<td>25</td>
<td>1</td>
<td>21/68</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Gandhi et al. 2006 ‡</td>
<td>Retrospective 1979 – 1998 USA</td>
<td>AMI; reperfusion 23/29</td>
<td>364/1807</td>
<td>70/67</td>
<td>55/41</td>
<td>5</td>
<td>262/917</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Schiele et al. 2006</td>
<td>Prospective 2000 – 2001 France</td>
<td>AMI; STEMI 44; reperfusion (STEMI) 44/78</td>
<td>175/549</td>
<td>70/68</td>
<td>38/33</td>
<td>1</td>
<td>29/53</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Svensson et al. 2007 ‡</td>
<td>Retrospective 1990-1991; 1995-1996 Sweden USA</td>
<td>AMI in 30 – 74 y old; thrombolysis 28/24</td>
<td>734/3090</td>
<td>63/61</td>
<td>46/34</td>
<td>7</td>
<td>356/803</td>
<td>2.11 (1.80,2.46)</td>
<td>Age, sex, smoking habits, prior disease (AMI, hypertension, angina), prior revascularisation</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Table S3.2: Baseline characteristics of the studies included in the meta-analysis (continued)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study design/Year of baseline data collection/Location</th>
<th>Setting including AMI phenotype (%)‡; and reperfusion (%) in the whole cohort Or in DM/No DM*</th>
<th>No of patients DM/ No DM</th>
<th>Mean age (y) DM/ No DM</th>
<th>Female (%) DM/ No DM</th>
<th>Follow-up (y)</th>
<th>Number of deaths DM/ No DM</th>
<th>Hazard ratio/ Odds ratio (95% CI) †</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kvan et al. 2007 ‡</td>
<td>Prospective 1999 – 2000 Norway</td>
<td>AMI; Non-Q wave AMI 65/ 58; thrombolysis 18/ 30 STEMI treated with primary PCI</td>
<td>121/779</td>
<td>75/71</td>
<td>38/35</td>
<td>70/273</td>
<td>2.72§ (1.7, 4.35)</td>
<td>Covariates in the logistic regression analysis: age, sex, smoking status</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>van der Schaaf et al. 2007</td>
<td>Retrospective 1997-2002 Netherlands</td>
<td></td>
<td>174/1134</td>
<td>NA</td>
<td>35/25</td>
<td>1</td>
<td>31/82</td>
<td>2.9§ (1.8, 4.3)</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Norhammar et al. 2007 ‡</td>
<td>Retrospective 1995-1997 Sweden</td>
<td>AMI</td>
<td>5679/22582</td>
<td>68/67</td>
<td>37/31</td>
<td>1</td>
<td>1686/3748</td>
<td>1.31 (1.24,1.38)</td>
<td>Propensity Score, inhospital and discharge treatments, revascularisation within 14 days of index AMI.</td>
<td>Fair</td>
</tr>
<tr>
<td>Norhammar et al. 2007 ‡</td>
<td>Retrospective 1998-2002 Sweden</td>
<td>AMI</td>
<td>9134/33427</td>
<td>68/66</td>
<td>37/29</td>
<td>1</td>
<td>1799/4044</td>
<td>1.44 (1.36,1.52)</td>
<td>Propensity Score, inhospital and discharge treatments, revascularisation within 14 days of index AMI.</td>
<td>Fair</td>
</tr>
<tr>
<td>Ishihara et al. 2007 ‡</td>
<td>Retrospective 1996 – 2003 Japan</td>
<td>STEMI; emergency angiography and primary PCI in 90%</td>
<td>212/590</td>
<td>64/ 63</td>
<td>25/20</td>
<td>3</td>
<td>32/54</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
</tbody>
</table>
Table S3.2: Baseline characteristics of the studies included in the meta-analysis (continued)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study design/ year of baseline data collection/ Location</th>
<th>Setting including AMI phenotype (%)<em>; and reperfusion (%) in the whole cohort Or in DM/No DM</em></th>
<th>No of patients DM/ No DM</th>
<th>Mean age (y)</th>
<th>Female (%) DM / No DM</th>
<th>Follow-up (y)</th>
<th>Number of deaths DM/ No DM</th>
<th>Hazard ratio/ Odds ratio (95% CI) †</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aronson et al. 2007</td>
<td>Prospective 2001-2005 Israel</td>
<td>AMI STEMI 66/77, thrombolysis 17/24, primary PCI 21/26</td>
<td>462/1101</td>
<td>66/62</td>
<td>31/20</td>
<td>4</td>
<td>108/170</td>
<td>NA/NA</td>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td>Hsu et al. 2007 ‡</td>
<td>Retrospective 2001-2003 Taiwan</td>
<td>First AMI; thrombolysis in 85</td>
<td>63/135</td>
<td>NA/NA</td>
<td>1</td>
<td>8/12</td>
<td>1.53§ (0.62,3.74)</td>
<td>NA/NA</td>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td>Koek et al. 2007 ‡</td>
<td>Retrospective 1995 Netherlands</td>
<td>First AMI</td>
<td>2018/19547</td>
<td>71/68</td>
<td>50/31</td>
<td>5</td>
<td>1127/6654</td>
<td>1.44 (1.35,1.53)</td>
<td>Age, previous CVD, ethnicity.</td>
<td>Fair</td>
</tr>
<tr>
<td>Hansen et al. 2007 ‡</td>
<td>Retrospective 2001-2003 Denmark</td>
<td>STEMI/NSTEMI; Primary PCI (STEMI) 67/78; Subacute PCI (NSTEMI) 35/51</td>
<td>48/286</td>
<td>71/67</td>
<td>31/38</td>
<td>4.4</td>
<td>21/67</td>
<td>NA/NA</td>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td>Cubbon et al. 2007 ‡</td>
<td>Prospective (EMMACE 2) 2003 UK</td>
<td>AMI</td>
<td>272/1370</td>
<td>71/70</td>
<td>40/36</td>
<td>1.5</td>
<td>99/352</td>
<td>NA/NA</td>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td>Cid-Alvarez et al. 2009</td>
<td>Prospective 2003-2007 Spain</td>
<td>AMI</td>
<td>253/558</td>
<td>NA/NA</td>
<td>1.5</td>
<td>1.5</td>
<td>69/82</td>
<td>NA/NA</td>
<td></td>
<td>Poor</td>
</tr>
</tbody>
</table>
Table S3.2: Baseline characteristics of the studies included in the meta-analysis (continued)

<table>
<thead>
<tr>
<th>Author/ Year</th>
<th>Study design/ year of baseline data collection/ Location</th>
<th>Setting including AMI phenotype (%)<em>; and reperfusion (%) in the whole cohort Or in DM/No DM</em></th>
<th>No of patients DM/ No DM</th>
<th>Mean age (y)</th>
<th>Female (%) DM / No DM</th>
<th>Follow - up (y)</th>
<th>Number of deaths DM/ No DM</th>
<th>Hazard ratio/ Odds ratio (95% CI) †</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hung et al. 2009</td>
<td>Prospective 2005-2007 Australia</td>
<td>AMI; STEMI 31/ 45; revascularisation (PCI/CABG) 47/61</td>
<td>423/1321</td>
<td>66/65</td>
<td>31/29</td>
<td>1</td>
<td>69/96</td>
<td>1.79 (1.18, 2.72)</td>
<td>Age, DM, prior AMI, Killip class, GRACE score, eGFR &lt; 60, need for dialysis, early invasive management, discharge treatment: aspirin, clopidogrel, statin, beta blocker, ACE-I</td>
<td>Good</td>
</tr>
<tr>
<td>Ouhoummane et al. 2009 ‡</td>
<td>Retrospective 1995-1997 Canada</td>
<td>First AMI</td>
<td>5132/18568</td>
<td>69/65</td>
<td>43/32</td>
<td>5</td>
<td>2553/5250</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Beck et al. 2009 ‡</td>
<td>Prospective 1998 – 2003 Germany</td>
<td>First MI; reperfusion or revascularisation 67/78</td>
<td>659/1631</td>
<td>63/60</td>
<td>28/26</td>
<td>3</td>
<td>161/230</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Squire et al. 2010 ‡</td>
<td>Retrospective 1993-2005 UK</td>
<td>AMI; thrombolysis 63/73</td>
<td>749/3951</td>
<td>68/67</td>
<td>39/31</td>
<td>1</td>
<td>234/913</td>
<td>1.52§ (1.24, 1.86)</td>
<td>Age, gender, prior AMI, CK, thrombolysis, smoking, yr of index admission, blood glucose</td>
<td>Fair</td>
</tr>
</tbody>
</table>
Table S3.2: Baseline characteristics of the studies included in the meta-analysis (continued)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study design/year of baseline data collection/Location</th>
<th>Setting including AMI phenotype (%)<em>; and reperfusion (%) in the whole cohort or in DM/No DM</em></th>
<th>No of patients DM/No DM</th>
<th>Mean age (y) DM/No DM</th>
<th>Female (%) DM/No DM</th>
<th>Follow-up (y)</th>
<th>Number of deaths DM/No DM</th>
<th>Hazard ratio/Odds ratio (95% CI) †</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Luca et al. 2010</td>
<td>Retrospective 2003 Poland</td>
<td>STEMI treated with primary PCI</td>
<td>877/6316</td>
<td>65/60</td>
<td>45/27</td>
<td>1.4</td>
<td>206/796</td>
<td>1.23 (1.04, 1.46)</td>
<td>Age, gender, prior AMI, hypercholesterolemia, clinical/angiographic features, shock, renal failure, time to treatment, no. of vessels stented, no. of stents, post procedure TIMI flow, failed PCI</td>
<td>Fair</td>
</tr>
<tr>
<td>Norhammar et al. 2010</td>
<td>Retrospective 2002-2007 Sweden</td>
<td>STEMI/NSTEMI treated with PCI</td>
<td>8467/37480</td>
<td>NA</td>
<td>NA</td>
<td>2.7</td>
<td>1660/3991</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
</tbody>
</table>
Table S3.2: Baseline characteristics of the studies included in the meta-analysis (continued)

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<tr>
<th>Author/Year</th>
<th>Study design/year of baseline data collection/Location</th>
<th>Setting including AMI phenotype (%) ; and reperfusion (%) in the whole cohort Or in DM/No DM*</th>
<th>No of patients DM/No DM</th>
<th>Mean age (y) DM/No DM</th>
<th>Female (%) DM / No DM</th>
<th>Follow-up (y)</th>
<th>Number of deaths DM/No DM</th>
<th>Hazard ratio/ Odds ratio (95% CI) †</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Mulder et al. 2010</td>
<td>Retrospective 1996, 1999, 2003, 2006 Netherlands</td>
<td>AMI</td>
<td>142/1026</td>
<td>NA</td>
<td>NA</td>
<td>5</td>
<td>54/197</td>
<td>1.1 (0.78,1.6)</td>
<td>Age, gender, prior AMI/CABG, hypertension, DM, hypercholesterolemia, smoking, FH of AMI, diagnosis of STEMI, anterolateral location, multi-vessel disease, admission blood glucose, initial reperfusion.</td>
<td>Fair</td>
</tr>
<tr>
<td>Claessen et al. 2010</td>
<td>Retrospective 1997-2007 Netherlands</td>
<td>STEMI treated with primary PCI.</td>
<td>539/3967</td>
<td>NA</td>
<td>37/27</td>
<td>5</td>
<td>151/714</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Rasoul et al. 2010</td>
<td>Prospective (Zwolle myocardial infarction study) Netherlands</td>
<td>First NSTEMI; revascularisation 70/77</td>
<td>138/709</td>
<td>68/63</td>
<td>36/29</td>
<td>1</td>
<td>11 /18</td>
<td>2.25 (1.05,3.9)</td>
<td>Age, gender, DM, hypertension, Killip class, revascularisation.</td>
<td>Fair</td>
</tr>
<tr>
<td>Nijjar et al. 2010</td>
<td>Retrospective 1994 – 2003 Canada</td>
<td>AMI, bi-ethnic cohort of Whites (95%) and South Asians (5%)</td>
<td>7416/33253</td>
<td>NA</td>
<td>38/32</td>
<td>3</td>
<td>2941/8972</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
</tbody>
</table>
### Table S3.2: Baseline characteristics of the studies included in the meta-analysis (continued)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study design/Year of baseline data collection/Location</th>
<th>Setting including AMI phenotype (%)<em>; and reperfusion (%) in the whole cohort or in DM/No DM</em></th>
<th>No of patients DM/No DM</th>
<th>Mean age (y) DM/No DM</th>
<th>Female (%) DM/No DM</th>
<th>Follow-up (y)</th>
<th>Number of deaths DM/No DM</th>
<th>Hazard ratio/Odds ratio (95% CI) †</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kahn et al. 2012 ‡</td>
<td>Retrospective 2005-2009 UK</td>
<td>STEMI treated with primary PCI; drug eluding stent 41/32</td>
<td>310/2276</td>
<td>65/62</td>
<td>33/27</td>
<td>1.8</td>
<td>43/148</td>
<td>1.50 (1.08, 2.09)</td>
<td>Age, gender, prior MI, no. of diseased coronary vessels.</td>
<td>Fair</td>
</tr>
<tr>
<td>Andersson et al. 2011</td>
<td>Prospective TRACE, DIAMOND_MI, BEAT 1990-1999 Denmark Retrospective (MONICA registry) Northern Sweden 1989-2006</td>
<td>AMI patients screened for the TRACE, DIAMOND-MI, BEAT studies.</td>
<td>1819/15093</td>
<td>69/67</td>
<td>38/30</td>
<td>18</td>
<td>1396/8985</td>
<td>1.45 (1.37, 1.54)</td>
<td>Age, sex, LVEF, COPD, hypertension, clinical heart failure, wall motion index score, year of hospital admission</td>
<td>Poor</td>
</tr>
<tr>
<td>Eliasson et al. 2011</td>
<td>Retrospective (MONICA registry) Northern Sweden 1989-2006</td>
<td>First AMI 25-64 year age</td>
<td>897/4944</td>
<td>NA</td>
<td>NA</td>
<td>6.8</td>
<td>396/1208</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Jensen et al. 2012</td>
<td>Retrospective 2002-2005 Denmark</td>
<td>STEMI treated with primary PCI and stent</td>
<td>316/3339</td>
<td>64/63</td>
<td>31/27</td>
<td>3</td>
<td>75/422</td>
<td>2.03 (1.59, 2.59)</td>
<td>Age, gender, co-morbidity index, stent type, stent length, reference vessel size, procedure time, glycoprotein IIb/IIIa use</td>
<td>Fair</td>
</tr>
<tr>
<td>Dziewierz et al. 2012 ‡</td>
<td>Retrospective (Euro transfer registry) 2005 – 2007 Europe</td>
<td>STEMI treated with primary PCI and early abciximab before the PCI</td>
<td>262/1388</td>
<td>69/64</td>
<td>38/26</td>
<td>1</td>
<td>27/97</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
</tbody>
</table>
Table S3.2: Baseline characteristics of the studies included in the meta-analysis (continued)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study design/year of baseline data collection/Location</th>
<th>Setting including AMI phenotype (%)<em>; and reperfusion (%) in the whole cohort Or in DM/No DM</em></th>
<th>No of patients DM/No DM</th>
<th>Mean age (y) DM/No DM</th>
<th>Female (%) DM / No DM</th>
<th>Follow-up (y)</th>
<th>Number of deaths DM/No DM</th>
<th>Hazard ratio/ Odds ratio (95% CI) †</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eitel et al. 2012</td>
<td>Prospective 2006–2008 Germany</td>
<td>STEMI treated with primary PCI with stents or thrombectomy or glycoprotein IIb/IIIa</td>
<td>88/323</td>
<td>68/64</td>
<td>41/21</td>
<td>1.7</td>
<td>10/14</td>
<td>3.4 (1.5, 7.7)</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Bot et al. 2012</td>
<td>RCT DepreMI) MIND-IT 1997-2002 UK</td>
<td>AMI</td>
<td>330/2374</td>
<td>66/61</td>
<td>30/21</td>
<td>10</td>
<td>95/344</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Lee et al. 2012 ‡</td>
<td>Retrospective 2007 – 2010 The Republic of Korea</td>
<td>AMI treated with PCI</td>
<td>921/1517</td>
<td>66/63</td>
<td>36/27</td>
<td>1</td>
<td>106/69</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Gholap et al. 2012 ‡</td>
<td>Retrospective cohort study (MINAP) 2002-2008 UK</td>
<td>AMI; reperfusion or revascularisation 50/61</td>
<td>835/3276</td>
<td>69/66</td>
<td>33/30</td>
<td>2.5</td>
<td>291/750</td>
<td>1.08 (0.86, 1.36)</td>
<td>Age, gender, smoking, prior disease (hypertension, CAD, DM), prior and discharge medications (aspirin, beta blockers, ACE-inhibitors, statins), inpatient use of loop diuretics, SBP, RR, eGFR, admission blood glucose, diagnosis of STEMI, ethnicity</td>
<td>Good</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Study design/ year of baseline data collection/ Location</td>
<td>Setting including AMI phenotype (%)<em>; and reperfusion (%) in the whole cohort Or in DM/No DM</em></td>
<td>No of patients DM/ No DM</td>
<td>Mean age (y)</td>
<td>Female (%) DM / No DM</td>
<td>Follow-up (y)</td>
<td>Number of deaths DM/ No DM</td>
<td>Hazard ratio/ Odds ratio (95% CI) †</td>
<td>Covariates used in the adjusted analysis</td>
<td>USPSTF Quality Rating**</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-------------------------</td>
<td>--------------</td>
<td>-----------------------</td>
<td>--------------</td>
<td>-----------------------------</td>
<td>---------------------------------</td>
<td>------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Park et al. 2012 ‡</td>
<td>Prospective 2005-2007 Korea</td>
<td>STEMI/NSTEMI treated with PCI</td>
<td>1412/3662</td>
<td>63/62</td>
<td>38/25</td>
<td>1</td>
<td>129/189</td>
<td>1.50 (1.03,2.19)</td>
<td>Age, gender, smoking, prior disease (hypertension, DM, dyslipidaemia, CAD), creatinine clearance, STEMI/NSTEMI, LVEF, Killip class, multi-vessel disease, ACC/AHA lesion type, stent type, concomitant drugs</td>
<td>Good</td>
</tr>
<tr>
<td>Nauta et al. 2012 ‡</td>
<td>Retrospective 1985-2008 Netherlands</td>
<td>AMI</td>
<td>2015/12419</td>
<td>NA</td>
<td>38/26</td>
<td>20</td>
<td>1672/8072</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>De Luca et al. 2013 ‡</td>
<td>Individual patient metaanalysis (DESERT) 2002-2005 Multinational</td>
<td>STEMI treated with primary PCI with drug-eluting vs. bare metal stents</td>
<td>972/5326</td>
<td>63/60</td>
<td>28/22</td>
<td>3.3</td>
<td>186/394</td>
<td>1.76 (1.35,2.29)</td>
<td>Age, gender, hypertension, hypercholesterolaemia, ischaemia time.</td>
<td>Fair</td>
</tr>
<tr>
<td>Chiang et al. 2013 ‡</td>
<td>Retrospective 1996 – 2005 Taiwan</td>
<td>AMI</td>
<td>20528/56028</td>
<td>66/66</td>
<td>37/25</td>
<td>5</td>
<td>10396/23031</td>
<td>1.47§ (1.42,1.52)</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Radomska et al. 2013 ‡</td>
<td>Prospective 2005-2006 Poland</td>
<td>STEMI</td>
<td>5346/20689</td>
<td>NA</td>
<td>47/31</td>
<td>1</td>
<td>1315/3063</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
</tbody>
</table>
Table S3.2: Baseline characteristics of the studies included in the meta-analysis (continued)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study design/ year of baseline data collection/ Location</th>
<th>Setting including AMI phenotype (%%)<em>; and reperfusion (%%) in the whole cohort Or in DM/No DM</em></th>
<th>No of patients DM/ No DM</th>
<th>Mean age (y) DM/ No DM</th>
<th>Female (%) DM / No DM</th>
<th>Follow-up (y)</th>
<th>Number of deaths DM/ No DM</th>
<th>Hazard ratio/ Odds ratio (95% CI) †</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanidas et al. 2014 ‡</td>
<td>RCT (INFUSE-AMI) USA, Europe</td>
<td>Anterior STEMI due to LAD lesion treated with bivalirudin supported primary PCI +/- intra-lesional abciximab +/- thrombus aspiration</td>
<td>51/400</td>
<td>65/60</td>
<td>35/25</td>
<td>1</td>
<td>6/20</td>
<td>1.56 (0.5, 3.86)</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Chen et al. 2014</td>
<td>Prospective 1992-2008 Taiwan</td>
<td>STEMI treated with primary PCI</td>
<td>306/653</td>
<td>NA</td>
<td>NA</td>
<td>16.6</td>
<td>34/28</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Arnold et al. 2014</td>
<td>Prospective (TRIUMPH AMI registry) 2005 – 2008 USA</td>
<td>AMI</td>
<td>887/1966</td>
<td>60/58</td>
<td>37/31</td>
<td>3</td>
<td>180/192</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Piccolo et al. 2014</td>
<td>RCTs, pooled analysis 2006 – 2011 European centres</td>
<td>STEMI; randomised to intracoronary vs intravenous abciximab at the time of primary PCI</td>
<td>578/2468</td>
<td>70/62</td>
<td>34/22</td>
<td>1</td>
<td>47/91</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
<tr>
<td>Lazzeri et al. 2015‡</td>
<td>Retrospective 2004-2011 Italy</td>
<td>First STEMI treated with primary PCI</td>
<td>276/929</td>
<td>71/68</td>
<td>33/26</td>
<td>1</td>
<td>37/80</td>
<td>NA</td>
<td>NA</td>
<td>Poor</td>
</tr>
</tbody>
</table>
Table S3.2: Baseline characteristics of the studies included in the meta-analysis (continued)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study design/ year of baseline data collection/ Location</th>
<th>Setting including AMI phenotype (%)<em>; and reperfusion (%) in the whole cohort Or in DM/No DM</em></th>
<th>No of patients DM/ No DM</th>
<th>Mean age (y) DM/ No DM</th>
<th>Female (%) DM / No DM</th>
<th>Follow-up (y)</th>
<th>Number of deaths DM/ No DM</th>
<th>Hazard ratio/ Odds ratio (95% CI) †</th>
<th>Covariates used in the adjusted analysis</th>
<th>USPSTF Quality Rating**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al. 2016 ‡</td>
<td>Prospective Aug – Nov 1995 UK</td>
<td>AMI</td>
<td>279/1874</td>
<td>71/70</td>
<td>47/38</td>
<td>20</td>
<td>237/1419</td>
<td>1.42 (1.21,1.65)</td>
<td>DM, Age, gender, prior MI, Prior CHF, hypertension, smoking status, PVD.</td>
<td>Fair</td>
</tr>
</tbody>
</table>

