Cognitive Impairment in Heart Failure

Jane Ann Cannon MBChB, MRCP (UK)

Submitted in fulfilment of the requirements for the degree
of
Doctor of Philosophy

BHF Glasgow Cardiovascular Research Centre
Faculty of Medicine
University of Glasgow

Date of submission August 2016

Acknowledgement

I am indebted to Professor John McMurray, not only for the opportunity to undertake this research project but also for his untiring supervision and professional support throughout my time working with him. I will always be grateful for his advice and guidance throughout my career in cardiology. I would also like to thank Professor Matthew Walters and Dr Karen Hogg for their expertise and insights.

I would like to express my sincere thanks to all the patients and healthy volunteers who participated in this study and who were so generous with their time. I am grateful for the financial support provided through a research fellowship from The British Society for Heart Failure and Servier.

Many people provided assistance with this study and I would especially like to acknowledge the help of Sister Kirsten Russell, Sister Eve Shannon, Mr David Barber, Mr Neil McInnes and Ms Caroline Wilson. I would like to thank all of the research nurses of the Glasgow Cardiovascular Research Centre and in particular my friend and colleague Sister Barbara Meyer. I am privileged to have worked with so many exceptional colleagues throughout this research including Dr Terry Quinn, Dr Niall Broomfield and Dr John Sharp. For your advice, time and patience and I am most grateful.

To colleagues who have become friends – Drs John Forbes, Natalie Sawdon, Jonathan Dalzell, Eugene Connolly, Ross Campbell, Colette Jackson and many more. Thank you for the welcomed distractions of nights out, cups of tea and mainly for listening to me rant on about this project - I am sure you have heard more about cognitive impairment than you ever wanted to! I am truly lucky to have the most supportive family. Bart, Suzanne, Martin and Margaret – any achievement of mine has been built upon the foundation of my wonderful family and I am grateful for your advice and support (even although I may not always show it!).

This thesis is dedicated to my mum Susan, who has always been there for me with encouragement and reassurance, my husband Graham, for his love, support and patience when I have needed it most and to my dad William, whom I will always love, always miss, and never forget.

Author's Declaration

The work described in this thesis was carried out while I was employed as a Clinical Research Fellow in the University Division of Cardiovascular and Medical Sciences at the British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow. Supervision was provided by Professor John McMurray, Professor Matthew Walters and Dr Karen Hogg.

Recruitment of patients from Greater Glasgow and Clyde Health Board was undertaken by me. I carried out all clinical examinations and follow up visits with the help of Sister Barbara Meyer. I was trained in the administration of the neuropsychological assessments by Dr Niall Broomfield and the calculation and interpretation of the scores was undertaken by Ms Rosalind Lees, Dr Niall Broomfield and Dr John Sharp. Construction of the database was performed by me and several database managers at the Robertson Centre for Biostatistics, University of Glasgow. The more complex statistical analyses were performed by Ms Nicola Greenlaw and Mr Robin Young under the supervision of Professor Ian Ford.

To date, work from this study has been presented at national and international meetings including the British Society for Heart Failure (2014, 2015), American Heart Association Scientific Sessions (2014), the International Congress on Vascular Dementia 2015 and the International Society of Vascular, Behavioural and Cognitive Disorders (2016). I confirm that this thesis has been composed by me solely and that it has not been submitted or accepted in any previous application for a degree. The writing of this thesis is entirely my own work. All sources of information within this thesis are specifically acknowledged.

Dr Jane A Cannon

August 2016

List of publications and presentations related to this work

Publications

Jane A Cannon, Li Shen, Pardeep S Jhund, Soren L Kristensen, Lars Køber, Fabian Chen, Jianjian Gong, Martin P. Lefkowitz, Jean L. Rouleau, Victor C. Shi, Karl Swedberg, Michael R. Zile, Scott D. Solomon, Milton Packer, John J.V. McMurray. On behalf of the PARADIGM-HF Investigators and Committees. Dementia-related adverse events in PARADIGM-HF and other trials in heart failure with reduced ejection fraction. European Journal of Heart Failure August 2016.doi:10.1002/ ejhf.687

Jane A. Cannon, Peter Moffitt, Ana Cristina Perez-Moreno, Karen J.+ Hogg, Matthew R. Walters, Niall M. Broomfield, Terence J. Quinn, John J.V. McMurray. Cognitive impairment and heart failure: systematic review and meta-analysis. Submitted to Journal of Cardiac Failure and under review.

Jane A Cannon, Li Shen, John JV McMurray. Clinical outcomes according to QRS duration and morphology in the irbesartan in patients with heart failure and preserved systolic function (I-PRESERVE) trial. European Journal of Heart Failure 2016;18, 1021-1031

Jane A Cannon, John JV McMurray, Terry J Quinn. "Hearts and Minds": association, causation and implication of cognitive impairment in heart failure. Alzheimer's Research and Therapy 2015;7(1):22

Jane A Cannon, Andrew R McKean, Pardeep S Jhund, John JV McMurray. What can we learn from RELAX-AHF compared to previous AHF trials and what does the future hold? Open Heart Journal 2015;2:e000283.

Jane A Cannon, Timothy Collier, Li Shen, Karl Swedberg, Henry Krum, Dirk J van Veldhuisen, John Vincent, Stuart Pocock, Bertram Pitt, Faiez Zannad, John JV McMurray. Clinical outcomes according to QRS duration and morphology in the Eplerenone in Mild Patients: Hospitalization and Survival study in Heart Failure (EMPHASIS-HF). European Journal of Heart Failure 2015 17, 707-716

Jane A. Cannon, John J. V. McMurray. Gut feelings about heart failure. JACC 2014; 64 (18): 1915-1916.

Jonathan R Dalzell, Jane A Cannon, Joanne Simpson, Roy S Gardiner, Mark C Petrie. Improving outcomes in cardiomyopathy. Expert Review of Cardiovascular Therapy Journal 2015;13(6): 665-71.

Jonathan R Dalzell, Jane A Cannon, Collette E Jackson, Ninian N Lang, Roy S Gardner. Emerging biomarkers for heart failure: an update. Biomark Med. 2014; 8(6):833-40.

Presentations

Abstract submitted to International Stroke Conference, American Stroke Association, Houston, Texas 2017.

Oral presentation and short-listed for European Young Investigator Award. The International Society for Vascular, Behavioural and Cognitive Disorders. Amsterdam, The Netherlands 2016.

European Society of Cardiology – Europrevent scientific meeting. Istanbul, Turkey 2016

Heart failure and comorbidity. Royal College of General Practitioners, London, UK. 2016

Oral presentation of original research work. British Geriatric Society Cardiovascular Specialist Interest Group Scientific Meeting, Royal College of Physicians, London, UK 2015

Cognitive impairment in heart failure. Oral presentation of original research work. 9th International Congress on Vascular Dementia, Ljubljana, Slovenia 2015

Dementia-related adverse effects in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). European Society of Cardiology Heart Failure Congress, Seville, Spain 2015

Cognitive impairment in heart failure: An update on the BSH fellowship. Oral presentation of original research work. British Society For Heart Failure annual meeting. Queen Elizabeth II conference centre, London. November 2015

The impact of dementia on heart failure mortality. American Heart Association annual meeting, Chicago, Illinois 2014

Cognitive impairment in heart failure. Oral presentation of original research work, British Society For Heart Failure annual meeting. Queen Elizabeth II conference centre, London. November 2014

Further funding awarded to support new projects related to this work

BMS investigator initiated award – neuroimaging correlates of cognitive impairment in cardiac disease, £30, 000.00

NHS Greater Glasgow & Clyde endowment fund – cognitive impairment in heart failure: Do cognitive screening measures predict non-compliance with medication in a heart failure cohort, £15, 000.00

British Heart Foundation centre of research excellence seed fund – using neuroimaging to describe the pathophysiology of cognitive decline in heart failure, £20, 000.00

Data used for joint application to BHF/Alzheimers/Stroke Association priority program award in collaboration with University of Edinburgh - under review

Table of Contents

Index of Tables

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

Chapter 9

Chapter 10

Index of Figures

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

Chapter 8

Chapter 11

Abbreviations

ACE:	Addenbrookes Cognitive Examination
ACE-i:	Angiotensin Converting Enzyme inhibitor
AD:	Alzheimer's Disease
ADL:	Activities of Daily Living
3MS:	Modified Mini Mental State Examination
AF:	Atrial Fibrillation
AHA:	American Heart Association
ALT:	Alanine Transaminase
AMT:	Abbreviated Mental Test
ANOVA:	Analysis of Variance
AR:	Aortic Regurgitation
ARB:	Angiotensin Receptor Blocker
AS:	Aortic Stenosis
AST:	Aspartate Transaminase
ALJD:	Adjective List of Janke & Debus
AV:	Atrioventricular
AVLT:	Auditory Verbal Learning Test
BFT:	Buscke-Fuld Test
BHF-GCRC:	British Heart Foundation – Glasgow Cardiovascular Research Centre
BMI:	Body Mass Index
BNP:	Brain Natriuretic Peptide
BP:	Blood Pressure
BSE:	British Society for Echocardiography
CABG:	Coronary Artery Bypass Graft
CAD:	Coronary Artery Disease
CAMCOG:	The Cambridge Cognitive Examination
CAN-TAB:	Cambridge Neuropsychological Test Automated Battery
CASP:	Critical Appraisal Skills Programme
CBTT:	Corsi's Block Tapping Test
CDS:	Cardiac Depression Scale

CHF:	Congestive Heart Failure
CI:	Cognitive Impairment
CI:	Confidence Interval
CIMS:	Complex Ideational Material Subtest
CMR:	Cardiac Magnetic Resonance
CO:	Cardiac Output
COPD:	Chronic Obstructive Pulmonary Disease
COWA:	Controlled Oral Word Association
CPET:	Cardiopulmonary Exercise Test
CRF:	Case Report Form
CRP:	C-Reactive Protein
CRT-D:	Cardiac Resynchronisation Therapy - Defibrillator
CRT-P:	Cardiac Resynchronisation Therapy - Pacemaker
CSF:	Cerebrospinal Fluid
CT:	Computerised Tomography
CV:	Cardiovascular
CVF:	Categorical Verbal Fluency
CVLT:	California Verbal Learning Test
DCT:	Digit Cancellation Test
DCM:	Dilated Cardiomyopathy
DRS:	Disability Rating Scale
DSM:	Diagnostic and Statistical Manual of Mental Disorders
DSST:	Digit Symbol Substitution Test
DST:	Digit Span Test
DT:	Deceleration Time
DTI:	Diffusion Tensor Imaging
DWI:	Diffusion Weighted Imaging
DWMC:	Deep White Matter Changes
ECG:	Electrocardiograph
EDTA:	Ethylene Diamine Tetra Acetic Acid
EF:	Ejection Fraction
eGFR:	Estimated Glomerular Filtration Rate

ESC:	European Society of Cardiology
ESR:	Erythrocyte Sedimentation Rate
ETT:	Exercise Tolerance Test
FAB:	Frontal Assessment Battery
FBC:	Full Blood Count
FLAIR:	Fluid attenuated inversion recovery
FTT:	Finger Tapping Test
GDS:	Geriatric Depression Scale
GLM:	Generalised Linear Model
HADS:	Hospital Anxiety and Depression Scale
Hb:	Haemoglobin
HC:	Healthy Control
HF:	Heart Failure
HFLS:	Heart Failure Liaison Service
HF-PEF:	Heart Failure with Preserved Ejection Fraction
HF-REF:	Heart Failure with Reduced Ejection Fraction
HR:	Heart Rate
ICD:	Implantable Cardioverter-Defibrillators
IDC:	Idiopathic Dilated Cardiomyopathy
IHD:	Ischaemic Heart Disease
IQ:	Intelligence Quotient
IQCODE:	Informant Questionnaire on Cognitive Decline in the Elderly
ISD:	Information Services Division
JVP:	Jugular Venous Pressure
KCCQ:	Kansas City Cardiomyopathy Questionnaire
LBBB:	Left Bundle Branch Block
LFT:	Liver Function Test
LGT-3:	Baeumlers Lern Gedächtnist
LV:	Left Ventricle/Ventricular
LVEDD:	Left Ventricular End Diastolic Diameter
LVEF:	Left Ventricular Ejection Fraction
LVH:	Left Ventricular Hypertrophy

LVSD:	Left Ventricular Systolic Dysfunction
LWHFQ:	Living With Heart Failure Questionnaire
MANOVA:	Multivariate Analysis of Variance
MCI:	Mild cognitive impairment
MDB:	Mental Deterioration Battery
MeSH:	Medical Subject Headings
MI:	Myocardial Infarction
MMSE:	Mini Mental State Examination
MoCA:	Montreal Cognitive Assessment Tool
MR:	Mitral Regurgitation
MRA:	Mineralocorticoid Receptor Antagonist
MRI:	Magnetic Resonance Imaging
MS:	Mitral Stenosis
MST:	Memory Scanning Test
MW:	Mann-Whitney Rank Test
NAART:	North American Adult Reading Test
NCSE:	Neurobehavioural Cognitive Status Examination
NHS:	National Health Service
NOAC:	Novel oral anticoagulant
NT-pro BNP:	N-terminal pro-BNP
NYHA:	New York Heart Association
OSA:	Obstructive Sleep Apnoea
PCI:	Percutaneous Coronary Intervention
PET:	Positron Emission Tomography
PND:	Paroxysmal Nocturnal Dyspnoea
PMT:	Prose Memory Test
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PT:	Prothrombin Time
PVD:	Peripheral Vascular Disease
PVWMC:	Periventricular White Matter Changes
RAAS:	Renin Angiotensin Aldosterone System
RAVL:	Rey Auditory Verbal Learning Test

RBANS:	Repeatable Battery for the Assessment of Neurocognitive Status
RBMT:	Rivermead Behavioural Memory Test
RCPM:	Raven's Coloured Progressive Matrices
RDW:	Red Cell Distribution Width
SCWT:	Stroop Colour Word Test
SD:	Standard Deviation
SDMT:	Symbol Digit Modalities Test
SIGN:	Scottish Intercolliegate Guidelines Network
SLUMS:	Saint Louis University Mental Status
SOB:	Shortness of Breath
SPECT:	Single Photon Emission Computerised Tomography
SSS:	Sick Sinus Syndrome
SVD:	Small Vessel Disease
SVT:	Supraventricular Tachycardia
SW:	Sulcal Widening
SWI:	Susceptibility Weighted Imaging
TFTs:	Thyroid Function Tests
TIA:	Transient Ischaemic Attack
TMT:	Trail Making Test
TR:	Tricuspid Regurgitation
TTE:	Transthoracic Echocardiography
U&Es:	Urea and Electrolytes
VE:	Ventricular Enlargement
VJT:	Verbal Judgement Test
VST:	Visual Scanning Test
VT:	Ventricular Tachycardia
VWST:	Verbal Word Span Test
WAIS:	Wechsler Adult Intelligence Scale
WBC:	White Blood Cell
WHO:	World Health Organisation
WLNS:	Wechsler Letter Number Sequencing
WMS:	Wechsler Memory Scale

WTAR:	Wechsler Test of Adult Reading

Summary

The clinical syndrome of heart failure is one of the leading causes of hospitalisation and mortality in older adults. Due to ageing of the general population and improved survival from cardiac disease the prevalence of heart failure is rising. Despite the fact that the majority of patients with heart failure are aged over 65 years old, many with multiple co-morbidities, the association between cognitive impairment and heart failure has received relatively little research interest compared to other aspects of cardiac disease.

The presence of concomitant cognitive impairment has implications for the management of patients with heart failure in the community. There are many evidence based pharmacological therapies used in heart failure management which obviously rely on patient education regarding compliance. Also central to the treatment of heart failure is patient self-monitoring for signs indicative of clinical deterioration which may prompt them to seek medical assistance or initiate a therapeutic intervention e.g. taking additional diuretic. Adherence and self-management may be jeopardised by cognitive impairment.

Formal diagnosis of cognitive impairment requires evidence of abnormalities on neuropsychological testing (typically a result ≥1.5 standard deviation below the age-standardised mean) in at least one cognitive domain. Cognitive impairment is associated with an increased risk of dementia and people with mild cognitive impairment develop dementia at a rate of 10-15% per year, compared with a rate of 1-2% per year in healthy controls.1 Cognitive impairment has been reported in a variety of cardiovascular disorders. It is well documented among patients with hypertension, atrial fibrillation and coronary artery disease, especially after coronary artery bypass grafting. This background is relevant to the study of patients with heart failure as many, if not most, have a history of one or more of these co-morbidities.

A systematic review of the literature to date has shown a wide variation in the reported prevalence of cognitive impairment in heart failure. This range in variation probably reflects small study sample sizes, differences in the heart failure populations studied (inpatients versus outpatients), neuropsychological tests employed and threshold values used to define cognitive impairment. The main aim of this study was to identify the prevalence of cognitive impairment in a representative sample of heart failure patients and to examine whether this association was due to heart failure per se rather than the common cardiovascular co-morbidities that often accompany it such as atherosclerosis and atrial fibrillation.

Of the 817 potential participants screened, 344 were included in this study. The study cohort included 196 patients with HF, 61 patients with ischaemic heart disease and no HF and 87 healthy control participants. The HF cohort consisted of 70 patients with HF and coronary artery disease in sinus rhythm, 51 patients with no coronary artery disease in sinus rhythm and 75 patients with HF and atrial fibrillation. All patients with HF had evidence of HF-REF with a LVEF <45% on transthoracic echocardiography. The majority of the cohort was male and elderly. HF patients with AF were more likely to have multiple co-morbidities.

Patients recruited from cardiac rehabilitation clinics had proven coronary artery disease, no clinical HF and a LVEF >55%. The ischaemic heart disease group were relatively well matched to healthy controls who had no previous diagnosis of any chronic illness, prescribed no regular medication and also had a LVEF >55%. All participants underwent the same baseline investigations and there were no obvious differences in baseline demographics between each of the cohorts.

All 344 participants attended for 2 study visits. Baseline investigations including physiological measurements, electrocardiography, echocardiography and laboratory testing were all completed at the initial screening visit. Participants were then invited to attend their second study visit within 10 days of the screening visit.

342 participants completed all neuropsychological assessments (2 participants failed to complete 1 questionnaire). A full comprehensive battery of neuropsychological assessment tools were administered in the 90 minute study visit. These included three global cognitive screening assessment tools (mini mental state examination, Montreal cognitive assessment tool and the repeatable battery for the assessment of neuropsychological status) and additional measures of executive function (an area we believe has been understudied to date). In total there were 9 cognitive tests performed. These were generally well tolerated.

Data were also collected using quality of life questionnaires and health status measures. In addition to this, carers of the study participant were asked to complete a measure of caregiver strain and an informant questionnaire on cognitive decline.

The prevalence of cognitive impairment varied significantly depending on the neuropsychological assessment tool used and cut-off value used to define cognitive impairment. Despite this, all assessment tools showed the same pattern of results with those patients with heart failure and atrial fibrillation having poorer cognitive performance than those with heart failure in sinus rhythm. Cognitive impairment was also more common in patients with cardiac disease (either coronary artery disease or heart failure) than age-, sex-

and education-matched healthy controls, even after adjustment for common vascular risk factors.

CHAPTER ONE

INTRODUCTION

1.1 Epidemiology and pathophysiology of heart failure

1.1.1 Definition and classification of heart failure

The European Society of Cardiology define heart failure (HF) as a clinical syndrome with typical signs and symptoms (including shortness of breath, ankle swelling and raised jugular venous pressure) that results from an abnormality of either cardiac structure or function, identified at rest.[2] HF can therefore be viewed as the final common pathway resulting from an initial insult to the myocardium, rather than a diagnosis in itself and an underlying aetiology should therefore be sought.

Contemporary terminology used to describe HF can be based upon left ventricular ejection fraction (LVEF), timing of symptoms or severity of symptoms. The classification relating to LVEF is important, not only because of prognosis (the lower LVEF, the poorer the survival) but also because the large clinical trials that have informed our current clinical practice have largely been based on those patients with heart failure and reduced ejection fraction (HF-REF). There is a sub-group of patients that present with signs and symptoms typical of HF but with preserved ejection fraction on echocardiography (HF-PEF). It has been postulated that inadequate myocardial relaxation preventing normal filling may be the underlying mechanism in these patients. Unfortunately, clinical trials conducted over the past decade have failed to alter the trajectory of this condition which shares the same substantial morbidity and mortality as that of HF-REF.

Some “De Novo” HF patients, experience symptoms for an indeterminate time period and present in a “sub-acute” or “acute” manner. In contrast to this, those patients who have had signs and symptoms of HF for some time are often said to have “chronic HF” and at any time they may experience “decompensation” of their clinical condition.

The most commonly used method of grading severity of HF is the New York Hospital Association (NYHA) classification (Table 1-1). This categorises HF patients according to their functional limitation due to the principal symptoms of HF i.e. dyspnoea and fatigue. Patients can change class at any time and this does not necessarily correlate with LVEF or duration of symptoms.

Table 1-1: New York Heart Association heart failure classification

NYHA Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations or breathlessness.
II	Mild limitation of physical activity. Comfortable at rest or with mild exertion but ordinary activity results in fatigue, palpitations or breathlessness.
III	Marked limitation of physical activity. Comfortable at rest but any ordinary activity causes fatigue, palpitations or breathlessness.
IV	Symptoms of HF at rest. Any physical activity causes exacerbation of symptoms.

1.1.2 Epidemiology of heart failure

The Framingham study published in 1971, described the natural history of HF and showed a prevalence of HF of 0.8% in those aged between 50 and 59, rising to 9.1% in those over 80 with incidence rates of 0.2% at age 54 and 0.4% at age 85.[3] This study relied on a clinical diagnosis of HF. However, more recent epidemiological studies have required objective evidence of HF to fulfil current diagnostic guidelines.[4] Estimates of the incidence and prevalence of HF in the literature will therefore vary depending on the definition of HF used, the diagnostic criteria and the cohort studied.

More recently, the prevalence of HF has been estimated between 1 to 2% of the adult population in developed countries increasing to ≥10% in patients over 70 years with more than half of these older patients having HF-PEF.[5] Data from the Framingham cohort has shown no increase in the incidence of HF since the 1970's, and this pattern is also broadly evident when looking at data from Medicare records. In fact, these records show a reduction in incidence rates from 57.5/1000 to 48.4/1000 person years in the 80-84 year age group in the period from 1994-2003.[4] However, despite the slight reduction in incidence, the prevalence rate rose significantly from 90/1000 to 120/1000 person years. These trends can be explained in part by the ageing of the general population and improved survival from cardiovascular disease.

In Scotland, a large primary care survey estimated the prevalence of HF to be 7.1 in 1000, increasing with age to 90.1 in 1000 among patients over 85 years of age.[6] The investigators found the incidence of HF to be 1.8 in 1000 in men and 2.2 in 1000 in women and this figure is in keeping with estimates from the UK (1.4 and 1.2/1000),[7] Finland (1.0 and 4.0/1000)[8] and the USA (3.4 and 2.4/1000).[9]

1.1.3 Aetiology and pathophysiology of heart failure

HF can result from a broad spectrum of structural or functional cardiac (or non-cardiac) disorders and is often the terminal manifestation resulting from an underlying cardiovascular disease process. Table 1-2 outlines both the common and less common causes of HF. Although determining the underlying aetiology can present a challenge to clinicians, it is important to do so for several reasons. Determining the underlying aetiology can allow for the initiation of specific therapeutic disease-modifying agents, highlight the need for further investigations, inform longer-term prognosis and indicate a need for family screening.

HF-REF is the best understood type of HF with regard to its underlying pathophysiology and treatment. It is often sub-divided into ischaemic and non-ischaemic. Common causes of non-ischaemic HF-REF include hypertension, valvular heart disease, arrhythmias, and certain forms of cardiomyopathy. The cardiomyopathies are a group of disorders defined by structural or functional abnormalities of the ventricular myocardium that are unexplained by flow limiting coronary artery disease or abnormal loading conditions i.e. they tend to be a diagnosis of exclusion.[10] Historically they have been classified into primary forms in which the heart is the only involved organ, and secondary forms resulting from a systemic disorder. The different types of cardiomyopathy include dilated, hypertrophic, arrhythmogenic right ventricular, restrictive and unclassified. They can be further divided into familial and non-familial forms.

Coronary artery disease (CAD) is the cause of approximately two thirds of HF cases.[11] CAD can either present acutely e.g. acute myocardial infarction or insidiously e.g. chronic stable angina/occult disease. Regardless of its mode of onset it triggers maladaptive physiological responses that eventually result in progressive impaired cardiac function.

