The Development and Course of Heart Failure after a Myocardial Infarction

Being a Thesis Submitted for the Degree of Doctor of Philosophy (PhD)

Department of Cardiology
Hull York Medical School
University of Hull

By

Dr Azam Torabi,
MD (Medical University of Tabriz, Iran)

2011

بسم الله الرحمن الرحيم

Abstract

Introduction: Robust epidemiological data on the incidence of myocardial infarction (MI) are hard to find, but synthesis of data from a number of sources indicates that the average hospital in the UK should admit about two patients with a first MI and one recurrent MI per 1000 population per year. Although age-adjusted incidence may be declining, this may be offset by greater longevity in the general population. The incidence of acute coronary syndromes (ACS) is much higher. The incidence and outcome of both ACS and of MI will depend greatly on how data are collected.

The cumulative incidence, persistence and resolution of heart failure (HF) after an MI in the general population are poorly described. Cardiac dysfunction subsequent to MI is a common cause for morbidity and mortality, however, there are few data on what proportion of long-term survivors of MI has important cardiac dysfunction and/or HF.

The aim of this thesis is to describe the incidence and outcome of MI in the general population and in different age groups, explain the natural history and prognosis of HF after an MI both during the index admission and long-term (6 year) follow-up in relationship to the presence of HF and also to determine the utility of amino-terminal pro-brain natriuretic peptide (NT-proBNP) alone and in conjunction with other clinical data, as a marker of left ventricular systolic dysfunction (LVSD) and subsequent prognosis in long-term survivors of MI. Subgroup data according to age and anaemia will also be reported.

Methods: Patients with a death or discharge diagnosis of MI in 1998 were identified from records of hospitals providing services to a local community of 560,000 people. Records

were scrutinized to identify the development of HF, defined as symptoms and signs consistent with that diagnosis and treated with loop diuretics. HF was considered to have resolved if diuretics could be stopped without recurrent symptoms. Analyses were done on the whole population and then sub-groups by age (<65, 65-75 and >75 years) and anaemia status. Anaemia was defined according to WHO criteria (men haemoglobin (Hb)<13; women Hb<12 g/dL) and categorized as definite (>1 g below threshold), borderline (within 1g of threshold) and (>1g above threshold).

In 2004, surviving patients were invited to attend for clinical assessment, an echocardiogram and measurement of NT-proBNP and were subsequently followed until 31st December 2009 using medical records.

Also in 2005, another group of patients admitted with ACS to cardiology or general medical wards were identified prospectively by trained nurses from 1st January to 31st December 2005. Patients with a death or discharge code of MI were also identified by the hospital information department and from Myocardial Infarction National Audit Project (MINAP) records.

Results: For the first cohort, 896 patients were identified of whom 54% had died by December 2005. During the index admission, 199 (22%) patients died, many with HF, and a further 182 (20%) patients developed HF that persisted until discharge, of whom 121 died subsequent to discharge. Of 74 patients with transient HF that resolved before discharge, 41 had recurrent HF and 38 died during follow-up. After discharge, 145 (33%) patients developed HF for the first time, of whom 76 died during follow-up. Overall, of 281 deaths occurring after discharge, of which 235(84%) were amongst patients who first developed HF.

Of 896 patients, 311 were aged <65, 297 aged 65-75 and 288 aged >75 years of whom, respectively, 24%, 57% and 82% had died by December 2005. During the index admission,

by age group, 24 (8%), 68 (23%) and 107 (37%) patients died in each group, many with HF, and a further 37 (12%), 63 (21%) and 82 (29%) developed HF that persisted until discharge. After discharge, 53 (24%), 55 (40%) and 37 (47%) patients developed HF for the first time. Overall, of 51, 102 and 128 deaths occurring after discharge, 35 (70%), 93 (91%) and 107 (85%) were among patients who first developed HF.

Of 855 patients with an available hemoglobin during index admission, 103 were anaemic, 280 were borderline and 472 were not anaemic based on the first available haemoglobin during the index admission. 300 patients had more than one measurement of haemoglobin, of which 125 (85 unchanged status from first assessment) had definite, 289 (237 unchanged) had borderline and 441 (424 unchanged) had no anaemia on the last available measurement. During the index admission, 77 patients (75%) with definite, 130 (46%) with borderline and 196 (42%) who had no anaemia on the first available haemoglobin developed HF, of whom 41 (53%), 50 (38%) and 60 (31%) died during the admission compared, respectively, to 7 (27%), 14 (9%) and 9 (3%) deaths in patients who did not develop HF. During a six year follow-up, 543 (64%) patients developed HF and 456 (53%) died. Amongst patients with HF during the index admission, the six year mortality rates in those with definite, borderline and no anaemia (last available index admission measurement) were, 90%, 84% and 64% (P=0.0001). In patients without HF on the index admission, 6-year mortality rates were 62%, 42% and 24% (P=0.0001). Anaemia (last available index admission measurement) predicted all-cause mortality independent of the presence of HF (p=0.055).

451 had died by 2004 and only 414 were available for follow-up, of whom 175 patients attended and had NT-proBNP measured. Of these, 51 (29%) patients had LVSD, 66 (38%) had NT-proBNP >50pmol/L (423pg/ml), 86 (49%) had one or the other and 31 (18%) had both. Patients with higher NT-proBNP were more likely to have HF (and be treated with

diuretics), LVSD (and therefore treatment with ACE inhibitors), a dilated atrium, substantial mitral regurgitation and atrial fibrillation (and therefore treatment with warfarin and digoxin) (p=0.0001). Thirty six patients died during follow-up; 28 (42%) with an NT-proBNP >50pmol/L (423pg/ml) (77% of all deaths). ROC curves suggested that NT-proBNP 56pmol/L (474pg/ml) had the highest sensitivity (78%) and specificity (77%) for predicting death (AUC 0.78). Echocardiography added little to the prognostic information provided by NT-proBNP alone.

In 2005, the prospective survey identified 1,731 admissions (1,439 patients) with ACS, of which 764 (704 patients) were for MI. The hospital information department reported only 552 admissions (544 patients) with MI and only 206 admissions (203 patients) were reported to MINAP. Using all three data-bases, 934 admissions (873 patients) for MI were identified, for which TnT was >1ug/L in 443, 0.04 to 1.0 in 435, <0.03 in 19 and not recorded in 37. A further 823 patients had plasma troponin T >0.03ug/L but did not have ACS ascertained by any survey method. Of 873 patients with MI, 146 died during admission (17% versus 22% in the 1998 cohort) and 218 by one year.

Conclusion: The incidence of ACS/MI is highly dependent on the methodology for case-ascertainment and the method used to identify cardiac damage (for instance the sensitivity of the troponin assay used). The development of HF precedes death in most patients who die in the short- or longer-term following an MI. The risk of developing HF and dying after an MI increases progressively with age and anaemia. In patients with a remote history of MI, elevated NT-BNP identifies patients with a high prevalence of LVSD. Regardless of age, most deaths are preceded by the development of HF. Anaemia is associated with a high mortality even in the absence of HF.

Prevention of HF, by reducing the extent of myocardial damage and recurrent MI and by subsequent good management could have a substantial impact on prognosis.

This thesis dedicated to:

My father, Khosro Torabi for his unceasing encouragement, and my mother, Eradat Mohammadi for her love

My husband Hossein, my daughter Mona and my son Majid, for their support, patience and for the hard times they went through during my study period

Acknowledgements

I wish to give special thanks to my supervisor, Prof John Cleland, for all his guidance, support and kindness from the time I met him. I also thank my second supervisor Prof Roger Watson for his encouragement, my colleague, Dr. Alan Rigby, for his teaching and support regarding the statistics.

This project was supported in part by the Hull and East Yorkshire Cardiac Trust Fund. I thank George Britchford, the hospital Records Department and the hospital staff for their assistance in collecting the data.

I thank the MINAP Coordinator, Neil Richardson, the hospital Information Department (John Taylor), the Chemical Pathology Laboratory staff (Lisa Dawson), and all the hospital staff who assisted in the collection of hospital data. I also wish to acknowledge the contribution of Janet Bristow who sadly passed away before the HIP study was complete.

Particular thanks to Gillie Porter, for helping on submitting my publications, Marilyn Etheridge and Carolyn Medlam for supporting me during this period and Yvonne Arrow for her clerical assistance. I would also like to extend my thanks to all my colleagues and their help during this study.

Finally, I would like to offer profuse thanks to my parents, my husband Dr Hossein Panahi, my daughter Mona, my son, Majid for all the love and great patience throughout the years, and my sisters and brothers, especially Mahdi, for their unconditional love and support throughout my life.

Table of Contents

Abstract…….……i

Acknowledgement.....vi

Table of Contents.....viii

List of Tables……xiv

List of Figures……..xvi

List of Abbreviation…….xviii

Published material…..…….……xxi

1 Chapter 1: The Development and Natural History of Heart Failure (HF) after Myocardial Infarction (MI) 1

1.1 Introduction 1

1.2 Literature Review 4

1.2.1 The Incidence of Myocardial Infarction: 5

1.2.2 What Is Already Known on the Incidence of Heart Failure or LVSD During Admission in Patients with a Myocardial Infarction?.....8

1.2.3 Heart Failure Developing and Recovering after Discharge from the Index Myocardial Infarction Hospitalisation 15

1.2.4 Results of the BNP Review: 17

1.3 The Evidence Gap 23

2 Chapter 2: METHOD OF STUDY: 24

2.1 Study population and process of contacting Patient.....24

2.2 Case Records Review.....26

2.3 Tests during follow up visit....29

2.4 Inclusion Criteria....30

2.5 Exclusion Criteria for Index Admission....30

2.6 2.6 Definitions....31

2.6.1 2.6.1 Definition of Myocardial Infarction....31

2.6.2 Definition of Heart Failure....31

2.6.3 Resolution of Heart Failure....32

2.6.4 Definition for left ventricular dysfunction (LVSD)....32

2.6.5 Definition of Renal Dysfunction....32

2.6.6 Definition for anaemia....32

2.6.7 Mode of Death:....33

2.6.8 Place of Death....34

2.7 Statistical Analysis:....35

3 Chapter 3: The Timing of Development and Subsequent Clinical Course of Heart Failure after a Myocardial Infarction....39

3.1 Introduction....39

3.2 Methods....40

3.2.1 Study population....40

3.2.2 Follow-up....40

3.2.3 Definition of Myocardial Infarction....40

3.2.4 Other Definitions....41

3.2.5 Resolution of Heart Failure....42
3.2.6 Statistical Analysis:....42
3.3 Results:....43
3.3.1 Overall Results....43
3.3.2 Mode of Death....57
3.3.3 Cox Model....57
3.4 Discussion....59
3.5 Study limitations....62
3.6 Conclusion:....64
4 Chapter 4: The development and course of Heart Failure after a Myocardial Infarction in different age groups....65
4.1 Introduction....65
4.2 Methods....65
4.2.1 Study population....65
4.2.2 Follow-up....66
4.2.3 Definition of Myocardial Infarction....66
4.2.4 Other Definitions....67
4.2.5 Resolution of Heart Failure....67
4.2.6 Statistical Analysis:....67
4.3 Results:....68
4.3.1 Overall results:....68
4.3.2 Long-Term Follow-up....78

4.3.3 Cox Model 82

4.4 Discussion 87

4.5 Study limitations 90

4.6 Conclusions: 91

5 Chapter 5: Anaemia after a Myocardial Infarction and Its Relationship to the Development of Heart Failure and Mortality 92

5.1 Introduction 92

5.2 Methods 92

5.2.1 Study population 92

5.2.2 Follow-up 93

5.2.3 Definition of Myocardial Infarction 93

5.2.4 Other Definitions 94

5.2.5 Statistical Analysis: 94

5.3 Results: 96

5.3.1 Overall Results 96

5.3.2 Mode of death 109

5.3.3 Cox Models 111

5.4 Discussion 113

5.5 Study limitations 114

5.6 Conclusion: 116

6 Chapter 6: Utility of NT-proBNP to Identify Left Ventricular Dysfunction and Adverse Prognosis in Patients with a Prior Myocardial Infarction 117

6.1 Introduction 117

6.2 Method 118

6.2.1 Study population 118

6.2.2 Definition of Myocardial Infarction 119

6.2.3 Heart failure, LVSD, LA dilatation and valve disease 120

6.2.4 Adjudication of Mode of Death 120

6.2.5 Statistical Analysis: 121

6.3 Results 122

6.3.1 Overall results 122

6.3.2 Long-Term Follow-up 127

6.3.3 ROC curve 128

6.3.4 Cox regression 134

6.4 Discussion: 134

6.5 Conclusion: 137

7 Chapter 7: The Incidence and Outcome of Patients Hospitalised for Acute Coronary Syndrome in 2005. The Hull Infarction Project 138

7.1 Background 138

7.2 Methods 139

7.2.1 Study population 139

7.2.2 HIP-2005 Definitions 139

7.2.3 MINAP criteria: 140

7.2.4 Hospital Coding System: 140

7.2.5 Laboratory-positive troponin T (TnT): 141

7.2.6 Statistical Analysis 141

7.3 Results 141

7.3.1 Overall Results 141

7.3.2 Mortality according Troponin T (TnT) during first admission in all patients identified by HIP-2005, HID, MINAP and Lab positive TnT 150

7.3.3 Loop diuretic and survival subsequent to discharge and by end of 2008 in patients with ACS identified by HIP-2005 153

7.3.4 Loop diuretics and left ventricular function 154

7.4 Discussion 154

7.5 Conclusion 158

References 159

Appendices 174

1. Consultant Letter 174

2.Consultant letter to patient 177

3. Patient Information Leaflet 179

4.Patient Consent Form 183

5. Gp letter 185

List of Tables

Table 1-1 Incidence of myocardial infarction 7

Table 1-2 Prevalence and incidence of heart failure in patients with myocardial infarction...14

Table 1-3 Progression of heart failure and mortality in randomised controlled trials of post-infarction left ventricular systolic dysfunction……..…17

Table 1-4 Prognosis of NT-BNP and BNP in patients with acute myocardial infarction…....19

Table 1-5 Prognosis of NT-BNP and BNP in randomised controlled trials in patients with acute coronary syndrome……..19

Table 1-6 Prognosis and diagnosis of NT-proBNP and BNP in patients late after myocardial infarction…….……..…22

Table 2-1 During the case note review the following data were collected……..28

Table 3-1 Patients characteristics recorded during the overall index admission overall and classified according to the development of heart failure (HF) and mortality during index admission [data are median (inter-quartile range) and number occurring (%)]……..….47

Table 3.2 Treatment during index admission and any time until 31st December 2005……..49

Table 3-3 Imaging evidence of left ventricular (LV) function during index admission or shortly thereafter.…….56

Table 3-4 Cox-regression models; for mortality in patients unadjusted and age-adjusted subsequent to discharge (n=667)…….…….58

Table 4.1 Patients Characteristics recorded during the Index Admission overall and classified according to the three different age group: >65 years old, 65-75 years old and >75 years old (data are median (inter-quartile range) and number occurring (%))……70

Table 4.2 1Treatment during index admission and any time until 31st December 2005……..72

Table 4.3 Imaging evidence of left ventricular function during index admission or shortly after……..……...83

Table 4-4 Mode of death in patients who died during index admission (n=199) and subsequent to discharge (n=281)……..85

Table 4-5 Cox-regression models; unadjusted and multivariate-adjusted procedures of mortality in patients subsequent to discharge (n=667)…….86

Table 5-1 Anaemia groups Changes between first and last available measurement……...96

Table 5.2 Patients Characteristics recorded during the Index Admission classified according to Anaemia status……...……..99

Table 5.3 Treatment during index admission and any time until 31st December 2005…100

Table 5.4 Imaging evidence of left ventricular function during index admission or shortly after and relationship to development of heart failure or death…….107

Table 5-5 Mortality and mode of death during index admission (N=181) and subsequent to discharge (n=275) according to anaemia status……..…110

Table 5.6 Cox-regression models; for mortality in patients subsequent to discharge (n=64) …….…….....……...….112

Table 6-1Patients Characteristics classified according to the NT-proBNP quartile…..….123

Table 6.2 Treatment during follow-up clinic…….…....126

Table 6-3 Imaging evidence of left ventricular function during follow-up clinic…….....126

Table 6.4 Patients Characteristics recorded during follow-up clinic overall and classified according to the LVSD Y/N and NT-proBNP >50……129

Table 6-5 Cox-regression models predicting mortality in patients attended for follow-up clinic during 2004 and 2005 (n=175)…….133

Table 7.1 Patient characteristics recorded during the index admission…….....148

List of Figures

Figure 1-1 Structure of Brain natriuretic peptide…….….4

Figure 1-2 Proportion of patients with HF and left ventricular systolic dysfunction (LVSD) within the first few days after a myocardial infarction in the TRACE study [1]……...…..…10

Figure 1-3 Proportion of patients with left ventricular systolic dysfunction (LVSD), transient or persistent heart failure (HF) and their outcome in RACE study……...…….…….11

Figure 3.1 Primary MI and Fist MI in 1998 and development of heart failure (HF) and mortality……..…….……..44

Figure 3.2 The proportions of patients developing different categories of heart failure (HF)……...…51

Figure 3.3 Mortality during index admission according to the development of HF during the index admission (transient or persistent)…….....52

Figure 3.4 Kaplan-Meier curves showing prognosis amongst patients discharged after the index myocardial infarction with and without persistent or transient heart failure (HF). …..53

Figure 3-5 Pie-chart showing the proportion of patients who died with or without preceding evidence of heart failure (HF) subsequent to discharge from index admission…….…..54

Figure 4-1 Flow diagram showing the sequence of development of heart failure and mortality over approximately 6 years in different age group……...…….74

Figure 4.2 The proportions of patients developing different categories of heart failure according different age groups…….77

Figure 4.3.a & b a and b:prognosis amongst patients discharged after the index myocardial infarction……..79

Figure 4-4 Mortality after index admission, with and without Heart failure any time……81

Figure 5-1 Prevalence of Heart Failure during index admission Y/N according to gender (men and women)……..……...…98

Figure 5-2 Flow diagram showing the sequence of development of heart failure and mortality over approximately 6 years in patients with (a) anaemia, (b) Borderline, (c) No anaemia according to first haemoglobin during admission…….……..102

Figure 5-3 Prevalence & Mortality according to anaemia groups and (a) heart failure and (b) LVSD…….105

Figure 5.4 Kaplan-Meier curves showing prognosis among patients discharged after the index hospitalisation……...111

Figure 6-1 NT pro-BNP test in patients with myocardial infarction…….……..122

Figure 6-2 Mortality within 12 month, 36months and by 31st December 2009 according to quartile of NT-proBNP (Median and IQR 35 (13-86) pmol/L)…….127

Figure 6-3 Mortality within 12 months, 36months and by end of 2009 according to (a) LVSD and (b) Lent atrial dilatation……..131

Figure 6-4 ROC Curve for all-cause mortality by 2010…… …….132

Figure 7.1 Incidence of ACS and myocardial infarction (MI) in (a) HIP, (b) HID and (c) MINAP……..…142

Figure 7.2 Incidence of myocardial infarction in all three data-sets (HIP, HID and MINAP)…….....145

Figure 7.3 patients with (a) MI and (b) ACS identified by HIP, HID and MINAP with highest TnT during any ACS admission in 2005……...146

Figure 7.4 Mortality by end of 2008 from first admission in all patients with ACS…….151

Figure 7.5 Probability of death within 30-day, one-year and 3-yearaccording to the troponin T level during index admission……..152

Figure 7.6 Survival until end of 2008 in patients with a first admission with ACS identified by HIP……153

List of Abbreviations

<	Less than
>	Greater than
<	Equal or Less than
>	Equal or Greater than
ARBs	Angiotensin receptor blockers;
ACS	Acute coronary syndrome
AF	atrial fibrillation
AMI	Acute Myocardial infarction
ARBs	Angiotensin receptor blockers
BMI	Body mass index
BNP	Brain natriuretic peptides
CK	Creatinine kinase
CK-MB	Creatinine kinase Mass
CABG	Coronary artery bypass grafting
COPD	Chronic obstructive pulmonary disease
CIs	Confidence intervals
DINAMIT	Defibrillator in Acute Myocardial Infarction Trial

ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
HF	Heart failure
ECG	Electrocardiogram
Hb	Haemoglobin
HRs	Hazard ratios
HIP	Hull Infarction Project
ICD	Implantable cardiac defibrillators
IQR	Inter-quartile range
K-M	Kaplan-Meier
LA	Left Atrial
LAD	Left atrial dilatation
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
LVMI	Left ventricular mass index
LVSD	Left ventricular systolic dysfunction
LVEF	Left ventricular ejection fraction

MINAP	Myocardial Infarction National Audit Project
MI	Myocardial infarction
MR	Mitral regurgitation
NSTEMI	Non ST elevation MI
NA	Not applicable or available
NT-proBNP	Amino-terminal pro-brain natriuretic peptide
PHF	Persistent HF
PTCA	Percutaneous transluminal coronary angioplasty
PCI	Percutaneous transluminal coronary angioplasty
QOL	Quality of life
RCT	Randomised control trial
ROC	Receiver operating characteristic
STEMI	ST-segment elevation myocardial infarction
SCD	Sudden cardiac death
THF	Transient HF
TnT	Troponin T
WHO	World Health Organization

Published Material:

Peer-Reviewed Publications

1. Antithrombotic agents. Oxford Textbook of Heart Failure, 2011
2. Declining In-Hospital Mortality and Increasing Heart Failure Incidence in Elderly Patients with First Myocardial Infarction. J Am Coll Cardiol, 2010; 55:79-81.
3. Clinical Trials Update from the European Society of Cardiology Heart Failure Meeting 2009: CHANCE, B-convinced, CHAT, CIBIS-ELD and Signal-HF. European HF J, 2009, 11(8): 802-805
4. The Timing of Development and Subsequent Clinical Course of Heart Failure after a Myocardial Infarction. Euro Heart Journal (2008) 29,859-870
5. "Epidemiology and management of heart failure and left ventricular systolic dysfunction in the aftermath of a myocardial infarction", Heart. 2005 May;91 Suppl 2:ii7-13; discussion ii31,ii43-8
6. Revised review of a paper "Mild Heart Failure is a Mortality Marker after a Non ST Segment Acute Myocardial Infarction", American Journal of Cardiology, November 2009.
7. Revised review of a paper "A high incidental rise in cardiac troponin I carries a higher mortality risk in older patients than in those with a diagnosed acute coronary syndrome", age and ageing, December 2009.

Presentations, Abstracts & Other Publications

1. Effect of timing of drug therapy, salt intake and exercise on non-invasive haemodynamics as measured by volume clamp technology (Nexfin, Bmeye) - HeartCycle European Union 7th Framework Programme. European HF congress, Gothenburg, Sweden, May 2011

2. The prevalence of extra-cranial carotid artery disease in patients with chronic heart failure. European HF congress, Gothenburg, Sweden, May 2011
3. Quality of Life and Mortality in Patients with Suspected Heart Failure.European HF congress, Gothenburg, Sweden, May 2011
4. Effect of data collection method on the hospital incidence of acute coronary syndrome. The Hull Infarction Project - 2005. Clinical Biosciences Institute Research Day, Daisy Building, Castle Hill Hospital, Hull, UK, 30 June 2010 (this also presented in Cardiac Monitoring Educational Meeting in Castle Hill Hospital, June 2010
5. Effect of data collection method on the hospital incidence of acute coronary syndrome. European society of cardiology (ESC) Congress, Stockholm, Sweden, Aug 2010.
6. Utility of NT-proBNP to Identify Left Ventricular Dysfunction and Adverse Prognosis in Patients with a Remote Myocardial Infarction. European HF congress, Berlin, Germany, May 2010
7. Does the Severity of LV Dysfunction or the Extent of Myocardial Scar Explain Elevations in Plasma Galectin-3 in Patients with Heart Failure? European HF congress, Berlin, Germany, May 2010
8. 2D STE-based strain imaging is superior to TDI-based strain imaging in differentiation of transmural from non-transmural chronic scar in post-MI patients with LV systolic dysfunction. European HF congress, Berlin, Germany, May 2010
9. Prevalence and Prognosis of Late Left Ventricular Systolic Dysfunction (LVSD) after Myocardial Infarction (MI). European HF congress, Nice, France, Jun 2009
10. Risk Stratification of Heart Failure Patients Using Decision Trees: an Analysis of Trans-European Network-Home-Care Management System (Ten-HMS) Study. European HF congress, Nice, France, Jun 2009

11. Prediction of Short-term Survival Using Repeated NT-ProBNP Measurements for Patients with Heart Failure: an Analysis of the Trans-European Network-Home-Care Management System (Ten-HMS) Study. European HF congress, Nice, France, Jun 2009
12. Prevalence and Prognosis of Heart Failure in Different age grope in Post MI Patients: is anaemia an independent predictor of survival? European Heart congress, Munich, Germany, Sep 2008
13. Prevalence and Prognosis of Anaemia in Post MI Patients: is anaemia an independent predictor of survival? European society of cardiology (ESC) Congress, Munich, Germany, Aug 2008
14. Prevalence and Prognosis of Anaemia in Post MI Patients, European HF congress, Milan, Italy, Jun 2008
15. Prevalence and Prognosis of Heart Failure in Different age grope in Post MI Patients. European HF congress, Milan, Italy, Jun 2008
16. “Contemporary Epidemiology of LVSD after Myocardial Infarction”. European Heart Failure meeting, Hamburg, Germany, July 2007
17. “Prevalence And Prognosis of Renal Dysfunction in Post MI Patients”, European Heart Failure meeting, Hamburg, Germany, July 2007
18. “Prevalence and Prognosis of HF in Post MI patients”, World Congress of Cardiology, Barcelona, 3-6 Sept 2006. (presented in Research meeting, University of Hull June 2006, also in the Cardiology big team meeting CHH 13 June 2006)
19. “Multi Model Diagnostic Tests To Assess Heart Failure Using ECG, Chest X-Ray and Echocardiogram In Patients With Suspected Heart Failure” British Cardiac Society, Glasgow, June 2007

20. “Prevalence and Prognosis of HF in Post MI patients”, World Congress of Cardiology, Barcelona, 3-6 Sept 2006. Also presented in Research meeting, University of Hull June 2006, also in the Cardiology big team meeting CHH 13 June 2006.
21. “Prognosis of developing Heart Failure following ST elevation (STEMI) and non ST elevation (NSTEMI) infarct”, HYMS meeting, UK, Apr 2005. Also presented in IRCE meeting, Leeds, UK, Jul 2005.
22. Prevalence and Incidence of Heart Failure and Left Ventricular Systolic Dysfunction in Post MI patients”, IRCE meeting, Leeds, UK, Jul 2005. (also presented in HYMS meeting, UK, Apr 2005).
23. Prevalence of broad QRS complex and HF in Post MI patients”, IRCE meeting, Manchester, UK, Jun 2004”

1 Chapter 1: The Development and Natural History of Heart Failure (HF) after Myocardial Infarction (MI)

1.1 Introduction

The aim of this thesis is to describe the incidence and timing of onset, persistence, resolution of heart failure developing after an acute myocardial infarction and its relationship to mortality both during and subsequent to the index admission for myocardial infarction. Although heart failure is a well recognised complication of myocardial infarction and one that is associated with a poor prognosis, very little is known about the natural history of heart failure after a myocardial infarction beyond these basic facts. Estimates of the incidence of myocardial infarction are inconsistent, depending highly on the diagnostic criteria applied and the method of case-ascertainment. Estimates of the incidence of heart failure after myocardial infarction are also inconsistent and usually confined to groups of patients who have survived to discharge and been managed by a cardiologist. There are few reports about what proportion of cases resolve or of the late development of heart failure and its relationship to recurrent ischaemic events. Conventionally, heart failure due to myocardial infarction is thought to be related to the size of the infarction. Large infarcts lead to the loss of a greater mass of myocardium with a reduction in ventricular contractility and greater adverse remodelling leading to a decline in left ventricular ejection fraction and left ventricular systolic dysfunction. The size of the infarct will depend on the coronary anatomy (patients with proximal coronary lesions subtending a large volume of myocardium are more likely to have large myocardial infarctions; proximal disease in the left anterior descending or left main coronary artery giving rise to the largest infarcts) amount of collateral blood flow, whether coronary artery occlusion is persistent or intermittent, reperfusion within a narrow

time window and the sensitivity of the cardiac myocytes to ischaemia. Factors such as left ventricular hypertophy may predispose to greater loss of myocytes. Anterior myocardial infarctions may be more likely to give rise to heart failure not only because they tend to cause larger infarctions but because they affect the left ventricular free wall which may be most likely to undergo adverse left ventricular remodelling [1].

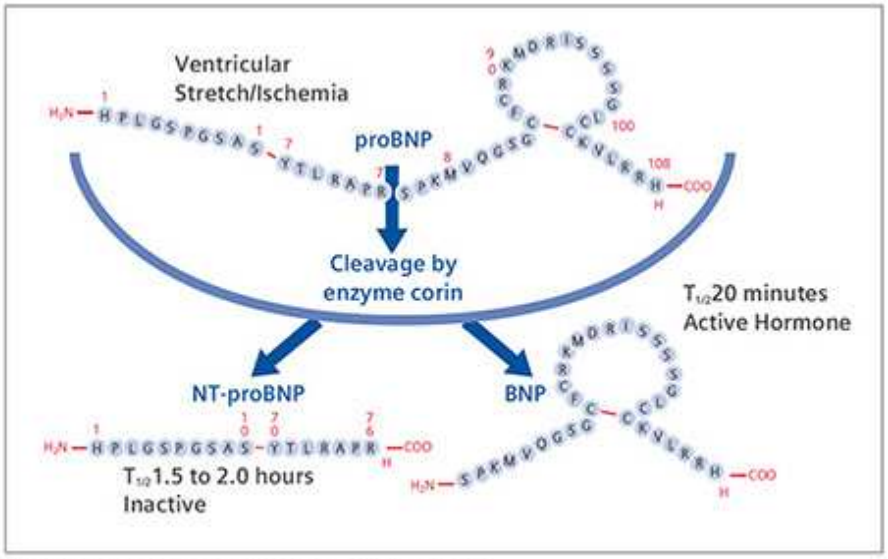
However, the incidence of heart failure appears much greater than the incidence of left ventricular systolic dysfunction. It is unknown whether heart failure or left ventricular systolic dysfunction is of greater prognostic significance. Heart failure may occur subsequent to a myocardial infarction for many reasons. Some patients will have pre-existing cardiac dysfunction and heart failure. Pre-existing dysfunction may reflect prior damage from coronary disease leading to predominantly systolic dysfunction. However, chronic hypertension can lead to left ventricular hypertophy, increased myocardial collagen content and diastolic myocardial dysfunction. Super-imposition of damage from myocardial infarction may cause heart failure when there is only a modest decline in left ventricular systolic function. Myocardial infarction may cause papillary muscle dysfunction and mitral regurgitation. More rarely, myocardial infarction may cause rupture of the inter-ventricular septum which is usually a catastrophic event with a high mortality.

Ventricular function probably improves more often than it declines in the aftermath of an acute myocardial infarction. A myocardial infarction can be considered to consist of an inner zone of irrecoverable myocardial necrosis and an outer zone where myocardium is ischaemic. This leads to myocardial stunning with loss of contractility. If ischaemia is severe and persists this may lead to myocardial cell death through apoptosis. If ischaemia resolves then stunned myocardium may recover contractility and ventricular function may improve. Sometimes the myocardium hangs in the balance for long periods, perhaps indefinitely,

without recovery of function but without cell death. Some of this is due to recurrent ischaemia and stunning. In other cases, myocardial hibernation may occur, either due to a metabolic defect in the myocardium itself or a critically low myocardial blood flow or simply the effects of chronic repetitive stunning[2]. One of the mechanisms by which beta-blockers improve ventricular function in patients with chronic heart failure is probably the relief of recurrent ischaemia and hibernation [2] and indeed myocardial ischaemia due to micro-vascular disease in the absence of epicardial disease may be one cause of dilated cardiomyopathy and account for why these patients get such a large and consistent response to beta-blockers. Observational studies have suggested that revascularisation can improve the function of stunned and hibernating myocardium although randomised controlled trials have been unable to show superiority over medical treatment alone [3 4 5]. It is unknown whether recovery of ventricular function leads to resolution of heart failure if it has already occurred or whether recovery can reduce the risk of developing heart failure in the future.

This thesis will review the literature related to the development and natural history of heart failure subsequent to an acute myocardial infarction and then describe, in detail, the development and natural history of heart failure in two large cohorts of patients drawn from a local population of about 560,000 patients who had a myocardial infarction either in 1998 (cohort 1) or 2005 (cohort 2).

Figure 1-1Structure of Brain natriuretic peptide



ProBNP molecule cleaved to BNP and NT-proBNP.

1.2 Literature Review

This chapter will review three main topics, a) the incidence of myocardial infarction, b) the time course of the development of heart failure after an acute myocardial infarction and c) the use of N-terminal brain natriuretic peptide after a myocardial infarction as a means to detect cardiac dysfunction and to predict prognosis.

The incidence and prevalence of heart failure and left ventricular systolic dysfunction and their combination after an acute myocardial infarction was extracted only from trials that enrolled 100 or more consecutive patients. The review was limited to English language papers. The electronic search for heart failure and myocardial infarction was carried out using Pub-med and Cochrane. This literature search was limited to publications between the 1st of January 1994 and 1st^{t} of January 2008. The key words used were “myocardial infarction and heart failure”. A systematic review of BNP for detecting HF and LVSD after MI was carried out in the same way with same limitation and same period as HF and MI in Pub-med and Cochrane, the studies with more than 500 cases after an acute MI and more than 50 cases in

patients with a remote MI were reviewed. The key words used were “myocardial infarction and brain natriuretic peptide”.

After applying the defined search criteria, a preliminary review of abstracts identified was carried out. Related abstracts were selected if they were considered relevant and their full text was reviewed. Only twenty full text papers & abstracts met our criteria for “heart failure and myocardial infarction” and only fourteen “myocardial infarction and brain natriuretic peptide”.

1.2.1 The Incidence of Myocardial Infarction:

It is probable that the incidence of MI varies around the world; although when age and sex matched populations are compared the differences may not be so great. MI is common in China, Australia, America and Europe, as evidence by large, relevant trials from each of these regions. Robust epidemiological data are hard to find because the majority of studies have restricted their interest either to certain age groups and/or only to patients with a hospital diagnosis and have been retrospective[6].

The British Heart Foundation estimates that there are about four MIs per thousand populations per year, but hospital discharge statistics in the UK suggest only half that amount. The MI National Audit Project (MINAP) for England (and Wales), which aims to report the outcome for all patients, not just with MI, but also other acute coronary syndromes either leading to hospitalisation or developing during admission, reported more than 78,000 myocardial infarctions in 2009-2010 [7] but points out that there was disproportionate under-reporting of myocardial infarction non ST elevation myocardial infarction, possibly because about half of these cases are not managed on cardiology wards. Adjusting for this MINAP believe there should have been about 100,000 cases in England & Wales or1.6 cases per

thousand population of all ages per year. However, there may well be additional under-reporting of STEMI so the total number of cases may be between 120,000 and 150,000 per year. But this excludes patients who die suddenly before reaching hospital and those with no or atypical symptoms who do not present to hospital. Perhaps 20-30% of people suffering an MI will die before they reach hospital[8 9]. About 25% of patients will have no symptoms or symptoms that are mistaken for a less serious problem and will not seek hospital attention or be referred to a cardiologist[10 11 12]. Thus the total burden of myocardial infarction in England & Wales may be close to 300,000 cases per year or six cases per thousand population of all ages per year (Table 1.1).

There are likely to be several reasons for the above discrepancies. It is unlikely that all cases are reported to MINAP as noted above. Cardiologists tend to focus on younger patients with a clear diagnosis of MI and few co-morbidities. For many years, many centres were under the illusion that MINAP was a register of cases who got thrombolysis – which made many hospitals look as though they were giving better care than was actually the case. It is likely that hospital statistics are an underestimate of hospital activity. We know, from a review of our own case records that when MI is reported on hospital death and discharge codes it is almost always appropriate but that a substantial number of cases with MI are not coded as such. The discrepancy between MINAP and the hospital discharge statistics almost certainly reflects selective reporting of obvious infarcts in younger patients with a typical presentation and relatively low co-morbidity; just the sort of patients who go into clinical trials. However, there is good evidence that it is the older patient with atypical presentation who is most likely to develop HF, has the worst prognosis but is less likely to receive effective care [10 11 12].

Table 1-1Incidence of myocardial infarction

Study	Years of data collection	Age limits	Population served	Cases	Incidence (events/ 1000/year)	Case fatality
MONICA[a] [6]	1985-1991	35-64 years	large	3,584	4.3	49% at 28 days
OXMIS [8]	1994-1995	<80 years	568,800	1,343	2.4	39% at 28 days
ARIC [9 13]	1987-1996	35-74 years	354,357	14,842	4.2	
BHF/NICE[14]	Uncertain	All ages	58 million	268,000	4.6	
Hospital Death & Discharge Statistics (England)[15]	2002-2003	All ages	50 million	105,476	2.1	
Hospital Death & Discharge Statistics (England)[16]	2005-2006	All ages	50 million	64,436	1.28	
Hospital Death & Discharge Statistics (Scotland) [17]	1990-2000	All ages	4.8 million	96,026 (225,512[b])	2.0 (4.7[b])	
Hospital Death & Discharge Statistics (Scotland) [18]	2000	All ages	4.8 million	~8,000 ~27,000	1.7 (5.7[b])	
MINAP[7]	2009-2010	All ages		78,574#	1.6 (>2.0#)	

[a]The definition included definite non-fatal myocardial infarction and possible, probable or definite CHD mortality. Cities from 21 countries were included in the study. Belfast and Glasgow represented the UK. They had a much higher than average incidence than the mean effect but only a slightly lower 28 day case fatality. # MINAP states that they know there is underreporting, especially of NSTEMI

[b]Cardiac chest pain including myocardial infarction and unstable angina

There are some serious consequences of selective reporting. Singling out a few patients and providing them with excellent care, while excluding patients with an intrinsically poor prognosis who have received less investigation and care, is the most efficient way of appearing to give good care when resources are limited. No doubt, as MINAP evolves and matures, the safe guards that have been built into the system will help prevent selective reporting. Using the number of events per hospital per thousand catchment population, together with the mean age and sex of the patients, as part of the published quality assurance for MINAP would be helpful.

Synthesising data from a number of sources, it is likely that the average hospital in the UK should admit about two patients with an MI per thousand populations (all ages) per year of which about one third will be a recurrent myocardial infarction.

Recent publications suggest that the age-adjusted risk of MI and coronary heart disease mortality are falling[6]. It is not clear that this has translated into an overall reduction in either[9 13]. As the proportion of older people in the population increases this may more than offset any gain in terms of a reduction in age-related morbidity. It is likely that the overall rate of MI in the population will increase, especially in people aged >70 years[19 20].

1.2.2 What Is Already Known on the Incidence of Heart Failure or LVSD During Admission in Patients with a Myocardial Infarction?

LVSD and HF are not synonymous[21]. Some patients suffer major left ventricular damage and yet remain asymptomatic. Between 30-50% of patients who develop HF do not have LVSD, mitral regurgitation or arrhythmias [22 23]. LVSD can be measured fairly objectively but symptoms and signs of HF are subjective and the threshold for diagnosis will vary widely amongst clinicians. Both LVSD and HF may occur early or develop late and both may recover. Many patients are given loop diuretics during the course of their MI and it is likely

that most of these patients have exhibited signs or symptoms of HF [24].Prescription of a loop diuretic is associated with a worse outcome [25 26].

There are few data on the contemporary existing natural history of these phenomena. Surveys indicate that only about 60% of patients with a MI have their ventricular function assessed[24]. Moreover, it is clear that patients with atypical presentation of infarction, who are often not cared for by a cardiologists, have a higher risk of developing LVSD and HF and have a higher mortality[10 11 12]. Cardiology focused studies and registries are likely to underestimate the incidence of post-MI heart failure. It is hoped that MINAP project will ensure that such selective reporting is avoided.

Perhaps the study of highest quality is the registry for the TRACE study, which underpinned a randomised controlled trial comparing placebo and trandolapril in Denmark, predominantly (76%) in patients with a first MI [21 27 28]. Of 6,526 patients in whom the wall-motion index was assessed, 2,606 patients (40%) developed major left ventricular systolic dysfunction. Amongst those who had LVSD, 74% developed features of HF and 30% of all patients had both LVSD and HF. However, 24% of patients had features of HF but did not have LVSD. Overall, about two thirds of patients had either HF or LVSD (Figures 1.2 and 1.3).

The VALIANT study which tested valsartan, alone or combined with the ACE-inhibitor (during 1999 to 2001). Of 5566 patients with MI, 27% developed LVSD. Amongst those who had LVSD, 30% developed HF and therefore only 8% of all patients assessed had both LVSD and HF. In patients who died during index admission 80%, had either HF, LVSD or both. However, documentation of mortality in patients with HF or LVSD alone was poor [29].

Figure 1-2Proportion of patients with HF and left ventricular systolic dysfunction (LVSD) within the first few days after a myocardial infarction in the TRACE study [1]

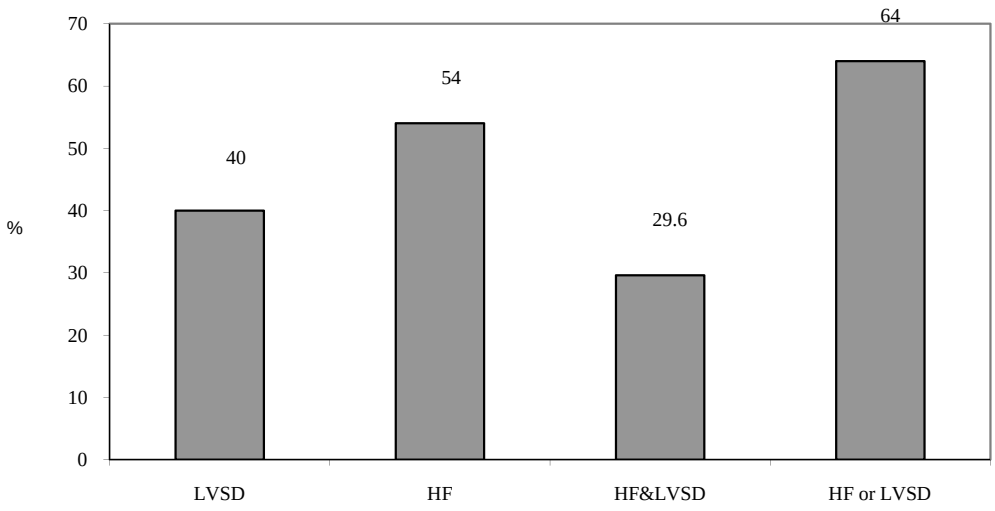
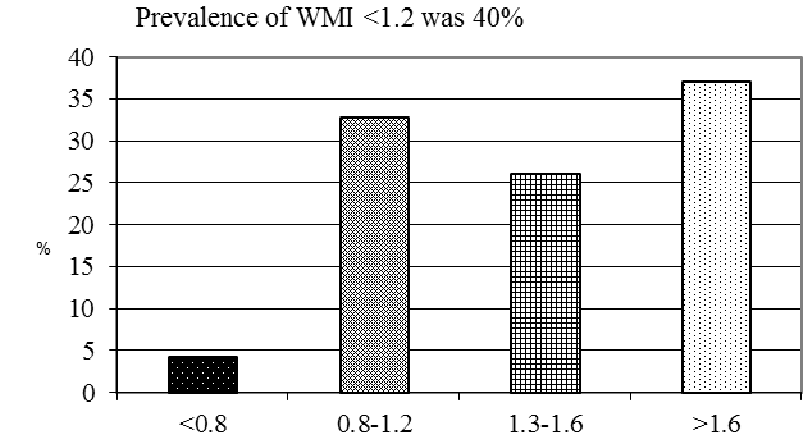
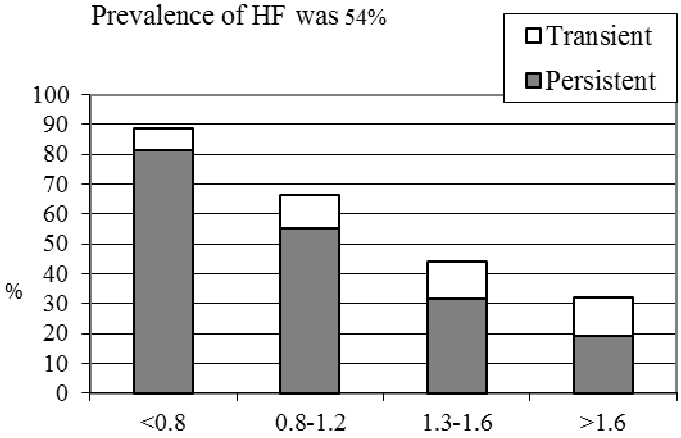
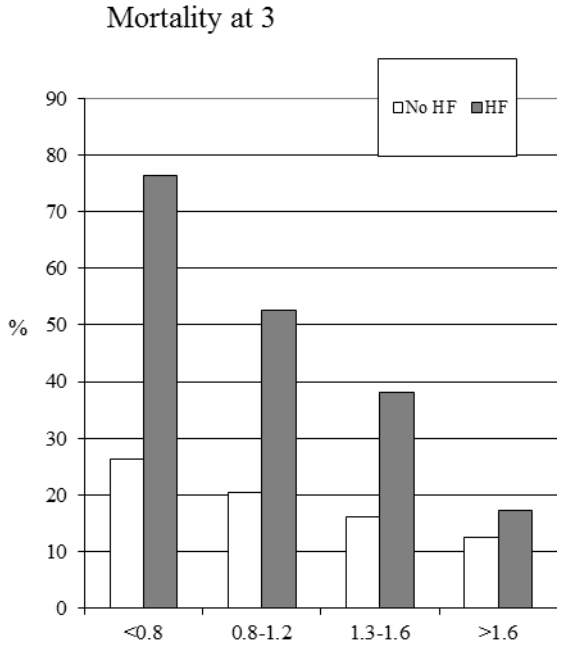


Figure 1-3Proportion of patients with left ventricular systolic dysfunction (LVSD), transient or persistent heart failure (HF) and their outcome in TRACE study







(patients divided into 4 groups: WMI <0.8, ≤0.8, <1.2, ≤1.2, ≤1.6 and >1.6, approximately corresponding to LV ejection fraction <0.25, ≤0.25, <0.35, ≤0.35, ≤ 0.50 and > 0.50 respectively [28].

WMI, wall motion index.

In another observational study of 3166 patients with MI and LV assessment, 33% developed LVSD. Amongst those who had LVSD, 71% developed HF and only 23% of all patients had both LVSD and HF. Overall development of HF was 1464 (46%) but 15% of them was prior to their hospitalisation and only 10% of them developed after 24 hours of admission[23].

Other population studies corroborate a prevalence of major LVSD acutely after an MI of about 40%, although lower rates are generally reported in clinical trials that recruited patients selectively from cardiology services (recruiting patients from cardiology services alone will tend to exclude older patients who often remain under the care of geriatricians) [24 30] (Figure 1.2).

Other studies have looked at Killip class or diuretic treatment only in the early days of admission with no further detail in other days[31]. The Worcester Heart Attack Study reported MI admissions during 13 annual period (from 1975 to 2001), development of HF during hospitalization was 37-45%, with the highest incidence of HF between 1981-1984 with 45% compared to 40% in the last period of study (2001)[32].

Prior to the widespread use of thrombolysis, ACE inhibitors and beta-blockers, studies suggested progressive LV remodelling occurred in a substantial proportion of patients, leading to an increasing prevalence of LVSD over time[33]. However, others focused on the delayed recovery from stunning and reported recovery from LVSD after MI [34 35]. It is likely that more aggressive therapy of MI has reduced the risk of adverse remodelling and improved the chances of recovery from LVSD[35]. However, modern treatment will also have kept a higher proportion of patients with severe LVSD alive but had little impact on those without major LVSD since their prognosis was already good[36]. Overall, it appears that the incidence of post-infarction HF has changed little[22 36 37 38]. Obviously, the

complex interactions between disease, outcome, and epidemiology require study rather than uncertain speculation.

The TRACE study suggested that >50% of patients having a MI would develop symptoms and/or signs of HF and in about one third of these cases HF will have been present prior to their MI [21]. This incidence of new-onset HF of about 40% is consistent with a systematic review of the literature[30], (Table1.2). Of patients who develop new onset symptoms of HF, about 70% will do so by the time of first hospital evaluation, while 30% will develop them later during the index admission.

On the other hand, registries and randomised controlled trials of acute coronary syndrome demonstrate lower percentage of patients developing heart failure after a myocardial infarction as they excluded the high risk patients such as history of HF and Killip class IV heart failure [39].

Table 1-2Prevalence and incidence of heart failure in patients with myocardial infarction

Study	Collection period	Exclusions	Number	Pre-existing HF	HF developing during index	HF developing developing after discharge	Total
US National Registry [38]	1994-2000	Shock or prior HF	606500		20.4%	8.6%	29.0%
TRACE [21]	1990-1992	Shock or inadequate echo visualisation of LV function	6676	17.7%	36.9% (805 within first 2 days)	NA	54.6% (11.4% transient only)
EHFS[24]	2000	Registry	10484	10%	~25%	NA	35%
Olmested County [22 40]	1979-1994	Registry	2171	11.8%	24.2% within 30 days	16.8% over 6.6 years	53.1%
Framingham[37]	1950-1989	Registry	546		9.7% within 28 days	10 years	
Hellerman review	NA	Population based	NA	37% (95% CI 25% to 48%)			NA
	NA	Registry	NA	36% (95% CI 19% to 51%)			NA
	NA	Trials	NA	18% (95% CI 11% to 35%)			NA
MONICA Project, Perth, Western Australia [41]	1984 &1993	History of HF and MI, if patients died within 28 days[a]	4006	none	22.4% within 28 days	10 years	NA

CI,confidence intervals; HF, heart failure; NA, not applicable or available; [a], only age 25-64 years included;

Other methods of data collection, and the clinical experience of some, suggest a lower incidence of HF. This could reflect a higher threshold for diagnosis, failure to include transient events, exclusion of patients with pre-existing HF, excluding patients with conditions such as cardiogenic shock and excluding patients who die soon after admission. Cardiology focused studies and registries are likely to underestimate the incidence of HF in post MI patients as they tend to exclude older, higher risk patients.