* If such information is reported.
† Risk of death in those with compared with those without diabetes.
‡ Event data on long-term mortality in those who survived to discharge or the first 30 days after index AMI is available.
§ Odds ratio.

** Please see Box S3.1 in this Appendix Three for details of the USPSTF criteria used for quality rating. Those studies not reporting adjusted data for mortality risk were rated as ‘poor’. In many of these studies, people with diabetes were older and had a higher prevalence of baseline cardiovascular risk factors which could have contributed to their higher mortality rates. Among the studies reporting adjusted data, those adjusting for key confounders (baseline difference in clinical characteristics, and risk factors, acute therapies for AMI and secondary prevention therapies post AMI) and also achieving >80% follow-up as per the requirement of the USPSTF criteria were only graded as ‘good’. The rest adjusted studies were graded as ‘fair’.

Abbreviations:
ACE-I, angiotensin converting enzyme inhibitors; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; Cardiac cath, cardiac catheterization; CHF, congestive heart failure; CHD, coronary heart disease; CK, creatinine kinase; COPD, chronic obstructive pulmonary disease; DM, Diabetes mellitus; eGFR, estimated glomerular function rate; GP IIb/IIIa, glycoprotein IIb/IIIa; MONICA project, monitoring trends and determinants in cardiovascular disease project; RR (95% CI), hazard ratio (95% confidence intervals); HR, heart rate; Ht, height; LAD, left anterior descending; LV- LVEF, left ventricular ejection fraction; PCI, percutaneous intervention; PVD, peripheral vascular disease; RCT, randomised controlled trial; SE, socioeconomic; SBP, systolic blood pressure; STEMI – NSTEMI, non-ST elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; Wt, weight; WBC, white blood cell count.

Study acronyms:
**BEAT**: Bucindolol Evaluation in Acute myocardial infarction; **CADILLAC**: Comparison of Angioplasty with Stenting, with or without Abciximab, to Lower Late Angioplasty Complications; **CCHP**: Corpus Christi Heart Project; **DepreMi**: Depression after Myocardial Infarction; **DIAMOND**: DIAgnosis Management and Outcome of Depression in primary care; **EMMACE**: Evaluation of the Methods and Management of Acute Coronary Events; **GUSTO**: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; **INFUSE-AMI**: The Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction; **MIDAS**: Myocardial Infarction Data Acquisition System; **MINAP**: Myocardial Infarction National Audit Programme; **MIND-IT**: Myocardial Infarction and Depression-Intervention Trial; **STENT PAM**: Primary Stenting in Acute Myocardial Infarction; **TAMI**: Thrombolysis and Angioplasty in Myocardial Infarction; **TRACE**: TRAndolapril Cardiac Evaluation; **TRIUMPH**: Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients’ Health status; **DESERT**: Drug-Eluting Stent in Primary Angioplasty.
Table S3.3. Risk of long-term mortality in patients with diabetes compared with those without diabetes (66/66 cohorts): Comparison of primary and sensitivity analyses

<table>
<thead>
<tr>
<th>Analysis and outcome</th>
<th>Hazard ratio (95% credible intervals)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pooled mean effect</td>
<td>Predicted effect in a new study</td>
</tr>
<tr>
<td>Primary analysis (Included all studies in Table S1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term mortality (unadjusted analysis)</td>
<td>1.82 (1.73, 1.91)</td>
<td>1.82 (1.32, 2.52)</td>
</tr>
<tr>
<td>SA1 (Excluded 12 studies in which data were derived from KM curves*)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long term mortality (unadjusted analysis)</td>
<td>1.80 (1.71, 1.90)</td>
<td>1.80 (1.33, 2.49)</td>
</tr>
<tr>
<td>SA2 (Excluded 3 studies in which data was derived from percentages†)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term mortality (unadjusted analysis)</td>
<td>1.81 (1.72, 1.91)</td>
<td>1.81 (1.32, 2.51)</td>
</tr>
<tr>
<td>SA3 (Excluded all 15 studies from SA1 and SA2 combined)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term mortality (unadjusted analysis)</td>
<td>1.79 (1.70, 1.89)</td>
<td>1.80 (1.32, 2.44)</td>
</tr>
</tbody>
</table>

SA=Sensitivity analysis
†List of studies excluded in SA2 (Table S3.2): Wahab et al. 2002, Svensson et al. 2007, and Hsu et al. 2007
Table S3.4. Risk of long-term mortality in patients with diabetes compared with those without diabetes, in the cohort of early survivors* (42/64 studies): Comparison of primary and sensitivity analyses

<table>
<thead>
<tr>
<th>Analysis and outcome</th>
<th>Hazard ratio (95% credible intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pooled mean effect</td>
</tr>
<tr>
<td>Primary analysis (Included 42/64 studies, unadjusted analysis)</td>
<td></td>
</tr>
<tr>
<td>Long term mortality (unadjusted analysis)</td>
<td>1.82 (1.70, 1.95).</td>
</tr>
<tr>
<td>SA1 (Excluded 9 studies in which data were derived from KM curves†)</td>
<td></td>
</tr>
<tr>
<td>Long term mortality</td>
<td>1.80 (1.67, 1.93)</td>
</tr>
<tr>
<td>SA2 (Excluded 3 studies in which data was derived from percentages††)</td>
<td></td>
</tr>
<tr>
<td>Long term mortality</td>
<td>1.81 (1.68, 1.94)</td>
</tr>
<tr>
<td>SA3 (Excluded all 12 studies from SA1 and SA2 combined)</td>
<td></td>
</tr>
<tr>
<td>Long term mortality</td>
<td>1.78 (1.66, 1.91)</td>
</tr>
</tbody>
</table>

SA=Sensitivity analysis
*Those who survived to discharge or first 30 days following the index AMI
††List of studies excluded in SA2 (Table S2): Wahab et al. 2002, Svensson et al. 2007, and Hsu et al. 2007
Box S3.1: The US Preventive Service Task Force (USPSTF) Quality Rating Criteria for the RCTs and cohort studies

Criteria

- Initial assembly of comparable groups:
  - RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups;
  - Cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- Important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs

Ratings based on above criteria

**Good:** Meets all criteria

1. Comparable groups assembled initially and maintained throughout the study
2. Follow up at least 80 percent
3. Reliable and valid measurement instruments are used and applied equally to the groups
4. Interventions are spelled out clearly
5. Important outcomes are considered
6. Appropriate attention to confounders in analysis

**Fair:**

1. Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up
2. Measurement instruments are acceptable (although not the best) and generally applied equally
3. Some but not all important outcomes are considered
4. Some but not all potential confounders are accounted for.
5. The important limitations noted in the “poor” category below are not observed

**Poor:**

1. Groups assembled initially are not close to being comparable or maintained throughout the study;
2. Unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment)
3. Key confounders are given little or no attention.

Final decision on rating of this article based on the above definition: Good/Fair/Poor
Figure S3.1: Early survivors* (42/64 studies): Unadjusted Hazard ratio (HR) for long-term mortality in people with diabetes in comparison to those without.

*Those survived to discharge or first 30 days following the index AMI HR greater than 1 indicates an increased risk of death in people with compared with those without diabetes.
Figure S3.2. Early survivors (42/64 studies): The risk of long-term mortality in people with diabetes compared with those without diabetes across different subgroups. HR greater than 1 indicates an increased risk of death in people with compared with those without diabetes.

Early survivors are those who survived to discharge or first 30 days following the index AMI. P value is for interaction.
*studies with a mixed population of patients with STEMI/NSTEMI/AMI.
Appendix Four: Supplementary material for Chapter Four

List of contents in this appendix:

Table S4.2

Table S4.3
## Supplementary Table S4.2: Univariate association of clinical variables with 30-day, 1-year, and total mortality in the survivors at discharge cohort. Data are hazard ratio (95% confidence intervals)

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Mortality N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 days</td>
</tr>
<tr>
<td></td>
<td>N= 3790</td>
</tr>
<tr>
<td><strong>Demographics variables</strong></td>
<td></td>
</tr>
<tr>
<td>Gender (Female vs Male)</td>
<td>0.585 (0.395 , 0.865)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>1.059 (1.041 , 1.077)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.985 (0.978 , 0.992)</td>
</tr>
<tr>
<td>Heart Rate (beats/min)</td>
<td>1.002 (0.994 , 1.010)</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>0.772 (0.646 , 0.922)</td>
</tr>
<tr>
<td>Admission plasma glucose (mmol/L)</td>
<td>1.069 (1.044 , 1.095)</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>0.957 (0.947 , 0.967)</td>
</tr>
<tr>
<td><strong>AMI phenotype</strong></td>
<td></td>
</tr>
<tr>
<td>NSTEMI vs STEMI</td>
<td>0.558 (0.367 , 0.850)</td>
</tr>
<tr>
<td><strong>Year of admission</strong></td>
<td></td>
</tr>
<tr>
<td>Oct 2002-Dec 2003</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>0.907 (0.551 , 1.494)</td>
</tr>
<tr>
<td>2005</td>
<td>0.490 (0.234 , 1.024)</td>
</tr>
<tr>
<td>2006</td>
<td>0.647 (0.334 , 1.252)</td>
</tr>
<tr>
<td>2007</td>
<td>0.402 (0.215 , 0.751)</td>
</tr>
<tr>
<td>2008</td>
<td>0.261 (0.115 , 0.589)</td>
</tr>
<tr>
<td>Test for Linear Trend (p-value)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Ethnicity (SA vs. WE)</strong></td>
<td>1.172 (0.726 , 1.891)</td>
</tr>
<tr>
<td><strong>Medical history (Yes vs No)</strong></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.417 (0.945 , 2.124)</td>
</tr>
<tr>
<td>Prior Diabetes</td>
<td>1.363 (0.874 , 2.124)</td>
</tr>
<tr>
<td>Prior Coronary Heart Disease §</td>
<td>1.427 (0.848 , 2.402)</td>
</tr>
<tr>
<td>Prior Hypertension</td>
<td>1.987 (1.315 , 3.002)</td>
</tr>
<tr>
<td><strong>Prior medication (Yes vs No)</strong></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.945 (0.633 , 1.412)</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>1.966 (1.306 , 2.960)</td>
</tr>
<tr>
<td>Statin</td>
<td>1.169 (0.759 , 1.799)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>1.174 (0.762 , 1.807)</td>
</tr>
<tr>
<td><strong>Inpatient treatment (Yes vs No)</strong></td>
<td></td>
</tr>
<tr>
<td>Initial Reperfusion</td>
<td>1.154 (0.774 , 1.720)</td>
</tr>
<tr>
<td>Loop Diuretic</td>
<td>3.199 (2.129 , 4.806)</td>
</tr>
<tr>
<td><strong>Discharge medication (Yes vs No)</strong></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.165 (0.107 , 0.253)</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>0.138 (0.086 , 0.221)</td>
</tr>
<tr>
<td>Statin</td>
<td>0.166 (0.108 , 0.255)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>0.176 (0.112 , 0.276)</td>
</tr>
</tbody>
</table>

SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)
**Supplementary Table S4.3:** Multivariate association of clinical variables with 30-day, 1-year, and total mortality in the survivors at discharge. Data are hazard ratio (95% confidence intervals)