HF-PEF is more common in older, female patients. It is less frequently due to CAD and is more often linked to hypertension and atrial fibrillation (AF) with the diagnosis being one of exclusion of other non-cardiac causes of breathlessness.[2] HF-PEF can be a precursor to HF-REF in certain causes of HF e.g. hypertension.[12] The pathophysiological basis of HF-PEF remains poorly understood: while an abnormality of diastolic function has been postulated as the underlying mechanism, this hypothesis has been disputed.[13]

Although any cardiac pathology can ultimately lead to HF, most is known about the pathophysiology of HF due to myocardial contractile failure leading to left ventricular systolic dysfunction (LVSD). Following on from the index event (or injury such as myocardial infarction), a loss of myocytes results in the reduction of stroke volume and in turn cardiac output (CO). As a consequence a number of compensatory mechanisms are then triggered in

an attempt to maintain CO. Although, initially effective, over time these compensatory mechanisms contribute to adverse remodelling of the myocardium and a further decline in cardiac function. The process of remodelling is complex and involves a number of haemodynamic, neurohormonal and structural changes which, in combination, result in changes to ventricular geometry, dimensions and ultimately function.[14]

The haemodynamic responses triggered by reduced CO lead to elevated left ventricular diastolic pressure and volume. Initially, the increased stretch applied to cardiac myocytes leads to enhancement of myocardial contractile force. This is the intrinsic adaptive process known as the Frank-Starling law.[15-17] While, within the normal range of end-diastolic volumes an increased haemodynamic load will result in enhanced myocardial contraction, studies have shown that increased preload in the presence of high end-diastolic volumes can lead to a decline in cardiac performance. This decline is often designated the descending limb of the Starling curve.[18]

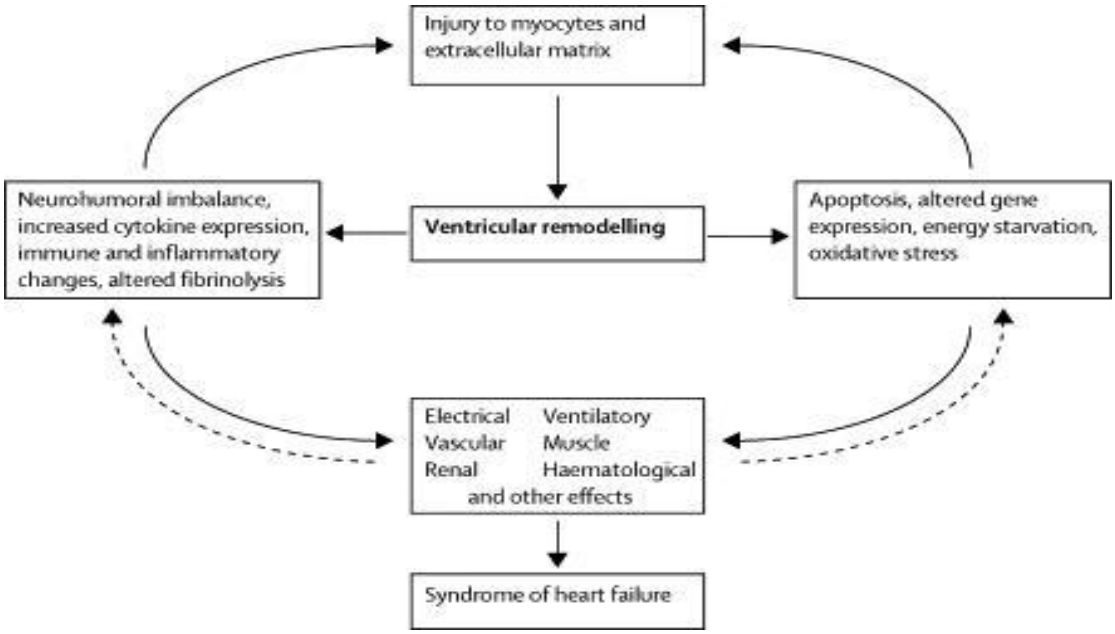
Through activation of the sympathetic nervous system and up-regulation of the renin-angiotensin aldosterone system, neurohormonal responses act synergistically to increase preload (mainly through vasoconstriction and salt and water retention).

Like other compensatory mechanisms over time, these processes too become deleterious by increasing myocardial afterload and stimulating further structural responses (including dilatation of damaged myocardium, hypertrophy of unaffected myocytes and fibrosis of necrotic myocardium) all of which result in further decline in cardiac function and a vicious cycle of progressive HF (Figure 1-1).

Table 1-2: Causes of heart failure

Common causes of heart failure	Less common causes of heart failure
Arrythmias • Atrial fibrillation	Cardiomyopathies • Familial • Peripartum • Toxins (cocaine, iron, copper)
Cardiomyopathies • Alcohol induced cardiomyopathy • Idiopathic cardiomyopathy	Congenital heart disease
Coronary artery disease	Endomyocardial disease • Radiotherapy • Carcinoid
Hypertension	High output • Thyrotoxicosis • Anaemia
Iatrogenic • Anthracyclines • Steroids	Infective • Chagas disease • Viral myocarditis • Human immunodeficiency virus • Lyme disease
Valvular heart disease • Degenerative • Rheumatic fever • Congenital	Infiltrative • Amyloid • Sarcoid • Neoplastic
	Metabolic • Endocrine (e.g. acromegaly) • Nutritional (e.g. thiamine deficiency) • Autoimmune (e.g. scleroderma)
	Neuromuscular • Friedreich's ataxia • Muscular dystrophy
	Pericardial disease • Calcification • Infiltration
	Storage disorders • Haemochromatosis • Fabry disease • Glycogen storage disease

Figure 1-1: Pathophysiology of heart failure due to left ventricular systolic dysfunction. Reproduced with permission from McMurray JJ et al[14]



1.1.4 Diagnosis of heart failure

There are three aspects to the diagnosis of HF. Firstly, the recognition of the cardinal symptoms (e.g. dyspnoea/fatigue) and signs (e.g. peripheral oedema) of the HF syndrome. Secondly, the demonstration of an abnormality of cardiac structure or function with the patient at rest. Finally, the identification of the underlying aetiology.

There is no symptom or sign of HF that is both sensitive and specific to HF and so clinical evaluation, on its own, is not sufficient to confirm the diagnosis. Many of the presenting symptoms are relatively insensitive in discriminating HF from other potential differential diagnoses and those symptoms which are more sensitive are less specific.[19] Many of the clinical signs result from salt and water retention and so are also non-specific (Table 1-3). In addition, these signs can change quickly depending on diuretic use/fluid intake and so are more difficult to assess in patients without clinical decompensation. Signs and symptoms are very useful when assessing response to treatment and can indicate clinical deterioration; which may prompt escalation of therapy.

If clinical HF is suspected, initial baseline investigations including 12 lead electrocardiography (ECG) and B-type natriuretic peptide (BNP) are recommended by both the European Society of Cardiology (ESC) and the Scottish Intercollegiate Guidelines Network (SIGN). [2;20]Less than

8% of patients presenting acutely with HF will have a normal ECG, however, its specificity is relatively poor (<60% at best).[21;22] With more chronic presentations, the ECG has an even lower negative predictive value (<10%).[21] However, the ECG is also a useful tool in assessing the potential underlying aetiology of heart failure e.g. arrhythmia/ischaemia and in guiding treatment e.g. rate control/device therapy.

The most commonly studied blood biomarker in HF is the naturally occurring, cardiomyocyte secreted, peptide BNP. The prohormone, pro-BNP, is released into the circulation from the ventricle in response to increased myocardial stretch, and cleaved into BNP (the active fragment) and N-terminal pro-hormone of brain natriuretic peptide (NT-pro BNP, inactive fragment) both of which can be measured in the plasma. It is well established that plasma levels of both BNP and NT-pro BNP are elevated in patients with LVSD[23] with the degree of elevation proportional to the severity of chronic HF.[24] Factors which may increase serum BNP levels include female sex, increasing age and renal impairment. Obesity can decrease serum BNP levels. The thresholds used in clinical practice are dependent on whether the patient presents with acute HF or with a more gradual onset. A normal BNP level in an untreated patient virtually excludes cardiac disease and suggests an alternative diagnosis should be sought. BNP levels can also be used to monitor response to treatment (levels fall when HF improves) and reflects patient prognosis (higher BNP levels are associated with increased mortality). If both the plasma BNP and 12 lead ECG are normal the chances of finding significant LVSD is <10%.[25] If either the ECG or plasma biomarkers are abnormal, the patient should be referred for echocardiography.[2]

Cardiac imaging plays a key role in the diagnosis of heart failure providing useful information regarding cardiac structure (e.g. cardiac dimensions/volumes) and function (e.g. LV ejection fraction/valvular function). For reasons of access, cost and accuracy transthoracic echocardiography is the most commonly employed cardiac imaging modality. Comprehensive echocardiographic assessment of LV function is, therefore, integral to the HF diagnostic pathway.

Echocardiography may be complemented by other imaging techniques depending on the information gained, local expertise and specific clinical questions e.g. cardiac magnetic resonance imaging (CMR) or computerised tomography (CT).

Additional investigations may be employed to determine the underlying aetiology, these will depend on the clinical history, examination and the suspected underlying diagnosis. These additional investigations may include right and left cardiac catheterisation for suspected constrictive or ischaemic aetiology, cardiac biopsy for suspected infiltrative diseases or genetic

testing for familial cardiomyopathy. Further investigations should be chosen according to their ability to answer specific clinical questions and take account of contraindications to, and risks of, specific tests.

Table 1-3: Sensitivity and specificity of signs and symptoms in diagnosing chronic heart failure. Adapted from 2007 SIGN guidelines *"Management of chronic heart failure"*[20]

Symptom	Sensitivity (%)	Specificity (%)
Dyspnoea	66	52
Orthopnoea	21	81
PND	33	76
Oedema	23	80
Sign	Sensitivity (%)	Specificity (%)
Raised JVP	10	97
3rd heart sound	31	95
Oedema	10	93
Tachycardia	7	99
Crepitations	13	99

PND, paroxysmal nocturnal dyspnoea; JVP, jugular venous pressure

1.1.5 Treatment of heart failure

The goals of treatment in HF are to reduce the burden of HF signs and symptoms, reduce HF hospitalisations and reduce mortality. There is a large, robust evidence base supporting both the use of pharmacological and device therapy in the treatment of chronic HF-REF.

For symptomatic relief, diuretics are the mainstay of treatment and should be initiated as soon as possible after a symptomatic patient presents. Loop diuretics and thiazide diuretics are both used; either in isolation or combination. These two classes of diuretic work on different parts of the nephron and inhibit the resorption of sodium and chloride, promoting salt and water diuresis. Consequently it is important to carefully monitor the patient's fluid status and urea/electrolytes.

Prognostically, the first medication that should be commenced is an angiotensin-converting enzyme (ACE) inhibitor. There is a large evidence base supporting the use of ACE-inhibitors in patients with HF-REF which clearly shows that their use improves morbidity and mortality.[26;27] ACE-inhibitors reduce the conversion of angiotensin I to angiotensin II (the main effector hormone of the renin angiotensin aldosterone system) and so reduce aldosterone release. Ultimately, this results in reduced sympathetic nervous system activity, reduced vasoconstriction and reduced inflammatory and pro-coagulant processes. If a patient is

intolerant of ACE-inhibitor therapy an angiotensin receptor blocker (ARB) should be tried in its place.[28]

Unless contraindicated and once euvolaemic all patients with HF-REF should be initiated on beta blocker therapy. Beta blockers have also been shown to substantially reduce morbidity and mortality.[29] In addition to reducing rates of sudden cardiac death, they can also improve left ventricular ejection fraction and have both anti-ischaemic and anti-arrhythmic properties.[30;31] There is a consensus that ACE-inhibitor/ARB and beta blocker therapies are complimentary and should be started as soon as possible after a diagnosis of HF-REF is made.

In patients who remain symptomatic despite treatment with ACE-inhibitor/ARB and beta blocker therapy, a mineralocorticoid receptor antagonist (MRA) should then be added; again to improve patient prognosis.[32;33] Other evidence based HF pharmacological treatments include ivabradine,[34] digitalis[35] and (in a more select population) the combination of isosorbide dinitrate/hydralazine.[36]

Ventricular arrhythmias are a common cause of mortality in HF patients. Although some of the pharmacological therapies listed above reduce the rates of arrhythmia, they do not completely remove it. Implantable cardioverter-defibrillators (ICDs) aim to prevent sudden cardiac death from ventricular arrhythmias. ICDs are recommended in patients who have had previous symptomatic ventricular arrhythmias, who are expected to survive for longer than one year, irrespective of LVEF. In terms of primary prevention, ICDs should be considered in patients with symptomatic HF (NYHA II-III), with LVEF ≤35%, who have had at least 3 months treatment with optimal medical therapy and are expected to survive for longer than one year. These recommendations are based on large published randomised controlled trials which all showed substantial reductions in mortality when ICDs are used in these subgroups of HF patients.[37-40]

Cardiac Resynchronisation Therapy (CRT) aims to minimise interventricular and intraventricular dys-synchrony. Minimising dys-synchrony increases LV filling time, decreases septal dyskinesis and reduces mitral regurgitation, and thus improves cardiovascular haemodynamics. Several studies demonstrate the beneficial effect of CRT on HF outcomes. CRT use is now recommended in symptomatic patients (NYHA III/IV) who are in sinus rhythm with evidence of dys-synchrony on ECG, that is QRS duration ≥120 milliseconds with left bundle branch morphology (LBBB), an EF ≤35% and who are expected to live for longer than one year.[41;42] In patients who do not have LBBB morphology the QRS duration should be at least 150 milliseconds duration. Those patients with milder symptoms (NYHA II) are required

to have a LVEF of ≤30% and QRS duration of ≥130milliseconds or ≥150milliseconds, depending on the presence or absence of LBBB morphology, respectively.[43]

No treatment has yet been shown to improve outcomes in HF-PEF and so the mainstay of current recommendations is symptomatic relief with diuretic therapy.[44-46] Attention should be paid to the treatment of any associated co-morbidities, such as, ensuring adequate ventricular rate control in patients with atrial fibrillation and optimising blood pressure control in those with hypertension.

1.1.6 Prognosis in heart failure

HF reduces the quantity and quality of life for afflicted individuals and exerts a substantial drain on healthcare services.[47] However, recent reports have suggested that the poor survival of patients hospitalised for HF[48] (as well as those in the community)[49] may be improving; perhaps due to the increased prescription of disease modifying agents such as beta-blockers and ACE-inhibitors.[27;30] Despite this, 25% of patients are re-admitted with signs and symptoms of HF within one month of discharge and 10-20% die in the 6 months after discharge with prognosis in individual patients being highly variable.[50] The development of a prognostic tool that would allow identification of those patients at greatest risk of death is therefore desired and is the subject of ongoing clinical research.

To date, many potential prognostic variables have been highlighted including age, sex, aetiology, NYHA status, LVEF and plasma natriuretic peptide concentrations. Overall scoring systems have also been developed using various combinations of parameters e.g. heart failure risk calculator.[51] Many of these variables are inter-related and whilst they may have strong prognostic power in univariate models, they are competitively removed in multivariate models of prognosis. These variables can change over time with a concomitant effect on prognosis.

The ideal prognostic tool would be cost-effective, easily accessible, minimally invasive, reproducible and both sensitive and specific to HF.

1.2 Heart failure and cognitive impairment

1.2.1 Definition of cognitive impairment

Cognition is the term used to describe a group of mental processes including attention/concentration, memory, language skills, orientation, and problem solving. It is the faculty for processing information, applying knowledge and changing preferences.[52] These

various processes are known as the domains of cognition and each domain can be studied individually. Any one of these domains can be impaired in isolation or in combination.

Cognitive impairment (CI) is an umbrella term that includes chronic as well as more acute problems, such as delirium; both of which can occur in HF. Chronic CI is a spectrum from mild CI (MCI) to dementia, with these two extremes sharing many of the same risk factors and underlying pathophysiology. There are many definitions of MCI in the literature with a division into those focusing on memory impairment and alternatives based on impairment of other domains e.g. language, orientation and attention/concentration.

Although generally first identified by memory difficulty, CI can occur without memory impairment. Even if memory is impaired, the individual may still have the ability to function in daily life. Formal diagnosis of CI requires evidence of abnormalities on neuropsychological testing (typically a result ≥1.5 standard deviation below the age-standardised mean) in at least one cognitive domain. CI is considered a pathological entity and not a function of normal aging. CI is associated with an increased risk of dementia and people with MCI develop dementia at a rate of 10-15% per year, compared with a rate of 1-2% per year in healthy controls.[1]

1.2.2 Cognitive assessment tools used to detect cognitive impairment in heart failure

To date, there are no tools specifically recommended for screening for CI in HF, although several instruments validated in the general population are potential candidates.

Multidomain Screening Tools:

Mini Mental State Examination (MMSE): Although originally developed as a screening test to distinguish "organic" from "non-organic" (e.g. schizophrenia) cognitive disorders, the MMSE is now the most commonly used measure of global cognition. Various cut-off values have been advocated for maximum sensitivity and specificity in differing populations and although the MMSE is not viewed to be sensitive at identifying earlier cognitive changes a cut-off score of ≤ 24 is often used to define CI (Table 1-4). When compared with the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) and the International Classification of Diseases 10 (ICD-10) criteria for dementia the MMSE was reported to have a sensitivity of 94% and specificity of 78%.[53]

Addenbrookes Cognitive Examination (ACE): This was developed in an attempt to address the deficiencies of the MMSE and was designed to be sensitive to the early stages of fronto-temporal dementia and Alzheimer's disease (AD). Based on a validation study, two cut-off

scores were suggested for clinical practice; the higher cut-off score of 88 has an increased sensitivity for the detection of dementia (94%) but lower specificity (89%); the lower cut-off score of 82 is less sensitive (84%) but was 100% accurate in correctly classifying non-demented controls (see Table 1-4).[54]

Montreal Cognitive Assessment (MoCA): This instrument was developed to identify older adults who present with MCI but perform within normal range on the MMSE. The results can be categorised as shown in Table 1-4.

Prolonged neurocognitive assessments are not always practical or feasible in the clinical setting and so the screening tests above are important in identifying patients that warrant further neurocognitive investigation. Domain-specific assessments, however, remain the gold standard in examining cognition.

Neuropsychological batteries: Cognition involves multiple cognitive processes working in unison. Individual cognitive domains can be examined using domain-specific measures. The collective term "battery" is often used when a number of these different tests are grouped together. The most frequently measured individual cognitive domains in HF studies are attention, working memory, delayed memory, learning and psychomotor speed.

The domain of "executive function" is an umbrella term for cognitive processes that regulate, control and manage other cognitive processes such as planning, problem solving, mental flexibility, and the initiation and monitoring of actions.[52] Executive function is particularly important in patients with HF as this determines how a person can recognise novel situations and adapt to them appropriately. Neuropsychological assessments of executive function have been greatly underused in studies of CI in HF to date, although in a few recent cases investigators have attempted to construct a neuropsychological battery to address this gap. For example, Bauer et al[55] tested a neuropsychological battery (Repeatable Battery for the Assessment of Neuropsychological Status [RBANS]) assessing multiple domains, including immediate memory, visuospatial, language, executive function, attention and delayed memory in patients with HF. Eighty community dwelling patients in NYHA class I-IV HF were enrolled, and although a healthy control group was not included, their results were compared with published age and education adjusted norms. Validity was documented by comparing the RBANS scores with individual, previously validated, neuropsychological tests and test-retest reliability was checked by retesting a subsample of 21 participants after 12 days. Both were satisfactory, supporting the use of this battery in patients with HF.

Informant based assessments: Fundamental to the diagnosis of CI is neuropsychological change over time. Patients themselves may struggle to make an objective assessment of personal change over a period of years and so one approach is to question someone familiar with the patient e.g. family member or friend. Informant based interviews retrospectively assess change in cognitive function over time and one commonly used example of this is the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). The preferred IQCODE format is a 16-item questionnaire designed to retrospectively ascertain change in cognitive and functional performance over a 10 year time period.[56] For each item the informant scores change on a 5-point ordinal hierarchical scale with responses ranging from 1: "has become much better" to 5: "has become much worse". This gives a sum score of 16 to 80 that can be averaged by the total number of completed items to give a final score of 1.0 to 5.0, where higher scores indicate greater decline. There are no "normative values" as the IQCODE is designed to assess pathological cognitive decline. A score of >3.6 is often used to differentiate "cases" and "non-cases".[57]

Other aspects of assessment: Cognitive scores need to be interpreted in the context of mood and previous peak intelligence therefore it is important to take these factors into consideration at the time of patient assessment.

The Wechsler Test of Adult Reading (WTAR) is intended as a measure of pre-morbid intelligence allowing us to classify an individual's pre-morbid IQ as low, average, high. This can then be used as a comparison to see the extent of cognitive decline on current testing – based on where they would have been, had they not had some kind of cerebral insult. The test typically takes 5-10 minutes and consists of 50 words with irregular spelling e.g. gnat. Each word is individually presented and examinees are asked to pronounce each. The total raw score is the maximum number of words correctly pronounced (0-50). The obtained raw score is converted to a standard score that is then compared to a predicted score. The predicted score is derived from demographic data based on the test's normative sample and then subtracted from the obtained WTAR score in order to assess the magnitude of difference.[58]

Cognitive defects within mood disorders have been studied extensively.[59-61] Although results have not always been consistent, an overall pattern of specific impairment has become evident. Patients with mood disorders have shown impaired performance specifically in tests of attention, executive function and memory.[62] Evidence that cognitive decline may develop in conjunction with mood disorders was demonstrated in a 7 year study following 600 healthy, elderly participants on measures of cognition and mood.[63] Participants with no depressive symptoms at baseline presented mild, yet progressive cognitive decline annually. With each additional depressive symptom present at baseline, the annual rate of cognitive decline

increased by 24%. Therefore the number of depressive symptoms at baseline was associated with increased risks of developing Alzheimer's Disease (AD).

The Hospital Anxiety and Depression Scale (HADS) is a brief (14 item), self-report measure of anxiety and depression. It was initially developed for use in the general medical outpatient clinic but is now widely used in both clinical practice and research.[64] Interpretation of the HADS is based primarily on the use of cut-off values and the tests authors recommend that, for both the anxiety and depression scales alike, raw scores of between 8 and 10 identify mild cases, 11-15 moderate cases and 16 or above severe cases.[65]

Clinical assessment: The gold standard method for diagnosing CI remains a comprehensive clinical assessment performed in specialist assessment services. This encompasses a detailed history and examination as well as clinical cognitive assessment using standardised instruments in combination with cerebral imaging where appropriate. The World Health Organisation clearly outlines the necessary clinical criteria required in order to fulfil the diagnosis of CI in their ICD-10 classification of mental and behavioural disorders.[66]

Table 1-4: Classification of cognitive screening tools

Screening Test	Score	Clinical Interpretation
Mini Mental State Examination Score	≥25	Normal
	21-24	Mild Cognitive Impairment
	10-20	Moderate Cognitive Impairment
	≤9	Dementia
Montreal Cognitive Assessment Score	>26	Normal
	23-26	Mild Cognitive Impairment
	17-22	Moderate Cognitive impairment
	≤16	Dementia
Addenbrookes Cognitive Examination Score	<88	Cognitive Impairment
	<82	Dementia

1.2.3 Potential pathophysiology of cognitive impairment in heart failure

1.2.3.1 Introduction

Historically, research describing the pathology of dementia has been polarised, with vocal proponents for 'amyloid' and 'cerebral small vessel disease' aetiologies. Increasingly these processes are recognised as co-existing with complex biological interactions.[67] The same is likely true of the pathogenesis of CI in HF. Chronic cerebral hypoperfusion and occult cardioembolic disease are examples of potential mechanistic explanations that have dominated the literature on cognition in HF. Both processes have face validity, have strong supporting scientific and observational data and yet have traditionally been studied in isolation.[68] Although here, the potential pathological mechanisms are discussed separately; it seems likely that both processes frequently coexist in patients with HF and may exert pathological synergy.

Although most of the postulated mechanisms are described in the context of HF-REF, issues of cerebral hypoperfusion, thrombotic disease and concomitant cardiovascular disease are also seen in HFPEF[2] and it seems likely they will factor in the pathogenesis of any cognitive decline seen in this syndrome.

1.2.3.2 Confounding from other disease

Co-existence of dementia and CI has been reported in a variety of cardiovascular disorders, including CAD, myocardial infarction and valvular heart disease. Midlife exposure to the common vascular risk factors of diabetes, hypertension and smoking is associated with later life cognitive decline.[69] This background is relevant to the study of patients with HF as many have a history of one or more of these co-morbidities. As discussed previously, dissecting the contribution of HF from concomitant vascular risk and disease is challenging but is essential for future studies that wish to describe the cognitive component of HF.

AF is a potential confounding condition worthy of separate discussion. The association of AF with cognitive decline is compelling.[70;71] Much of the CI associated with AF is driven by cardioembolic stroke. However, cognitive decline is also seen in patients with AF and no history of clinical stroke, possibly representing occult embolic disease.[70] AF is common in HF and the prevalence increases with severity of disease. Up to 50% of patients with 'end-stage' HF have AF.[72] Increasing use of ambulatory monitors is discovering substantial undetected paroxysmal AF and so these figures may be underestimates. While AF is a factor in the pathogenesis of some HF-related CI, it is probably not the sole explanation. Where studies have

controlled for the presence of AF in their HF patient population, there remains substantial prevalent CI.[69;73-76]

With the increasingly sophisticated interventional toolkit available to cardiologists, the effect of invasive and interventional procedures on cognition should be considered. Acute and chronic neurological deficits associated with cardiac surgery are well described[77] while interventions such as cardiac catheterisation and transcatheter aortic valve replacement have also been associated with post-procedure CI.[78] The mechanism of neurological insult associated with these procedures is likely a combination of reduced cerebral perfusion and embolic disease.

As well as 'physical' conditions, mood disorder may also represent an important confounder of association between HF and CI. Clinically important depression and anxiety are common in patients with HF. Depression is found in nearly 30% of HF patients and is associated with poor outcomes.[79] There is a complex interplay between cognitive decline (particularly in the context of 'small vessel disease'), mood disorder and systemic vascular disease that is poorly understood but likely to be relevant to HF. Mood disorders are particularly important to detect as they can respond to intervention, making mood disorder in HF a potentially treatable form of cognitive decline.