Another potential way of assessing the proportion of patients with HF after MI is to measure the amount of loop diuretic used, since the predominant use of these agents is for the management of fluid retention caused by heart or renal failure. Surveys suggest that a third or more of patients admitted with an acute coronary syndrome will be treated with a diuretic and it is likely that most of these patients have shown signs or symptoms of HF [24]. The Euro Heart survey of Acute Coronary syndromes suggested that about 35% of all patients with MI will receive in-patient diuretic therapy but did not distinguish loop from thiazide diuretic[24].

Estimates of the proportion of patients that have or will develop heart failure during the index admission vary from as low as 9% up to 55%[21 27 37]which may be transient or persist (Table 1.2). Overall, the literature review suggests about 40% of patients should have heart failure or LVSD identified during an admission for MI or about one patient per thousand population per year.

1.2.3 Heart Failure Developing and Recovering after Discharge from the Index Myocardial Infarction Hospitalisation

Not all patients who develop HF in the acute post-infarction period will develop chronic HF. The TRACE study suggested that the signs and symptoms of HF would be transient in about 15% of patients with major LVSD and 40% of patients without major LVSD[28] (Figure 1.2).

The incidence of HF developing for the first time after discharge from the index admission is even more uncertain. The Framingham study (population of Framingham about 65,000), based on rather limited evidence suggested that, although mortality had declined after an MI, the risk of HF had not, which the authors ascribed to improved survival amongst patients who had sustained major ventricular damage[37]. However, late-onset HF (>29 days after the event) may have been reduced by up to 50% although this analysis is based effectively on only 15 cases. The incidence of late-onset HF in Framingham was only 1% per year. The Olmsted County study, which identified 2,171 infarcts over 15 years from a population of about 130,000, suggested that 12% of patients had pre-existing HF and that 41% of patients would develop new onset HF (using the Framingham Criteria, which does not require LVSD to be present) over 6.6 years giving a combined total of 53% for the development of HF. Most new cases developed during the index hospitalisation, with an annual incidence thereafter of about 3%[22 36 40]. Moller demonstrated 7% of patients were hospitalized for new or worsening HF during 40 months follow up but they did not clarify the numbers of cases that were due to new onset HF[42]. Recurrent MI was not reported to be an independent determinant of developing HF [36 40]. However, the Framingham Criteria were designed to be specific rather than sensitive to a diagnosis of HF [43]and therefore the Framingham and Olmsted County studies may have substantially underestimated of the risk of developing heart failure after an MI.

Three substantial studies of post-infarction LV systolic dysfunction that excluded patients with more severe heart failure developing during the index admission give some further insights[44 45 46 47] (Table 1.3). However, patients with ‘mild’ HF during the index admission were not excluded from these studies.

Table 1-3Progression of heart failure and mortality in randomised controlled trials of post-infarction left ventricular systolic dysfunction

Study	Year	HF at baseline	Diuretic use at baseline	Follow up	Subsequent HF event	Overall mortality
SAVE [46]	1987-1990	~40%	35%	42 months	15.5 %	22.5%
CAPRICRN[44 45]	1996-1999	NA	34%	15 months	13.1%	13.6%
EFHESUS [47]	1999-2001	90%	60%	16 months	11.1%	15.6%
HF, heart failure						

1.2.4 Results of the BNP Review:

According to ESC new guideline[48] clinical skills and cardiac imaging are not the only measures of cardiac dysfunction after an MI. Brain natriuretic peptides (BNP) and NT-proBNP provide an alternative simple method for detecting cardiac function, although as the concentration of these peptides are also dependent on renal function, they should really be considered a marker of cardio-renal dysfunction. Atrial fibrillation, low body mass index, left atrial hypertension (due to left ventricular systolic or diastolic dysfunction or mitral valve disease) and pulmonary hypertension may all cause a rise in NT-proBNP and are all associated with adverse cardiovascular outcomes. The relationship between NT-proBNP and this broad range of predictors of an adverse cardiovascular outcome is its strength as a tool with which to assess prognosis but both a strength and weakness when it comes to diagnosis. In health, NT-proBNP rises with age (perhaps reflecting declining renal function and reduce ventricular compliance) and is higher in women. These demographic trends are swamped by changes induced by the onset of disease and female sex. As older people are more prone disease it may not be intelligent to have age-corrected normal values [49].

Patients who have increased plasma concentrations of N terminal pro B-type natriuretic peptide (NT-proBNP) and BNP after an acute MI have a higher HF hospitalisation rate and worse prognosis (Table 1.4). Some of the studies demonstrated that NT-proBNP

concentration has negative correlation with LV EF after MI[50 51]. The ability to predict a poor outcome is independent and additive to that of LVSD[52 53 54].

Table 1-4Prognosis of NT-BNP and BNP in patients with acute myocardial infarction

study	Natriuretic peptide test	Time of blood test	number	Age limitation	f-up	BNP & LVSD	Predictor of
Richards[54]	N-BNP >median	24-96 hours[a]	666 hospital admission	<85	3 years		Death or HF hospitalisation
Khan[55 56]	Log NT-proBNP	3-5 days[a]	983 concecutive MI[b]		343 days	Was elevated in pts with LVSD	Death and HF and LV EF
Bjorklund[57]	NT-BNP	Before stsrting lysis	782 STEMI-RCT	≥18y	1 year		death
[a]after the onset of symptoms; [b]echocardiography parameters were available on 584 subjects. RCT; randomised control trial							

Table 1-5Prognosis of NT-BNP and BNP in randomised controlled trials in patients with acute coronary syndrome.

study	Collection data	Natriuretic peptide test	Time of blood test	number	Age limitation	f-up	NT-proBNP Predicted
Scirica[58]	RCT	BNP	baseline	4162		24 months	HF admission
Galvani[59]	Hospital registry	NT-proBNP	3 hours	1756		30 days	Death & severe HF
Westerhout[60]	RCT	NT-proBNP	baseline	7800	>21 years	30 days/1 year[a]	death & Death/MI
Morrow[61]	RCT[b]	NT-proBNP	baseline	1676		30 days/1 year[c]	Death & CHF
James[52]	RCT	NT-proBNP	baseline	6809		1 year	death
Omland[62]	Coronary care unit admission	NT-BNP	3 days	609	18-80	51 months	death
James[63]	RCT	BNP	baseline	2525		10 months	death
[a]HF admission after 30days of randomisation, 30 days f-up for death and death/MI and 1 year f-up for death. [b]NSTE- ACCS, [c]new CHF within 30 days and 1-year mortality. CHF, congestive heart failure.							

Accordingly, patients who have LVSD and elevated NT-proBNP have the worst outcome, those with LVSD alone or elevated NT-proBNP alone have an intermediate prognosis, and those without LVSD and normal NT-proBNP have a good prognosis[54]. If it is accepted that it is important to stratify risk in patients with MI in order to identify patients who do or do not need intensive treatment, then a combination of cardiac imaging, natriuretic peptide, and stress testing for ischaemia provides a robust strategy for risk profiling.

The studies also indicated the increase level of plasma concentrations of NT-proBNP and BNP provide a powerful prognostic value amongst patients with acute coronary syndrome and associated with higher mortality and HF hospitalisation rate (Table 1.5).

In most of the previous studies BNP measurements were performed during the acute phase of MI or ACS, only limited surveys investigated the role of BNP in the chronic phase. An audit of patients with a prior history of MI conducted in primary care showed that BNP concentration was of some use for excluding only those patients with severe LV dysfunction, but was unable to discriminate between patients with lesser degree of LVSD and preserved LV function [64]. Another study on 418 outpatients with previous MI suggested that NT-proBNP could be used to identify patients with a reduced LVEF (cut point of 260 pg/ml for EF<45% and 348pg/ml for detecting EF <35%) [65]. Another study assessed 52 stable patients after MI and found that NT-proBNP was independently related to LV volumes and LVEF [66]. Another study on 141 asymptomatic patients with previous MI showed that there was a correlation between LVEF and BNP concentration only in patients with a reduced LVEF but not in those without LVSD [67] (Table 1.6).

There is a paucity of data to assess the relationship between the severity of LV dysfunction and NT-proBNP concentration in patients with a remote MI. The studies that investigated the

prognostic value of NT-BNP were based on measurements made in the acute setting of an MI and there is no documentation on analysis of the prognostic power of the NT-proBNP measurement on the remote cases.

Table 1-6 Prognosis and diagnosis of NT-proBNP and BNP in patients late after myocardial infarction.

study	Collection data	Natriuretic peptide test	Time of blood test	number	Age limitation	f-up	BNP and LV function	Multivariare-- Predictor of
Luchner [65]	MI registery	NT-BNP	Study time	418	<75 years		Cut off value: 384pg/dl for detecting EF<35 and 260pg/dl for detecting EF<45	in multivariate model, NT-BNP was independent & significant predictors of HF, EF, LVMI and GFR
Watanabe[67]	Cross sectional study[a]	BNP	Study time	141		-	Negative correlation between EF & BNP in low EF group, no correlation between EF & BNP in normal EF group	
Orn[66]	RCT	NT-BNP	Study time, 1months,1 year, >4years	52		>4 years	Log BNP was related to end diastolic volume index	Increasing age, no use of early statin therapy and LV end diastolic volume were significantly independent variables of NT-BNP at >4 years
McClure[64]	Primary care	BNP	Study time	134			Low BNP can exclude severe LVSD[b]	

[a] Outpatients with history of MI & no HF symptoms during last year. [b] Only can exclude severe LVSD but unable to discriminate between patients with moderately severe dysfunction and those with preserved LV function. MI; myocardial infarction, LV; left ventricular, HF; heart failure, EF; ejection fraction, GFR; glumoral filtration rate, RCT; randomised control trial, LVSD; left ventricular systolic dysfunction.

1.3 The Evidence Gap

There is a paucity of data investigating the prevalence of HF and LVSD following MI in all patients. The percentages of patients developing HF during index admission varies amongst studies, many of which selectively reported from cardiology services and randomised control trial which tend to exclude older people, patients with prior MI, those with severe haemodynamic compromise and 'fragile' patients; all the groups at highest risk of developing heart failure and of dying. The development of transient and recurrent HF are poorly documented as is the contribution of recurrent myocardial infarction. If recurrent myocardial infarction rarther than ventricular remodelling is the most important factor driving the progression of heart failure this might require a major change in strategy. Finally, there are few contemporary data on the long-term development of heart failure after myocardial infarction and its importance as a determinant of longer term prognosis.

It is known that the plasma concentration of BNP after acute MI provide powerful prognostic value and associated with higher mortality, HF hospitalisation rate and other non-fatal ischaemic events (MI and re admission for ACS) independent of the other factors furthermore the higher concentration of BNP are associated with coronary artery disease, it also has been reported that BNP is a useful screening test for LV dysfunction and it co-related with LV ejection fraction (EF). There is less data on BNP in patients with a remote MI to show the diagnostic value for detecting LV dysfunction and HF. The role of BNP for detecting patients with worse prognosis, who need more follow-up and effective treatment in patients with prior MI, is unclear.

2 Chapter 2: METHOD OF STUDY:

2.1 Study population and process of contacting Patient

I. This study was approved by the Local Research Ethics Committee.

II. All patients with a death or discharge diagnosis of acute MI (International Classification Codes I21.0, I21.1, I21.2, I21.4, I21.9, I22.0, I22.1, I22.8 and I22.9) "between" the 1st of January and 31st of December 1998 were identified for us by the Hull & East Yorkshire Hospitals Trust Information Department (UK) that provide all of the acute cardiac services for about 560,000 people living in a geographically distinct part of the United Kingdom. Case note of all patients screened and follow-up data were collected until 31st December 2005. Restricting the cohort to cases in 1998 ensured that all patients had roughly equal duration of follow-up. Recruitment of consecutive cases using the hospital coding criteria helped to reduce ascertainment bias and increase the representativeness of the population. For instance inclusion only of patients cared for by a cardiologist would have biased the sample towards inclusion of younger patients. However, it is possible that some patients will have been missed by this procedure. To deal with this and finding out the incidence of MI between different databases, during 2005, we compared the hospital coding criteria and Myocardial Infarction National Audit Project (MINAP) records, Hull Infarction Project (HIP-2005) and all troponin T (TnT) >0.03 ug/L reported by lab (see chapter 7).

III. All patients who were alive by May 2004 were identified and a "Consultant Letter" (see appendix) sent, at the request of the ethics committee, either to the consultant who cared for the patient in 1998 or to a consultant who subsequently cared for the

patient, requesting permission for us to contact the patient asking them to attend the clinic at the Academic Department of Cardiology, Hull Royal Infirmary or Castle Hill hospital and to sign the "Consultant Letter to Patient" (see appendix) template. The exception to this rule was patients under the care of Professor Cleland, since he was supervising the project, and patients. Professor Cleland was designated as the cardiologist caring for the patient if none of the current cardiologists were or had cared for the patient.

IV. A "patient information leaflet" and invitation letter (see appendix), which were approved by the local ethics committee and trust board, were sent to all patients who were alive by May 2004. The hospital patient administration system (Clinicom) was used to identify patients who had died immediately prior to sending the letter.

V. Patients who responded favourably to the "Consultant Letter to Patient" were invited to attend Hull Royal Infirmary or Castle Hill hospital for follow up. They were asked to provide consent using the "Patient Consent Form" (see appendix).

VI. The patients' family doctors were informed if patient(s) chose to participate and of any clinically relevant results by patients by using the "GP Letter" (see appendix).

2.2 Case Records Review

The case records of all patients, regardless of whether they were able to attend for follow-up, were reviewed to identify:

- Their usual address since only patients residing in Hull and East Yorkshire were included in the survey. Since Hull and East Yorkshire NHS Trust is the sole provider of acute care in the region this enabled tracking of recurrent hospitalisations.
- the evidence in support of a diagnosis of acute myocardial infarction on the index admission
- whether the patient developed transient or persistent heart failure during the index admission
- mortality during the index admission
- clinical course subsequent to discharge including
    - Development or resolution of heart failure
    - Readmission for acute coronary syndromes
    - Readmission for heart failure

If no hospital record existed after January 1st 2004, the family practitioner was contacted to ascertain the patient's current therapy and HF status.

During the case note review the following data were collected: age, sex, height, weight, history of hypertension, history of MI, history of diabetes, history of heart failure, blood pressure, supra ventricular tachycardia, ventricular tachycardia, cardiology seen during index admission, blood test (full blood count, Urea & Electrolytes, blood glucose, cholesterol, CK and CK-MB), chest X-ray, electro-cardiogram, any cardiac image (echocardiography, angiography and radionuclide), coronary artery bypass graft, medication (thrombolysis,

diuretics, angiotension converting enzyme inhibitors, heparin, insulin, inothrop, nitrate, calcium blockers, aspirin, warfarin, oral hypoglycaemic agents, β-blockers, Digoxin, angiotensin-II receptor antagonists, statins and onset of diabetes (Table 2.1). Also the occurrence of major events, such as recurrent MI, death, LV systolic dysfunction, angina admission and stroke were recorded by end of December 2005 (followed six years).

Table 2-1During the case note review the following data were collected:

Demographics	Dates	History	Clinical Features	Laboratory Values	ECG & CX-Ray & Imaging Data	Therapy	Events	Death data
Age	Index Admission	Hypertension	Blood pressure	Serum Creatinine	chest X-ray	PTCA	Mortality	Place
Sex	Index Discgarge	Diabetes	smoking	Urea	Cardiomegaly	CABG	HF	Mode of death
Height	Daete of LV measurement	MI	HF during admission	Haemoglobin	Upper lobe vein distension	Thrombolysis	Re MI	Terminal HF
Weight	Date of birth	HF	Shock	Sodium	Pulmonary oedema	Diuretic	CVA	Cardiogenic shock
Current Smoking	Onset of Diabetes	LVSD	supra ventricular tachycardia	Potassium	Pleural effusion	Loop diuretic	Chest pain admission	Stroke
Ex smoking	Date of 1st reMI	PTCA	ventricular tachycardia	Glucose	Radionuclide	Thiazide diuretic	Diabetes	Cardiac procedure
Alcohol	Date of any cardiac image	CABG	HF in discharge	Cholesterol	Coronary angiography	Beta-blockers		Other cardiovascular
Managed by cardiologist	Last recorded as alive	Family history		Peak CK	electro cardiogram	ACE-inhibitor		Cancer
	Date of Death			CK-MB	Rate	ARB		Infection
					Rhythm	Statin		Other non-cardiovascular
					QRS conduction	Spironolactone		Autopsy
					QRS ≥120	Aspirin		
					Type of MI	Clopidogrel		
					LBBB, Pace	Heparin		
					ST segment elevation	warfarin		
					Echocardiography	Calcium channel blockers		
					Major LVSD	Insulin		
					Major Mitral regurgitation	oral hypoglycaemic agents		
					Major other valve disease	Inotropic therapy		
					Radionuclide	Nitrate		
					LVEF 35-39%	Digoxin		
					LVEF <35%			
					Angiography			
					Major LVSD			
					Vessel disease			
					LMCA disease			

LV, left ventricular; MI, myocardial infarction; HF, heart failure; LVSD, left ventricular systolic dysfunction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; ck, creatine kinade; ECG, electro cardiogram; LBBB, left bundle brunch block; LMCA, left main coronary artery; ACE inhibitor, angiotension converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CVA, cerebrovascular accident.

2.3 Tests during follow up visit

Patients who attended for the follow up visit were asked about their medical history, symptoms and Current drug therapy, physical examination, blood tests including: Full blood count, Lipid Profile, urea, electrolytes, and blood glucose.

The following additional tests were also performed:

- Symptoms and quality of life using the Euro Heart Failure Questionnaire (see appendix)
- NT-proBNP blood test as a marker for cardiac dysfunction.

Venous blood samples for analysing NT proBNP:

- were obtained from patients when they attended for follow up visit. Blood samples were immediately centrifuged at 4^{oC} (Termo centra CL3R) for 15 minutes at 3000 RCM (revolution per minute) within 30 minutes and pipetted plasma into small cryovials and stored in a –80ºC freezer until analysis.
- Plasma NT-BNP levels were determined using a commercial assay (Elecsys 2010, Roche analysis).

- 12-lead electrocardiogram (ECG). (G E Medical, Model: Mac 5000)
- 24 hour ambulatory ECG monitoring (a few number of patients only have been offered this test as availability was limited). (Reynolds, Life card CF)

- Echocardiography with Tissue Doppler Imaging (GE Medical, VIVID-5).
    - Ventricular dimensions were measured by M-mode. Two-dimentional, apical two and four-chamber views were taken for volume measurements and ejection fraction calculated by Simpson’s biplane method. Left ventricular ejection fraction (LVEF)

<40% or a qualitative report of moderate or severe LVSD on echocardiography. Left Atrial (LA) dimension was measured as the antero-septal diameter from the parasternal long axis view and considered as dilated if >3.8cm. Valve disease was assessed by colour flow Doppler from multiple echocardiographic views. Mitral regurgitation was graded as mild, moderate or severe.

2.4 Inclusion Criteria

Patients with a death or discharge code for an AMI between 1st of January and 31st of December 1998 identified from the Hull & East Yorkshire Hospitals NHS Trust Information Department.

2.5 Exclusion Criteria for Index Admission

- Patients who had been transferred from outside of the Hull and East Yorkshire area or who were just visiting the area

- Patients who had missing case notes.
- Patients who had no confirmation of AMI in their records during 1998 and had a coding mistake.

2.6 2.6 Definitions

2.6.1 2.6.1 Definition of Myocardial Infarction

At least **two** of the following five criteria had to be identified during case note review to confirm a diagnosis of MI.

1. History of prolonged cardiac chest pain.

2. An increase in biomarkers consistent with MI, which in 1998 was usually creatinine kinase (CK) or CK-MB mass. These were considered abnormal if they were twice the upper limit of normal values.

3. Progressive electrocardiographic changes consistent with MI or new onset left bundle branch block.

4. Sudden unexpected death

5. Autopsy evidence of MI

2.6.2 Definition of Heart Failure

Heart failure was defined clinically either as signs and symptoms consistent with that diagnosis (principally breathlessness and signs of fluid retention) resulting in treatment with loop diuretics or patients who died shortly after developing evidence of major cardiac dysfunction, such as cases of cardiogenic shock or pulmonary oedema or patients in whom post mortem examination definite heart failure. These patients were identified as a special subset so that the contribution of this group of patients to overall outcome could be identified:

- Cardiogenic shock was defined as an arterial pressure <100mmHg due to low cardiac output requiring inotropic therapy or an intra-aortic balloon pump. For patients with an

un-recordable blood pressure, a systolic pressure of 50mmHg was entered as a default value for statistical purposes.

- Patients who had evidence of HF/ LVSD and were on dialysis due to renal failure were counted as if they were receiving loop diuretic.

2.6.3 Resolution of Heart Failure

Consistent with European Society of Cardiology Guidelines [68], resolution of HF was defined as the withdrawal of loop diuretics without the recurrence of symptoms.

2.6.4 Definition for left ventricular dysfunction (LVSD)

Criteria for LVSD were left ventricular ejection fraction (LVEF) <40% or a qualitative report of moderate or severe LVSD on echocardiography, first-pass radionuclide ventriculography or contrast angiography. Evidence of LVSD was not required for a diagnosis of heart failure.

2.6.5 Definition of Renal Dysfunction

Renal dysfunction was defined as estimated glomerular filtration rate (eGFR) <60 mls/min/1.73m^2, using the four-variable formula derived from the modification of diet in renal disease study (4V MDRD):

GFR= 186 * [serum creatinine/88.4$^{)-1.154}$ *Age$^{-0.203}$ * (0.742 if female) *(1.212 if African Caribbean)[69].

2.6.6 Definition for anaemia

Anaemia was defined according to WHO criteria as a haemoglobin concentration <13g/dL in men and <12g/dL in women.

2.6.7 Mode of Death:

2.6.7.1 Sudden (presumed arrhythmic) cardiac death (SCD);

Sudden cardiac death was defined as one or more of the following:

- Unwitnessed death or witnessed sudden death in the absence of other cause of death such as severe heart failure, stroke, cardiac procedures, aortic dissection or aneurysm rupture, end stage cancer, severe infection such as septicaemia, major surgery or other end-stage disease
- Resuscitated cardiac arrest in the absence of other causes of death (as above) if the patient died within the following 72 hours.
- Absence of evidence of an explanation for death other than sudden (arrhythmic) death on autopsy.

2.6.7.2 Heart Failure Deaths

Patients who died at home but had persistent severe symptoms of heart failure or recurrent hospital admissions for worsening heart failure and patients who were admitted to hospital for or with worsening heart failure during and who developed cardiogenic shock, pulmonary oedema, or severe heart failure were considered to have died of heart failure.

2.6.7.3 Stroke deaths

Stroke was defined as the sudden onset of focal neurological signs that persisted for at least 24 hours or resulting in death. Deaths within 30 days of a stroke were deemed deaths due to stroke unless another more proximate cause was evident. Stroke occurring within 24 hours of thrombolysis for myocardial infarction were deemed cardiac procedure related rather than deaths due to stroke.

2.6.7.4 Cardiovascular Procedure Related Deaths

Patients who died during or after angiography, angioplasty, coronary artery bypass graft (CABG), valve surgery or vascular surgery and those who died due to stroke within 24hours of thrombolysis for myocardial infarction were considered cardiac procedure related deaths.

2.6.7.5 Other cardiovascular

This included aortic dissection and pulmonary embolism. It is recognised that a proportion of such events will not be clinically recognised and will often be recorded as sudden cardiac death.

2.6.7.6 Cancer

Patients who were diagnosed with advanced, incurable cancer.

2.6.7.7 Infection

Patients who died due to severe infection, usually bronchopneumonia or septicaemia.

2.6.7.8 Other non cardiovascular

Patients who died subsequent to any major non-cardiovascular surgery, end-stage renal failure, end-stage chronic obstructive pulmonary disease (COPD), emphysema, asbestosis, severe GI bleeding, bowel obstruction, general debility and pancreatitis.

2.6.8 Place of Death

Death was reported as in-hospital, out-of-hospital (if patients died in ambulance or sheltered accommodation/nursing home, we categorised as a death out-of-hospital).

2.7 Statistical Analysis:

Data were entered into a Microsoft Access database and analysed using SPSS (version 13.0). Key outcomes were the proportion of patients who died and mortality rate. Continuously distributed data are presented as median and inter-quartile range. Categorical data are presented as percentages. Groups of patients with and without heart failure were compared by the Chi-squared test. Logistic regression was used to look at relationship between HF and gender. The incidence rate of HF per person-year of follow-up was calculated for the first year and for subsequent years of follow-up[70]. This was only calculated for those discharged without HF or in whom HF had resolved by the time of discharge. Ninety-five percent confidence intervals were calculated using boot strapping with 1000 re-substitutions[71].

Kaplan-Meier (K-M) curves were generated to illustrate patients' survival overall and in relevant subgroups. K-M curves were compared by the log-rank test. Cox regression was used to look at mortality, from which hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The Cox regression model is semi-parametric in the sense that no assumption concerning event-free survival times is necessary. The Cox regression model is based on the assumption that the effect of a risk factor, expressed as a hazard ratio, is constant over time. The purpose of this model was not to develop a risk stratification tool but rather to determine the extent to which a particular clinical pathway altered outcome. We present age-adjusted models in the text rather than adopting a formal statistical approach to model building (i.e., taking an epidemiological stance). The assumption of proportionality of the Cox model covariates was tested by plotting residuals[72 73 73]. Linearity of continuous data was checked by including a squared term.

Heart Failure status was categorised into six groups:

1. No HF at any time (this was the reference group)

2. Patients with HF on the index admission and persisting at follow up until death or end of follow-up
3. Persistent HF on the index admission that resolved subsequent to discharge.
4. Transient HF on the index admission that resolved prior to discharge but recurred during follow-up.
5. Transient HF on the index admission that resolved prior to discharge and did not recur prior to death or end of follow-up
6. Patients who did not develop HF on the index admission but who later developed HF during follow-up.

Development and course of HF according to age was categorised into three groups:

1. <70 years,
2. 70 to 79 years
3. > 79 years.

Development and course of HF according to sex

1. Women
2. Men

Development and course of HF according to development of ST elevation (more than 2mm in chest leads and more than 1mm in limb leads) was categorised into four groups:

1. ST elevation
2. No ST elevation.
3. Left bundle branch block (LBBB)
4. Unknown

Development and course of HF and renal dysfunction according to renal function (out come by eGFR) was categorised into four groups:

1. eGFR less than 30 ml/min,
2. 30-59 ml/min,
3. More than 59 dl/min.
4. Not known

Development and course of HF and anaemia was categorised into three groups:

1. According to WHO criteria with >1 g below WHO threshold being definite anaemia
2. 1 g above or below WHO threshold as borderline
3. >1g above WHO threshold as not anaemia

Development and course of HF according to presence of diabetes was categorised into three groups:

1. Any diagnosis of diabetes and the following subgroups
   - Diet only at discharge
   - Metformin at discharge
   - Other oral therapy at discharge
   - Insulin at discharge
2. No diabetes at discharge (with blood glucose measured)
3. No diagnosis of diabetes and no measure of glucose

Development and course of HF according to the smoking was categorised into four groups:

1. Current smoking
2. Ex-smoking
3. not smoking
4. not known

Development and course of HF according to the type of MI in ECG was categorised into four groups:

1. Any anterior site (V2-V4)ST elevation
2. Other site rather than Anterior
3. Left bundle branch block (LBBB) and Pace maker inserted
4. No ECG report

3 Chapter 3: The Timing of Development and Subsequent Clinical Course of Heart Failure after a Myocardial Infarction1

3.1 Introduction

Heart failure (HF) is a common complication of myocardial infarction (MI), which may develop early or late. Once it has developed it may persist or resolve, and if it resolves it may re-occur. The cumulative incidence and resolution or persistence of HF after a MI is poorly described.

Surveys suggest that one-third or more of patients admitted with an acute coronary syndrome (ACS) will be treated with a diuretic and it is likely that this will often be for signs or symptoms of HF [24 74]. Surveys also suggest that between 9 and 55% of patients have or will develop HF during admission for MI [21 27 37 74],which may be transient or persist. The incidence of HF developing for the first time after discharge from the index admission is poorly described, with incomplete data regarding numbers surviving until discharge and confusion about how best to present incidence rates and therefore comparison between studies is difficult. Despite differences in statistical presentation, these studies would seem to suggest that most new cases of HF in those hospitalised with an MI develop during admission or early after discharge [22 38 40]. Studies also suggest that patients who develop HF are at much greater risk of dying, whether or not they also have left ventricular systolic dysfunction (LVSD)[28 74]. However, few reports exist about the outcome of HF that is either transient or develops only subsequent to discharge. Also, it is unclear what proportion of cases occurring late after the index infarction is because of recurrent MI. We set out to identify the timing of onset, persistence, resolution, and outcome of HF developing after an MI.

[1] This chapter has already been published in European Heart Journal (see: Azam Torabi et al, 2008).

3.2 Methods

3.2.1 Study population

One hospital group in Hull and the East Riding of Yorkshire (UK) provide all of the acute cardiac services for about 560,000 people living in a geographically distinct part of the United Kingdom. Patients with a discharge diagnosis of acute MI during 1998 were identified from the Hospitals Information Department and their case notes screened. Patients who were transferred from another region, those with missing case notes, or in whom acute MI could not be confirmed from their records were excluded.

This study was approved by the Local Research Ethics Committee.

3.2.2 Follow-up

This was a retrospective analysis designed in 2004. The case records of all patients were reviewed to identify use of loop diuretics and if so whether this was due to symptoms or signs of HF. Follow-up data were collected until 31st December 2005. If no recent hospital record existed, the family practitioners of patients or patients themselves were contacted to ascertain the patient's current therapy and HF status. The occurrence of major events, such as recurrent MI, and stroke were recorded.

3.2.3 Definition of Myocardial Infarction

At least two of the following five criteria had to be identified during case note review to confirm a diagnosis of MI.

1. History of prolonged cardiac chest pain.

2. An increase in biomarkers consistent with MI, which in 1998 was usually creatinine kinase (CK) or CK-MB mass. These were considered abnormal if they were twice the upper limit of normal values.
3. Progressive electrocardiographic changes consistent with MI or new onset left bundle branch block (LBBB).
4. Sudden unexpected death
5. Autopsy evidence of MI

3.2.4 Other Definitions

HF was clinically defined either as signs and symptoms consistent with that diagnosis (principally breathlessness and signs of fluid retention) resulting in treatment with loop diuretics or patients who died shortly after developing evidence of major cardiac dysfunction, such as cases of cardiogenic shock or pulmonary oedema. The latter group of patients were identified as a special subset so that the contribution of this group of patients to overall outcome could be identified. Cardiogenic shock was defined as an arterial pressure <100mmHg because of low cardiac output requiring inotropic therapy or an intra-aortic balloon pump. For patients with an un-recordable blood pressure, a systolic pressure of 50mmHg was entered as a default value for statistical purposes. Use of loop diuretics for the treatment of hypertension or renal failure was not included in the definition of HF. Evidence of LVSD was not required for a diagnosis of HF. Criteria for LVSD were left ventricular ejection fraction (LVEF) < 40% or a qualitative report of moderate or severe LVSD on echocardiography, first-pass radionuclide ventriculography, or contrast angiography.

3.2.5 Resolution of Heart Failure

Consistent with European Society of Cardiology Guidelines [68], resolution of HF was defined as the withdrawal of diuretics without the recurrence of symptoms.

3.2.6 Statistical Analysis:

Data were entered into a Microsoft Access database and analysed using SPSS version 13.0 (UK,Ltd). Key outcomes were the proportion of patients who died and mortality rate. Continuously distributed data are presented as median and inter-quartile range (IQR). Categorical data are presented as percentages. Groups of patients with and without HF were compared by the Chi-squared test. Logistic regression was used to look at the relationship between HF and gender. The incidence rate of HF per person-year of follow-up was calculated for the first year and for subsequent years of follow-up [70]. This was only calculated for those discharged without HF or in whom HF had resolved by the time of discharge. Values for 95% confidence intervals (CIs) were calculated using boot strapping with 1000 re-substitutions [71].

Kaplan-Meier (K-M) curves were generated to illustrate patients' overall survival and in relevant subgroups. K-M curves were compared by the log-rank test. Cox regression was used to look at mortality, from which hazard ratios (HRs) and 95% CI were calculated. The Cox regression model is semi-parametric in the sense that no assumption concerning event-free survival times is necessary. The Cox regression model is based on the assumption that the effect of a risk factor, expressed as HR, is constant over time. The purpose of this model was not to develop a risk stratification tool, but rather to determine the extent to which a particular clinical pathway altered outcome. We present age-adjusted models in the text rather than adopting a formal statistical approach to model building (i.e., taking an epidemiological stance). The assumption of proportionality of the Cox model covariates was

tested by plotting residuals[72 73]. Linearity of continuous data was checked by including a squared term.

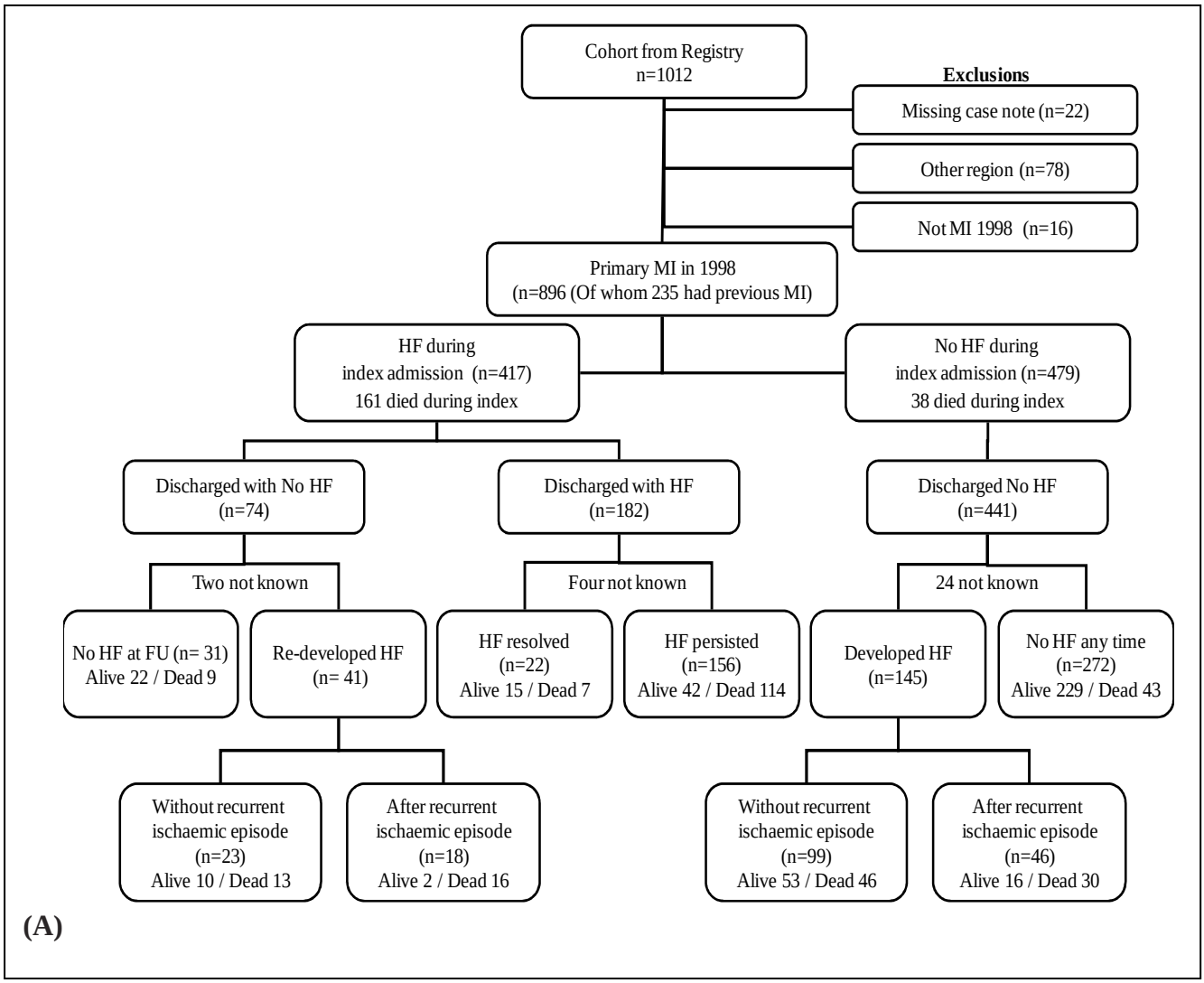
HF status was categorised into six groups: (i) No HF at any time (this was the reference group); (ii) Patients with HF on the index admission and persisting at follow-up until death or end of follow-up; (iii) Persistent HF (PHF) on the index admission that resolved subsequent to discharge; (iv) Transient HF (THF) on the index admission that resolved prior to discharge but recurred during follow-up; (v)THF on the index admission that resolved prior to discharge and did not recur prior to death or end of follow-up; (vi) Patients who did not develop HF on the index admission, but who later developed HF during follow-up.

3.3 Results:

3.3.1 Overall Results

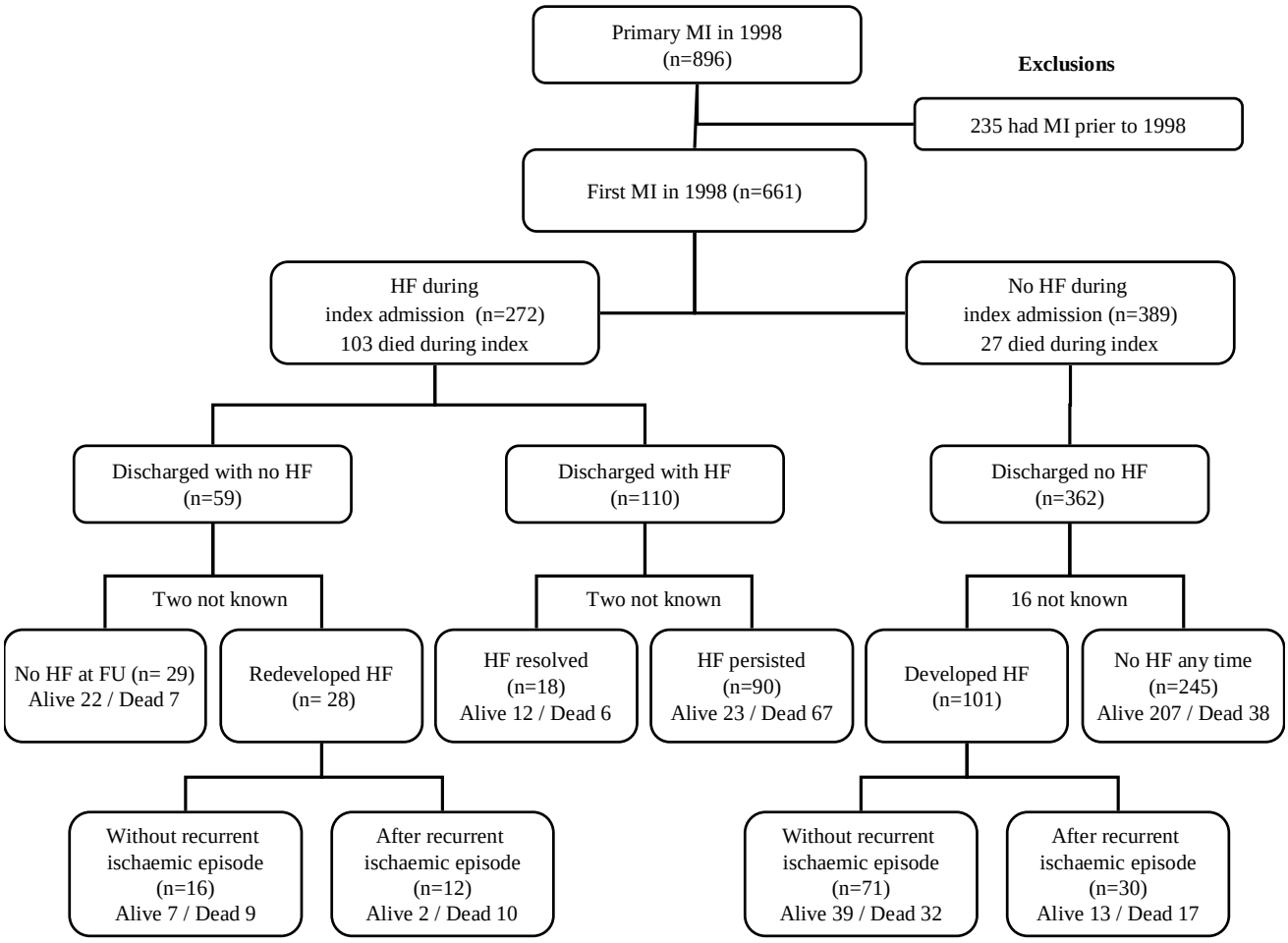
Of 1,012 patients with a death or discharge diagnosis of acute MI in 1998, 116 were excluded from further analysis (78 because they had been transferred for acute management from another region, 22 because of lack of relevant documents for the event, and in 16 cases because the diagnosis of MI could not be confirmed from the record). Of the 896 patients for the main analysis, 661 had no prior history of MI (Figure 3.1b). Thirty patients (3.3%) were lost to follow-up after the index admission. Documentation of the index event was generally good with little in the way of missing key data.

Figure 3-1Primary MI and Fist MI in 1998 and development of heart failure (HF) and mortality



Flow diagram showing the sequence of development of heart failure (HF) and relationship with recurrent ischemic episodes and mortality over approximately 6 years in patients admitted with an acute myocardial infarction (MI) to the Hull and East Yorkshire Hospitals Group during 1998. Follow-up data were incomplete in 30 patients. See text for details. (B) Flow diagram showing the sequence of development of HF and relationship with recurrent ischemic episodes and mortality over approximately 6 years in patients who had a first acute MI (without prior MI) in the Hull and East Yorkshire Hospitals Group during 1998. Follow-up data were incomplete in 20 patients (two with transient HF (THF), two with persistent HF (PHF) during the index admission, and 16 in patients with no HF during index admission, one of whom was reported to have died by the administrative system.

(B)


Primary MI in 1998
(n=896)
Exclusions
235 had MI prier to 1998
First MI in 1998 (n=661)
HF during
index admission (n=272)
103 died during index
No HF during
index admission (n=389)
27 died during index
Discharged with no HF
(n=59)
Discharged with HF
(n=110)
Discharged no HF
(n=362)
Two not known
Two not known
16 not known
No HF at FU (n= 29)
Alive 22 / Dead 7
Redeveloped HF
(n= 28)
HF resolved
(n=18)
Alive 12 / Dead 6
HF persisted
(n=90)
Alive 23 / Dead 67
Developed HF
(n=101)
No HF any time
(n=245)
Alive 207 / Dead 38
Without recurrent
ischaemic episode
(n=16)
Alive 7 / Dead 9
After recurrent
ischaemic episode
(n=12)
Alive 2 / Dead 10
Without recurrent
ischaemic episode
(n=71)
Alive 39 / Dead 32
After recurrent
ischaemic episode
(n=30)
Alive 13 / Dead 17

The median age of the patients was 70 (IQR 61-78) years and 333 (37%) were women (Table 3.1). Of men, 141 (25%) and of women, 147 (44%), were aged >75 years. There was a prior history of hypertension in 300 (33%), MI in 235 (26%), HF in 134 (15%) and diabetes in 82 (9%). In addition, 33 (4%) patients were newly diagnosed with diabetes during the index admission. Sixty-two percent were managed, at least in part, by a cardiologist during their index admission. ST-segment elevation myocardial infarction (STEMI) was present in 518 (58%) and non-STEMI in 316 patients (35%). Forty seven patients had LBBB, five patients were in a paced rhythm, and 10 had no ECG recording available from the time of admission. During the index admission, patients with HF were more often treated with ACE-inhibitors, nitrates, digoxin and insulin. However, patients who developed HF on the index admission were less likely to receive beta-blockers ($p<0.0005$) (Table 3.2).

Overall, 480 patients (54%) had died by December 2005. Figure 3.1a describes the sequence of events that led to the development of HF and/or death. Figure 3.2 shows the overall proportion of patients who developed HF at any time during follow-up and their categorisation according to persistence, remission, and timing of development of HF.HF was present during the index admission in 417 (47%) patients and these patients were older (75(67-81) vs. 66(57-74) years; ($p<0.0001$) and more likely to be women [54% vs. 42% in men; ($p=0.001$). The median age of women with HF was 77 (IQR 71-84) and in men with HF was 73 (IQR range 64-79). In a logistic model, the relationship between HF and sex was no longer significant ($p=0.46$) after adjustment for age. During the index hospitalization, 161 patients (39%) with HF died; 71 of them fulfilled the definition of cardiogenic shock. Only 38 (8%) patients who did not fulfil the criteria for HF died during the index admission (Figure 3.3). HF resolved in 74 patients (18%) and therefore only 182 patients (20%) were discharged with PHF of whom 70 had HF prior to admission.

Table 3-1Patients characteristics recorded during the overall index admission overall and classified according to the development of heart failure (HF) and mortality during index admission [data are median (inter-quartile range) and number occurring (%)].

Variables (units) [missing data]	Overall	No HF during index admission	HF during index admission	P-value	Survived index	Died on Index	P-value
	896	479	417		697	199	
Age (years) [0]	70 (61-78)	66 (57-74)	75 (67-81)	<0.0005	68 (59-76)	76 (71-83)	<0.0005
Women [0]	333 (37%)	153 (32%)	180 (43%)	0.001	250 (36%)	83 (42%)	0.133
Current smoker [87]	303 (37%)	202 (44%)	101 (29%)		261 (40%)	42 (28%)	
Ex smoker	255 (32%)	126 (27%)	129 (37%)	<0.0005	213 (32%)	42 (28%)	<0.0005
History of Hypertension [40]	300 (35%)	138 (30%)	162 (41%)	0.004	224 (33%)	76 (41%)	0.049
History of Diabetes [3]	82+33a (13%)	42 (9%)	73 (18%)	<0.0005	78 (11%)	37 (19%)	<0.0005
Prior MI [1]	235 (26%)	90 (19%)	145 (35%)	<0.0005	166 (24%)	69 (35%)	0.008
History of HF [4]	134 (15%)	4 (1%)	130 (31%)	<0.0005	76 (11%)	58 (30%)	<0.0005
Prior CABG	39 (4%)	9 (2%)	30 (7%)	<0.0005	29 (4%)	10 (5%)	0.598
Prior PTCA	14 (2%)	7 (1%)	7 (2%)	0.794	10 (1%)	4 (2%)	0.564
Managed Primarily by Cardiologist	558 (62%)	317 (66%)	241 (58%)	0.01	466 (67%)	92 (46%)	<0.0005
Index Admission ECG							
ST segment elevationb [10]	518 (58%)	270 (57%)	248 (60%)	<0.0005	406 (59%)	112 (58%)	<0.0005
Non ST elevation [10]	316 (36%)	192 (41%)	124 (30%)		261 (38%)	55 (29%)	
QRS > 120 [23]	199 (22%)	58 (12%)	141 (34%)	<0.0005	124 (18%)	75 (39%)	<0.0005
Anterior site [10]	422 (48%)	195 (41%)	227 (55%)	<0.0005	322 (46%)	100 (52%)	<0.0005
Chest X-ray							
Pulmonary oedema [227]	160 (24%)	18 (5%)	142 (43%)	<0.0005	101 (19%)	59 (45%)	<0.0005
Cardiomegaly	156 (23%)	45 (13%)	111 (33%)	<0.0005	125 (23%)	31 (24%)	0.005
Upper Lobe Vein Distension	159 (24%)	49 (15%)	110 (33%)	<0.0005	125 (23%)	34 (26%)	0.004
Pleural effusion	73 (11%)	13 (4%)	60 (18%)	<0.0005	50 (9%)	23 (18%)	<0.0005

Physical Examination							
Heart Rate [9]	78 (64-97)	72 (61-86)	87 (69-107)	<0.0005	75 (63-90)	92 (72-109)	<0.0005
Atrial fibrillation (yes/no) [2]	153 (17%)	31 (6%)	122 (29%)	<0.0005	97 (14%)	56 (28%)	<0.0005
Systolic blood pressure[5]	140 (120-160)	140 (125-160)	136 (115-160)	0.007	142 (125-162)	126 (101-142)	<0.0005
Blood Tests (on admission)							
Peak creatinine kinase [49]	828 (376-1901)	880 (382-1850)	749 (348-1941)	0.096	888 (390-1919)	623 (256-1698)	0.721
Cholesterol [353]	5.5 (4.8-6.4)	5.6 (4.9-6.3)	5.4 (4.6-6.4)	0.08	5.5 (4.9-6.4)	5 (4.2-6.2)	0.27
Sodium [29]	137 (135-139)	137 (136-139)	137 (134-139)	<0.0005	137 (135-139)	136 (134-138)	<0.0005
Creatinine [127]	105 (89-129)	97 (83-111)	119 (97-157)	<0.0005	101 (86-120)	134 (106-198)	<0.0005
Anaemia in first available haemoglobinc[41]	206 (24%)	81 (18)	125 (31%)	<0.0005	132 (20%)	74 (41%)	<0.0005

CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction; ECG, electrocardiogram. Percentages are shown are of those in whom measurements were made.