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>30 days</th>
<th>1 Year</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 3792</td>
<td>106(2.80)</td>
<td>363(9.60)</td>
</tr>
<tr>
<td><strong>Admission demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (Female vs Male)</td>
<td>0.848 (0.467, 1.538)</td>
<td>1.026 (0.774, 1.360)</td>
<td>1.113 (0.912, 1.358)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>1.077 (1.040,1.115)</td>
<td>1.058 (1.042, 1.075)</td>
<td>1.071 (1.059, 1.083)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>0.981 (0.971, 0.990)</td>
<td>0.994 (0.989, 0.998)</td>
<td>0.996 (0.993, 0.999)</td>
</tr>
<tr>
<td>Heart Rate (beat/min)</td>
<td>0.998 (0.987,1.008)</td>
<td>1.004 (1.000, 1.009)</td>
<td>1.007 (1.004, 1.010)</td>
</tr>
<tr>
<td>Admission plasma glucose (mmol/L)</td>
<td>1.095 (1.047,1.146)</td>
<td>1.046 (1.017,1.077)</td>
<td>1.042 (1.021, 1.064)</td>
</tr>
<tr>
<td>eGFR (mL/min)</td>
<td>0.994 (0.977, 1.011)</td>
<td>0.978 (0.970, 0.987)</td>
<td>0.985 (0.980, 0.991)</td>
</tr>
<tr>
<td><strong>AMI phenotype</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nSTEMI vs STEMI</td>
<td>0.253 (0.125, 0.512)</td>
<td>0.643 (0.486, 0.852)</td>
<td>0.826 (0.679, 1.005)</td>
</tr>
<tr>
<td><strong>Year of admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year of admission</td>
<td>0.826 (0.701, 0.974)</td>
<td>0.956 (0.887, 1.030)</td>
<td>0.926 (0.873, 0.981)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(SA vs WE)</td>
<td>2.021 (0.932, 4.384)</td>
<td>1.118 (0.760, 1.643)</td>
<td>0.950 (0.718, 1.258)</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Yes vs No)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.722 (0.934, 3.177)</td>
<td>0.949 (0.710, 1.270)</td>
<td>0.920 (0.752, 1.124)</td>
</tr>
<tr>
<td>Prior Diabetes</td>
<td>0.638 (0.313, 1.303)</td>
<td>0.907 (0.656, 1.255)</td>
<td>1.080 (0.860, 1.356)</td>
</tr>
<tr>
<td>Prior CHD §</td>
<td>1.093 (0.467, 2.560)</td>
<td>1.117 (0.751, 1.661)</td>
<td>1.328 (1.015, 1.738)</td>
</tr>
<tr>
<td>Prior Hypertension</td>
<td>1.836 (0.985, 3.421)</td>
<td>1.152 (0.868, 1.529)</td>
<td>1.112 (0.914, 1.354)</td>
</tr>
<tr>
<td><strong>Prior medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Yes vs No)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.951 (0.509, 1.778)</td>
<td>1.088 (0.810, 1.462)</td>
<td>1.086 (0.883, 1.336)</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>1.707 (0.929, 3.136)</td>
<td>1.403 (1.045, 1.883)</td>
<td>1.127 (0.913, 1.392)</td>
</tr>
<tr>
<td>Statin</td>
<td>0.961 (0.463, 1.997)</td>
<td>0.974 (0.699, 1.358)</td>
<td>0.992 (0.782, 1.258)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>0.685 (0.351, 1.339)</td>
<td>1.059 (0.784, 1.429)</td>
<td>1.093 (0.883, 1.353)</td>
</tr>
<tr>
<td><strong>Inpatient treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Yes vs No)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop Diuretic</td>
<td>1.029 (0.568,1.867)</td>
<td>1.598 (1.172, 2.179)</td>
<td>1.484 (1.203, 1.830)</td>
</tr>
<tr>
<td><strong>Discharge medication</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Yes vs No)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.543 (0.235,1.256)</td>
<td>1.027 (0.702, 1.503)</td>
<td>1.228 (0.925, 1.631)</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>0.357 (0.167, 0.763)</td>
<td>0.730 (0.529, 1.007)</td>
<td>0.795 (0.633, 0.997)</td>
</tr>
<tr>
<td>Statin</td>
<td>1.191 (0.448, 3.170)</td>
<td>0.844 (0.574, 1.240)</td>
<td>0.712 (0.542, 0.935)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>0.425 (0.176, 1.027)</td>
<td>0.673 (0.475, 0.955)</td>
<td>0.955 (0.734, 1.243)</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; SBP, Systolic blood pressure; eGFR, estimated Glomerular filtration rate calculated using the MDRD formula; STEMI, ST elevation myocardial infarction; nSTEMI, non-ST elevation myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

§ any of angina/ myocardial Infarction; / percutaneous Intervention (PCI)/ coronary artery bypass grafting (CABG)
Appendix Five: Supplementary material for Chapter Five

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Table S5.1: Association of clinical variables with mortality over the entire follow-up post acute myocardial infarction in the Whole cohort and in the White European and South Asian subgroups: Cox proportionate hazards univariate analysis

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All cause mortality over the entire follow-up period (Median 912 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole Cohort</td>
</tr>
<tr>
<td></td>
<td>N=1043/4111(25.3%)</td>
</tr>
<tr>
<td>Admission Demographics</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>0.85 (0.72, 1.01)</td>
</tr>
<tr>
<td>(South Asian vs White Europeans)</td>
<td></td>
</tr>
<tr>
<td>Gender (Female vs Male)</td>
<td>0.56 (0.49, 0.63)</td>
</tr>
<tr>
<td>Age (year)(^{-1})</td>
<td>1.08 (1.07, 1.09)</td>
</tr>
<tr>
<td>SBP (mmHg)(^{-1})</td>
<td>0.99 (0.99, 0.99)</td>
</tr>
<tr>
<td>Heart Rate (beat/min)(^{-1})</td>
<td>1.01 (1.01, 1.01)</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/L)(^{-1})</td>
<td>0.75 (0.71, 0.79)</td>
</tr>
<tr>
<td>Admission plasma glucose (mmol/L)(^{-1})</td>
<td>1.06 (1.05, 1.07)</td>
</tr>
<tr>
<td>eGFR (mL/min)(^{-1})</td>
<td>0.96 (0.96, 0.96)</td>
</tr>
<tr>
<td>AMI Phenotype</td>
<td></td>
</tr>
<tr>
<td>NSTEMI vs STEMI</td>
<td>0.94 (0.83, 1.06)</td>
</tr>
<tr>
<td>Year of Admission</td>
<td></td>
</tr>
<tr>
<td>Oct 2002-Dec 2003 (Reference)</td>
<td>1</td>
</tr>
<tr>
<td>2004</td>
<td>0.92 (0.78, 1.08)</td>
</tr>
<tr>
<td>2005</td>
<td>0.70 (0.56, 0.87)</td>
</tr>
<tr>
<td>2006</td>
<td>0.72 (0.57, 0.90)</td>
</tr>
<tr>
<td>2007</td>
<td>0.68 (0.56, 0.83)</td>
</tr>
<tr>
<td>2008</td>
<td>0.54 (0.42, 0.69)</td>
</tr>
<tr>
<td>Medical History (Yes vs No)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.17 (1.03, 1.33)</td>
</tr>
<tr>
<td>Prior Diabetes</td>
<td>1.65 (1.45, 1.89)</td>
</tr>
<tr>
<td>Prior CHD</td>
<td>1.11 (0.93, 1.33)</td>
</tr>
<tr>
<td>Prior Hypertension</td>
<td>1.46 (1.29, 1.65)</td>
</tr>
</tbody>
</table>
Table S5.1 (Continued): Association of clinical variables with mortality over the entire follow-up post acute myocardial infarction in the Whole cohort and in the White European and South Asian subgroups: Cox proportionate hazards univariate analysis

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>All cause mortality over the entire follow-up period (Median 912 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whole Cohort (N=1043/4111 (25.3%))</td>
</tr>
<tr>
<td>Pre-Admission Medication</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.91 (0.80, 1.03)</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>1.45 (1.27, 1.66)</td>
</tr>
<tr>
<td>Statin</td>
<td>1.17 (1.03, 1.34)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>1.59 (1.40, 1.80)</td>
</tr>
<tr>
<td>Admission treatment</td>
<td></td>
</tr>
<tr>
<td>Reperfusion/Revascularisation</td>
<td>0.47 (0.41, 0.53)</td>
</tr>
<tr>
<td>Loop Diuretic</td>
<td>4.00 (3.51, 4.56)</td>
</tr>
<tr>
<td>Discharge Medication</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.38 (0.34, 0.43)</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>0.36 (0.32, 0.41)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>0.41 (0.36, 0.46)</td>
</tr>
<tr>
<td>Statin</td>
<td>0.31 (0.27, 0.35)</td>
</tr>
</tbody>
</table>

SBP=systolic blood pressure; eGFR=estimated glomerular filtration rate; STEMI = NSTEMI = non-ST elevation myocardial infarction; CHD=coronary heart disease; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker
Table S5.2: Association between ethnicity (South Asian versus White Europeans) and mortality following acute myocardial infarction, in the subgroups of patients with ST elevation MI and non-ST elevation MI: Cox proportionate hazards multivariate analysis*

<table>
<thead>
<tr>
<th>Mortality time periods</th>
<th>Multivariate analysis*</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>STEMI (N=2397, SA 17.5%)</td>
<td>Model 1A</td>
<td>Model 2A</td>
<td>Model 1B</td>
<td>Model 2B</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
<td>HR (95% CI)</td>
<td>p value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Over entire follow-up, median 912 days</td>
<td></td>
<td>1.05 (0.83, 1.32)</td>
<td>0.706</td>
<td>1.01 (0.80, 1.29)</td>
<td>0.930</td>
<td>1.22 (0.93, 1.61)</td>
</tr>
<tr>
<td>(STEMI 621/2397, NSTEMI 422/1714)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early mortality 0 - 30 days</td>
<td></td>
<td>1.26 (0.92, 1.72)</td>
<td>0.158</td>
<td>1.20 (0.87, 1.66)</td>
<td>0.277</td>
<td>1.37 (0.81, 2.30)</td>
</tr>
<tr>
<td>(STEMI 299/2397; NSTEMI 111/1714)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long term mortality in 30-day survivors</td>
<td></td>
<td>0.85 (0.60, 1.21)</td>
<td>0.355</td>
<td>0.85 (0.60, 1.22)</td>
<td>0.370</td>
<td>1.18 (0.86, 1.63)</td>
</tr>
<tr>
<td>(STEMI 322/2098, NSTEMI 311/1603)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality &gt;30 days - 1 year</td>
<td></td>
<td>0.72 (0.41, 1.27)</td>
<td>0.260</td>
<td>0.72 (0.41, 1.27)</td>
<td>0.256</td>
<td>1.21 (0.74, 1.96)</td>
</tr>
<tr>
<td>(STEMI 139/2098, NSTEMI 130/1603)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality &gt;1 year - 3 years</td>
<td></td>
<td>1.25 (0.71, 2.18)</td>
<td>0.442</td>
<td>1.29 (0.73, 2.27)</td>
<td>0.387</td>
<td>1.15 (0.69, 1.90)</td>
</tr>
<tr>
<td>(STEMI 104/1954, NSTEMI 129/1470)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality &gt; 3 years - end of follow-up</td>
<td></td>
<td>0.61 (0.27, 1.38)</td>
<td>0.237</td>
<td>0.60 (0.26, 1.37)</td>
<td>0.225</td>
<td>1.19 (0.56, 2.54)</td>
</tr>
<tr>
<td>(STEMI 79/1110, NSTEMI 52/708)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Missing data were imputed. STEMI = NSTEMI = non-ST elevation myocardial infarction

Variables included in the multivariate Cox regression models:
Model 1A, 1B: age, gender, prior diabetes, prior hypertension, prior CHD, smoking history
Model 2A, 2B: Model 1 plus admission glucose, estimated glomerular function rate (eGFR), in-patient diuretic use, acute reperfusion/revascularisation, secondary prevention therapies at discharge
Table S5.3: Association between diabetes and mortality following acute myocardial infarction, in subgroups of White European and (WE) and South Asians (SA) patient.: Cox proportionate hazards multivariate analysis*

| Mortality time periods (Number deaths/total number of survivors in WE and SA ethnic groups) | Multivariate analysis |
|---|---|---|---|---|
| | White Europeans N=3381 | South Asians N=730 |
| | Model 1E | Model 2E | Model 1F | Model 2F |
| Over entire follow-up (median 912 days) | 1.52 (1.29, 1.78) | 0.000 | 1.10 (0.92, 1.31) | 0.293 | 1.67 (1.21, 2.32) | 0.002 | 1.27 (0.88, 1.84) | 0.209 |
| Early mortality 0 - 30 days (WE 336/3381, SA 74/730) | 1.30 (0.99, 1.70) | 0.56 | 0.85 (0.63, 1.14) | 0.269 | 1.64 (1.02, 2.65) | 0.041 | 1.49 (0.81, 2.71) | 0.197 |
| Long term mortality in 30-day survivors (WE 542/3045, SA 91/656) | 1.66 (1.36, 2.03) | <0.001 | 1.23 (0.98, 1.54) | 0.069 | 1.68 (1.08, 2.62) | 0.021 | 1.34 (0.81, 2.21) | 0.259 |
| Mortality >30 days - 1 year WE 231/3045, SA 38/656 | 1.66 (1.22, 2.24) | 0.001 | 1.20 (0.86, 1.66) | 0.284 | 1.58 (0.78, 3.13) | 0.188 | 1.39 (0.64, 3.03) | 0.412 |
| Mortality >1 year - 3 years (WE 196/2808, SA 37/618) | 1.45 (1.04, 2.04) | 0.031 | 1.07 (0.73, 1.57) | 0.719 | 1.58 (0.80, 3.11) | 0.187 | 1.15 (0.53, 2.52) | 0.726 |
| Mortality > 3 years - end of follow-up (WE 115/1480, SA 16/305) | 2.11 (1.37, 3.26) | 0.001 | 1.67 (1.02, 2.73) | 0.042 | 2.76 (0.84, 9.03) | 0.093 | 3.13 (0.72, 13.57) | 0.128 |

*Missing data were imputed. WE, White Europeans; SA, South Asians

Variables included in the multivariate Cox regression models: Model 1E, 1F: age, gender, prior CHD, prior hypertension, smoking history, type of AMI. Model 2E, 2F: Model 1E/F plus admission glucose, estimated glomerular function rate (eGFR), in-patient diuretic use, acute reperfusion/revascularisation, secondary prevention therapies at discharge.
Appendix Six: Supplementary material for the SWEET-Heart study

List of contents in this appendix

Ethics approval letter
Ethics substantial amendments letter
Participant letter of invitation
Reply slip
Patient information sheet
Consent form
Questionnaire Booklet
The Algorithm showing versions of letters to be sent to the participants and their General Practitioners (GP)
Patient Result letters, 1 - 6
GP Result letters, 1 - 6
The Sweet-Heart study poster
27 July 2010

Professor Kamlesh Khunti
Professor of Primary Care Diabetes & Vascular Medicine
University of Leicester
Department of Health Sciences
22-26 Princess Road West
Leicester
LE1 6TP

Dear Professor Khunti,

Study Title: Screening White Europeans and Ethnic South Asians for glucose intolerance following heart attack. (The SWEET-Heart study)

REC reference number: 10/H0402/46
Protocol number: 1.0

Thank you for your letter of 26 July 2010, responding to the Committee’s request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see “Conditions of the favourable opinion” below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to...
the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation’s involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<table>
<thead>
<tr>
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<tr>
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<td></td>
<td>01 February 2010</td>
</tr>
<tr>
<td>Investigator CV: Dr Nitin Narayan Gholap</td>
<td></td>
<td>17 May 2010</td>
</tr>
<tr>
<td>Protocol</td>
<td></td>
<td>08 July 2010</td>
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<td>GP Results Letter 1 (Normal)</td>
<td>1</td>
<td>17 May 2010</td>
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<tr>
<td>GP Results Letter 6 (Diabetes with symptoms)</td>
<td>1</td>
<td>17 May 2010</td>
</tr>
<tr>
<td>Statistical Review</td>
<td></td>
<td></td>
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<tr>
<td>Protocol approval letter CLARHC Scientific Committee</td>
<td></td>
<td>07 June 2010</td>
</tr>
<tr>
<td>Patient Result Letter 1 (Normal)</td>
<td>1</td>
<td>17 May 2010</td>
</tr>
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<td>Pre-Diabetes - The end !!!!!...or a new beginning?</td>
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<td>Covering Letter</td>
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<tr>
<td>Summary/Synopsis: Flowchart</td>
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<td>Letter from Sponsor</td>
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<td>Advertisement: Poster</td>
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<td>Letter of invitation to participant</td>
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<tr>
<td>Letter of invitation to participant: Pilot</td>
<td>1.0</td>
<td>17 May 2010</td>
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<tr>
<td>Response to Request for Further Information</td>
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<td>26 July 2010</td>
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<tr>
<td>Participant Information Sheet: WITHOUT Diabetes</td>
<td>2</td>
<td>08 July 2010</td>
</tr>
<tr>
<td>Participant Information Sheet: - Pilot (with Diabetes)</td>
<td>2</td>
<td>08 July 2010</td>
</tr>
<tr>
<td>Participant Consent Form</td>
<td>2</td>
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</tr>
<tr>
<td>Participant Consent Form: - Pilot</td>
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<tr>
<td>Questionnaire: IPAQ</td>
<td></td>
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<tr>
<td>GP Results Letter 2 (Pre-Diabetes Transients)</td>
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<tr>
<td>GP Results Letter 3 (Pre-Diabetes)</td>
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</table>
Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

Please quote this number on all correspondence

Yours sincerely,
10/H0402/48 – Further Information Favourable Opinion letter re-issued to correct list of documents – 10 September 2010

Mr Ken Willis
Chair

Email: susie.cornick-willis@nottspct.nhs.uk

Enclosures:

“After ethical review – guidance for researchers”

Copy to:

Graham Hewitt, University of Leicester

R&D office for NHS care organisation at lead site - UHL
National Research Ethics Service
NRES Committee East Midlands - Northampton
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS
Tel: 0115 8839368
Fax: 0115 8839294

13 May 2011

Professor Kamlesh Khunti
Professor of Primary Care Diabetes & Vascular Medicine
University of Leicester
Department of Health Sciences
22-28 Princess Road West
Leicester
LE1 6TP

Dear Professor Khunti

Study title: Screening White Europeans and Ethnic South Asians for glucose intolerance following heart attack. (The SWEET-Heart study)

REC reference: 10/H0402/46
Amendment number: SA1 4th April 2011
Amendment date: 11 April 2011

The above amendment was reviewed at the meeting of the Sub-Committee held on 21 April 2011.