1.2.3.3 Systemic inflammation and amyloid

Several recent studies have demonstrated the formation of tangle and plaque-like structures and fibrillar deposits (that is, the 'hallmark' lesions of Alzheimer's disease (AD) dementia) within the myocardium of patients with hypertrophic cardiomyopathy and idiopathic dilated cardiomyopathy.[80] Mis-folded proteins in the form of intermediate oligomers have also been described in cardiac tissue, with a distribution similar to that observed in the brain of patients with AD,[80] raising the possibility of a common myocardial and cerebral pathology in a subset of patients with HF.

The systemic inflammatory state recognised in patients with HF may also contribute to CI.[81] It is postulated that inflammatory mediators influence cognition via diverse cytokine-mediated interactions between neurons and glial cells. In vitro and animal models support the inflammation and cognitive decline hypothesis and studies in humans with HF are emerging, although data are far from definitive at present.[81]

1.2.3.4 Acute and chronic hypoperfusion

A mechanistic link between hypotension and CI, mediated via chronic cerebral hypoperfusion and loss of the normal autoregulation of cerebral perfusion pressures, has been postulated. Many diseases, including diabetes mellitus and depression, are associated with impaired reactivity of cerebrovascular perfusion autoregulatory systems and this state seems to confer a higher risk of cognitive decline.[82] HF patients often have systemic hypotension and in the context of disordered autoregulation this could lead to further insults to cerebral perfusion. Cerebral perfusion abnormalities have been demonstrated in HF patients, with reactivity more impaired in patients with greater severity of HF.[68]

These hypoperfusion cognitive problems are not necessarily 'vascular' dementia. In animal models, reduced cerebral blood flow triggers a neurotoxic cascade that culminates in accumulation of amyloid and hyperphosphorylated tau proteins, the classical precursors of AD. If chronic hypoperfusion is causative, then improving cerebral blood flow should reduce cognitive decline.

There is some evidence to support this view in patients with severe HF who have undergone cardiac transplant, pacemaker or cardiac resynchronisation therapy, and in whom measures of cognition have stabilised or improved post-procedure.[83-85]

1.2.3.5 Thrombosis and cerebral infarction

The potential importance of AF-related cardioembolism has been discussed. Cardioembolism is also seen in HF with sinus rhythm where ventricular function is the most important determinant of thrombus formation and potential embolic cerebral infarction.[86] Down regulation of thrombomodulin, structural changes in the cardiac chambers and potential blood stasis in the context of reduced myocardial contractility are associated with thrombus formation that may in turn lead to arterial events of clinical stroke or occult cerebral infarction.[86] This systemic prothrombotic phenotype increases risk of all thrombo-embolic diseases and HF is also associated with venous thromboembolism.[87;88] This is not surprising, as abnormalities in all three constituents of Virchow's Triad (abnormal blood constituents, abnormal vessel wall and abnormal blood flow) are present in HF. Neurohormonal activation seen in HF is associated with increased production of thrombogenic factors such as von Willebrand factor, thromboxane A2 and endothelin. The end result is a hypercoagulable state with increased serum levels of circulating fibrinogen, fibrinopeptide A and D-dimer (amongst others) resulting in platelet and thrombin activation and ultimately leading to plasma hyperviscosity and thrombosis.[89] A relationship between all these circulating markers of thrombosis and haemostasis and cognitive decline, particularly 'vascular dementia', has been

described.[90] It would seem intuitive that anticoagulation may prevent sequelae of thrombosis; however, studies of formal anticoagulation in HF with sinus rhythm have been equivocal. To date, no large study of anticoagulation in HF describing cognitive outcomes has been published.

1.2.4 Treatment implications of cognitive impairment in heart failure

There is an impressive evidence base to support pharmacological interventions in HF-REF. Historically HF trials have described clinical outcomes such as death, vascular events and hospitalisation with decompensated HF. There has been little focus on cognition or dementia as trial outcome or as a case mix adjuster. In fact for many of the trials that inform the HF evidence base, dementia or CI will have been an exclusion criterion. Where trialists have attempted to describe cognitive effects of HF treatment, results have been neutral.[91]

Central to the treatment of HF is relatively complex multi-drug pharmacological treatment with attendant need for careful biochemical surveillance and self- monitoring. To achieve optimal outcomes requires strict adherence to prescribed evidence-based therapy.[2] Poor adherence is linked to an elevated risk of hospitalisation and death, whereas appropriate self-management may reduce these risks.[2] It seems intuitive that ensuring adherence and self-management would be especially challenging in the context of CI.

Interventions with ACE-inhibitors have been a mainstay of HF-REF therapy for decades. ACE is also important in neurotransmitter modulation and there are theoretical reasons to believe that ACE-inhibitors may have an effect on cognitive decline. Cognitive sub-studies of the Cardiovascular Health Study and the Italian Longitudinal Study on Ageing[92;93] both reported that subjects treated with ACE-is had equivalent rates of incident dementia compared with those treated with other anti-hypertensives. However, there were intriguing within-class differences in cognitive outcomes - for example, between centrally and non-centrally active agents and between differing drug potencies.[93] The other pillars of HF-REF therapy, beta-blockers and MRA's, may also influence cognition. Although no studies specific to HF are available, there is hypertension literature suggesting theoretical cognitive effects of beta-blockade but inconclusive evidence that this is clinically important.[94] Cognitive effects of MRAs have been demonstrated in animal models but human data are limited.[95]

Novel approaches to pharmacological intervention in HF are being developed, with the natriuretic peptide system a key therapeutic target. These peptides possess differing degrees of haemodynamic, neurohormonal, renal and cardiac effects which may be favourable in the HF setting and may augment the effects of RAAS blockade. Studies using inhibitors of neprilysin (also known as neutral endopeptidase), an enzyme involved in the breakdown of

endogenous natriuretic peptides, have yielded encouraging results.[96] Based on this experience a phase III trial comparing the angiotensin receptor neprilysin inhibitor molecule LCZ696 to the ACE-i enalapril was undertaken in chronic HF-REF (PARADIGM-HF). This trial was recently stopped for benefit of LCZ696 over enalapril.[97] However, cardiac optimism must be tempered by caution regarding potential non-cardiac, cognitive adverse effects. Mutations in the neprilysin gene have been associated with familial forms of AD and neprilysin-deficient mice show an AD phenotype.[98]

In the light of non-definitive data, how should we treat a patient with HF and CI? Cognitive enhancing medication such as acetylcholinesterase inhibitors have recognised effects on the cardiac conduction system, occasionally causing bradycardia, sick sinus syndrome or other arrhythmias (including torsades de pointes) resulting from QT prolongation through excessive cholinergic stimulation. One recent study showed donepezil to be safe in patients without symptomatic heart disease and actually reduced levels of plasma brain natriuretic peptide in patients with subclinical HF.[99]

Although there are no data to suggest cognitive benefits of standard HF therapy, there are equally no signals of harm. Given the beneficial effects of pharmacological therapy on mortality and hospitalisation, it would seem sensible to consider these evidence-based medical interventions for all HF patients, tailoring the intervention to suit the patient. A multidisciplinary approach with frequent review and medication titration seems to work well. Prescribers need to be alert to the potential effects of CI on concordance with sometimes complex drug regimens. Early use of compliance aids and involvement of family or carers may help in this regard. The goal of management of HF is to provide 'seamless care' in both the community and hospital to ensure the treatment of every patient is optimal.

Despite the plethora of publications and guidelines, the data consistently show a lower uptake of evidence-based investigations and therapies in older patients with consequent higher rates of HF hospitalizations and mortality.[100] The current shift away from concentration on individual drug therapies to a focus on systems of care that allow effective treatment delivery is welcomed.

1.3 Aims of study

CI is well documented in a range of cardiovascular disorders such as CAD,[101] hypertension[102] and AF.[103] This is relevant to the study of HF patients, as we know that many, if not most, have a history of one or more of these co-morbidities. The documented prevalence in of CI in HF in current literature varies hugely – from 30 to 80% (see chapter 2). This variation probably

reflects variation in study design, HF severity, sample size, neuropsychological assessment tools and the diagnostic criteria employed in the various studies.

This study aims to provide a more comprehensive evaluation of cognition in HF by using larger sample sizes, performing an extensive neuropsychological assessment using a "domain-based" battery of tools and including both cardiac and healthy control participants. Particular attention has been paid to the domain of executive function which is involved in the handling of novel situations. It enables an individual to recognise a new situation, process the information and formulate a plan accordingly. This is obviously key to patients involved in symptom recognition and self-management and has been understudied in HF literature to date. The hypotheses of this study are three-fold.

Firstly we hypothesise that patients with HF will attain lower cognitive scores than those age and sex matched healthy control participants. Secondly, HF patients will attain lower cognitive scores than age and sex matched cardiac controls. Thirdly, not with-standing the first two hypotheses, patients with a combination of HF and AF (either permanent or paroxysmal) will have poorer cognition than those with HF and no history of AF.

The aims of this study are:

- To determine the prevalence of CI in the stable, CHF outpatient population.
- To determine if the underlying cause of HF (ischaemic versus non ischaemic) affects the prevalence of CI in CHF.
- To determine if the presence of AF affects the prevalence of CI in CHF.
- To determine if the "pattern" of CI differs between cohorts i.e. global CI versus impaired executive function.
- To compare different cognitive assessment tools including MMSE, MoCA and RBANS
- To determine if CI is associated with:
    - Mood
    - Carer burden
    - Markers of self-care

Ultimately, this study aims to determine whether CI is a feature of HF *per se* rather than the cardiovascular co-morbidity characterising HF.

CHAPTER TWO

SYSTEMATIC REVIEW OF THE LITERATURE

2.1 Introduction

The clinical syndrome of HF imposes an immense burden of symptoms on patients, reduces quality of life and is one of the leading causes of hospitalisation and mortality, particularly in more developed countries.[5] Due to aging of the population and improved survival from CAD prevalence of HF is expected to double within the next 40 years.[104] These arguments of high symptomatic and economic burden and increasing absolute numbers in the context of an ageing population equally apply to the syndromes of cognitive impairment CI and in particular, dementia.

CI has been reported in a variety of cardiovascular disorders. It is described in patients with hypertension,[102] AF[103] and CAD, especially after coronary artery bypass grafting (CABG).[101] Many patients with HF, if not most, have a history of one or more of these co-morbidities. The pathogenesis of CI remains poorly described but putative mechanisms such as cerebral hypoperfusion; cumulative cerebrovascular insults and systemic inflammation may all be relevant in cardiac disease. Central to the treatment of HF is a relatively complex multi-drug pharmacological treatment which requires careful biochemical surveillance, strict adherence and high level self-management.[2] Successful self-management may be jeopardised by CI.

Thus, there are plausible reasons to suspect an association between HF and cognitive decline. Understanding this association is important, particularly as CI may impact on HF management. A literature describing CI in the HF population is available but papers are published in disparate specialty medical journals (cardiology, neurology, psychiatry), sample sizes can be modest and results are inconsistent. Individually these papers provide little insight into the link between the two conditions. In this situation a comprehensive synthesis of all published literature with summary statistics can give useful information.

2.2 Methods

This systematic review was designed, conducted and reported according to the "Preferred Reporting Items for systematic reviews and meta-analyses" (PRISMA) guidelines.[105] A search protocol was created and is available on an open access web-based resource (PROSPERO, registration number CRD42014015485).[106]

The primary aim was to describe an association between HF and CI (where CI is a syndrome including mild cognitive impairment, multi-domain cognitive impairment and varying severities of dementia). Two independent researchers trained in systematic review, performed all aspects of searching, selection, extraction and assessment (J.A.C & P.M) any disagreements were referred to a third arbitrator (T.J.Q).

2.2.1 Inclusion/exclusion criteria

The eligibility criteria were defined prior to any literature searches and were outlined as follows:

1. Studies published in English.
2. Studies with at least 50 human participants.
3. Original research published in peer reviewed scientific journals.
4. Studies presenting data on CI and HF with the following study designs: prospective cohorts, cross sectional population studies and case-control studies.
5. Studies using at least one validated measure of cognition or clinical diagnosis made according to recognized criteria.
6. Studies including patients with a formal clinical diagnosis of HF.

Randomized controlled trials that collected cognitive data as primary or secondary outcome were excluded as the included participants may not be generalizable to an unselected HF population. Abstracts were included in the search but, for the final selection of studies only those that had been fully published in peer reviewed journals were included. Papers were not excluded on the basis of year of publication.

2.2.2 Search strategy

A sensitive search strategy based around concepts of [heart failure] and [cognition/dementia/cognitive testing] was created. Where available validated search strings were used and supplemented with MeSH terms and other controlled vocabulary. (figure 2-1

outlines the search strategy and review profile). Multidisciplinary databases were searched from inception until 31st May 2015: MEDLINE (OVID), EMBASE (OVID), CINAHL (EBSCO), PsychINFO (EBSCO), Web of Science (Thomson Reuters) and CENTRAL (Cochrane Library). Where the facility was available, the "explode" function was used in those databases. Bibliographies of included papers and relevant reviews were searched for further possible titles and the process was repeated until no new titles were found. Where the same data were presented in more than one publication the primary (first) publication was used.

After de-duplication, titles generated from the initial database searches were screened and if felt to be relevant, then the full text was reviewed.

2.2.3 Data extraction

For papers eligible for inclusion, data were extracted to a pre-specified and piloted proforma. Information regarding diagnosis of HF, with particular focus on subtypes of HF (HF-PEF or HF-REF); severity of HF (symptomatic or objective marker); sampling frame (outpatient or inpatient/mixed) and cognitive assessment or criteria employed were collated.

2.2.4 Risk of bias and generalizability assessment

Internal and external validity were assessed using the approach outlined in critical appraisal skills (CASP) guidance.[105] The CASP checklists were used for cohort and case-control studies and domains were assessed relating to sampling frame, case ascertainment (dementia and HF) and confounding to create a semi-quantitative assessment. A paper was defined as low risk of bias where the following criteria were met: samples recruited had robust diagnosis of HF based on current ESC guidelines; cognitive function was assessed using standardized cognitive assessment tools or diagnosis made using validated classification system; confounding factors taken into account in the analyses of results.

For longitudinal studies a follow up period of 18 months was deemed to be an appropriate timescale to assess for the development of cognitive impairment. For each study external validity was considered including whether the results could be applied to a contemporary HF population.

2.2.5 Data analyses

A summary of key findings were formatted into tables to inform a narrative synthesis of the included papers. Meta-analyses were performed to give summary estimates in those instances where more than 3 papers used a similar study design and contained comparable cognitive assessments. Heterogeneity was assessed through visual inspection of forest plots and

quantitatively using Higgins I^2 and potential publication bias was assessed using a funnel plot. All meta-analyses were run with both a fixed and random effects model.

Differing statistical approaches were pre-specified depending on the study design. For case-control data we calculated relative risks comparing proportions with CI in the HF population versus the healthy control population. For cross-sectional studies point estimates of prevalence of CI / dementia were described. It was intended to assess rates of incident CI/dementia and calculate summary hazard ratios in prospective studies.

A sensitivity analysis was pre-specified, restricted to those studies judged as low risk of bias on validity assessment and subgroup analyses were pre-specified restricted to outpatient populations only. All analyses were performed using Stata version 14 (Stata Corp, College Station, Texas).

2.3 Results

From 18000 titles identified, 350 abstracts were selected for review, 87 full manuscripts were assessed and 37 papers (n=8411 participants) were eligible for inclusion in the final review. Figure 2-1 outlines the search strategy and review process.

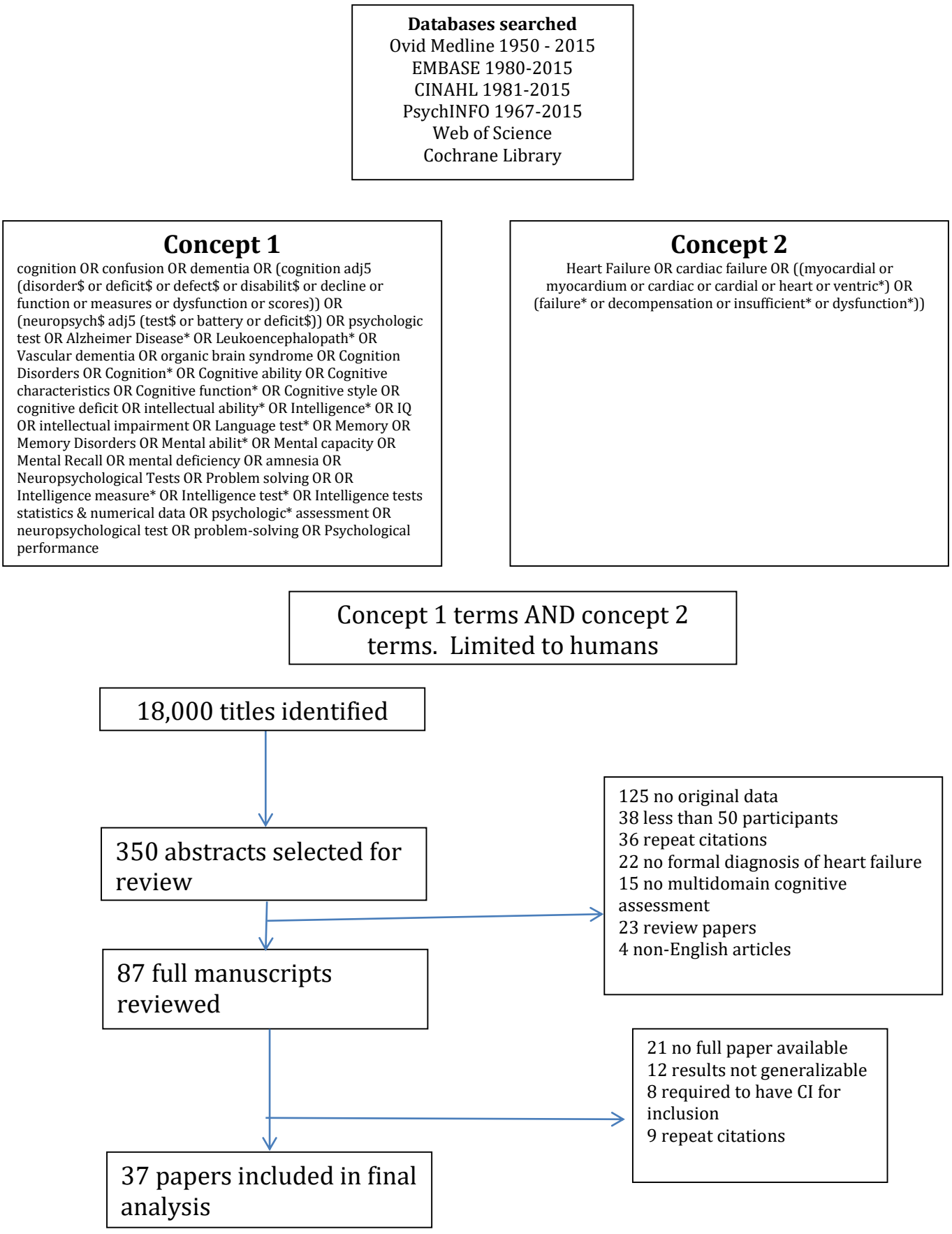


Figure 2-1: Search strategy and review profile for systematic review

2.3.1 Narrative review of included studies

7 case control studies were included (representing 1781 participants),[55;107-112] 4 of which included healthy participants as the control group[107-110] with the other 3 comparing rates of CI between HF cohorts i.e. between those with HF-PEF and HF-REF.[55;111-113] 26 cross-sectional studies were included[73;74;100;114-136] (representing 4177 participants) the majority of which (n=18) recruited patients from the outpatient setting.[100;114-118;121-123;127-129;131-136] Only 4 studies (with 2513 participants) examined for incident cognitive function/ dementia in patients with HF over prospective longitudinal follow up.[137-140] All key study characteristics are summarised in tables 2-1 - 2-3.

Table 2-1: Design of case-controlled studies

Study	Sample	Population	CV Measures/Criteria	Cognitive assessment tool used
Bauer et al 2011[55]	51 HF-REF patients 29 HF-PEF patients	Outpatients only	LVEF NYHA	RBANS Neuropsychological battery
Bratzke-Bauer et al 2013[112]	47 HF-REF patients 33 HF-PEF patients	Outpatients only	LVEF NYHA	MMSE RBANS Neuropsychological battery
Callegari et al 2002[107]	64 HF patients 321 healthy control participants	Consecutive admissions	LVEF<50% NYHA I-III CPET Right heart catheterisation	Neuropsychological battery
Festa et al 2011[111]	169 HF-REF patients 38 HF-PEF patients	Outpatients only	LVEF	Neuropsychological battery
Pressler et al 2010[110]	249 HF patients 63 healthy control participants 102 general medical patients	Outpatients only	NYHA LVEF	MMSE Neuropsychological battery
Sauvé et al 2009[108]	50 HF patients 50 healthy control participants	Outpatients only	LVEF≤40% NYHA II-IV	Neuropsychological battery
Trojano et al 2003[109]	149 HF NYHA II patients 159 HF NYHA III/IV patients 207 non HF control patients	Consecutive admissions	No measure of LV function NYHA II-IV	MMSE Neuropsychological battery

Table 2-2: Design of cross sectional studies

Study	Sample	Population	CV Measures /Criteria	Cognitive assessment tool used
Alosco et al 2014[114]	110 CHF patients	Outpatients	LVEF NYHA II-IV	3MS
Alosco et al 2012[117]	157 CHF patients	Outpatients	2 minute step test NYHA	Neuropsychological battery
Alosco et al 2013[116]	52 CHF patients	Outpatients	Cardiac Index	MMSE RBANS
Alosco et al 2014[115]	179 CHF patients	Outpatients	LVEF NYHA II-IV	Neuropsychological battery
Antonelli et al 2003[119]	369 CHF patients	Consecutive admissions	NYHA	MMSE Neuropsychological battery
Arslanian- Engoren et al 2014[120]	53 CHF patients	Inpatients	NYHA	Cogstate battery
Athilingam et al 2011[121]	90 CHF patients	Outpatients	NYHA LVEF Cardiac index & 6 minute walk test	MMSE MoCA
Baldasseroni et al 2010[122]	80 CHF patients	Outpatients	NYHA 6 minute walk test LVEF MLHFQ	MMSE
Cacciatore et al 1998[123]	92 CHF participants	Outpatients	NYHA	MMSE
Cameron et al 2010[124]	93 CHF patients	Consecutive admissions	LVEF NYHA Self-care HF index	MMSE MoCA
Debette et al 2007[74]	83 HF patients	Consecutive admissions	LVEF<45% NYHA I-IV	MMSE
Dodson et al 2013[125]	282 decompensated HF patients	Non-consecutive admissions	HF diagnosis based on documentation in medical records	MMSE
Feola et al 2007[73]	60 CHF patients	Inpatients	LVEF NYHA II-IV BNP	Neuropsychological battery

Feola et al 2013[126]	303 CHF patients	Consecutive admissions	LVEF NYHA BNP 6 minute walk test Non-invasive CO	MMSE
Gallagher et al 2013[127]	128 CHF patients	Outpatients	NYHA MLHFQ	MoCA
Garcia et al 2011[128]	116 CHF patients	Outpatients	NYHA 2 minute step test	3MS Neuropsychological battery
Ghanbari et al 2013[129]	239 CHF patients	Outpatients	NYHA LVEF	MMSE
Hajduk et al 2013[130]	577 CHF patients	Inpatients	Not specified	MoCA Neuropsychological battery
Harkness et al 2013[100]	100 CHF patients	Outpatients	LVEF ≤45% NYHA I-III Self-care in HF index	MMSE MoCA
Hawkins et al 2014[131]	231 CHF patients	Outpatients	NYHA	Neuropsychological battery
Hawkins et al 2012[132]	250 CHF patients	Outpatients	LVEF	RBANS Neuropsychological battery
Hjelm et al 2013[133]	137 CHF patients	Outpatients	NYHA LVEF BNP	MMSE Neuropsychological battery
Jesus et al 2006[134]	83 CHF patients	Outpatients	LVEF	MMSE
Miller et al 2012[118]	140 HF patients	Outpatients only	No measure of LV function No NYHA classification 2 minute step test	Neuropsychological battery
Steinberg et al 2011[135]	55 HF patients	Outpatients only	LVEF≤45% NYHA I-III 6 Minute Walk Test	MMSE Neuropsychological battery
Vogels et al 2007[136]	58 CHF patients	Outpatients	LVEF NYHA	MMSE Neuropsychological battery

BNP, brain natriuretic peptide; CHF, chronic heart failure; CO, cardiac output; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota living with heart failure questionnaire; MMSE, mini mental state examination; MoCA, Montreal cognitive assessment tool; 3MS, modified mini mental exam; NYHA, New York heart association; RBANS, repeatable battery for the assessment of neuropsychological status

Table 2-3: Design of longitudinal studies

Study	Sample	Population	CV Measures /Criteria	Cognitive assessment tool used	Follow up period
Almeida et al 2012[137]	77 CHF patients with LVEF <40% 73 CAD patients with LVEF >60% 81 controls with no CAD/CHF	Outpatients	LVEF 6 minute walk test	MMSE Neuropsychological battery	24 months
Hjelm et al 2012[138]	95 HF patients 607 non-CHF controls	Outpatients	HF diagnosis based on documentation in medical records	Neuropsychological battery	10 years
Qiu et al 2006[139]	205 CHF patients 1096 controls	Outpatients	Not specified	MMSE	9 years
Riegel et al 2012[140;141]	279 consecutive HF patients (HF-REF & HF-PEF)	Outpatients	NYHA I-IV LVEF	Neuropsychological battery	6 months

CAD, coronary artery disease; CHF, chronic heart failure; HF, heart failure; HF-PEF, heart failure preserved ejection fraction; HF-REF, heart failure reduced ejection fraction; LVEF, left ventricular ejection fraction; MMSE, mini mental state examination; NYHA, New York heart association;

Available longitudinal studies included ambulatory patients with HF followed for between six months and ten years.[138;141] Within the prospective study rubric, various study designs were employed including comparison of HF-PEF and HF-REF and comparison of HF with healthy controls. The heterogeneity precluded any attempt at meta-analysis. Three studies compared HF and non-HF groups,[137-139] where follow-up was longer than two years the HF group seemed to have greater decline in cognition. (table 2-4).