Example interpretation: patients who had HF during the index admission had a higher heart rate compared to patients without HF; also those who died on the index admission had a higher heart rate than those who survived. This same patern occurred for creatinine, but the revers pattern was found for sodium, peak creatinine kinase, cholesterol and systolic blood pressure.

aThirty-three cases newly diagnosed as diabetic on index admission.

bP-value for ST calculated between three groups [ST-elevation, no ST-elevation, and other (left bundle branch block and pace)]

cAnaemia: WHO criteria for anaemia are used (male <13g/dL and female <12g/dL).

Table 3-2Treatment during index admission and any time until 31st December 2005.

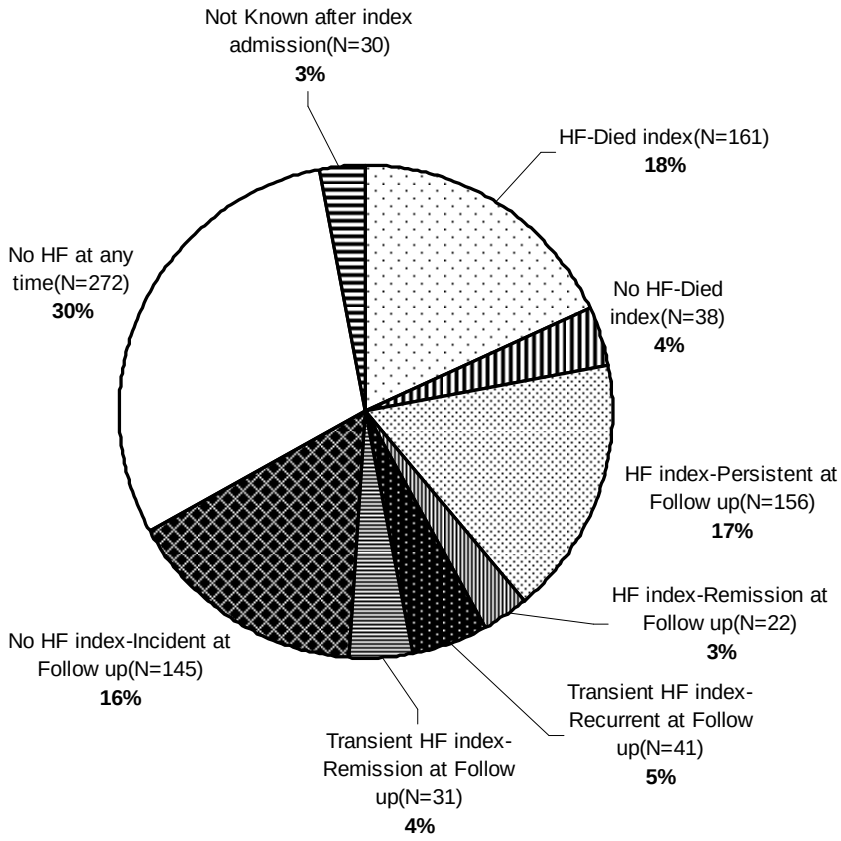
Variables (units) [missing data]	All	No HF during index admission	HF during index admission	P-value	Survived index	Died on Index	P-value
n	**896**	**479**	**417**		**697**	**199**	
Revascularisation during admission							
Thrombolysis [0]	372	225 (47%)	147 (35%)	<0.0005	323 (46%)	49 (25%)	<0.0005
PCI [0]	20	15 (3%)	5 (1.2%)	0.05	20 (3%)		0.016
CABG [0]	8	1 (0.2%)	7 (1.7%)	0.021	6 (1%)	2 (1%)	0.85
Treatment at any time during admission							
Parenteral							
Loop diuretic [7]	262	0	262 (65%)	<0.0005	155 (22%)	107 (54%)	<0.0005
Nitrates [3]	309	153 (32%)	156 (37%)	0.212	255 (37%)	54 (27%)	0.028
Inotropic therapy [2]	94	3 (0.6%)	93 (22%)	<0.0005	29 (4%)	65 (33%)	<0.0005
Heparin [15]	694	387 (81%)	307 (77%)	0.037	579 (85%)	115 (58%)	<0.0005
Insulin [1]	79	30 (6.3%)	49 (11.8%)	0.008	59 (8%)	20 (10%)	0.134
Oral							
Aspirin [2]	792	455 (95%)	336 (81%)	<0.0005	658 (94%)	134 (68%)	<0.0005
Clopidogrel [2]	7	5 (1%)	2 (0.5%)	0.630	6 (1%)	1 (1%)	0.026
Warfarin [2]	35	3 (0.6%)	20 (4.8%)	<0.0005	25 (4%)	10 (5%)	0.019
Statin [2]	406	281 (59%)	125 (30%)	<0.0005	393 (56%)	13 (7%)	<0.0005
ACE inhibitors [2]	354	130 (27%)	224 (54%)	<0.0005	307 (44%)	47 (24%)	<0.0005
ARBs [2]	8	1 (0.2%)	7 (1.7%)	0.065	6 (1%)	2 (1%)	0.029
Beta-blockers [2]	497	360 (75%)	137 (33%)	<0.0005	465 (67%)	32 (16%)	<0.0005
Nitrates [2]	320	146 (31%)	174 (42%)	0.002	260 (37%)	60 (30%)	0.006
Calcium-channel blockers [2]	215	104 (22%)	111 (27%)	0.227	172 (25%)	43 (22%)	0.021
Loop diuretic [3]	297	5 (1%)	292 (70%)	<0.0005	217 (31%)	80 (41%)	0.033
Thiazide diuretic [1]	18	9 (2%)	9 (2%)	0.620	13 (2%)	5 (3%)	0.146
Spironolactone [1]	1	1 (0.2%)		0.418	1		0.150
Digoxin [2]	68	6 (1%)	62 (15%)	<0.0005	41 (6%)	27 (14%)	<0.0005
Oral hypoglycaemic agent [2]	21	11 (2%)	10 (2%)	0.990	17 (2%)	4 (2%)	0.028
Revascularisation at Any Time							
PCI [0]	94	77 (16%)	17 (4%)	<0.0005	94 (13%)	0	<0.0005
CABG [0]	98	67 (14%)	31 (4%)	0.002	96 (14%)	2 (1%)	<0.0005

Treatments at Any Time[a]							
ACEi (seven cases prior to index were on ACE-inhibitors) [2]	496	249 (52%)	247 (59%)	0.091	449 (64%)		
ARBs [2]	44	24 (5%)	20 (5%)	0.984	40 (6%)		
Beta-blockers [2]	541	378 (79%)	163 (39%)	<0.0005	509 (73%)		
Loop diuretic [2]	539	151 (32%)	388 (93%)	<0.0005	401 (58%)		
Thiazide diuretic [2]	68	47 (10%)	21 (5%)	0.017	63 (9%)		
Spironolactone [2]	64	25 (5%)	39 (9%)	0.037	64 (9%)		
Digoxin [2]	110	30 (6%)	80 (19%)	<0.0005	81 (12%)		
Insulin [1]	93	38 (8%)	55 (13%)	0.020	73 (10%)		
Oral hypoglycaemic agent [2]	72	46 (10%)	26 (6%)	0.111	67 (10%)		
Aspirin [2]	805	461 (96%)	345 (83%)	<0.0005	671 (96%)		
Statin [2]	530	367 (77%)	163 (39%)	<0.0005	517 (74%)		

PCI, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; ARBs, angiotensin receptor blockers;
[a]LData on patients who died during the index admission treatment is not shown since it could not have changed.

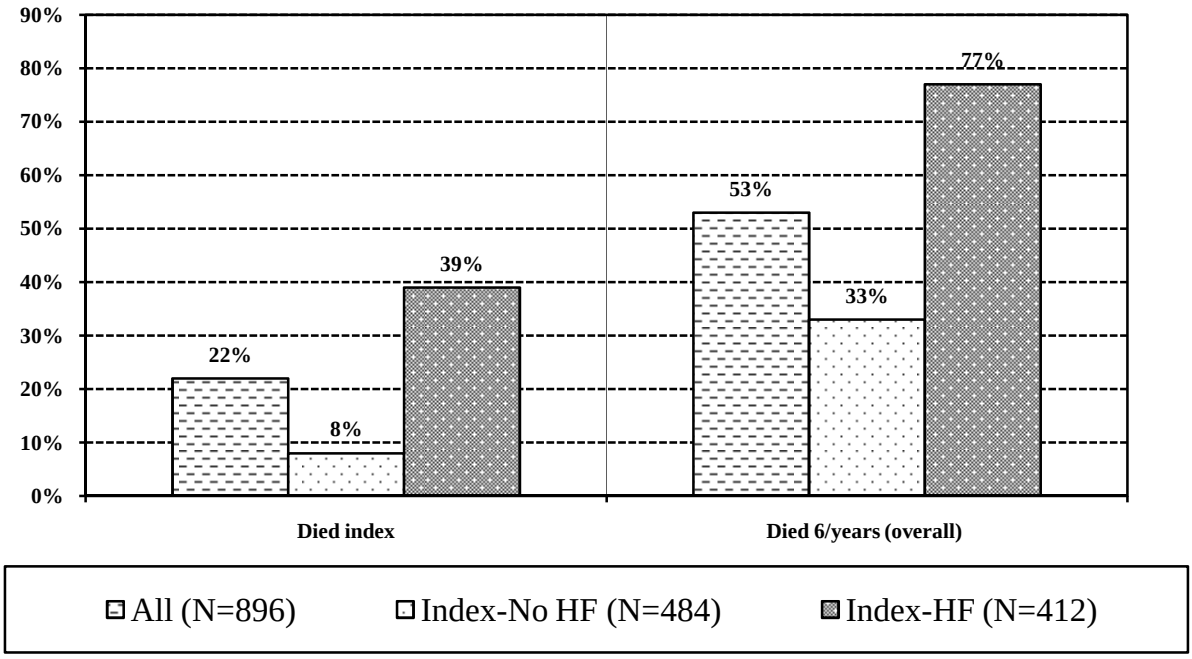
In patients who's HF persisted until discharge, only 27 had their diuretics discontinued subsequently. Two of these patients developed renal failure and progressed to dialysis. Diuretics were stopped in three patients because of hypotension and electrolyte disturbances with a recurrence in symptoms and subsequent death. In the remaining 22 patients, diuretics were withdrawn without a recurrence of HF symptoms. Of the 182 patients with PHF at the time of discharge, 121 (66%) died within 6 years.

Figure 3-2The proportions of patients developing different categories of heart failure (HF)



Pie-chart showing the proportions of patients developing different categories of heart failure (HF) according to early mortality, timing of onset and persistence. See methods for definitions of transient, persistent, remission and recurrence.

Figure 3-3Mortality during index admission according to the development of HF during the index admission (transient or persistent).



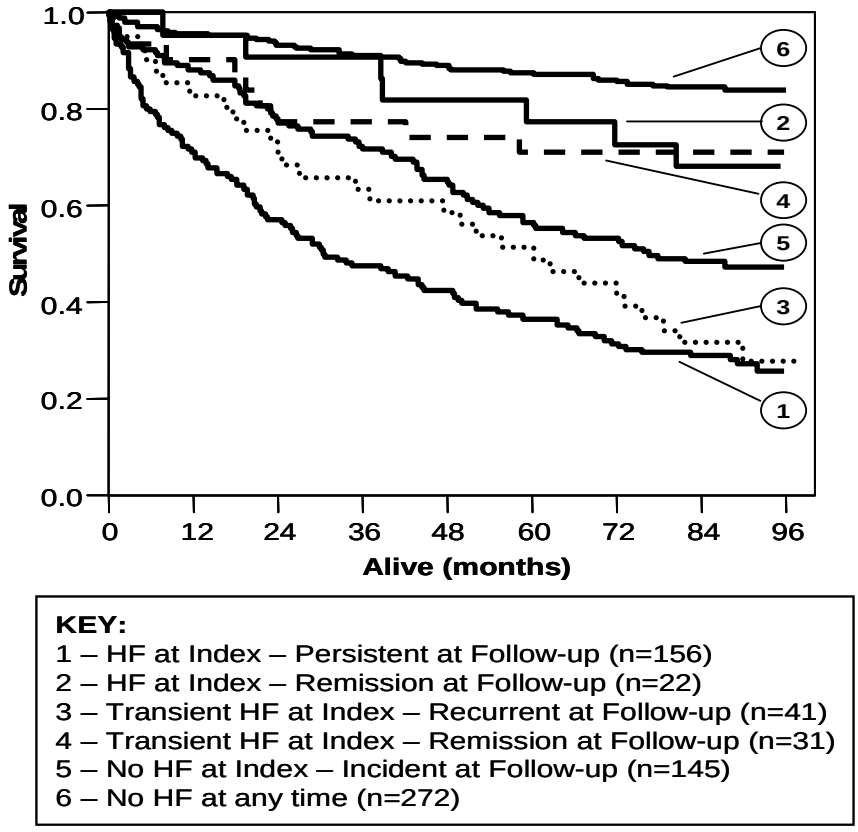
Of 74 patients with THF during the index admission, 41 (55%) had recurrence of HF (THF in eight), which occurred during admission for ACS or within 30 days of discharge in 18 patients. Thirty eight (51%) of these patients died during follow-up, of which 29 were after the recurrence of HF (five after THF).

Of 441 patients discharged without any occurrence of HF, follow-up data were available for 417, of whom 145 (35%) subsequently developed HF, 58 of these in the year after the index admission. HF was transient during follow-up in 26 patients (18%). Late onset HF occurred in 46 (32%) cases during admission for ACS or within 30 days of discharge. Of the 145 patients who developed HF after discharge, 76 (52%) died (six after transient HF) compared with 46 (16%) among the 296 patients who never developed HF at any time.

Thus, of 278 deaths occurring subsequent to discharge following an MI, 235 (84%) occurred subsequent to the development of THF or PHF (Figures 3.4 and 3.5). In those patients who did not have HF at the time of discharge and in whom follow-up records were available

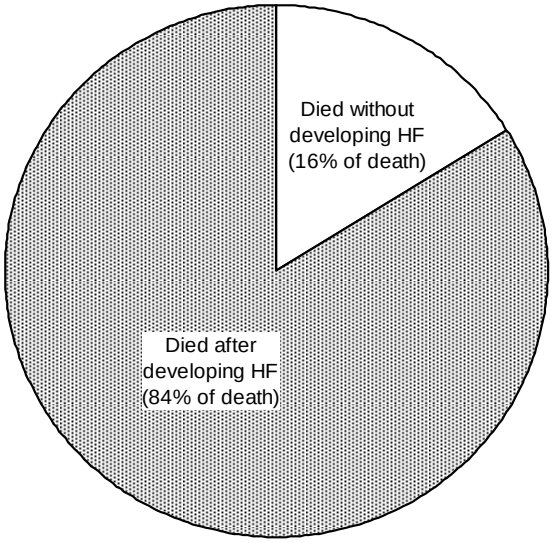
(n=489), the incidence of HF was 0.194 (95% CI 0.154 – 0.239) per person-year within the first year and 0.048 (95% CI 0.039 – 0.057) per person-year thereafter.

Figure 3-4Kaplan-Meier curves showing prognosis amongst patients discharged after the index myocardial infarction with and without persistent or transient heart failure (HF).



For statistical comparisons see Table 3.4.

Figure 3-5Pie-chart showing the proportion of patients who died with or without preceding evidence of heart failure (HF) subsequent to discharge from index admission.



A report on left ventricular function during or shortly after the index admission was available in 507 (77%) surviving patients and 71 patients who died during the index admission (Table 3.3). Of 255 (30%) patients reported to have LVSD during or within 90 days of admission, 46 (18%) died during the index admission, 82 (32%) developed PHF, 30 (12%) developed THF, 50 (20%) developed HF only after discharge, eight (3%) died after discharge without documented HF (one with no follow-up data), and 34 (14%) survived without documentation of HF (four with no follow-up data). A further 26(3%) patients had a prior diagnosis of LVSD without any imaging during index or within 90 days of index admission of whom 16 (62%) died during the index admission and seven after discharge. Overall, 108 (49%) patients with documented LVSD died after discharge, 98 (91%) of whom also had HF. Of 297 patients documented not to have major LV systolic dysfunction, nine (3%) died during the index admission, 34 (11%) developed PHF, 25 (8%) developed THF, 54 (18%) developed HF only after discharge, 20 (7%) died after discharge but without developing HF (one with no follow-up data), and 142 (50%) survived without developing HF (12 with no follow-up data).

Overall, 67 (38%) patients who were documented not to have LVSD died after discharge, 46 (69%) of whom had HF.

Of 283 (33%) patients for whom no report of LV function was identified, 128 (45%) died during the index admission, 49 (17%) developed PHF, 13 (5%) developed THF, 29 (10%) developed HF only after discharge, 14 (5%) died after discharge without documented HF (one with no follow-up data), and 44 (16%) survived without documentation of HF (five with no follow-up data). Overall, 85 (49%) patients, who had no assessment of LV function reported in their records, died after discharge; 80 (94%) of them also had HF.

Table 3-3Imaging evidence of left ventricular (LV) function during index admission or shortly thereaftera

Images [missing data]	All 861	No HF during index admission 458	HF during index admission 403	P-value	Survived index 662	Died on Index 199	P-value
Contrast angiography	**93**	**60**	**33**		**87**	**6**	
Left main coronary artery [2]	10	6 (10%)	4 (12%)	0.551	10 (11%)	1 (16%)	0.837
Three-vessel disease[b]	42	27 (45%)	15 (47%)		41	2 (33%)	
Two-vessel disease	25	17 (28%)	8 (25%)		23	2 (33%)	
One-vessel disease	24	15 (25%)	9 (28%)		22	2 (33%)	
NVD	1	1	0	0.824	1	0	0.926
LVSD (LV assessed n=59) [33]	13	7 (16%)	6 (38%)	0.048	13	0	0.034
Echocardiography	**283**	**106**	**177**		**226**	**57 (29%)**	
Major LVSD [4]	141	31 (29%)	110 (63%)	<0.0005	96 (43%)	45 (83%)	<0.0005
Moderate or severe mitral regurgitation [12]	39	3 (3%)	36 (20%)	<0.0005	24 (11%)	15 (29%)	0.001
Moderate or severe other valve disease[6]	11	1 (1%)	10 (6%)	0.118	8 (4%)	3 (5%)	0.818
Radionuclide	**357**	**251**	**106**		**249**	**2**	
LVEF 35-39%	42	27 (11%)	15 (14%)		42 (17%)	0	
LVEF <35%	110	51 (20%)	59 (57%)	<0.0005	108 (43%)	2 (100%)	0.105
LVSD Prior to index[c]	**26**	**1**	**15**		**9**	**16**	
LV assessment by any technique Δ	578	329 (72%)	249 (62%)	0.002	507 (77%)	71 (36%)	<0.0005
Moderate or severe LVSD by any technique [283]	281	100 (30%)	181 (73%)	<0.0005	219 (43%)	62 (87%)	<0.0005

[a]The imaging test indicating the most severe left-ventricular impairment on index admission or first available within 90 days after index admission (excluding 35 cases with recurrent acute myocardial infarction within 90 days, since the image may not reflect the damage from their index infarction). Percentages shown are of those in whom measurements were made.

[b]Four cases had graft occlusion, six cases had ventricular septal defect, and one had mitral valve rupture during index admission. Two patients had prior valve replacement and aortic regurgitation or stenosis or mitral stenosis.

[c]Left ventricular systolic dysfunction (LVSD) Prior to index admission without imaging during index admission or shortly after. Δ LV assessed in 578 cases of which 26 cases had LVSD prior to index admission and LVSD on index admission in 392 cases, 500 cases within 30 days, 37 cases within 31-60 days, and 15 cases within 61-90 days. Two cases had angiography done privately with no result in case note.

3.3.2 Mode of Death

Of 199 patients who died during the index admission, the mode of death was considered to be sudden cardiac death (SCD) in 55 cases (14 after arrhythmia), HF in 114, stroke in two, cardiac procedure-related in four, other cardiac in eight, infection in four, cancer in one, and other non-cardiac in 11 patients.

Of 281 patients who died after the index admission, 168 died during a re-admission to hospital and 113 died out of hospital. Out of hospital deaths were usually poorly documented but were probably sudden because of arrhythmias or vascular events. Fifteen patients had severe HF, one died of self-poisoning, nine had advanced cancer, one had severe pulmonary hypertension, and two had stroke. Among patients who died out of hospital, 83 (73%) had either THF or PHF, 48 of whom had documented LVSD, 19 documented absence of important LVSD at last cardiac imaging prior to death. Sixteen had no assessment of LV function. 30 (27%) had no HF, seven of whom had asymptomatic LVSD, 13 had documented absence of LVSD at last cardiac imaging prior to death and also ten had no assessment of LV function. Of those who died on re-admission, nine were attributed to SCD, 68to HF of whom 39 fulfilled the definition of cardiogenic shock prior to death, 11 to stroke, two to cardiac procedures, four to other cardiac causes, 22 to infection, 24 to cancer and 27 to other non-cardiac causes. One patient had missing notes.

3.3.3 Cox Model

The age-adjusted models are presented in Table 3.4. Patients with PHF at follow-up had a high mortality when compared with those having no HF. Adjusting for other factors such as creatinine, anaemia, beta blockers, smoking, diabetes, prior MI, history of HF, gender, ST-

elevation and non ST-elevation, SVT, PTCA, CABG and Q wave in discharge did not alter the nature of these relationships (though obviously the HRs were different).

Table 3-4Cox-regression models; for mortality in patients unadjusted and age-adjusted subsequent to discharge (n=667).

		Univariable		Age Adjusted	
Variable Name	N	HR	P-value	HR	P-value
HF Status[a]	272				
PHF-persistent at follow-up	156	7.822 (5.497-11.131)	<0.0005	4.732 (3.270-6.848)	<0.0005
PHF-resolved at follow-up	22	0.753 (0.352-1.613)	0.466	0.677 (0.316-1.450)	0.315
THF-redevelop HF	41	2.4444 (1.550-3.854)	<0.0005	2.409 (1.527-3.798)	<0.0005
THF-remission at follow-up	31	0.656 (0.329-1.309)	0.232	0.775 (0.388-1.549)	0.471
No HF-developed HF	145	1.434 (1.046-1.967)	0.025	1.499 (1.093-2.057)	0.012
MI after discharge	145	2.655 (2.075-3.398)	<0.0005	2.011 (1.565-2.584)	<0.0005
Angina admission	111	0.395(0.260-0.601)	<0.0005	0.419 (0.275-0.637)	<0.0005
HF, heart failure; MI, myocardial infarction; HR, hazard ratio; THF, transient HF during index admission; PHF, persistent HF during the index admission. [a]with reference to no HF any time (index admission and follow-up).					

3.4 Discussion

This report suggests that the prognosis of MI is much worse than many contemporary clinical trials suggest, and that death is usually preceded by the development of HF. Of 896 patients with a hospital diagnosis of acute MI in 1998, 562 (62.7%) had or developed HF in the following 6 years. The high proportion of patients who develop HF after an MI might seem surprising, as ischaemic heart disease is common and the prevalence of HF only about 1%. This reflects the poor prognosis of HF, often a short-lived illness usually terminated by death, and suggests that the burden of HF may be better described by its incidence rather than prevalence[75]. HF is also often under-represented in health-care statistics, because events such as death or hospitalization are ascribed to the cause of HF rather than its presence. Death is usually a complex process and attributing death to only one reason is often inappropriate. For instance, a patient could die of a lethal arrhythmia in the setting of worsening HF induced by a recurrent ischaemic event. This patient died as a consequence of a constellation of events. What is important is to identify which interventions might produce worthwhile benefit for patients.

A systematic review suggested that the crude incidence of HF for any reason in the overall population is 1.3/1,000/year[76]. Extrapolating from our data, the population incidence of HF related to MI may be about 0.7/1,000/year. As population studies suggest that only about half the cases of HF are preceded by an MI [77 78], our data appear consistent with the overall situation but provide a rather different perspective. New-onset HF after discharge was more common than in previous reports [22 38 40], perhaps reflecting the intensity of surveillance or the definition used in our study. However, effective treatment of MI is likely to reduce mortality to a greater extent in patients with large MIs who are then likely to survive to develop HF. Therefore, our study provides some support for the widely held suspicion that

good post-infarction care will increase rather than decrease the incidence and prevalence of HF [74].

Understanding the natural history of patients who have had an MI with and without HF may help inform therapeutic choices. Amongst patients who had HF, it was present in 23.1% prior to the index infarct, many of whom had had a previous MI, it developed for the first time during the index hospital admission in 51.1% and within 30 days of a further coronary event in 6.1%. Only 19.4% of patients developed HF more than 30 days after the index infarction without a further hospitalization for MI. Not all MIs present with typical symptoms and may manifest as worsening HF or sudden death[79 80 81 82]. Thus, most cases of HF observed in this cohort occurred in close proximity to an acute coronary event. This has two important implications. Firstly, it challenges the concept that HF is often because of progressive LV remodelling with a long prodrome. Most cases of HF may have a sudden and rather unpredictable onset because of MI or arrhythmias, which would account for why most first diagnosis of HF occurs in hospital[83]. Secondly, it reinforces the view that treatment directed at reducing the extent of acute myocardial damage and prevention of re-infarction might have important effects on the development of HF[84 85 86 87 88 89].Trials of statins[90 91], ACE-inhibitors[15 92], aldosterone antagonists[93] and beta-blockers[94] , although not aspirin [95], appear to reduce the risk of HF after MI, which is partly mediated by reducing further coronary events. It is widely believed that these treatments can also reduce the risk of recurrent MI in patients with HF, thereby improving survival [96]. However, a recent large study suggested that rosuvastatin could reduce non-fatal vascular events but not mortality, perhaps because vascular events were not an important driver of outcome [97]. Similarly, anti-thrombotic agents have failed, so far, to reduce mortality in HF [98]. Other treatments, such as ACE-inhibitors, aldosterone antagonists, and beta-blockers, appear more effective at reducing mortality than coronary events in patients with established

HF, although it has been argued that this reflects their ability to prevent some patients with MI from dying suddenly [96]. Treatment directed solely at preventing progressive LV remodelling in the years after MI might have only a minor role in the prevention of HF in this population, as few patients who developed HF did so remote from an acute coronary event. However, treatments aimed predominantly at ventricular remodelling may have an important role in slowing the progression of HF once it has developed.

About 40% of the deaths that occur within approximately six years after a MI occur during the index admission and 35% during a subsequent re-admission. Most of these deaths were associated with severe HF. About one-quarter of patients died out of hospital. Most of these patients had developed HF prior to death, although only about 10% reported deteriorating symptoms in the month before death. Little information could be obtained on the mode of death in these patients but adjudication committees of clinical trials, that often obtain more detailed data, assign most of these to sudden death and assume that arrhythmias rather than recurrent vascular events are the cause [96]. Accordingly, widespread implantation of a defibrillator theoretically might reduce mortality amongst discharged patients by about 30%. However, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) [99] showed that implantation of a defibrillator early after MI did not reduce mortality, perhaps because this intervention cannot reduce the commonest mode of death in these patients which is worsening HF. More aggressive pharmacological therapy [47] may be the best way to manage the risk of both sudden death and worsening HF. Whether early implantation of a device that also provides bi-ventricular pacing could improve prognosis awaits the outcome of further trials[100].

The prognosis of HF in this study was worse than suggested by either randomized controlled trials [101 102]or many surveys of MI [24]. However, using the GRACE registry score, the

predicted in-hospital mortality for our patients was 22%[103]. The lower mortality observed in other cohorts most likely represents case-selection, with preference being given to recruitment of younger patients, who tend to be managed by cardiologists, in trials and surveys and the exclusion of cardiogenic shock and severe HF. Age was a powerful determinant not only of prognosis but also of the likelihood of being referred to a cardiologist in our study.

As reported by others[21], LVSD and clinical evidence of HF carried independent prognostic information. Patients who had both did worse than those who had either alone. Potential markers of the metabolic stress of a large infarction and the development of HF, including renal dysfunction and hyponatraemia were also independent predictors of an adverse outcome and each a potential target for therapy.

3.5 Study limitations

Patients with THF developing either during or after the index admission that subsequently resolved permanently had a HR <1 which may seem surprising (Table 3.4). There were few such patients in these cohorts, the CIs around the HR were wide and overlapped that of patients who never developed HF. Patients with THF had to survive long enough to permit HF to resolve and this may have introduced methodological bias favouring outcome in patients with THF. A similar potential bias towards an over-optimistic assessment of survival exists for patients with late-onset HF who had a poor outcome when compared with those who never developed HF. Also, exclusion of patients with recurrent or late-onset HF and a poor prognosis from the groups with only THF will bias outcome favourably in the latter groups. A less likely explanation for the lower mortality in patients with THF is that their intrinsic risk is similar to patients who never had HF, but that they received the prognostic

benefits of treatment for HF. We also acknowledge a potential pessimistic bias in assessing outcome in patients with PHF, as patients who die early have less opportunity to recover and therefore less opportunity to be labeled as THF[104]. Ultimately, this analysis is descriptive and not designed to show whether one group does better than another but rather the outcome in each individual clinical group of patients.

Our study will have missed patients who died of their MI before reaching hospital and patients who, if they had symptoms, were not recognized as having had an MI. Epidemiological studies suggest that about one-third of patients with MI die before they reach hospital[6], and that about one-quarter of patients who survive an MI do not have symptoms that lead to urgent hospital referral[26 105 106]. It is likely that the hospital records system failed to code some infarcts, although false-positive coding was rare. For these reasons, this study substantially underestimates the true incidence of MI in the community. The survey was of patients managed in 1998. Significant changes in prevention and management have occurred and may have altered outcome. In 2005, 704patients had a death or discharge diagnosis MI reported in our hospital of which78 died (11% compared to 22% in 1998). We defined HF as HF symptoms that led to treatment with loop diuretics but some patients may have been managed with thiazides. Not all patients had LV function assessed. Also, as systematic attempts were not made to withdraw diuretics, we may have under-estimated the transitory nature of HF in some cases. A simple, robust definition of HF remains elusive. However, patients who receive loop diuretics and who have cardiovascular disease clearly have a poor prognosis whether or not they have a low EF [26]. Ultimately, HF is a clinical syndrome that relies on a doctor’s skill in assessing a patient in the light of appropriate investigations.

The prevalence of diabetes mellitus was similar to that reported in another large trial from the same county in England, but is towards the lower end of the spectrum reported in the literature [38 41]. This may reflect under-reporting of milder cases of diabetes, as it was not routine practice to obtain fasting blood glucose in these patients. However, surveys reporting high levels of diabetes have generally included large numbers of patients from North America, where the prevalence of diabetes is probably, genuinely higher than in our region.

Another potential limitation of our analysis is that patients who died early had less opportunity to recover or to develop late-onset HF. It is unclear how useful attempts at adjusting for this problem would be. Ultimately, our study is not trying to build a risk model, but to establish the proportion of patients who develop HF after an MI, to describe its time of onset, whether it resolves and the consequences of each in terms of mortality.

3.6 Conclusion:

The development of THF or PHF precedes death in the great majority of patients who die within 6 years of an MI. Most patients who develop HF after an MI do so shortly after an initial or recurrent coronary event suggesting that reducing infarct size and recurrent events rather than ventricular remodelling may be a more successful strategy to prevent HF. Improved management of HF and its important co-morbidities such as renal dysfunction and diabetes may slow the rate of progression and improve quality of life and prognosis in such patients.

4 Chapter 4: The development and course of Heart Failure after a Myocardial Infarction in different age groups

4.1 Introduction

Heart failure (HF) is a common complication of myocardial infarction (MI), which may develop early or late and once it has developed it may persist or resolve, and if it resolves it may re-occur [107].A growing proportion of patients with MI are aged >65 years and older patients are at greater risk of developing HF and have a poorer prognosis[108 109 110]. Surprisingly, the complex pattern and timing of the development and resolution of HF and the importance of such distinctions has never been quantified in relationship to age [109 111]. Understanding the drivers of morbidity and mortality after MI is important, given the large gap between mortality rates reported in clinical trials of MI compared to those reported in epidemiological studies. Improved understanding of which patients are at risk and the nature of the risk could help focus attention on patients at greater need, to ensure that they receive appropriate therapy and that they are targeted for recruitment into clinical trials, which are currently struggling to show substantial differences in outcome partly because their event rates are so low. Treatment can only help patients who are at risk of the problem you are trying to prevent.

4.2 Methods

4.2.1 Study population

One hospital group in Hull and the East Riding of Yorkshire (UK) provides all of the acute cardiac services for about 560,000 people living in a geographically distinct part of the United Kingdom. Patients with a discharge diagnosis of acute MI during 1998 were identified

from the Hospitals Information Department and their case notes screened. Patients who were transferred from another region, those with missing case notes or in whom acute MI could not be confirmed from their records were excluded. The study was approved by the Local Research Ethics Committee.

4.2.2 Follow-up

This was a retrospective analysis designed in 2004. The case records of all patients were reviewed to identify use of loop diuretics and if so whether this was due to symptoms or signs of HF. Follow-up data were collected until 31st December 2005. If no recent hospital record existed, the family practitioners of patients or patients themselves were contacted to ascertain the patient's current therapy and HF status. The occurrence of major events, such as recurrent MI, and stroke were recorded.

4.2.3 Definition of Myocardial Infarction

At least **two** of the following five criteria had to be identified during case note review to confirm a diagnosis of MI.

1. History of prolonged cardiac chest pain.
2. An increase in biomarkers consistent with MI, which in 1998 was usually creatinine kinase (CK) or CK-MB mass. These were considered abnormal if they were twice the upper limit of normal values.
3. Progressive electrocardiographic changes consistent with MI or new onset left bundle branch block.
4. Sudden unexpected death
5. Autopsy evidence of MI

4.2.4 Other Definitions

Heart failure was clinically defined either as signs and symptoms consistent with that diagnosis (principally breathlessness and signs of fluid retention) resulting in treatment with loop diuretics or patients who died shortly after developing evidence of major cardiac dysfunction, such as cases of cardiogenic shock or pulmonary oedema. Cardiogenic shock was defined as an arterial pressure <100mmHg because of low cardiac output requiring inotropic therapy or an intra-aortic balloon pump. For patients with an un-recordable blood pressure, a systolic pressure of 50mmHg was entered as a default value for statistical purposes. Use of loop diuretics for the treatment of hypertension or renal failure was not included in the definition of HF. Criteria for left ventricular systolic dysfunction (LVSD) were left ventricular ejection fraction (LVEF) < 40% or a qualitative report of moderate or severe LVSD on echocardiography, first-pass radionuclide ventriculography or contrast angiography. Patients according to their age were categorised into three groups: (i) <65 years old; (ii) 65-75 years old and (iii) >75 years old.

4.2.5 Resolution of Heart Failure

Consistent with European Society of Cardiology Guidelines[68], resolution of heart failure was defined as the withdrawal of diuretics without the recurrence of symptoms.

4.2.6 Statistical Analysis:

Data were entered into a Microsoft Access database and analysed using SPSS Inc, version 13.0 (UK, Ltd). Key outcomes were the proportion of patients who died and all-cause mortality. Continuously distributed data are presented as median and inter-quartile range (IQR). Categorical data are presented as percentages. Groups of patients with and without HF were compared by the Chi-squared test. Kaplan-Meier (K-M) curves were generated to

illustrate patients' overall survival, and in subgroups. K-M curves were compared by the log-rank test on the appropriate degrees-of-freedom. Cox regression was used to look at mortality, from which hazard ratios (HRs) and 95% CIs were calculated. The Cox regression model is semi-parametric in the sense that no assumption concerning event-free survival times is necessary. The Cox regression model is based on the assumption that the effect of a risk factor, expressed as a HR, is constant over time. The assumption of proportionality of the Cox model covariates was tested by plotting residuals[72 73]. Linearity of continuous data was checked by including a squared term. We did not build a model using automated selection methods. Models explained survival on the basis of their biological relevance to heart failure[112]. Hence, we adopted an epidemiological approach to model building.

Heart failure status was categorised into six groups: (i) No HF at any time (this was the reference group for statistical comparisons); (ii) Patients with HF on the index admission and persisting at follow up until death or end of follow-up; (iii) Persistent HF on the index admission that resolved subsequent to discharge; (iv) Transient HF on the index admission that resolved prior to discharge but recurred during follow-up; (v)Transient HF on the index admission that resolved prior to discharge and did not recur prior to death or end of follow-up; (vi) Patients who did not develop HF on the index admission but who later developed HF during follow-up.

4.3 Results:

4.3.1 Overall results:

Of 1,012 patients with a death or discharge diagnosis of acute MI in 1998, 116 were excluded from further analysis because they were transfered from another region or due to a lack of confirmation of MI in the patient-record. This left 896 patients for analysis, of whom 311

(35%) were aged <65 years, 297 (33%) were aged 65-75 years and 288 (32%) were aged >75 years (Table 4.1). Of these patients,16, 8 and 6 from each group respectively were lost to follow-up after the index admission. About one third of patients were women, with the proportion increasing with age. About 25% of patients had a prior history of MI and about 15% had a history of HF preceding the index event, rising from 7% in those aged <65 years to 25% in those aged >75 years. ST-segment elevation myocardial infarction (STEMI) was present in 193 (62%), 174 (59%) and 151 (53%). Fewer older patients were managed primarily by a cardiologist.

During the index admission, younger patients were more often treated with aspirin, statin, beta-blockers, intravenous nitrate and heparin. Older patients were more likely to receive loop diuretics and digoxin (p=0.0005) (Table 4.2). Primary angioplasty was not done in this hospital group in 1998. 159, 127 and 86 patients received thrombolysis in aged <65 years 65-75 years and aged >75 respectively.

Table 4-1 Patients Characteristics recorded during the Index Admission overall and classified according to the three different age group: >65 years old, 65-75 years old and > 75 years old (data are median (inter-quartile range) and number occurring (%)).

Variables (units)	Missing data	All	<65 years old	65-75 years old	>75 years old	P value
n		896	311(35%)	297 (33%)	288 (32%)	
Age (years)	0	70 (61-78)	58(51-61)	71 (68-73)	81 (78-85)	0.0001
Women	0	333 (37%)	66 (21%)	120 (40%)	147 (51%)	0.0001
Current smoker	87	303 (37%)	166 (55%)	97 (35%)	40 (17%)	0.0001
Ex smoker		255 (32%)	85(30%)	96 (35%)	74 (32%)	
History of Hypertension	40	300 (35%)	81 (27%)	105 (37%)	114 (42%)	0.006
History of Diabetes	3	82 + 33a (13%)	33 (11%)	45 (15%)	37 (13%)	0.290
Prior MI	1	234 (26%)	73 (24%)	73 (25%)	89 (31%)	0.153
History of HF	4	134 (15%)	22 (7%)	39 (13%)	73 (25%)	0.0001
Prior CABG		39 (4%)	19 (6%)	14 (5%)	6 (2%)	0.051
Prior PTCA		14 (2%)	10 (3%)	4 (1%)	0	0.006
Managed Primarily by Cardiologist		558 (62%)	233 (75%)	186 (63%)	139 (48%)	0.0001
Index Admission ECG						
ST segment elevation[b]	10	518 (58%)	193 (62%)	174 (59%)	151 (53%)	0.001
Non ST elevation	10	316 (36%)	110 (36%)	104 (35%)	102 (36%)	
ARS $\geq$120	23	199 (23%)	41 (13%)	70 (24%)	88 (31%)	0.0001
Anterior site	10	422 (47%)	132 (43%)	151 (52%)	139 (49%)	0.052
Chest X-ray						
Pulmonary oedema	227	160 (24%)	33 (14%)	54 (24%)	73 (33%)	0.0001
Cardiomegaly		156 (23%)	42 (18%)	47 (21%)	67 (30%)	0.018
Upper Lobe Vein Distension		159 (24%)	50 (22%)	51 (23%)	58 (26%)	0.388
Pleural effusion		73 (11%)	15 (7%)	23 (10%)	35 (16%)	0.014
Physical Examination						
Heart Rate	9	78 (64-97)	73 (61-88)	76 (64-98)	85 (68-101)	0.0001
Atrial fibrillation (yes/no)	2	153 (17%)	19 (6%)	56 (19%)	78 (27%)	0.0001
Systolic blood pressure	5	140 (120-160)	132 (121-142)	140 (120-160)	140 (120-160)	0.610
HF during index[c]		417 (47%)	82 (29%)	143 (48%)	192 (67%)	0.0001
Discharged with HF		182 (20%)	37 (12%)	63 (21%)	82 (28%)	0.0001

Died during index admission[d]		199 (22%)	24 (8%)	68 (23%)	107 (37%)	0.0001
Blood Tests (on admisssion)		828 (376-1901)				
Peak CK	49	828 (376-1901)	1062(418-2262)	767 (369-1779)	684 (318-1651)	0.018
Cholesterol	353	5.5 (5-6.4)	5.5(4.9-6.3)	6 (5-6)	5 (5-6)	0.591
Sodium	29	137 (135-139)	137(136-139)	137 (135-139)	137 (135-138)	0.001
Creatinine	127	105 (89-129)	95(83-108)	108 (90-132)	117 (96-149)	0.0001
Anaemia in 1st available Hb[e]	41	206(24%)		67 (24%)	105 (38%)	0.0001

CABG, coronary artery bypass; PTCA, percutaneous transluminal coronary angioplasty; ECG, electrocardiogram. Percentages are shown are of those in whom measurements were made. CK = creatine kinase. Example interpretation: older patients hadhigh creatinine levels compare to younger patients. Many of these associations show dose-response. The differences for Na are exaggerated because of the relative large sample sizes between the three groups, and the relatively low standard deviations (in other words, this is a statistical quirk).

[a]Thirty-two cases newly diagnosed as diabetic on index admission.

[b]P-value for ST calculated between three groups (STE, No STE and other (LBBB and pace).

[c]Heart failure during index admission. Of deaths during the index admission, in age <65, 65-75 and >75 years respectively 12, 27, and 33 patients developed cardiogenic shock. [d] Anaemia: WHO criteria for anaemia are used (male <13 dg/dL; female <12 g/dl)

Table 4-2Treatment during index admission and any time until 31st December 2005.

Variables (units)	missing data	All	<65 years old	65-75 years old	>75 years old	P value
n		896	311 (35%)	297 (33%)	288 (32%)	
Revascularisation during admission						
Thrombolysis	0	372	159 (51%)	127 (43%)	86 (30%)	0.0001
PCI	0	20	16 (0.05%)	4 (0.01%)	0(%)	0.0001
CABG	0	8	4 (0.01%)	3 (0.01%)	1 (<0.01%)	0.459
Treatment During Admission						
Parenteral						
Loop diuretic	7	262	49 (16%)	91 (31%)	122 (42%)	0.0001
Nitrates	3	309	125 (40%)	103 (35%)	81 (28%)	0.019
Inotropic therapy	2	94	22 (0.07%)	34 (11%)	38 (13%)	0.121
Heparin	15	694	264 (86%)	234 (80%)	196 (70%)	0.0001
Insulin	1	79	28 (0.09%)	34 (11%)	17 (0.06)	0.104
Oral						
Aspirin	2	792	302 (97%)	251 (85%)	239 (83%)	0.0001
Clopidogrel	2	7	3 (1%)	4 (1%)	0	0.321
Warfarin	2	35	7 (2%)	14 (5%)	14 (5%)	0.332
Statin	2	406	214 (69%)	141 (48%)	51 (18%)	0.0001
ACE inhibitors	2	354	126 (41%)	120 (41%)	108 (38%)	0.782
ARBs	2	8	2 (1%)	2 (1%)	4 (1%)	0.689
Beta-blockers	2	497	236 (76%)	163 (55%)	98 (34%)	0.0001
Nitrates	2	320	90 (29%)	107(36%)	123 (43%)	0.008
Calcium channel blockers	2	215	70 (23%)	82 (28%)	63 (22%)	0.364
Loop diuretic	3	297	58 (19%)	94 (32%)	145 (50%)	0.0001
Thiazide diuretic	1	18	4 (1%)	7 (2%)	7 (2%)	0.495
Spironolactone	1	1		1		
Digoxin	2	68	6 (2%)	22 (7%)	40 (14%)	0.0001
Oral hypoglycaemic agent	2	21	4 (1%)	6 (2%)	11 (4%)	0.241
Revascularisation at Any Time						
PCI	0	94	72 (23%)	20 (8%)	2 (1%)	0.0001
CABG	0	98	58 (19%)	35 (12%)	5 (2%)	0.0001
Treatments at Any Time						
ACE-inhibitors	2	496	197 (63%)	170 (57%)	129 (45%)	0.0001
ARBs	2	44	26 (8%)	11 (4%)	7 (2%)	0.009
Beta-blockers	2	541	256 (82%)	173 (58%)	99 (35%)	0.0001
Loop diuretic	2	539	130 (42%)	187 (63%)	222 (77%)	0.0001
Thiazide diuretic	2	68	30 (10%)	20 (8%)	18 (6%)	0.287
Spironolactone	2	64	28 (9%)	20 (8%)	17 (6%)	0.301
Digoxin	2	110	16 (5%)	38 (13%)	56 (20%)	0.0001
Insulin	1	92	33 (11%)	39 (13%)	20 (7%)	0.083
Oral hypoglycaemic agent	2	67	26 (8%)	24 (8%)	17 (6%)	0.499
Aspirin	2	805	304 (98%)	256 (86%)	245 (85%)	0.0001
Statin	2	530	269 (86%)	189 (64%)	72 (25%)	0.0001

PCI, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; ARBs, angiotensin receptor-blockers.

Overall, 75 (24%) patients <65 years, 170 (57%) 65-75 years and 235 (82%) >75 years had died by December 2005. Figure 4.1a, b and c describes the sequence of events that led to the development of HF and/or death. Figure 4.2 shows the overall proportion of patients who developed HF at any time during follow-up and their categorisation according to persistence, remission and timing of development of HF in different age groups. During the index hospitalization, 82 patients (26%) <65 years, 143 (48%) patients 65-75 years and 192 patients (67%) >75 years developed HF. Twenty four patients (8%) <65 years died, of whom 19 (79%) had HF, 68 (23%) patients 65-75 years died, of whom 53 (78%) also had HF and 107 patients (37%) >75 years died, of whom 89 (83%) died after developing HF. Heart failure resolved in 26 (32%)patients <65 years, in 27 (19%) patients 65-75 years and in 21 (11%) patients >75 years and therefore only 37 (12%) patients <65 years, 63 (21%) patients 65-75 years and 82 (28%) patients >75 years were discharged with persistent heart failure of whom 13, 26 and 31 respectively had HF prior to admission.

Figure 4-1Flow diagram showing the sequence of development of heart failure and mortality over approximately 6 years in different age group

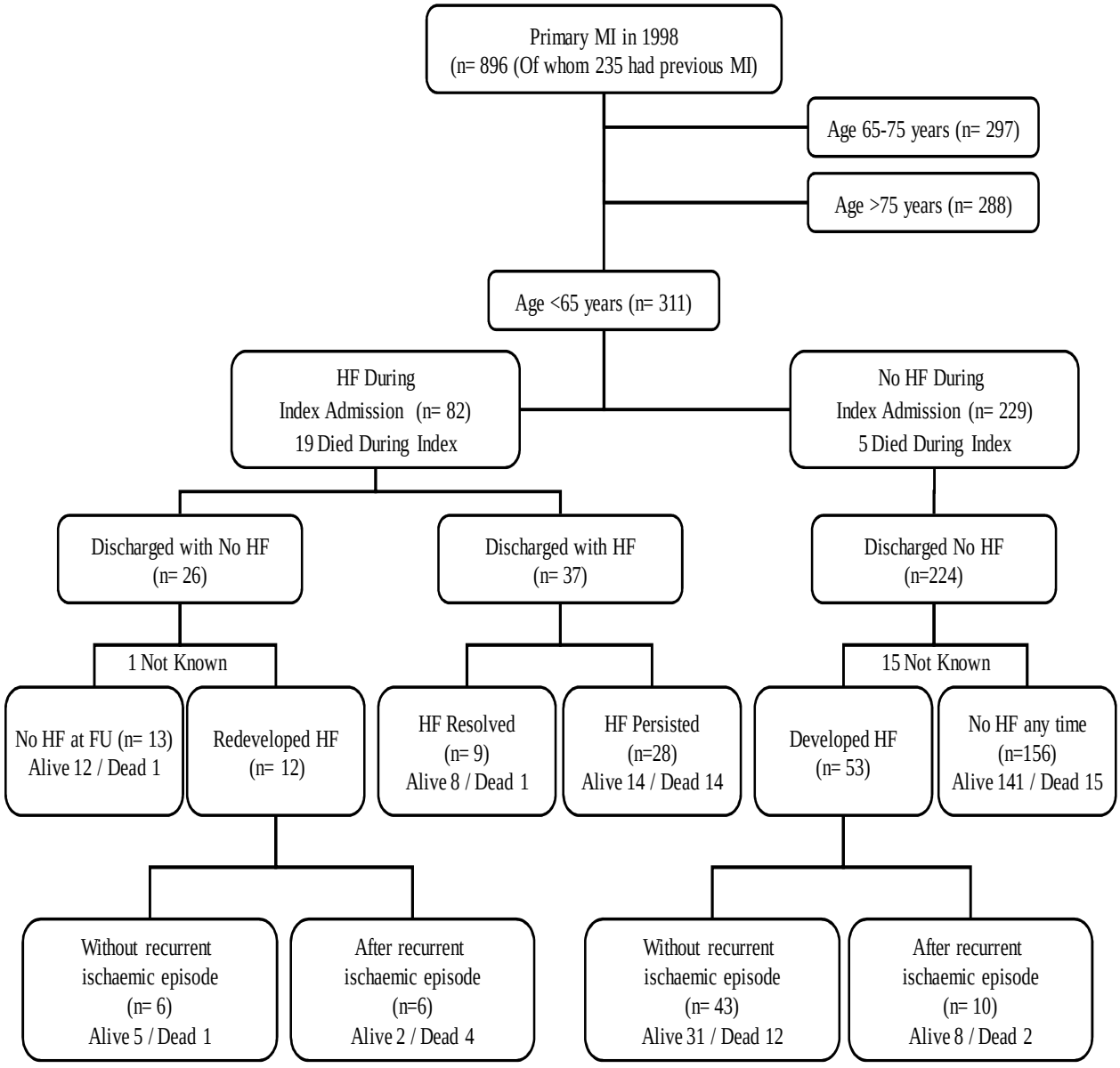


Fig 4.1.a: Flow diagram showing the sequence of development of heart failure (HF) and relationship with recurrent ischemic episodes and mortality over approximately 6 years in patients less than 65 years old which admitted with an acute myocardial infarction (MI) to the Hull and East Yorkshire Hospitals Group during 1998. Follow-up data were incomplete in 16 patients. See text for details.