Ethical opinion

The Committee asked you to provide assurance that participants are given at least 12 hours to give consent or to provide justification if this cannot be implemented. You provided justification for the reduced consenting period. The Sub-Committee was satisfied that in the circumstances a 6 hour acceptance window would be acceptable, but stressed that the 6 hours is a minimum window which must be adhered to.

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

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<td>GP Result letter 5 (DIABETES) (FAX)</td>
<td>2</td>
<td>13 March 2011</td>
</tr>
<tr>
<td>GP Result Letter 6 (Diabetes with symptoms) FAX</td>
<td>2</td>
<td>13 March 2011</td>
</tr>
<tr>
<td>Patient No further study visits letter</td>
<td>1</td>
<td>04 April 2011</td>
</tr>
<tr>
<td>Patient Rearranging Follow Up Appointment Letter</td>
<td>1</td>
<td>04 April 2011</td>
</tr>
<tr>
<td>Letter of invitation to participant</td>
<td>2</td>
<td>13 March 2011</td>
</tr>
<tr>
<td>Participant Information Sheet: Patient Information Sheet</td>
<td>3</td>
<td>13 March 2011</td>
</tr>
</tbody>
</table>

*This Research Ethics Committee is an advisory committee to East Midlands Strategic Health Authority
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees In England*
### Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

### R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

### Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

10/H0402/46: Please quote this number on all correspondence

Yours sincerely

Mr Ken Willis
Chair

E-mail: lisa.gregory@nottspot.nhs.uk

**Enclosures:** List of names and professions of members who took part in the review

**Copy to:** Graham Hewitt, University of Leicester
Mrs Carolyn Maloney, University Hospital Leicester - Research and Development Office
NRES Committee East Midlands - Northampton

Attendance at Sub-Committee of the REC meeting on 21 April 2011

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr Mike Newman</td>
<td>Consultant Gynaecologist</td>
<td>Expert</td>
</tr>
<tr>
<td>Mr Ken Willis</td>
<td>Medical Devices Manager</td>
<td>Lay</td>
</tr>
</tbody>
</table>

Also in attendance:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mrs Lisa Gregory</td>
<td>Committee Coordinator</td>
</tr>
</tbody>
</table>
The SWEET-Heart Study, Leicester

Date

To

Dear

Invitation to join a study on impact of high blood glucose levels on complications following a heart attack

Up to half of the people admitted with heart attack have high blood glucose levels with undetected type 2 diabetes or so called Pre-diabetes. Many of them would have no symptoms from the high blood glucose levels. Having diabetes or higher than normal blood glucose level puts them at a higher risk of developing complications such as heart failure or death following a heart attack. Furthermore, South Asian people suffer from heart attacks at a younger age and die early due to its complications and this is thought to be due to the excess rates of diabetes in this ethnic population. Early detection and treatment of diabetes and higher than normal blood glucose levels following a heart attack can reduce the serious complications.

Based on information provided by the consultant looking after you on the ward, we are inviting you to participate in an important research study looking at the rates of undetected diabetes and higher than normal blood glucose levels and its impact on complications in people from multiethnic population admitted with heart attack. This study is being conducted by the Diabetes Research Team at the Leicester Royal Infirmary.

I am enclosing an Information Sheet giving details of the study and why you have been chosen.

Once you have read the information sheet, a doctor or nurse may approach you and ask if you are interested in taking part. Or, if you would definitely like to participate in the study, please complete and sign the enclosed form and return it to the ward staff in the provided envelope. The research team will then arrange an appointment with you.

If you feel that you need further information please call the Research Team on either 0116 2585446 or 0759097861 or tick the appropriate box on the provided form and someone from the Research Team will contact you to discuss the study further.

If you do not wish to receive any further invitations to participate in this research please let us know by ticking the appropriate box on the enclosed form.

Yours sincerely

Prof Melanie Davies
Professor of Diabetes, University Hospitals of Leicester

The SWEET-Heart Study, Leicester

Name of Participant
Address of Participant

Hospital Number:

I have read the information sheet provided and would like to take part in the SWEET-Heart Study. □

I have read the information sheet and would like to hear more about the SWEET-Heart Study. □

I do not want to take part in the SWEET-Heart Study (No further information is required). □

Signed: ___________________________ Date: ___________________________

Date of Birth: ___________________________

Do you already have diabetes? □Yes □No □Not sure

Are you taking part in any other clinical trial? □Yes □No □Not sure

Please include a suitable time for us to see you on the ward.

Please see me: □ Morning (9am-12pm) □ Afternoon (12pm-5pm) □ Evening (5pm-8pm)
PATIENT INFORMATION SHEET

The SWEET-Heart Study

A study of early detection of Type 2 diabetes and Pre-Diabetes following a Heart attack in patients from a multi-ethnic population

Principal Investigators: Professor Kamlesh Khunti, Professor Melanie Davies

You are being invited to take part in a research study. Because joining a research study is an important decision, we have put together some information to explain why the research is being done and how it may benefit you. Feel free to take your time to read this leaflet. You can talk it over with your family or friends, and if anything is not clear, or you would like to know more, we have put a name and contact number at the end of the leaflet so you can talk directly to us about being invited to take part in this research study.

What is the purpose of this study

In a healthy person without diabetes, a part of our body called the pancreas produces insulin, which helps the sugar in the food we eat to be stored in the body (mainly in muscle and the liver), and used for energy. In people with Type 2 diabetes, the pancreas is worn out, and cannot produce enough insulin to do this. As a result less sugar is stored into muscles and the liver while sugar levels in the blood become high. Importantly people with Type 2 diabetes are at a much higher risk of developing heart attack, stroke and damage to the kidneys, eyes and feet. Also once you have type 2 diabetes it doesn’t go away and becomes more serious over time.

In people with Pre-diabetes blood sugar levels are higher than normal but NOT enough for a diagnosis of diabetes. You may hear it called Impaired Glucose Tolerance (IGT) or Impaired Fasting Glucose (IFG) depending on which test was used to detect it. People with Pre-diabetes are more likely to develop type 2 diabetes and may already be experiencing some health problems because of it. Just like diabetes if you have pre-diabetes you are at a higher risk of developing a heart disease and/or stroke.

Type 2 diabetes and Pre-diabetes are rapidly increasing all over the world. As results the number individuals with heart disease are also steadily rising. Also type 2 diabetes is three to six fold more common in people from South Asian (SA) ethnic group. This puts SA people at a higher risk of developing heart disease.
Research shows that up to three quarters of people admitted with heart attack have type 2 diabetes or pre-diabetes. However many of them wouldn’t know about it. Also the current method of screening for Type 2 diabetes using a fasting blood test may not diagnose it in up to one third of them. Having type 2 diabetes or Pre-diabetes puts them at a higher risk of developing complications such as recurrence of heart attack in future, heart failure or death following heart attack. This situation is likely to be worse in SA people due to the high rates of diabetes in this ethnic population.

Research has shown that early detection and treatment of type 2 diabetes or Pre-diabetes following heart attack can significantly reduce the risk of developing such serious complications. However it is important that everyone admitted with heart attack is screened for type 2 diabetes using the most reliable screening method, so that no one remains undiagnosed. Currently there isn’t enough research information available on how common type 2 diabetes or pre-diabetes is following heart attack, in a multiethnic population in the UK. Also information is lacking on the reliability and benefits of different screening methods available for diagnosing type 2 diabetes following heart attack.

This study aims to find out how many people admitted with heart attack also have Type 2 diabetes or Pre-diabetes and haven’t being diagnosed before. We also aim to find out how best to pick it up early so that measures to control it can be started in time to avoid some of the serious complication. The study is part of an educational qualification that one of the doctors’ from the research team is undertaking.

Why have I been chosen?

You have been chosen because we are inviting everyone admitted with heart attack and not previously known to have Type 2 diabetes or pre-diabetes. If the heart specialist looking after you on the ward or a research registrar has given you a copy of this leaflet, it means you are eligible to join the study, and this is our invitation to you.

Do I have to take part?

No! Taking part is entirely up to you, although of course we hope that enough people will come forward to help us run the study. Even if you decide to take part now, and change your mind later, you can stop whenever you wish. And whatever decision you make, either now or during the study (if you decide to take part), will not affect the quality of care you receive.

What will happen to me if I take part?

First of all, we will arrange the first screening visit with you on the ward before your discharge from hospital. This visit will take around three hours and will be in the morning. We will ask you to fast (not eat any food after midnight) for this visit however that doesn’t mean that you are obliged to take part when we see you. Also, please be assured that this visit will not delay your planned discharge from the hospital. If you get discharged from the hospital before we arrange the first screening visit on the ward, we will invite you to return for the screening visit in our research clinic at the hospital. During the visit you will meet our
team and you can ask any questions you might have before signing our consent form. If you agree to take part, you will then undergo screening for type 2 diabetes by having the Oral Glucose Tolerance Test (OGTT) and some extra blood tests.

Regardless of the results of your first OGTT we will invite you for a second OGTT in 6 to 8 weeks times following discharge from the hospital. This is because to diagnose diabetes we need two results on two separate occasions. This second screening visit will take place in our diabetes research centre at the Leicester Royal Infirmary or Glenfield General Hospital and you can choose the most convenient day for you. This visit will also take around three hours in the morning and in addition to the OGTT you will undergo some of the extra blood tests measured before.

You, your GP and your heart specialist will receive a copy of the results within two weeks of the second visit. If the results are abnormal we will write to you before two weeks and if necessary someone we will telephone you to let you know the results.

**What is an Oral Glucose Tolerance Test (OGTT)?**

Firstly, you do not have anything to eat or drink after midnight. Although you may have water. We will then take some blood to check your blood sugar levels, recent average blood sugar level - the HbA1c test - and health of your kidneys. You will then have a sugary drink (Lucozade). After 2 hours you will have your blood sugar levels measured again to see how well your body is dealing with the sugar intake. We will also take some additional blood samples to check levels of Insulin and certain proteins in the blood (biomarkers) that may show whether you are at a higher risk of diabetes.

**What are the extra blood tests for?**

In the last few years research has shown that certain proteins in the blood are linked to lifestyle and the risk of developing diabetes and heart disease. We will measure levels of such proteins in your blood whilst we are taking fasting blood samples. This is to see how the amounts of these proteins differ in people from different ethnic populations and during the course of admission and 6 to 8 weeks after a heart attack.

Research has also shown that the amount of Insulin produced in your body, in relation to sugar rise, relates to the risk of developing diabetes and heart disease. We would also like to measure your Insulin level at fasting, at 30 minutes, one hour and two hour following the Lucozade drink. We will only do this at the first oral glucose tolerance test.

During the first visit, we will take a total of 60 mls (12 teaspoons) of blood from your arm, over two hours, using a cannula inserted into a vein in your arm. If you already have a cannula inserted by your doctor on the ward (which most people will have) all blood sample during the first visit will be collected through this cannula. However if the cannula has been removed we will need to insert a new cannula to obtain blood samples. It will be removed after we have taken the final sample.

During the second visit we will take total 40 mls (8 teaspoon) of blood over two hours using only a syringe a needle (no need for a cannula insertion).
Other tests

We will also ask you to collect a first morning urine sample for each visit to check for excess amounts of protein leakage (albumin-creatinine ratio) from your kidney. This research is also looking at ethnic differences in the amount of such protein leakage and its relation to development of complications in people with heart attack.

In between the blood tests one of our team will ask you to complete a questionnaire about your health, physical activity, eating habits and overall wellbeing. We will also ask you about your past medical history, any medications you are taking, your occupation, smoking habits and history of diabetes and heart disease in your family. It should take about 30 to 45 minutes to complete. We will also measure your height, weight, waist circumference and blood pressure.

What else does this study involve?

This study is also investigating, in the first year following heart attack, the rates of complications. For this we will use your information held by the NHS and records maintained by the General Registrar office. To do this we need to have your permission to go through your hospital records and also pass on your details and NHS number to the Hospital Episode Statistics (HES), Office of National Statistics (ONS), and Morbidity Query Information Export SynTax (MIQUEST) - a methodology used to access information from GP computer records. These official sources (HES, ONS and MIQUEST) will give us information about your illnesses and hospital admissions in the first year following heart attack.

Optional assessments

We would also like to collect some further important measurements and information about you. However these are optional – it is for you to decide whether or not you would like to have them done.

Firstly, we would like to store some of your blood samples long term and use them for future diabetes research. This is likely to involve research looking at any new types of proteins linked to the risk of diabetes and heart disease, found in future. Any such study that we want to do in future will have ethics committee approval. We will store the sample in our secure freezers for up to 10 years, after which we will we will transfer them into a bio-bank. All stored samples will be marked with an identification code. When you donate your samples you will be ‘gifting’ them to us, but you can at any time request them to be destroyed if they have not been used. If you are happy for us store your sample in longer term for this purpose then you will have to tick a box on the consent form.

Mortality Tagging: Secondly we also want to be able to check the health status of people participating in our study in the longer term at two, five and ten year’s time. This is called mortality tagging. It is also done with the help of ONS as discussed before and we need to have your permission to pass your details to ONS for this specific purpose. However if you want, you can opt out of this part of the study involving mortality tagging in long term by not ticking the box at the bottom of the consent form.
What will my results show? :

After analysing the two OGTT results it will show one of the following:

- You don’t have type 2 diabetes or pre-diabetes.
- You have diabetes
- You have pre-diabetes

What if my results are normal?

If your results are normal then you and your GP will receive a copy of the results of all your tests within two weeks of your second appointment. Some people may follow less healthy lifestyle after an ‘all clear’ result. If so this would be an unwanted feature of screening for diabetes. Some written information highlighting benefits of a healthy lifestyle may be a simple answer to this problem.

What if my results show I have diabetes?

You will have a confirmed diagnosis of type 2 diabetes if both the OGTT results show your blood sugar levels are in diabetes range. However in some patients who have symptoms of diabetes only one abnormal test is enough to confirm the diagnosis of diabetes. In any case you will be telephoned within two working days to inform you of the results and you will be referred to your GP for appropriate treatment. The good news is that the earlier type 2 diabetes is detected the better it can be treated with resulting benefits of reduced chances of developing long term complications.

Also it is likely that the diagnostic criteria of diabetes in the UK will change in near future and include the recent average blood sugar level – the HbA1c test in it. In the HbA1c test part of the red cells in the blood to which sugar is attached is measured. This part of red blood cells then gives a good indication of average blood sugar level over the previous 6 to 8 weeks. If the change in diagnostic criteria is to happen during the course of this study, some people may be considered as having type 2 diabetes based on their HbA1c test although they were previously not diagnosed to have it based on the results of the two OGTT. If your diabetes diagnosis status change and if you were considered to have type 2 diabetes based on the new HbA1c criteria, we will immediately inform you and refer you to your GP for appropriate treatment.

What if my results show I have pre-diabetes?

Past research shows that 50% of people with pre-diabetes go on to develop diabetes within 10 years. Also SA people are more likely to progress to diabetes compared to white people. However, we also know that if people can make lifestyle changes then they can significantly reduce their chances of getting diabetes and sometimes get their blood sugar levels back to normal range. If the test results show that you have pre-diabetes we will provide you with information to make lifestyle changes. However as you recently had a heart attack which can
limit your ability to undergo any physical exercises as normal, you need to discuss any such recommendations on physical activity with your heart specialist. Currently there are no tablet treatments available for people with pre-diabetes; however this is being researched across the country.

**Will my GP be informed of my results?**

Yes, your family doctor will be informed of all results of the tests taken at both the visits.