Table 2-4: Results from longitudinal studies

Study	Sample	Age (Years)	Hazard Ratio (at last follow-up)	Follow up period	Cognitive outcome	Change over time
Almeida et al 2012[137]	77 CHF patients with LVEF <40% 73 CAD patients with LVEF >60% 81 controls with no CAD/CHF	68 (10) 68 (10) 69 (11)	N/A	24 months	CAMCOG	CAMCOG scores in CHF group declined by 0.9 points over 2 years No other differences between groups
Hjelm et al 2012[138]	95 HF patients 607 non-CHF controls	84(3)	1.258 (95%CI: 0.95-1,66)	10 years	Neuropsychological battery	HF patients: Significant decline in episodic memory & spatial performance compared with controls.
Qiu et al 2006[139]	205 CHF patients 1096 Controls	83 (5) 81 (5)	1.84 (95%CI: 1.35-2.51)	9 years	Dementia (DSM diagnosis)	Over 9 years 85% CHF patients developed CI & 65% of controls developed CI
Riegel et al 2012[140]	279 consecutive HF patients (HF-REF & HF-PEF)	62 (12)	N/A	6 months	DSST	No significant change in cognition over 6 months (HF-REF and HF-PEF) Minimal improvement in DSST (53 (18)- 58 (18)) in both groups likely due to learned effect

CAD, coronary artery disease; CAMCOG, Cambridge cognition examination; CHF, chronic heart failure; CI, cognitive impairment; DSST, digit symbol substitution test; HF, heart failure; HF-PEF, heart failure preserved ejection fraction; HF-REF, heart failure reduced ejection fraction; N/A, not applicable

2.3.2 Quantitative analyses

Of all eligible studies n=20 (n=2290 participants) cross-sectional[73;116;142,74;100;118;118;121-130;132-136] and n=4 (n=1414 participants) case-control were suitable for quantitative summary analyses.[107-110] There was substantial heterogeneity across all analyses (I2: 98.5% for cross-sectional; 71.5% for case-control) and random effects data are preferentially reported in the text (both models presented in the forest plots).

For cross-sectional studies describing prevalence of CI; there was a spread in reported values from 0.1 (95% CI: 0.07-0.14) to 0.79 (95% CI: 0.75-0.82). Summarising the data, overall prevalence was 0.43 (95%CI: 0.30-0.55). For subgroup analysis restricted to those studies including only outpatients (n=14 papers; 1620 participants),[100;116;118;121-123;127-129;132-136] results were similar 0.40 (95% CI: 0.28-0.52); as were summary results in the sensitivity analysis restricted to low risk of bias studies (n=13 papers; 2012 participants) 0.44 (95%CI: 0.29-0.59).[100;116;121-124;127-130;132;133;136] (Figures 2-2 – 2-4). There were insufficient studies to allow for the proposed subgroup analysis looking at HF-PEF and HF-REF.

For case-controlled studies, n=4 papers (1414 participants) compared rates of CI and dementia in HF versus non-HF controls.[107-110] Overall the random effects model showed a 1.55 relative risk (95% CI: 1.23- 1.95) of CI in the HF cohort (figure 2-5). There were insufficient data to allow comparison between those case controlled studies comparing HF-PEF and HF-REF.

A funnel plot showing effect estimates against study size for the cross sectional data is shown in figure 2-6. This shows a relatively symmetrical funnel shape suggesting publication bias was not a major issue.

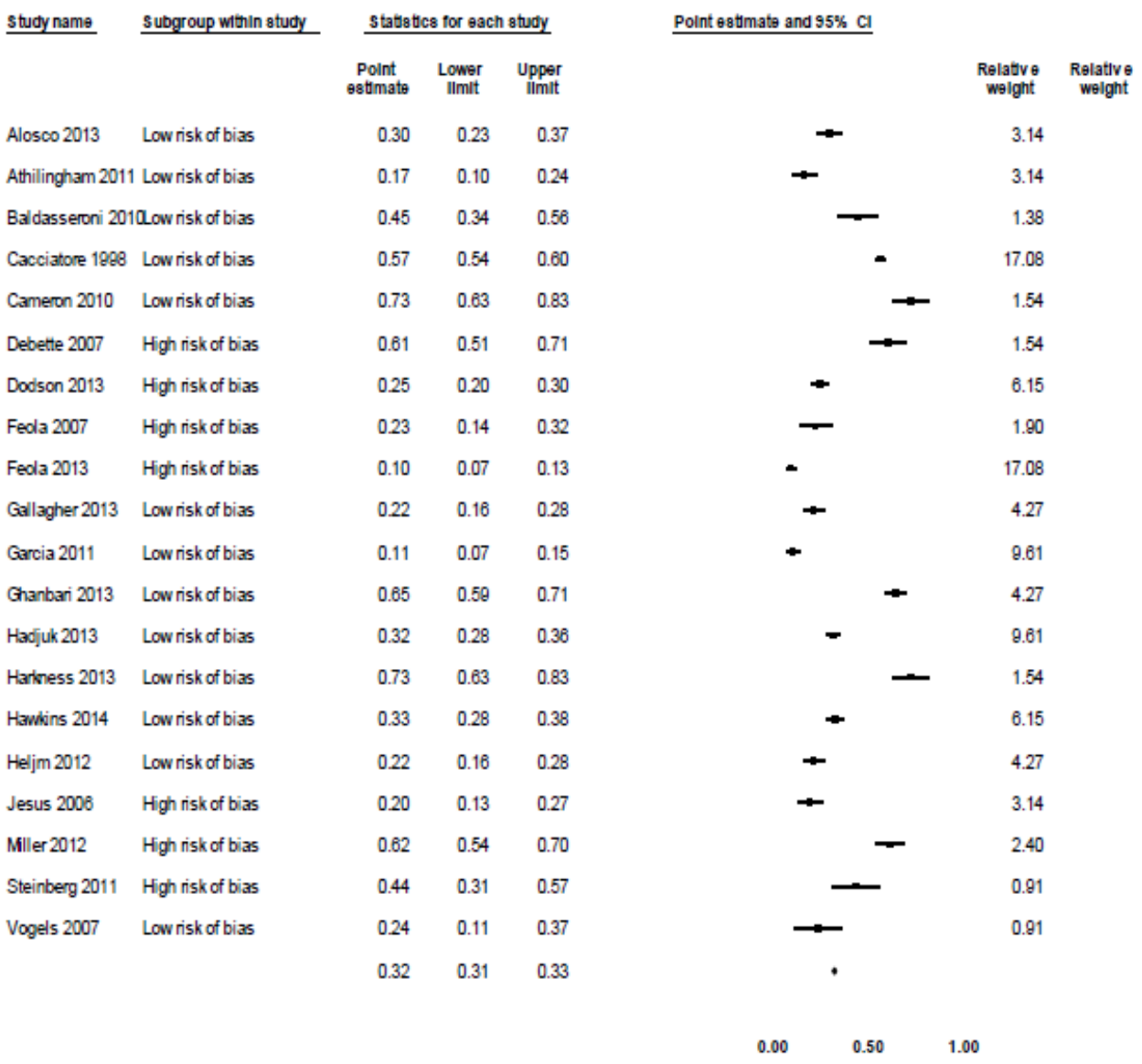


Figure 2-2: Forrest plot of all cross-sectional studies (N=20) showing overall point estimate of 0.32 (95% CI: 0.31 – 0.33) for the risk of cognitive impairment in heart failure.

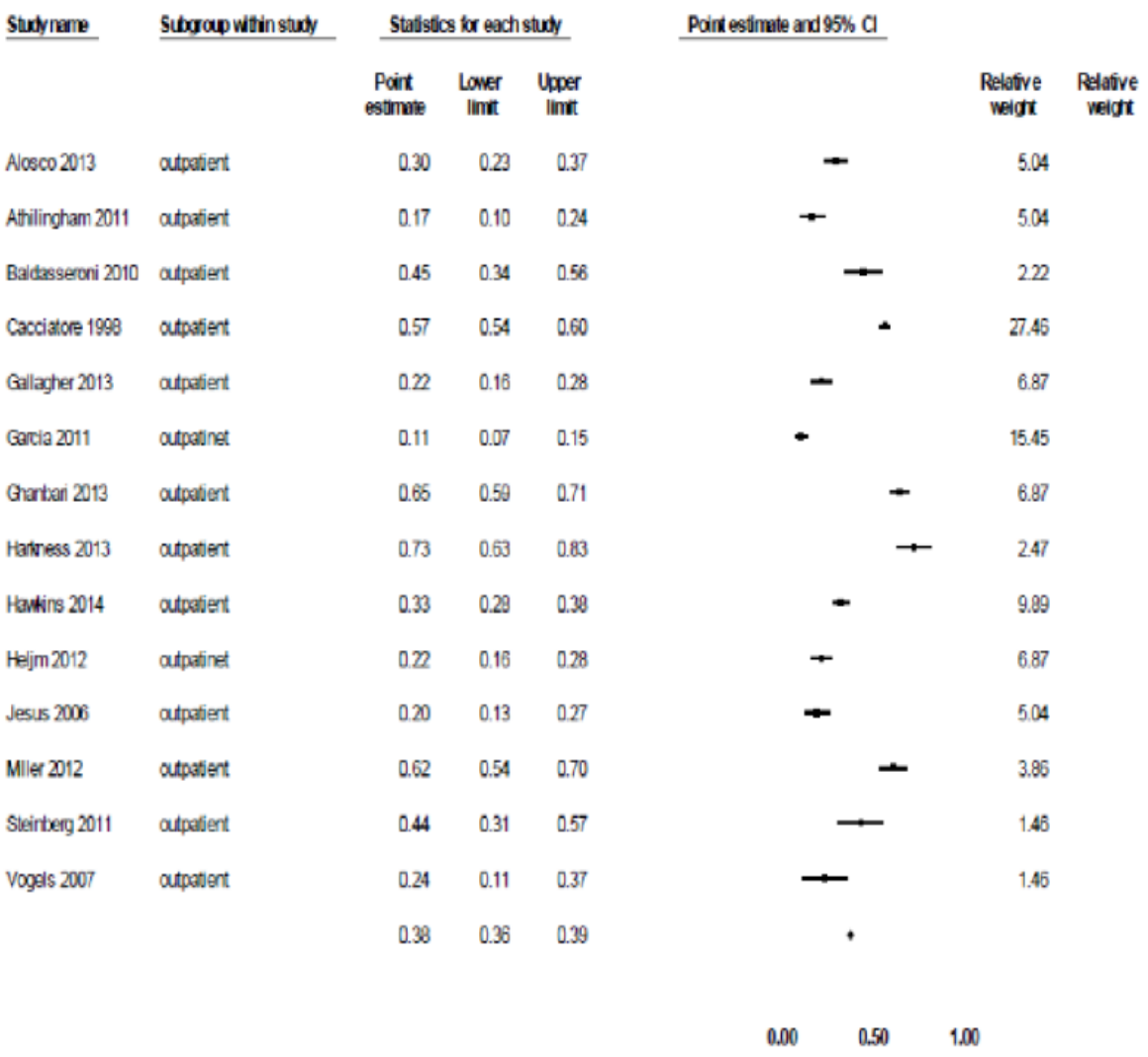


Figure 2-3: Forrest plot of cross sectional studies which recruited from outpatient populations only (N= 14) showing point estimate of 0.38 (95% CI: 0.36 -0.39) for the risk of cognitive impairment in heart failure.

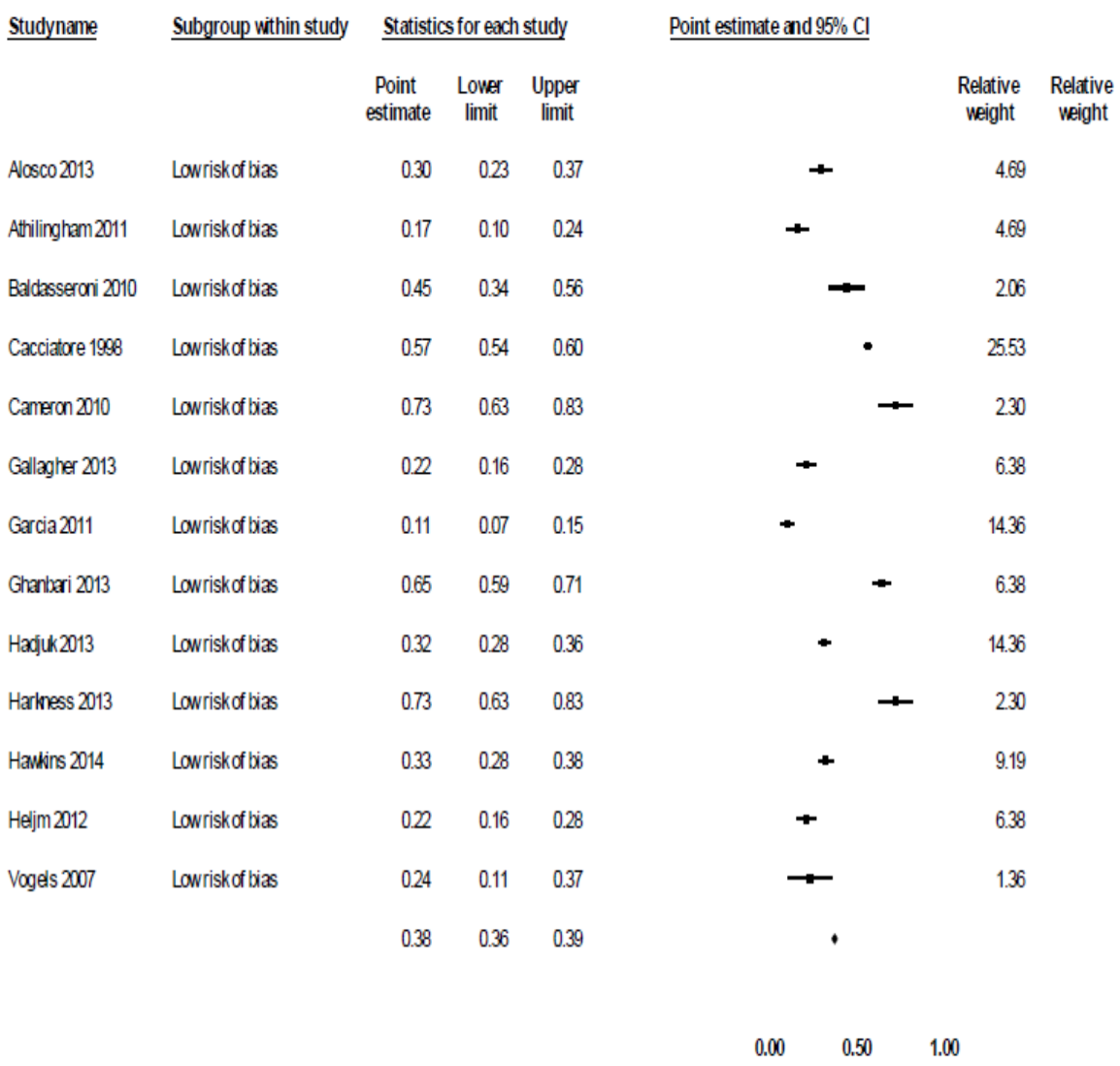


Figure 2-4: Forest plot of cross sectional studies which were found to have a "low risk" of study bias (N=13) showing overall point estimate of 0.38 (95% CI: 0.36-0.39) for the risk of cognitive impairment in heart failure.

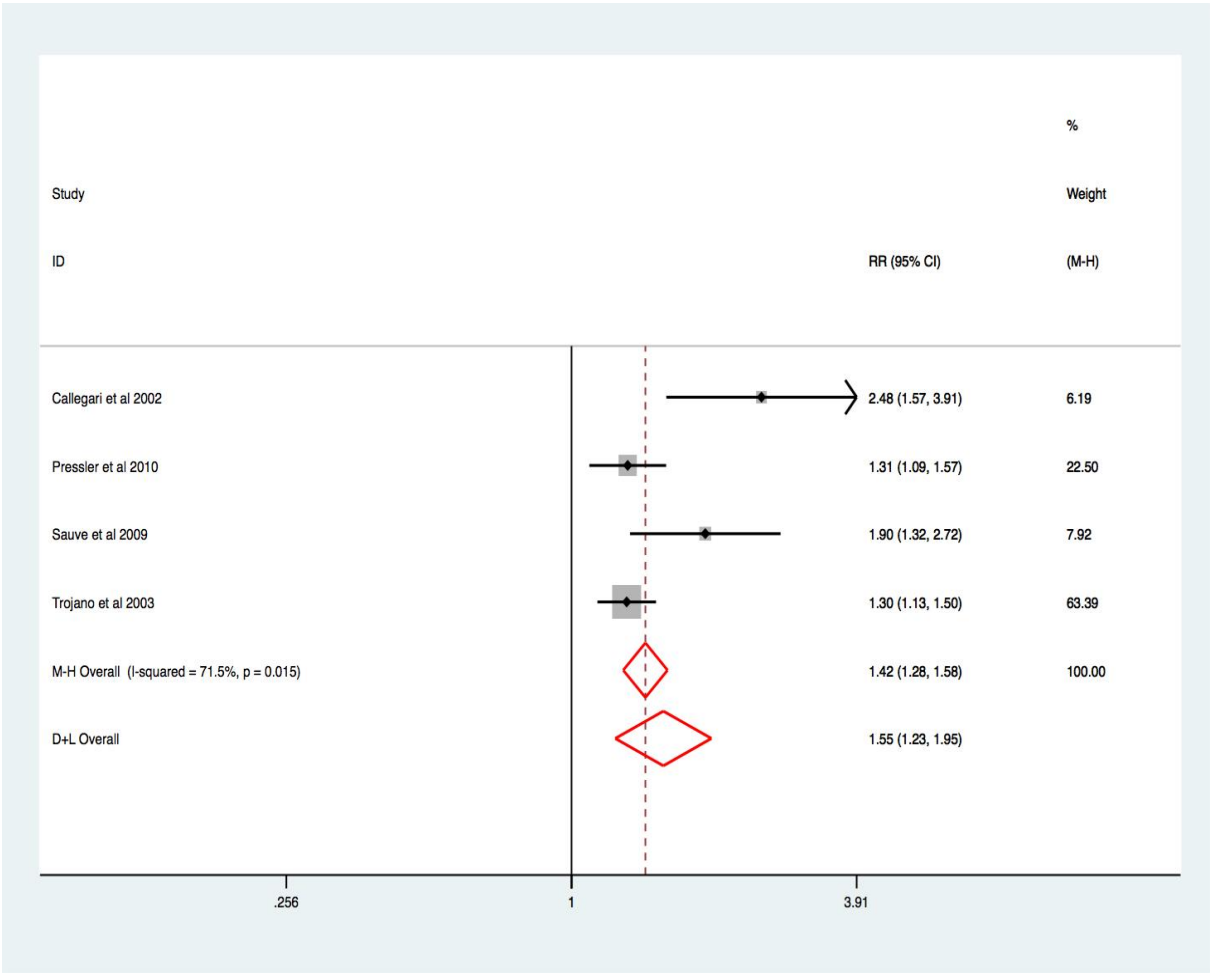


Figure 2-5: Forrest plot showing case controlled studies comparing heart failure cohort vs. healthy controls

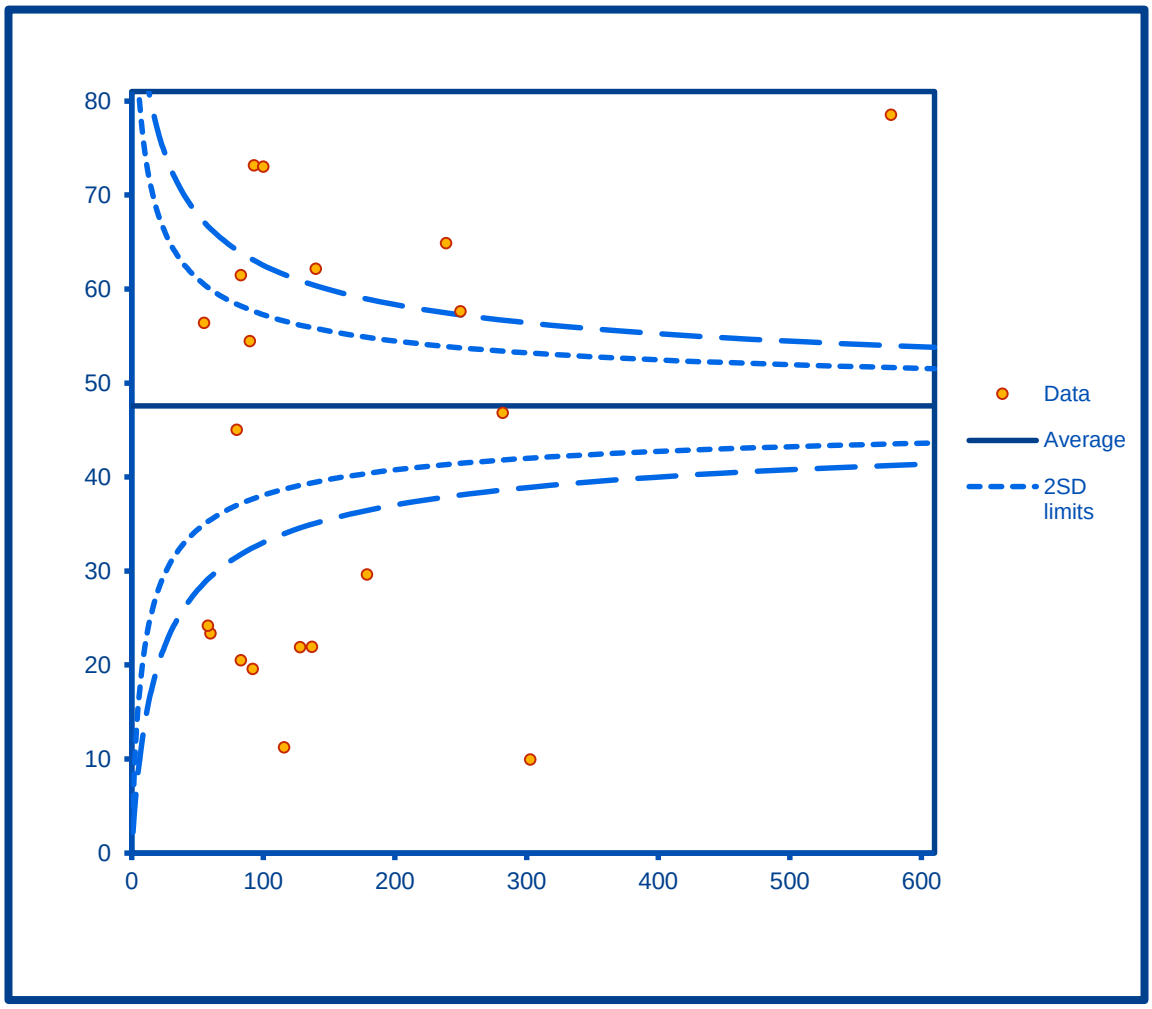


Figure 2-6: Funnel plot of cross-sectional data

2.4 Discussion

A strong association between HF and cognitive problems have been demonstrated in this systematic review. Summary data suggest that in an unselected HF population around 40% will have CI or dementia. Subgroup and sensitivity analyses confirm that this high prevalence is robust and not driven by poor quality studies or by inclusion of significant numbers who were unwell with decompensated HF. Case-control data suggest that compared to matched controls with no HF, those with HF have significantly increased risk of CI.

Observational data are susceptible to a variety of biases. The variability of the prevalence rates for CI that are reported in the reviewed studies probably results from the differences in the populations studied and the differences in the range and specificity of the instruments used to assess cognition. The heterogeneity of samples including patients and control subjects who had previous neurological injuries poses an additional limitation on the samples in most of the studies included.

The ideal study design looking at the association between HF and CI would involve longitudinal follow up of a group of patients with HF (but free of CI at inception) with regular administration of standardised cognitive assessment tools and comparison with a group of age-, sex- and education-matched control cardiac patients as well as healthy control participants. For completion a group of cardiac patients (without HF) should be included to control for underlying cardiac conditions such as AF and CAD. No study using that specific design was found in this review.

The strengths of this review include a comprehensive search strategy based on validated search terms and interrogation of cross-disciplinary electronic databases. All papers were quality assessed using a robust method tailored specifically to the study question. Due to lack of information in some of the manuscripts included, it was not possible to include all of the papers in the pre-specified analyses. A further limitation of the summary analyses is the substantial clinical heterogeneity between studies and participants.

To put the prevalence estimate of 40% into context, the estimated prevalence of CI/ dementia in the UK in adults over 65 years old is 7.1% (based on 2013 data). The total number of people with dementia in the UK is forecast to increase to over 1 million by 2025 and over 2 million by 2051 if age-specific prevalence remains stable. This increasing prevalence is driven by ageing of the general population and existence of other co-morbid factors – of which HF could be an important contributor.