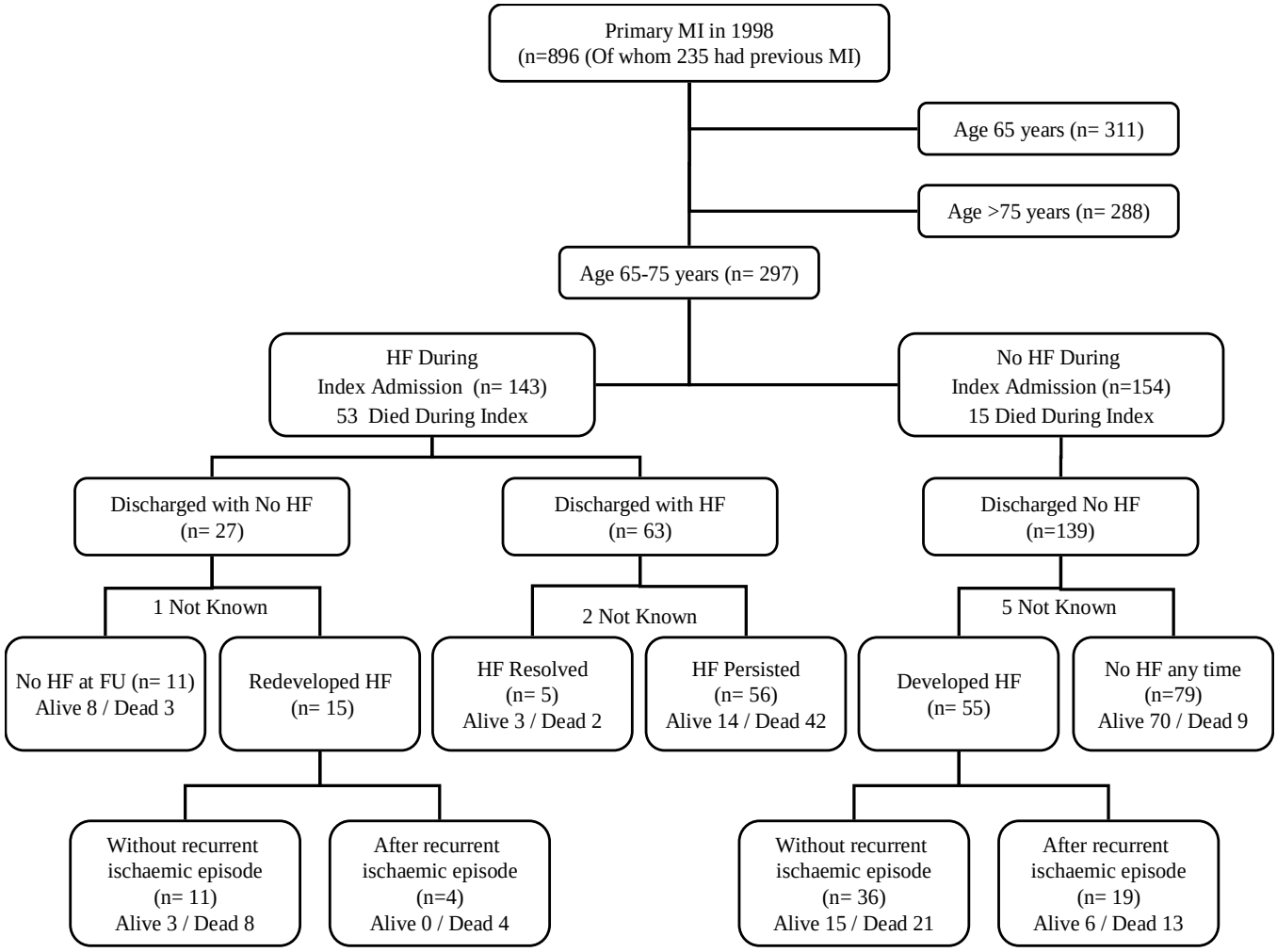


Fig 4.1.b Flow diagram showing the sequence of development of heart failure and relationship with recurrent ischemic episodes and mortality over approximately 6 years in patients 65 to 75 years oldwhich admitted with an acute myocardial infarction to the Hull and East Yorkshire Hospitals Group during 1998. Follow-up data were incomplete in 8 patients. See text for details.

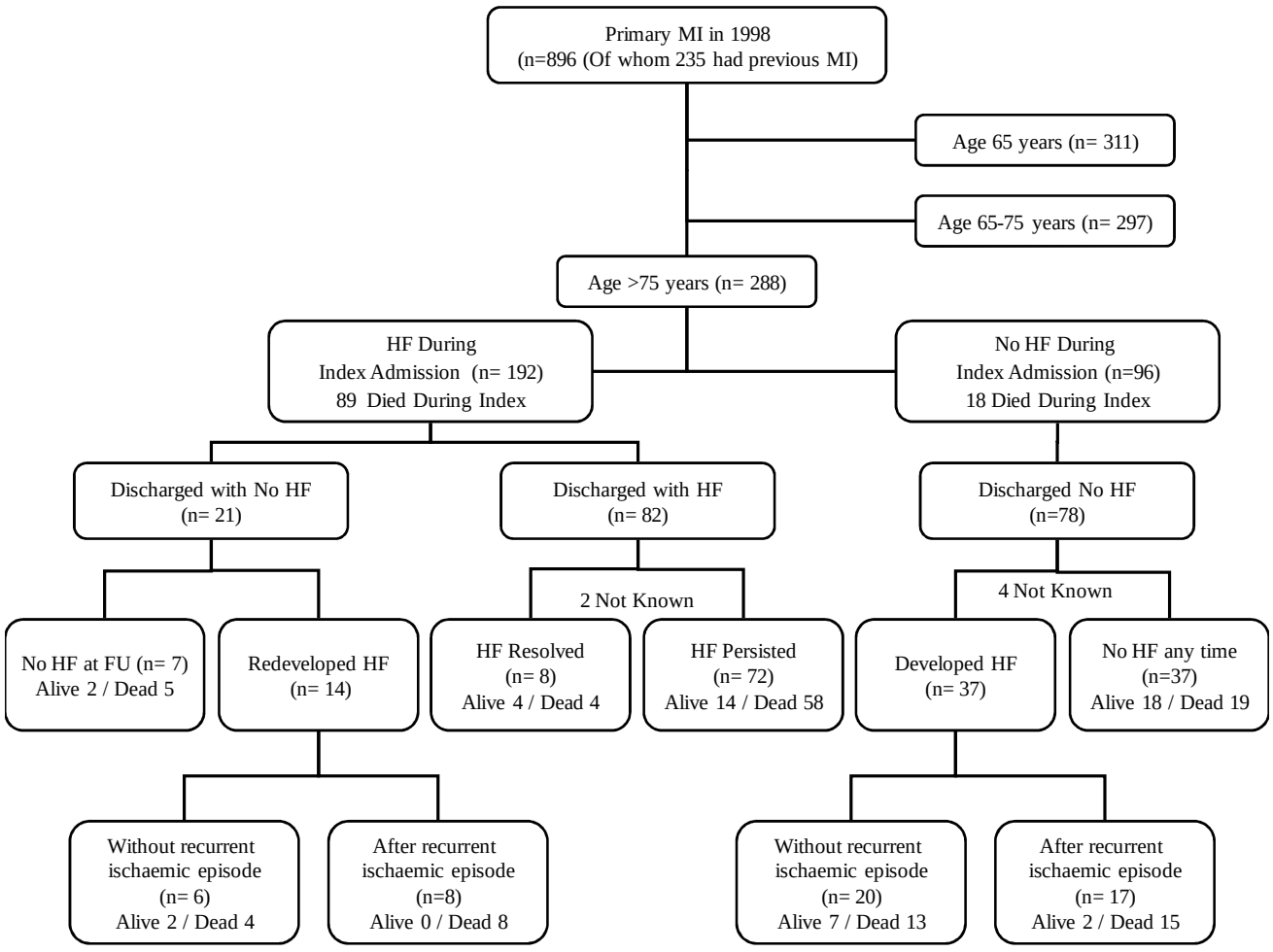
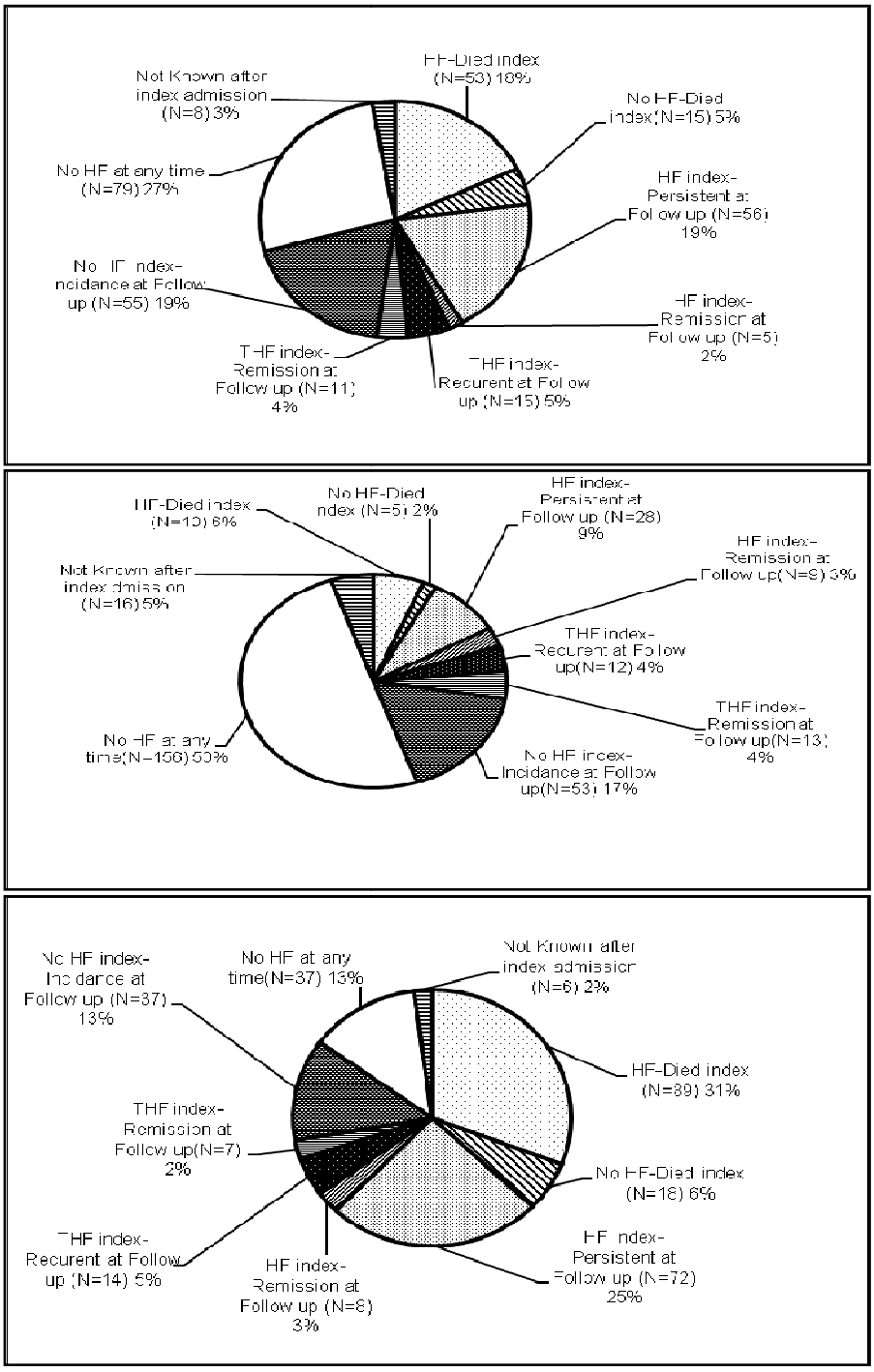


Fig 4.1.c Flow diagram showing the sequence of development of heart failure and relationship with recurrent ischemic episodes and mortality over approximately 6 years in patients more than 75 years oldwhich admitted with an acute myocardial infarction to the Hull and East Yorkshire Hospitals Group during 1998. Follow-up data were incomplete in 6 patients. See text for details.

Figure 4-2The proportions of patients developing different categories of heart failure according different age groups.



Pie chart showing the proportions of patients developing different categories of heart failure according to early mortality, timing of onset and persistence according to different age group (>65 years, 65-75 years and >75 years). See methods for definitions of transient (THF), persistent (PHF), remission and recurrent heart failure (HF).

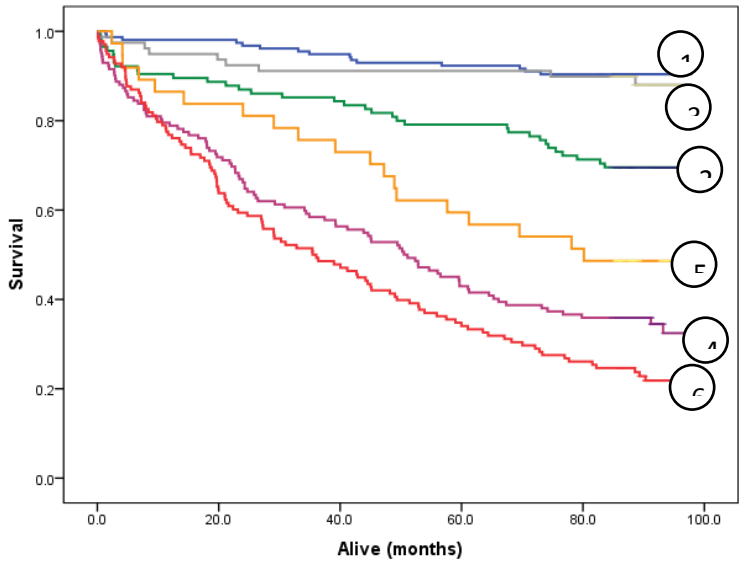
4.3.2 Long-Term Follow-up

Amongst 37, 63 and 82 patients <65, 65-75 and >74 years with persistent heart failure at discharge, crude mortalities at six years were 41%, 70% and 76% respectively (two patients aged 65-75 years and two aged>75 years lost follow-up). Amongst 26, 27 and 21 patients with transient heart failure during the index admission in the three age groups during, 46%,56% and 67% had recurrence of HF and 23%, 56% and 81% died. Of 224, 139 and 78 patients in the three age groups who were discharged without developing HF, 15 were lost to follow-up and, of the remainder, 25%, 41% and 50% subsequently developed HF, which usually persisted. Of 53, 55 and 37 patients who developed HF after discharge, 26%, 62% and76% died in each age group respectively, compared to 10%, 12% and 51% in patients who never developed HF at any time. Thus of 271, 221 and 175 patients aged <65, 65-75 and >75 years who were discharged and followed-up, 115, 142 and 138 had or developed transient or persistent HF and 50 (18%), 102 (46%) and 126 (72%) subsequently died, of whom 35 (70%), 93 (91%) and 107 (85%) respectively occurred subsequent to the development of HF (Figures 4.3a, b and 4.4).

A report on LV function during or shortly after the index admission was available in 228 (83%), 175 (81%) and 104 (60%) surviving patients in the above mentioned patient groups and in 16, 24 and 31 patients who died during the index admission (Table 4.3). The outcome of these patients is shown in detail in Table 4.3. Overall, stratified by age, 26 (31%), 48 (59%) and 34 (63%) patients with documented LVSD (including LVSD prior to the index admission) died after discharge, of whom 20 (77%), 46 (96%) and 32 (94%) also had heart failure.

Figure 4-3.a &b a and b:prognosis amongst patients discharged after the index myocardial infarction

a:



KEY:

1: <65 years- Never HF (n=156)

2: <65 years- HF any time (n=115)

3: 65-75 years- Never HF (n=79)

4: 65-75 years- HF any time (n=142)

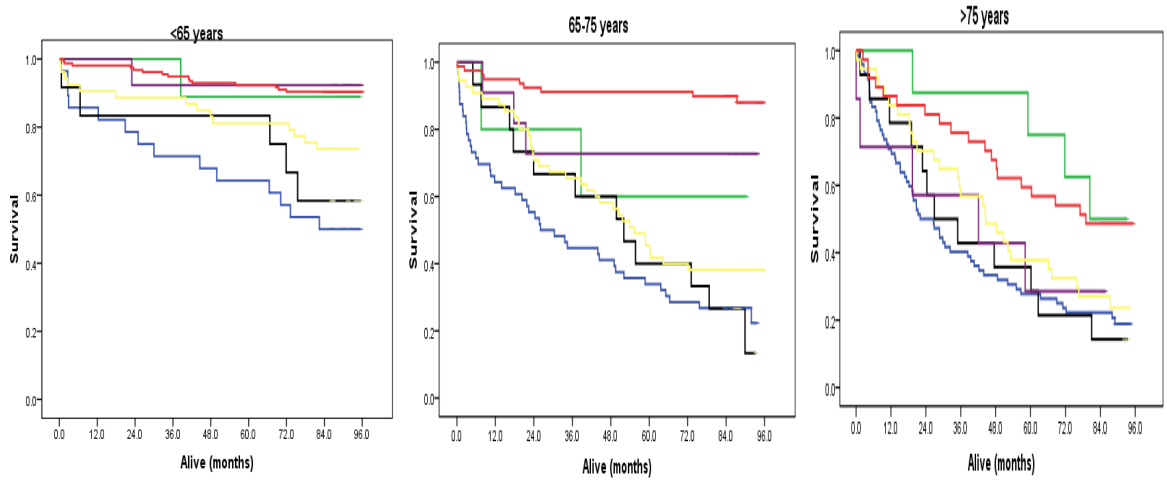
5: >75 years- Never HF (n= 37)

6: >75 years- HF any time (n= 138)

Group ID	2	3	4	5	6
	sig	sig	sig	sig	sig
2	0.0001				
3	0.650	0.002			
4	0.0001	0.0001	0.0001		
5	0.0001	0. 019	0.0001	0.88	
6	0.0001	0.0001	0.0001	0.49	0.003

Kaplan-Meier curves showing prognosis amongst patients discharged after the index myocardial infarction in different age groups (>65 years, 65-75 years and >75 years) with any HF (persistent or transient) and those who never developed HF.

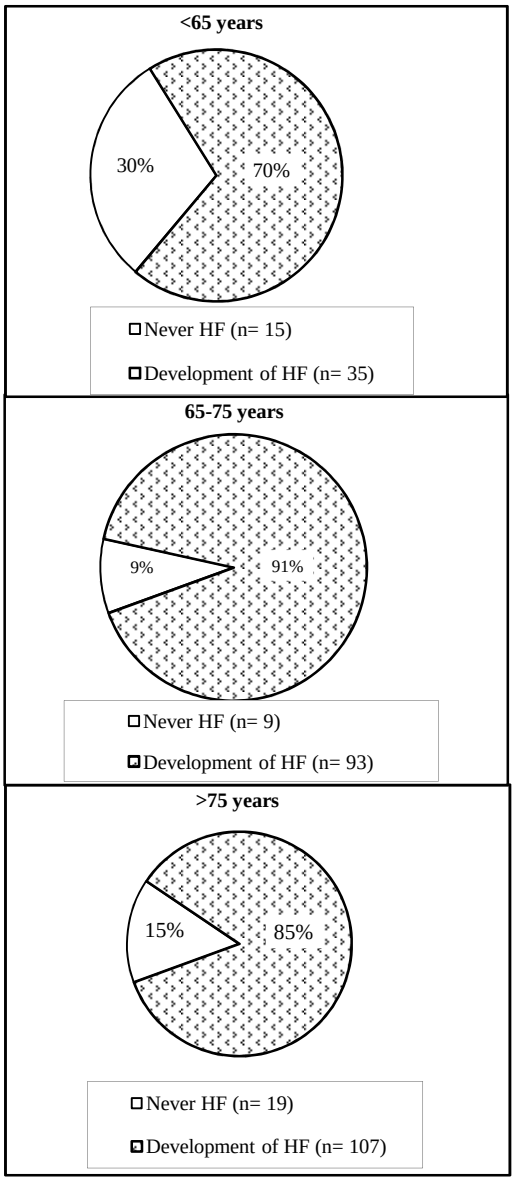
B:



KEY	<65 years	65-75 years	>75 years
HF at Index- Persistent at Follow-Up	28	56	72
HF at Index- Remission at Follow-Up	9	5	8
Transient HF at Index- Recurrent at Follow-Up	12	15	14
Transient HF at Index- Remission at Follow-Up	13	11	7
No HF at Index- Incident at Follow-Up	53	55	37
No HF at any time	156	79	37

Kaplan-Meier curves showing prognosis amongst patients discharged after the index myocardial infarction with and without transient or persistent heart failure according to different age group (>65 years, 65-75 years and >75 years). For statistical comparisons see Table 5.6. Numbers in table are numbers of patients.

Figure 4-4 Mortality after index admission, with and without Heart failure any time and



Pie-chart showing the proportion of patients in different age groups (>65 years, 65-75 years and >75 years) who died, subsequent to discharge from index admission, with or without preceding evidence of heart failure.

Of 51, 102 and 128 patients aged <65, 65-75 and >75 years who died after the index admission, 23 (45%), 67 (66%) and 78 (61%) patients died during a re-admission to hospital (Table 4. 4). Little detailed information was available for out-of-hospital deaths but review of existing data suggested that most were unexpected and probably sudden.

4.3.3 Cox Model

Patients who had or developed HF during the index admission had the poorest survival across all age groups Figure 4.3a and 4.3b a. Univariate age-stratified models are presented in Table 4.5. Patients with persistent HF had the highest mortality. This effect was most marked for those patients in the middle-aged group (65-75 years old) and less pronounced for patients aged >75 years, most of whom developed HF and who had a poor outcome whether or not they developed HF.

Table 4-3Imaging evidence of left ventricular function during index admission or shortly after

	Missing Data	All	**Age<65 years**	**Age 65-75 years**	**Age>75 years**	**p-value**
n		**861**	**296**	**284**	**281**	
Contrast angiography		**93**	**64**	**24**	**5**	
Left main coronary artery	2	10	6 (10%)	3 (13%)	1 (20%)	0.855
Three-vessel disease[b]		42	25 (39%)	13 (54%)	4 (80%)	0.539
Two-vessel disease		25	20 (31%)	5 (21%)		
One-vessel disease		25	18 (28%)	6 (25%)	1 (20%)	
LVSD (LV assessed n=59)	33	13	11 (25%)	2 (13%)	0	0.210
Echocardiography		**283**	**96**	**100**	**87**	
Major LVSD	4	141	44 (46%)	51 (51%)	46 (55%)	0.029
Moderate or severe mitral regurgitation	12	39	9 (9%)	14 (14%)	16 (18%)	0.519
Moderate or severe other valve disease	6	11	1 (1%)	5 (5%)	5 (6%)	0.329
Radionuclide		**357**	**176**	**123**	**58**	
LVEF 35-40%		42	46 (26%)	39 (32%)	25 (43%)	0.087
LVEF <35%		110	18 (10%)	18 (15%)	6 (10%)	
LV assessment by any technique	**319**	**552**	**237 (80%)**	**192 (68%)**	**123 (44%)**	
Moderate or severe LVSD (any technique)[c]		**281**	**98**	**101**	**82**	
Died index admission		62	15 (15%)	19 (19%)	28 (34%)	0.006
Discharged with persistent HF		91	24 (26%)	33 (33%)	34 (41%)	
Discharged after transient HF		30	12 (13%)	13 (14%)	5 (7%)	
Developed HF after discharge		50	21 (23%)	23 (24%)	6 (9%)	
Died after discharge-transient or persistent HF		99	19 (19%)	48 (48%)	32 (39%)	
Survived despite transient or persistent HF		72	8 (8%)	21 (21%)	13 (16)	
Died after discharge without developing HF	1	10	6 (6%)	2 (2%)	1 (1%)	
Survived without developing HF[e]	4	38	20 (20%)	11 (11%)	8 (10%)	
Total Deaths	1	170	40 (41%)	69 (69%)	61 (74%)	
No Major LVSD (any technique)		**297**	**146**	**98**	**53**	
Died index admission		9	1 (1%)	5 (5%)	3 (6%)	0.0001
Discharged with persistent HF		34	5 (3%)	14 (14%)	15 (28%)	
Discharged after transient HF		25	10 (7%)	9 (9%)	6 (11%)	
Developed HF after discharge		54	24 (16%)	19 (19%)	11 (21%)	
Died after discharge-transient or persistent HF		46	4 (3%)	22 (22%)	20 (38%)	
Survived despite transient or persistent HF	3	67	35 (24%)	20 (21%)	12 (23%)	
Died after discharge without developing HF	2	21	7 (5%)	5 (5%)	9 (17%)	

Survived without developing HF	11	154	99 (71%)	46 (48%)	9 (17%)	
Total Deaths	2	76	12 (8%)	32 (33%)	32 (60)	
No Report of LV function by any technique		**283**	**52**	**85**	**146**	
Died index admission		128	8 (15%)	44 (52%)	76 (52%)	0.0001
Discharged with persistent HF		49	6 (12%)	13 (15%)	30 (21%)	
Discharged after transient HF		13	2 (4%)	3 (4%)	8 (5%)	
Developed HF after discharge		29	3 (6%)	8 (9%)	18 (12%)	
Died after discharge-transient or persistent HF		70	6 (12%)	16 (19%)	48 (33%)	
Survived despite transient or persistent HF		21	5 (10%)	8 (9%)	8 (5%)	
Died after discharge without developing HF		15	5 (10%)	2 (2%)	8 (5%)	
Survived and did not develop HF		49	28 (54%)	15 (18%)	6 (4%)	
Total Deaths		213	19 (37%)	62 (73)	132 (90%)	

[a]The imaging test indicating the most severe left-ventricular impairment on index admission or 1st available within 90 days after index admission (excluding 35 cases with recurrent acute myocardial infarction within 90 days since the image may not reflect the damage from their index infarction). Percentages are shown are of those in whom measurements were made.
[b]Four cases had graft occlusion, one cases had no vessel disease, six cases had ventricular septal defect, one cases had mitral valve rupture during index admission and two patients had prior valve replacement. [c]aortic regurgitation or stenosis or mitral stenosis.
[c]Twentypatientshad prior LVSD without any LV assessment during or shortly after index admission.

Table 4-4 Mode of death in patients who died during index admission (n=199) and subsequent to discharge (n=281)

	All	Age<65 years	Age 65-75 years	Age>75 years
	896	311 (35%)	297 (33%)	288 (32%)
Died during index admission				
Total	199	24	68	107
SCD	55	6	18	31
HF	114	16	38	60
Stroke	2	0	0	2
Cardiac procedures related	4	0	1	3
Other cardiac	8	1	3	4
Infection	4	0	2	2
Cancer	1	0	0	1
Other non cardiac	11	1	6	4
Died after the index admission	281	51	102	128
Died during a re-admission				
Total	168[a]	23	67	78
SCD	9	2	3	4
HF	68	8 (35%)	30 (45%)	30 (39%)
Stroke	11	1	4	6
Cardiac procedures related	2	0	2	0
Other cardiac	4	1	1	2
Infection	22	2	7	13
Cancer	24	6	8	10
Other non cardiac	27	3	12	12
Died out of hospital[b]				
Total	113	28	35	50
Severe HF[c]	16	7	5	4
Advanced cancer	9	2	2	5
Stroke	2	1	0	1
Any transient or persistent HF	83	17	29	37
Any HF with LVSD prior to death[d]	48	12	20	16
Any HF with no LV assessment	16	2	3	11
Any HF with No LVSD	19	3	6	10
Never HF	30	11	6	13
Never HF but LVSD prior to death	7	5	2	0
Never HF with no LV assessment	10	2	2	6
Never HF and No LVSD	13	4	2	7

[a]one patient with age >75 years had missing data during last admission.
[b]with age 65-75 years one patients died of self-poisoning, with age <65 years one patient had three vessel disease and was waiting for CABG , one patient had three vessel disease and was waiting for PTCA and another had LAD disease but were not suitable for surgery and one patient 65-75 year old had severe pulmonary hypertension.
[c]Severe HF during one month prior to death of whom two had missed HF(chest X-rays report were pulmonary oedema after death).
[d]LVSD in last cardiac imaging prior to death
P-values not calculated owing to small cell numbers.

Table 4-5Cox-regression models; unadjusted and multivariate-adjusted procedures of mortality in patients subsequent to discharge (n=667).

			Univariate			Multivariable Adjusted	
Variable Name	N		HR	P value		HR	P value
<65 years old	271						
Heart Failure Status*	156	30.559			24.632		
PHF-persistent at f/up	28	26.103	6.701 (3.230-13.902)	<0.0005	20.904	5.889 (2.754-12.593)	<0.0005
PHF-resolved at f/up	9	0.618	0.450 (0.061-3.301)	0.432	0.436	0.507 (0.068-3.802)	0.509
THF-redevelop HF	12	2.667	2.543 (0.830-7.793)	<0.102	2.378	2.420 (0.787-7.439)	<0.123
THF-remission at f/up	13	1.203	0.319 (0.042-2.456)	0.273	1.160	0.326 (0.042-2.508)	0.281
No HF-developed HF	53	1.035	1.512 (0.682-3.351)	0.309	0.915	1.478 (0.664-3.287)	0.339
Re-admission with MI	39	9.474	2.638 (1.422-4.893)	0.002	2.607	1.747 (0.888-3.437)	<0.106
Re-admission with angina	51	0.019	0.950 (0.462-1.955)	0.890	0.027	0.938 (0.435-2.022)	<0.870
65-75 years old	221						
Heart Failure Status*	79	49.172			46.855		
PHF-persistent at f/up	56	44.738	11.798 (5.724-24.315)	<0.0005	42.600	11.408 (5.492-23.697)	<0.0005
PHF-resolved at f/up	5	0.136	1.309 (0.313-5.483)	0.712	0.225	1.416 (0.337-5.960)	0.635
THF-redevelop HF	15	6.317	2.683 (1.243-5.791)	0.012	4.199	2.143 (1.036-4.856)	0.040
THF-remission at f/up	11	0.796	0.578 (0.173-1.929)	0.372	1.089	0.526 (0.157-1.758)	0.297
No HF-developed HF	55	4.398	1.753 (1.037-2.962)	0.036	2.433	1.525 (0.897-2.592)	0.119
Re-admission with MI	47	21.711	2.660 (1.763-4.015)	<0.0005	3.718	1.522 (0.993-2.334)	0.054
Re-admission with angina	39	11.348	0.267 (0.124-0.576)	0.001	8.644	0.305 (0.138-0.673)	0.003
>75 years old	175						
Heart Failure Status*	37	14.914			12.452		
PHF-persistent at f/up	72	11.415	2.452 (1.457-4.127)	0.001	7.580	2.114 (1.241-3.603)	0.006
PHF-resolved at f/up	8	1.572	0.523 (0.190-1.441)	0.210	2.580	0.434 (0.157-1.202)	0.108
THF-redevelop HF	14	3.293	1.872 (0.951-3.684)	0.070	3.266	1.869 (0.948-3.682)	0.071
THF-remission at f/up	7	0.463	1.381 (0.545-3.504)	0.496	1.184	1.689 (0.657-4.338)	0.277
No HF-developed HF	37	0.335	1.152 (0.713-1.861)	0.563	0.328	1.151 (0.711-1.863)	0.567
Re-admission with MI	59	7.351	1.641 (1.147-2.349)	0.007	1.516	1.269 (0.868-1.855)	0.218
Re-admission with angina	21	9.641	0.321 (0.157-0.658)	0.002	7.531	0.357 (0.171-0.745)	0.006

*with reference to No HF any time (index admission and follow up).
THF, transient HF during the index admission; PHF, persistent heart failure during the index admission; MI, myocardial infarction.

4.4 Discussion

This analysis shows that the development of heart failure after a myocardial infarction increases steeply with age, that most patients who die subsequent to a myocardial infarction will first develop heart failure and that heart failure is a powerful adverse prognostic factor. Patients aged <65 years were least likely to develop heart failure but nonetheless, over six years of follow-up, 50% developed heart failure and 70% of deaths in this age group occurred subsequent to the development of HF. For patients aged 65-75 years, 73% developed heart failure during follow-up and 91% of deaths in this age group occurred subsequent to the development of HF. In patients aged >75 years, 87% developed heart failure but the prognosis was poor even amongst patients who did not develop overt heart failure. Few patients (only 34 of 281 or 12% of those evaluated) who had substantial LVSD after myocardial infarction escaped death or the development of heart failure over the subsequent six years. However, about half of patients who did not have substantial LVSD still went on to develop heart failure, of whom a large proportion died. Thus the prevention and management of heart failure rather than of LVSD may be the most important therapeutic target in patients with heart failure.

This cohort of patients was enrolled prior to the widespread adoption of primary angioplasty and before national audits were introduced to improve the quality of care. Treatments to restore coronary perfusion were suboptimal. Studies show that thrombolysis and primary percutaneous angioplasty can reduce myocardial damage[113 114 115] leading to improved long-term recovery of cardiac function [116 117 118] and reduced mortality [119 120 121 122]. This should lead to a reduction in the incidence of heart failure, although evidence in support of this hypothesis is scant. Use of ACE inhibitors [123], angiotensin receptor blockers[124 125], aldosterone receptor antagonists[93], beta-blockers [45] and statins

[126]were not used optimally by contemporary standards. Greater use might have assisted recovery in ventricular function, reduced the development of heart failure and improved prognosis. Aspirin was used widely but was rarely used in combination with clopidogrel. The need for long-term anti-platelet therapy after MI is now under question, especially in patients who have developed HF [48 127 128]. Studies of patients with heart failure and coronary disease suggest no survival advantage [48 98 129 130] from aspirin in patients with heart failure but a substantial increase in admissions with exacerbations of HF.

Hopefully, improvements in care have improved the prognosis of patients with myocardial infarction [131]. However, a repeat survey in our hospital conducted in 2005, with much higher uptake of guideline-indicated therapy, revealed a three year mortality which was still in excess of 30%, suggesting that the prognosis of heart failure in epidemiologically representative cohorts of patients, not just those who get to the catheter laboratory, remains poor. Overall, our cohort of patients was most unlike that observed in clinical trials. The median age in our cohort in 1998 was 70 years and 35% were women [107]. This had changed little by 2005 and is similar to that reported by the Myocardial Infarction National Audit Programme (MINAP) in the UK in 2003-2005 (mean age 69 years and 36% women [132]. The Euro Heart Survey of Acute Coronary Syndromes reported a mean age of just 63 years and 29% women amongst patients with an ST elevation MI and 66 years and 36% in those with MI but not ST elevation [24]. In contemporary clinical trials, such as the Platelet Inhibition and Patient Outcomes (PLATO) study, the median age was only 62 years and only 28% were women[133]. One year mortality, including in-patient deaths, was only 6% compared to in-patient and one year mortalities of 22% and 31% in 1998 and 11% and 19% in 2005 in our epidemiological cohort. The TRITON-TIMI 38 study was a randomized controlled trial comparing a new thienopyridine, prasugrel, to one of the first agents in this class, clopidogrel conducted between 2004 and 2007. Prasugrel has a faster and more

consistent effect on the inhibition of platelet activation than clopidogrel, the activity of which may be dependent on genetic factors. TRITON-TIMI 38 included very few patients aged >75 years (only 13%). Patients aged ≥75 years were more likely to reach the primary end-point (cardiovascular death, MI or stroke) than the majority of patients who were aged <65 years (18.3% versus 10.6% over a median follow-up of 15 months for those assigned to clopidogrel. The relative and absolute gain of those assigned to prasugrel were lower in the older age group but with a substantial increase in the risk of haemorrhagic complications leading the regulators to the conclusion that the risks outweighed benefit in patients aged >75 years with a low body weight (<60kg) [134].As low body weight indicates, in general, a worse prognosis in patients with cardiovascular disease [135] this should be a very high risk population but at 15 months only 16.0% of those assigned to clopidogrel had reached a primary endpoint compared to a one year mortality of 19% in the overall population in our 2005 cohort. This could be reflect differences in care but more likely reflects differences in case ascertainment and selection. Old, frail and sick patients may either decline to participate in trials or investigators, for a variety of reasons including compassion, may avoid enrolling them. Moreover, patients in TRITON-TIMI 38 had to be eligible for PCI to participate and many multi-morbid, older patients may be deemed unfit for such a procedure. A low threshold for the detection of MI with the use of more sensitive troponin assays may also lead to an apparent improvement in prognosis, as small MIs will generally have a better prognosis than large ones.

The patients with the worst prognosis, those aged >75 years are poorly represented in clinical trials (only 15% in the PLATO trial with a 1.4% absolute reduction in mortality from 5.9% with copidogrel to 4.6% with ticagrelor; $p<0.001$) and may well receive an inferior quality of care. Clinical trials amongst older patients with acute coronary syndromes could highlight the needs of this patient group and also provide a group at high risk of a poor outcome that would

allow the benefits of an effective therapy to be clear. The prognosis of patients enrolled in many contemporary trials of acute coronary syndrome is now so good it is difficult to make any improvement. However, older patients may also be at greater risk of side effects such as bleeding and renal dysfunction making the challenge of finding effective therapy greater. It is also possible that outcome in older patients is more resistant to change with therapy.

The problem may not be so much chronological as biological age. Older patients had more co-morbid conditions such as atrial fibrillation, conducting system disease, respiratory disease, renal dysfunction, anaemia and, worst of all, heart failure. In a sense, age is a surrogate for the drivers of an adverse outcome. Investigation and management of these co-morbidities could be an important pathway to improved outcomes. Patients aged 65-75 years are at intermediate risk and it is in patients at intermediate risk where the greatest therapeutic gains may occur. It is difficult to reduce risk in a group already at low risk, whereas in patients at high risk, an effective therapy may still not be effective enough to make a meaningful difference in outcome [136]. Identifying and managing modifiable risk is key and it may be best to target the intermediate age group at intermediate risk to achieve the greatest benefit.

4.5 Study limitations

The survey was of patients managed in 1998. Substantial changes in management have occurred and should have altered outcome. New cohorts of patients should be recruited but must inevitably reflect practice from a previous era if long follow-up is required. Not all patients had LV function assessed. Since systematic attempts were not made to withdraw diuretics, we may have under-estimated the transitory nature of heart failure in some cases. A simple, robust definition of heart failure remains elusive. However, patients who receive loop

diuretics and who have cardiovascular disease clearly have a poor prognosis whether or not they have a low ejection fraction[26]. Ultimately, heart failure is a clinical syndrome that relies on a doctor's skill in assessing a patient in the light of appropriate investigations.

The prevalence of diabetes mellitus was similar to that reported in another large trial from the same county in England but is towards the lower end of the spectrum reported in the literature (15, 16). This may reflect under-reporting of milder cases of diabetes, as it was not routine practice to obtain fasting blood glucose [137]. However, surveys reporting high levels of diabetes have generally included large numbers of patients from North America, where the prevalence of diabetes is probably, genuinely higher than in our region.

4.6 Conclusions:

In conclusion, the development of transient or persistent HF precedes death in the great majority of patients who die within six years of an MI in all age groups. Improved management of cardiac dysfunction and HF and its important co-morbidities such as anaemia and renal dysfunction may slow the rate of progression and improve quality of life and prognosis in such patients.

5 Chapter 5: Anaemia after a Myocardial Infarction and Its Relationship to the Development of Heart Failure and Mortality

5.1 Introduction

Anaemia is common in patients who have had an acute myocardial infarction (AMI), predicts a high 1-year [138] and 30-day all-cause and cardiovascular mortality [139 140] and is associated with the development of heart failure (HF) [140 141].Anaemia is also common in patients with heart failure, may exacerbate its symptoms [142]and is also associated with poor prognosis[143]. Not surprisingly, patients who develop heart failure with or without LVSD as a consequence of AMI are also commonly anaemic and this also predicts an adverse prognosis [144]. Interestingly, there is little evidence of a dose effect with mild and moderate anaemia predicting a similarly poor outcome. However, the interplay between anaemia and heart failure after AMI and their relative prognostic significance is uncertain. We set out to explore these relationships and their association with short- and long-term prognosis after AMI.

5.2 Methods

5.2.1 Study population

One hospital group in Hull and the East Riding of Yorkshire (UK) provide all of the acute cardiac services for about 560,000 people living in a geographically distinct part of the United Kingdom. Patients with a discharge diagnosis of acute MI during 1998 were identified from the Hospitals Information Department and their case notes screened. Patients who were transferred from another region, those with missing case notes or in whom AMI could not be

confirmed from their records were excluded. The study was approved by the Local Research Ethics Committee.

5.2.2 Follow-up

This was a retrospective analysis designed in 2004. The case records of all patients were reviewed to identify use of loop diuretics and if so whether this was due to symptoms or signs of heart failure. Follow-up data were collected until 31st December 2005. If no recent hospital record existed, the family practitioners of patients were contacted to ascertain the patient's current therapy and heart failure status. The occurrence of major events, such as recurrent MI, and stroke were recorded.

5.2.3 Definition of Myocardial Infarction

At least **two** of the following five criteria had to be identified during case note review to confirm a diagnosis of MI.

1. History of prolonged cardiac chest pain. (n = 657)
2. An increase in biomarkers consistent with MI, which in 1998 was usually creatinine kinase (CK) ratio or CK-MB mass. These were considered abnormal if they were twice the upper limit of normal values. (CK >200 n = 737)
3. Progressive electrocardiographic changes consistent with MI or new onset left bundle branch block. (n = 539)
4. Sudden unexpected death (n = 46)
5. Autopsy evidence of MI (n = 10)

5.2.4 Other Definitions

Heart failure was defined clinically either as signs and symptoms consistent with that diagnosis (principally breathlessness and signs of fluid retention) resulting in treatment with loop diuretics or patients who died shortly after developing evidence of major cardiac dysfunction, such as cases of cardiogenic shock or pulmonary oedema. For patients with an un-recordable blood pressure, a systolic pressure of 50mmHg was entered as a default value for statistical purposes. Use of loop diuretics for the treatment of hypertension or renal failure was not included in the definition of heart failure. Evidence of LVSD was not required for a diagnosis of heart failure. Criteria for LVSD were left ventricular ejection fraction (LVEF) < 40% or a qualitative report of moderate or severe LVSD on echocardiography, first-pass radionuclide ventriculography or contrast angiography. The World Health Organization (WHO) criteria for anaemia is a haemoglobin (Hb) <12g/dL in women and <13g/dL in men. Mean Hb values for healthy men and women in the report on which this was based were 13.3+/-0.9g/dL for women and 15.2+/-0.9g/dL for men [145]. We categorised patients according to the first available Hb reported during the index admission into those who had definite anaemia (>1 g below threshold), borderline anaemia (within 1g above or below the threshold) or who were not anaemic (>1g above threshold).

5.2.5 Statistical Analysis:

Data were entered into a Microsoft Access database and analysed using SPSS (version 13.0). Key outcomes were the proportion of patients who died and mortality rate. Continuously distributed data are presented as median and inter-quartile range. Categorical data are presented as percentages. Groups of patients with and without anaemia and/or heart failure were compared by the Chi-squared test on 2 degrees-of-freedom.

Kaplan-Meier (K-M) curves were generated to illustrate patients' survival overall, and in relevant subgroups. K-M curves were compared by the log-rank test. Cox regression was used to look at mortality, from which hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The Cox regression model is semi-parametric in the sense that no assumption concerning event-free survival times is necessary. The Cox regression model is based on the assumption that the effect of a risk factor, expressed as a hazard ratio, is constant over time.

The assumption of proportionality of the Cox model covariates was tested by plotting residuals[72 73]. Linearity of continuous data was checked by including asquared term.

We present age-adjusted models and looked at the relationship between all-cause mortality and the following variables: sex, HF, LVSD, creatinine and anaemia (according to last Hb during index admission). We adopted an epidemiological approach to model building rather than a more formal statistical approach. Hence, models were built that explained survival on the basis of their biological relevance to heart failure [112].

HF status was categorised into four groups: (i) No HF during index admission as a reference group; (ii) patients with HF prior to index; (iii) persistent HF (PHF) during the index admission; (iv) transient HF (THF) during index admission. Anaemia status was categorised into three groups as described in the method section but we used the last Hb during index admission.

5.3 Results:

5.3.1 Overall Results

Of 896 patients with confirmed myocardial infarction during 1998, no report of Hb during the index admission could be found in 41 cases. This left 855 patients for analysis, of which 103 had definite, 280 had borderline and 472 had no anaemia based on the first available haemoglobin during the index admission. Of these patients, 2, 8 and 18 from each group respectively were lost to follow-up after the index admission. The distribution of Hb in men and women with and without heart failure is shown in figure 5.1. 300 patients had more than one measurement of haemoglobin, of which 125 had definite, 289 had borderline and 441 had no anaemia on the last available measurement. Changes between first and last available measurement are shown in Table 5.1. The median (IQR) haemoglobin changed from 13.70(13.70-14.80) to 13.50 (13.50-14.60) and the prevalence of definite anaemia rose from 12% to 15%.

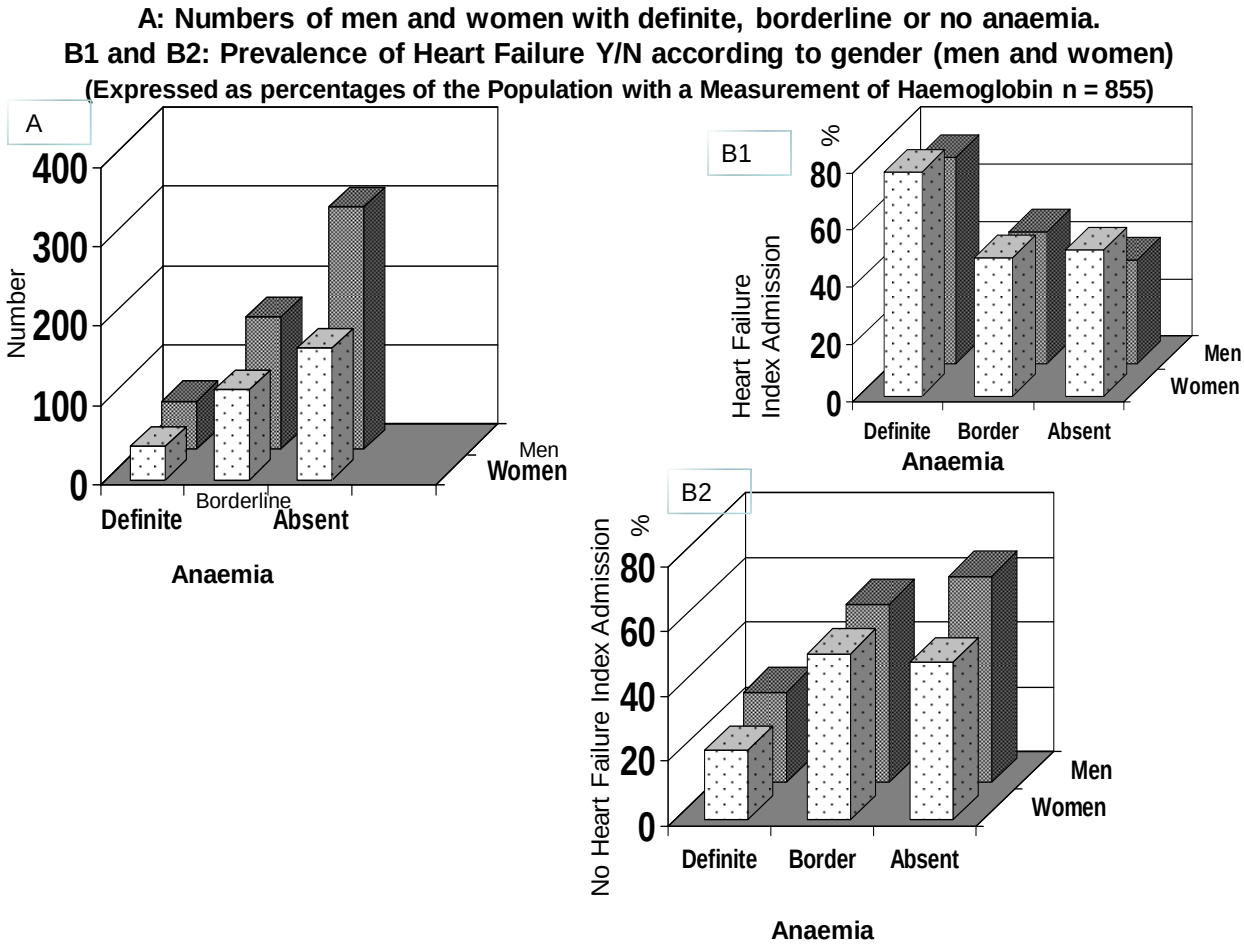
Table 5-1 Anaemia groups Changes between first and last available measurement

Baseline ➔ Follow-up🡻	None	Borderline	Definite	Total
None	424	17	0	441
Borderline	34	237	18	289
Definite	14	26	85	125
Total	472	280	103	855

The characteristics of the patients according to first available haemoglobin are shown in Table 5.2.The median age of the patients was 70 (interquartile range 61-78) years and 321 (38%) were women. There was a prior history of hypertension in 284 (33%), MI in 223 (26%), heart failure in 130 (15%) and diabetes in 78 (9%). Additionally, 22 (3%) patients were newly diagnosed with diabetes during the index admission. Sixty-two percent were managed, at least in part, by a cardiologist during their index admission. ST segment elevation myocardial infarction (STEMI) was present in 495 (58%) and non-STEMI in 301 patients (35%). Forty seven patients had Left Bundle Branch Block (LBBB), five patients were in a paced rhythm, and seven had no ECG recording available from the time of admission. Patients without anaemia were, on average, younger ($p<0.0001$) (Table 5.2) but, using a sex-specific threshold for the definition of anaemia, the prevalence was similar in men and women. Patients with anaemia were less likely to receive aspirin ($p<0.0001$) compared to those with borderline or no anaemia (Table 5.3). Older patients (>75 years old) were less likely to be treated with aspirin compared to younger patients (<65 years old).