**Will there be any side effects?**

You may suffer from slight discomfort while the cannula is being inserted or the blood sample is being taken using a needle and syringe from your arm. Some people do experience bruising after cannula insertion or blood samples have been taken. Rarely the vein used to insert the cannula may become swollen however this usually settles within few days. You may have a negative feeling or perceive a reduction in health if you are found to have type 2 diabetes on screening. On the other hand you may feel motivated that you are diagnosed as having diabetes at an early stage and have a chance to control the disease in time to avoid long term complications.

**What do I have to do if I want to take part in this study?**

If you decide to take part in the study you will be asked to sign a consent form. You will be given a copy of this patient information sheet and a copy of the signed consent form to keep for your own records. If you need an interpreter to help you when you attend for visits at the hospital we can arrange this for you.

**What are the possible benefits of taking part?**

We hope that all people in the study will avoid developing some of the complications of diabetes such as heart problems, eye problems and kidney problems, however, this cannot be guaranteed. The information we get from this study may help us to treat future patients with diabetes better to stop or prevent complications happening.

**Will I get travelling expenses?**

Travel costs will be reimbursed up to £15, which includes parking charges and public transport fares, so please keep all your receipts. If driving, you will also need to record your mileage.

**What if something goes wrong?**

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone’s negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated
during the course of this study, the normal National Health Service complaints mechanisms are available to you. You can phone the hospital’s Patient Information and Liaison Service (PILS) on freephone: 0808 178 8337. You can also email your complaint by filling in an online form on the hospital website: www.ahl-tr.nhs.uk/patients/support-and-advice/making-a-complaint.

Will my taking part in this study be kept confidential?

Absolutely! All information that is collected about you during the course of the research will be kept strictly confidential. All your research data will be handled by to the co-ordinating centre at the University hospitals of Leicester NHS trust and any information about you, which leaves the co-ordinating centre, will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?

The results of the study may be published in a professional journal, but you will not be identified by name in any publications.

Who is organising and funding the research?

This research is being undertaken under the CLAHRC programme and funded through money from the Department of Health. The study is coordinated by the University hospitals of Leicester NHS trust.

Who has reviewed the study?

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

If you require any further information about the study you can contact the SWEET-Heart study team on 07590978861.

Many thanks for taking the time to read this patient information sheet.
The SWEET-Heart Study Consent Form  Version 2, 8th July 2010

Principal Investigator: Professor Kamlesh Khunti, Professor MJ Davies

Study ID

1. I confirm that I have read and understand the patient information sheet version 2, dated 8th July 2010 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, without my medical or legal rights being affected.

3. I understand that sections of my medical notes may be looked at by responsible individuals from the SWEET-Heart team, from regulatory authorities or the NHS trust, where it is relevant to me taking part in research. I give permission for these individuals to have access to my records.

4. I agree to my GP being informed of my participation.

5. I agree to take part in the above study.

i. I consent for my anonymised blood sample to be stored and used for future research related to biomarker in diabetes and heart disease. I understand this is a free choice and does not affect my participation in the study.

ii. I consent for my anonymised stored blood samples to be transferred to a biobank after 10 years of being stored if they have not been used.

iii. I understand that information held by the NHS and records maintained by the General Register Office may be used to keep in touch with me and follow up my health status.

iv. I agree to being contacted with details of future research and my details to be stored on a computer database for this purpose.

Name of patient __________________________ Date __________ Signature __________________________

Name of person taking the consent (if different from researcher) __________________________ Date __________ Signature __________________________

Researcher __________________________ Date __________ Signature __________________________

Three copies required: 1 copy for patient; 1 copy for the researcher pack, 1 copy (original) for the medical notes

SWEET Heart Consent form v2, 8th July 2010
Study ID: 

Name:______________________________

Date: ____________________________

Date of Birth: _____________________

Male □ Female □

Questionnaire Booklet

Please fill out all the questions contained in this booklet. The answers you give are important to us and will be treated with the utmost confidentiality.
Section A - Occupation

B1. What is your current work status?

- In work - full time i.e. more than 30 hours per week
- part time work i.e. less than 30 hours per week
- keeping house
- wholly retired from work
- waiting to start a new job already obtained
- unemployed and looking for work
- out of work as temporarily sick
- permanently sick or disabled

Other: please specify

B2. Please could you give us some details about your present or last job.

What is (was) the name or title of your job?

______________________________

What kind of work do (did) you do in your job?

______________________________

What training or qualifications are (were) needed for your job?

______________________________

Are (were) you working:

- as an employee
- as self-employed

Do (did) you supervise or have management responsibility for the work of other people?
B3. Do you have a partner?

Yes [ ] No [ ]

If your answer is No, please go to B4

If yes

B3a. What kind of work does (did) s/he do in his/her job?

___________________________________________________________

B3b. What training or qualifications are (were) needed for his/her job?

___________________________________________________________

B3c. Is (was) s/he working.....

- as an employee [ ]
- as self-employed [ ]

B3d. Does (did) s/he supervise or have management responsibility for the work of other people?

- No [ ]
- Yes; 1-24 people [ ]
- Yes; 25 or more people [ ]

B4. At what age did you finish full time education? ________ years

B5. Does your household have any cars or vans normally available for its use?
Do you own or rent your home?

- Own it/buying it
  - Yes □ No □
- Rent it
  - Yes □ No □

B6a. What is your legal marital status?

- Married □
- Unmarried □
- Divorced/Separated □
- Widow/Widower □

B6b. Have you ever cohabited with someone without being married?

- I am cohabiting with someone now □
- I have cohabited with someone in the past □
- I have never cohabited with someone □
Section B - Your Health – and – Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

1. Overall, how would you rate your health during the past week? [Mark with a ☐ in the one box that best describes your answer.]

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
<th>Very poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
</tbody>
</table>

2. During the past week, how much did physical health problems limit your usual physical activities (walking, climbing stairs)?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Very little</th>
<th>Somewhat</th>
<th>Quite a lot</th>
<th>Could not do physical activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
</tbody>
</table>

3. During the past week, how much difficulty did you have doing your daily work, both inside and outside the home, because of your physical health?

<table>
<thead>
<tr>
<th>None at all</th>
<th>A little bit</th>
<th>Some</th>
<th>Quite a lot</th>
<th>Could not do daily work</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
</tbody>
</table>

4. How much bodily pain have you had during the past week?

<table>
<thead>
<tr>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
</tbody>
</table>
5. **During the past week**, how much energy did you have?

- Very much
- Quite a bit
- Some
- A little
- None

☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

6. **During the past week**, how much did your physical health or emotional problems limit your usual social activities with family or friends?

- Not at all
- Very little
- Somewhat
- Quite a lot
- Could not do social activities

☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

7. **During the past week**, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?

- Not at all
- Slightly
- Moderately
- Quite a lot
- Extremely

☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

8. **During the past week**, how much did personal or emotional problems keep you from doing your usual work, studies, or other daily activities?

- Not at all
- Very little
- Somewhat
- Quite a lot
- Could not do daily activities

☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5
Section C - Anxiety & Depression

Instructions - Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your clinician to know how you feel.

You do not have to think too much to answer. For these questions, spontaneous answers are the most important.

Read every sentence. Place an X on the answer that best describes how you have been feeling during the LAST WEEK.

1. I feel tense or wound up:
   - Most of the time
   - A lot of the time
   - From time to time
   - Not at all

2. I still enjoy the things I used to enjoy
   - Definitely as much
   - Not quite as much
   - Only a little
   - Hardly at all

3. I get a sort of frightened feeling as something awful is about to happen
   - Very definitely and quite badly
   - Yes, but not too badly
   - A little but it doesn’t worry me
   - Not at all

4. I can laugh and see the funny side of things
   - As much as I always could
   - Not quite as much now
   - Definitely not so much now
   - Not at all

5. Worrying thoughts go through my mind
   - A great deal of the time
   - A lot of the time
   - From time to time but not often
   - Only occasionally

6. I feel cheerful
   - Not at all
   - Not often
   - Sometimes
   - Most of the time

7. I can sit at ease and feel relaxed
   - Definitely
   - Usually
   - Not often
   - Not at all

8. I feel as if I am slowed down
   - Nearly all of the time
   - Very often
   - Sometimes
   - Not at all

9. I get a sort of frightened feeling like butterflies in the stomach

10. I have lost interest in my appearance
11. I feel restless, as if I had to be on the move
- Not at all
- Occasionally
- Quite often
- Very often

12. I look forward with enjoyment to things
- Definitely
- I don’t take as much care as I should
- I may not take quite as much care
- I take just as much care as ever

13. I get a sudden feeling of panic
- Very often indeed
- Quite often
- Not very often
- Not at all

14. I can enjoy a good TV or radio programme or book
- Often
- Sometimes
- Not often
- Very seldom
SECTION D - Physical Activity

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active during the last 7 days before admission to hospital. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the vigorous activities that you did in the last 7 days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

1. During the last 7 days, on how many days did you do vigorous physical activities like heavy lifting, digging, aerobics, or fast bicycling?
   ______ days per week
   □ No vigorous physical activities ➔ Skip to question 3

2. How much time did you usually spend doing vigorous physical activities on one of those days?
   ______ hours per day
   ______ minutes per day
   □ Don’t know/Not sure

Think about all the moderate activities that you did in the last 7 days. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the last 7 days, on how many days did you do moderate physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.
   ______ days per week
   □ No moderate physical activities ➔ Skip to question 5
4. How much time did you usually spend doing moderate physical activities on one of those days?

   _____ hours per day
   _____ minutes per day

   ☐ Don’t know/Not sure

Think about the time you spent walking in the last 7 days. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the last 7 days, on how many days did you walk for at least 10 minutes at a time?

   _____ days per week

   ☐ No walking ➔ Skip to question 7

6. How much time did you usually spend walking on one of those days?

   _____ hours per day
   _____ minutes per day

   ☐ Don’t know/Not sure

The last question is about the time you spent sitting on weekdays during the last 7 days. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the last 7 days, how much time did you spend sitting on a week day?

   _____ hours per day
   _____ minutes per day

   ☐ Don’t know/Not sure
SECTION E - Eating Habits Questionnaire

Purpose
The purpose of this questionnaire is to get an idea of your usual eating habits. For the listed foods, we would like to know how many servings you eat in a typical day or week. A serving is an average portion that would be served at a meal. If you usually eat more than one serving of the food at a time, you should count all the servings you eat.

Instructions
For each food listed, tick the box that describes the number of servings that you usually eat. If you never eat a particular food, tick the box under “None”.

Please do not leave any lines blank.

<table>
<thead>
<tr>
<th>Breads &amp; Rolls</th>
<th>None</th>
<th>Less than 1 a day</th>
<th>1 to 2 a day</th>
<th>3 to 4 a day</th>
<th>5 or more a day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. White bread or rolls, chapattis or parathas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Brown bread or rolls, or brown chapattis, or parathas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Wholemeal bread or rolls, chapattis, or parathas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Breakfast cereals</th>
<th>None</th>
<th>Less than 1 a week</th>
<th>1 to 2 a week</th>
<th>3 to 5 a week</th>
<th>6 or more a week</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Sugared type: Frosties, Coco Pops, Ricicles Sugar Puffs Rice or Corn type: Corn Flakes, Rice Krispies, Special K</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Porridge or Ready Brek Wheat type: Shredded Wheat, Weetabix, Fruit 'n Fibre, Puffed Wheat, Nutri-grain, Start Muesli type: Alpen, Jordan's</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
About how many **servings per week** do you eat of the following foods?
(Please tick one box on each line)

<table>
<thead>
<tr>
<th>Vegetable foods</th>
<th>None</th>
<th>Less than 1 a week</th>
<th>1 to 2 a week</th>
<th>3 to 5 a week</th>
<th>6 to 7 a week</th>
<th>8 to 11 a week</th>
<th>12 or more a week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasta, rice, or dishes made from grains such as millet, semolina and cornmeal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INCLUDE: plain boiled rice, rice and peas, pilau and biryani</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potatoes (excluding chips), yams, cassava, plantains, breadfruit, sweet potatoes or taro/eddo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peas, lentils (dhal) or beans (including baked beans)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other types of vegetables (cooked or raw as in salads)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit (including fresh, frozen or canned fruit)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

About how many **servings per week** do you eat of the following foods?
(Please tick one box on each line)

<p>| Cheese (any except cottage)                                                    |      |                    |               |               |               |               |                  |
| Beef, pork, or lamb (for vegetarians; nuts)                                    |      |                    |               |               |               |               |                  |
| INCLUDE: burgers, sausages, bacon, ham, meat pies, meat curries, casserole, and processed meat |      |                    |               |               |               |               |                  |
| Chicken or turkey (including processing types)                                  |      |                    |               |               |               |               |                  |
| Fish (NOT fried fish)                                                           |      |                    |               |               |               |               |                  |
| ANY fried food                                                                  |      |                    |               |               |               |               |                  |
| INCLUDE: fried fish, fried chicken                                            |      |                    |               |               |               |               |                  |</p>
<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Less than a quarter pint</th>
<th>About a quarter pint</th>
<th>About half a pint</th>
<th>1 pint or more</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>17. Cakes, pies, puddings, pastries or Indian sweets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>18. Sweet or savoury snacks such as chocolate, crisps, biscuits, Bombay mix, sev and chanachur</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**About how much of the following types of milk do you yourself use in a day**, for example in cereal, tea, or coffee? (Please tick one box on each line)

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Less than a quarter pint</th>
<th>About a quarter pint</th>
<th>About half a pint</th>
<th>1 pint or more</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>19. Full cream (silver top) or Channel Islands (gold top)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>20. Semi-skimmed (green or red striped top)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>21. Skimmed (blue checked top)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**About how many rounded teaspoons per day** do you usually use of the following types of spreads, for example on bread, sandwiches, toast, potatoes, or vegetables?

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>1 a day</th>
<th>2 a day</th>
<th>3 a day</th>
<th>4 a day</th>
<th>5 a day</th>
<th>6 a day</th>
<th>7 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>22. Butter, ghee or margarine such as sunflower or olive spread, Flora, Vitalite, Clover, Olivio, Stork, Utterly Butterly</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>23. Low fat spreads (e.g. Shape, Delight, Flora Lite, half fat butter, half fat ghee, etc)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**What type of fat do you usually use for the following purposes?**

(Please tick one box on each line)

<table>
<thead>
<tr>
<th></th>
<th>Solid cooking fat (White Flora, Cookeen)</th>
<th>Hard margarine (Stork) or ghee</th>
<th>Low fat spread (Flora Light, Olivite, St. Ivel Gold) or peanut oil</th>
<th>No fat used</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>24. As a spread</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1 a day</td>
<td>2 a day</td>
<td>3 a day</td>
</tr>
<tr>
<td>----------------------</td>
<td>------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Fruit, vegetables or salad</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Include: fresh, frozen, chilled, dried, canned or 100% juice. (NOT potatoes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

25. For frying
26. For baking or cooking

About how many portions of fruit, vegetables, or salad do you usually eat in a day?

Thank You for completing this Questionnaire.
Appendix B (The SWEET-Heart Study, Protocol): The Algorithm

Algorithm showing versions of the ‘Result Letters’ to be send to the GPs and Patients, informing the outcomes of successive OGTTs and the final diagnosis. (Please follow a similar pattern of connecting arrows at a time to navigate through the diagram)

1st OGTT

- Normal range
- Pre-diabetes range
- Diabetes range

2nd OGTT

- Normal range
- Pre-diabetes range
- Diabetes range

Diagnosis

- Normal
  (Letter 1)
- Pre-diabetes
  (Letter 3)
- Pre-diabetes
  (Transient)
  (Letter 2)

3rd OGTT

- Diabetes
  (Letter 4)

Diagnosis

- Diabetes
  (Letter 5)
- Diabetes
  (Letter 6)

Symptoms present

Appendix B: (The SWEET-Heart study Protocol) v1 4th May 2010
Dear «Pat_Title» «Pat_FirstName» «Pat_LastName»

09/01/2017

Patient ID: «Pat_ID»
Appointment Date: «Appt_Date»
Height: «Pat_Height»m
Weight: «Pat.Weight»kg
Body Mass Index: «Pat_BMI»kg/m²
Blood pressure: «BPavesys»/«BPaveda» mmHg

<table>
<thead>
<tr>
<th>BloodTests</th>
<th>First Visit «ApptDate»</th>
<th>Second Visit «ApptDate»</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium:</td>
<td>«Sodium»mmol/L</td>
<td>«Sodium»mmol/L</td>
</tr>
<tr>
<td>Potassium:</td>
<td>«Potassium»mmol/L</td>
<td>«Potassium»mmol/L</td>
</tr>
<tr>
<td>Urea:</td>
<td>«Urea»mmol/L</td>
<td>«Urea»mmol/L</td>
</tr>
<tr>
<td>Creatinine:</td>
<td>«Creatinine»umol/L</td>
<td>«Creatinine»umol/L</td>
</tr>
<tr>
<td>eGFR:</td>
<td>«eGFR»mL/min</td>
<td>«eGFR»mL/min</td>
</tr>
<tr>
<td>Fasting Glucose:</td>
<td>«Fasting Glucose»mmol/L</td>
<td>«Fasting Glucose»mmol/L</td>
</tr>
<tr>
<td>120 Minute Glucose:</td>
<td>«120M_Glucose»mmol/L</td>
<td>«120M_Glucose»mmol/L</td>
</tr>
</tbody>
</table>

Urine ACR:

I would like to thank you for taking part in the SWEET-Heart study.