Data generated from this review are in keeping with previously published reviews describing the prevalence of CI in HF. Vogels et al published a systematic review looking at this association in 2007.[143] Across 22 studies, HF was associated with an increased risk of CI (reported prevalence between 30-80%). Whether the increased risk of CI in HF is due to the clinical syndrome of HF itself – or the atherosclerotic risk factors commonly underlying it remains less clear. Other systematic reviews have shown associations between CI and other cardiovascular disorders such as AF,[144] stroke[145] and CAD.[146] Many potential confounding variables are relevant to these groups of patients and so although the association with impaired cognition is clear, a causal relationship is harder to prove - or disprove.

Preserving cognitive function and quality of life within the growing population of elderly patients with heart failure requires an awareness of this potential complication in the early stages of heart disease. Although the idea of concomitant CI and HF will be familiar to most clinicians it is not routinely screened for in the cardiology outpatient setting. Cognitive screening is not currently recommended in the European Society of Cardiology heart failure guidelines and this is in part due to the lack of standardised screening tools that are accessible, easy to administer in a timely fashion and that have clear clinical cut-off scores. Although this systematic review clearly shows a high prevalence of CI in the HF population recent observational data suggests that informal assessment of cognition by a cardiologist is insufficiently sensitive with 3 in 4 patients with CI not recognised as such in routine consultations. Cognitive assessment tools may have a role in research and practice, although first we should reach a consensus on appropriate assessment score cut-offs in this population and outline specific cognitive profiles in these patients. Although clearly important, systematic data on cognitive impairment in heart failure does not remove the need for prospective studies and experimental models to clarify the pathogenesis of this condition.

In conclusion, much of the heterogeneity in the prevalence of cognitive impairment/dementia seen in the HF population can be explained by differences in study methodology and case mix. Although numerous studies assessing prevalence were found, there was a dearth of studies investigating the incidence of CI in HF which should be addressed in future research. Once the incidence and prevalence of CI in HF are better defined the consequences of this association and the possible underlying mechanisms also need to be evaluated.

CHAPTER THREE

METHODS

Chapter 3: Methods

3.1 Introduction

This chapter will outline the methods used in this clinical cross sectional study. Ethical approval for the study was gained from the West of Scotland Research Ethics Service in November 2012 and an overview of the individual patient journey is shown in Figure 3-1. The methods used for patient identification, recruitment, data collection and data analysis will all be described.

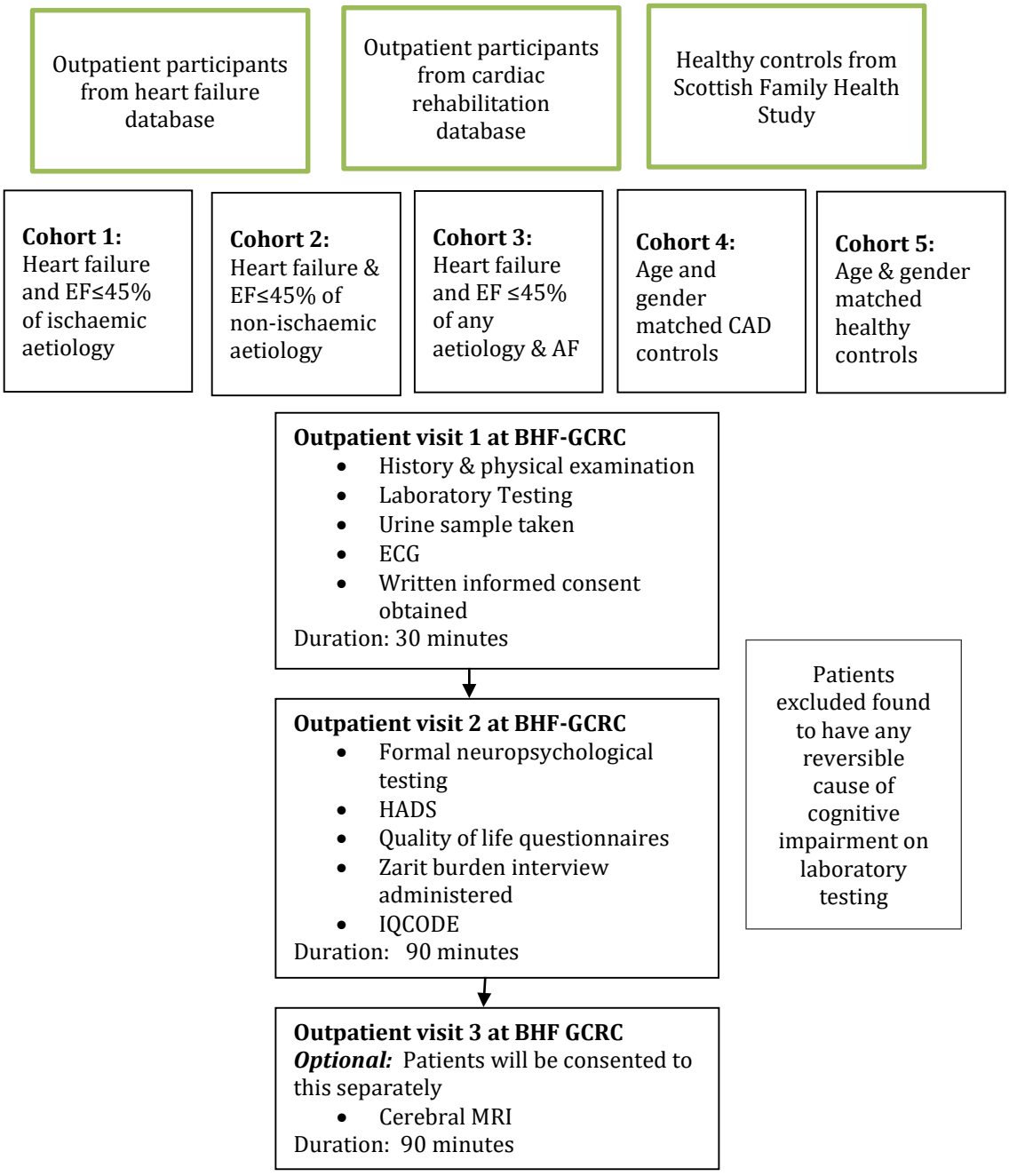


Figure 3-1: Flow diagram of patient assessments

3.2 Participant identification and recruitment

3.2.1 The outpatient heart failure cohorts

All HF patients in this study were recruited via the heart failure liaison service (HFLS) at the Royal and Western Infirmaries in Glasgow, the Royal Alexandra Hospital in Paisley and Stobhill Hospital, Glasgow. The Western Infirmary, Glasgow had a catchment population of over 250,000 people and covered the North-West of the city. Glasgow Royal Infirmary also has a catchment population of over 250,000 people from the North East of the city and part of East Dumbartonshire. Ambulatory care is shared between Glasgow Royal Infirmary and Stobhill Hospital – with cardiology outpatient clinics being held at both sites. The Royal Alexandra hospital in Paisley is a large district general hospital with a wide catchment area ranging from Renfrewshire to Oban and Argyll. All participant recruitment took place between March 2013 and December 2014.

NHS Greater Glasgow and Clyde has one of the largest, most comprehensive and longest running community based specialist HF nurse services which allowed access to a city-wide population of patients with systolic HF. This service serves a total population of approximately one million inhabitants. Any patient identified as having systolic HF (defined by EF ≤45% on echocardiography, radionuclide ventriculography or angiography) can be referred to the HFLS for follow up in the community; either from primary or secondary care.

I screened all patients referred to the HFLS between March 2013 and December 2014 and patient contact was made if the patient fulfilled the study inclusion criteria (listed below).

3.2.2 The outpatient coronary artery disease cohort

The CAD cohort was recruited from cardiac rehabilitation teams based at the same four hospital sites listed above. Patients admitted to hospital with an uncomplicated MI, unstable angina or following (either elective or emergency) coronary angiography +/- percutaneous coronary intervention (PCI) are followed up by a cardiac rehabilitation team. All patients referred for cardiac rehabilitation between March 2013 and December 2014 were screened and contacted if the enrolment criteria were fulfilled (see below).

3.2.3 The healthy control cohort

Generation Scotland is a Scottish Government funded initiative which draws from collaboration between Scottish university medical schools, the NHS and willing volunteers. It is a research resource which has recruited over 21,000 healthy volunteers from all over Scotland to participate in the Scottish Family Health Study. Age and sex matched healthy

controls from within the same geographical area as our HF and CAD groups were recruited from this database. These participants had all previously given consent to Generation Scotland for re-contact in future studies.

Inclusion Criteria

All participants were required to be able to provide written, informed consent and be over 60 years of age. Otherwise, the inclusion criteria varied depending on the particular study cohort as outlined below:

Cohort 1: Heart failure of ischaemic aetiology in patients in sinus rhythm

This cohort included ambulatory subjects with CHF and a reduced LVEF (≤45%) secondary to CAD without the exclusions listed below. The presence of CAD was defined as previous MI (documented in medical notes) or ≥50% stenosis in ≥1 epicardial coronary artery either on CT or invasive coronary angiography.

Cohort 2: Heart failure of non-ischaemic aetiology in patients in sinus rhythm

This cohort included ambulatory subjects with CHF and a reduced LVEF (≤45%) of non-ischaemic aetiology, without the exclusions listed below. Non-ischaemic aetiology was defined by the absence of CAD on coronary angiography (either CT or invasive) or myocardial perfusion/ischaemia imaging (including stress echocardiography, single photon emission computerised tomography [SPECT], positron emission tomography [PET] or CMR) with no previous clinical history of MI.

Cohort 3: Heart failure of any aetiology and atrial fibrillation

This cohort included ambulatory subjects with CHF and a reduced LVEF (≤45%) of any aetiology without the exclusions listed below. These patients were required to have a documented diagnosis of AF (either paroxysmal or permanent).

Cohort 4: Coronary artery disease control group

This cohort included ambulatory subjects with known CAD, LVEF >55% and no clinical HF, without the exclusions listed below. CAD was defined as either previous documented MI or CAD of ≥50% stenosis in ≥1 epicardial coronary artery on either CT or invasive coronary angiography.

Cohort 5: Healthy control group

This cohort included ambulatory subjects with no history of chronic illness, on no regular medication without the exclusions listed below.

Exclusion criteria

- History of hospital discharge within the past 3 months
- Previous cardiac arrest
- Previous cardiac surgery
- History of stroke
- Significant hearing/visual impairment or language barrier preventing completion of study assessments
- AF on 12 lead ECG or a history of paroxysmal AF (except cohort 3)
- Depression as defined by HADS score >10 or clinically evident depression/anxiety
- Participants younger than 60 years of age
- Known neurodegenerative disease including known dementia
- History of alcohol excess (i.e. >21 units/week for men and >14 units/week for females)
- Inability to provide informed consent

Any patient with a co-morbid diagnosis that could potentially result in altered cognition were excluded e.g. alcohol excess, previous cardiac arrest, previous cardiac surgery and stroke. It is well documented that mood interacts with cognition and so patients with clinically significant anxiety or depression (either listed in their past medical history or defined by HADS score>10) were also excluded. Although there are recent data suggesting that delirium can persist for up to 12 months post hospital discharge, the ICD-10 classification defines delirium as "transient and of fluctuating intensity with most cases recovering within four weeks or less".[147;148] Any patient discharged from hospital within the past 3 months was therefore excluded – in an attempt to minimise inclusion of patients with delirium. The other exclusion criteria listed pertain to the participant's ability to provide written, informed consent.

Consent

Initial contact was made by a member of the patients "usual care" team i.e. a member of the HFLS or cardiac rehabilitation team for cohorts 1-4. In the case of cohort 5, contact was initially made by a member of Generation Scotland. Potential eligible participants were given basic information regarding the study protocol and if there were no objections, a written patient (or participant) information sheet was then sent (appendices I&II, pages 199-207). After 72 hours the potential participant was re-contacted and if at that stage they remained willing to

participate, an appointment card detailing the time and location of the first study visit was sent (appendix III). Informed, written consent was obtained at study visit one (appendices IV&V). In addition to study participation, permission was also requested for future re-contact regarding further research related to this study and for participant details to be "flagged" for follow-up with Information Services Division(ISD) of NHS Scotland, allowing identification of deaths and readmissions to hospital.

3.3 Study visit 1

3.3.1 Data collection

Every participant recruited into this study was allocated a unique and anonymous study identification number. They were invited to attend 2 study visits (with an optional third study visit) held at the British Heart Foundation Glasgow Cardiovascular Research Centre (BHF-GCRC). A large amount of clinical data was collected at each study visit and so the components of each visit will be discussed separately.

At study visit 1, data were obtained by a thorough review of the patients' medical case notes as well as from clinical history and examination. Other methods of obtaining data included searching various hospital database systems for echocardiography, coronary angiography and radiological reports. Data were recorded under the following headings on the case report form (CRF) for study visit 1; participant demographics, HF symptoms, aetiology of HF, medical history, medications, vital signs, CV examination, recent echocardiography results and results from baseline investigations performed at visit 1 which included ECG, urinalysis and blood tests (appendix VI).

Demographic details collected included participant age, sex, race and date of most recent hospital discharge. Although direct age and sex comparisons have been made in previous study populations other variables are also known to influence cognition. Data were therefore collected regarding whether the participant lived alone or with a family member, marital status, functional ability with activities of daily living and years of education; all of which are known to have an impact upon cognition.

The clinical assessment of HF involved both detailed patient history and thorough clinical examination. Patients were asked about the burden of HF symptoms using the NYHA classification system (Table 1-2) in addition to other surrogate markers of HF severity including; HF duration, previous HF hospitalisation and specialist healthcare professionals coordinating care. A detailed family history, past medical history and drug history were also recorded.

The underlying aetiology of HF was recorded in the CRF. To fulfil the criteria for ischaemic cardiomyopathy the patient was required to have had a definite previous MI recorded in their clinical notes or >50% stenosis in ≥ 1 epicardial coronary artery demonstrated on either invasive or CT coronary angiography. If an ischaemic cause was excluded, other potential causes listed in the CRF included; idiopathic dilated cardiomyopathy (DCM), hypertension, alcohol, valvular, unknown or other. The recorded underlying aetiology was based on information from the patients' medical notes, clinical history and echocardiographic findings.

All participants were required to have had a transthoracic echocardiogram (TTE) performed in the 6 months prior to enrollment. If this had not been performed as part of routine care an echocardiogram was requested prior to study visit 1 at the participants' local cardiology outpatient services. All study subjects had a TTE performed by an accredited British Society of Echocardiography (BSE) sonographer. Data from the most recent TTE was recorded in the CRF (appendix VI). Specific information documented included; left ventricular end-diastolic diameter (LVEDD), the presence or absence of left ventricular hypertrophy (LVH), the grade of LVSD (categorized as mild/mild-moderate/moderate/moderate-severe/severe), documentation of any valvular heart disease (including a qualitative assessment of severity) and calculated EF by Simpson's biplane method (where available).

During clinical examination, objective evidence of HF was noted and this was summarised using the Killip classification system (Table 2-1). The Killip score was introduced in 1967 for clinical assessment of patients following acute MI, stratifying them according to the severity of their post-MI HF. The original report by Killip and Kimball demonstrated poorer prognosis in those patients with a higher Killip score.[149] In addition to a detailed cardiovascular examination, vital signs including height, weight, blood pressure, heart rate, temperature, oxygen saturations and respiratory rate were recorded. It has previously been hypothesised that larger neck circumference may confer higher risk of obstructive sleep apnoea which may, in turn impact on cognition.[150] Neck circumference was therefore also documented in the CRF.

Table 3-1: Killip classification of heart failure

Killip class	Clinical examination findings
I	No clinical signs of heart failure
II	Findings of mild-moderate heart failure e.g. lung crackles/gallop rhythm/ third heart sound/raised JVP
III	Frank pulmonary oedema
IV	Cardiogenic shock – hypotension and evidence of peripheral vasoconstriction

3.3.2 Baseline investigations

Although there are no clear data to support or refute the use of "routine" laboratory tests in the assessment of patients with suspected dementia, the American Academy of Neurology does recommend screening for any potentially reversible causes of CI including vitamin B12 deficiency and hypothyroidism.[151] In contrast to this, a number of laboratory tests are considered mandatory in the ongoing assessment and monitoring of patients with HF and can provide valuable information regarding patient prognosis.[152]

Each participant in this study therefore had a full panel of biochemical and haematological blood tests taken. These results provided information regarding HF severity and prognosis and highlighted any biochemical or haematological potentially reversible cause of CI. The following blood tests were taken at study visit 1; Urea and electrolytes (U&E), liver function tests (LFT), thyroid function tests (TFT), glucose, bone profile, C-reactive protein (CRP), lipid profile, BNP, full blood count (FBC), haematinics, erythrocyte sedimentation rate (ESR) and coagulation screen. All bloods except BNP were analysed in the Western Infirmary haematology and biochemistry laboratories within 4 hours of collection. The BNP samples were collected in potassium ethylene diamine tetra acetic acid (EDTA) tubes and sent to the department of biochemistry at Gartnavel General Hospital in Glasgow for testing. Plasma BNP was measured using the Architect Assay (Abbott Laboratories, Abbott Park, IL, USA). These samples were analysed in batches once a week.

Although advances in the identification of genetic markers of AD and other dementias have raised awareness of the familial nature of some dementias, there are currently no genetic markers recommended for routine diagnostic purposes. Over recent years there has been intense interest in developing markers related to the neuropathology of AD in the cerebrospinal fluid (CSF) e.g. CSF β-amyloid$_{1-42}$ and CSF tau.[153;154] Examination of CSF was out-with the scope of this study and no serum biomarkers have yet been identified in the detection

of CI. In addition to the blood tests listed above, each participant also had a urine dipstick test and if this was abnormal, full urinalysis and microscopy was performed.

Every participant in this study has a 12 lead ECG performed at study visit 1. The ECG is a useful tool in the diagnosis of HF and can allude to the underlying aetiology e.g. ischaemia/arrhythmia. There are a number of ECG abnormalities that may be relevant in a patient with HF and specific ECG abnormalities confer prognostic information in HF. Specific ECG parameters were recorded in the CRF (appendix VI). Particular attention was paid to the cardiac rhythm on the ECG as this had implications with regards to which study cohort participants were recruited into. In addition to rhythm, ventricular rate, QRS duration, QRS morphology, the presence of changes suggesting myocardial ischaemia and the presence of LVH was also documented.

Eligible participants (based on the inclusion and exclusion criteria) without any obvious potential causes of reversible CI were then invited to attend study visit 2. The second study visit was also held at the BHF-GCRC within 7 days of visit 1.

3.4 Study visit 2

3.4.1 Assessment of global cognition

On arrival to study visit 2, participants were asked about any change in their medical condition or symptom burden. They were asked regarding hospital re-admission or any change to their current medication. Their vital signs (including BP, HR and weight) were recorded and a focused cardiovascular examination was performed. These findings were all recorded in the CRF (appendix VII). Provided there was no change in their medical condition or any recent hospital admission a full battery of neuropsychological assessments were then administered.

The same neuropsychological assessments were administered to each participant in the same order lasting up to 90 minutes. The time of day that the tests were completed was recorded on the CRF as it has been suggested this can have an impact on performance. In the design of this study we included cognitive assessment tools that focused on global cognition as well as more specialist assessment tools looking at the individual domains of cognition. Each will be discussed in turn below.

3.4.1.1 Mini mental state examination

The Mini mental state examination (MMSE) is the most commonly used clinical measure of global cognition. Developed in 1975 by Folstein et al, it was originally intended as a brief screening test to quantitatively assess the severity of CI and to document changes in cognition over time.[155] It was not intended as an isolated diagnostic tool to identify patients with dementia.

The MMSE is divided into 2 sections with a maximum score of 30 (appendix VII). The first section requires only verbal responses and assesses temporal and spatial orientation, memory (registration, repetition and recall of 3 objects) and attention (spelling "world" backwards). The second section tests language and visuospatial functions. It requires the subject to name simple objects, follow verbal and written commands, write a sentence and copy two intersecting pentagons.

In the original study by Folstein et al, the MMSE score differed significantly in 69 patients with dementia syndromes, affective disorder (major depressive disorder) and affective disorder with CI when compared to 63 age matched controls.[155] Good concurrent validity was also demonstrated when compared to the verbal and performance intellectual quotient of the Wechsler adult intelligence scale (WAIS) as well as good test-re-test and inter-rater reliability.[155]

The threshold score taken as the "cut-off" normative value for the MMSE has a large impact on its clinical interpretation and the commonly used classification is outlined in Table 1-4. The MMSE was shown to be sensitive to age and years of education in a population study of 18,056 participants.[156] In this study sample, ages ranged from 18 to greater than 85 years old and from people with no education to those having several years of higher education. The researchers reported MMSE scores as mean, median and percentile distributions specific for age and education level. They found an inverse relationship between MMSE score and age ranging from a median of 29 for those 18 to 24 years of age, to 25 for individuals greater than 80 years old. The median MMSE score was 29, 26 and 22 for those with at least 9 years of education, 5 to 8 years of education and less than 5 years of education, respectively. Therefore age and years of education must also be taken into consideration when interpreting results of the MMSE.[157]

The MMSE has several limitations. It lacks sensitivity to pick up subtle changes in cognition and as such has a "ceiling effect"; possibly resulting in false-negative diagnoses.[158] In addition to this the MMSE does not include any measure of executive function and this domain has been

found to be altered early in the course of Alzheimer's disease. In addition to possible "ceiling effects", it is sometimes described as having "floor effects" with the difficulty in assessing memory, language and perceptual problems in patients with severe CI. As with many of these cognitive assessment tools, there is also the issue of a "learned effect" which may occur if they are administered repeatedly at short time intervals.[159]

3.4.1.2 Montreal cognitive assessment tool

The Montreal Cognitive Assessment tool (MoCA) was initially developed in 1996 by Ziad Nasreddine in Montreal, Quebec.[160] It can be administered in under 10 minutes and has a total possible score of 30. The cut-off score indicating MCI is 26 (Table 1-4). In contrast to the MMSE, the MoCA corrects for low educational attainment by adding one point to the participants final score for ≤12 years of formal education. It assesses a number of individual cognitive domains including short term memory recall, visuospatial ability, executive function, attention, concentration, working memory, language and orientation to time and place. See appendix VIII.

The original validation study, found the MoCA to have better sensitivity for detecting MCI when compared to the MMSE (90% and 18% respectively).[160] In this study these 2 cognitive screening tools were used in the assessment of 94 patients meeting mild cognitive impairment clinical criteria supported by psychometric measures. Both the MMSE and MoCA demonstrated good specificity (100% and 87% respectively). Subsequently this tool has been shown to be a sensitive screening measure for MCI in patients with cardiovascular disease,[161] in patients with CHF[162;163] and neurocognitive problems.[164;165] When the MoCA was directly compared to the MMSE in a cohort of CHF patients it detected in excess of a third more CHF patients with cognitive scores suggestive of MCI than the MMSE.[166]

3.4.2 Assessment of individual cognitive domains

3.4.2.1 Repeatable battery for the assessment of neuropsychological status

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a brief, individually administered test consisting of 5 indexes. These include attention, language, visuospatial/constructional abilities, and immediate and delayed memory. The test comprises 12 subtests which yield 5 index scores and a total scale score and can be administered by trained examiners in approximately 40 minutes (Table 3-2). Appendix IX illustrates the RBANS scoring sheet onto which the final scores are entered under the separate cognitive domains.

Table 3-2: Description of repeatable battery for the assessment of neuropsychological status subtests

Index/Subtest	Description
	Immediate Memory
List learning	A list of 10 semantically unrelated words is orally presented, and the examinee is asked to recall as many words as he or she can. This process is repeated over 4 learning trials.
Story memory	A short story is orally presented, and the examinee is asked to retell the story from memory. The same story is presented a second time, and the examinee is again asked to retell the story from memory.
	Visuospatial/Constructional
Figure copy	The examinee is shown a multipart geometric drawing and is asked to make an exact copy while the drawing remains on display.
Line orientation	The examinee is presented with a drawing that consists of 13 equal lines radiating out from a single point to form a semi-circular fan shaped pattern. All lines are numbered (1-13). Below this drawing are 2 lines that match 2 of the lines in the array above. The examinee is asked to identify which 2 lines they match. 10 trials are given, with different sets of test lines on each trial.
	Language
Picture naming	The examinee is presented with a series of pictured objects and is asked to name each one. A semantic cue is provided only if an object is obviously misperceived.
Semantic fluency	The examinee is given one minute to name as many exemplars as possible from a given semantic category.
	Attention
Digit span	The examiner reads a string of digits and asks the examinee to repeat the digits in the same order. The length of the digit string increases by one on each trial.
Coding	The examinee is presented with a page filled with rows of boxes with a number from 1 to 9 above each box (in a random sequence), and a blank space below the number. At the top of the page is a key with a unique, simple, geometric shape beneath each of the numbers, 1 to 9. Using the key, the examinee is asked to fill in the number corresponding to each shape, for as many boxes as the examinee can complete in 90 seconds.
	Delayed Memory
List recall	The examinee is asked to recall the list of 10 words learned in the list learning subtest.
List recognition	The examinee is read 20 words (10 targets, 10 distractors) and asked to indicate whether each word was on the word list.
Story memory & figure recall	The examinee is asked to re-tell the story they learned earlier and draw the figure shown earlier from memory.

The normative information from the RBANS manual, which is used to calculate the index and total scores, was based on 540 healthy adults who ranged in age from 20 to 89 years old.[167] RBANS was developed with a three-fold purpose:

- As a stand-alone "core" battery for the detection and characterisation of dementia in the elderly
- As a neuropsychological "screening" battery for use when lengthier standardised assessments are inappropriate
- For repeat evaluations when an alternate form is desirable in order to control for content practice effects.