Of855 patients, 103 had definite, 280 had borderline and 472 had no anaemia based on the first available haemoglobin during the index admission.Figures5.2a, 5.2b and 5.2c describe the sequence of events that led to the development of heart failure and/or death in these groups. During the index admission, 77 patients (75%) with definite, 130 (46%) with borderline and 196 (42%) who had no anaemia developed HF, of whom 41 (53%), 50 (38%) and 60 (31%) died during the index admission compared, respectively, to 7 (27%), 14 (9%) and 9 (3%) deaths in patients who did not develop HF. (Figure 5.3a).

Figure 5-1Prevalence of Heart Failure during index admission Y/N according to gender (men and women)



Panel A

Data are expressed as a number of the whole population (n=855) stratified by gender and anaemia status determined by the first measurement of haemoglobin during the index admission

Panel B1 and B2

Prevalence of index admission heart failure and no heart failure reported only during the index admission in relationship to gender and to anaemia status determined by the first measurement of haemoglobin during the index admission.

Table 5-2Patients Characteristics recorded during the Index Admission classified according to Anaemia status

Variables (units)	missing data	Overall	Anaemia [a]			P value
			Definite	Borderline	None	
N		855	103	280	472	
Age (years)	0	70 (61-78)	78 (71-82)	76 (68-83)	72 (65-79)	0.0001
Patients Aged <65 years	0	296 (35%)	13 (13%)	69 (25%)	214 (45%)	0.0001
Patients Aged >75 years	0	275 (32%)	55 (53%)	115 (41%)	105 (22%)	
Women	0	321 (38%)	42 (41%)	113 (40%)	166 (35%)	0.281
Current smoker	76	304 (39%)	19 (23%)	85 (33%)	200 (46%)	0.0001
Ex smoker		234 (30%)	27 (33%)	89 (35%)	118 (27%)	
History of Hypertension	37	284 (35%)	41(41%)	105 (39%)	138 (31%)	0.029
History of Diabetes	3	78+32[b] (13%)	14 (14%)	34 (12%)	62 (13%)	0.607
Prior MI	0	223 (26%)	33 (32%)	75 (27%)	115 (24%)	0.261
History of HF	4	130 (15%)	33 (32%)	45 (16%)	52 (11%)	0.0001
Prior CABG		36 (42%)	3 (3%)	13 (5%)	20 (4%)	0.755
Prior PTCA		14 (2%)	2 (2%)	4 (1%)	8 (2%)	0.930
Managed Primarily by Cardiologist		532 (62%)	51 (50%)	163 (58%)	318 (67%)	0.001
Index Admission ECG						
ST segment elevation[c]	7	495 (58%)	52 (52%)	160 (57%)	283 (60%)	0.592
Non ST elevation	7	301 (35%)	40 (40%)	101 (36%)	160 (34%)	
QRS $\geq$120	18	192 (23%)	30 (31%)	64 (23%)	98 (21%)	0.120
Anterior site	7	406 (48%)	46 (46%)	101 (48%)	226 (48%)	0.923
Chest X-ray						
Pulmonary oedema	202	157 (24%)	30 (37%)	48 (22%)	79 (22%)	0.014
Cardiomegaly		155 (24%)	25 (31%)	59 (27%)	71 (20%)	0.044
Upper Lobe Vein Distension		158 (24%)	26 (32%)	51 (23%)	81 (23%)	0.205
Pleural effusion		73 (11%)	18 (22%)	26 (12%)	29 (8%)	0.001
Physical Examination						
Heart Rate (b/min)	6	78 (64-97)	86 (66-102)	78 (65-96)	77 (64-96)	0.466
Atrial fibrillation (yes/no)	1	148 (17%)	30 (29%)	51 (18%)	67 (14%)	0.001
HF during index[d]		403 (47%)	77 (75%)	130 (46%)	196 (42%)	0.0001
Systolic BP (mm/Hg)	4	140 (120-160)	130 (110-150)	140 9120-160)	140 (123-160)	0.003
Blood Tests (on admission)						
Peak CK	33	828(374-1902)	595 (312-1225)	700 (327-1705)	1011 (411-2130)	0.008
Cholesterol (mmol/L)	326	6 (5-6)	5 (4-6)	6 (5-6)	6 (5-6)	0.560
Sodium	11	137 (135-139)	137 (134-139)	137 (135-139)	137 (135-139)	0.011
Creatinine	103	105 (89-128)	124 (96-165)	106 (87-129)	103 (87-121)	0.0001

CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; ECG, electrocardiogram. Percentages are shown are of those in whom measurements were made. CK = creatine kinase. Example interpretation: patients who had anaemia had a lower ck compared to patients with no anaemia. Also patients who had anaemia had a higher creatinine during the index admission compared to patients with borderline and no anaemia. The differences for Na are exaggerated because of the relative large sample sizes between the three groups, and the relatively low standard deviations (in other words, this is a statistical quirk).

[a]Anaemia: WHO criteria for anaemia are used(men<13 dg/dL; women<12 g/dL), Definite anaemia is defined as >1g below these thresholds Borderline is within 1g above or below these thresholds

[b]Thirty-two cases newly diagnosed as diabetic on index admission.

[c]P-value for ST calculated between three groups (STE, No STE and other (LBBB and pace).

[d]Heart failure during index admission.

Table 5-3Treatment during index admission and any time until 31st December 2005.

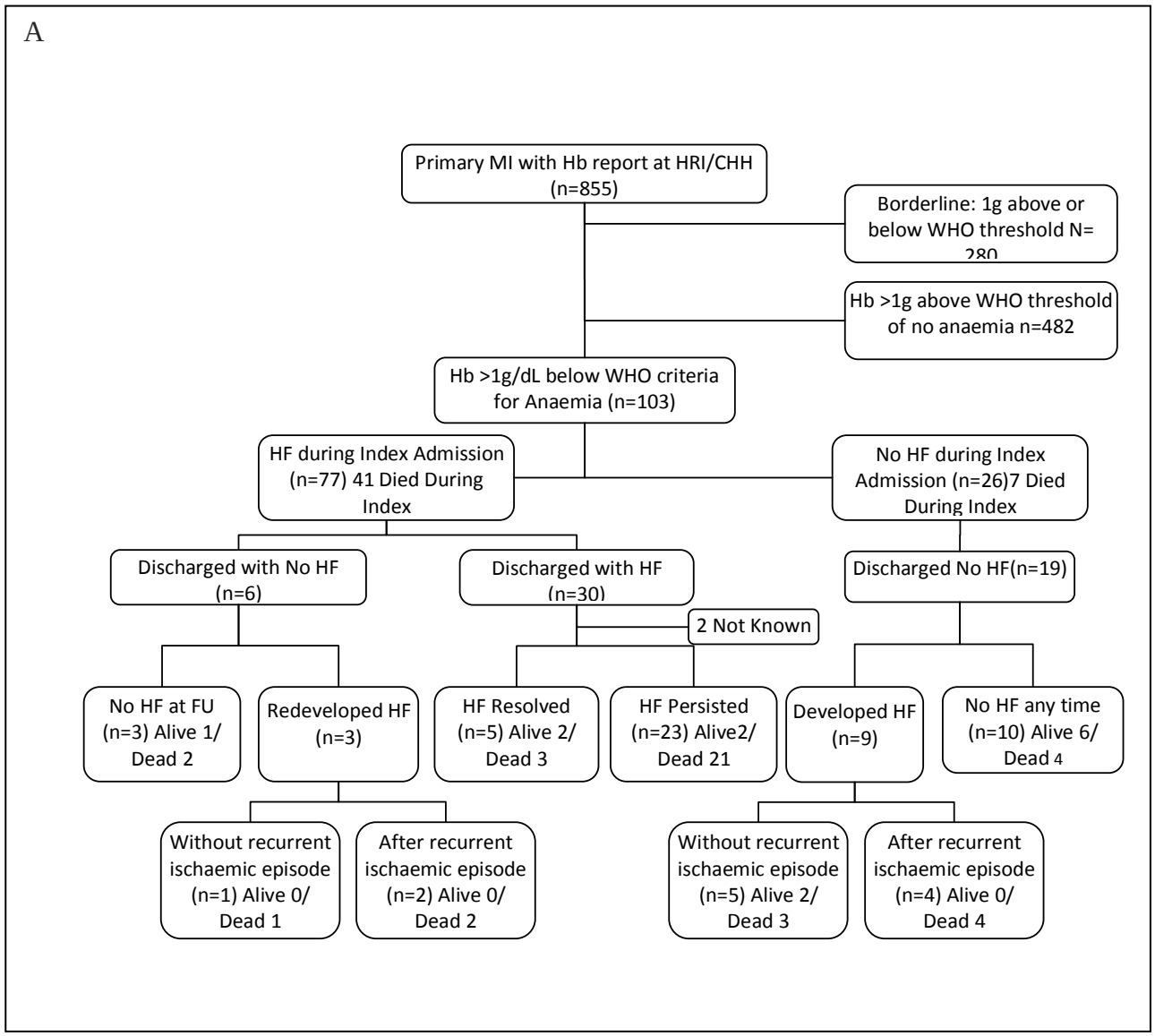
			Anaemia			
Variables (units)	missingdata	Overall	Definite*	Borderline*	None*	P value
n		855	103	280	472	
Revascularisation during admission						
Thrombolysis	0	354	22 (21%)	108 (39%)	255 (54%)	0.0001
PCI	0	18	2 (2%)	4 (1%)	12 (3%)	0.585
CABG	0	8	2 (2%)	1	5 (%)	0.331
Treatment at any time during admission						
Parenteral						
Loop diuretic	6	257	50 (49%)	81 (29%)	126 (27%)	0.0001
Nitrates	2	300	37 (36%)	93 (33%)	170 (36%)	0.676
Inotropic therapy	1	88	18 (17%)	25 (9%)	45 (10%)	0.116
Heparin	13	673	72 (71%)	217 (78%)	384 (83%)	0.091
Insulin	1	77	7 (7%)	21 (8%)	49 (10%)	0.506
Oral						
Aspirin	1	757	75 (73%)	255 (91%)	427 (91%)	0.0001
Clopidogrel	1	6	2 (2%)	4 (1%)	0	0.074
Warfarin	1	35	4 (4%)	14 (5%)	17 (4%)	0.792
Statin	1	388	17 (17%)	112 (40%)	259 (55%)	0.0001
ACE inhibitors	1	341	38 (37%)	110 (39%)	193 (41%)	0.832
ARBs	1	7	1 (1%)	3 (1%)	3 (1%)	0.869
Beta-blockers	1	478	35 (34%)	149 (53%)	294 (62%)	0.0001
Nitrates	1	308	53 (51%)	108 (39%)	147 (31%)	0.002
Calcium channel blockers	1	205	30 (30%)	63 (23%)	112 (24%)	0.617
Loop diuretic	0	291	59 (57%)	98 (35%)	134 (28%)	0.0001
Thiazide diuretic	0	17	2 (2%)	5 (2%)	10 (2%)	0.951
Spironolactone	0	1	0	0	1	0.666
Digoxin	1	65	16 (16%)	20 (7%)	29 (6%)	0.021
Oral hypoglycaemic agent	1	19	2 (2%)	8 (3%)	9 (2%)	0.813
Revascularisation at any time						
PCI	0	90 (11%)	2 (2%)	24 (9%)	64 (14%)	0.001
CABG	0	94 (11%)	5 (5%)	24 (9%)	65 (14%)	0.009
Treatments at any time						
ACE inhibitor	1	477	46 (45%)	152 (54%)	279 (59%)	0.074
ARBs	1	41	1 (1%)	15 (5%)	25 (5%)	0.334
Beta-blockers	1	522	39 (38%)	166 (59%)	317 (67%)	0.0001
Loop diuretic	1	523	83 (81%)	183 (65%)	257 (55%)	0.0001
Thiazide diuretic	1	66	5 (5%)	21 (8%)	40 (8%)	0.660
Spironolactone	1	64	6 (6%)	23 (8%)	35 (7%)	0.837
Digoxin	1	106	18 (17%)	38 (14%)	50 (11%)	0.289
Insulin	0	91	7 (7%)	26 (9%)	59 (13%)	0.175
Oral hypoglycaemic agent	1	72	2 (2%)	17 (6%)	51 (11%)	0.016
Aspirin	1	770	77 (75%)	259 (93%)	434 (92%)	0.0001
Statin	1	506	24 (23%)	151 (54%)	331 (70%)	0.0001

PCI, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; ARBs, angiotensin receptor-blockers.
*For definitions see foot note of table 5.2

Of patients who did not have HF during the index admission, a further 9 (47%), 58 (43%) and 73 (27%) patients with, respectively, definite, borderline and no anaemia subsequently went on to develop HF. Amongst patients with persistent heart failure at discharge, crude mortalities at six years were 23 (77%), 43 (75%) and 53 (58%) in those with definite, borderline or no anaemia. Of patients who developed HF after discharge, 7 (78%), 38 (66%) and 29 (40 %) died respectively in those with definite, borderline or no anaemia, compared to 4 (40%), 14 (18%) and 26 (13%) patients who never developed HF at any time.

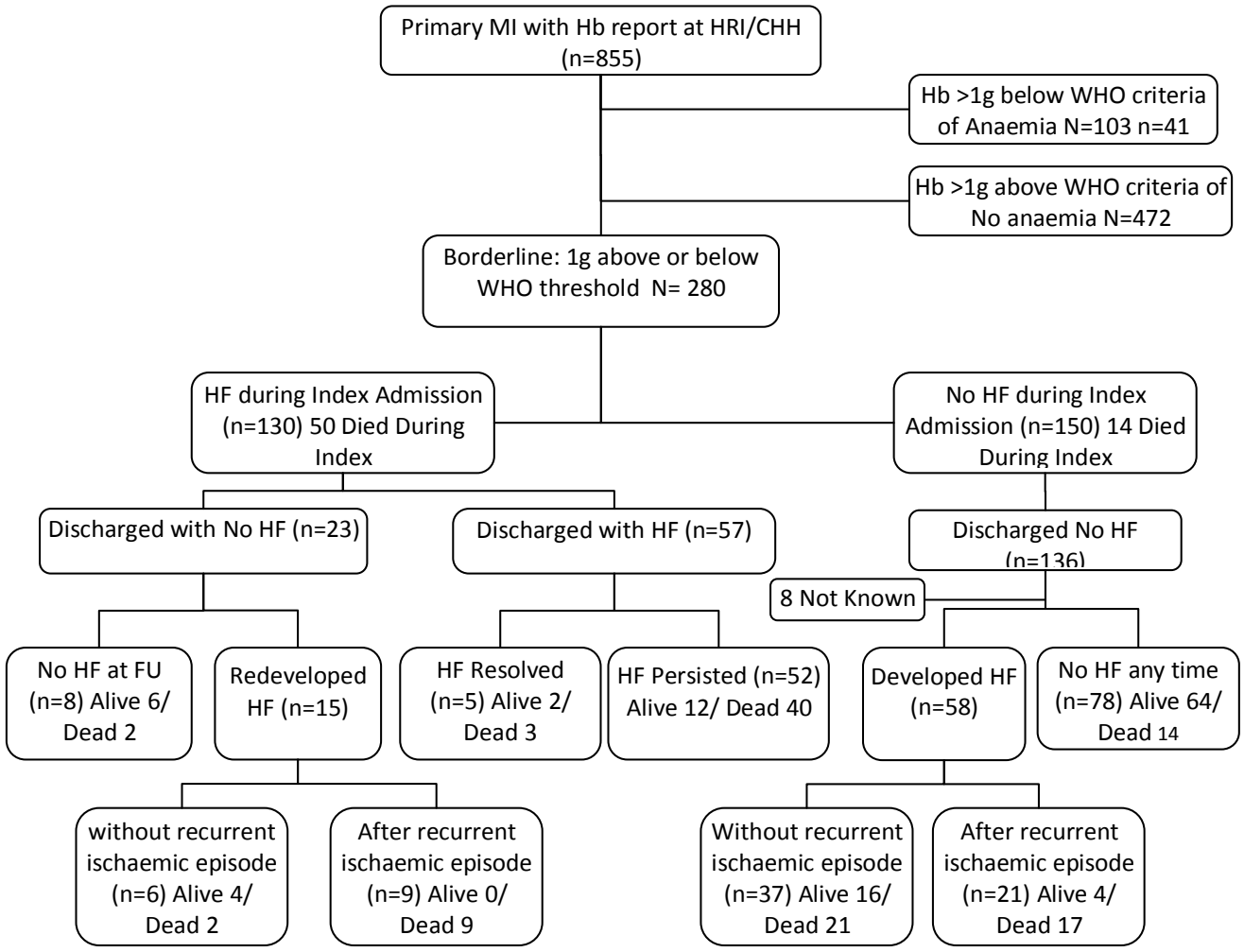
Of 53, 208 and385 patients with, respectively, definite, borderline or no anaemia based on the first haemoglobin who survived to discharge, 39 (74%), 106 (51%) and 127 (33%) subsequently died and of these 35 (90%), 92 (87%) and 102 (80%) occurred after developing transient or persistent HF. Overall, 86 (83%) patients with definite, 188 (67%) with borderline and 269 (57%) without anaemia developed HF, of which 87 (84%), 172 (61%) and 197 (42%) had died by December 2005. Based on the last, rather than first haemoglobin, of 125, 289 and 441 patients with, respectively, definite, borderline or no anaemia, 87 (70%), 172 (60%) and 197 (45%) subsequently died and of these 76 (87%), 144 (84%) and 162 (82%) occurred after developing transient or persistent HF. Overall, 101 (81%) patients with definite, 200 (69%) patients with borderline and 242 (55%) patients without anaemia developed HF, of which 89 (88%), 155 (76%) and 138 (57%) had died by December 2005.

Figure 5-2Flow diagram showing the sequence of development of heart failure and mortality over approximately 6 years in patients with (a) anaemia, (b) Borderline, (c) No anaemia according to first haemoglobin during admission.



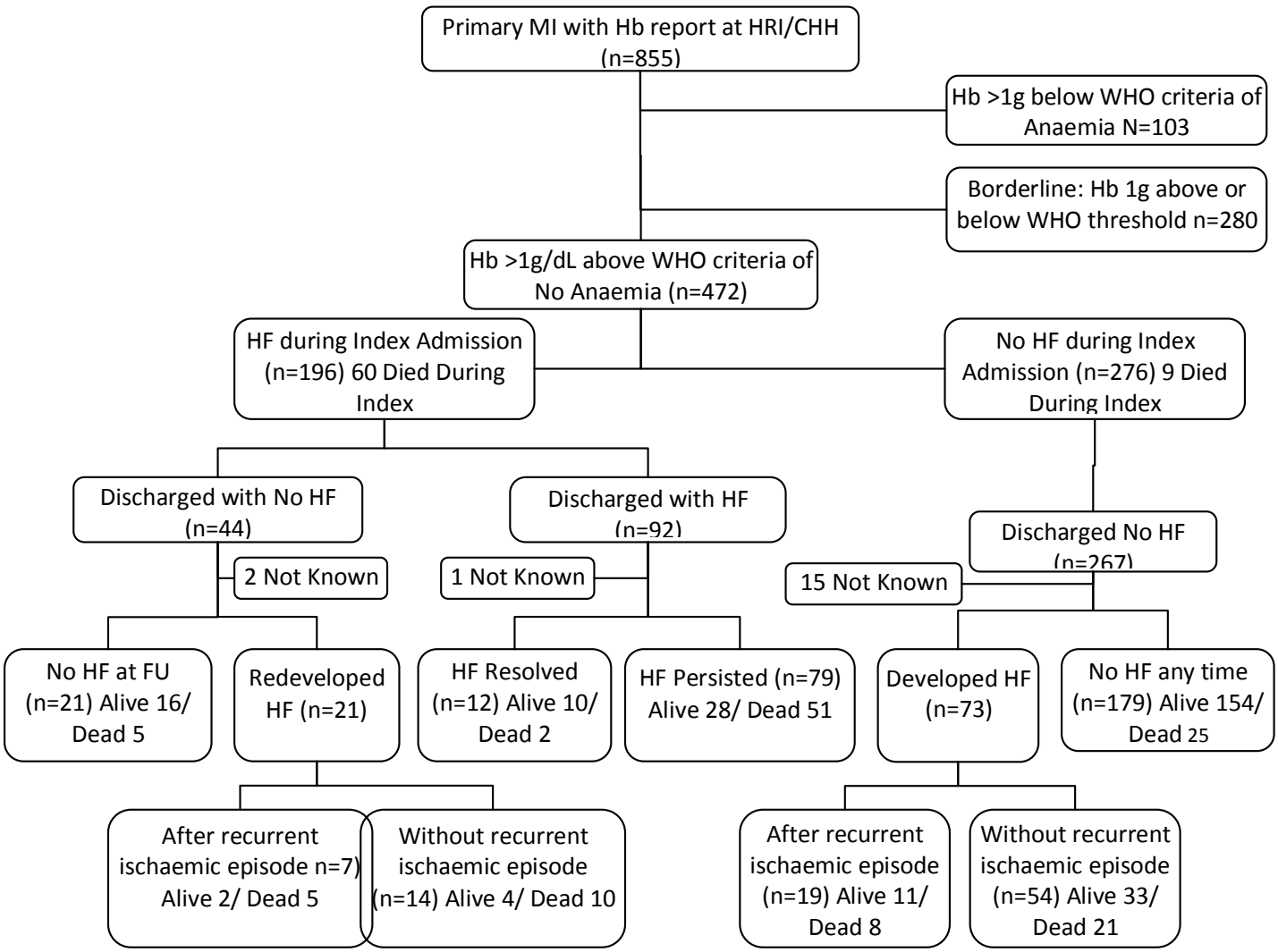
Flow diagram showing the sequence of development of heart failure and relationship with recurrent ischemic episodes and mortality over approximately 6 years in patients admitted with an acute myocardial infarction and Hb >1g/dL below WHO criteria for anaemia to the Hull and East Yorkshire Hospitals Group during 1998. Follow-up data were incomplete in 2 patients. See text for details.

b



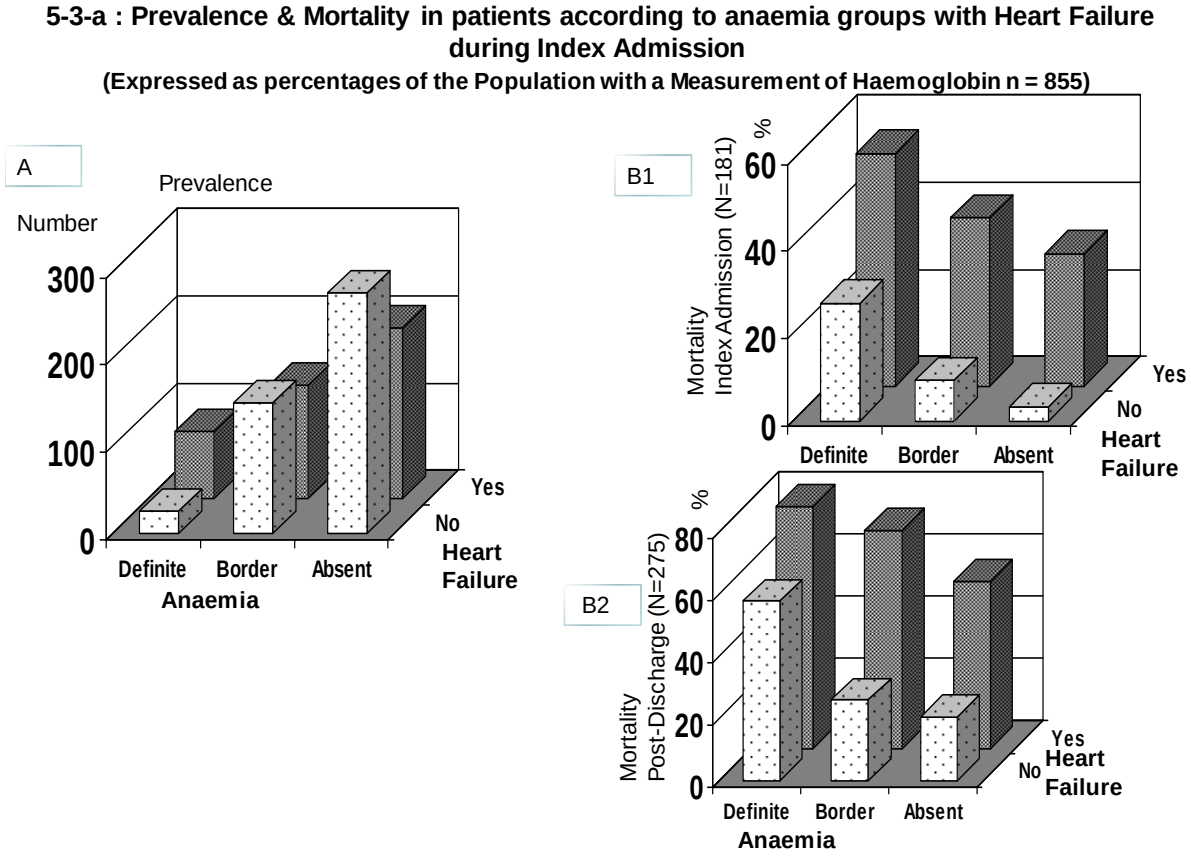
Flow diagram showing the sequence of development of heart failure and relationship with recurrent ischemic episodes and mortality over approximately 6 years in patients admitted with an acute myocardial infarction and Hb 1g above or below WHO threshold as borderline to the Hull and East Yorkshire Hospitals Group during 1998. Follow-up data were incomplete in 8 patients. See text for details.

c



Flow diagram showing the sequence of development of heart failure and relationship with recurrent ischemic episodes and mortality over approximately 6 years in patients admitted with an acute myocardial infarction and Hb >1g/dL above WHO criteria for anaemia to the Hull and East Yorkshire Hospitals Group during 1998. Follow-up data were incomplete in 2 patients. See text for details.

Figure 5-3Prevalence & Mortality according to anaemia groups and (a) heart failure and (b) LVSD.



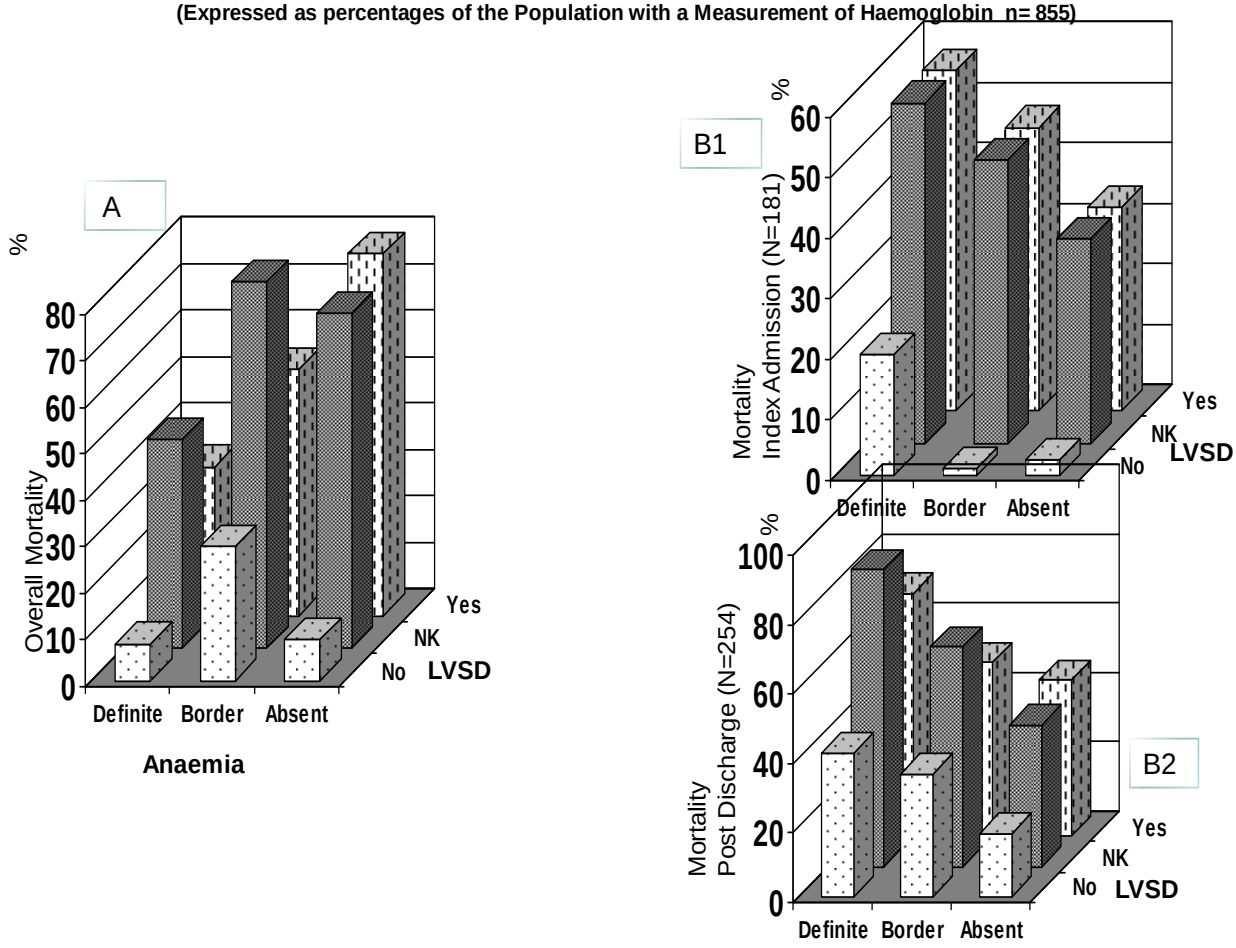
Panel A

Overall mortality in relationship to heart failure reported during the index admission only and to anaemia status determined by the first measurement of haemoglobin during the index admission.

Panel B1 and B2

Index admission and post-discharge mortality in relationship to heart failure reported during the index admission only and to anaemia status determined by the first measurement of haemoglobin during the index admission.

5-3-b:Prevalence & Mortality in Patients with and without LVSD During index Admission or Shortly after
(Expressed as percentages of the Population with a Measurement of Haemoglobin n= 855)



b:

Panel A:

Overall mortality in relationship to LVSD reported during the index admission or shortly after and to anaemia status determined by the first measurement of haemoglobin during the index admission (n=456).

Panel B1 and B2:

Index admission and post-discharge mortality in relationship to LVSD reported during the index admission or shortly after and to anaemia status determined by the first measurement of haemoglobin during the index admission.

Table 5-4Imaging evidence of left ventricular function during index admission or shortly after and relationship to development of heart failure or death

Variables (units) [missing data]	missing data	Overall	Anaemia			P value
			Definite*	Borderline*	None*	
n		820	101	267	452	
Contrast angiography		88	4	26	58	
Left main coronary artery	2	8	0	2 (8%)	6 (11%)	0.792
Three-vessel disease[b]		39	2 (50%)	10 (38%)	27 (47%)	0.979
2VD		25	1 (25%)	8 (31%)	16 (28%)	
1VD		23	1 (25%)	8 (31%)	14 (24%)	
LVSD (LV assessed n=57)	31	13	1 (33%)	4 (25%)	8 (21%)	0.861
Echocardiography		281	34	90	157	
Major LVSD	4	139	23 (70%)	43 (49%)	73 (47%)	0.055
Moderate or severe mitral regurgitation	12	37	9 (29%)	10 (11%)	18 (12%)	0.031
Moderate or severe other valve disease	6	10	1 (3%)	7 (8%)	2 (1%)	0.031
Radionuclide		340	21	102	217	
LVEF 35-39%		40	2 (10%)	13 (13%)	25 (12%)	0.116
LVEF <35%		105	10 (48%)	37 (36%)	58 (27%)	
LV assessment by any technique	**264**	**556**	**53**	**169**	**334**	
Moderate or severe LVSD (any technique)[c]		**271**	**38 (72%)**	**89 (53%)**	**144 (43%)**	
Died index admission		59	18 (47%)	17 (19%)	24 (17%)	0.002
Discharged with persistent HF		90	14 (37%)	25 (28%)	51 (35%)	
Discharged after transient HF		29	3 (10%)	10 (12%)	16 (12%)	
Developed HF after discharge		48	2 (6%)	21 (25%)	25 (19%)	
Died after discharge without developing HF	1	8	0	1 (1%)	7 (5%)	
Survived without developing HF[e]	3	37	1 (3%)	15 (17%)	21 (15%)	
Died after discharge - transient or persistent HF		96	14 (37%)	35 (39%)	47 (33%)	0.19
Survived despite transient or persistent HF	1	71	5 (13%)	27 (30%)	45 (31%)	
Total Deaths	2	163	32 (84%)	53 (60%)	78 (54%)	
No Major LVSD (any technique)		**285**	**15**	**80**	**190**	
Died index admission		9	3 (20%)	1 (1%)	5 (3%)	0.005
Discharged with persistent HF		33	3 (20%)	13 (16%)	17 (9%)	
Discharged after transient HF		25	0	6 (8%)	19 (10%)	
Developed HF after discharge		51	3 (20%)	18 (23%)	30 (16%)	
Died after discharge without developing HF[g]	2	21	2 (13%)	6 (8%)	13(7%)	
Survived without developing HF[h]	11	146	4 (27%)	36 (47%)	106 (56%)	
Died after discharge - transient or persistent HF		46	3 (20%)	22 (28%)	21 (11%)	0.023

Survived despite transient or persistent HF		63	3 (20%)	15 (19%)	45 (24%)	
Total Deaths	2	76	8 (53%)	29 (36%)	39 (21%)	
No Report of LV function by any technique		**264**	**48**	**98**	**118**	
Died index admission		113	27 (65%)	46 (47%)	40 (34%)	0.004
Discharged with persistent HF		48	12 (25%)	17 (17%)	19 (16%)	
Discharged after transient HF		13	3 (6%)	3 (3%)	7 (6%)	
Developed HF after discharge		29	3 (6%)	14 (14%)	12 (10%)	
Died after discharge without developing HF	1	14	2 (4%)	6 (6%)	6 (5%)	
Survived without developing HF[j]	5	47	1 (2%)	12 (12%)	34(29%)	
Died after discharge - transient or persistent HF		69	16 (33%)	27 (28%)	26 (22%)	0.21
Survived despite transient or persistent HF		21	2 (42%)	7 (7%)	12 (10%)	
Total Deaths	1	196	45 (94%)	79 (81%)	72 (61%)	

[*] For definitions see foot note of table 5.2

[a]The imaging test indicating the most severe left-ventricular impairment on index admission or 1st available within 90 days after index admission. Percentages are shown are of those in whom measurements were made.

[b]Four cases had graft occlusion, six had ventricular septal defect and one had mitral valve rupture during index admission. Two patients had prior valve replacement and aortic regurgitation or stenosis or mitral stenosis.

[c]Twenty patients had prior LVSD without any LV assessment during or shortly after index admission.

#LV assessed in 556 cases of whom LVSD reported only prior to admission in 25 cases, on index admission in 193 cases, a further 41 cases within 30 days, 8 cases within 31-60 days and 4 cases within 61-90 days.

A report on left ventricular function during or shortly after the index admission was available in 32 (58%), 151 (70%) and 305 (76%) surviving patients in the above mentioned patient groups and in 21, 18 and 29 patients who died during the index admission (Table 5.4). Overall, stratified by Hb, 14 (70%), 36 (51%) and 54 (45%) patients with documented LVSD died after discharge, of whom 14 (100%), 35 (97%) and 47 (87%) also had heart failure (Figure 5.3b). Of patients in whom LVSD was excluded, 5 (42%), 28 (41%) and 34 (18%) died of whom 3 (60%), 22 (79%) and 21 (62%) also had heart failure.

Of 275 deaths that occurred subsequent to discharge, 231 (84%) were preceded by the development of transient or persistent heart failure. Of these 275 deaths, 39, 108 and 128 patients had, respectively, definite, borderline and no anaemia on the first haemoglobin during the index admission and of these 35 (90%), 94 (87%) and 102 (80%) also had transient or persistent HF (Figures 5.3b and 5.4). Based on the last, rather than first haemoglobin, 42, 123 and 110 patients had, respectively, definite, borderline and no anaemia on the first haemoglobin during the index admission and of these 39 (93%), 107 (87%) and 85 (77%) also had transient or persistent HF.

5.3.2 Mode of death

Of 181 patients who died during the index admission, 165 cases were cardiac related. Of 275 patients who died after the index admission, 166 died during a re-admission to hospital and 109 died out of hospital. In patients who died out of hospital, 16 had severe heart failure, one died of self-poisoning, nine had advanced cancer and two had a stroke and one had three vessel diseases and was waiting for PCI (Table 5.5). Information on the precise cause of death was lacking in 79 cases and in most cases appeared to be sudden.

Table 5-5Mortality and mode of death during index admission (N=181) and subsequent to discharge (n=275) according to anaemia status.

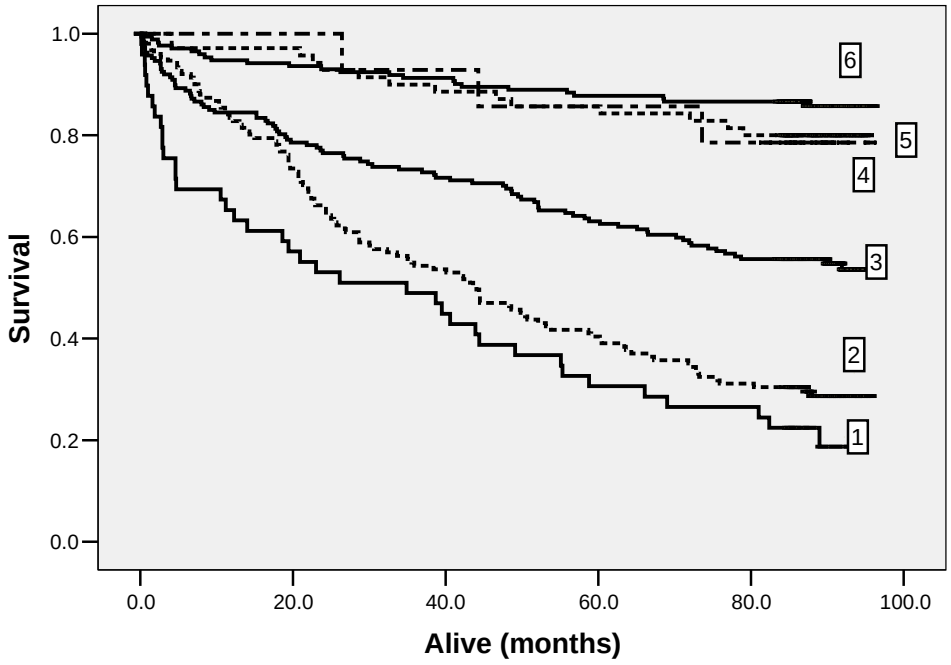
		Anaemia		
	Overall	**Definite***	**Borderline***	**None***
n	**820**	**101**	**267**	**452**
Died during index admission				
Total	**181**	**48**	**64**	**69**
Sudden cardiac death	46	9	16	21
HF	106	24	39	43
Stroke	2	1	1	0
Cardiac procedures related	3	1	1	1
Other cardiac	8	4	3	1
Infection	4	2	2	
Cancer	1	1	0	0
Other non cardiac	11	6	2	3
Died after the index admission	**275**	**39**	**108**	**128**
Died during a re-admission				
Total	**166**	**28#**	**67**	**71**
SCD	9	3	3	3
HF	66	5	30	31
Stroke	11	2	4	5
Cardiac procedures related	2	0	1	1
Other cardiac	4	1	1	2
Infection	22	7	9	6
Cancer	24	5	10	9
Other non cardiac	27	4	9	14
Died out of hospital				
Total	**109**	**11**	**41**	**57**
Severe HF	16[c]	1	5	10
Advanced cancer	9	1	4	4
Stroke	2	1	1	0
Any transient or persistent HF	**81**	**19**	**40**	**31**
Any HF with LVSD prior to death[a]	46	4	18	24
Any HF with no LV assessment	16	2	3	11
Any HF with No LVSD	19	2	7	10
Never HF	28	1	10	17
Never HF but LVSD prior to death	6	0	2	4
Never HF with no LV assessment	9	1	3	5
Any HF and No LVSD	13	0	5	8

* For definitions see foot note of table 5.2

#Missing data for the last admission for one cases

[a] LVSD in last cardiac imaging prior to death

Figure 5-4Kaplan-Meier curves showing prognosis among patients discharged after the index hospitalisation



Key:
1. Anaemia- HF at any time (n=49)
2. Bord erline- HF at any time (n=151)
3. No Anaemia- HF at any time (n=187)
4. Anaemia- Never HF (n=14)
5. Borderline- Never HF (n=72)
6. No Anaemia- Never HF (n=173)

Kaplan-Meier curves showing prognosis among patients discharged after the index myocardial infarction with anaemia, borderline and no anaemia according to last recorded Hb during index admission with and without heart failure at any time (persistent or transient) (N=646).

5.3.3 Cox Models

Patients with anaemia were more likely to die (Table 6). This relationship was mostly retained after further adjustment for sex, HF, LVSD, GFR and the other variables listed in table 6. (HR=1.379, 95% CI=0.982, 1.935, p=0.055). Substituting, the last available with the first available haemoglobin the link was slightly weakened.

Table 5-6Cox-regression models; for mortality in patients subsequent to discharge (n=646).

			Univariable			Age Adjusted	
Variable Name	**N**	**Wald**	**HR**	**P value**	**Wald**	**HR**	**P value**
No anaemia*	360	49.743		**0.0001**	**5.794**		**0.055**
Borderline	223	30.996	2.090 (1.612-2.708)	**0.0001**	3.252	1.291 (0.978-1.704)	**0.071**
Anaemia	63	19.873	2.115 (1.521-2.940)	**0.0001**	2.876	1.339 (0.956-1.876)	**0.090**
HF status[a]	397	105.586		0.0001	21.964		0.0001
New PHF during index admission	111	42.306	2.703 (1.998-3.657)	0.0001	6.820	1.528 (1.112-2.101)	0.009
New THF during index admission	67	1.216	1.224 (0.847-1.770)	0.282	1.519	1.266 (0.870-1.843)	0.218
Prior HF	71	44.198	2.779 (2.054-3.760)	0.0001	10.191	1.673 (1.220-2.295)	0.001
LV function status	275	57.164		0.0001	19.895		0.0001
LVSD[b]	224	45.111	2.957 (2.148-4.072)	0.0001	12.058	1.809 (1.295-2.527)	0.001
Not reported LV	275	15.077	1.598 (1.257-2.031)	0.0001	8.899	1.459 (1.138-1.869)	0.003
Sex (Female, n= 239)		19.847	0.582 (0.458-0.738)	0.0001	2.422	1.233(0.947-1.605)	0.120
Glomerular filtration Rate[c]	646	51.387	0.969 (0.960-0.977)	0.0001	4.053	0.991 (0.981-1.000)	0.044
Age (as a continues variable)	646	149.183	1.073 (1.061-1.085)	0.0001	44.007	1.048 (1.033-1.062)	0.0001

HR, hazard ratio; HF, heart failure; LV, left ventricular; THF, transient HF during index admission; PHF, persistent HF during index admission

*Anaemia status was according to last Hb available during index admission.

[a]with reference to No HF during index admission; [b]With reference to no left ventricular systolic dysfunction during index admission. [c]four-variable formula derived from the modification of diet in renal disease study (4V MDRD): [GFR= 186* (Creat/88.4)-1.154 *Age-0.203* 0.742 if female *1.212 if African Caribbean] were used to calculate glomerular filtration rate, In patients with no creatinine report during index admission (74 cases) median creatinine were used.

5.4 Discussion

This report confirms that anaemia is common in patients with AMI and is associated with the development of heart failure. Anaemia predicts a worse prognosis, largely because of its association with heart failure and renal dysfunction. Indeed, anaemia was rare in the absence of heart failure and, since ascertainment heart failure. The development of clinical heart failure rather than anaemia was the more powerful predictor of an adverse outcome but anaemia had some additional, independent prognostic value. In the absence of heart failure, anaemia had relatively little influence on prognosis, although very few patients had definite anaemia but not heart failure. In patients with heart failure, the presence of 'definite' anaemia indicated a poor one-year mortality and the prognosis of 'borderline' anaemia was as poor as that of 'definite' anaemia in the longer term. Patients with definite anaemia were older and presumably frailer with more co-morbidities which may account for why a higher proportion of deaths were non-cardiac (59%), including due to cancer (19%), in this group.

Anaemia may just be associated with and a marker of heart failure, but the two conditions could also be causally linked. The cardiovascular system is designed, amongst other things, to supply enough oxygen to the metabolising tissues. Anaemia reduces the oxygen carrying power of the blood. The cardiovascular system can adapt first by extracting a higher proportion of oxygen, leading to a reduction in mixed venous oxygen saturation, and then by raising cardiac output. In an already damaged heart this may lead to heart failure. Anaemia may also be a sign of iron deficiency and iron deficiency can impair metabolism of both cardiac and skeletal muscle and other metabolic processes requiring iron [146]. Widespread use of aspirin could be responsible for an epidemic of mostly subclinical duodenal ulceration [26 147] leading to iron deficiency amongst patients with known coronary artery disease [26 127]. Chronic cardiac dysfunction is associated with anaemia. This is often due to iron

deficiency and again may be aspirin related or related to reduced absorption in the gut either due to mucosal dysfunction or hepcidin overproduction [148] that prevents iron transport. Heart failure is also linked to cytokine activation that may lead to bone marrow resistance to the effects of erythropoietin. Heart failure is also associated with renal dysfunction which may lead to inadequate production of erythropoietin [149]. Thus, heart failure and anaemia may reflect yet another set of 'vicious cycles' where worsening of one condition begets worsening of the other.

A further possible cause of anaemia in the setting of AMI is cardiac dysfunction causing salt and water retention leading to plasma volume expansion and a reduction in haemoglobin concentration without a reduction in red blood cell mass [150]. This might be expected to progress as heart failure develops and might improve with plasma volume contraction in response to diuretic therapy. Anaemia appears more prevalent around the time of decompensation of heart failure [151] and haemoglobin often rises after re-compensation after discharge. Treatments given for AMI, including ACE inhibitors [152] and carvedilol [153] will often cause a modest fall in Hb and yet improve prognosis rather than make it worse. The reasons why these agents cause a fall in Hb is controversial but may simply due to arterial and, more importantly, venous relaxation leading to plasma volume expansion[154]. ACE inhibitors may also interfere with erythropoietin production [155]. Major haemorrhage due to the use of anti-thrombotic and thrombolytic interventions is associated with an adverse prognosis [156].

5.5 Study limitations

The survey was of patients managed in 1998. Significant changes in prevention and management have occurred and may have altered outcome. Not all patients had LV function

assessed. Patients with less severe heart failure may not have received loop diuretics and it is possible that not all patients who received a loop diuretic were identified. Also, since systematic attempts were not made to withdraw diuretics, we may have under-estimated the transitory nature of heart failure in some cases. A simple, robust definition of heart failure remains elusive. However, patients who receive loop diuretics and who have cardiovascular disease clearly have a poor prognosis whether or not they have a low ejection fraction[26]. Ultimately, heart failure is a clinical syndrome that relies on a doctor's skill in assessing a patient in the light of appropriate investigations.

We obtained measurements of Hb predominantly from only one time-point. Only a minority of patients had a second measurement of Hb (Table 5.1). Hb may vary with the progression of heart failure, the impact of cardiovascular therapies, the availability of haematinics and changes in plasma volume. Serial measurement of Hb during admission and subsequent follow-up may have demonstrated a stronger link between anaemia and prognosis [157].

Another potential limitation of our analysis is that patients who died early had less opportunity to recover or to develop late-onset heart failure. It is unclear how useful attempts at adjusting for this problem would be.

We did not collect information on haematinic deficiencies, although in patients with cardiovascular disease and anaemia, iron deficiency is common as is a normochromic normoytic anaemia without associated deficiency in iron or vitamin B12 or folic acid. The latter is often associated with renal dysfunction and an increase in inflammatory markers such as C-reactive protein and termed 'anaemia of chronic disease'. Neither did we collect serial information on medical therapy to investigate changes over time that might have been associated with anaemia. Such analyses are complex to do and even more complex to interpret. For instance, a patient with anaemia may be more likely to be taking aspirin, which

can cause blood loss and iron deficiency, but may also be more likely to stop aspirin because they have become anaemic. Sorting out which is the ‘chicken’ and which is the ‘egg’ may be impossible in an observational study.

5.6 Conclusion:

In conclusion, in patients with AMI, anaemia is associated with a greater risk of developing HF. Most patients who die in the six years subsequent to an MI first develop HF. Whether treatment for anaemia would alter the risk of developing heart and/or improve outcome awaits investigation.

6 Chapter 6: Utility of NT-proBNP to Identify Left Ventricular Dysfunction and Adverse Prognosis in Patients with a Prior Myocardial Infarction

6.1 Introduction

Myocardial infarction is a common cause of cardiac dysfunction, which is a major determinant of subsequent prognosis. Patients with severe myocardial damage often die in the acute phase or go on to develop heart failure. Ventricular dysfunction and heart failure may resolve if myocardial stunning rather than necrosis is extensive. On the other hand, ventricular dysfunction and heart failure may develop as a late complication of myocardial infarction either due worsening ventricular function due to recurrent ischaemic damage or adverse ventricular remodelling or due to the development of other complications such as atrial fibrillation or renal dysfunction. These complex and competing risks make it difficult to predict the prevalence of chronic left ventricular systolic dysfunction (LVSD) or heart failure amongst long-term survivors of a myocardial infarction.