**I would like to advise you that your glucose tolerance tests are normal.**

If you require any more information please contact the SWEET-Heart study team on 0116 2525429.

Yours sincerely

Dr Nitin Gholap
Research Registrar, Diabetes & Endocrinology

SWEET Heart Patient Result Letter 1 (NORMAL) v1 17 May 2010
Dear «Pat_Title» «Pat_LastName»

Patient ID: «Pat_ID»
Appointment Date: «ApptDate»
Height: «Pat_Height»m
Weight: «Pat_Weight»kg
Body Mass Index: «Pat_BMI»kg/m²
Blood pressure: «BPavesys»/«BPavedia» mmHg

<table>
<thead>
<tr>
<th>BloodTests</th>
<th>First Visit «ApptDate»</th>
<th>Second Visit «ApptDate»</th>
</tr>
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<td>Sodium</td>
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</tr>
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<td>120 Minute Glucose</td>
<td>«120M_Glucose» mmol/L</td>
<td>«120M_Glucose» mmol/L</td>
</tr>
</tbody>
</table>

Urine ACR:

I would like to thank you for taking part in the SWEET-Heart study.

I would like to advise you that your second glucose tolerance test (OGTT) is normal. However your first OGTT showed pre-diabetes and this increases your risk of developing diabetes in future.

We advice annual fasting blood sugar checks at your GP surgery in one year’s time.

If you require any more information please contact the SWEET-Heart study team on 0116 2525429.

Yours sincerely

Dr Nitin Gholap
Research Registrar, Diabetes & Endocrinology

SWEET Heart Patient Result Letter 2 (PRE-DIABETES transient) v1.17 May 2010
The SWEET-Heart Study, Leicester

09/01/2017&08/08/2040

Dear «Pat_Title» «Pat_LastName»

<table>
<thead>
<tr>
<th>Patient ID: «Pat_ID»</th>
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<tbody>
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<td>Height: «Pat_Height»m</td>
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<tr>
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</tr>
<tr>
<td>Body Mass Index: «Pat_BMI»kg/m2</td>
<td>Body Mass Index: «Pat_BMI»kg/m2</td>
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<tr>
<td>Blood pressure: «BPavessys»/«BPavedia» mmHg</td>
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</table>

<table>
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<th>Second Visit «ApptDate»</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium: «Sodium»mmol/L</td>
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</tr>
<tr>
<td>Potassium: «Potassium»mmol/L</td>
<td>«Potassium»mmol/L</td>
<td>«Potassium»mmol/L</td>
</tr>
<tr>
<td>Urea: «Urea»mmol/L</td>
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<td>Creatinine: «Creatinine»umol/L</td>
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</tr>
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<td>120 Minute Glucose: «120M_Glucose»mmol/L</td>
<td>«120M_Glucose»mmol/L</td>
<td>«120M_Glucose»mmol/L</td>
</tr>
</tbody>
</table>

| Urine ACR: | |
|------------| |

I would like to thank you for taking part in the SWEET-Heart study.

I would like to advise you that your glucose tolerance test is not completely normal. You do not have diabetes, but you do have pre-diabetes. This increases your risk of developing Diabetes in the future. However, this is less likely to occur if you can make changes to your lifestyle. We have included an information booklet about Pre-Diabetes. Since you recently suffered a heart attack which can affect your ability to take physical exercise as normal, please discuss the recommendation in the booklet on physical activity with your heart specialist during your next visit.

We also advise annual fasting blood sugar checks at your GP surgery in one year's time to see if you have gone on to develop diabetes.

If you require any more information please contact the SWEET-Heart study team on 0116 2525429.

Yours sincerely

Dr Nitin Gholap
Research Registrar, Diabetes & Endocrinology

SWEET Heart Patient Result Letter 3 (Pre-Diabetes) v1 17 May 2010
Dear «Pat_Title» «Pat_LastName»

09/01/2017

Patient ID: «Pat_ID»
Appointment Date: «ApptDate»
Height: «Pat_Height»m
Weight: «Pat_Weight»kg
Body Mass Index: «Pat_BMI»kg/m²
Blood pressure: «BP_average»/«BP_average» mmHg

<table>
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</table>

Urine ACR:

I would like to thank you for taking part in the SWEET-Heart study.

I would like to advise you that your second glucose tolerance test (OGTT) has shown that you have high blood sugar levels in the diabetes range. However, your first OGTT test did not show diabetes. To confirm diabetes, OGTT showing diabetes range results on two separate occasions are needed.

In view of this, we will arrange you to have another OGTT within two weeks time.

If you require any more information please contact the SWEET-Heart study team on 0116 2525429.

Yours sincerely

Dr Nitin Gholap
Research Registrar, Diabetes & Endocrinology

SWEET Heart Patient Result Letter 4 (Recall for third OGTT) v1 17 May 2010
Dear «Pat_Title» «Pat_LastName»,

Patient ID: «Pat_ID»
Appointment Date: «ApptDate»
Height: «Pat_Height»m
Weight: «Pat_Weight»kg
Body Mass Index: «Pat_BMI»kg/m^2
Blood pressure: «BPavsys» mmHg

<table>
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<th>First Visit «ApptDate»</th>
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<tr>
<td>Fasting Glucose</td>
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</tr>
<tr>
<td>120 Minute Glucose</td>
<td>«120M_Glucose» mmol/L</td>
<td>«120M_Glucose» mmol/L</td>
</tr>
<tr>
<td>Urine ACR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

I would like to thank you for taking part in the SWEET-Heart study.

I would like to advise you that your glucose tolerance tests are abnormal and confirms that you have diabetes.

The results of this test have been forwarded to the diabetes consultant in the hospital and your GP. The hospital diabetes team will arrange an appointment to see you in the next 2 weeks to discuss your diagnosis in more detail and initiate an appropriate treatment.

If you require any more information please contact the SWEET-Heart study team on 0116 2525446.

Yours sincerely

Dr Nitin Gholap
Research Registrar Diabetes
Dear «Pat_Title» «Pat_LastName»

09/01/2017

Patient ID: «Pat_ID»
Appointment Date: «ApptDate»
Height: «Pat_Height»m
Weight: «Pat_Weight»kg
Body Mass Index: «Pat_BMI»kg/m2
Blood pressure: «BPavsys»/«BPavdia» mmHg

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<tr>
<td>Fasting Glucose</td>
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</tr>
<tr>
<td>120 Minute Glucose</td>
<td>«120M_Glucose» mmol/L</td>
<td>«120M_Glucose» mmol/L</td>
</tr>
</tbody>
</table>

Urine ACR:

I would like to thank you for taking part in the SWEET-Heart study.

I would like to advise you that your glucose tolerance test has shown that you have high blood sugar levels in the diabetes range. As you also have symptoms of diabetes the test confirms that you have type 2 diabetes.

The results of this test have been forwarded to the diabetes consultant in the hospital and your GP. The hospital diabetes team will arrange an appointment to see you in the next 2 weeks to discuss your diagnosis in more detail and initiate an appropriate treatment.

If you require any more information please contact the SWEET-Heart study team on 0116 2525429.

Yours sincerely

Dr Nitin Gholap
Research Registrar, Diabetes & Endocrinology

SWEET Heart Patient Result Letter 6 (DIABETES with symptoms) v3 13th March 2011
The SWEET-Heart Study, Leicester

09/01/2017

Dear <GP_Title> <GP_LastName>

The following patient attended Oral Glucose Tolerance Tests (OGTT) for the SWEET-Heart Study on <ApptDate> during his recent admission with acute myocardial infarction and at follow up visit on <ApptDate>. The results of the OGTTs and general health screen are listed below:

Patient ID: <Pat_ID>

Patient: <Pat_Title> <Pat_FirstName> <Pat_LastName>

Address: <Pat_AddressLine1>, <Pat_Towns>, <Pat_Postcode>

Date of Birth: <Pat_Dob>

Height: <Pat_Height> m  Weight: <Pat_Weight> kg  BMI: <Pat_BMI> kg/m²

Blood Pressure: <BP_sys>/<BP_dia> mmHg

Current Smoker: <SmokerText> if yes, number of cigarettes per day <Pat_NoPerDay>

<table>
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<th>Blood Results</th>
<th>First Visit &lt;ApptDate&gt;</th>
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<tr>
<td>Sodium</td>
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</tr>
<tr>
<td>Creatinine</td>
<td>Result &lt;Creatinine&gt; umol/L</td>
<td>Result &lt;Creatinine&gt; umol/L</td>
</tr>
<tr>
<td>eGFR</td>
<td>Result &lt;eGFR&gt; mL/min</td>
<td>Result &lt;eGFR&gt; mL/min</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Result &lt;HbA1c&gt; %</td>
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<tr>
<td>Fasting Glucose</td>
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</tr>
<tr>
<td>120 Minute Glucose</td>
<td>Result &lt;M_120M_Glucose&gt; mmol/L</td>
<td>Result &lt;M_120M_Glucose&gt; mmol/L</td>
</tr>
</tbody>
</table>

Urine albumin: creatinine ratio Results Results

This patient was shown to have normal glucose test results.

Yours Sincerely

Dr Nitin Gholap
Research Registrar, Diabetes & Endocrinology

Cc: <Admitting Cardiologist - Name and Address>

SWEET Heart GP Result Letter 1 (Normal) v1 17 May 2010
08/01/2017 to 06/02/2018

Dear «GP_Title» «GP_LastName»,

The following patient attended Oral Glucose Tolerance Tests (OGTT) for the SWEET- Heart Study on «ApptDate» during their recent admission with acute myocardial infarction and at a follow up visit on «ApptDate». The results of the OGTT and general health screen are listed below.

Patient ID: «Pat_ID»

Patient: «Pat_Title» «Pat_FirstName» «Pat_LastName», «Pat_AddressLine1», «Pat_AddressLine2», «Pat_Town», «Pat_Postcode».

Date of Birth: «Pat_Dob»

Height: «Pat_Height»m  Weight: «Pat_Weight»kg  BMI: «Pat_BMI»kg/m²

Blood Pressure: «BP_sys»/«BP_dia» mmHg

Current Smoker: «Pat_IsCurrentSmoker» If yes, number of cigarettes per day: «Pat_NoPerDay»

<table>
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<th>Blood Results:</th>
<th>First Visit «ApptDate»</th>
<th>Second Visit «ApptDate»</th>
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<td>Result «120M_Glucose» mmol/L</td>
</tr>
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</table>

Urine albumin: creatinine ratio: Results: Results

This patient was shown to have normal glucose tolerance on the second test. However his first test showed pre-diabetes and this can increase his risk of developing diabetes in the future.

Therefore we advise annual fasting blood glucose checks at your surgery.

Yours sincerely

Dr Nitin Gholap
Research Registrar, Diabetes & Endocrinology

Cc: «Admitting Cardiologist - Name and Address»
09/01/2017

Dear <GP_Title> <GP_LastName>

The following patient attended Oral Glucose Tolerance Tests (OGTT) for the SWEET-Heart Study on <ApptDate> during his recent admission with acute myocardial infarction and at follow up visit on <ApptDate>. The results of the OGTTs and general health screen are listed below:

Patient ID: <Pat_ID>

Patient: <Pat_Title> <Pat_FirstName> <Pat_LastName>

Address: <Pat_AddressLine1>, <Pat_Town>, <Pat_Postcode>

Date of Birth: <Pat_Dob>

Height: <Pat_Height>m  Weight: <Pat_Weight>kg  BMI: <Pat_BMI>kg/m^2

Blood Pressure: <BPsys>/<BPdia>mmHg

Current Smoker: <SmokerText> if yes, number of cigarettes per day <Pat_NoParDay>

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<td>Result &lt;M_120M_Glucose&gt;mmol/L</td>
</tr>
</tbody>
</table>

Urine albumin: creatinine ratio Results

This patient was shown to have pre-diabetes.

There is evidence to show that this can be prevented from progressing to diabetes and the patient has been advised on the benefit of weight reduction and healthy eating.

Yours Sincerely

Dr Nitin Gholap  
Research Registrar, Diabetes & Endocrinology

Cc: « Admitting Cardiologist - Name and Address »

SWEET Heart Study GP Result Letter 3 (Pre-diabetes) v1 17 May 2010
The SWEET-Heart Study, Leicester

340

09/01/2017

Dear GP Title and LastName,

The following patient attended Oral Glucose Tolerance Tests (OGTT) for the SWEET-Heart Study on [ApptDate] during his recent admission with acute myocardial infarction and at a follow up visit on [ApptDate]. The results of the OGTTs and general health screen are listed below:

Patient ID: Pat_ID

Patient: Pat_Title, Pat_FirstName and Pat_LastName

Address: Pat_AddressLine1, Pat_Town, Pat_Postcode

Date of Birth: Pat_Dob

Height: Pat_Height m 
Weight: Pat_Weight kg 
BMI: Pat_BMI kg/m²

Blood Pressure: BP_sys mmHg/ BP_dia mmHg

Current Smoker: SmokerText

Blood Results:

<table>
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<td>Result</td>
</tr>
<tr>
<td>Urine albumin</td>
<td>Results</td>
<td>Results</td>
</tr>
</tbody>
</table>

This patient was shown to have diabetes range blood glucose levels on his second OGTT. However his first OGTT test did not show diabetes. To confirm diabetes, OGTTs showing abnormal results on two separate occasions are needed.

In view of this he will be recalled to have another Oral Glucose Tolerance test within two weeks time to confirm the diagnosis of diabetes.

Yours Sincerely

Dr Nitin Gholap
Research Registrar, Diabetes & Endocrinology

Cc: Admitting Cardiologist - Name and Address
The SWEET-Heart Study, Leicester

Dear [GP_Title] [GP_LastName],

The following patient attended oral glucose tolerance tests (OGTT) for the SWEET-Heart Study on [AppDate] during his recent admission with acute myocardial infarction and at follow up visit on [AppDate]. The results of the OGTTs and general health screen are listed below:

Patient ID: [Pat_ID]

Patient: [Pat_Title] [Pat_FirstName] [Pat_LastName]

Address: [Pat_AddressLine1], [Pat_AddressLine2], [Pat_Town], [Pat_Postcode]

Date of Birth: [Pat_Dob]

Results of initial screening:

Height: [Pat_Height]m Weight: [Pat_Weight]kg BMI: [Pat_BMI]kg/m²

Blood Pressure: [BPpavsys]/[BPvedia]mmHg

Current Smoker: [SmokerText] if yes, number of cigarettes per day [Pat_NoPerDay]

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Urine albumin:creatinine ratio: Results

The results of the test confirm that your patient has type 2 diabetes.

I would be grateful if you could make the necessary arrangements to see your patient in clinic, to initiate diabetes treatment.

If you feel that you need any further information from us at this stage please do not hesitate to contact me.

Yours sincerely

Dr Nitin Gholap
Research Registrar, Diabetes & Endocrinology
09/01/2017

Dear «GP_Title» «GP_LastName»

The following patient attended an Oral Glucose Tolerance Test (OGTT) for the SWEET-Heart Study on «ApprDate» during his recent admission with acute myocardial infarction. The results of the OGTT and general health screen are listed below:

Patient ID: «Pat_ID»

Patient: «Pat_Title» «Pat_FirstName» «Pat_LastName»

Address: «Pat_AddressLine1», «Pat_Town», «PatPostcode»

Date of Birth: «Pat_Dob»

Height: «Pat_Height»m Weight: «Pat_Weight»kg  BMI: «Pat_BMI»kg/m²

Blood Pressure: «BPavesys»/«BPavedia»mmHg

Current Smoker: «SmokerText»If yes, number of cigarettes per day «Pat_NoPerDay»

Urine albumin: creatinine ratio (ACR):

**Blood Results:**

<table>
<thead>
<tr>
<th></th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>«Sodium»mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>«Potassium»mmol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>«Urea»mmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>«Creatinine»umol/L</td>
</tr>
<tr>
<td>eGFR</td>
<td>«eGFR»mL/min</td>
</tr>
<tr>
<td>HbA1c</td>
<td>«HbA1c»%</td>
</tr>
<tr>
<td>Fasting Glucose</td>
<td>«Fasting Glucose»mmol/L</td>
</tr>
<tr>
<td>120 Minute Glucose</td>
<td>«M_120M_Glucose»mmol/L</td>
</tr>
</tbody>
</table>

This patient who has symptoms of diabetes was also shown to have high blood sugar levels in diabetes range on the OGTT. **This confirms that he does have type 2 diabetes.**

I would be grateful if you could make the necessary arrangements to see your patient in Clinic, to initiate diabetes treatment.

If you feel that you need any further information from us at this stage please do not hesitate to contact me.