Available normative RBANS data were then extended by a study which looked at a population of 718 community dwelling older adults in the USA.[168] This study provided age- and education -corrected subtest, index and total scale scores for each domain of cognition. Results from this study were similar to the original RBANS standardisation sample and are presented in table 3-3. Based on all of these data, the current clinical accepted thresholds are shown in table 3-4. For index and total scale scores a mean score of 100 with a standard deviation of 15 is accepted as "average range". Patients scoring 2 standard deviations below the mean score for the population sample are classed as "impaired".

Table 3-3: Repeatable battery for the assessment of neuropsychological status index scores for total study sample and by each midpoint age range from the Oklahoma Longitudinal Assessment of Health Outcomes in Mature Adults (OKLAHOMA) study[168]

	Duff et al final sample	Midpoint age 70	Midpoint age 75	Midpoint age 80	Midpoint age 85
Immediate memory	95.2 (18.0)	95.9 (17.6)	95.5 (17.3)	94.0 (18.4)	94.4 (19.7)
Visuospatial	102.7 (17.5)	103.3 (17.2)	102.2 (17.4)	101.9 (18.5)	101.0 (18.9)
Language	95.4 (11.2)	95.3 (11.0)	94.7 (11.6)	95.8 (11.7)	96.7 (13.0)
Attention	99.9 (16.1)	100.5 (15.6)	99.8 (15.9)	99.3 (16.6)	99.1 (18.3)
Delayed memory	98.9 (17.0)	100.5 (16.2)	98.5 (17.7)	95.7 (18.1)	95.7 (18.1)
Total scale	97.9 (15.9)	98.8 (15.4)	97.6 (16.1)	96.6 (17.1)	96.8 (18.1)

Data are presented as means (SD)

Table 3-4: Repeatable battery for the assessment of neuropsychological status clinical classification threshold scores

Clinical classification	Total scale score
Very superior	≥130
Superior	≥120 & ≤129
High average	≥110 & ≤119
Average	≥90 & ≤110
Low average	≥80 & ≤89
Borderline	≥70 & ≤79
Extremely low	≤69

After this comprehensive battery was constructed, its feasibility was then documented in a group of patients with chronic HF by Bauer et al.[55] The final sample consisted of 80 community dwelling NYHA class I-IV individuals with HF and reliability and validity measures documented by this study supported the continued use of this battery in the HF population.[55]

3.4.3 Additional measures of executive function

The cognitive domain of executive function has been understudied in the HF population to date. This is relevant to patients with HF, as "executive function" is an umbrella term used to describe various cognitive processes involved in the handling of novel situations. It is a faculty for recognising these situations, processing information and formulating plans accordingly. This is obviously key to patients involved in symptom recognition and self-management. Individual "bolt-on" assessments of executive function were therefore added to the other standard measures of global and domain-specific cognition.

3.4.3.1 Wechsler letter number sequencing

The Wechsler Adult Intelligence Scale (WAIS) intelligence quotient (IQ) tests are the primary instruments used to measure adult intelligence in clinical practice. The original WAIS (Form I) was published in 1955 by David Wechsler and has been updated over recent years.[169]

The current version of the test, the WAIS-IV, was released in 2008 and is composed of 10 core subtests one of which is the test of Wechsler Letter Number Sequencing (WLNS). This subtest assesses attention and executive function by asking examinees to repeat sequences of number and letters in both numerical and alphabetical order (see appendix VII). The WAIS-IV has been standardised on a sample of 2,200 people in the United States ranging from 16 to 90 years of age.[170] In a normal distribution, the IQ range of one standard deviation above and below the mean is where approximately 68% of all adults would fall.[171]

3.4.3.2 Trail making test parts A and B

The Trail Making Test (TMT) is one of the most popular neuropsychological assessment tools used to assess speed of processing, mental flexibility and executive function. The TMT consists of 2 parts; A and B. TMT-A asks an individual to draw lines sequentially connecting 25 encircled numbers. The requirements are similar for TMT-B except the participant now has to alternate between numbers and letters. The score on each part represents the length of time required to complete the test (see appendix X).

Performance on the TMT varies with age and years of education but not gender.[175] Based on a study of 911 community dwelling individuals normative values were therefore stratified into 11 age groups (18-89 years) and 2 education levels (0-12 and > 12 years) allowing more accurate interpretation of these scores and translation into clinical practice.[172] These normative values are available in appendix XI.

3.4.3.3 Controlled oral word association test

Original time-limited, verbal fluency tests date back to the Thurstone's Word Fluency Test, which formed part of the primary mental abilities test. This originally asked participants to write words beginning with a specific letter over a relatively long period of time e.g. 5 minutes. This has gradually evolved and in the current version this test of phonemic verbal fluency and executive function records the number of words beginning with the same designated letter said by the participant in one minute (appendix VII). The name of the test was changed to controlled oral word association (COWA) test to avoid confusing the phrase "word fluency". The letters F, A and S have continued to be used as a measure of verbal fluency in the neurosensory centre comprehensive examination for aphasia.[173]

As education may play a role and because gender differences have been reported (with females performing at a superior rate to age-matched males) a normative sample stratified according to age, education and sex was examined in a study by Ruff et al in 1996.[174] The total sample of 360 normal volunteers ranged in age between 16 and 70 years and in education from 7 to 22 years. Care was taken to ensure the population was heterogeneous with respect to age and education. To assess test-retest reliability, 30% of the sample was retested after a 6 month delay. A three-way analyses of variance (age x gender x education) was carried out on the mean number of words for all three letters. Age had no significant effect. However, gender moderated the effect of education on the number of words produced. The interaction of gender and education was ordinal, with the effect of years of education positively predicting COWA performance for both men and women. Therefore the effect of education was significant ($p<0.0001$), and differences due to education alone accounted for a greater proportion of total

variance (8%). The current accepted cut-off scores for COWA (F, A & S) are shown in table 3-5.

Table 3-5: Normative values for F, A, S stratified for age and years of education

	Age 16-59 years			**Age 60-79years**			**Age 80-95years**		
	Education (Years)			Education (Years)			Education (Years)		
	0-8	9-12	13-21	0-8	9-12	13-21	0-8	9-12	13-21
Percentile Score									
90	48	56	61	39	54	59	33	42	56
80	45	50	55	36	47	53	29	38	47
70	42	47	51	31	43	49	26	34	43
60	39	43	49	27	39	45	24	31	39
50	36	40	45	25	35	41	22	29	36
40	35	38	42	22	32	38	21	27	33
30	34	35	38	20	28	36	19	24	30
20	30	32	35	17	24	34	17	22	28
10	27	28	30	13	21	27	13	18	23
Mean (SD)	38.5 (12)	40.5 (10.7)	44.7 (11.2)	25.3 (11.1)	35.6 (12.5)	42.0 (12.1)	22.4 (8.2)	29.8 (11.4)	37.0 (11.2)

SD, standard deviation

3.4.3.4 Animal naming test

Semantic fluency is another method of assessing verbal fluency. Individuals are asked to generate names from a specified category in one minute and the category of animals is most frequently employed (see appendix VII). Tombaugh et al stratified normative values by age (16-59, 60-79 and 80-95 years) and years of education (0-8, 9-12 and 13-21) in 735 community dwelling volunteers.[175] Unlike with the phonemic verbal fluency tests, age accounted for more variance than years of education in this assessment tool (education 13.6% vs. age 23.4%) and gender was found to account for less than 1% of the variance. Table 3-6 shows the accepted normative values for the animal naming test stratified by age and years of education.

Table 3-6: Normative values for animal naming test stratified for age and years of education

	Age 16-59 years			Age 60-79years			Age 80-95years		
	Education (Years)			Education (Years)			Education (Years)		
	0-8	9-12	13-21	0-8	9-12	13-21	0-8	9-12	13-21
Percentile Score									
90	-	26	30	20	22	25	18	19	24
75	-	23	25	17	19	22	16	17	20
50	-	20	23	14	17	19	13	14	16
25	-	17	18	12	14	16	11	12	14
10	-	15	16	11	12	13	9	11	12
Mean (SD)		19.8 (4.2)	21.9 (5.4)	14.4 (3.4)	16.4 (4.3)	18.2 (4.2)	13.1 (3.8)	13.9 (3.4)	16.3 (4.3)

SD, standard deviation

3.4.3.5 Frontal assessment battery

The frontal assessment battery (FAB) is a bedside tool that takes approximately 10 minutes to administer and is used in the assessment of executive function. It consists of six questions which explore both cognitive and behavioural domains under the control of the frontal lobes. The FAB was initially designed in 2000 in a study of 42 normal subjects and 121 patients with various degrees of frontal lobe dysfunction.[176] They found a cut-off score of 12 had a sensitivity of 77% and a specificity of 87% in differentiating between frontal lobe dementia and Alzheimer's dementia. A copy of the FAB is shown in appendix XII.

3.4.4 Measure of pre-morbid intelligence quotient

3.4.4.1 Wechsler test of adult reading

The Wechsler test of adult (WTAR) reading provides a tool for estimating premorbid intellectual functioning. When assessing individuals for possible CI, it is necessary to know whether their current cognitive state represents a decline from their pre-morbid level. The inclusion of a marker of pre-morbid IQ is something which has been neglected in current HF and cognition literature to date.

The WTAR is based on a reading-recognition paradigm, requiring the reading and pronunciation of words that have irregular phonetic translation but not requiring knowledge of word meaning. Examinees are given a card with 50 words written on it. They are asked to read these words aloud and given one mark for each word pronounced correctly (see appendix XIII). The use of words with irregular pronunciation minimises the assessment of the examinee's current ability to apply standard pronunciation rules and maximises the assessment of the examinee's previous learning of the word. Pronunciation guidance is given

to the examiner both in written and audio format (see appendix XIV). The raw score is converted to a standard score based on age, sex and years of education normative values.[177] The standard score is then compared to the predicted score for each examinee. Predicted scores are derived from the individuals' level of education. The UK standardisation sample and demographic-predicated WTAR scores are shown in Appendix XV.

3.4.5 Informant questionnaire on cognitive decline in the elderly

The informant questionnaire on cognitive decline in the elderly (IQCODE) was developed as an alternative way of measuring cognitive decline from a pre-morbid level using informant reports.[178] This is useful in patients who are unable to undergo direct testing because of lack of co-operation, acute illness or low levels of literacy. There are a large number of informant questionnaires available and of these the IQCODE is the most commonly used.

26 items are included in the questionnaire which asks the informant to comment on any perceived changes in cognition over the past 10 years. Each item is rated on a 5 point scale from 1 – "much improved" to 5 – "much worse" (see appendix XVI). The ratings are then averaged over the 26 items to give an overall score from 1-5. A variety of cut-off values have been proposed for use in cognitive screening and these vary depending on whether the study population are inpatient or outpatient. A cut-off of 3.6 or above has been generally accepted as abnormal.[179]

This scale was designed to reflect improvement in cognition as well as decline, to allow for the questionnaire to be used in treatment trials and following acute illness. The IQCODE has high reliability and is relatively unaffected by education and as it provides information complimentary to cognitive tests, harnessing them together improves screening accuracy.[179]

3.4.6 Measures of symptom burden and self-care

The following 3 questionnaires were administered to all patients in each of the HF cohorts. Patients were given these questionnaires at the end of study visit 2 and asked to complete them at their leisure and return them by post to the BHF-GCRC (see appendix XVII & XVIII).

3.4.6.1 Kansas City Cardiomyopathy Questionnaire

One of the most commonly used disease-specific health related quality of life questionnaires (HRQoL) in HF is the Kansas City Cardiomyopathy Questionnaire (KCCQ).[180] This 23-point questionnaire quantifies physical limitation, symptoms (frequency, severity and change over time), quality of life, knowledge and social function (see appendix XVII). It is scored by assigning each response an ordinal value, beginning with 1 for the response that implies the

lowest level of functioning and adding together the scores within each domain. Scale scores are transformed into a 0-100 range by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100. To aid the interpretation of scores, two summary scores have been developed. A functional status score includes the physical limitation and symptom domains and a clinical summary score can be calculated by combining the functional status with the quality of life and social limitation domains.

3.4.6.2 Self-Care of Heart Failure Index

The self-care of heart failure index was initially published in 2004 and assesses a patient's ability to monitor their symptoms, implement a treatment strategy based on their symptoms and assess their response to that treatment strategy.[181] The questionnaire is divided into 3 sections looking at maintenance actions (e.g. low salt diet), management actions (e.g. taking extra diuretic) and patient confidence in their actions (see appendix XVIII). Each of the 3 scales is standardised to a 0-100 range and results should be interpreted individually. A score of ≥70 can be used as the cut-point to judge self-care adequacy in research. A change in scale more than one half of a standard deviation is considered clinically relevant.[182]

3.4.6.3 EQ-5D

The EQ-5D is a standardised instrument for use as a measure of health outcome. The EQ-5D descriptive system can be converted to a single index value for health status, based on the respondent's responses to the various questions. It records the level of self-reported problems on mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The index values, presented in country specific value sets, are a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years. Index values were derived from the descriptive system using the crosswalk link function online calculator. In addition to this, there is a visual analogue scale which records the respondent's self-rated health status from 0-100, where the endpoints are labelled "best imaginable health state" and "worst imaginable health state" (see appendix XVII).

3.4.7 Measure of care-giver strain

3.4.7.1 Zarit Burden Interview

Community care of patients with chronic illness has many advantages but often places a major burden on family members and other care-givers. Increased care-giver burden has been associated with increased hospital admissions, higher incidence of elder mistreatment and increased clinical depression amongst family care-givers.[183;184] The identification of risk

factors associated with negative care-giving outcomes therefore has important clinical implications for quality of care and service utilisation.

The Zarit Burden Interview was initially developed in 1980 and revised in 1985.[185] It is a 22-item scale developed to assess the severity of caregiver perceptions of burden or stress in caring for a patient. Each item is answered on a 5 point scale: o for never, 1 for rarely, 2 for sometimes, 3 for quite frequently and 4 for nearly always. The scores for each item are added and the total ranges from 0 to 88 with higher scores indicating greater burden (see appendix XIX). Although the use of absolute cut-off values does not replace the need for comprehensive clinical evaluation, a study by Rankin et al in 1994 identified a cut-off score as 10 as both sensitive and specific in identifying care-givers experiencing depressive symptoms and in need of further support in the community.[183]

3.4.8 Assessment of mood

Mood disorder is common among patients with HF.[186] A recent meta-analysis published in the Journal of the American College of Cardiology found approximately 1 in 5 patients meet the criteria for major depression based on clinical interviews and substantially higher rates of clinically significant depression are present among patients assessed with questionnaires.[187] Rates of mortality, clinical events, rehospitalisation and general health care use are markedly higher among HF patients diagnosed with mood disorder and the current HF ESC guidelines include the provision of adequate psychological support to patients and family and/or caregivers.[188]

The HADS questionnaire (described in chapter 1.2.2) was administered to all participants in this study as a measure of anxiety and depression (see appendix XVI). It is recommended that, for both the anxiety and depression scales alike, raw scores of between 8 and 10 identify mild cases, 11-15 moderate cases and 16 or above severe cases.[65]

3.5 Database construction

All paper copies of the case record forms were kept in a locked filing cabinet at the BHF Glasgow Cardiovascular Research Centre. An electronic database was created in the Robertson Centre for Biostatistics at the University of Glasgow to store these data. Data were manually entered into the electronic database and verified by two independent database managers working in the Robertson Centre. No patient identifying material was entered into the electronic database; patients were anonymised and identified by their unique study identification number. All data were checked manually and also underwent pre-specified electronic data validation checks which resulted in the production of a large number of queries. All queries were investigated

and data appropriately amended in the central database. This robust system ensured quality control of the data processed.

3.6 Power calculation and statistical analyses

The sample size of approximately 240 patients with HF and 160 participants without HF has 90% power at a 5% significance level to detect differences between groups for a continuous outcome measure of 0.36 standard deviation (SD) units, based on a two-sample t-test. This compares favourably with the differences in cognitive measures previously found between HF patients and controls of 0.5-0.8 SD units.

Categorical variables are summarised with the number and proportion of participants falling within each category. Continuous variables are summarised using the number available, mean, SD, median, 25th and 75th quartiles and minimum and maximum values. Analyses were performed using R for windows v3.0.0 or SAS for Windows v9.3, or higher versions of these programs. A probability value of $p<0.05$ was considered significant.

To assess whether cognition differed between patients with HF and healthy controls, or HF and cardiac controls, Generalised Linear Models (GLM) were used to compare cases and the healthy/cardiac controls for each of the cognitive assessment tools. Models were fitted with various levels of adjustment:

1. Model adjusted for age and sex only
2. As for model 1, with the addition of general demographic and clinical confounders (co-morbidity count, race, education level [using WTAR], medication count)
3. As for model 2, with the addition of cognitive confounders (history of depression, HADS score, antidepressant use)
4. As for model 3, with the addition of vascular risk factors (smoking, systolic blood pressure, diabetes mellitus, BMI, previous MI, chronic kidney disease [defined as eGFR<60], hypertension)

GLM's were also fitted to assess whether cognition differed between the HF cohorts for the cognitive assessment tools. Models were adjusted according to the same covariates specified above in models 1-4 along with additional covariates supplied in a fifth model:

5. As for model 4, with the addition of HF clinical severity covariates (NYHA class, CHF >2years, previous HF hospitalisation, BNP and specialist co-ordinating care)

The HF groups were compared in the following two analyses:

(a) HF with AF versus HF without AF (here HF was included irrespective of CAD status)
(b) HF with CAD versus HF groups without CAD (here HF was included irrespective of AF status)

Using established binary and multiple cut-point definitions for each questionnaire, comparable analysis using the covariates from the continuous outcomes indicated above were done using either binary or ordinal logistic regression, as appropriate. Results for all analyses are presented as the estimated difference between groups alongside corresponding 95% confidence intervals and p-values.

CHAPTER FOUR

CLINICAL CHARACTERISTICS OF HEART FAILURE COHORTS

Chapter 4: Clinical characteristics of heart failure cohorts

4.1 Introduction

This chapter will outline the recruitment of ambulatory patients with chronic, stable heart failure into this study and detail the reasons for exclusion from participation. The main focus of this chapter is to describe in detail their clinical characteristics including demographic details, signs and symptoms of heart failure, past medical history, medication use and examination findings. The results of basic investigations including electrocardiography, echocardiography and blood tests will also be described. Significance testing was not routinely performed for each variable – only in certain pre-selected variables where a significant association was postulated.

4.2 Results

4.2.1 Recruitment of study cohort

Recruitment into this study took place between March 2013 and December 2014. Heart failure patients attending outpatient clinics at Glasgow Royal Infirmary, Western Infirmary Glasgow, Royal Alexandra Hospital and Stobhill hospital were screened for eligibility. Patients with heart failure were recruited into 1 of 3 HF cohorts:

Cohort 1. Heart failure of ischaemic aetiology in sinus rhythm (HF CAD)
Cohort 2. Heart failure of non-ischaemic aetiology in sinus rhythm (HF no CAD)
Cohort 3. Heart failure of any aetiology and atrial fibrillation (HF AF)

The final numbers recruited into each of these HF cohorts is illustrated in figure 4.1.

A total of 520 patients with heart failure were screened for inclusion however 324 were excluded from participation. The main reasons for exclusion are illustrated in figure 4.2. The reasons for exclusion included: History of AF (for HF cohorts 1&2), previously diagnosed neurological illness (including previous stroke, traumatic brain injury, cerebral palsy and former diagnosis of cognitive impairment / dementia), age <60 years, recent discharge from hospital, previous cardiac surgery (including CABG and valve replacement surgery), patient refusal, history of alcohol excess, previous cardiac arrest, ejection fraction >45%, terminal illness and inability to provide informed consent (due to language barrier / sensory impairment).

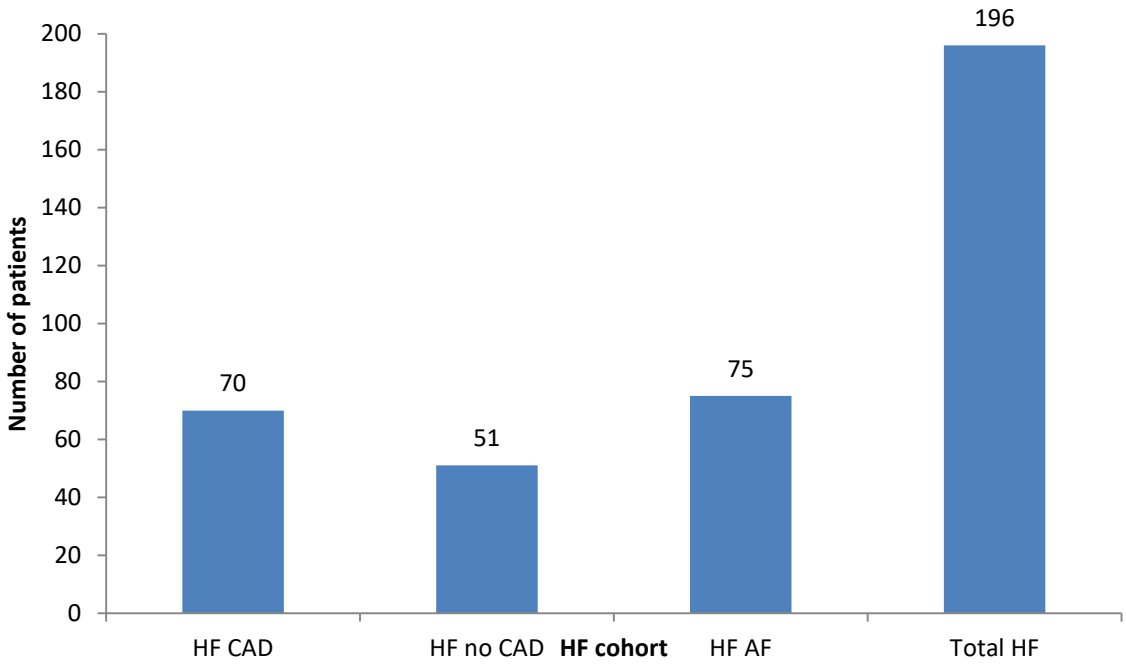


Figure 4-1: Final numbers recruited into each heart failure cohort

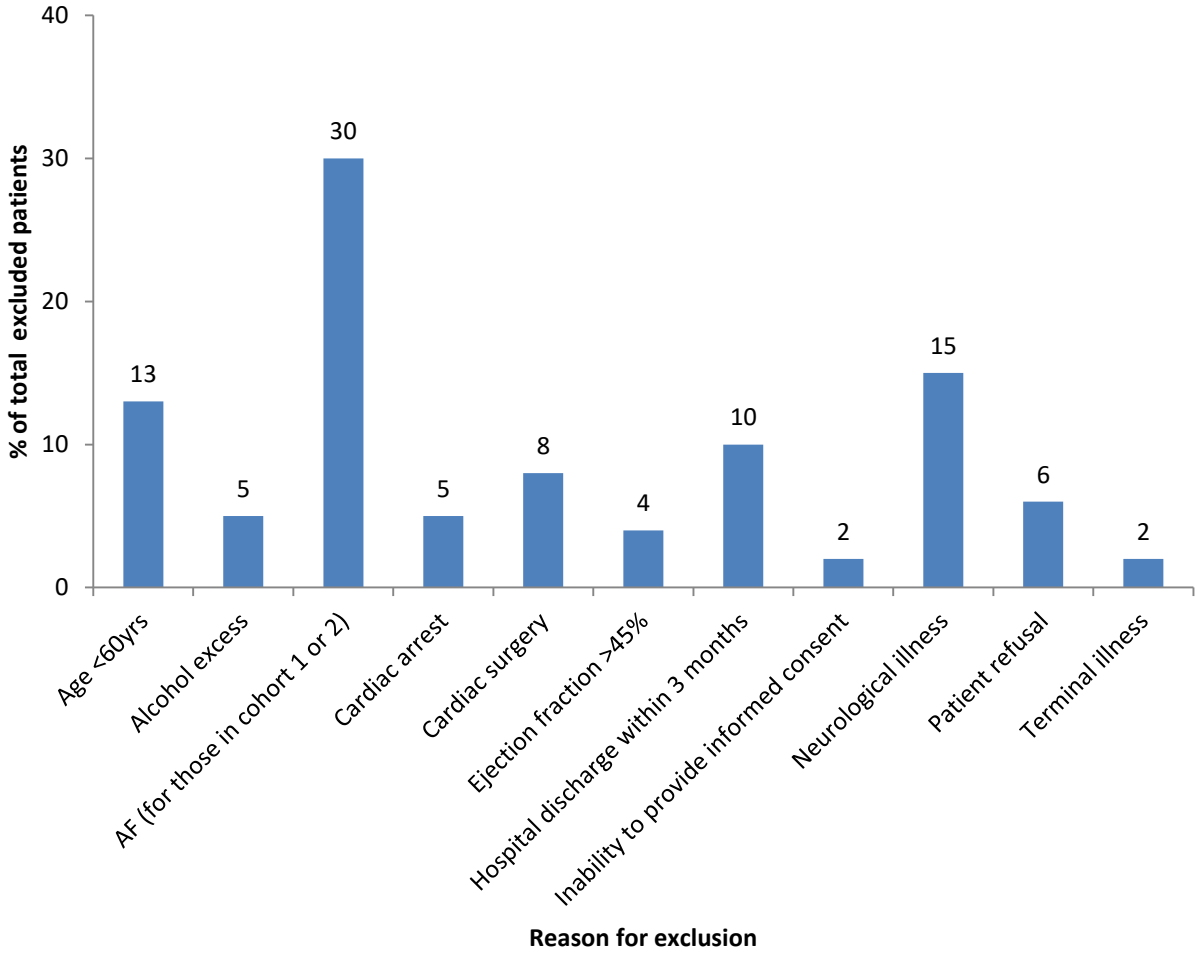


Figure 4-2: Breakdown of reasons for exclusion into study for heart failure patients

4.2.2 Demographics of heart failure cohorts

The clinical demographics of patients recruited into HF cohorts 1-3 are shown in table 4-1. The 3 HF groups were relatively well matched for age and sex. The majority of HF patients recruited into the study were male (70%) with an overall mean (SD) age of 71 (8) years and a wide overall range in age from 60-94 years. 99% of the total HF population were white with the remaining 1% being South-Asian. Education status was also well matched between the HF cohorts as assessed by total years of education and full scale IQ. A higher proportion of those with HF secondary to CAD were current smokers (60%) with approximately half of the 3 HF cohorts drinking alcohol within recommended limits.