Amino-terminal pro-brain natriuretic peptide (NT-proBNP) is a powerful predictor of an adverse prognosis in the setting of an acute myocardial infarction partly reflecting it's strong association with LVSD [50 51]. Patients with both LVSD and an elevated NT-proBNP in the setting of an acute myocardial infarction are reported to have a worse outcome compared to those with either LVSD or an elevated NT-proBNP alone [54].Several studies have shown that measurement of natriuretic peptides are of limited value in identifying patients with left ventricular systolic dysfunction remote from the time of myocardial infarction, although normal values generally exclude severe LVSD[64 65]. Natriuretic peptides may reflect other factors including LV diastolic dysfunction, atrial fibrillation, cardiac valve disease and renal

dysfunction. Also, assessment of cardiac function is prone to large observer errors[67]. None of these reports provide information on the utility of measuring NT-proBNP in long-term survivors of myocardial infarction as a convenient and inexpensive means of monitoring cardiovascular risk. We set out to determine the utility of NT-proBNP alone and in conjunction with other clinical data, as a marker of cardiac dysfunction and prognosis in patients who had survived a myocardial infarction for approximately 6 years.

6.2 Method

6.2.1 Study population

The Hull and East Yorkshire Hospitals (UK) serve a population of approximately 560,000 people. Patients with a discharge diagnosis of acute myocardial infarction during 1998 were identified from the Hospitals Information Department. All patients who were alive by May 2004 and lived in Hull were invited for assessment during 2004 and 2005 for:

- Medical history
- Symptom and quality of life assessment using the Euro Heart Failure Questionnaire[158]
- Physical examination
- Blood tests for standard haematology, biochemistry and lipid profiles, glucose and NT-proBNP. Venous blood was drawn after 15 min at rest and either sent to the hospital routine laboratory or, for NT-proBNP, immediately centrifuged at 4^{o}C (Termo centra CL3R) for 15 minutes at 3000 RPM (revolution per minute) and supernatant plasma stored within 30 minutes in 1.5ml cryovials at –80ºC until analysis. Plasma NT-BNP levels were determined using a commercial assay (Elecsys 2010, Roche analysis) with units given as pmol/L (1pmol/L = 8.457pg/ml).
- Electrocardiogram (ECG)

- Echocardiogram with Tissue Doppler Imaging (GE Medical, VIVID-5). Ventricular dimensions were measured by M-mode. Two-dimensional, apical two-and four-chamber views were taken for volume measurements and ejection fraction calculated by Simpson's biplane method. Left ventricular systolic dysfunction (LVSD) was defined as a left ventricular ejection fraction (LVEF) <40% or a qualitative report of moderate or severe LVSD on echocardiography[107]. Left atrial (LA) dimension was measured as the antero-septal diameter from the parasternal long axis view and considered as dilatated if >3.8cm. Valve disease was assessed by colour flow Doppler from multiple echocardiographic views. Mitral regurgitation was graded as mild, moderate or severe.

The case records of all patients were reviewed and followed-up until December 31st 2005. All-cause mortality was subsequently followed through the regional medical records system until 31st December 2009. Out of hospital deaths are automatically reported to the hospital. Survival was confirmed using patient centre (hospital electronic records) during 2010. The study was approved by the Local Research Ethics Committee. Patients who attended for review provided written informed consent.

6.2.2 Definition of Myocardial Infarction

At least two of the following five criteria had to be identified during case note review to confirm a diagnosis of MI.

1. History of prolonged cardiac chest pain.
2. An increase in biomarkers consistent with MI, which in 1998 was usually creatinine kinase (CK) or CK-MB mass. These were considered abnormal if they were twice the upper limit of normal values.

3. Progressive electrocardiographic changes consistent with MI or new onset left bundle branch block.
4. Sudden unexpected death
5. Autopsy evidence of MI

6.2.3 Heart failure, LVSD, LA dilatation and valve disease

Heart failure was defined clinically either as signs and symptoms consistent with that diagnosis (principally breathlessness and signs of fluid retention) resulting in treatment with loop diuretics or patients who died shortly after developing evidence of major cardiac dysfunction, such as cases of cardiogenic shock or pulmonary oedema. Use of loop diuretics for the treatment of hypertension or renal failure was not included in the definition of heart failure. LVSD was not required for a diagnosis of heart failure. Patients who moved out of the region were excluded. Body mass index (BMI) was calculated weight/height^2.

6.2.4 Adjudication of Mode of Death

Death was ascribed to only one of the following primary modes: sudden cardiac death, heart failure, stroke, cardiovascular procedure related deaths, other cardiovascular, cancer, infection or other non-cardiovascular. Each mode other than the primary mode could also be reported as contributory. So, a patient with metastatic prostate cancer and heart failure but who had a high probability of survival for more than a year who then died suddenly would be reported as having a primary mode of sudden death but with heart failure and cancer as contributory factors.

6.2.5 Statistical Analysis:

Data were entered into a Microsoft Access database and analysed using SPSS (version 17.0). Continuously distributed data are presented as median and inter-quartile range. Categorical data are presented as percentages. Patients were classified according to the NT-BNP quartile during follow-up clinic and were compared by the Chi-squared test on 3 degrees-of-freedom. Key outcomes were the proportion of patients who had LVSD and all-cause mortality. Receiver operating characteristic (ROC) curves [159] were calculated for NT-proBNP. Cox regression was used to look at the relationships between all-cause mortality and a limited subset of the variables (age, sex, diabetes, NYHA, quality of life (QOL), systolic BP, AF, body mass index (BMI), haemoglobin (Hb), urea, NT-proBNP, left ventricular systolic dysfunction (LVSD), left atrial dilatation (LAD) and mitral regurgitation (MR). Serum urea, serum creatinine and eGFR were highly collinear and therefore only serum urea, which was most strongly associated with an adverse outcome on univariate analysis, was entered in the multi-variable model. All variables were included in the Cox model. The proportionality of hazards assumption was checked for all variables by residual inspection[72]. Follow-up time was censored at 31 December 2009. Goodness-of-fit was measured by the Wald Chi-squared statistic. Given the few deaths (n=36) QOL was considered as a continuous variable in the Cox models. Missing values for continuous variables were imputed by the median; for categorical variables inclusion of an additional category. An arbitrary level of 5% statistical significance (2-tailed) was assumed.

6.3 Results

6.3.1 Overall results

Of 896 patients with a confirmed myocardial infarction during 1998, 451 had died and 31 had moved out of the region leaving414who were alive and potentially available to participate in May 2004. These patients were invited to attend for follow-up. Overall, 189 patients (47%) attended but through administrative or laboratory errors measurement of NT-proBNP was obtained in only 175 patients. The median [and interquartile (IQR) range] of NT-proBNP was 35pmol/L [13 to 86pmol/L] (Figure 6.1 and Table 6.1).

Figure 6-1NT pro-BNP test in patients with myocardial infarction

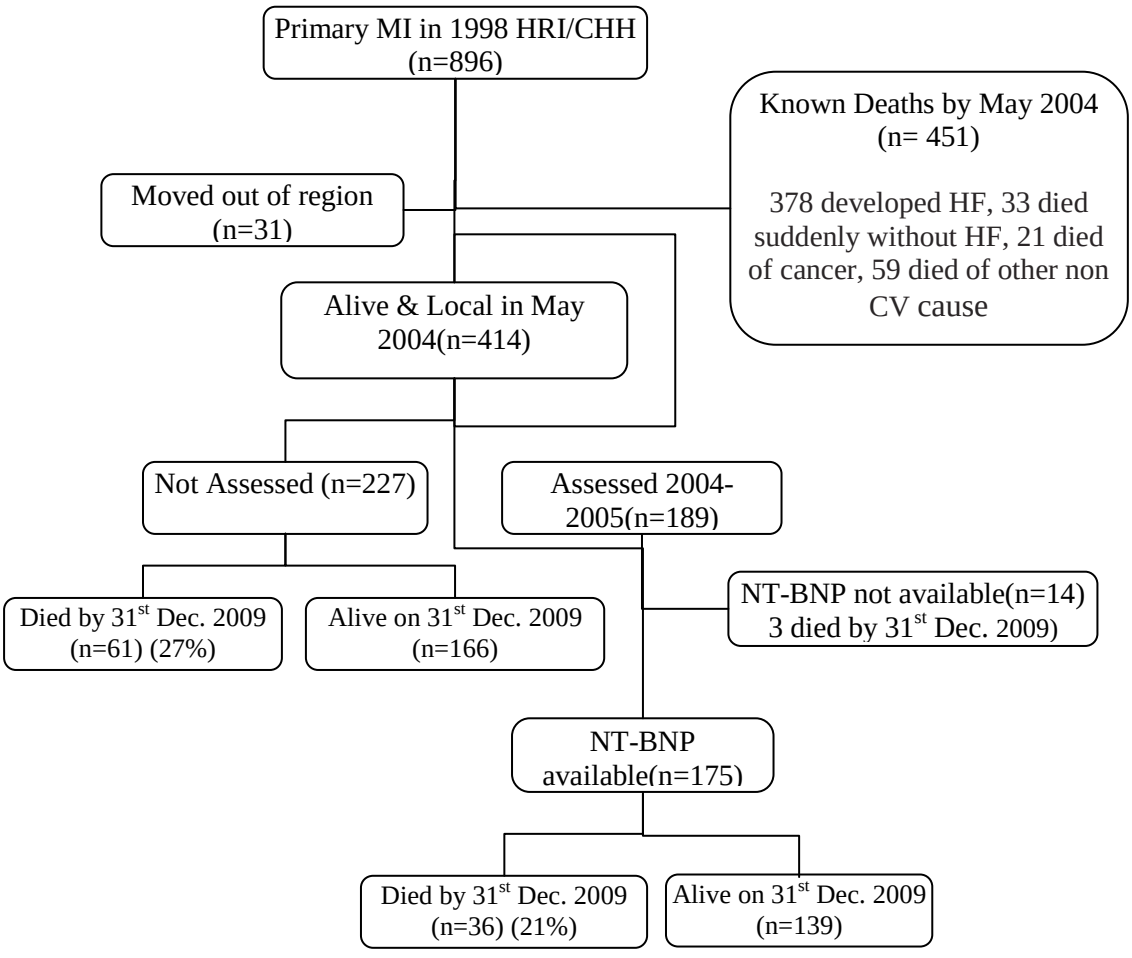


Table 6-1Patients Characteristics classified according to the NT-proBNP quartile

data are median (inter-quartile range) and number occurring (%). Assessments were conducted blind to NT-proBNP values.						
Variables (units) [patients with missing data]	**Overall**	**1st Quartile <13 pmol/L**	**2nd Quartile 13-35 pmol/L**	**3rdQuartile >35-86 pmol/L**	**4thQuartile>86 pmol/L**	**p-value**
n	**175**	**43**	**44**	**44**	**44**	
Age (years) [0]	68 (63-75)	64 (58-68)	67 (65-77)	69(65-75)	72 (67-77)	0.0001
Women [0]	42 (24%)	7 (16%)	13 (30%)	11 (25%)	11 (25%)	0.533
Current smoker [3]	31 (18%)	7 (17%)	9 (21%)	8 (19%)	7 (16%)	0.662
Ex-smoker	103 (60%)	29 (69%)	22 (52%)	26 (59%)	26 (59%)	
Non smoker	38 (22%)	6 (14%)	11 (26%)	10 (23%)	11 (25%)	
History of Hypertension	105 (60%)	17 (40%)	23 (52%)	35 (80%)	30 (68%)	0.001
History of Diabetes	32 (18%)	6 (14%)	4 (9%)	11 (25%)	11 (25%)	0.128
History of heart failure	73 (42%)	9 (21%)	13 (30%)	18 (41%)	33 (75%)	0.0001
History of SVT	35 (20%)	1 (2%)	3 (7%)	8 (18%)	23 (52%)	0.0001
Prior CABG	46 (26%)	4 (9%)	10 (23%)	13 (30%)	19 (43%)	0.004
Prior PTCA	49 (28%)	17 (40%)	12 (27%)	10 (23%)	10 (23%)	0.225
Clinic ECG						
Heart Rate	61 (54-70)	61 (56-68)	59 (51-69)	60 (53-68)	65 (54-82)	0.039
AF (yes/no)	19 (11%)	0	0	6 (14%)	13 (30%)	0.0001
Any Anterior Q-wave	28 (16%)	4 (9%)	9 (20%)	7 (16%)	8 (18%)	0.524
Other pathological Q-wave	52 (30%)	12 (28%)	16 (36%)	10 (23%)	14 (32%)	0.548
LBBB/Pace/ICD	24 (14%)	1 (2%)	3 (7%)	8 (19%)	12 (27%)	0.003
No Q-wave	71 (41%)	27 (63%)	16 (36%)	19 (43%)	10 (23%)	0.004
QRS $\geq$120 [23]	29 (17%)	3 (7%)	4 (9%)	7 (16%)	15 (34%)	0.002
Physical Examination						
NYHA I	94 (54%)	34 (79%)	27 (61%)	24 (55%)	9 (20%)	0.0001
NYHA II	60 (34%)	6 (14%)	13 (30%)	17 (39%)	24 (55%)	
NYHA III/IV	21 (12%)	3 (7%)	4 (9%)	3 (7%)	11 (25%)	
Body mass index [2]	27 (24-31)	28 (26-32)	28 (25-31)	27 (24-32)	25 (22-29)	0.066
Systolic blood pressure	139 (126-154)	140 (126-157)	138 (130-154)	141 (130-165)	133 (117-153)	0.578
Quality of life						
Overall health (Poor) #	38 (56%)	7 (16%)	8 (19%)	8 (19%)	16 (40%)	0.038
Overall quality of life (Poor) #	27 (16%)	4 (9%)	3 (7%)	5 (12%)	15 (37%)	0.001

Blood Tests						
Cholesterol [6]	4.2 (3.8-4.8)	4.4 (3.9-4.8)	4.3 (3.7-4.9)	4 (3.8-4.7)	4.2 (3.7-4.9)	0.881
Sodium [2]	140 (139-141)	140 (138-141)	140 (139-142)	140 (139-141)	140 (137-143)	0.954
Potassium [5]	4.3 (4.1-4.6)	4.2 (3.9-4.6)	4.4 (4.1-4.5)	4.4 (4-4.6)	4.4 (4.1-4.7)	0.143
Creatinine [2]	98 (85-118)	93 (81-101)	95 (84-106)	101 (81-117)	120 (100-144)	0.0001
Haemoglobin [1]	14.2 (13-15)	14.9 (14-15.5)	14.2 (12.9-14.9)	13.9 (13.5-14.7)	13.2 (12.2-14.7)	0.001
Anaemia [1]	34 (19%)	2 (5%)	10 (23%)	6 (14%)	16 (36%)	0.001
Urea [2]	5.8 (4.7-7)	5.2 (4.2-6)	6 (4.9-6.7)	5.6 (4.8-7)	6.9 (5.8-9.8)	0.0001
Glucose [6]	5.7 (5.2-6.6)	5.7 (5.2-6.9)	5.7 (5.2-6.6)	5.8 (4.9-6.7)	5.8 (5.4-7.4)	0.338
Outcome						
Death	**36 (21%)**	**3 (7%)**	**4 (9%)**	**6 (14%)**	**23 (52%)**	0.0001
Death if in Sinus Rhythm	**25 (14%)**	**3 (7%)**	**4 (9%)**	**4 (9%)**	**14 (32%)**	0.0019
Death within 12 months	8 (5%)	0	2 (5%)	0	6 (14%)	0.006
Death >12 to 36 months	15 (9%)	2 (5%)	1 (2%)	3 (7%)	9 (20%)	0.011
Cardiovascular Death	19 (11%)	1 (2%)	1 (2%)	6 (14%)	11 (25%)	0.0011
Heart Failure Death	8 (5%)	0	0	0	8 (18%)	0.0001
Sudden Death	12 (7%)	1 (2%)	1 (2%)	5 (11%)	5 (11%)	0.13
Non-cardiovascular death	17 (10%)	2 (5%)	3 (7%)	0	12 (27%)	0.026
Cancer Deaths	8 (5%)	2 (5%)	3 (7%)	0	3 (7%)	0.37

SVT, Supra ventricular tachycardia; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; LBBB/ Pace/ ICD, left bundle branch block or pace maker or intra cardiac device.
Patients ranked quality of life on a seven-point scale with the worst three ranks (quite poor, poor and very poor) counted as poor.

The median (IQR) age of 70 (61-78) years for the whole population at the time of the index myocardial infarction in 1998 was and 37% were women. The median (IQR) age of the 175 patients at the time of assessment was 68 (63-75) years and 42 (24%) were women. Prior histories of hypertension (n = 105; 60%), of transient or persistent heart failure (n = 73; 42%) and of diabetes (n = 32; 18%) were common. Q-waves were present on the ECG in 80 (46%) and left bundle brunch block (LBBB) in 18 patients, four patients were in a paced rhythm and two had implantable cardiac defibrillators (ICD).Patients in the highest quartile of NT-proBNP were, on average, older (p=0.0001) (table 6.1) and more often had a history of heart failure (p=0.0001), paroxysmal or persistent atrial fibrillation (AF) (p=0.0001) and CABG (p=0.005). These patients were more likely to receive warfarin, ACE-inhibitors, loop diuretics and digoxin (Table 6.2) and to have LVSD, left atrial dilatation and moderate or severe mitral regurgitation (Table 6.3). Indeed, 38 (88%) of patients in the highest quartile of NT-proBNP had one or more echocardiographic features of cardiac dysfunction or atrial fibrillation versus only 28% (mainly left atrial dilatation) amongst patients in the lowest quartile. In a logistic regression model the relationship between NT-proBNP quartile and LVSD and LA dilatation remained significant after adjustment for age and creatinine.

Table 6-2Treatment during follow-up clinic.

Variables (units) [missing data]	Overall	1st Quartile<13 Pmol/L	2nd Quartile 13-35 Pmol/L	3rdQuartile >35-86 Pmol/L	4thQuartile> 86 Pmol/L	p-value
N	**175**	**43**	**44**	**44**	44	
Treatments at f-up						
Aspirin	137 (79%)	38 (86%)	38 (84%)	37 (86%)	26 (59%)	0.003
Clopidogrel	16 (9%)	3 (7%)	5 (11%)	5 (11%)	3 (7%)	0.786
Warfarin [2]	16 (9%)	1 (2%)	1 (2%)	1 (2%)	13 (30%)	0.0001
Statin	149 (85%)	39 (91%)	40 (91%)	38 (86%)	32 (73%)	0.055
ACE inhibitors	86 (49%)	10 (23%)	19 (43%)	25 (57%)	32 (73%)	0.0001
ARBs##	14 (8%)	4 (9%)	5 (11%)	3 (7%)	2 (5%)	0.666
Beta-blockers	108 (62%)	22 (51%)	31 (71%)	30 (68%)	25 (57%)	0.197
Nitrates	38 (22%)	10 (23%)	8 (18%)	8 (18%)	12 (27%)	0.681
Nicorandil	18 (10%)	4 (9%)	3 (7%)	3 (7%)	8 (18%)	0.244
Calcium channel blockers	29 (17%)	10 (23%)	5 (11%)	5 (11%)	9 (21%)	0.309
Loop diuretic	53 (30%)	6 (14%)	8 (18%)	13 (30%)	26 (59%)	0.0001
Thiazide diuretic	13 (7%)	6 (14%)	2 (5%)	3 (7%)	2 (5%)	0.290
Digoxin	11 (6%)		1 (2%)	3 (7%)	7 (16%)	0.012
Oral hypoglycaemic agent	14 (8%)	4 (9%)	2 (5%)	6 (14%)	2 (5%)	0.331
ARBs, angiotensin–II receptor antagonists.						

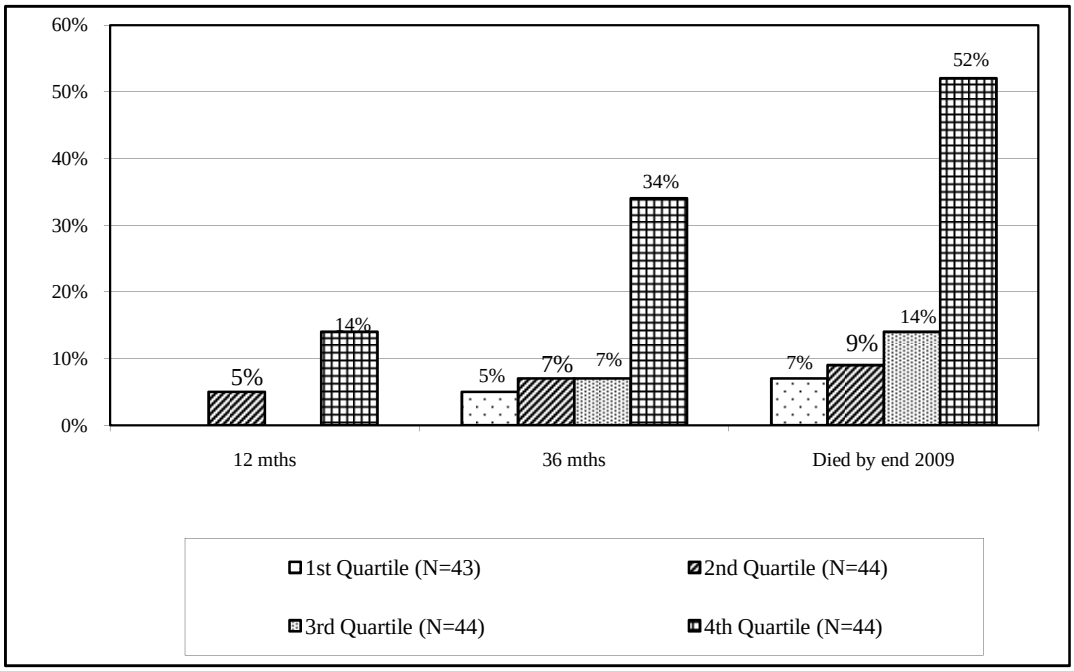
Table 6-3Imaging evidence of left ventricular function during follow-up clinic

Variables (units) [missing data]	Overall	1st Quartile< 13 Pmol/L	2nd Quartile 13-35 Pmol/L	3rdQuartile>35-86 Pmol/L	4thQuartile>86 Pmol/L	p-value for trend
N	**175**	**43**	**44**	**44**	44	
Echocardiography						
Major LVSD	51 (29%)	3 (7%)	9 (21%)	17 (39%)	22 (50%)	0.0001
Left atrial (LA) dilatation [9]	73 (44%)	9 (21%)	15 (38%)	22 (54%)	27 (63%)	0.0001
Moderate or severe mitral regurgitation [2]	20 (11%)	0	1 (2%)	2 (5%)	17 (36%)	0.0001
Moderate or severe disease of other valve[2]	14 (8%)	1 (2%)	3 (7%)	3 (7%)	7 (16%)	0.03
LVSD or Moderate or Severe Valve Disease [2]	63 (36%)	4 (9%)	12 (27%)	19 (45%)	28 (64%)	0.0001
LVSD or LA dilatation [6]	93 (57%)	11 (26%)	19 (48%)	29 (67%)	34 (79%)	0.0001
Any of the Above [6]	97 (57%)	12 (28%)	19 (48%)	29 (67%)	37 (86%)	0.0001
Any of the Above or AF	99 (59%)	12 (28%)	19 (48%)	30 (70%)	38 (88%)	0.0001
LVSD = left ventricular systolic dysfunction. Major is LVEF ≤40% either measured or semi-quantitatively. Other valve disease: moderate or severe tricuspid or pulmonary valve disease.						

6.3.2 Long-Term Follow-up

Median follow-up time was 1759 days (IQR 1548-1963). Of the 227 eligible patients who failed to attend the clinic or in whom no NT-proBNP value was obtained, 61 (27%) subsequently died. Of the 175 patients who had a measurement of NT-proBNP, 36 (21%) subsequently died prior to the 31st December 2009, of whom 23 (52%) were in the highest quartile of NT-proBNP (Figure 6.2). Twelve patients died suddenly, of whom 8 had heart failure, although this was severe in only one case. Five patients died primarily of progressive heart failure and it was contributory in a further four (one sudden death, one COPD deaths, one chest infection and one stroke death). Two patients died of stroke, six of infection (mainly pulmonary), eight of cancer and two died of other non-cardiac causes (dementia-related). All of the heart failure deaths occurred in patients in the highest quartile of NT-proBNP, while eleven of the twelve sudden deaths occurred in those with above median NT-proBNP. However, non-cardiovascular deaths were also more common in the highest quartile of NT-proBNP.

Figure 6-2Mortality within 12 month, 36months and by 31st December 2009 according to quartile of NT-proBNP (Median and IQR 35 (13-86) pmol/L)



Fifty one patients had LVSD of whom 31 (61%) also had an NT-proBNP ≥50 pmol/L (median and IQR 100 (80-367)pmol/L) and 20 did not (median and IQR 28 (19-37)pmol/L) (Table 6.4). Of 124 patients with no LVSD, thirty five patients (28%) had an NT-proBNP ≥50pmol (median and IQR 124 (66-199)pmol/L) and 89 did not (median and IQR (14 (8-27)pmol/L). Patients with an NT-proBNP ≥50pmol/L had a high mortality whether LVSD was present (42%) or not (43%). Patients with an NT-proBNP <50pmol/L had a lower mortality whether LVSD was present (10%) or not (7%). Indeed, only two of 109 patients with NT-proBNP <50pmol/L died within one year of assessment, compared to seven (11%) of 66 with NT-proBNP >50pmol/L. Echocardiography added little to the prognostic information provided by NT-proBNP alone (figure 6.3a, b and 6.4a, b).

6.3.3 ROC curve

Receiver-operator curves (ROC) suggest that 56pmol/L (474pg/ml) had the optimal sensitivity (78%) and specificity (77%) for predicting death (AUC 0.78, 95% CI=0.69, 0.87) (Figure 6. 4a). If only patients (n = 152) in sinus rhythm (25 deaths) were included, the cut-point was unchanged but sensitivity improved to 84% with some loss of specificity 68%. (Figure 6.4b).

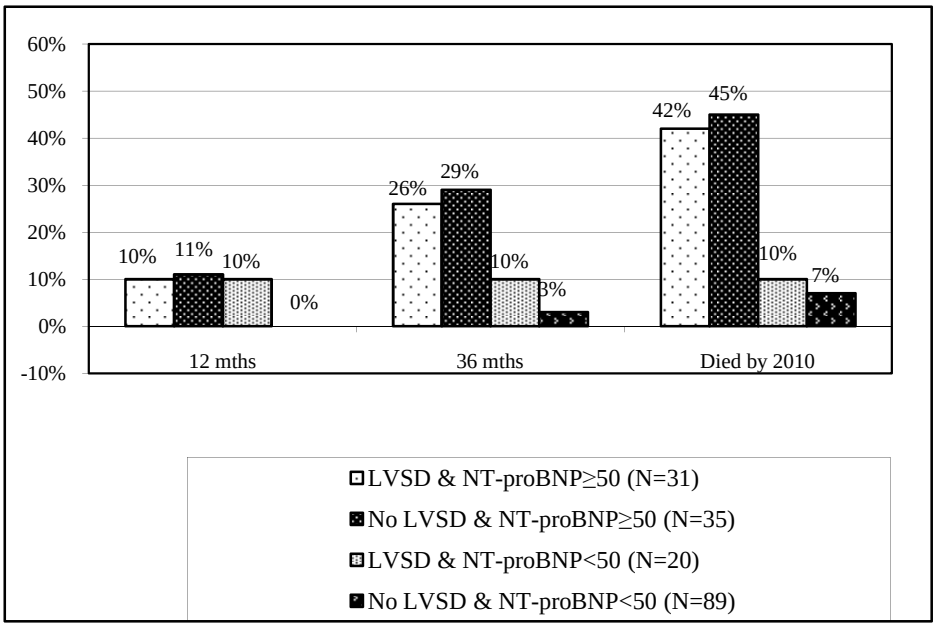
Table 6-4Patients Characteristics recorded during follow-up clinic overall and classified according to the LVSD Y/N and NT-proBNP >50

Variables (units) [missing data]	Overall	No LVSD with proBNP<25	NoLVSD with proBNP25-50	LVSD with proBNP<50	No LVSD &proBNP≥50	LVSD & proBNP ≥50	P-value
n	**175**	**64**	**25**	**20**	**35**	**31**	
Age (years) [0]	68 (63-75)	66 (60-70)	70 (66-77)	65 (61-72)	72 (67-80)	70 (66-75)	0.005
Women [0]	42 (24%)	15 (23%)	8 (32%)	4 (20%)	7 (20%)	8 (26%)	0.840
Current smoker [3]	31 (18%)	12 (19%)	3 (12%)	5 (26%)	4 (11%)	7 (23%)	0.607
Ex-smoker	103 (60%)	39 (63%)	16 (64%)	11 (58%)	23 (66%)	14 (45%)	
Non smoker	38 (22%)	11 (18%)	6 (24%)	3 (16%)	8 (23%)	10 (32%)	
History of Hypertension	105 (60%)	30 (47%)	16 (62%)	13 (65%)	27 (77%)	19 (61%)	0.055
History of Diabetes	32 (18%)	6 (9%)	3 (12%)	5 (25%)	12 (34%)	6 (19%)	0.102
History of heart failure	73 (42%)	18 (20%)	13 (28%)	11 (55%)	18 (51%)	25 (81%)	0.0001
History of SVT	35 (20%)	4 (6%)	2 (8%)	1 (5%)	17 (49%)	11 (35%)	0.0001
Prior CABG	46 (26%)	11 (17%)	3 (12%)	4 (20%)	14 (40%)	14 (45%)	0.005
Prior PTCA	49 (28%)	20 (31%)	5 (20%)	7 (35%)	11 (31%)	6 (19%)	0.593
Clinic ECG							
Heart Rate [1]	61 (54-70)	60 (55-64)	57 (51-68)	66 (54-72)	65 (56-74)	64 (58-81)	0.076
AF (yes/no)	19 (11%)	0	0	0	12 (34%)	7 (23%)	0.0001
Any Anterior Q-wave	28 (16%)	4 (6%)	6 (24%)	8 (40%)	2 (6%)	8 (26%)	0.0001
Other pathological Q-wave	52 (30%)	21 (33%)	7 (28%)	5 (25%)	14 (40%)	5 (16%)	0.282
LBBB/Pace/ICD	24 (14%)	2 (3%)	1 (4%)	5 (25%)	3 (9%)	13 (42%)	0.0001
No Q-wave	71 (41%)	37 (58%)	11 (44%)	2 (10%)	16 (46%)	5 (16%)	0.0001
QRS ≥120 [23]	29 (17%)	4 (6%)	2 (8%)	4 (20%)	7 (20%)	12 (39%)	0.0001
Physical Examination							
NYHA I	94 (54%)	52 (81%)	16 (62%)	7 (35%)	14 (40%)	5 (16%)	0.0001
NYHA II	60 (34%)	10 (16%)	8 (32%)	9 (45%)	16 (46%)	18 (58%)	
NYHA III/IV	21 (12%)	2 (3%)	1 (4%)	4 (20%)	5 (14%)	8 (26%)	
Body mass index [2]	27 (24-31)	28 (26-31)	28 (24-31%)	28 (25-32)	27 (25-30)	24 (22-28)	0.166
Systolic blood pressure	139 (126-154)	143 (130-154)	141 (132-165)	131 (113-144)	144 (133-159)	121 (115-151)	0.004
Blood Tests							

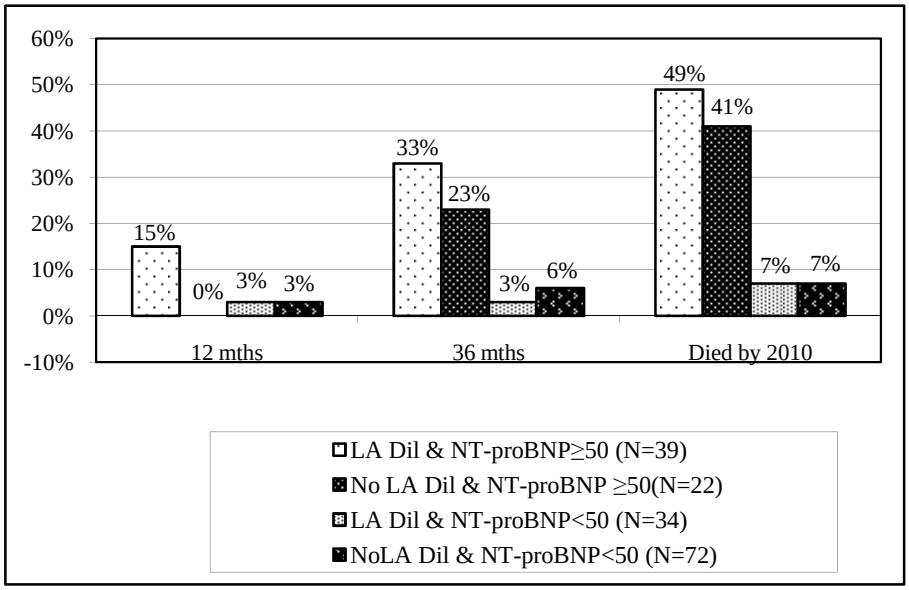
Cholesterol [6]	4.2 (3.8-4.8)	4.4 (3.9-4.9)	4 (3.7-4.6)	4.2 (4.1-4.8)	4.2 (3.8-5)	4.2 (3.7-4.8)	0.768
Sodium [2]	140 (139-141)	140 (139-141)	140 (140-142)	139 (138-141)	140 (139-142)	140 (138-141)	0.713
Potassium [5]	4.3 (4.1-4.6)	4.2(4-4.5)	4.4 (4.1-4.6)	4.4 (4.1-4.8)	4.4 (4.1-4.6)	4.4 (4.1-4.6)	0.313
Creatinine [2]	98 (85-118)	92 (82-1100)	96 (85-108)	104 (88-113)	113 (91-143)	114 (100-126)	0.0001
Haemoglobin[1]	14.2 (13-15)	14.6 (13.8-15.3)	13.9 (12.8-14.8)	13.8 (13.2-14.4)	13.6 (12.1-14.7)	14.2 (12.7-14.7)	0.010
Anaemia [1]	34 (19%)	4 (6%)	6 (24%)	5 (25%)	13 (38%)	6 (19%)	0.013
Urea [2]	5.8 (4.7-7)	5.4 (4.3-6.2)	5.8 (4.6-7.4	5.5 (5.1-6)	6.6 (5-9.4)	6.8 (5.7-7.8)	0.0001
Glucose [6]	5.7 (5.2-6.6)	5.6 (5.2-6.5)	5.8 (5.4-6.5)	5.9 (5.2-6.9)	6.2 (5.5-8.9)	5.6 (5.1-6.3)	0.162
Outcome							
Death	**36 (21%)**	**4 (6%)**	2 (8%)	**2 (10%)**	**15 (43%)**	**13 (42%)**	0.0001
Death within 12 months	9 (5%)	0	0	2 (10%)	4 (11%)	3 (10%)	0.068
Death >12 to 36 months	23 (13%)	3 (4%)	0	0	7 (20%)	5 (16%)	0.009
Death if in Sinus Rhythm	25 (14%)	4 (6%)	2 (8%)	2 (10%)	9 (26%)	8 (26%)	0.02
CV Death	19 (11%)	1 (2%)	1 (4%)	1 (5%)	10 (29%)	6 (19%)	0.002
Heart Failure Death	9 (5%)	0	0	0	5 (14%)	4 (13%)	0.0034
Sudden Death	12 (7%)	1 (2%)	1 (4%)	1 (5%)	6 (17%)	3 (10%)	0.051
Non-CV death	16 (9%)	3 (5%)	1 (4%)	1 (5%)	4 (11%)	7 (23%)	0.045
Cancer	8 (5%)	3 (5%)	1 (4%)	1 (5%)	0	3 (10%)	0.46

SVT, Supra ventricular tachycardia; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; LBBB/ Pace/ ICD, left bundle branch block or pace maker or intra cardiac device. CV = cardiovascular

Figure 6-3Mortality within 12 months, 36months and by end of 2009 according to (a) LVSD and (b) Lent atrial dilatation.



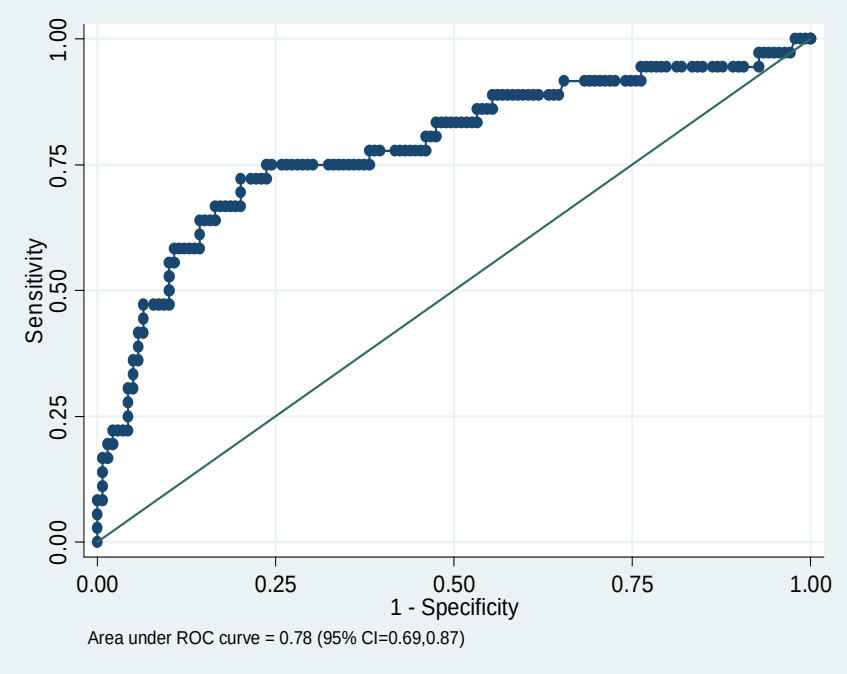
Mortality within 12 months, 36months and by end of 2009 according to LVSD and NT-proBNP ≥50 pmol/L (423 pg/ml)



Mortality within 12 months, 36months and by end of 2009 according to left atrial (LA) dilatation and NT-proBNP≥50 pmol/L (423 pg/ml)

Figure 6-4 ROC Curve for all-cause mortality by 2010

All patients n=175



Patients with sinus rhythm n=152

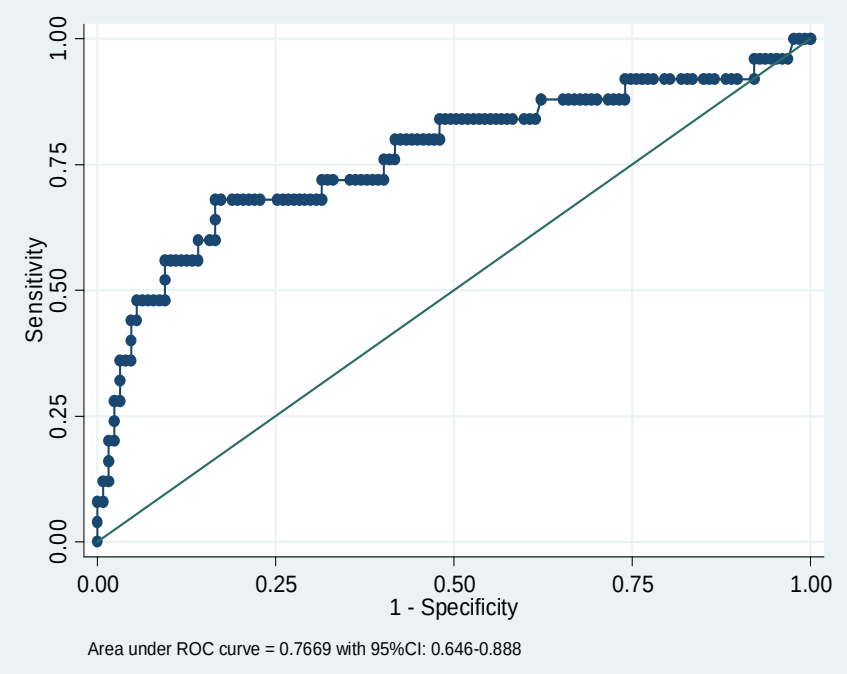


Table 6-5Cox-regression models predicting mortality in patients attended for follow-up clinic during 2004 and 2005 (n=175).

Variables ranked according to Wald χ^2 value on univariate analysis									
	Univariate			**Multivariable with BNP**			**Multivariable without BNP**		
Variable Name	**HR**	**Wald**	**P value**	**HR**	**Wald**	**P value**	**HR**	**Wald**	**P-value**
NT-proBNP (pmol/L)	1.004 (1.003-1.005)	44.178	0.0001	**1.003 (1.000-1.005)**	**4.397**	**0.036**			
NYHA III	7.572 (3.682-15.573)	30.278	0.0001	**4.497 (1.359-14.878)**	**6.065**	**0.014**	**4.636 (1.450-14.827)**	**6.688**	**0.010**
Quality of life	1.807 (1.462-2.232)	30.024	0.0001	**1.628 (1.137-2.331)**	**7.079**	**0.008**	**1.770 (1.240-2.524)**	**9.912**	**0.002**
Urea (mmol/L)	1.157 (1.079-1.241)	16.642	0.0001	1.052 (0.912-1.214)	0.492	0.483	0.981 (.867-1.111)	0.087	0.768
Haemoglobin (g/dl)	0.672 (0.554-0.816)	16.183	0.0001	**0.708 (0.538-.933)**	**6.026**	**0.014**	**0.669 (0.509-.881)**	**8.212**	**0.004**
Mitral regurgitation	4.282 (2.051-8.943	14.988	0.0001	0.582 (0.145- 2.336)	0.582	0.445	1.174 (.389-3.539)	0.081	0.776
Age (years)	1.070 (1.031-1.111)	12.803	0.0001	**1.077 (1.018-1.140)**	**6.646**	**0.010**	**1.083 (1.026-1.142)**	**8.451**	**0.004**
Atrial fibrillation	3.713 (1.717-8.028)	11.118	0.001	0.319 (0.065-1.577)	1.964	0.161	0.780 (0.228-2.669)	0.157	0.692
NYHA II	3.653 (1.489-8.962)	8.006	0.005	1.895 (.539-6.659)	0.993	0.319	1.767 (.499-6.254)	0.779	0.377
Left atrial dilatation	2.316 (1.174-4.569)	5.874	0.015	1.917 (0.795- 4.622)	2.098	0.147	1.854 (.773-4.444)	1.914	0.167
LVSD*	1.951 (1.005-3.787)	3.902	0.048	1.037 (0.423- 2.539)	0.006	0.937	1.054 (0.442-2.515)	0.14	0.905
Systolic BP (mm/Hg)	0.985 (0.970-1.001)	3.549	0.060	0.993 (.975-1.011)	0.641	0.423	0.993 (.976-1.010)	0.670	0.413
Sex (Men)	1.197 (0.543-2.635)	0.198	0.656	**3.052 (1.146-8.130)**	**4.984**	**0.026**	**3.106 (1.162-8.306)**	**5.100**	**0.024**
Diabetes	1.074 (0.470-2.452)	0.029	0.886	1.780 (.726-4.366)	1.589	0.208	1.685 (.691-4.107)	1.318	0.251
BMI (wt/h^2)	0.998 (0.935-1.064)	0.005	0.943	1.000 (.992-1.008)	0.001	0.992	1.000 (.997-1.003)	0.001	0.981
LVSD; left ventricular fat, BMI, body mass index									

6.3.4 Cox regression

In a multi-variable analysis, the strongest predictors of survival were age, NYHA class, quality of life, haemoglobin and NT-proBNP. Neither echocardiographic variables nor measures of renal function provided additional prognostic information (Table 6.5). The strongest echocardiographic predictor of an adverse outcome was the presence of moderate or severe mitral regurgitation, followed by left atrial dilatation and only then by the presence of LVSD but none entered the multi-variable model. When NT-proBNP was removed from the model, the relationship between death and quality of life and with haemoglobin became much stronger but echocardiographic measures or renal function still did not enter the model. The presence of AF was a powerful univariate predictor of an adverse outcome, but after adjusting for NT-proBNP and, to a lesser extent, other variables tended to be associated with better outcomes.

6.4 Discussion:

This analysis suggests that screening long-term survivors of myocardial infarction using NT-proBNP may be a useful method to identify patients with an adverse prognosis in whom a more aggressive diagnostic and treatment strategy is justified. Blood for NT-proBNP can be taken in the community and by non-specialists and sent using routine transport as for other standard blood tests to a central laboratory or measured using a point-of-care device. About one third of patients will have an NT-proBNP $\geq$50pmol/L, of whom about 42% will die within the subsequent 3 years compared to only 7% in those with an NT-proBNP <50pmol/L. An NT-proBNP $\geq$50pmol/L identified all nine deaths where heart failure (100%) was the primary or contributory cause, nine of twelve (75%) sudden deaths and 11 of 16 (69%) non-cardiovascular deaths. In the United Kingdom, patients who have had a myocardial

infarction are assessed annually thereafter to assess cardiovascular status and risk by their family doctor, who will often not have specialist cardiology knowledge or skill. Testing for NT-proBNP is simple, relatively inexpensive and identifies an adverse outcome with greater precision than more complex and expensive tests, such as echocardiography. Accordingly, it might be considered for inclusion as part of this routine assessment. Whether it needs to be done annually or less frequently requires further evaluation.

Several previous reports [65 67 160] have suggested that NT-proBNP lacks sufficient sensitivity and specificity for the detection of LVSD to make it a useful clinical tool for clinical practice. The problem may lie with the deficiencies of cardiac imaging or in the way that it is reported rather than with NT-proBNP. Patients with LVSD and a normal NT-proBNP had a fairly good prognosis. None died of heart failure in the subsequent three years and only one died suddenly four months after the test. This may be because patients who have a normal NT-proBNP have less severe LVSD or because the report on the echocardiogram was inaccurate and a false-positive result. Conventionally, an elevated NT-proBNP in the absence of LVSD has been counted as a false positive. However, these patients have a poor outcome and the echocardiogram is usually not normal. Many of these patients have a dilated left atrium suggesting the presence of left ventricular diastolic dysfunction or mitral regurgitation. A prior history of hypertension was more common in patients with an elevated NT-proBNP and could be the cause of diastolic LV function. The diagnostic strength of NT-proBNP is its ability to identify patients with an adverse outcome for a variety of reasons, including both systolic and diastolic left and right ventricular dysfunction, atrial fibrillation, valve disease and renal dysfunction. The diagnostic weakness of NT-proBNP is its inability to distinguish the reasons why an adverse outcome is likely, which requires further investigation.

This study is rather small to draw confident conclusions about the ability of NT-proBNP to predict the mode of death. However, NT-proBNP appears to be a better predictor of death from progressive heart failure than of sudden death as reported previously in a large study [161]. It is rare for a patient to die of heart failure within the following few years unless NT-proBNP is grossly elevated[161]. NT-proBNP also identifies an increased risk of sudden death[162] but risk begins to rise when NT-proBNP is only modestly elevated. NT-proBNP was also a surprisingly good predictor of non-cardiovascular deaths and again this is consistent with reports that NT-proBNP is at least as good at predicting all-cause mortality as it is in predicting cardiovascular deaths [162], Patients with cancer or lung disease may be more likely to die if they have serious underlying heart disease, whilst lung congestion may be a substrate for lung infection. On the other hand, lung disease may cause pulmonary hypertension and right ventricular overload[39] and cancers may cause wasting, leading to cachexia and cardiac dysfunction [163].

An increase in NT-proBNP was associated with many adverse prognostic factors and may have little to add to them as noted in some other clinical settings[62]. However, NT-proBNP is simple to administer, relatively inexpensive and objective. The assay has high precision although day-to-day variation reflecting diet and other physiological variations may be substantial. NT-proBNP performed better when patients with atrial fibrillation were excluded from the model. Other data suggests that the relationships between NT-proBNP, other measures of cardiac function and prognosis are disturbed in the presence of atrial fibrillation. For a given plasma concentration of NT-proBNP, patients with atrial fibrillation will have less evidence of important cardiac dysfunction [164] and a better prognosis [162].

The prevalence of echocardiographic abnormalities and the risk of death both increase progressively as NT-proBNP rises. NT-proBNP is a continuous variable with a wide

distribution. The higher the NT-proBNP, the worse the outlook. Any threshold value used to identify disease or risk is, to some extent, arbitrary. Accordingly, it may be better to use a system of graduated risk rather than a single threshold. For instance, in our clinical practice, NT-proBNP <25pmol/L is considered low-risk and requiring no special actions while values ≥50pmol/L are of concern and require investigation. Values between 25-50pmol/L are considered a 'grey-zone' requiring repeat NT-proBNP evaluation and more intensive control of traditional risk-factors rather than referral for further investigation.

This analysis has many limitations. Many patients died prior to the study. Other studies show that NT-proBNP is a powerful marker when measured early after a myocardial infarction [50 51]. A major limitation of this analysis is that 54% of surviving patients did not attend. Mortality in this group was 27%; very similar to that observed in the studied cohort (21%). The number of deaths in this analysis is relatively small and therefore we had limited statistical power [44 165].

6.5 Conclusion:

In patients who have had a myocardial infarction and survived several years, an elevated NT-proBNP identifies those with an adverse prognosis in whom investigation and more intensive treatment may be justified. Echocardiography provides little or no additional prognostic information but may inform therapeutic choices.

7 Chapter 7: The Incidence and Outcome of Patients Hospitalised for Acute Coronary Syndrome in 2005. The Hull Infarction Project.

7.1 Background

Although acute coronary syndromes (ACS), including myocardial infarction (MI), are common, there is a lack of robust epidemiological data about their incidence [74]. Case ascertainment and selection could have a major impact on incidence and outcome statistics. This creates difficulty in planning appropriate resources, doubt about the efficacy of coronary prevention at a population level and uncertainty about the overall effectiveness of management of acute coronary syndromes.