Yours Sincerely

Dr Nitin Gholap
Research Registrar, Diabetes & Endocrinology

Cc: «Admitting Cardiologist - Name and Address»
• Are you admitted with a Heart Attack?
• Are you interested in participating in a study?

The SWEET-Heart Study
A study looking at the impact of high blood sugar levels and undetected diabetes on complications following a Heart Attack.

If interested please speak to any member of the staff on the ward or contact the research team on extension 7065429 or mobile 07884283386.
Appendix Seven: Publications related to the work in this thesis

Peer-reviewed publications (copies of articles are presented below in the listed order)


Gholap NN, Davies M, Patel K, Sattar N, Khunti K. Type 2 diabetes and Cardiovascular disease in South Asians. *Primary Care Diabetes* 2011;5:45-56

The published articles (pp. 346-363 & pp. 373-393) have been removed from the electronic version of this thesis due to copyright restrictions.

The unabridged version can be consulted, on request, at the University of Leicester Library.
Is admission blood glucose concentration a more powerful predictor of mortality after myocardial infarction than diabetes diagnosis? A retrospective cohort study

Nitinay Narayan Ghapal,¹ Rajnikant Laxmishanker Mehta,¹ Leong Ng,2,3 Melanie J Davies,² Kamlesh Khunti,¹ Iain B Squire2,3

ABSTRACT
Objective: To explore the relative association of admission blood glucose levels and antecedent diabetes on early and long-term survival in a contemporary UK population of patients with ST elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI).

Setting: Tertiary care centre.

Participants: 4111 (20.3% known diabetes) consecutive patients admitted with acute myocardial infarction (58.3% STEMI) between October 2002 and September 2008.

Primary and secondary outcome measures: All-cause mortality at 30 days and 1 year. The relative association of admission blood glucose and of antecedent diabetes with mortality was assessed using multivariate Cox regression analysis. Furthermore, we compared these relationships in patients with STEMI to those with NSTEMI.

Results: By 30 days and 1 year, 409 (9.9%) and 677 (16.5%) of patients died. After adjusting for covariates, diabetes did not show independent association with mortality at any time point in the entire cohort (HR 30 days 0.93 (95% CI 0.83 to 1.03); 1 year 1.00 (0.77 to 1.30)) or in subgroups of STEMI (HR 30 days 1.03 (0.65 to 1.64); 1 year 1.08 (0.77 to 1.51)) and NSTEMI (HR 30 days 0.62 (0.26 to 1.56); 1 year 0.87 (0.56 to 1.36)). In contrast, after adjusting for covariates, admission glucose showed robust and independent association with mortality in the entire cohort (HR 30 days 1.97 (1.04 to 1.10); 1 year 1.05 (1.03 to 1.08)), and in the subgroup of STEMI (30 days 1.07 (1.03 to 1.10); 1 year 1.07 (1.04 to 1.10)), and NSTEMI (HR 30 days 1.07 (1.00 to 1.14); 1 year 1.02 (0.97 to 1.06)).

Conclusions: Admission glucose is strongly associated with mortality in all presentations of acute myocardial infarction (AMI), irrespective of established diabetes diagnosis. The increased risk is maintained up to 1 year. Future studies are required to assess the impact of active management of elevated blood glucose in improving mortality in individuals admitted with AMI.

ARTICLE SUMMARY

Article focus
Robust associations are seen for both measures of glycaemia—the diagnosis of diabetes, and elevated blood glucose levels on admission, with poor outcomes in patients with ST elevation myocardial infarction (STEMI).

We explored the less known, relative association of admission blood glucose levels and antecedent diabetes on early and long-term survival in a contemporary UK population of patients with STEMI and non-STEMI (NSTEMI).

Key messages
In patients with both STEMI as well as NSTEMI, admission glucose is more strongly associated with mortality than is antecedent diabetes diagnosis.

The increased risk associated with admission glucose is evident during the index admission, at 30 days, 1 year and beyond and is apparent in those surviving to discharge.

Conversely, after multivariate adjustment for covariates, including admission glucose is not associated with mortality.

Strengths and limitations of this study
This is a study of a large cohort of patients with both STEMI and NSTEMI managed in contemporary clinical practice in a tertiary care centre.

A statistically robust association was seen for admission glucose with both short-term and long-term mortality after adjusting for many important confounders.

Our data lack information on glucose-lowering intervention, patients with undiagnosed diabetes and other potentially relevant variables which were not considered in the analysis.
Admission blood glucose and mortality post myocardial infarction

INTRODUCTION

For patients with acute myocardial infarction (AMI) the risk of adverse outcome is increased by the concomitant diagnosis of diabetes mellitus (diabetes). In addition, elevated blood glucose concentration, a common finding at admission in patients with AMI, is also associated with increased risk of adverse outcome, irrespective of prior diabetes. In some studies, the association between admission blood glucose concentration and adverse outcome was more powerful in patients without, compared to those with, prior diabetes. Indeed, we previously reported more powerful association with 36hrs and 1 year mortality after ST-elevation myocardial infarction (STEMI) for admission blood glucose concentration, compared to the diagnosis of diabetes.

While a causal relationship is unproven, there are numerous potential pathophysiological mechanisms by which hyperglycaemia may impact toxicity during myocardial ischaemia. Indeed, observational data suggest that elevated blood glucose may contribute directly to adverse outcome after AMI. Prognosis is worse for patients in whom hyperglycaemia persists in the 24-48 h after AMI compared to those in whom blood glucose normalises.

In patients without prior diabetes, insulin-based treatment of hyperglycaemia after AMI is associated with improved prognosis. Further, in randomised, controlled trials (RCTs) of intensive, insulin-based blood glucose management during admission with AMI, survival benefit was evident only when intervention effectively lowered blood glucose concentrations.

While the relationship between blood glucose concentration and outcome after AMI has largely been described in patients with STEMI, the majority of acute coronary syndromes in contemporary practice are non-ST-elevation AMI (NSTEMI). The aim of the current analysis was to compare the relative strength of association with 30-day and 1-year mortality of antecedent diabetes diagnosis and admission blood glucose concentration in patients with STEMI and with NSTEMI, and in those with and without a history of diabetes, in a multicentre population. We also assessed the relevance of blood glucose concentration, recorded soon after admission to hospital, with AMI, to mortality in patients surviving to discharge.

METHODS

Data were from consecutive admissions between 1 October 2002 and 30 September 2008, to the two coronary care units of a large teaching hospital serving the population of Leicestershire, UK (approximately 946,000 residents in 2004). For all patients, as part of the hospital’s mandatory commitment to the Myocardial Ischaemia National Audit Project (MINAP), we record clinical and demographic data including information on diagnosis (STEMI/NSTEMI), ECG site of infarct, medical history, coronary heart disease risk factors and prescribed medication. Data are re-linked to mortality information and include self-reported coding for ethnicity, for which local coverage is thorough. Approximately 10% of the local population are of South Asian ethnic origin, over twice the UK national average.

Patients were categorised as having a diagnosis of diabetes if this was self-reported by the patient, or on the basis of medication prescribed prior to admission. All patients with AMI routinely underwent blood glucose measurement, in most cases within first 12 h after admission with their blood samples assayed in the hospital laboratory. We used such first-recorded admission glucose levels for this analysis. All diagnoses of AMI were verified prior to submission to the national MINAP database; the diagnosis of AMI was made according to the joint ESC/ACC/AHA/WHF definition. Patients were categorised as STEMI or NSTEMI, according to the final discharge diagnosis recorded in the MINAP database. For patients with multiple AMI admissions during the study period, we considered only the first event. The number of cases admitted with AMI during the study period determined the sample size.

Survival was measured from the date of first admission to the date of death or of censoring at 30 September 2009. Mortality data are supplied to the hospital on a monthly basis via the UK Office for National Statistics. Follow-up data on mortality were available for all the patients. The predefined primary outcome measure was 30-day, and 1-year, all-cause mortality.

The study was approved by the local research ethics committee. The data used in this analysis were gathered during routine care and as part of the MINAP, managed by the Royal College of Physicians. We collected data pertaining to admission with AMI.

Statistical analysis

Baseline characteristics were compared between groups using independent two-sample t-tests for continuous variables and \( \chi^2 \) tests for categorical variables. Mortality at 30 days and at 1 year, in the entire cohort, and in those patients surviving to discharge, was calculated.

We calculated mortality proportions for patients admitted from 1 October 2002 to 30 September 2008 with follow-up censored at 30 September 2009. Survival probabilities were calculated using Kaplan-Meier (KM) analyses and patient groups compared using survival analysis log rank test. Relative risk of mortality, as a function of clinical variables, was examined using Cox proportional hazards techniques. We initially assessed the unadjusted, univariate association with outcome for admission blood glucose and for diabetes, and for other potentially relevant clinical and demographic variables (age, sex, ethnicity (White European, South Asian), smoking, type of AMI (STEMI, NSTEMI), prior history (hypertension, any coronary artery disease, cerebrovascular or peripheral vascular disease), admission systolic blood pressure and heart rate, estimated glomerular filtration rate (eGFR), coronary revascularisation during index admission, preadmission and discharge drug therapy (antiplatelet, \( \beta \)-blocker, statin, ACE inhibitor/angiotensin receptor blocker) and index...
Admission blood glucose and mortality post myocardial infarction

Demographic and clinical covariates with univariate association (p<0.10) with mortality at 30 days or 1 year were entered into multivariate models (Cox proportional hazards). All quantitative variables were entered as continuous variables into the model. Patients with missing data (table 1) were not excluded but their values were set as missing. Statistical significance for all comparisons was set at p<0.05 (two-sided). Data are presented as HR and 95% CI. We used fractional polynomials to model admission glucose to account for any non-linearity and assessed its independent association with mortality in subgroups with and without diabetes. Analyses were carried out using SPSS V.18.

<table>
<thead>
<tr>
<th>Table 1 Baseline characteristics at admission stratified by diabetes status</th>
<th>All, n=4111</th>
<th>Known DM, n=835 (20.3%)</th>
<th>Not known DM, n=3276 (79.7%)</th>
<th>p Value*</th>
<th>Missing value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>66.4 (13.3)</td>
<td>68.6 (11.8)</td>
<td>65.8 (13.6)</td>
<td>&lt;0.005</td>
<td>0.0</td>
</tr>
<tr>
<td>Women (%)</td>
<td>1224 (29.8)</td>
<td>276 (33.1)</td>
<td>948 (28.9)</td>
<td>0.022</td>
<td>0.0</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>White European</td>
<td>3381 (82.2%)</td>
<td>545 (61.1)</td>
<td>2836 (86.8)</td>
<td>&lt;0.005</td>
<td>0.0</td>
</tr>
<tr>
<td>South Asian</td>
<td>730 (17.8%)</td>
<td>290 (39.7)</td>
<td>440 (60.3)</td>
<td></td>
<td>0.0</td>
</tr>
<tr>
<td>Medical history (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2048 (50.3)</td>
<td>584 (70.0)</td>
<td>1464 (45.0)</td>
<td>&lt;0.005</td>
<td>1.0</td>
</tr>
<tr>
<td>Current/ex-smoker</td>
<td>1396 (33.7)</td>
<td>292 (33.6)</td>
<td>1084 (35.5)</td>
<td>0.527</td>
<td>7.1</td>
</tr>
<tr>
<td>Coronary heart disease†</td>
<td>491 (12.1)</td>
<td>149 (17.9)</td>
<td>342 (10.6)</td>
<td>&lt;0.005</td>
<td>0.9</td>
</tr>
<tr>
<td>CVA</td>
<td>254 (6.3)</td>
<td>86 (10.3)</td>
<td>168 (5.2)</td>
<td>&lt;0.005</td>
<td>1.2</td>
</tr>
<tr>
<td>PVD</td>
<td>154 (3.8)</td>
<td>42 (5.0)</td>
<td>112 (3.5)</td>
<td>0.041</td>
<td>1.2</td>
</tr>
<tr>
<td>Heart failure</td>
<td>190 (4.7)</td>
<td>76 (9.1)</td>
<td>114 (3.5)</td>
<td>&lt;0.005</td>
<td>1.2</td>
</tr>
<tr>
<td>Type of infarction (%)</td>
<td>STEMI</td>
<td>2397 (58.3)</td>
<td>417 (49.9)</td>
<td>1980 (60.4)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>1714 (41.7)</td>
<td>418 (49.9)</td>
<td>1296 (39.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>81.1 (24.3)</td>
<td>85.5 (25.3)</td>
<td>80.0 (24.0)</td>
<td>&lt;0.005</td>
<td>1.5</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>136.5 (28.4)</td>
<td>157.7 (30.7)</td>
<td>136.2 (27.7)</td>
<td>0.202</td>
<td>1.0</td>
</tr>
<tr>
<td>Biochemical data</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Peak CK (IU/L normal range &lt;200)</td>
<td>1113.5 (1810.4)</td>
<td>939.9 (1270.3)</td>
<td>1156.4 (1917)</td>
<td>&lt;0.005</td>
<td>7.6</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>116.4 (63.8)</td>
<td>128.8 (76.1)</td>
<td>113.1 (59.8)</td>
<td>&lt;0.005</td>
<td>16.8</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>63.0 (22.2)</td>
<td>57.7 (20.6)</td>
<td>64.4 (21.7)</td>
<td>&lt;0.005</td>
<td>16.6</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.1 (1.3)</td>
<td>4.4 (1.2)</td>
<td>5.2 (1.3)</td>
<td>&lt;0.005</td>
<td>16.6</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>13.7 (1.9)</td>
<td>13.0 (1.9)</td>
<td>13.9 (1.8)</td>
<td>&lt;0.005</td>
<td>66.6</td>
</tr>
<tr>
<td>Plasma glucose (mmol/l)</td>
<td>8.8 (4.2)</td>
<td>12.0 (5.5)</td>
<td>7.9 (3.3)</td>
<td>&lt;0.005</td>
<td>14.9</td>
</tr>
<tr>
<td>Therapies (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior to index admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>2671 (65.0)</td>
<td>622 (74.5)</td>
<td>2049 (62.5)</td>
<td>&lt;0.005</td>
<td>0.0</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>990 (25.6)</td>
<td>295 (35.2)</td>
<td>725 (22.6)</td>
<td>&lt;0.005</td>
<td>6.0</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>1097 (26.3)</td>
<td>407 (50.0)</td>
<td>690 (22.5)</td>
<td>&lt;0.005</td>
<td>5.8</td>
</tr>
<tr>
<td>Statins</td>
<td>1083 (28.0)</td>
<td>389 (48.7)</td>
<td>694 (22.6)</td>
<td>&lt;0.005</td>
<td>5.8</td>
</tr>
<tr>
<td>In-hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reperfusion therapy‡</td>
<td>2414 (58.7)</td>
<td>419 (50.2)</td>
<td>1955 (60.9)</td>
<td>&lt;0.005</td>
<td>0.0</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>1502 (37.4)</td>
<td>436 (52.7)</td>
<td>1066 (33.4)</td>
<td>&lt;0.005</td>
<td>2.3</td>
</tr>
<tr>
<td>AI discharge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>2701 (66.1)</td>
<td>529 (65.3)</td>
<td>2172 (68.8)</td>
<td>0.057</td>
<td>3.5</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>2513 (63.3)</td>
<td>483 (56.9)</td>
<td>2030 (64.3)</td>
<td>0.013</td>
<td>3.5</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>2493 (62.9)</td>
<td>495 (56.9)</td>
<td>1998 (63.4)</td>
<td>0.222</td>
<td>3.6</td>
</tr>
<tr>
<td>Statins</td>
<td>2704 (67.7)</td>
<td>537 (60.5)</td>
<td>2167 (68.2)</td>
<td>0.167</td>
<td>2.8</td>
</tr>
</tbody>
</table>

All values are mean (SD) or number (%).

*Known diabetes versus not-known diabetes.
†Any of angiography/myocardial infarction/percutaneous intervention (PCI)/coronary artery bypass grafting (CABG).
‡Thrombolysis or coronary intervention (PCI or CABG) or both.
ARF, argininosuccinate receptor blocker; CK, creatinine kinase; CVA, cerebrovascular accident; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate calculated using the MDRD formula; MDRD, modification of diet in renal disease; NSTEMI, non-ST elevation myocardial infarction; PVD, peripheral vascular disease; STEMI, ST elevation myocardial infarction; SBP, systolic blood pressure.
Admission blood glucose and mortality post myocardial infarction

RESULTS
The study population was the 4111 patients admitted between 1 October 2002 and 30 September 2008 with discharge diagnosis of AMI (STEMI 2397, 58.3%) and for whom a minimum of 365 days follow-up was available from the date of admission. For this cohort, median follow-up was 912 (range 0–2556) days; for 3792 (92.2%) patients surviving to discharge from the index admission, median follow-up was 1031 (range 1–2556) days.

Demographic details of the study population are presented in table 1. Prior diabetes was recorded in 835 (20.3%) patients compared to those without, patients with antecedent diabetes were on average older (65.6 vs 65.8 years, p=0.002), more likely to be female (33.2% vs 28.9%, p=0.022) and to have prior cardiovascular comorbidities. Presentation with NSTEMI was more prevalent in cases with diabetes (59.1%), compared to those without (30.6%), prior diabetes (p<0.005). Mean glucose level was higher in patients with diabetes (12.9±5.5 mmol/l) compared to those without (7.9±3.3 mmol/l) (p<0.005). Mean peak creatinine kinase was lower in patients with diabetes.