Table 4-1: Basic demographics of patients recruited into heart failure cohorts

	HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)	Total HF (n=196)
Age (years)	71.0 ± 8.1	69.4 ± 7.5	71.0 ± 8.6	70.6 ± 8.1
Age range (years)	60-86	60-87	60-94	60-94
Sex (% males)	49 (70)	32 (63)	56 (75)	137 (70)
Education (total years)	11 [10, 14]	11 [10, 14]	12 [10, 15]	11 [10, 14]
Full scale IQ	104 [79, 118]	100 [70, 117]	100 [70, 118]	103 [70, 118]
Smoker	42 (60)	24 (47)	35 (47)	101 (52)
Current alcohol	36 (51)	24 (47)	39 (52)	99 (51)

Data are presented as means ± SD or median [Q1, Q3] for continuous data and N (%) for categorical data.

4.2.3 Diagnosis of heart failure

To fulfil the entry criteria into this study, HF patients were required to have objective evidence of reduced left ventricular ejection fraction on echocardiography in addition to documented clinical evidence of HF, thus fulfilling the current ESC definition of HF-REF. Therefore, all patients recruited into HF cohorts 1-3 had an ejection fraction of <45% on transthoracic echocardiography, performed within 6 months of entry into this study. In addition to EF I also looked at other surrogate measures of HF severity including HF duration, prior hospital admissions with HF, specialist co-ordinating care and serum BNP concentration. See table 4-2.

Of the 70 patients recruited into HF cohort 1 (HF CAD) 66 (94%) had ≥50% stenosis in one or more coronary artery on invasive coronary angiography with the remaining 4 having a documented prior myocardial infarction based on clinical history, cardiac enzymes and ECG findings.

CAD was excluded on invasive coronary angiography in 32 (63%) of the 51 patients recruited into HF cohort 2 (HF of non-ischaemic aetiology). The remaining 19 patients had CAD excluded on stress echocardiography (n=7), CMR (n=3) and CT coronary angiography (n=9). After exclusion of CAD no cause of HF was found in 25% of this cohort. The other underlying aetiologies recorded listed in table 4-3.

Table 4-2: Heart failure characteristics

	HF CAD (n=70)	**HF no CAD (n=51)**	**HF AF (n=75)**
Ejection fraction	34.1 ± 6.7	33.7 ± 7.1	34.9 ± 7.1
HF duration >2 years	42 (60.0)	18 (35.3)	52 (69.3)
Previous HF hospitalisation	52 (74.3)	34 (66.7)	61 (81.3)
HF specialist co-ordinating care	64 (91.4)	45 (88.2)	67 (89.3)
BNP (pg/ml)	162 [11, 3425]	208 [12, 2271]	214 [13, 1160]

Data are presented as means ± SD or median [Q1, Q3] for continuous data and N (%) for categorical data.

Table 4-3: Aetiology of heart failure

	HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)
Ischaemic aetiology	70 (100)	0 (0)	42 (56)
Idiopathic dilated cardiomyopathy	0 (0)	16 (31)	2 (3)
Hypertensive cardiomyopathy	0 (0)	6 (11)	0 (0)
Cardiomyopathy secondary to valvular heart disease	0 (0)	7 (13)	2 (3)
Unknown aetiology	0 (0)	13 (25)	15 (20)
Other aetiology of heart failure	0 (0)	10 (19)	14 (18)

Data are presented as means ± SD or median [Q1, Q3] for continuous data and N (%) for categorical data.

4.2.4 Heart failure symptom burden

Study participants were asked about symptoms of HF when they attended the initial screening visit and at return visit 1. Table 4-4 displays the frequencies of HF symptoms recorded at return visit 1. Most HF patients recruited had NYHA class II HF with smaller proportions having NYHA I or NYHA III HF. No patients with NYHA class IV were recruited into this study.

Table 4-4: Symptoms of heart failure

	HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)
NYHA I	19 (27.1)	18 (35.3)	16 (21.3)
NYHA II	37 (52.9)	21 (41.2)	45 (60.0)
NYHA III	14 (20.0)	12 (23.5)	14 (18.7)
Orthopnoea	16 (22.9)	10 (19.6)	11 (14.7)
PND	16 (22.9)	10 (19.6)	17 (22.7)
Ankle swelling	33 (47.1)	20 (39.2)	41 (54.7)
Wheeze	15 (21.4)	11 (21.6)	18 (24.0)
Palpitations	10 (14.3)	5 (9.8)	8 (10.7)

Data are presented as N (%)

4.2.5 Medical history

Table 4-5 illustrates the common co-morbid conditions found in the HF cohorts. Common risk factors for cardiovascular disease are displayed including treated hypertension, hypercholesterolaemia and diabetes mellitus. Since cerebrovascular disease was an exclusion to this study, none of the study participants had a documented past history of previous stroke or TIA. Although, as previously discussed, mood disorder is common in patients with HF only 2% of this HF population had a prior history of depression. Due to the interaction between mood and cognition, patients with clinically significant depression were excluded from this study. Those patients with a historical past medical diagnosis of depression documented in medical casenotes but not being actively treated were allowed to participate.

Arrhythmias are a common cause of morbidity and mortality in HF. Of 196 patients with HF enrolled, over one third (38.8%) had a previously documented arrhythmia. Documented arrhythmias included supraventricular arrhythmia (SVT), ventricular tachycardia (VT), sick sinus syndrome (SSS) and atrioventricular (AV) block. The prevalence of device therapy was relatively low, with the highest proportion of complex cardiac devices being present in those with ischaemic cardiomyopathy.

A family history of cardiac disease was recorded for each patient enrolled into this study. Between 24 and 51% of each cohort gave a family history of CAD with less aware of any history of cardiomyopathy.

As part of the past medical and social history taken, participants were asked about their living arrangements (whether they lived independently or with someone) and regarding any input from social services supplying help with activities of daily living.

Table 4-5: Prevalence of co-morbid conditions in heart failure cohorts

	HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)
Previous MI	68 (97.1)	0 (0)	37 (49.3)
Treated hypertension	61 (87.1)	29 (56.9)	71 (94.7)
Hypercholesterolaemia	61 (87.1)	21 (41.2)	61 (81.3)
Diabetes Mellitus	19 (27.1)	10 (19.6)	20 (26.7)
Diet controlled	3 (4.3)	2 (3.9)	3 (4.0)
Oral therapy	12 (17.1)	6 (11.8)	13 (17.3)
Insulin	4 (5.7)	2 (3.9)	4 (5.3)
Hypothyroidism	3 (4.3)	5 (9.8)	3 (4.0)
Peripheral arterial disease	10 (14.3)	3 (5.9)	4 (5.3)
Prior arrhythmia	10 (14.3)	4 (7.8)	62 (82.7)
SVT	3 (4.3)	0 (0)	46 (61.3)
VT	3 (4.3)	1 (2.0)	7 (9.3)
SSS	2 (2.9)	0 (0)	8 (10.7)
AV Block	2 (2.9)	3 (5.9)	1 (1.3)
Conventional pacemaker	4 (5.7)	1 (2.0)	8 (10.7)
CRT-D	2 (2.9)	1 (2.0)	5 (6.7)
CRT-P	9 (12.9)	2 (3.9)	1 (1.3)
Primary prevention ICD	4 (5.7)	0 (0)	5 (6.7)
Valvular heart disease	26 (37.1)	25(49.0)	39 (52.0)

Depression	2 (2.9)	2 (3.9)	0 (0)
Family history CAD	36 (51.4)	13 (25.5)	18 (24.0)
Family history cardiomyopathy	5 (7.1)	13 (25.5)	3 (4.0)
Lives alone	24 (34.3)	14 (27.5)	30 (40.0)
Employed carers	5 (7.1)	1 (2.0)	7 (9.3)

Data are presented as N (%). AV, atrioventricular; CAD, coronary artery disease; CRT-D, cardiac resynchronisation therapy – defibrillator; CRT-P, cardiac resynchronisation therapy – pacemaker; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; SVT, supraventricular tachycardia; VT, ventricular tachycardia; SSS, sick sinus syndrome

4.2.6 Medication use

Table 4-6 shows the frequencies of prescription of HF medication in each HF cohort. 166 out of the total 196 (85%) patients with HF were prescribed regular diuretic (including both loop and thiazide diuretics). Most patients were treated with either ACE inhibitor or ARB (89.9% of the total HF population) with slightly fewer patients established on regular beta blocker therapy (84.7%). Less than half of the HF patients (42.3%) were prescribed a mineralocorticoid receptor antagonist (MRA). Digoxin was more commonly used in the HF with AF cohort, probably reflecting its use as a rate-control agent.

Previous systematic reviews have looked at the association between cognition and antiplatelet/anticoagulant medication use.[189;190] I therefore collected data on the prescription of any antiplatelet or anticoagulant and these data are presented in table 4-7. 84% of those patients with HF and AF were formally anticoagulated with warfarin (73.3%) or a novel oral anticoagulant [(NOAC) 10.7%].

Other cardiovascular and non-cardiovascular medications are presented in table 4-8. A range of other medications were prescribed reflecting the large number of co-morbidities frequently associated with HF. Recent data have highlighted antihistamine and incontinence medications as potential cognitive confounders. These were not frequently prescribed in our HF cohorts.[191;192]

Table 4-6: Heart failure medication use

	HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)
Diuretic	62 (88.6)	44 (86.3)	60 (80.0)
Beta blocker	64 (91.4)	41 (80.4)	61 (81.3)
ACE or ARB	63 (90.0)	48 (94.1)	65 (86.7)
ACE Inhibitor	50 (71.4)	39 (76.5)	50 (66.7)
ARB	13 (18.6)	12 (23.5)	16 (21.3)
MRA	32 (45.7)	18(35.3)	33 (44.0)
Ivabradine	2 (2.9)	0 (0)	1 (1.3)
Digoxin	1 (1.4)	1 (2.0)	22 (29.3)
Hydralazine	3 (4.3)	0 (0)	2 (2.7)

Data are presented as N (%). ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist

Table 4-7: Antiplatelet and anticoagulant use

	HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)
Any antiplatelet therapy	57 (81.4)	28 (54.9)	21 (28.0)
Aspirin	49 (70.0)	22 (43.1)	17 (22.7)
Clopidogrel	20 (28.6)	6 (11.8)	4 (5.3)
Any anticoagulant therapy	9 (12.9)	13 (25.5)	63 (84.0)
Warfarin	8 (11.4)	11 (21.6)	55 (73.3)
NOAC	1(1.4)	2 (3.9)	8 (10.7)

Data are presented as N (%). NOAC, novel oral anticoagulant

Table 4-8: Other medication use

	HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)
Calcium channel blocker	4 (5.7)	2 (3.9)	9 (12.0)
Nicorandil	10 (14.3)	3 (5.9)	7 (9.3)
Long acting nitrate	14 (20.0)	2 (3.9)	9 (12.0)
Oral hypoglycaemic	15 (21.4)	8 (15.7)	18 (24.0)
Statin	56 (80.0)	29 (56.9)	52 (69.3)
Any lipid lowering drug	59 (84.3)	29 (56.9)	52 (69.3)
Anxiolytic	4 (5.7)	1 (2.0)	3 (4.0)
Antidepressant	4 (5.7)	2 (3.9)	2 (2.7)
Incontinence medication	4 (5.7)	1 (2.0)	11 (14.7)
Antihistamine	1 (1.4)	0 (0)	0 (0)
Bronchodilator	18 (25.7)	8 (15.7)	12 (16.0)

Data are presented as N (%)

4.2.7 Clinical examination findings

4.2.7.1 Routine physiological measurements

Routine physiological measurements were taken for each study participant at the initial screening visit and again at return visit 1. Table 4-9 lists the physiological measurements taken at return visit 1. From height and weight measurements, body mass index (BMI) was calculated for each patient. According to the World Health Organisation (WHO) BMI classification, the mean BMI of patients in HF cohorts 1 & 2 (27.4, 28.4) fell into the overweight range (BMI >25) with the mean BMI of the HF and AF cohort (30.4) falling into the obese category (BMI >30).

Neck circumference is thought to play a role in the pathogenesis of obstructive sleep apnoea (OSA). Due to the potential link between OSA and cognition I recorded neck circumference for each participant. A neck circumference over 16cm in females and 17cm in males is associated with an increased risk of developing OSA.

Table 4-9: Physiological measurements taken at return visit 1

		HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)
Height (cm)	Median Mean (SD)	167 166.5 (9.3)	168 166.3 (9.3)	170 167.2 (13.6)
Weight (Kg)	Median Mean (SD)	75.9 78.8 (19.6)	75.5 81.2 (22.0)	85.0 87.7 (17.9)
BMI	Median Mean (SD)	27.4 28.3 (5.9)	28.4 29.0 (6.1)	30.4 31.5 (7.1)
Neck circumference males (cm)	Median Mean (SD)	17.4 17.2 (1.7)	17.8 17.9 (2.5)	18.0 17.8 (2.0)
Neck circumference females (cm)	Median Mean (SD)	15.8 15.0 (2.5)	15.2 14.6 (2.2)	16.0 15.9 (2.1)
Systolic BP (mmHg)	Median Mean (SD)	135 136.9 (23.1)	133 138.2 (24.3)	137 137.9 (21.3)
Diastolic BP (mmHg)	Median Mean (SD)	70 72.1 (9.9)	76 75.7 (11.5)	79 77.7 (11.6)
Heart rate (BPM)	Median Mean (SD)	69.5 69.5 (12.5)	70.0 72.1 (12)	70.0 71.5 (12.3)
SpO_2 (%)	Median Mean (SD)	97 96.6 (2.0)	97 97.1 (1.4)	97 96.9 (1.7)
Respiratory rate (BPM)	Median Mean (SD)	16 15.5 (1.7)	16 15.2 (1.8)	16 15.3 (1.8)
Temperature (˚C)	Median Mean (SD)	36.0 36.3 (0.8)	36.5 36.5 (0.7)	36.2 36.2 (0.8)

Data are presented as means (SD) or median [Q1, Q3]. BP, blood pressure; BPM, beats per minute; cm, centimetres; Kg, kilogram; mmHg, millimetres of mercury

4.2.7.2 Cardiovascular examination signs

Each study participant had a full cardiovascular examination performed at return visit 1. The main findings are presented in table 4-10. Of the physical signs of heart failure listed below, peripheral oedema, followed by pulmonary crackles were most commonly found. Over 50% of patients in each cohort had a murmur on auscultation of their heart.

Table 4-10: Cardiovascular examination findings

	HF CAD (n=70)	**HF no CAD (n=51)**	**HF AF (n=75)**
Elevated JVP	1 (1.4)	4 (7.8)	3 (4.0)
Palpable apex	5 (7.1)	9 (17.6)	8 (10.7)
Displaced apex	2 (2.9)	5 (9.8)	7 (9.3)
Third heart sound	0 (0)	0 (0)	1 (1.3)
Cardiac Murmur	36 (51.4)	30 (58.8)	49 (65.3)
Pulmonary crackles	27 (38.6)	24 (47.1)	32 (42.7)
Pleural effusion	1 (1.4)	0 (0)	2 (2.7)
Peripheral oedema	25 (35.7)	25 (49.0)	35 (46.7)
Ascites	1 (1.4)	0 (0)	0 (0)
Carotid bruit	1 (1.4)	5 (9.8)	3 (4.0)

Data are presented as N (%). JVP, jugular venous pressure

4.2.8 Electrocardiography

Each study participant had a 12 lead ECG performed at their initial screening visit. This was performed on a calibrated ECG machine by an operator competent in the recording of an electrocardiogram. The most common ECG findings are presented in table 4-11 below. Of the patients recruited into the HF and AF category, n= 55 (73%) had evidence of AF on their baseline study ECG. n=15 (20%) were in normal sinus rhythm and n=5 (7%) had a paced rhythm on surface ECG. The remaining 121 patients with HF had no evidence (past or present) of AF. The overall mean ventricular rate was higher in those with AF on their ECG compared to those in SR (71±14bpm vs. 67±11bpm). The highest proportion of LBBB morphology was

found in those patients with HF and CAD (21%). The HF cohort with the longest mean QRS duration was those with non-ischaemic cardiomyopathy.

Table 4-11: Electrocardiographic findings in heart failure cohorts

	HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)
Ventricular rate (bpm)	66.7 ± 10.2	71.1 ± 13.0	71.3 ± 14.0
Sinus rhythm	58 (82.9)	48 (94.1)	15 (20.0)
Atrial fibrillation	0 (0.0)	0 (0.0)	55 (73.3)
Paced rhythm	12 (17.1)	3 (5.9)	5 (6.7)
LBBB	15 (21.4)	13 (25.5)	12 (16.0)
RBBB	1 (1.4)	1 (2.0)	2 (2.7)
Mean QRS duration (ms)	115.8 ± 27.6	119.4 ± 29.0	118.1 ± 27.9
Median QRS duration(ms)	108.0 [94.0, 136.0]	114.0 [94.0, 144.0]	112.0 [94.0, 142.0]
Mean QTc interval (ms)	441.7 ± 27.4	440.7 ± 28.5	437.3 ± 33.5
Median QTc interval (ms)	437.5 [422.0, 465.0]	439.0 [421.0, 464.0]	441.0 [415.0, 457.0]

Data are presented as means ± SD or median [Q1, Q3] for continuous data or N (%) for categorical data. BPM, beats per minute; LBBB, left bundle branch block; ms, milliseconds; RBBB, right bundle branch block

4.2.9 Echocardiography

All HF patients recruited into this study had a transthoracic echocardiogram performed within 6 months of recruitment by an accredited British Society of Echocardiography sonographer. These were performed at the patient's local cardiology outpatient department and were requested at the time of recruitment (if they had not had one performed in the 6 months prior to recruitment). All HF patients recruited into this study had a left ventricular ejection fraction <45% and the other common echocardiogram findings are presented in table 4-12.

Left ventricular ejection fraction was relatively well matched across the 3 HF cohorts. A higher proportion of those with non-ischaemic cardiomyopathy had significant valve pathology (defined as at least moderate), a higher proportion of severe LVSD and left ventricular dilatation.

Table 4-12: Echocardiographic findings in heart failure cohorts

	HF CAD (n=70)	**HF no CAD (n=51)**	**HF AF (n=75)**
Dilated LV	39 (55.7)	41 (80.4)	38 (50.7)
LVH	8 (11.4)	9 (17.6)	17 (22.7)
Mild LVSD	9 (12.9)	10 (19.6)	14 (18.7)
Moderate LVSD	33 (47.1)	19 (37.3)	31 (41.3)
Severe LVSD	28 (40)	22 (43.1)	30 (40)
At least moderate AS	1 (1.4)	3 (5.9)	1 (1.3)
At least moderate AR	0	2 (3.9)	1 (1.3)
At least moderate MS	0	0	0
At least moderate MR	13 (18.6)	17 (33.3)	18 (24.0)
At least moderate TR	4 (5.7)	2 (3.9)	3 (4.0)

Data are presented as N (%) for categorical data. AR, aortic regurgitation; AS, aortic stenosis; LV, left ventricle; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; MR, mitral regurgitation; MS, mitral stenosis; TR, tricuspid regurgitation

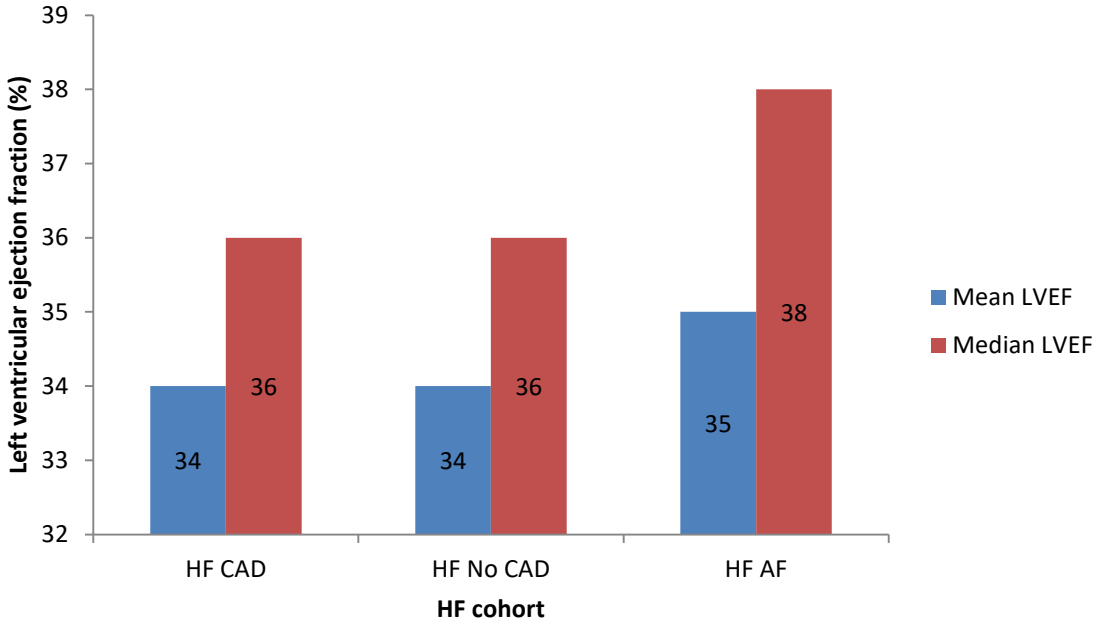


Figure 4-3: Distribution of left ventricular ejection fraction by heart failure cohort

4.2.10 Biochemistry

All HF patients (n= 196) enrolled into this study had a full battery of biochemical blood tests checked at their initial screening visit. The following biochemical tests were performed in each patient: U&E, LFT, CRP, BNP, TFT, glucose, calcium, phosphate, urate and cholesterol. All biochemical analyses were performed at the Western Infirmary Glasgow within 4 hours of collection, with the exception of plasma BNP which was batched and sent to the department of biochemistry at Gartnavel General Hospital in Glasgow for testing.

There were a mixture of normally distributed and skewed data, therefore mean and median values are both presented in this section. Biochemical parameters measured were similar across the 3 HF cohorts. The BNP and U&E results are shown in table 4-13. eGFR was calculated using the 4-variable MDRD formula and severe renal dysfunction was categorised by an eGFR <30ml/min/1.73m^2. Most patients enrolled had normal (eGFR >60ml/min/1.73m^2) or mildly impaired renal function (eGFR ≥30 & <60ml/min/1.73m^2). See figure 4-4.

Median plasma BNP was elevated in each of the 3 separate HF groups (>35 pg/mL for patients presenting in a non-acute manner) with an overall median plasma BNP of 204.5g/mL for the total HF population. There was a large range in concentrations of plasma BNP which is illustrated in figure 4-5.