In late 1998 the United Kingdom launched the Myocardial Infarction National Audit Project (MINAP) and required all hospital trusts to report all MIs initially and subsequently a much broader range of patients [166]. Between 2000 and 2002, more than 100,000 cases had been reported to MINAP [167 168]. These reports suggest that the quality of care for ACS in the UK is good or excellent. However, there are deep concerns about the completeness of the MINAP returns and case-selection which could distort the true pattern of care.

We conducted a retrospective audit of all patients coded for MI in our region in 1998. This identified 896 patients of whom 562 (63%) developed heart failure and 480 (54%) died during approximately six years' follow-up [107]. We now report a new audit of MIs occurring in 2005 from the same region using the same and three additional methods for case-ascertainment. This gave us the opportunity of comparing the hospital incidence of MI using three different approaches and of making a historical comparison from the same region at a time of major changes in treatment and services.

7.2 Methods

7.2.1 Study population

One hospital group in Hull and the East Riding of Yorkshire (UK) provides all the acute cardiac services for about 560,000 people, of whom about 300,000 are aged >35 years, living in a geographically distinct part of the United Kingdom. Patients who were transferred from another region were excluded from all analyses. The Hull Infarction Project (HIP-2005) employed specialist cardiac nurses to try to identify all patients with acute coronary syndrome (ACS) admitted during 2005to the acute assessment or cardiac monitoring units and other medical wards. Case records were reviewed to verify the medical diagnosis, use of loop diuretics, and concentrations of troponin T (TnT), which used a conventional (non high-sensitivity) assay at this time. Results of imaging tests were obtained whenever available and treatment at discharge was recorded. The hospital information department was asked to provide all death and discharge data for acute MI and patients reported to MINAP in 2005. We also received a report of all positive (>0.03ug/L) troponin T (TnT) tests done by the hospital laboratory, the sole provider of the service to the region. Survival status was recorded until 31st December 2008.

7.2.2 HIP-2005 Definitions

Acute coronary syndrome was defined as a diagnosis made by a cardiologist or, if the TnT was elevated, by a cardiac specialist nurse or a non-specialist doctor. ACS was sub-classified as an MI or unstable angina by cardiologists. When the cardiologist did not specify, patients who had an elevated TnT or ST segment elevation on the electrocardiogram were considered to have had a MI and those who did not were reported as unstable angina. Patients with sudden death or cardiac arrest that was considered likely to be due to an acute coronary

syndrome were included in the survey and considered to have had an MI if they had left bundle branch block or ST segment elevation or had a pre-existing increase in TnT.

Assessments of left ventricular function within one year of admission were recorded. Criteria for left ventricular systolic dysfunction were left ventricular ejection fraction (LVEF) < 40 % or a qualitative report of moderate or severe left ventricular systolic dysfunction on echocardiography, first-pass radionuclide ventriculography, or contrast angiography. TnT was defined as positive if >0.03ug/L and strongly positive if >1.0ug/L.

7.2.3 MINAP criteria:

MINAP seeks to enrol all patients with symptoms suggestive of an acute coronary syndrome admitted to hospital in England and Wales (population about 50 million)[169], although we suspect, in practice, that many hospitals report only patients who have been considered for thrombolysis or coronary intervention. From January 2004 until March 2005, 88,782 patients were reported to have had an MI by MINAP [170] although only 49,116 discharges were reported from March 2008 until March 2009 [171]. The discharge diagnosis of ACS is made by the medical staff caring for the patient in the light of standard investigations including clinical history, ECG and troponin. Patients' data are entered by clinical audit staff into a central database [131 169].

7.2.4 Hospital Coding System:

The coding department has specialised coding staff who review and code the case-notes of all deaths and discharges regardless of cause, including data from post-mortem examinations. The codes are used to generate central returns to the NHS and for reimbursement. Acute MI was coded as I21 and complications following acute MI as I23. These codes are recorded on an electronic patient administration system.

7.2.5 Laboratory-positive troponin T (TnT):

TnT (Roche Diagnostics) is only measured in a single laboratory in the region. All results are stored on an electronic data-base. Values >0.03ug/L are considered positive.

7.2.6 Statistical Analysis

Data were entered into a Microsoft Excel database then imported into Access database and analysed using SPSS (version 16.0). Categorical data are presented as percentages. Continuously distributed data are presented as median and inter-quartile range (IQR). Estimating the probability of death at day 30, one year and three years was calculated by using moving average estimator curves in patients who had TnT report after dividing them into patients with and without a diagnosis of ACS.

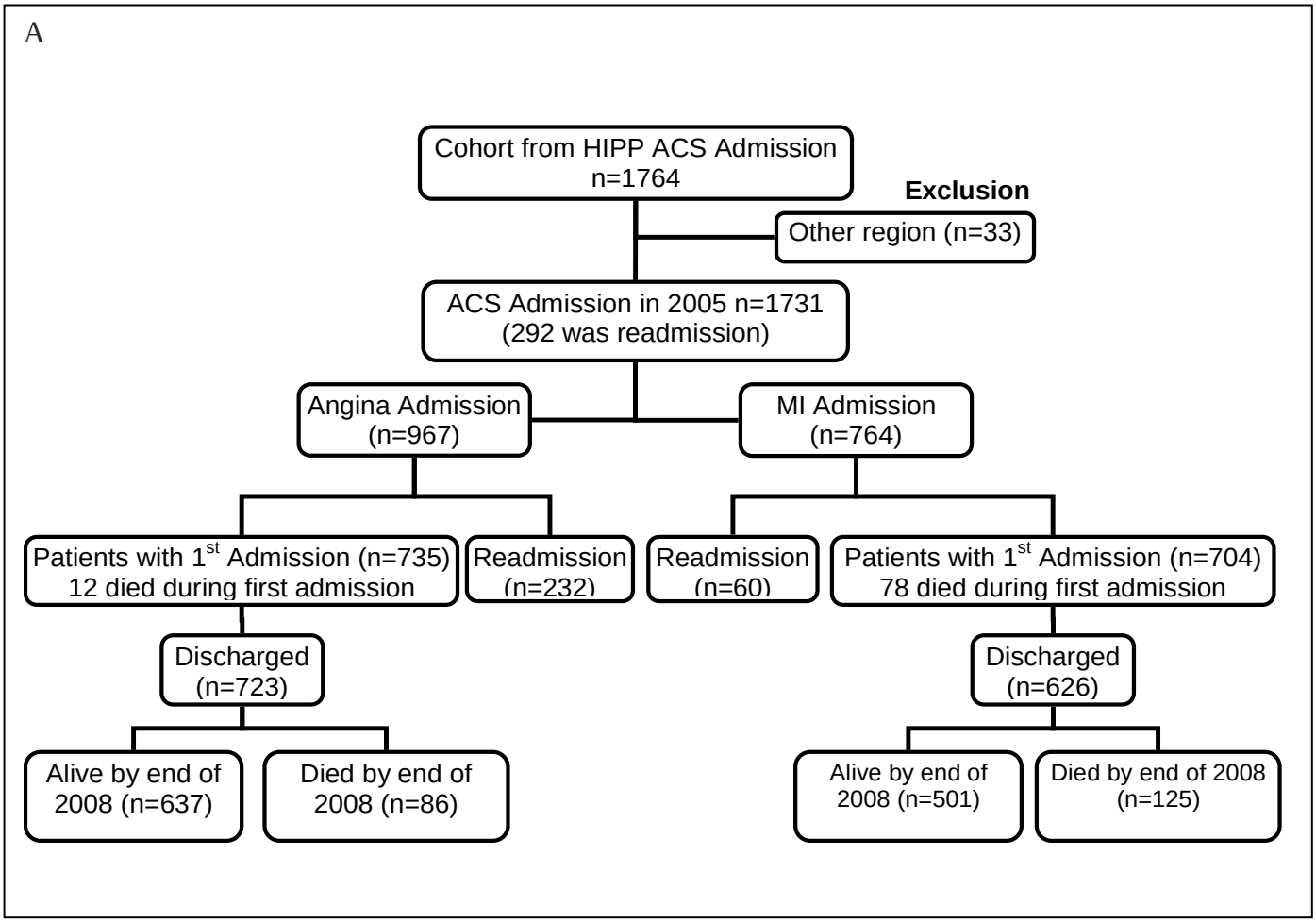
7.3 Results

7.3.1 Overall Results

Of 1764 admission identified with ACS by HIP-2005, 33 were excluded from further analysis because they had been transferred from another region. This left 1439 unique patients with 1731 admissions for the main analysis, of which 292 were readmissions within the same year, including 148 with one readmission and 55 with multiple readmissions. Of the 1,731 admissions identified in HIP-2005, 764 (704 patients and 60 readmissions) were classified as MI and 967 (735 patients and 232 readmissions) as angina (Figure 7.1a). Of 1,439 patients with ACS identified by HIP-2005, there was a prior history of hypertension in 541 (38%), MI in 246 (17%) and diabetes in 227 (16%). During the index hospitalization, only about half were managed, at least in part, by a consultant cardiologist and only 199 (14%) patients had percutaneous transluminal coronary angioplasty (PTCA).

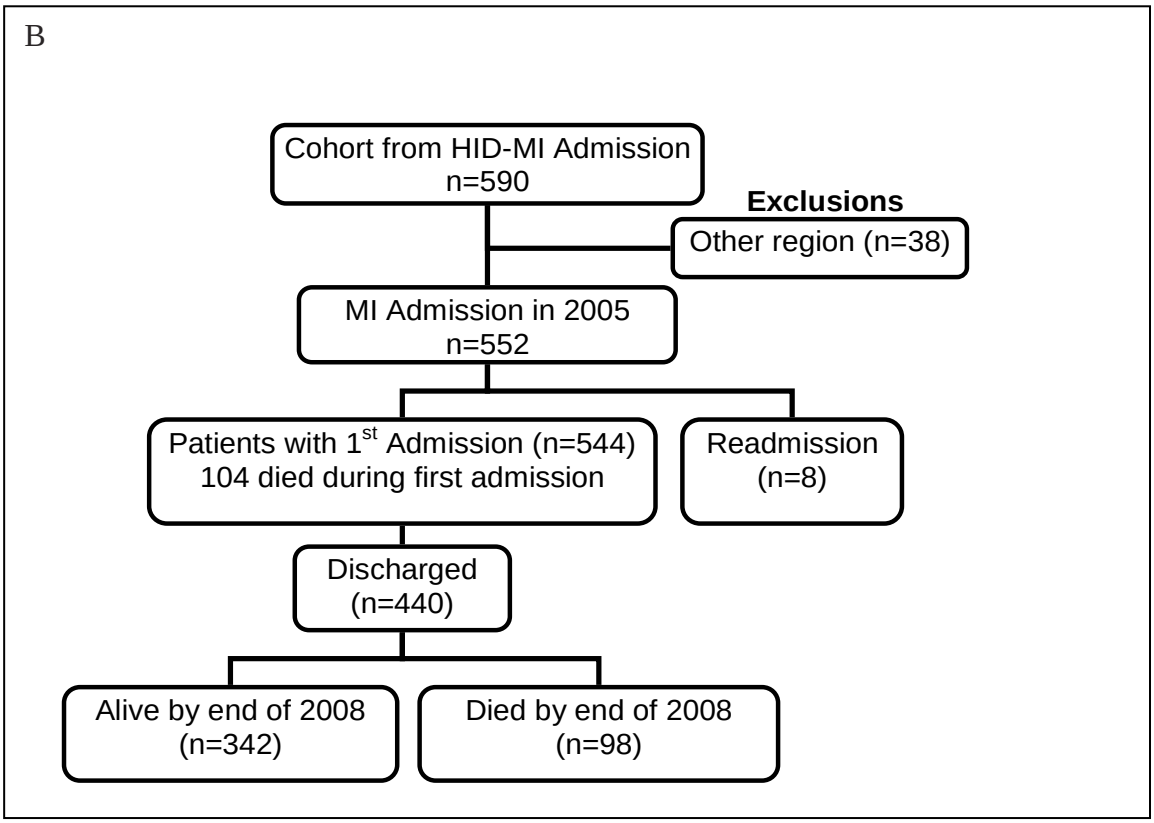
Using the hospital information department, only 552 admissions with MI (544 patients and 8 readmissions) were identified and using MINAP, only 206 admissions (203 patients and 3 readmissions) for MI. (Figure 7.1b and c).

Figure 7-1Incidence of ACS and myocardial infarction (MI) in (a) HIP, (b) HID and (c) MINAP

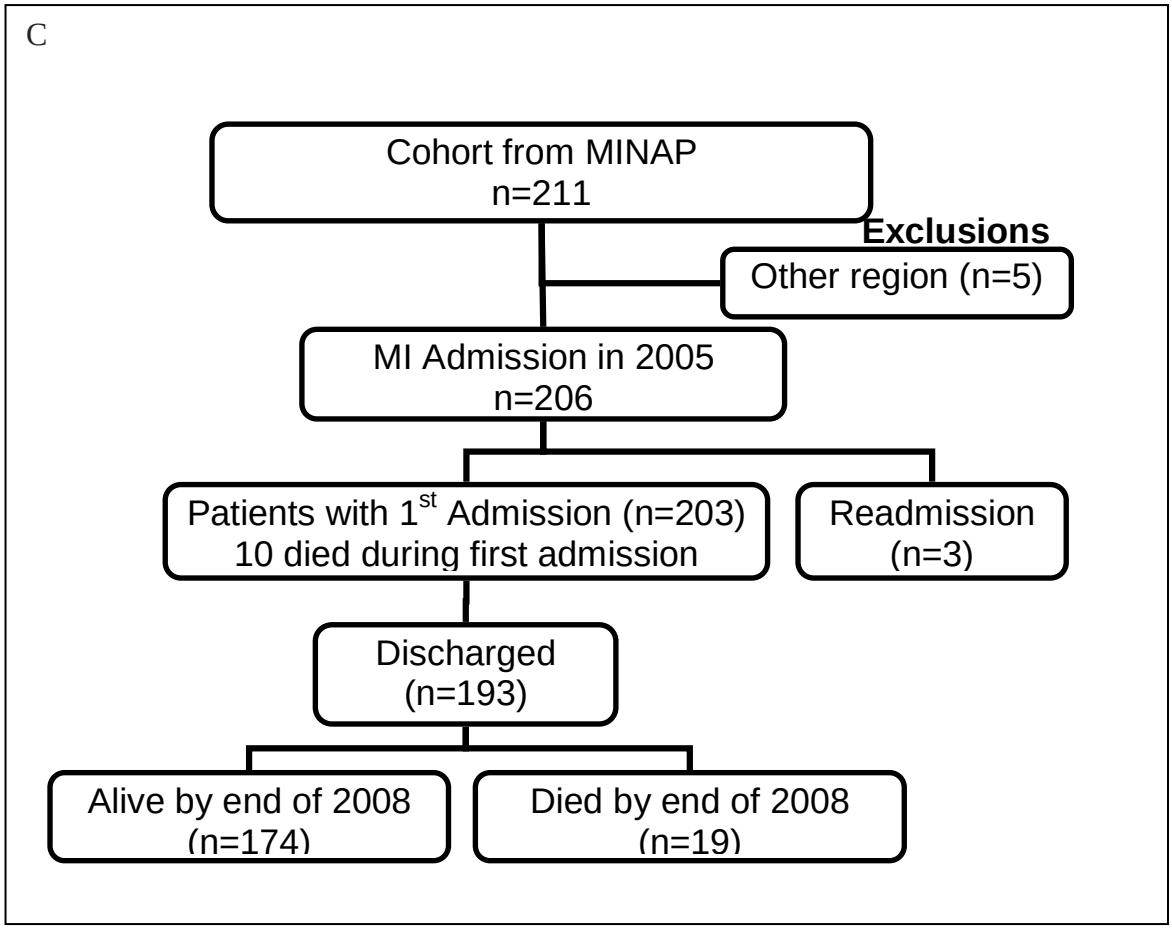


Flow diagram showing the incidence of ACS and myocardial infarction (MI) identified by (A) the Hull Infarction Project (HIP), (B) the Hospital Information Department (HID), (C) the Myocardial Infarction National Audit Project (MINAP) and (D) Laboratory report of troponin T (TnT) during 2005 and sequence of mortality until end of 2008. See text for details

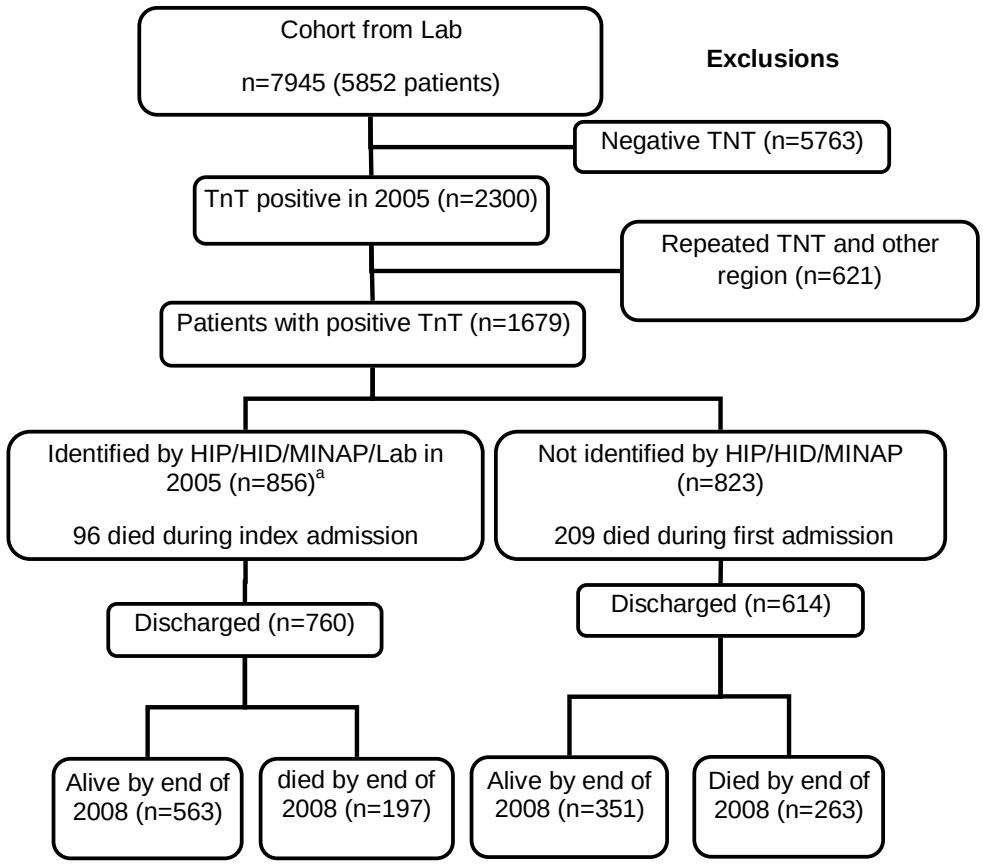
B


Cohort from HID-MI Admission
n=590
Exclusions
Other region (n=38)
MI Admission in 2005
n=552
Patients with 1st Admission (n=544)
104 died during first admission
Readmission
(n=8)
Discharged
(n=440)
Alive by end of 2008
(n=342)
Died by end of 2008
(n=98)

C

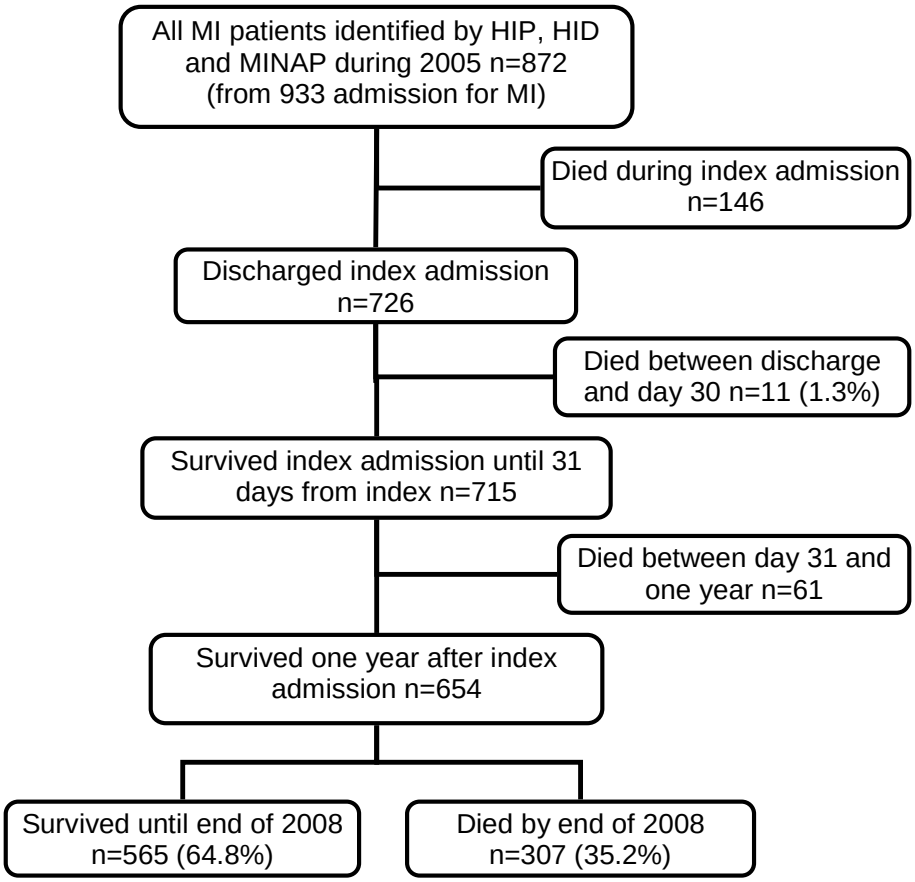

Cohort from MINAP
n=211
Exclusions
Other region (n=5)
MI Admission in 2005
n=206
Patients with 1st Admission (n=203)
10 died during first admission
Readmission
(n=3)
Discharged
(n=193)
Alive by end of 2008
(n=174)
Died by end of 2008
(n=19)

D



Of the 764 admissions (704 patients) identified by HIP-2005 with MI, 388 (381 patients) were also identified by hospital discharge codes and 186 (183 patients) by MINAP. Hospital discharge codes identified an additional 164 admissions (163 patients) with MI not identified by HIP-2005, of whom 140 patients had an elevated TnT, including 80 who had values >1.0ug/L. In addition, five patients were identified as MI by MINAP but not by other methods; two of these were identified as angina by HIP-2005, three had a negative troponin and two had no record of troponin being measured. Overall, the three methods of surveillance identified 933 admissions (872 patients) with MI and 1896 admissions (1,603 patients) with ACS (figure 7.2, 7.3a and 3b).

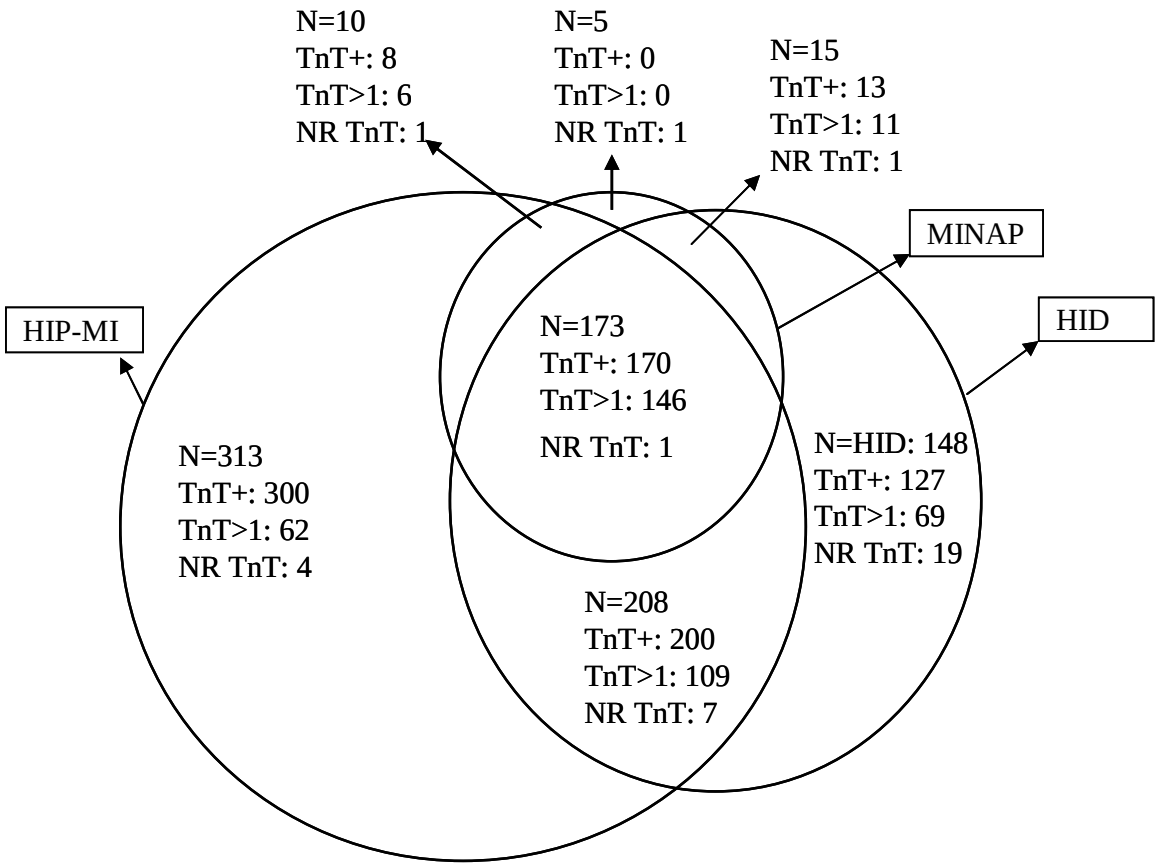
Figure 7-2Incidence of myocardial infarction in all three data-sets (HIP, HID and MINAP)



Flow diagram showing the incidence of myocardial infarction in all three data-sets (Hull Infarction Project (HIP), Hospital Information Department (HID) and the Myocardial Infarction National Audit Project (MINAP)) during 2005 and sequence of mortality during index admission, 30 days, one year and until 31 December 2008. See text for details.

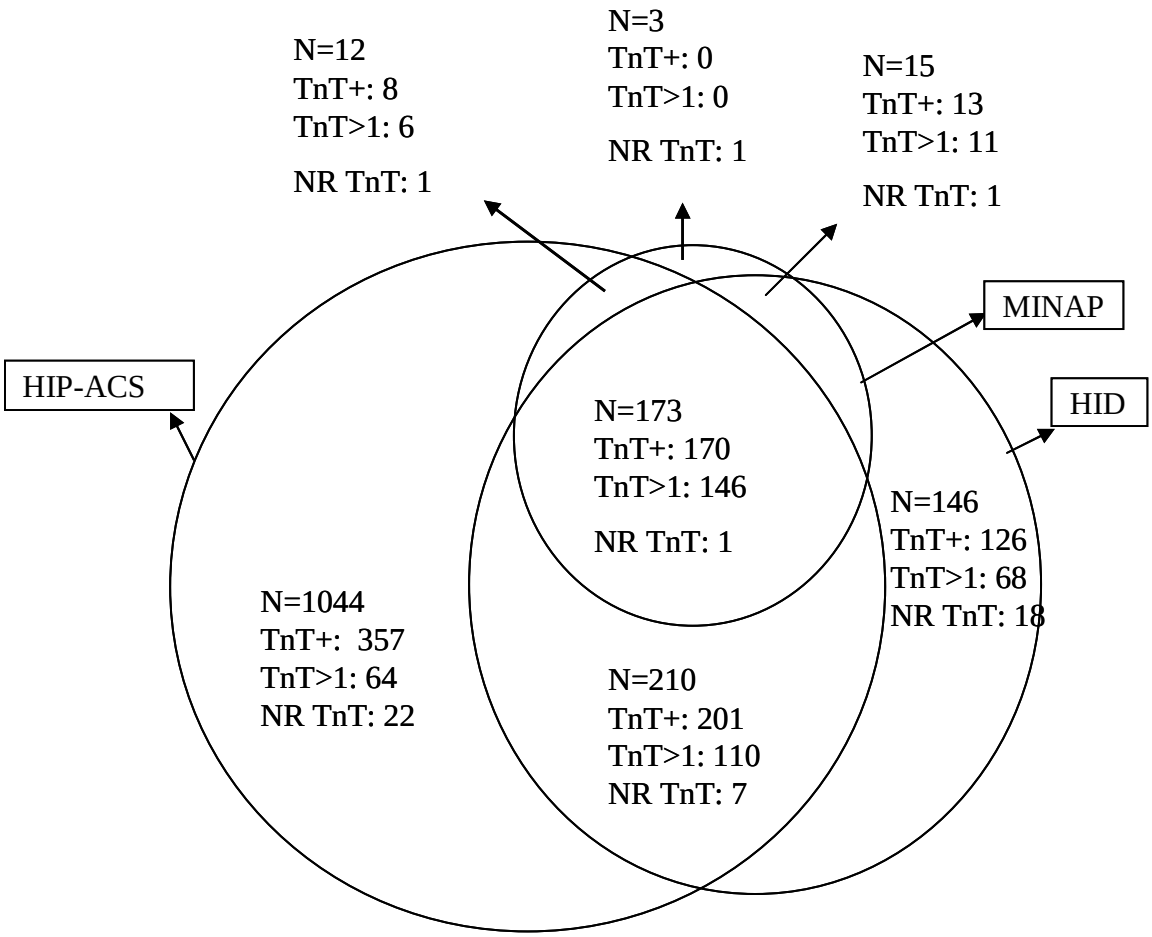
Figure 7-3patients with (a) MI and (b) ACS identified by HIP, HID and MINAP with highest TnT during any ACS admission in 2005

a:



Venn diagram showing patients with MI identified by the Hull Infarction Project (HIP) (n=704), patients with MI identified by the Hospital Information Department (HID) (n=544) and patients with MI identified by the Myocardial Infarction National Audit Project (MINAP) data (n=203) with highest troponin T (TnT) during any acute coronary syndrome admission in 2005, (positive (+ve), >1 and not reported (NR) TnT).

b:



Venn diagram showing patients with acute coronary syndrome (ACS) identified by HIP (n=1439), patients with MI identified by hospital information department (HID) (n=544) and patients with MI who identified by MINAP data (n=203) with highest troponin T (TnT) during any acute coronary syndrome admission in 2005. (positive (+ve), >1 or not reported (NR) TnT).

Table 7-1Patient characteristics recorded during the index admission

Data are median (inter-quartile range) and number occurring (%)						
Variables	ACS-HIP *[missing data]*	MI-HIP *[missing data]*	MI-HID*[missing data]*	MI-MINAP*[missing data]*	TnT +ve Only *[missing data]*	Any Case *[missing data]*
n	1439	704	544	203	823	2,426
Age (years)	67 (58-77)	69 (59-78)	71 (60-80)	65 (56-73)	77 (69-84)	72 (61-81)
Age>75-men	181 (21%)	113 (24%)	95 (27%)	18 (13%)	211 (47%)	440 (32%)
Age>75-women	224 (38%)	117 (49%)	102 (54%)	18 (29%)	250 (67%)	511 (50%)
Women	591 (41%)	241 (34%)	189 (35%)	63 (31%)	375 (46%)	1029 (42%)
TnT≥0.03ug/L	724 (50%) *[34]*	678 (98%) *[13]*	510 (99%) *[27]*	191 (96%) *[4]*	823	1698 (71%) *[51]*
TnT>1.0 [a] ug/L	324 (23%)*[34]*	323 (47%)*[13]*	335 (65%) *[27]*	163 (82%) *[4]*	85 (10%)	491 (21%) *[51]*
Loop Diuretic ug/L	305(21%)	162(23%)	n	15 (12%) *[81]*	n	n
Aspirin	1027 (71%)*[2]*	517 (74%)*[2]*	n	144 (97%) *[55]*	n	n
ACE inhibitor	589 (41%)*[1]*	374 (53%)*[1]*	n	121 (92%) *[71]*	n	n
Angiotension receptor blocker (ARB)	82 (6%)*[1]*	30 (4%)*[1]*	n	2 (3%) *[127]*	n	n
Beta-blocker	873 (61%)*[1]*	473 (67%)*[1]*	n	120 (91%) *[71]*	n	n
Aldosterone Antagonist	59 (4%)*[1]*	37(5%)*[1]*	n	5 (4%) *[82]*	n	n
Statin	979 (68%)	513 (73%)	n	132 (95%) *[64]*	n	n
Report on LV Function Available	703 *[736]*	409 *[295]*	293 *[251]*	125 [78]	298 *[525]*	1055 *[1371]*
LVSD	236 (34%)	173 (42%)	142 (48%)	47 (38%)	134 (45%)	401 (38%)
In-Patient Mortality	87 (6%)	78 (11%)	104 (19%)	10 (5%)	209 (25%)	342 (14%)
30-day Mortality	96 (7%)	84 (12%)	101 (19%)	12 (6%)	187 (23%)	343 (14%)
One year Mortality	179 (12%)	134 (19%)	149 (27%)	19 (9%)	334 (41%)	597 (25%)
Overall Mortality by end of 2008	301 (21%)	203 (29%)	202 (37%)	29 (14%)	472 (57%)	877 (36%)
Any case, all ACS-HIP (MI and unstable angina in HIP), MI HID, MI MINAP and TnT +ve; ACS, acute coronary syndrome; MI, myocardial infarction; HIP, Hull Infarction Project; HID, Hospital Information Department; MINAP, Myocardial Infarction National Audit Project; TnT +ve, positive troponin T. Any case means a patient who belonged to any one of the other groups.						

The laboratory reported 7,945 TnT tests (2,300 with positive TnT) in 5,852 patients during 2005. After excluding patients from other regions, of 1679 patients with a positive TnT, 823 patients were not reported as ACS by any of the other three routes of ascertainment. Eighty five (10%) of these had values of TnT>1ug/L. These patients were older than other groups (Figure 7.1d and Table7.1).

The characteristics of the patients using each survey method are shown in table 7.1. The median age of the patients identified by HIP-2005 with ACS was 67 (interquartile range (IQR) 58-77) years, and with MI was 69 (IQR 59-78) years compared to 71 (IQR 60-80),65 (IQR 56-73) and 77 (IQR 69-84) years identified by HID, by MINAP and by a positive TnT only. The proportion of women in each group was 591 (41%), 241 (34%), 189 (35%), 63 (31%) and 375 (46%) respectively.

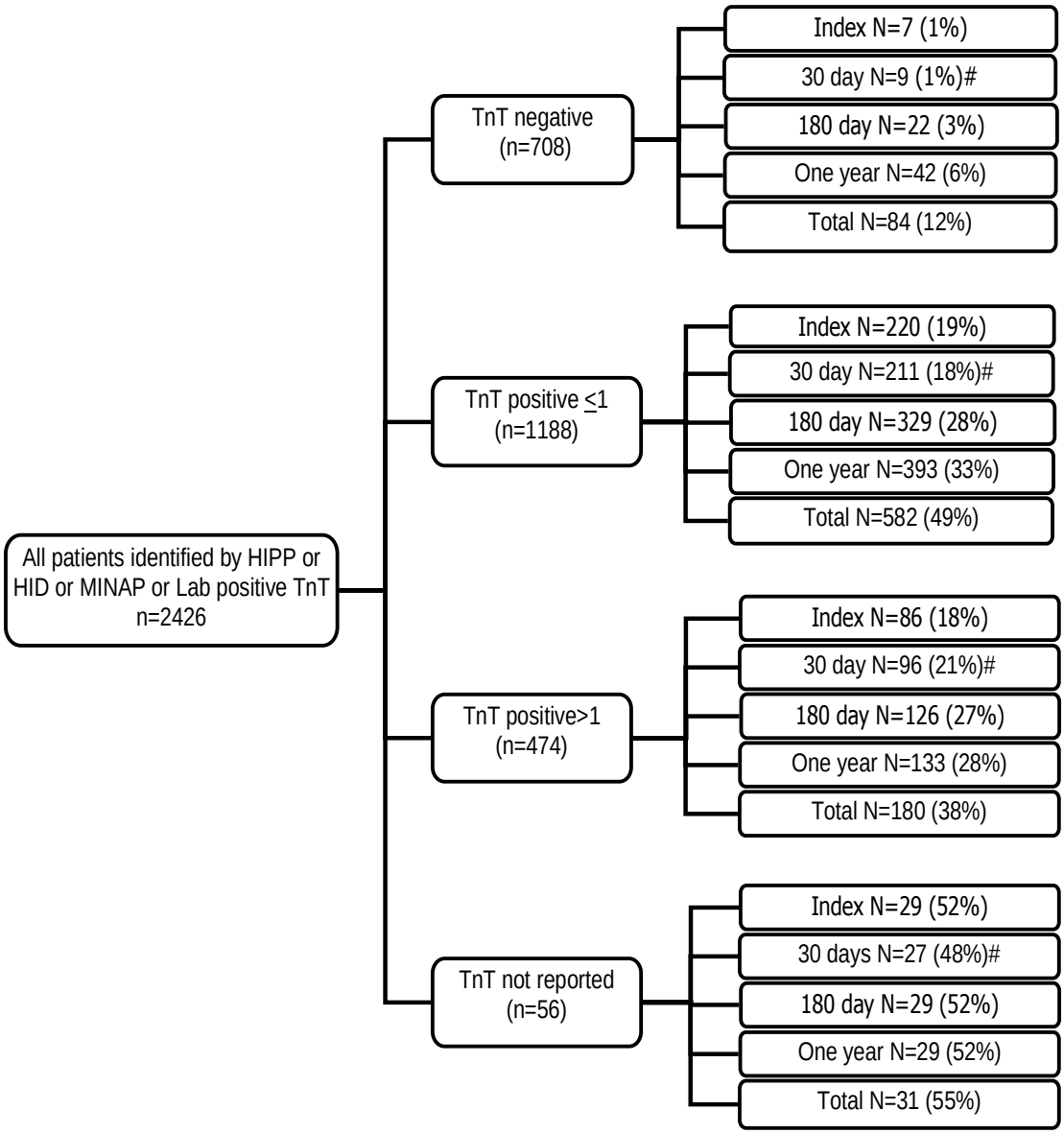
In HIP-2005, ST segment elevation (STEMI) was present in 328 (23%) patients on their first admission and an additional 9 patients had STEMI during readmission. Seventy one (5%) patients had left bundle branch block (LBBB), of whom 43were diagnosed as angina and 28 were managed as MI. Thrombolysis was given to 227 of 356 (64%) patients during their first admission and an additional 4 patients on readmission. The ‘door to needle’ time was available for228admissions and the median time was 30 minutes (IQR 20-63). This compares to 203 patients with STEMI or MI with LBBB identified by Hull MINAP (of whom three had a further readmission with STEMI), of whom 197 got thrombolysis with a door to needle time of 30 (IQR 20-51) minutes. Similar data were not available for patients identified by the hospital information department or laboratory TnT.

7.3.2 Mortality according Troponin T (TnT) during first admission in all patients identified by HIP-2005, HID, MINAP and Lab positive TnT

Overall 2,426 patients were identified by HIP-2005, HID, MINAP or a positive TnT as potentially having an ACS. Of these, TnT was ≤0.03ug/L in 708, >0.03 to 1.0ug/L in 1188, >1.0 ug/L in 474 and was not done in 56 patients (Figure 7.4). Of 708 patients with TnT≤0.03ug/L, 84 (12%) had died by 2009 of whom seven (1%) died during the index hospitalization and 42 (6%) during the first year. Of 1188 patients with TnT 0.04 to 1.0ug/L, 582(49%) patients had died by 2009of whom 220 (19%) died during the index hospitalization and 393 (49%) during the first year. Of 474 patients with TnT>1.0ug/L, 180 (38%) patients died, of whom 86(18%) died during the index hospitalization and 133 (28%) during the first year.

Of 1662 patients with an elevated TnT, only 839 (50%) were diagnosed with ACS by one of the survey methods. Of 1547 patients with ACS by at least one survey method, 708 (46%) had a negative TnT. There was a dramatic increase in mortality in patients with values of TnT>0.03ug/L but mortality was similar regardless of concentration above this level (Figure 7.5). Patients with a positive TnT who were not identified to have ACS by one of the survey methods had a worse prognosis (41%) at one year than those with ACS, whether they were TnT positive (23%; p=0.0001) or not (6%; p=0.0001). This was also true at 30 days and at 3 years (Figure 7.5).

Figure 7-4Mortality by end of 2008 from first admission in all patients with ACS

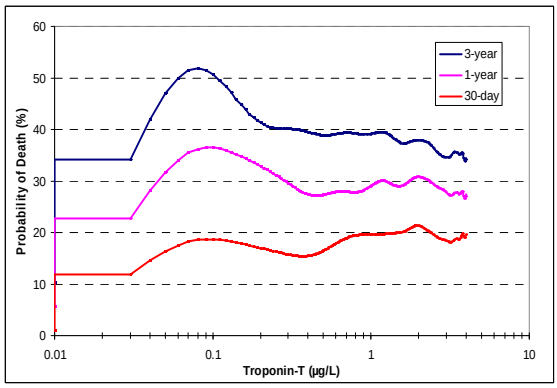


Mortality by end of 2008 from first admission in all patients with ACS identified by HIP, MI identified by HID, MINAP and positive Troponin T (TnT) during 2005 according to TnT measured during first admission.

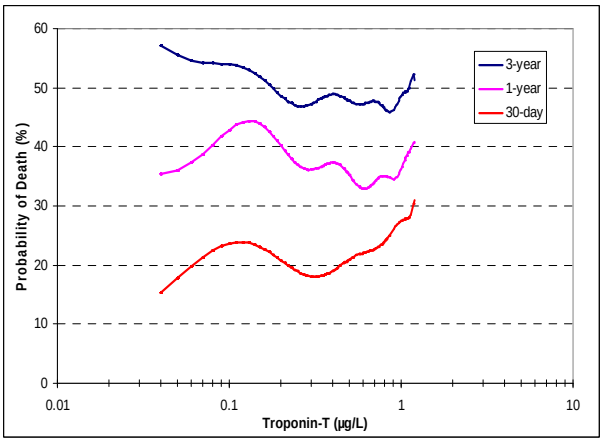
note that number may be smaller than for index admission because some people died during an index admission that lasted >30 days.

Figure 7-5Probability of death within 30-day, one-year and 3-yearaccording to the troponin T level during index admission

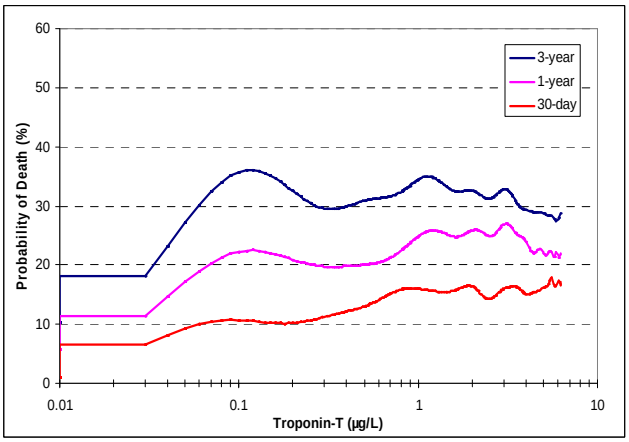
All Patients:



Patients with No Diagnosis of ACS:



Patients with Diagnosis of ACS:

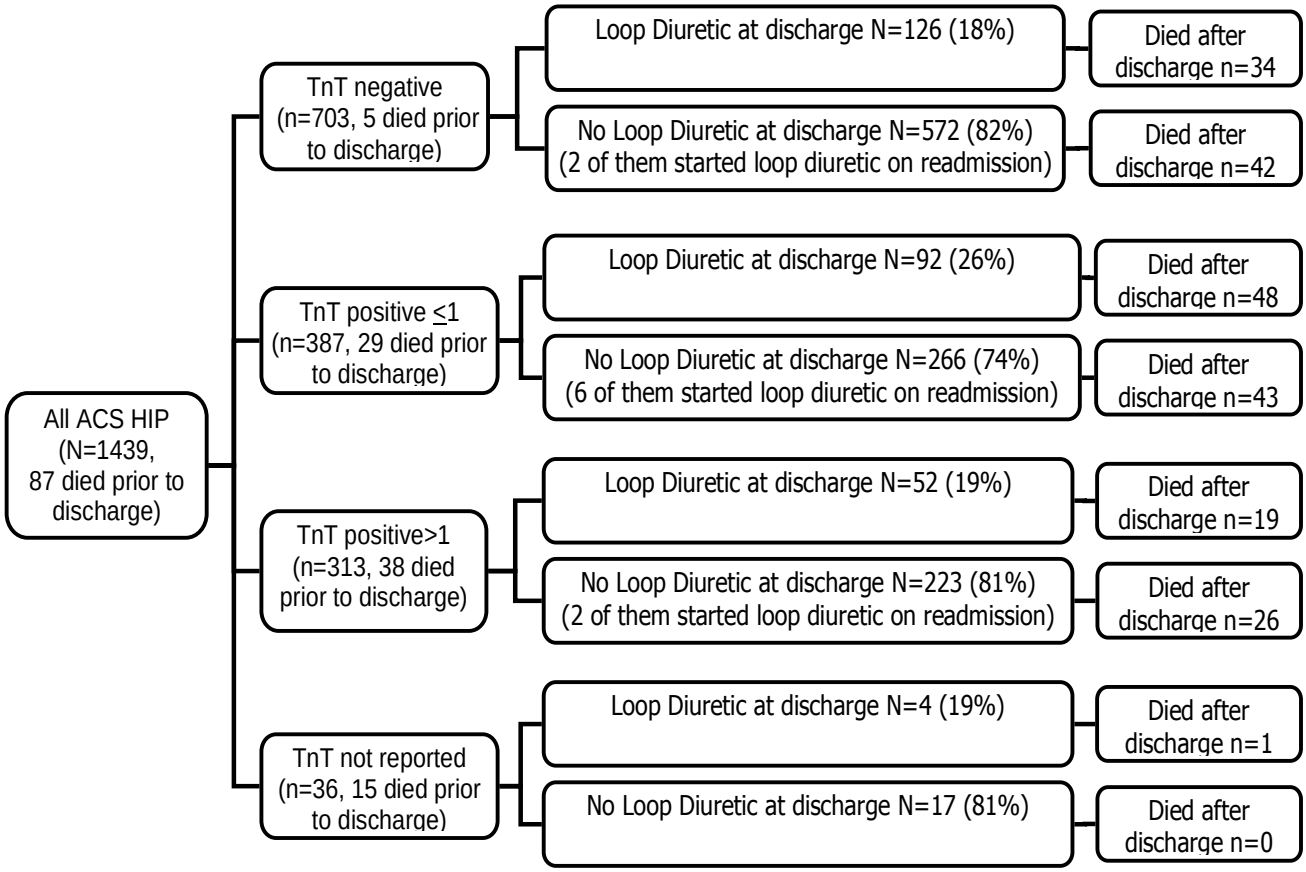


Probability of death within 30-day, one-year and 3-year according to the troponin T level during index admission in all patients identified by HIP, HID, MINAP or by positive TnT (n=2426), patients identified as an ACS or MI by HIP, HID or MINAP (n=1547) and in patients with no diagnosis of ACS but positive Troponin T (TnT) during 2005 (n=823) (56 patients with no report of TnT were excluded).

7.3.3 Loop diuretic and survival subsequent to discharge and by end of 2008 in patients with ACS identified by HIP-2005

Information on diuretic treatment was available in 1439 ACS patients from HIP-2005. Of 703 patients with TnT≤0.03ug/L, 698 survived the index admission of whom 126 (18%)were, and 572 were not, discharged on a loop diuretic, of whom 34 (27%) and 42 (7%) subsequently died. Of 700 patients with TnT>0.03ug/L included in HIP-2005, 633 survived the index admission of whom 144(23%) were, and 489(77%) were not, discharged on a loop diuretic, of whom 67 (47%) and 69 (14%) subsequently died (Figure 7.6).

Figure 7-6Survival until end of 2008 in patients with a first admission with ACS identified by HIP



Survival until end of 2008 in patients with a first admission with ACS identified by HIP according to treatment with loop diuretic at discharge. Troponin T (TnT) measured during first admission.

7.3.4 Loop diuretics and left ventricular function

Of 1352 patients with ACS identified by HIP-2005 who survived the index admission, no record of an assessment of LV function could be identified for 685 (51%) patients from their case notes or hospital systems during the subsequent year. Of 667, who had LV function assessed, 206 (30%) had LVSD. Mortality was 31% in those with LVSD, 12% in those without LVSD and 14% for those who had no reported assessment of LV function.

7.4 Discussion

This report demonstrates that the incidence of ACS is highly dependent on the method of ascertainment, with a ten-fold difference depending on the criteria applied. Identifying a high proportion of those who have ACS or MI is important when assessing therapeutic intervention rates and outcomes provided by services. An audit may appear excellent when applied to a subset of carefully selected patients but when applied to all those requiring care may appear poor. No single survey method identified more than 60% of the total possible population with ACS of 2,426 patients. The incidence of MI seems only slightly less dependent on the method of ascertainment with a three-fold difference between MINAP and HIP-2005 assessments. The high mortality amongst patients with a positive TnT but who were not identified by any other survey method gives cause for concern and is the subject of further investigation. Clearly, surveys that focus on cardiology wards and interventions are likely to miss many patients admitted elsewhere with ACS, especially in high risk groups such as older people or those with other important medical co-morbidities.