During the index admission administration of loop diuretics was more frequent (52.7% vs 33.4%, p<0.005) and, for patients with STEMI, coronary reperfusion therapy less frequent (50.2% vs 60.9%, p<0.005), in patients with diabetes. Other than for slightly less use of β-blockers and aspirin in patients with diabetes, patterns of prescription of secondary prevention therapies at discharge were similar in the two groups.

Mortality—univariate analysis
Deaths during hospitalisation, over 30 days, 1 year and the entire period of follow-up numbered 319 (7.8%), 409 (9.9%), 627 (15.6%) and 1041 (25.3%), respectively. Age, female sex, higher admission heart rate, higher eGFR, lower systolic blood pressure and presentation with STEMI (compared to NSTEMI), as well as prior smoking and hypertension, each showed univariate association with mortality risk over all time periods (table 2). Loop diuretic was associated with a 3–4 fold increase in mortality during follow-up. Survival improved over the period of observation.

Prior diabetes showed strong univariate association with mortality risk over all time periods HR 30 days 1.49 (1.12 to 1.95); 1 year 1.58 (1.35 to 1.86); all follow-up 1.66 (1.44 to 1.90) (table 2). The strength of association between glucose and mortality was consistent at 30 day and at 1 year, each mmol/l increase in admission glucose concentration being associated with a 6–7% increase in hazard of mortality over all time periods.

Postdischarge mortality
In those surviving to discharge (N=3792), 106 (2.8%), 365 (9.6%) and 726 (19.1%) died by 30-day, 1-year and over all follow-up (see online supplementary table S2A). Univariate associations with mortality were similar to those in the entire population. Prior diabetes showed univariate association with increased risk of death at all times, although this was not statistically significant at 30 days (HR 1.36, 0.87 to 2.12). For admission glucose, the strength of association with postdischarge mortality was very similar to that in the entire cohort, with 5–7% increase risk per mmol/l increase in glucose (see online supplementary table S2A).

Mortality—multivariate analysis
Table 3 shows the results of multivariate analysis. Age, lower admission systolic blood pressure and higher heart rate, lower eGFR, prescription of loop diuretic and STEMI (compared to NSTEMI) each retained independent association with mortality, as did prescription of individual discharge medications. After covariate adjustment, diabetes did not retain independent association with mortality at any time. In contrast, adjustment for covariates had little impact on the risk of mortality associated with admission glucose concentration.

Postdischarge mortality
For patients surviving to discharge, associations between clinical variables and the risk of mortality were similar to those seen in the entire cohort (see online supplementary table S5). While there was no association between prior diabetes and risk of mortality at any time (HR 30 days 0.64 (0.31 to 1.30); 1 year 0.91 (0.66 to 1.26); all follow-up 0.98 (0.86 to 1.16)), glucose concentration retained powerful association with the primary endpoint. This was evident at 30 days (HR per mmol/l 1.14, 95% CI 1.05 to 1.15), 1 year (1.05, 1.02 to 1.08) and over all follow-up (1.04, 1.02 to 1.06).

Admission glucose concentration: influence on mortality in patients with or without diabetes
We repeated multivariate analysis including a term for interaction between diabetes diagnosis and admission glucose concentration. While numerically greater in individuals without diabetes (figure 1), there was no conventional statistically significant difference in the association between mortality and admission glucose concentration for those with and without diabetes (30 days HR 1.00 (95% CI 0.97 to 1.03), p=0.95; 1 year 0.99, 0.97 to 1.02, p=0.66; entire follow-up 0.99, 0.97 to 1.01, p=0.42).

Diabetes and glucose after AMI: influence on mortality in STEMI and NSTEMI
After adjustment for covariates, diabetes showed no statistically significant association with mortality at any time period, either for STEMI or NSTEMI (table 4). The strength of association between blood glucose and mortality was very similar in the first 30 days after STEMI or NSTEMI. The strength of this relationship declined with time only after NSTEMI.
Discussion

It is well known that both prior diabetes diagnosis and admission blood glucose concentration are associated with adverse outcome after AMI. In this report, we compared the relative association of these two measures of dysglycemia with survival after STEMI as well as NSTEMI. Irrespective of the type of AMI, the univariate association with mortality risk for antecedent diabetes (40% excess at 30 days, 55% at 1 year) was no longer apparent after adjustment for relevant covariates including admission glucose concentration. In contrast, the excess risk associated with increasing glucose was not reduced after adjustment, was similar in those with and without known diabetes, and remained relevant in patients discharged alive from the index event.

In our previous report of over 9000 patients with STEMI, admitted in 1995–2004, the 50% increase in 30-day and 1-year mortality risk associated with known diabetes was attenuated by half on covariate adjustment and remained completely when admission blood glucose concentration was included in the analysis. The current report confirms these observations and extends them to a contemporary period, and to patients with NSTEMI as well as STEMI, in whom the strength of association between admission blood glucose concentration and 30-day mortality risk was similar, and concentration dependent. Importantly, the excess risk, around 7% for each 1 mmol/L increase in admission glucose concentration, was maintained up to and beyond 1 year from the index infarction. Further, this phenomenon was
### Table 3
Multivariate association of clinical variables with 30-day, 1-year and total mortality in the entire cohort

<table>
<thead>
<tr>
<th>N=4111</th>
<th>Mortality, N (%)</th>
<th>1 year</th>
<th>All (median 912 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 days</td>
<td>409 (9.95)</td>
<td>677 (16.5)</td>
</tr>
<tr>
<td>Admission demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (female vs male)</td>
<td></td>
<td>1.268 (0.885 to 1.819)</td>
<td>1.094 (0.865 to 1.383)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>1.059 (1.040 to 1.078)</td>
<td>1.062 (1.048 to 1.075)</td>
<td>1.073 (1.062 to 1.083)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>0.987 (0.981 to 0.992)</td>
<td>0.991 (0.987 to 0.995)</td>
<td>0.993 (0.990 to 0.996)</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>1.007 (1.001 to 1.013)</td>
<td>1.006 (1.002 to 1.010)</td>
<td>1.007 (1.005 to 1.010)</td>
</tr>
<tr>
<td>Admission plasma glucose (mmol/l)</td>
<td>1.072 (1.042 to 1.104)</td>
<td>1.059 (1.037 to 1.081)</td>
<td>1.053 (1.038 to 1.071)</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>0.987 (0.978 to 0.996)</td>
<td>0.982 (0.977 to 0.990)</td>
<td>0.988 (0.983 to 0.993)</td>
</tr>
<tr>
<td>NSTEMI versus STEMI</td>
<td>0.411 (0.282 to 0.597)</td>
<td>0.558 (0.443 to 0.704)</td>
<td>0.700 (0.587 to 0.834)</td>
</tr>
<tr>
<td>Ethnicity (South Asian vs White European)</td>
<td>1.355 (0.893 to 2.057)</td>
<td>1.155 (0.851 to 1.568)</td>
<td>0.996 (0.779 to 1.273)</td>
</tr>
<tr>
<td>Medical History (yes vs no)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.125 (0.788 to 1.607)</td>
<td>0.953 (0.749 to 1.213)</td>
<td>0.942 (0.786 to 1.130)</td>
</tr>
<tr>
<td>Prior diabetes</td>
<td>0.904 (0.631 to 1.382)</td>
<td>1.001 (0.770 to 1.300)</td>
<td>1.134 (0.927 to 1.396)</td>
</tr>
<tr>
<td>Prior coronary heart disease*</td>
<td>0.717 (0.402 to 1.278)</td>
<td>0.898 (0.632 to 1.277)</td>
<td>1.111 (0.864 to 1.428)</td>
</tr>
<tr>
<td>Prior hypertension</td>
<td>1.291 (0.969 to 1.784)</td>
<td>1.155 (0.913 to 1.461)</td>
<td>1.193 (0.949 to 1.533)</td>
</tr>
<tr>
<td>Preadmission medication (yes vs no)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.944 (0.667 to 1.335)</td>
<td>0.989 (0.781 to 1.252)</td>
<td>1.010 (0.842 to 1.213)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>1.288 (0.898 to 1.849)</td>
<td>1.363 (1.067 to 1.742)</td>
<td>1.173 (0.970 to 1.419)</td>
</tr>
<tr>
<td>Statin</td>
<td>0.963 (0.729 to 1.296)</td>
<td>0.977 (0.688 to 1.355)</td>
<td>0.938 (0.743 to 1.136)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>0.719 (0.497 to 1.042)</td>
<td>0.932 (0.728 to 1.194)</td>
<td>1.017 (0.840 to 1.232)</td>
</tr>
<tr>
<td>Admission treatment (yes vs no)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>1.416 (0.993 to 2.019)</td>
<td>1.703 (1.322 to 2.195)</td>
<td>1.532 (1.268 to 1.851)</td>
</tr>
<tr>
<td>Discharge medication (yes vs no)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.297 (0.157 to 0.562)</td>
<td>0.656 (0.479 to 0.887)</td>
<td>0.861 (0.676 to 1.097)</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>0.257 (0.133 to 0.494)</td>
<td>0.584 (0.423 to 0.753)</td>
<td>0.671 (0.544 to 0.829)</td>
</tr>
<tr>
<td>Statin</td>
<td>0.625 (0.295 to 1.339)</td>
<td>0.683 (0.484 to 0.963)</td>
<td>0.629 (0.490 to 0.808)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>0.470 (0.229 to 0.968)</td>
<td>0.610 (0.443 to 0.839)</td>
<td>0.850 (0.668 to 1.081)</td>
</tr>
</tbody>
</table>

*Any of angina/myocardial infarction/percutaneous intervention (PCI)/coronary artery bypass grafting (CABG).

Data are HR (95% CI).

ARBI, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate calculated using the MDRD formula; MDRD, modification of diet in renal disease; NSTEMI, non-ST elevation myocardial infarction; SBP, systolic blood pressure; STEMI, ST elevation myocardial infarction.

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![Figure 1](image-url)

Unadjusted odds of 30-day mortality according to admission blood glucose concentration in people with and without diabetes. The bars represent the number of people at various glucose levels. Solid lines indicate OR while dotted lines indicate 95% CI. Solid bars and black lines indicate patients with diabetes. Clear bars and red lines indicate patients without diabetes.

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Attenuated with time only for patients with NSTEMI and was evident even in those patients who survived to discharge from hospital, two potentially important clinical observations. These findings are in contrast to one previous report which reported the association between admission glucose and mortality to be confined to in-hospital deaths following either STEMI or NSTEMI. They are however in keeping with the vast majority of reports in this area.1-3,9-11

In contrast to most previous reports,3-9,11 we observed no independent association between diabetes and mortality risk after AMI. However, to our knowledge and unlike the present report, none of these studies adjusted for admission blood glucose, and each reported individual relationships between mortality after AMI and either diabetes diagnosis2,4,8 or blood glucose concentration.2,3,8,11-15,21 The current analysis and our previous study29 are the only reports to compare the relative association with outcome of both diabetes and blood glucose concentration. Both studies demonstrate a much stronger relationship between survival and blood glucose, and the loss of association between mortality...
and diabetes when blood glucose is considered. Owing to incomplete data and potential association between outcomes, we could not assess whether outcomes varied by diabetes therapies. However, previous studies have reported an independent association of admission blood glucose with mortality regardless of diabetic therapy used.6,7 These observations are of potential clinical significance. While admission blood glucose concentration after AMI is on average higher in patients with compared to those without, known diabetes,6 there is considerable overlap, as seen in the current report (figure 1). While many patients presenting with AMI will have previously undiagnosed diabetes,25 blood glucose at the time of admission with AMI is not a reliable indicator of the subsequent diagnosis of diabetes.25 In routine practice, the management of hyperglycaemia after AMI is influenced by the presence of prior diabetes diagnosis.2 In both European13 and North American5 settings, the majority (>65%) of patients presenting with hyperglycaemia in the context of AMI, and not previously known to have diabetes, do not receive active management of blood glucose. In the presence of a true, direct toxic effect upon prognosis of elevated blood glucose, failure to correct hyperglycaemia may represent suboptimal clinical care, and patients without known diabetes may be particularly disadvantaged. In particular, our demonstration that the relationship between glucose concentration and subsequent outcome is evident in NSTEMI as well as STEMI is of clear clinical relevance in terms of the overall management of patients presenting with AMI.

The strength of association between diabetes and mortality risk after AMI has been reported to increase with time from the event.27 While we observed such a trend on univariate analysis, this was attenuated in multivariate analysis, an observation which may relate to our inclusion of blood glucose as a covariate. A previous meta-analysis suggested a stronger association between admission blood glucose and adverse outcome.2 While we could not demonstrate formal statistical evidence of such a phenomenon, our data show convincingly that the relationship between glucose and outcome is at least as powerful in patients without known diabetes. Blood glucose soon after admission represents an easily identified, clinically relevant marker of risk after AMI, which should be assessed rapidly irrespective of diabetes status.
Admission blood glucose and mortality post myocardial infarction

An important observation from this study is the persisting association between admission blood glucose concentration and mortality risk in patients surviving to discharge, in both NSTE-AMI and STEMI. While in keeping with the possibility that blood glucose concentration at admission reflects the degree of individual physiological stress, or is a marker of the extent of infarction, our findings are as much in keeping with a direct, adverse influence on prognosis of acute hyperglycaemia. The mechanisms by which elevated glucose may be directly cardiotoxic have been summarised elsewhere and include attenuation of ischemic preconditioning, QT prolongation, increased thrombophilia and endothelial dysfunction. Furthermore, clinical studies overwhelmingly support a possible causal link between hyperglycaemia and adverse prognosis after AMI. Hyperglycaemia persisting at 24 h after admission is associated with adverse outcome.

While observational studies show consistently the adverse association between hyperglycaemia and outcomes post-AMI, results of the RCTs of active management of blood glucose have been inconsistent. However, in such trials, effective reduction in blood glucose with an intervention after AMI was associated with improved prognosis. The guidelines from professional societies in this area differ in their recommendations. In the North American guidelines, intensive glucose control is recommended in patients with AMI and significant hyperglycaemia (blood glucose levels >10.0 mmol/l) admitted in an intensive care unit. In contrast, the National Institute for Health and Clinical Excellence guidance recommends against routine use of intensive insulin therapy to manage hyperglycaemia (blood glucose levels >11.0 mmol/l) in patients with acute coronary syndrome. The latter guidelines highlighted a need for randomised controlled trials addressing specific gaps in knowledge this area.

Our report is subject to the limitations inherent in all observational cohort studies. Our results are from a single centre study. In the early years of the MINAP project, data on only STEMI were collected. Furthermore, data collected for MINAP was gathered mainly from a setting of coronary care unit. Selection bias could be the reason behind the overall low numbers of AMI cases (4111) recruited in our study over a 6-year period in a catchment population of one million. However, baseline and clinical outcome parameters in our study are similar to previous studies. Selection bias could also explain relatively high proportion of patients with STEMI (68.4%) compared to NSTE-AMI in our cohort. We therefore conducted subgroup analysis for people with STEMI and NSTE-AMI and compared their outcomes. Blood glucose concentration used in this analysis was that first recorded for the index admission, and is likely to have varied in timing relative to symptom onset. Our database lacks information on left ventricular (LV) ejection fraction, evidence of heart failure and a number of other potentially relevant variables. Information on body mass index, an indicator of underlying metabolic syndrome and associated dysglycaemia, was not available. Further, we have no information regarding the number of patients who were given a diagnosis of diabetes during, or subsequent to, the index admission. However, if elevated glucose contributes directly to prognosis, active management is likely to confer greater benefit when delivered as early as possible, irrespective of subsequent diabetes status. Thus, we suggest the first-recorded blood glucose concentration to be highly relevant to guiding appropriate management in individual patients, irrespective of residual LV function. While we have no information on interventions or changes to therapy after discharge, it is unlikely that these impacted on outcome in a major way, as the strongest association between mortality and glucose was in the first 30 days. Findings of our study based on real-life practice are applicable to other populations treated in similar setting.

In summary, admission blood glucose concentration is a powerful, routinely available marker of mortality risk after AMI. After adjustment for admission blood glucose, known diabetes is not associated with adverse outcome. The association between blood glucose concentration and mortality risk is of similar magnitude in patients with and without known diabetes, is evident for NSTE-AMI as well as STEMI, and persists beyond 1 year from the index event, including in patients surviving to discharge. Future studies are merited of the impact of active management of blood glucose in patients with all presentations of acute coronary artery disease, irrespective of diabetes diagnosis.

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Contributions: NG, IS and KK conceived the idea of the study and were responsible for the design of the study. NG and RM were responsible for undertaking the data analysis and produced the tables and graphs. IS, KK and MJ provided input into the data analysis. The initial draft of the manuscript was prepared by NG and IS and then circulated repeatedly among all authors for critical revision. IS was responsible for the acquisition of the data and IS, NG, RM, KK and MJ contributed to the interpretation of the results.

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