Our data from 2005 suggest an annual incidence of MI of 1.56 per thousand population, of ACS 2.86 per thousand and of ACS or positive TnT, 4.33 per thousand. In our region, using MI identified by hospital discharge statistics alone, the incidence of MI has dropped by 40%

from 1.66 per thousand per year in 1998 to 0.97 in 2005. This compares to 64,436 admissions in England for acute MI using hospital episode statistics, which gives a rate of 1.29 per thousand in 2005 [16].Of these, 49,017 patients were reported as STEMI [172] and 13,489 with non-STEMI [173], which suggests substantial under-reporting of non-STEMI. These incidence rates appear lower than historical reports from the UK [16]. However, the reports have often quoted rates excluding younger people from the denominator rather than using the whole population. If only people aged >35 years are considered, as has been done previously[74], then our local incidence of MI is closer to three per thousand. This is remarkably similar to the rate of clinically overt myocardial infarction reported in the Hypertension Outcomes Trial (HOT) [174] in 1998. However, these data are also likely to be an underestimate of the rate of MI in the community, as up to 30% of people with an MI may die before they reach hospital[8 9], and up to 40% of patients do not have symptoms that either cause them to seek medical attention or be referred to hospital [10 11 12 174].

With improvement in the diagnostic tests for MI we may expect that the incidence of MI should increase, especially that of non-STEMI that would otherwise be defined as unstable angina in the absence of a marker of myocardial damage. In our region, in 2005, the diagnosis of MI was based on Troponin T which had a higher sensitivity for diagnosis of MI compared to creatine kinase/CK-MB in 1998. A higher sensitivity Troponin-T assay has now been introduced will further increase the proportion of ACS that is defined as MI. Assuming the incidence of ACS does not change, the incidence of MI will rise. The detection of still smaller MIs will also lead to an apparent improvement in prognosis. Only adjustment of risk for other prognostic markers will enable detection of any real improvement in outcomes for MI. However, high-sensitivity Troponin-T will also increase the number of false-positive test results. Based on hospital discharge statistics alone, there appeared to be a 40% fall in the incidence of MI between 1998 and 2005. This might be a true effect and reflect improved

management through recommendations for lifestyle changes, better management of hypertension, widespread use of statins and appropriate revascularisation procedures [134]. In 1998, only 45% of MI patients were treated with statins in 1998 compared to 73% and 95% in HIP and MINAP data respectively during 2005. Alternatively, it is possible that treatments have had a greater impact on the size and severity of MI than on its incidence. Retrospective access to plasma from a large, representative cohort of patients with ACS in order to measure high-sensitivity Troponin-T would be necessary to investigate this possibility further. Ultimately, lack of rigorous case-ascertainment and consistent diagnostic criteria thwart the accurate description of the incidence of MI and whether it has changed. However, there seems little doubt that the age-adjusted prognosis of MI has improved dramatically in the last decade, provided the patients is referred to and reaches hospital.

About half of patients with a positive TnT were not identified as having ACS by any of the survey methods. There are reasons other than ACS for elevation in TnT, including strenuous exercise, heart failure, trauma, renal failure, sepsis, pulmonary embolism and myocarditis [175 176]. Undoubtedly, some of our patients with elevated TnT that were not identified in our surveys will not have had ACS. However, it is also likely that the diagnosis of ACS was missed in some cases and uncertain in others. For instance, in patients with heart failure, TnT is often elevated, especially although not exclusively during acute exacerbations [177]. Post-mortem data suggests a substantial rate of sub-clinical myocardial infarction in patients with heart failure dying suddenly or from progressive deterioration [81 82]. The high mortality rate amongst patients with elevated TnT who were not identified with ACS may well indicate a group of patients with high rates of heart and renal failure. This requires further exploration of patient characteristics and the contribution of myocardial damage to the elevated troponin and poor outcome.

In contrast to a previous report[178], on a much smaller patient population, we found that three month mortality was similarly high in patients with modest or substantial increases in TnT. Our hospital policy is to conduct, for most patients, a single TnT measurement at least 12 hours after the onset of symptoms. Single measurements may be a poor guide to the extent of myocardial damage. Alternatively, even modest increases in TnT may indicate the presence of unstable plaque and the threat of further events that provoke arrhythmias or cause substantial cardiac damage.

The outcome from myocardial infarction in our unselected population remains very different from that reported amongst patients in randomised controlled trials of ACS. The exclusion of high-risk, elderly patients with multiple co-morbidities from trials probably accounts for most of the disparity. However, failure to refer patients for cardiology advice and failure of cardiologists to undertake timely intervention may also contribute to poor outcomes. However, in-patient mortality for MI has dropped from 22% in 1998, a mortality that was consistent with the international GRACE score, to 11% in 2005, although some of the difference might be accounted for by differences in survey method. Use of more sensitive assays and new diagnostic criteria may increase the incidence of MI by detecting small infarcts that, in turn, may lead to an apparent decrease in the incidence of heart failure and of mortality after MI. Patients with small MIs have a low incidence of heart failure and a good prognosis. Improved detection and treatment of small MIs may reduce the rate of recurrent events and delay or prevent the development of heart failure in the longer term. However, in the short- to medium-term, the incidence and of heart failure and prognosis will be driven by patients who have sustained a large MI and if such cases are not prevented or managed effectively, the incidence of heart failure in the community may be little affected. Moreover, if patients with extensive MI who would have died of shock or heart failure on the index admission are managed well, they are highly likely to be discharged with or soon develop

chronic heart failure. Good management of MI could thus increase the incidence and prevalence of heart failure at the same time as improving prognosis.

Since this survey, a regional primary angioplasty service has been implemented for STEMI that may improve outcomes. However, standards of care appear much worse as case ascertainment increases, which is probably true of any hospital practice. As noted in the present study and previous studies here [107] and elsewhere [179], it is patients who develop clinical evidence of heart failure who fare particularly badly. Heart failure precedes the majority of deaths after myocardial infarction [180].

7.5 Conclusion

The incidences of ACS and MI are highly dependent on the method of case ascertainment but incidence rates of patients hospitalised with MI appear to have fallen in the last decade. Failure to identify older, high-risk patients leads to over-optimistic estimations about the prognosis of ACS, underestimation of the resources needed to manage it and misleading perceptions about the adequacy of care that may lead to complacency. TnT and use of diuretics appear simple clinical markers of prognosis. Even slight elevation in TnT indicates a poor outcome whether or not a patient is diagnosed with ACS.

References

Reference List

1 St John SM, Lee D, Rouleau JL, et al. Left ventricular remodeling and ventricular arrhythmias after myocardial infarction. *Circulation* 2003 May 27;**107**(20):2577-82.

2 Cleland JG, Pennell DJ, Ray SG, et al. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial. *Lancet* 2003 Jul 5;**362**(9377):14-21.

3 Cleland JG, Calvert M, Freemantle N, et al. The Heart Failure Revascularisation Trial (HEART). *Eur J Heart Fail* 2011 Feb;**13**(2):227-33.

4 Joyce D, Loebe M, Noon GP, et al. Revascularization and ventricular restoration in patients with ischemic heart failure: the STICH trial. *Curr Opin Cardiol* 2003 Nov;**18**(6):454-7.

5 Sparrow P, Loh P, Nikitin N, et al. Chronically ischaemic hibernating myocardium reduces prediction of recovery by delayed enhancement cardiac magnetic resonance imaging in heart failure secondary to coronary disease with no symptoms of angina [abstract]. *Heart (Supplement II)* 2008;**94**(A84).

6 Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, et al. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. *Lancet* 1999 May 8;**353**(9164):1547-57.

7 Myocardial Ischaemia National Audit Project (MINAP). website 2010 September 30Available from: URL: http://old.rcplondon.ac.uk/clinical-standards/organisation/partnership/Pages/MINAP-.aspx

8 Volmink JA, Newton JN, Hicks NR, et al. Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. The Oxford Myocardial Infarction Incidence Study Group. *Heart* 1998 Jul;**80**(1):40-4.

9 Rosamond WD, Chambless LE, Folsom AR, et al. Trends in the incidence of myocardial infarction and in mortality due to coronary heart disease, 1987 to 1994. *N Engl J Med* 1998 Sep 24;**339**(13):861-7.

10 Brieger D, Eagle KA, Goodman SG, et al. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. *Chest* 2004 Aug;**126**(2):461-9.

11 Dorsch MF, Lawrance RA, Sapsford RJ, et al. Poor prognosis of patients presenting with symptomatic myocardial infarction but without chest pain. *Heart* 2001 Nov;**86**(5):494-8.

12 Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction. An update on the Framingham study. *N Engl J Med* 1984 Nov 1;**311**(18):1144-7.

13 Rosamond WD, Folsom AR, Chambless LE, et al. Coronary heart disease trends in four United States communities. The Atherosclerosis Risk in Communities (ARIC) study 1987-1996. *Int J Epidemiol* 2001 Oct;**30 Suppl 1**:S17-S22.

14 British Heart Foundation. Coronary Heart Disease Statistics. 2004.

15 Hospital Episode Statistics: Healthcare Resource Groups, 2002-03. 2003.

16 Hospital Episode Statistics: Primary diagnosis: summary, 2005-06. 8 A.D. p. 1-213.

17 Murphy NFea. Hospital- discharge rates for suspected acute coronary syndromes between 1990 and 2000: population based analysis. *BMJ* 2004 Jun 12;**328**(7453):1413-4.

18 Murphy NF, MacIntyre K, Capewell S, et al. Hospital discharge rates for suspected acute coronary syndromes between 1990 and 2000: population based analysis. *BMJ* 2004 Jun 12;**328**(7453):1413-4.

19 Alpert JS, Thygesen K, Antman E, et al. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000 Sep;**36**(3):959-69.

20 McKenna CJ, Forfar JC. Was it a heart attack? Troponin positive acute coronary syndrome versus myocardial infarction. *BMJ* 2002;(324):377-8.

21 Kober L, Torp-Pedersen C, Jorgensen S, et al. Changes in absolute and relative importance in the prognostic value of left ventricular systolic function and congestive heart failure after acute myocardial infarction. TRACE Study Group. Trandolapril Cardiac Evaluation. *Am J Cardiol* 1998 Jun 1;**81**(11):1292-7.

22 Hellermann JP, Goraya TY, Jacobsen SJ, et al. Incidence of heart failure after myocardial infarction: is it changing over time? *Am J Epidemiol* 2003 Jun 15;**157**(12):1101-7.

23 Moller JE, Brendorp B, Ottesen M, et al. Congestive heart failure with preserved left ventricular systolic function after acute myocardial infarction: clinical and prognostic implications. *Eur J Heart Fail* 2003 Dec;**5**(6):811-9.

24 Hasdai D, Behar S, Wallentin L, et al. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). *Eur Heart J* 2002 Aug;**23**(15):1190-201.

25 Cleland J, Yassin A, Arrow Y, et al. Outcome of patients discharged on loop diuretic therapy with or without a diagnosis of heart failure [abstract]. *Eur J Heart Failure (suppl)* 2009;**8**(2).

26 Cleland JG, Shelton R, Nikitin N, et al. Prevalence of markers of heart failure in patients with atrial fibrillation and the effects of ximelagatran compared to warfarin on the incidence of morbid and fatal events: a report from the SPORTIF III and V trials. *Eur J Heart Fail* 2007 Jun;**9**(6-7):730-9.

27 Kober L, Torp-Pedersen C. Clinical characteristics and mortality of patients screened for entry into the Trandolapril Cardiac Evaluation (TRACE) study. *Am J Cardiol* 1995 Jul 1;**76**(1):1-5.

28 Kober L, Torp-Pedersen C, Pedersen OD, et al. Importance of congestive heart failure and interaction of congestive heart failure and left ventricular systolic function on prognosis in patients with acute myocardial infarction. *Am J Cardiol* 1996 Nov 15;**78**(10):1124-8.

29 Velazquez EJ, Francis GS, Armstrong PW, et al. An international perspective on heart failure and left ventricular systolic dysfunction complicating myocardial infarction: the VALIANT registry. *Eur Heart J* 2004 Nov;**25**(21):1911-9.

30 Hellermann JP, Jacobsen SJ, Gersh BJ, et al. Heart failure after myocardial infarction: a review. *Am J Med* 2002 Sep;**113**(4):324-30.

31 Hanania G, Cambou JP, Gueret P, et al. Management and in-hospital outcome of patients with acute myocardial infarction admitted to intensive care units at the turn of the century: results from the French nationwide USIC 2000 registry. *Heart* 2004 Dec;**90**(12):1404-10.

32 Goldberg RJ, Spencer FA, Yarzebski J, et al. A 25-year perspective into the changing landscape of patients hospitalized with acute myocardial infarction (the Worcester Heart Attack Study). *Am J Cardiol* 2004 Dec 1;**94**(11):1373-8.

33 St John SM, Pfeffer MA, Moye L, et al. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial. *Circulation* 1997 Nov 18;**96**(10):3294-9.

34 Christian TF, Gitter MJ, Miller TD, et al. Prospective identification of myocardial stunning using technetium-99m sestamibi-based measurements of infarct size. *J Am Coll Cardiol* 1997 Dec;**30**(7):1633-40.

35 Solomon SD, Glynn RJ, Greaves S, et al. Recovery of ventricular function after myocardial infarction in the reperfusion era: the healing and early afterload reducing therapy study. *Ann Intern Med* 2001 Mar 20;**134**(6):451-8.

36 Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004 Jul 21;**292**(3):344-50.

37 Guidry UC, Evans JC, Larson MG, et al. Temporal trends in event rates after Q-wave myocardial infarction: the Framingham Heart Study. *Circulation* 1999 Nov 16;**100**(20):2054-9.

38 Spencer FA, Meyer TE, Gore JM, et al. Heterogeneity in the management and outcomes of patients with acute myocardial infarction complicated by heart failure: the National Registry of Myocardial Infarction. *Circulation* 2002 Jun 4;**105**(22):2605-10.

39 Steg PG, Dabbous OH, Feldman LJ, et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). *Circulation* 2004 Feb 3;**109**(4):494-9.

40 Hellermann JP, Jacobsen SJ, Redfield MM, et al. Heart failure after myocardial infarction: clinical presentation and survival. *Eur J Heart Fail* 2005 Jan;**7**(1):119-25.

41 Najafi F, Dobson AJ, Hobbs M, et al. Temporal trends in the frequency and longer-term outcome of heart failure complicating myocardial infarction. *Eur J Heart Fail* 2007 Sep;**9**(9):879-85.

42 Moller JE, Hillis GS, Oh JK, et al. Wall motion score index and ejection fraction for risk stratification after acute myocardial infarction. *Am Heart J* 2006 Feb;**151**(2):419-25.

43 Mosterd A, Deckers JW, Hoes AW, et al. Classification of heart failure in population based research: an assessment of six heart failure scores. *Eur J Epidemiol* 1997 Jul;**13**(5):491-502.

44 Dargie H.J. Design and methodology of the CAPRICORN trial - a randomised double blind placebo controlled study of the impact of carvedilol on morbidity and mortality in patients with left ventricular dysfunction after myocardial infarction. *Eur Heart Failure J* 2000;**2**:325-32.

45 Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001 May 5;**357**(9266):1385-90.

46 Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med* 1992 Sep 3;**327**(10):669-77.

47 Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003 Apr 3;**348**(14):1309-21.

48 Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008 Oct;**29**(19):2388-442.

49 Frankenstein L, Clark AL, Goode K, et al. The prognostic value of individual NT-proBNP values in chronic heart failure does not change with advancing age. *Heart* 2009 May;**95**(10):825-9.

50 Khan SQ, Kelly D, Quinn P, et al. Cardiotrophin-1 predicts death or heart failure following acute myocardial infarction. *J Card Fail* 2006 Oct;**12**(8):635-40.

51 Verges B, Zeller M, Desgres J, et al. High plasma N-terminal pro-brain natriuretic peptide level found in diabetic patients after myocardial infarction is associated with an increased risk of in-hospital mortality and cardiogenic shock. *Eur Heart J* 2005 Sep;**26**(17):1734-41.

52 James SK, Lindahl B, Siegbahn A, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation* 2003 Jul 22;**108**(3):275-81.

53 Richards AM, Nicholls MG, Yandle TG, et al. Neuroendocrine prediction of left ventricular function and heart failure after acute myocardial infarction. The Christchurch Cardioendocrine Research Group. *Heart* 1999 Feb;**81**(2):114-20.

54 Richards AM, Nicholls MG, Espiner EA, et al. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. *Circulation* 2003 Jun 10;**107**(22):2786-92.

55 Khan SQ, Dhillon O, Struck J, et al. C-terminal pro-endothelin-1 offers additional prognostic information in patients after acute myocardial infarction: Leicester Acute Myocardial Infarction Peptide (LAMP) Study. *Am Heart J* 2007 Oct;**154**(4):736-42.

56 Khan SQ, Dhillon OS, O'Brien RJ, et al. C-terminal provasopressin (copeptin) as a novel and prognostic marker in acute myocardial infarction: Leicester Acute Myocardial Infarction Peptide (LAMP) study. *Circulation* 2007 Apr 24;**115**(16):2103-10.

57 Bjorklund E, Jernberg T, Johanson P, et al. Admission N-terminal pro-brain natriuretic peptide and its interaction with admission troponin T and ST segment resolution for early risk stratification in ST elevation myocardial infarction. *Heart* 2006 Jun;**92**(6):735-40.

58 Scirica BM, Morrow DA, Cannon CP, et al. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. *J Am Coll Cardiol* 2006 Jun 6;**47**(11):2326-31.

59 Galvani M, Ottani F, Oltrona L, et al. N-terminal pro-brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes. *Circulation* 2004 Jul 13;**110**(2):128-34.

60 Westerhout CM, Fu Y, Lauer MS, et al. Short- and long-term risk stratification in acute coronary syndromes: the added value of quantitative ST-segment depression and multiple biomarkers. *J Am Coll Cardiol* 2006 Sep 5;**48**(5):939-47.

61 Morrow DA, de Lemos JA, Sabatine MS, et al. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non-ST-elevation myocardial infarction: B-type natriuretic peptide and prognosis in TACTICS-TIMI 18. *J Am Coll Cardiol* 2003 Apr 16;**41**(8):1264-72.

62 Omland T, Persson A, Ng L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation* 2002 Dec 3;**106**(23):2913-8.

63 de Lemos JA, Morrow DA, Bentley JH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001 Oct 4;**345**(14):1014-21.

64 McClure SJ, Caruana L, Davie AP, et al. Cohort study of plasma natriuretic peptides for identifying left ventricular systolic dysfunction in primary care. *BMJ* 1998 Aug 22;**317**(7157):516-9.

65 Luchner A, Hengstenberg C, Lowel H, et al. NT-ProBNP in outpatients after myocardial infarction: interaction between symptoms and left ventricular function and optimized cut-points. *J Card Fail* 2005 Jun;**11**(5 Suppl):S21-S27.

66 Orn S, Manhenke C, Squire IB, et al. Plasma MMP-2, MMP-9 and N-BNP in long-term survivors following complicated myocardial infarction: relation to cardiac magnetic resonance imaging measures of left ventricular structure and function. *J Card Fail* 2007 Dec;**13**(10):843-9.

67 Watanabe I, Tani S, Washio T, et al. Relationship between the plasma levels of brain natriuretic peptide and left ventricular ejection fraction in asymptomatic patients with previous myocardial infarction. *Int Heart J* 2005 Nov;**46**(6):1007-14.

68 Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005 Jun;**26**(11):1115-40.

69 Fleming JS, Nunan TO. The new BNMS guidelines for measurement of glomerular filtration rate. *Nucl Med Commun* 2004 Aug;**25**(8):755-7.

70 Glynn RJ, Buring JE. Ways of measuring rates of recurrent events. *BMJ* 1996 Feb 10;**312**(7027):364-7.

71 Efron B, Tibshirani R. Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. *Statistical Science* 1986;**1**:54-77.

72 Schoenfeld D. Partial residual estimation for the proportional hazards regression model. *Biometrika* 1982;**69**:239-41.

73 Grambsch M, Therneau T. Proportional hazards tests and diagnostics based on weight residuals. *Biometrika* 1994;**81**:515-26.

74 Cleland JG, Torabi A, Khan NK. Epidemiology and management of heart failure and left ventricular systolic dysfunction in the aftermath of a myocardial infarction. *Heart* 2005 May;**91 Suppl 2**:ii7-13.

75 Lloyd-Jones DM, Larson MG, Leip EP, et al. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002 Dec 10;**106**(24):3068-72.

76 Cowie MR, Wood DA, Coats AJ, et al. Incidence and aetiology of heart failure; a population-based study. *Eur Heart J* 1999 Mar;**20**(6):421-8.

77 Cleland JG, Cohen-Solal A, Aguilar JC, et al. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. *Lancet* 2002 Nov 23;**360**(9346):1631-9.

78 Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. *Eur Heart J* 2003 Mar;**24**(5):442-63.

79 Cleland JG, Coletta AP, Nikitin NP, et al. Clinical trials update from the American College of Cardiology: Darbepoetin alfa, ASTEROID, UNIVERSE, paediatric carvedilol, UNLOAD and ICELAND. *Eur J Heart Fail* 2006 May;**8**(3):326-9.

80 STOKES J, III, DAWBER TR. The silent coronary: the frequency and clinical characteristics of unrecognized myocardial infarction in the Framingham study. *Ann Intern Med* 1959 Jun;**50**(6):1359-69.

81 Uretsky BF, Thygesen K, Armstrong PW, et al. Acute coronary findings at autopsy in heart failure patients with sudden death: results from the assessment of treatment with lisinopril and survival (ATLAS) trial. *Circulation* 2000 Aug 8;**102**(6):611-6.

82 Orn S, Cleland JG, Romo M, et al. Recurrent infarction causes the most deaths following myocardial infarction with left ventricular dysfunction. *Am J Med* 2005 Jul;**118**(7):752-8.

83 Cleland JG, Clark AL, Caplin JL. Takingheart failure seriously, Diagnosis and initiation of treatment are the aspects to concentrate on. *BMJ* 2000;**3321**:1095-6.

84 Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, et al. Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. *J Am Coll Cardiol* 2007 Jan 30;**49**(4):422-30.

85 Sutton AG, Campbell PG, Graham R, et al. One year results of the Middlesbrough early revascularisation to limit infarction (MERLIN) trial. *Heart* 2005 Oct;**91**(10):1330-7.

86 Ellis SG, Da Silva ER, Spaulding CM, et al. Review of immediate angioplasty after fibrinolytic therapy for acute myocardial infarction: insights from the RESCUE I, RESCUE II, and other contemporary clinical experiences. *Am Heart J* 2000 Jun;**139**(6):1046-53.

87 Rebuzzi AG, Niccoli G, Ferrante G. Acute myocardial infarction interventional procedures: primary percutaneous coronary intervention versus facilitated percutaneous coronary intervention, rescue angioplasty, rescue excimer laser. *Minerva Cardioangiol* 2007 Feb;**55**(1):73-82.

88 Zeymer U, Schroder R, Machnig T, et al. Primary percutaneous transluminal coronary angioplasty accelerates early myocardial reperfusion compared to thrombolytic therapy in patients with acute myocardial infarction. *Am Heart J* 2003 Oct;**146**(4):686-91.

89 Hochman JS, Lamas GA, Buller CE, et al. Coronary intervention for persistent occlusion after myocardial infarction. *N Engl J Med* 2006 Dec 7;**355**(23):2395-407.

90 Kjekshus J, Pedersen TR, Olsson AG, et al. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. *J Card Fail* 1997 Dec;**3**(4):249-54.

91 LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005 Apr 7;**352**(14):1425-35.

92 Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. *N Engl J Med* 1992 Sep 3;**327**(10):685-91.

93 Pitt B, Gheorghiade M, Zannad F, et al. Evaluation of eplerenone in the subgroup of EPHESUS patients with baseline left ventricular ejection fraction <or=30%. *Eur J Heart Fail* 2006 May;**8**(3):295-301.

94 Houghton T, Freemantle N, Cleland JG. Are beta-blockers effective in patients who develop heart failure soon after myocardial infarction? A meta-regression analysis of randomised trials. *Eur J Heart Fail* 2000 Sep;**2**(3):333-40.

95 Cleland JG. Is aspirin "the weakest link" in cardiovascular prophylaxis? The surprising lack of evidence supporting the use of aspirin for cardiovascular disease. *Prog Cardiovasc Dis* 2002 Jan;**44**(4):275-92.

96 Cleland JG, Massie BM, Packer M. Sudden death in heart failure: vascular or electrical? *Eur J Heart Fail* 1999 Mar;**1**(1):41-5.

97 Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007 Nov 29;**357**(22):2248-61.

98 Cleland JG, Findlay I, Jafri S, et al. The Warfarin/Aspirin Study in Heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004 Jul;**148**(1):157-64.

99 Gronefeld G, Connolly SJ, Hohnloser SH. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT): rationale, design and specific aims. *Card Electrophysiol Rev* 2003 Dec;**7**(4):447-51.

100 Yao G, Freemantle N, Calvert MJ, et al. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. *Eur Heart J* 2007 Jan;**28**(1):42-51.

101 Gerschutz GP, Bhatt DL. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study: to what extent should the results be generalizable? *Am Heart J* 2003 Apr;**145**(4):595-601.

102 Scheen AJ. [The CHARISMA study: in search of the best antiplatelet strategy for cardiovascular prevention]. *Rev Med Liege* 2006 Sep;**61**(9):656-61.

103 Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003 Oct 27;**163**(19):2345-53.

104 Zhou Z, Rahme E, Abrahamowicz M, et al. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol* 2005 Nov 15;**162**(10):1016-23.

105 Sigurdsson E, Thorgeirsson G, Sigvaldason H, et al. Prevalence of coronary heart disease in Icelandic men 1968-1986. The Reykjavik Study. *Eur Heart J* 1993 May;**14**(5):584-91.

106 Kannel WB, Abbott R. Incidence and prognosis of unrecognized myocardial infarction. *N Engl J Med* 1994;**311**(1):1144-7.

107 Torabi A, Cleland JG, Khan NK, et al. The timing of development and subsequent clinical course of heart failure after a myocardial infarction. *Eur Heart J* 2008 Apr;**29**(7):859-70.

108 Ennezat PV, Lamblin N, Mouquet F, et al. The effect of ageing on cardiac remodelling and hospitalization for heart failure after an inaugural anterior myocardial infarction. *Eur Heart J* 2008 Aug;**29**(16):1992-9.

109 Tang EW, Wong CK, Restieaux NJ, et al. Clinical outcome of older patients with acute coronary syndrome over the last three decades. *Age Ageing* 2006 May;**35**(3):280-5.

110 Kober L, Torp-Pedersen C, Ottesen M, et al. Influence of age on the prognostic importance of left ventricular dysfunction and congestive heart failure on long-term survival after acute myocardial infarction. TRACE Study Group. *Am J Cardiol* 1996 Jul 15;**78**(2):158-62.

111 Herlitz J, Karlson BW, Bang A, et al. Survival, mode of death, reinfarction and use of medication during a period of 5 years after acute myocardial infarction in different age groups. *Cardiology* 1996 Nov;**87**(6):529-36.

112 Harrell FJ, Lee K, Califf R, et al. Regression modelling strategies for improved prognostc prediction.*Statistics in Medicine* : 1984. p. 143-52.

113 Bertini M, Mollema SA, Delgado V, et al. Impact of time to reperfusion after acute myocardial infarction on myocardial damage assessed by left ventricular longitudinal strain. *Am J Cardiol* 2009 Aug 15;**104**(4):480-5.

114 Koren G, Weiss AT, Hasin Y, et al. Prevention of myocardial damage in acute myocardial ischemia by early treatment with intravenous streptokinase. *N Engl J Med* 1985 Nov 28;**313**(22):1384-9.

115 Sheehan FH, Braunwald E, Canner P, et al. The effect of intravenous thrombolytic therapy on left ventricular function: a report on tissue-type plasminogen activator and streptokinase from the Thrombolysis in Myocardial Infarction (TIMI Phase I) trial. *Circulation* 1987 Apr;**75**(4):817-29.

116 Bax M, de Winter RJ, Schotborgh CE, et al. Short- and long-term recovery of left ventricular function predicted at the time of primary percutaneous coronary intervention in anterior myocardial infarction. *J Am Coll Cardiol* 2004 Feb 18;**43**(4):534-41.

117 Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003 Jan 4;**361**(9351):13-20.

118 Parodi G, Memisha G, Carrabba N, et al. Prevalence, predictors, time course, and long-term clinical implications of left ventricular functional recovery after mechanical reperfusion for acute myocardial infarction. *Am J Cardiol* 2007 Dec 15;**100**(12):1718-22.

119 Boersma E, Maas AC, Deckers JW, et al. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996 Sep 21;**348**(9030):771-5.

120 Canto JG, Every NR, Magid DJ, et al. The volume of primary angioplasty procedures and survival after acute myocardial infarction. National Registry of Myocardial Infarction 2 Investigators. *N Engl J Med* 2000 May 25;**342**(21):1573-80.

121 Morrison LJ, Verbeek PR, McDonald AC, et al. Mortality and prehospital thrombolysis for acute myocardial infarction: A meta-analysis. *JAMA* 2000 May 24;**283**(20):2686-92.

122 Spaulding C, Morice MC, Lancelin B, et al. Is the volume-outcome relation still an issue in the era of PCI with systematic stenting? Results of the greater Paris area PCI registry. *Eur Heart J* 2006 May;**27**(9):1054-60.

123 GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. *Lancet* 1994 May 7;**343**(8906):1115-22.

124 Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004 Sep 23;**351**(13):1285-95.

125 Velazquez EJ, Pfeffer MA, McMurray JV, et al. VALsartan In Acute myocardial iNfarcTion (VALIANT) trial: baseline characteristics in context. *Eur J Heart Fail* 2003 Aug;**5**(4):537-44.

126 Wilhelmsen L, Pyorala K, Wedel H, et al. Risk factors for a major coronary event after myocardial infarction in the Scandinavian Simvastatin Survival Study (4S). Impact of predicted risk on the benefit of cholesterol-lowering treatment. *Eur Heart J* 2001 Jul;**22**(13):1119-27.

127 Cleland JG. Long-term aspirin for coronary artery disease: are we being deceived by a biased presentation of the evidence? *Future Cardiol* 2010 Mar;**6**(2):141-6.

128 Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009 Apr 14;**53**(15):e1-e90.

129 Executive summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline. *J Card Fail* 2006 Feb;**12**(1):10-38.

130 Massie BM, Collins JF, Ammon SE, et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation* 2009 Mar 31;**119**(12):1616-24.

131 Birkhead JS, Walker L, Pearson M, et al. Improving care for patients with acute coronary syndromes: initial results from the National Audit of Myocardial Infarction Project (MINAP). *Heart* 2004 Sep;**90**(9):1004-9.

132 Gale CP, Manda SO, Weston CF, et al. Evaluation of risk scores for risk stratification of acute coronary syndromes in the Myocardial Infarction National Audit Project (MINAP) database. *Heart* 2009 Mar;**95**(3):221-7.

133 Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009 Sep 10;**361**(11):1045-57.

134 Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007 Nov 15;**357**(20):2001-15.

135 Messerli FH, Christie B, DeCarvalho JG, et al. Obesity and essential hypertension. Hemodynamics, intravascular volume, sodium excretion, and plasma renin activity. *Arch Intern Med* 1981 Jan;**141**(1):81-5.

136 Cleland JG, Tavazzi L, Daubert JC, et al. Cardiac resynchronization therapy: are modern myths preventing appropriate use? *J Am Coll Cardiol* 2009 Feb 17;**53**(7):608-11.

137 Norhammar A, Tenerz A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 2002 Jun 22;**359**(9324):2140-4.

138 Al FN, Lawrence-Nelson J, Kostis JB, et al. Effect of anemia on 1-year mortality in patients with acute myocardial infarction. *Am Heart J* 2002 Oct;**144**(4):636-41.

139 Lipsic E, van dH, I, Voors AA, et al. Hemoglobin levels and 30-day mortality in patients after myocardial infarction. *Int J Cardiol* 2005 Apr 20;**100**(2):289-92.

140 Wu WC, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001 Oct 25;**345**(17):1230-6.

141 Sabatine MS, Morrow DA, Giugliano RP, et al. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. *Circulation* 2005 Apr 26;**111**(16):2042-9.

142 Archbold RA, Balami D, Al Hajiri A, et al. Hemoglobin concentration is an independent determinant of heart failure in acute coronary syndromes: cohort analysis of 2310 patients. *Am Heart J* 2006 Dec;**152**(6):1091-5.

143 Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. *Circulation* 2003 Jan 21;**107**(2):223-5.

144 Valeur N, Nielsen OW, McMurray JJ, et al. Anaemia is an independent predictor of mortality in patients with left ventricular systolic dysfunction following acute myocardial infarction. *Eur J Heart Fail* 2006 Oct;**8**(6):577-84.

145 Geneva WHO. WHO/UNICEF/UNU. Iron deficiency anemia: assessment, prevention, and control.
2001 (WHO/NHD/01.3). www.who.int/nut/documents/ida_. 2001.

146 Anker SD, Comin CJ, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009 Dec 17;**361**(25):2436-48.

147 Taha AS, McCloskey C, Prasad R, et al. Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomised, double-blind, placebo-controlled trial. *Lancet* 2009 Jul 11;**374**(9684):119-25.

148 Beaumont C, Delaby C. Recycling iron in normal and pathological states. *Semin Hematol* 2009 Oct;**46**(4):328-38.

149 von HS, Jankowska EA, Ponikowski P, et al. Anemia in heart failure: an overview of current concepts. *Future Cardiol* 2011 Jan;**7**(1):119-29.

150 Androne AS, Katz SD, Lund L, et al. Hemodilution is common in patients with advanced heart failure. *Circulation* 2003 Jan 21;**107**(2):226-9.

151 Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. *Circulation* 2003 Jan 21;**107**(2):223-5.

152 Clark AL, Cleland JG. Anemia and chronic heart failure: are we asking the right questions? *Circulation* 2005 Sep 20;**112**(12):1681-3.

153 Komajda M, Anker SD, Charlesworth A, et al. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. *Eur Heart J* 2006 Jun;**27**(12):1440-6.

154 Clark AL, Cleland JG. Anemia and chronic heart failure: are we asking the right questions? *Circulation* 2005 Sep 20;**112**(12):1681-3.

155 Clark AL, Cleland JG. Anemia and chronic heart failure: are we asking the right questions? *Circulation* 2005 Sep 20;**112**(12):1681-3.

156 John G.F.Cleland, Azam Torabi, Jufen Zhang, et al. Antithrombotic agents. In: Theresa A.McDonagh, Roy S.Gardner, Andrew L.Clark, Henry Dargie, editors. *Oxford Textbook of Heart Failure*. 1st ed. 2011.

157 Komajda M, Anker SD, Charlesworth A, et al. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. *Eur Heart J* 2006 Jun;**27**(12):1440-6.

158 Cleland JG, Swedberg K, Cohen-Solal A, et al. The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. *Eur J Heart Fail* 2000 Jun;**2**(2):123-32.

159 Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982 Apr;**143**(1):29-36.

160 McGowan JH, Cleland JG. Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. *Am Heart J* 2003 Sep;**146**(3):388-97.

161 Wedel H, McMurray JJ, Lindberg M, et al. Predictors of fatal and non-fatal outcomes in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA): incremental value of apolipoprotein A-1, high-sensitivity C-reactive peptide and N-terminal pro B-type natriuretic peptide. *Eur J Heart Fail* 2009 Mar;**11**(3):281-91.

162 Cleland JG, McMurray JJ, Kjekshus J, et al. Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). *J Am Coll Cardiol* 2009 Nov 10;**54**(20):1850-9.

163 Xu H, Crawford D, Hutchinson KR, et al. Myocardial dysfunction in an animal model of cancer cachexia. *Life Sci* 2010 Dec 14.

164 Shelton RJ, Clark AL, Goode K, et al. The diagnostic utility of N-terminal pro-B-type natriuretic peptide for the detection of major structural heart disease in patients with atrial fibrillation. *Eur Heart J* 2006 Oct;**27**(19):2353-61.

165 Peduzzi P, Concato J, Feinstein AR, et al. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol* 1995 Dec;**48**(12):1503-10.

166 MINAP hospital reports. **Myocardial ischaemia national audit project (MINAP)**. MINAP hospital reports 2008 November 12Available from: URL: The Cardiac Network of Wales

167 Brkhead J, Pearson M, Norris RM, et al. The national audit of myocardial infarction: a new development in the audit process. *Clinical Excellence* 2002 Sep 1;**4**(4):379-85.

168 Birkhead J. Where are we today? Early results from MINAP, the National Audit of Myocardial Infarction Project. *Heart* 2003 May;**89 Suppl 2**:ii13-ii15.

169 Quinn T, Weston C, Birkhead J, et al. Redefining the coronary care unit: an observational study of patients admitted to hospital in England and Wales in 2003. *QJM* 2005 Nov;**98**(11):797-802.

170 Birkhead JS, Weston C, Lowe D. Impact of specialty of admitting physician and type of hospital on care and outcome for myocardial infarction in England and Wales during 2004-5: observational study. *BMJ* 2006 Jun 3;**332**(7553):1306-11.

171 Prepared on behalf of the MINAP Steering Group. Myocardia Ischaemia National Audit Project (MINAP) How the NHS manages heart attacks. 2009 Jun.

172 Horne S, Weston C, Quinn T, et al. The impact of pre-hospital thrombolytic treatment on re-infarction rates: analysis of the Myocardial Infarction National Audit Project (MINAP). *Heart* 2009 Apr;**95**(7):559-63.

173 Birkhead JS, Weston CF, Chen R. Determinants and outcomes of coronary angiography after non-ST-segment elevation myocardial infarction. A cohort study of the Myocardial Ischaemia National Audit Project (MINAP). *Heart* 2009 Oct;**95**(19):1593-9.

174 Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet* 1998 Jun 13;**351**(9118):1755-62.

175 Mockel M, Schindler R, Knorr L, et al. Prognostic value of cardiac troponin T and I elevations in renal disease patients without acute coronary syndromes: a 9-month outcome analysis. *Nephrol Dial Transplant* 1999 Jun;**14**(6):1489-95.

176 Krahn J, Parry DM, Leroux M, et al. High percentage of false positive cardiac troponin I results in patients with rheumatoid factor. *Clin Biochem* 1999 Aug;**32**(6):477-80.

177 Omland T, de Lemos JA, Sabatine MS, et al. A Sensitive Cardiac Troponin T Assay in Stable Coronary Artery Disease. *N Engl J Med* 2009 Nov 25.

178 Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. *N Engl J Med* 1996 Oct 31;**335**(18):1333-41.

179 Ezekowitz JA, Kaul P, Bakal JA, et al. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. *J Am Coll Cardiol* 2009 Jan 6;**53**(1):13-20.

180 Torabi A, Rigby AS, Cleland JG. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. *J Am Coll Cardiol* 2009 Dec 29;**55**(1):79-81.

Appendices

1. Consultant Letter

University headed paper

Dear Dr ……Trust Consultant ….

I am a research fellow working for Professor John Cleland in the Academic Department of Cardiology of the University of Hull, based at Hull & East Yorkshire Hospitals Trust. I am working on a research project studying the occurrence of heart failure in patients who suffered an MI in 1998 and to investigate the predictive capacity of N-terminal B Natriuretic Peptide (NT-BNP) in heart failure.

I am seeking your agreement and help in recruiting patients who, following the occurrence of an MI in 1998, either were either admitted under your care or are currently under your care. In line with Caldicott principles, the first contact with these individuals should be from the clinician who either cared for them at the time of the infarct or are currently caring for them. The patients (see attached list) were identified to me by the Information Department. Should you approve that your patients can participate in this study, I would be most grateful if you would sign the attached template letter. I will then make copies of the template letter, add to the copies the name and address of each patient and arrange for the letters to be sent to them. If you have any objections please notify Professor Cleland in writing.

Circulatory levels of NT-BNP are known to increase when heart function is impaired. By measuring the level of NT-BNP in patients with suspected heart failure, it may be possible to filter-out patients who do not require further assessment, thereby reducing hospital waiting times for echocardiography and specialist referral. It may therefore be possible for us to

assess heart function using just a blood test. However, the amount of NT-BNP in the blood is also increased if kidney function is impaired and as such it is not yet clear whether this test alone can be used to distinguish between heart and kidney problems. It is therefore possible that measuring NT-BNP levels in combination with a test for kidney function may be very useful indeed.

This study requires the patient to visit the Department of Academic Cardiology, Hull Royal Infirmary, for blood tests (including NT-BNP and renal function (urea)). Patients will be reimbursed travel expenses or provided with transport to the Department. If the level of NT-BNP is high, they will be asked to return for further tests for heart failure including an ECG and an echocardiogram. They may also be asked to wear a 24 hour ambulatory ECG. The patient may also be invited to participate if they have a normal level of NT-BNP in order to act a control group.

I would be grateful if you would indicate whether you would like to be informed of patients' test results.

You will be informed should any patient agree to participate.

Thank you for your consideration,

Yours sincerely,

Dr A Torabi

Research Fellow in Cardiology
Dept of Academic Cardiology
Floor 3, Haughton Building
Hull Royal Infirmary

Anlaby Road
Hull, HU3 2JZ
Phone 01482 675016.
Cc Patient’s GP

2.Consultant letter to patient

Hull Royal Infirmary
Anlaby Road
Hull
HU3 2JZ

Dear…….

I am writing to invite you to take part in a research study. The study is being carried out, by the Department of Cardiology, the University of Hull, based at Hull & East Yorkshire Hospitals Trust. As well as being a research department, the Unit also runs cardiology clinics as part of the NHS program to provide care for heart patients in Hull and East Riding. You have been contacted because you were in the care of a consultant at this hospital with a heart attack in 1998.

What is this study about?

We are currently inviting people who had a heart attack in 1998 to volunteer to take part in a research study that we hope will help doctors to find a simpler way to check for heart damage.

The current way that doctors check for heart damage is expensive and time consuming We would like to test a new, quick and inexpensive blood test that measures a substance present in our blood, called N-terminal brain natriuretic peptide (or more simply, NT-BNP). More NT-BNP is thought to be in our blood when the heart has not made a full recovery.

It is hoped that this simple blood test will enable doctors to detect and treat heart problems earlier than is currently possible. It will also help the NHS to use its resources more effectively because the test may help GPs to decide which patients are more likely to need assessment by a hospital specialist.

What does taking part involve?

If you decide that you would like to take part (or you would like more information) about the study we ask that you contact us on the telephone number at the end of this letter to arrange a date to visit us. During your visit to us, we will discuss the study with you in more detail and you will be given time to decide if you would like to take part. You can discuss taking part with family, friends or even your GP. If you do agree to take part, we will ask you to do the following:

- provide a sample of blood to allow the level of NT-BNP and some other routine blood tests to be measured.
- have some further tests, such as an **Echocardiogram** (to look at the heart beating, a bit like the scan used to look at babies during pregnancy) and an **Electrocardiogram**, or **ECG** (to look at how your heart is performing).
- you may also be asked to wear a smaller walkman-like version of the ECG, called an **Ambulatory ECG**, to record your heart's performance for 24 hours. This will be attached to you by sticky tape. You will be asked to wear it when you go home and to return it to us the following day.

Please remember, your participation in this study is voluntary, and your care in the NHS will not be affected if you do not decide to take part. Your local doctor has been informed about this study. If you agree to take part, your doctor will be informed of that decision too.

What do I do now?

If you would like to take part in this study please telephone our reception on:

01482 624073

You can also call this number if you feel that you might like to take part, but you need to know more about the study before you decide what to do. Dr Azam Torabi, the study's researcher, will be pleased to discuss the study with you.

Yours sincerely,

Prof JGF Cleland, or Drs Alamgir, Caplin or Kaye

3. Patient Information Leaflet

Hull Royal Infirmary
Anlaby Road
Hull
HU3 2JZ

A Study to Assess the Use of NT-BNP

as a Marker of Cardiac Dysfunction in Post-MI Patients

You are invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not to take part.

Thank you for reading this.

About NT-BNP

We have known about the existence of Coronary Artery Disease for many years. We know that people with Coronary Artery Disease are more likely to develop heart problems. Improvements in modern medicine have improved the treatment of heart disease, but, unfortunately, some people still develop these problems. Detecting these problems early will alert your doctor so that treatment can be discussed with you that may stop or slow down their development.

It has recently been discovered that the level of a substance produced in blood - called **"N-terminal B NatriureticPeptide"** or **NT-BNP** for short -increased when heart function was impaired.This discovery may allow us to assess heart function as well as kidney function by a simple blood test. At the moment, however, assessing heart function is much more complex and requires special heart scans. However, the amount of NT-BNP in the blood is also increased if kidney function is impaired. Therefore, it is not yet clear whether this test alone can be used to distinguish between heart and kidney problems. It is therefore possible that NT-BNP combined with a simple test for kidney function may be very useful indeed.

In order to resolve these uncertainties, we wish to measure NT-BNP along with routine tests for heart and kidney function in about 700 people with Coronary Artery Disease.

We are receiving some support for the study from a company called Roche Diagnostics, who are developing the kit to measure NT-BNP. The company will have access to the data we acquire, but only in an anonymised form.

Study Requirements

If you agree to take part, we will invite you to the hospital for approximately $1^1/_2$ hours. We will take blood from you for measuring NT-BNP and to check your kidney function.

We will ask you a standard set of questions that we ask all patients who attend our special clinics for heart problems.

You will be asked to blow into a machine so that we can ensure that any breathlessness you might have is not due to lung problems.

Special heart tests include:

- an**electrocardiogram (ECG)** This measures small electrical signals from your heart muscle using wires attached to your chest, arms and legs by sticky tape.
- possibly a **24 hour ambulatory ECG.** This takes about half an hour. We may then attach you to a 24 hour ECG tape machine (a bit like a 'Walkman') using wires and sticky tape and you will go home. You will return 24 hours later to have the tape removed or we can arrange for the tape to be picked up.
- an**echocardiogram (ECHO)** This uses sound waves to build a picture of your heart moving inside your chest (a bit like the scan used to look at babies during pregnancy). You will be asked to lie on your side on a couch in a

darkened room. Some warm jelly will be put on your chest and a plastic probe pressed against your skin.

What are the potential risks and inconveniences for me?

There are no potential risks to you if you take part in this study. You will be required to visit our Department to give a blood sample and undergo some tests as described above. You may experience some bruising as a result of giving the blood.

If we do identify important heart or kidney problems, the results will be discussed with you and your GP and the best available advice and treatment offered. Your GP will be informed of your participation in this study.

Your Rights

You are under no obligation to take part in the study. You may withdraw at any time. If you withdraw it will in no way affect your future care.

All blood samples will be stored securely with in the Department for an indefinite period. They will be anonymised so that only staff working within the Department can trace the samples directly to you. All computerised data will be anonymised in the same manner and stored on password-protected computers within the Trust. Some data will be shared with Roche in order that they can develop their NT-BNP assay, but your confidentiality will be kept at all times. We may use the blood samples for other heart failure related studies but we will obtain your consent before we do this.

If you have decided to take part in the study, you will be asked to sign a consent form, a copy of which will be given to you. You will also be asked to sign a second consent form to join another study being run in this clinic called the **Heart Care Study**. The **Heart Care Study** is a large study that looks at the health of the heart during regular visits to the department to the clinic. If you agree to take part in the **Heart Care Study**, you will be asked to visit the clinic on average three times a year and it will also allow us to use the results of your tests in both studies.

You are under no obligation to take part in the second study and your healthcare will not be affected by your decision.

More details about the **Heart Care Study** are available upon arrival at the clinic, or alternatively can be sent to you upon request.

If you would like more information or would like to speak to someone please contact:

Dr Azam Torabi, Research Fellow in Cardiology, Academic Department of Cardiology, 3rd Floor Haughton Building, Hull Royal Infirmary, Anlaby Road HULL HU3 2JZ. Telephone 01482 675016.

Hull and East Yorkshire Hospitals NHS Trust

4.Patient Consent Form

Hull Royal Infirmary
Anlaby Road
Hull
HU3 2JZ

Consent Form

A Study to Assess the Use of NT-BNP

as a Marker of Cardiac Dysfunction after a

Heart Attack (MI)

(The Post-MI NT-BNP Study)

Name of Researcher: Dr Azam Torabi,
Academic Cardiology, Hull Royal Infirmary
Telephone 01482 675016

1. I confirm that I have read and understood the information sheet dated 20 April 2004 (version 4.0) for the above study and have been given a copy to keep. I have had the opportunity to ask questions and understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. ☐

2. I give permission for my medical records to be looked at and information taken from them to be analysed in strict confidence by the team. ☐

Subsequent data collected will be kept anonymous and can be used for scientific publications.

3. I understand that the medical information collected may be shared with Roche (who make the NT-BNP measurement kits) anonymously so that it will not be possible for Roche to identify me personally. ☐

4. I agree that the anonymised data and samples obtained from me during this study may be used in future heart care related studies. ☐

5. *I understand that information on me will be stored on a secure* computer and that analyses will be conducted confidentially. ☐

This information may be used for scientific publications but my identitywill remain anonymous

6. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of Person taking consent	Date	Signature
Researcher	Date	Signature

1 for patient; 1 for researcher; 1 to be with hospital notes

Hull and East Yorkshire Hospitals NHS
NHS Trust

5. Gp letter

Hull Royal Infirmary
Anlaby Road
Hull
HU3 2JZ

Dear Dr …….

Re: <<patient name, DOB, address, unit number>>.

Your patient has attended the Department of Academic Cardiology and provided an informed consent to participate in the Post MI Study and Heart Care Study

The Post MI Study involves investigating the occurrence and current status of heart failure in all patients who suffered an MI in 1998 and also attended Hull and East Yorkshire hospitals. Prior to contacting the patient, permission of the Consultant Cardiologists to contact the patient was obtained.

The tests involved include blood tests (haemoglobin, urea & electrolytes and NT-BNP – a marker of cardiac dysfunction) an ECG, an echocardiogram and possibly a 24-hour tape.

As per the normal practice of this Department's Heart Care Study, a QED report is enclosed for your information.

Should you wish for further information, please contact me on the number below.

Yours sincerely,

Dr Azam Torabi
Research Fellow in Cardiology
Dept of Academic Cardiology
Floor 3 Haughton Building,
Hull Royal Infirmary
Anlaby Road
Hull
HU3 2JZ
Telephone 01482 675016