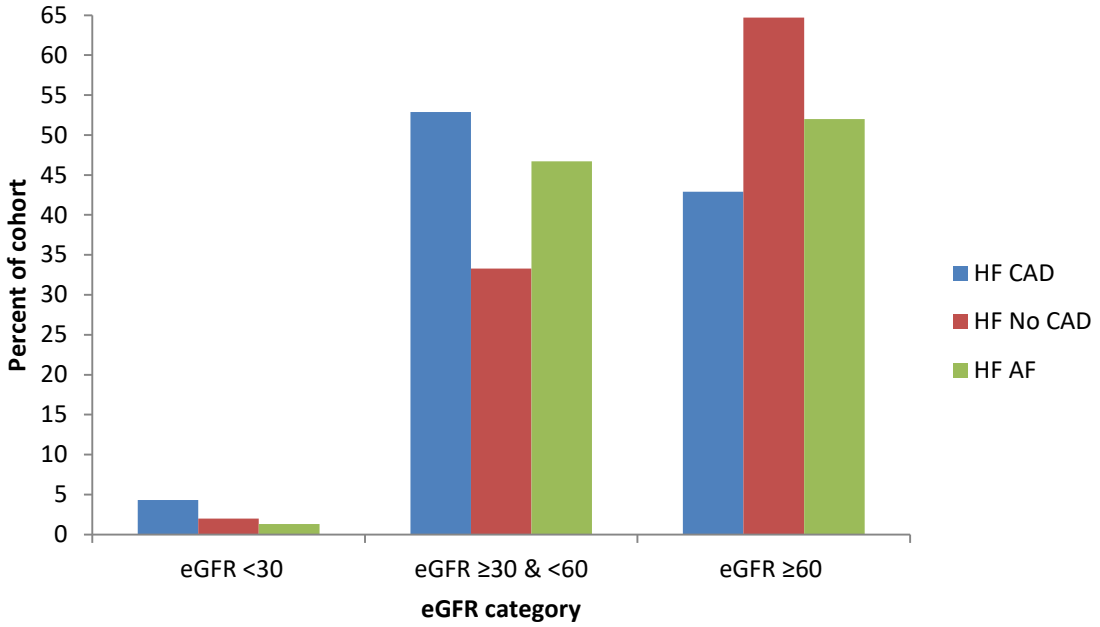


Figure 4-4: Distribution of eGFR by heart failure cohort

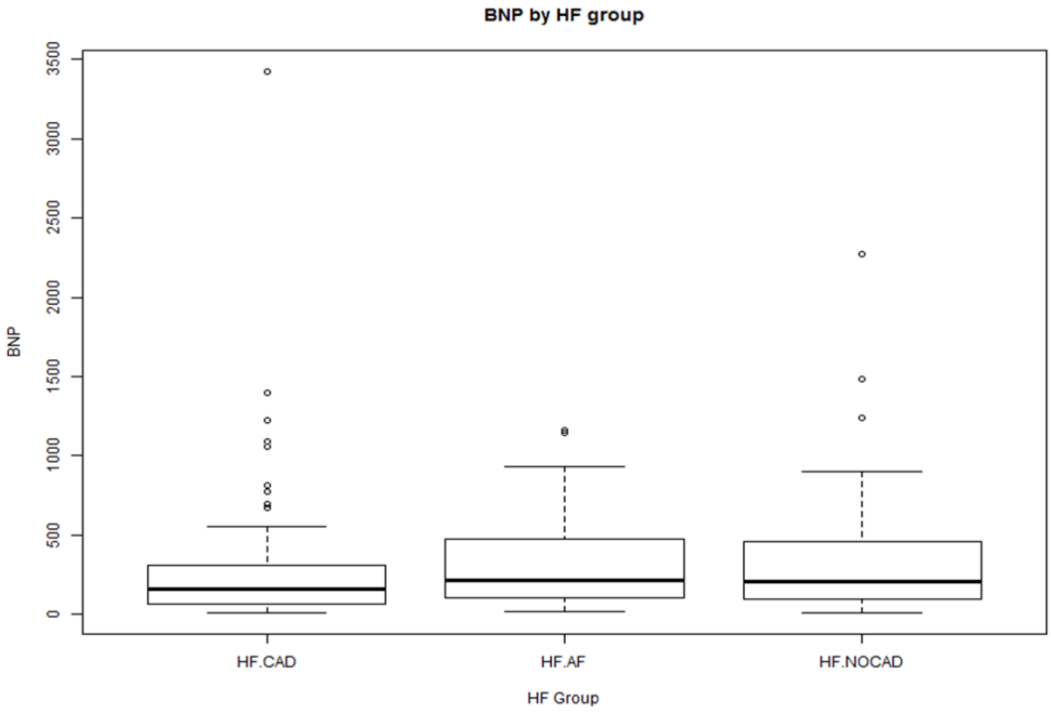


Figure 4-5: Distribution of BNP by heart failure cohort

Table 4-13: BNP and renal function results in heart failure cohorts

	HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)	Reference range/Units
Mean BNP	298.4 (480.2)	358.8 (421.8)	326.8 (289.8)	<35 pg/ml
Median BNP	162 [68, 305]	208 [98, 470]	214 [105, 493]	<35 pg/ml
Mean sodium	138.0 (2.8)	138.3 (3.1)	138.1 (3.0)	133-146 mmol/l
Median sodium	138 [137, 140]	138 [137, 140]	138 [137, 140]	133-146 mmol/l
Mean potassium	4.3 (0.4)	4.4 (0.3)	4.3 (0.5)	3.5-5.3 mmol/l
Median potassium	4.3 [4.1, 4.6]	4.4 [4.2, 4.6]	4.3 [4.1, 4.6]	3.5-5.3 mmol/l
Mean urea	9.9 (4.4)	7.8 (3.2)	8.8 (3.8)	2.5-7.8 mmol/l
Median urea	8.9 [7, 11.2]	7.0 [5.5, 10.3]	7.9 [6.3, 10.3]	2.5-7.8 mmol/l
Mean creatinine	112.7 (36.9)	93.3 (34.8)	104.1 (33.9)	40-130 µmol/l
Median creatinine	112 [81, 135]	85 [67, 110]	102 [74, 125]	40-130 µmol/l
Mean eGFR	61.9 (23.6)	75.4 (27.0)	67.4 (22.1)	>60ml/min/1.73m^2
Median eGFR	56.9 [26.3, 115.0]	74.8 [28.2, 161.8]	65.2 [27.8, 110.9]	>60ml/min/1.73m^2

Data are presented as means (SD) or median [Q1, Q3]. BNP, brain natriuretic peptide; eGRF, estimated glomerular filtration rate

The mean concentration of liver enzymes bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase and albumin were within normal local reference ranges and are shown in table 4-14.

Table 4-14: Liver function test results in heart failure cohorts

	HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)	Reference range /Units
Mean bilirubin	11.2 (4.3)	13.2 (7.8)	15.0 (8.4)	<20 mmol/l
Median bilirubin	10 [8, 14]	11 [8, 15]	14 [9, 17]	<20 mmol/l
Mean AST	20.7 (8.8)	22 (8.2)	23.5 (8.1)	<40 mmol/l
Median AST	19 [16, 23]	21 [16, 25]	22 [18, 28]	<40 mmol/l
Mean ALT	18.4 (9.2)	19.5 (8.6)	22.1 (11.7)	<50 mmol/l
Median ALT	16 [12, 22]	18 [13, 26]	18 [15, 26]	<50 mmol/l
Mean alkaline phosphatase	89.5 (29.5)	93.9 (42.2)	92.2 (35.1)	30-130 mmol/l
Median alkaline Phosphatase	83.5 [71, 107]	83 [69, 106]	82 [68, 106]	30-130 mmol/l
Mean albumin	37.1 (2.8)	37.3 (3.8)	36.9 (2.7)	35-50 mmol/l
Median albumin	37 [35, 39]	38 [35, 40]	37 [35, 39]	35-50 mmol/l

Data are presented as means (SD) or median [Q1, Q3]. ALT; alanine transaminase AST; aspartate transaminase

The other biochemical tests measured at the initial screening visit are shown in table 4-15. All HF patients had normal thyroid function test results. Due to the interaction between thyroid function and cognition, abnormal thyroid function would have been a potential confounder and so these patients would not have been eligible for participation. Mean and median CRP values were within normal limits in each of the HF groups. Random glucose levels were checked with the highest mean values found in those patients with non-ischaemic cardiomyopathy. Fasting blood glucose levels were not checked. In patients receiving lipid lowering therapy, mean and median total cholesterol levels were less than 5mmol/l. Of those patients not receiving lipid lowering therapy, patients with both ischaemic and non-ischaemic cardiomyopathy had total mean and median cholesterol levels outwith the reference range. All groups had slightly elevated mean urate levels.

Table 4-15: Results of other biochemical tests measured in heart failure cohorts

	HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)	Reference range/ Units
Mean TSH	2.1 (2.1)	2.1 (3.2)	1.8 (1.1)	0.35-5.00 mU/L
Median TSH	1.6 [1.1, 2.6]	1.5 [1.1, 2.0]	1.7 [1.1, 2.4]	0.35-5.00 mU/l
Mean T4	14.1 (2.3)	14.2 (2.4)	14.2 (1.9)	9.0-21.0 pmol/l
Median T4	13.6 [12.3, 15.7]	14.0 [12.8, 15.0]	14.0 [12.6, 15.9]	9.0-21.0 pmol/l
Mean urate	0.5 (0.1)	1.2 (5.3)	0.5 (0.2)	0.2-0.43 mmol/l
Median urate	0.5 [0.4, 0.5]	0.4 [0.4, 0.5]	0.5 [0.4, 0.6]	0.2-0.43 mmol/l
Mean CRP	8.1 (12.2)	4.9 (5.5)	6.5 (11.6)	0-10 mg/l
Median CRP	3.5 [2.0, 9.0]	3.0 [1.0, 6.0]	4.0 [3.0, 8.0]	0-10 mg/l
Mean glucose	6.9 (3.5)	7.3 (4.9)	7.0 (3.1)	3.5-6.0 mmol/l
Median glucose	5.6 [5.1, 6.8]	5.5 [4.8, 7.0]	5.8 [5.2, 7.8]	3.5-6.0 mmol/l
Mean total cholesterol on lipid lowering therapy	4.1 (0.8)	4.3 (1.2)	3.8 (0.8)	<5.0 mmol/l
Mean total cholesterol not on lipid lowering therapy	5.5 (1.2)	5.2 (1.4)	4.8 (1.1)	<5.0 mmol/l
Median total cholesterol on lipid lowering therapy	4.0 [3.6, 4.7]	4.1 [3.4, 4.9]	3.7 [3.2, 4.2]	<5.0 mmol/l
Median total cholesterol not on lipid lowering therapy	5.3 [4.8, 6.0]	5.1 [4.4, 6.3]	4.7 [3.9, 5.3]	<5.0 mmol/l

Data are presented as means (SD) or median [Q1, Q3]. CRP, C-reactive protein; TSH, thyroxine stimulating hormone

4.2.11 Haematology

Full blood count, haematinics and coagulation screens were checked for each patient recruited into this study. There were a mixture of normally distributed and skewed data, therefore mean and median values are both presented in this section. These results are shown in tables 4-16 – 17.

Table 4-16: Full blood count results in heart failure cohorts

	HF CAD (n=70)	**HF no CAD (n=51)**	**HF AF (n=75)**	**Reference range/ Units**
Mean WBC count	7.7 (1.9)	8.1 (3.0)	8.0 (2.1)	4.0-11.0 $x10^9$/l
Median WBC count	7.5 [6.7, 8.6]	7.7 [6.0, 9.1]	7.8 [6.5, 9.3]	4.0-11.0 $x10^9$/l
Mean Hb	129.1 (20.0)	133.6 (14.9)	134.3 (15.1)	115-165 g/L
Median Hb	130.5 [116, 144]	135.0 [125, 146]	137.0 [123, 143]	115-165 g/L
Mean RDW	16.3 (12.1)	15.0 (2.5)	14.7 (1.4)	11.6-14.6 %
Median RDW	14.1 [13.2, 15.0]	14.2 [13.4, 15.3]	14.4 [13.8, 15.4]	11.6-14.6 %
Mean platelet count	239.3 (82.1)	228.3 (89.4)	213.9 (60.2)	150-400 $x10^9$/l
Median platelet count	225.5 [187, 274]	211 [160, 263]	205 [180, 253]	150-400 $x10^9$/l
Mean lymphocyte count	1.9 (0.7)	1.8 (0.7)	1.9 (0.9)	1.5-4.0 $x10^9$/l
Median lymphocyte count	1.9 [1.4, 2.3]	1.7 [1.3, 2.3]	1.8 [1.3, 2.1]	1.5-4.0 $x10^{9/l}$
Mean ESR	16.4 (13.9)	9.0 (7.0)	13.9 (13.8)	1-12 mm/h
Median ESR	13.5 [6, 22]	8.0 [2, 12]	10.0 [5, 18]	1-12 mm/h

Data are presented as means (SD) or median [Q1, Q3]. ESR, erythrocyte sedimentation rate; Hb, haemoglobin; RDW, Red Cell Distribution Width; WBC, White Blood Cell

Table 4-17: Haematinic results in heart failure cohorts

	HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)	Reference range/ Units
Mean vitamin B12	417.1 (187.3)	367.1 (183.6)	399.8 (135.5)	200-900 pg/ml
Median vitamin B12	364 [302, 488]	324 [239, 425]	377.5 [292, 460]	200-900 pg/ml
Mean serum folate	6.2 (4.5)	5.3 (2.8)	6.2 (4.4)	3.1-20 µg/L
Median serum folate	4.5 [3.5, 7.2]	4.8 [3.1, 7.0]	4.6 [3.4, 7.4]	3.1-20 µg/L
Mean serum ferritin	185 (172)	168.8 (177.1)	154 (171.5)	15-200 ng/mL
Median serum ferritin	153 [68, 238]	126 [45, 225]	98 [39, 212]	15-200 ng/mL

Data are presented as means (SD) or median [Q1, Q3]

All patients with HF recruited into this study had a normal haemoglobin, lymphocyte count, WBC count and platelet count. In keeping with no evidence of anaemia, there was also no evidence of vitamin B12 deficiency, iron deficiency nor folate deficiency seen when haematinics were checked. All 3 HF cohorts had an elevated mean red blood cell distribution width with both the ischaemic cardiomyopathy cohort and HF and AF cohort having elevated mean ESR levels.

85 out of a total of 196 HF (43%) patients were formally anticoagulated with either warfarin or a novel oral anticoagulant. Coagulation results therefore varied significantly. The overall mean prothrombin time (PT) for those receiving formal anticoagulation versus those not on anticoagulation was 27.8s (8.6) vs. 11.5s (2.1) respectively. These results are demonstrated in figure 4-6.

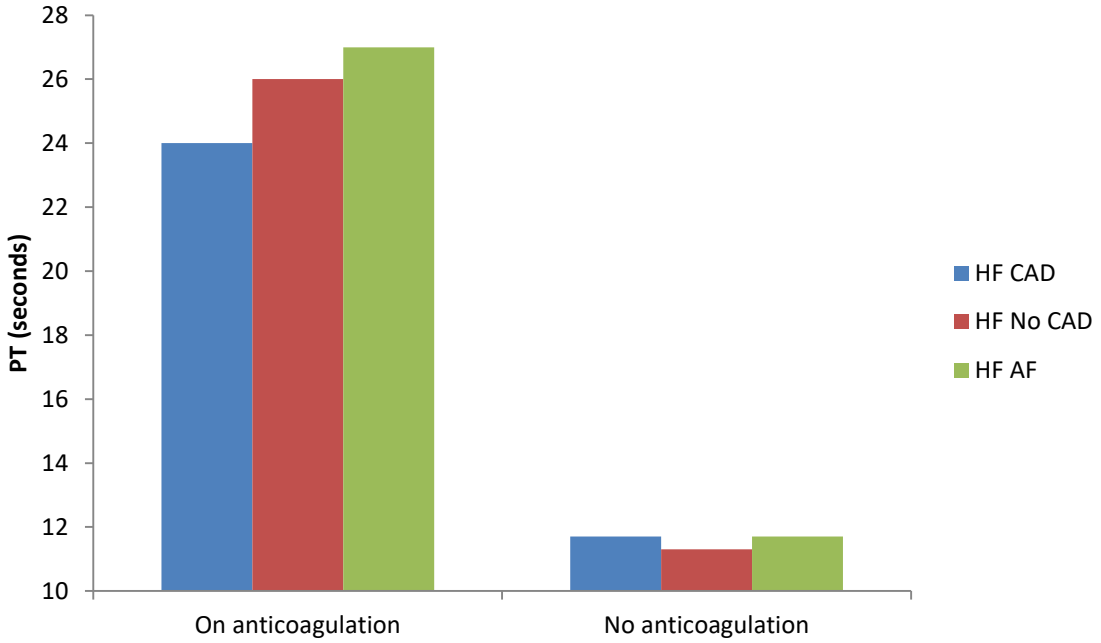


Figure 4-6: Mean pro-thrombin time on anticoagulation vs. no anticoagulation by heart failure cohort

4.3 Summary

This chapter described in detail the process of study recruitment as well as the clinical characteristics of the HF cohort recruited into this study. Of the 520 HF patients screened in the cardiology outpatient department, 196 fulfilled the criteria for inclusion. All of these HF patients had evidence of HF-REF with a LVEF <45% on transthoracic echocardiography. They were a cohort of stable, community-dwelling HF patients who had not been recently discharged from hospital.

In keeping with results from published studies of HF epidemiology,[5] the mean age of our population was 71 years with 70% of our total HF population being male. Those a history of AF had a higher proportion adverse HF prognostic indicators including longer duration of heart failure, higher rates of previous HF hospitalisation and higher concentrations of plasma BNP. Of those patients with non-ischaemic cardiomyopathy 22% had no clear cause of their HF identified.

Although a significant proportion of this cohort were elderly, with significant co-morbidities and polypharmacy, over one third (35%) lived at home alone and less than 10% (6.7%) had any employed carers to help with activities of daily living. The majority of these patients were on treatment with regular diuretic for symptomatic relief in addition to disease modifying medication. 84% of those patients with AF were formally anticoagulated – the majority with warfarin.

Consistent with an outpatient sampling frame, basic physiological measurements were stable for each of the HF groups. The majority of patients were in NYHA class II with lung crepitations and peripheral oedema being commonly found on physical examination. Across the 3 HF cohorts, most patients had objective evidence of either moderate or severe LVSD based on LVEF. Those with non-ischaemic cardiomyopathy in sinus rhythm were more likely to have a dilated left ventricle and prolonged QRS duration – most frequently with a left bundle branch block morphology on ECG. Apart from elevated plasma BNP levels there were no significant biochemical or haematological findings on laboratory testing. This is indicative of the fact that any potentially reversible causes of cognitive impairment precluded enrolment into this study.

CHAPTER FIVE

CLINICAL CHARACTERISTICS OF CONTROL COHORTS

5.1 Introduction

This chapter will discuss the recruitment of both disease and healthy control groups into this study. Their clinical characteristics including demographic details, past medical history, medication use and examination findings will be described in detail. Results of basic investigations including electrocardiography, echocardiography and blood tests will also be described with the differences between these 2 control groups highlighted. Significance testing was not routinely performed for each variable – only in certain pre-selected variables where a significant association was postulated. I chose to include both healthy controls (HC) and cardiac controls (CAD CONT) into this study to allow us to control for underlying cardiac conditions that often are present in HF. In my literature review (outlined in chapter 2) I found no study that has previously used this specific design.

5.2 Results

5.2.1 Recruitment of study control cohorts

5.2.1.1 Cardiac control cohort

Patients attending cardiac rehabilitation clinics between March 2013 and December 2014 at Glasgow Royal Infirmary, Western Infirmary Glasgow, Royal Alexandra Hospital and Stobhill hospital were screened for eligibility. These patients were required to have coronary artery disease on CT or invasive coronary angiography (defined as >50% stenosis in ≥1 coronary artery) or a clinical history of previous myocardial infarction with supporting evidence including elevated serum cardiac enzymes, dynamic ECG changes and clinical history consistent with acute myocardial ischaemia. They could not have any clinical history of heart failure and were required to have a LVEF >55% on transthoracic echocardiography.

Of the 197 patients screened at the cardiac rehabilitation clinic 61 were included in the final sample. 136 patients were excluded for a variety of reasons and these are shown in table 5-1. The most common reason for exclusion was age<60 years old followed by patient refusal to participate. In contrast to the HF cohorts, no patients were excluded because of previous cardiac arrest or inability to provide informed consent due to sensory or language difficulties.

Some patients are referred for cardiac rehabilitation following cardiac surgery and in this cohort 13% of those screened had to be excluded due to previous cardiac surgery. Those who develop LVSD following acute myocardial infarction are often followed up at the HF clinic rather than by the cardiac rehabilitation team and so only 4% of those screened were excluded on the basis of having a reduced LVEF.

Table 5-1: Reasons for exclusion into study for cardiac control patients

Reason for exclusion	Number (% of those excluded)
Age <60 years	64 (47)
Alcohol excess	4 (3)
AF	8 (6)
Cardiac surgery	18 (13)
Ejection fraction< 55%	5 (4)
Hospital discharge within 3 months	5 (4)
Neurological illness	10 (7)
Patient refusal	21 (15)
Terminal illness	1 (1)

Data are presented as N (%) for categorical data. AF, atrial fibrillation.

5.2.1.2 Healthy control cohort

The healthy control cohort was recruited from the Generation Scotland database (see chapter 3). These are healthy participants who have previously volunteered to take part in clinical research projects and whose details are held in a central database. Participants recruited into this cohort were required to have no previous history of heart failure or coronary artery disease. They were required to have no diagnosis of any chronic illness and to be on no regular medication. Candidates who fulfilled these criteria were contacted by the Generation Scotland team and asked if they were willing to participate.

The first 100 participants to reply were invited to attend for an initial screening visit. 13 of these volunteers were then excluded because of prescription of regular medication and previously undisclosed past medical history including previous stroke, hypertension, diabetes and connective tissue disease. The remaining 87 healthy volunteers gave written informed consent and participated in the study visits.

5.2.2 Demographics of control cohorts

5.2.2.1 Demographics of control cohorts

The clinical demographics of the control cohorts are shown in table 5-2. The two control cohorts had participants of similar age range. Those recruited into the healthy control cohort were more likely to be female, non-smokers with higher average years of education and higher full scale IQ.

Table 5-2: Basic demographics of participants recruited into control cohorts

	CAD CONT (n=61)	**HC (n=87)**
Age (years)	67.5 ± 6.3	70.3 ± 6.7
Age range (years)	60-92	59 – 85
Sex (% males)	43 (71)	55 (63)
Education (total years)	13 [11, 15]	15 [12, 18]
Full scale IQ	103 [70, 117]	112 [75, 117]
Smoker	37 (61)	13 (15)
Current alcohol	41 (67)	65 (75)

Data are presented as means (SD), median [Q1, Q3] or N (%) for categorical data.

5.2.2.2 Comparison between control and HF cohorts

When compared, the mean age of patients with CAD and no HF was lower than the mean age of those with HF (67.5 versus 70.6, p=0.0149) as was the mean age of the healthy control participants (70.3 versus 70.6, p= 0.8613). 70% of HF patients recruited into this study were male compared to 71% of patients recruited into the cardiac control group and 63% of healthy volunteers. These differences were not statistically significant when between group comparisons were made - firstly between HF patients and CAD controls (p=1.0000) and secondly between HF patients and healthy controls (p=0.3310). Healthy control participants were more likely to be female, have longer years of education, were less likely to smoke and more likely to consume alcohol. Table 5-3 shows a summary of the statistically significant p-values when between group comparisons of baseline characteristics were made.

Table 5-3: Summary of statistically significant differences in baseline demographics between groups

	Total HF (N=196)	CAD CONT (N=61)	HC (N=87)	HF vs CAD CONT p-value	HF vs HC p-value
Age (years)	70.6 ± 8.1	67.5 ± 6.3	70.3 ± 6.7	0.0149	0.8613
Education (total years)	11 [10, 14]	13 [11, 15]	15 [12, 18]	0.0169	<0.0001
Current alcohol	99 (51)	41 (67)	65 (75)	0.0323	0.0002

Data are presented as means (SD), median [Q1, Q3] or N (%) for categorical data.

5.2.3 Medical history

As previously described, those participants recruited into the healthy control cohort could not have any past medical history of chronic disease. Figure 5-1 shows the common co-morbid conditions found in the cardiac control cohort.

Patients recruited into the cardiac control cohort were required to have coronary artery disease confirmed either on CT or invasive coronary angiography (defined as >50% stenosis in ≥1 coronary artery) or a clinical history of previous myocardial infarction. 60 out of the 61 patients included had undergone previous coronary angiography (with invasive or CT) with 45 of them having going on to have percutaneous coronary intervention performed. 52 patients had a previous diagnosis of myocardial infarction and 36 (59%) described ongoing symptoms of angina.

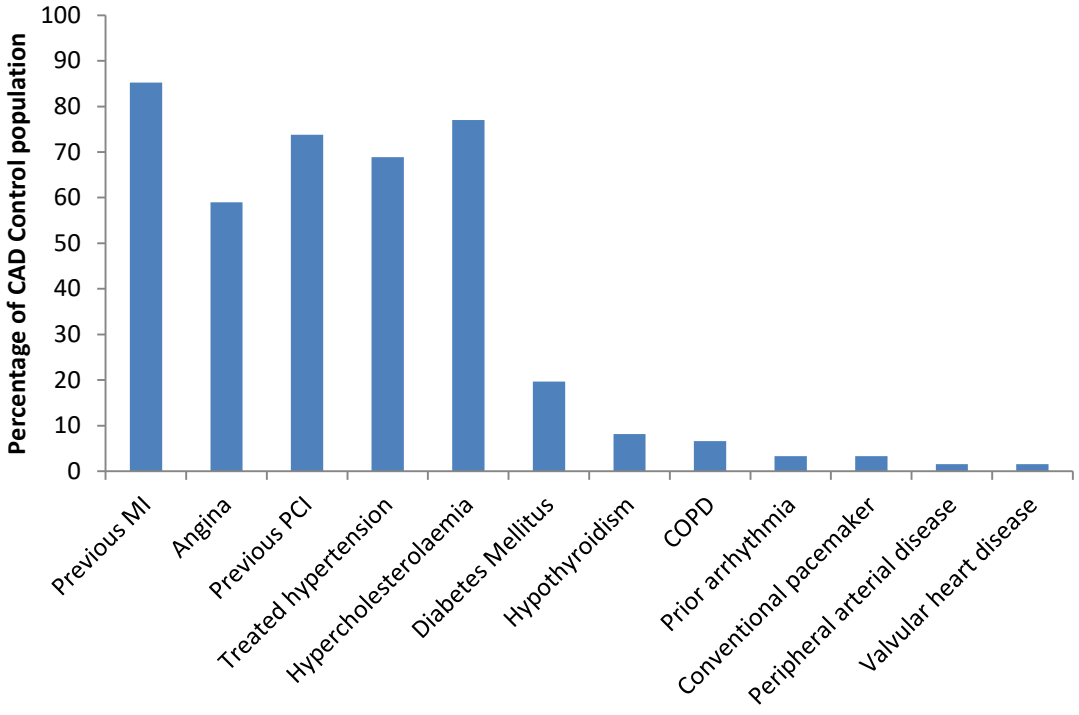


Figure 5-1: Prevalence of co-morbid conditions in the cardiac control population

Other cardiovascular risk factors including hypertension, hypercholesterolaemia and diabetes were also common in this cohort. Of the 12 patients diagnosed with diabetes 9 were treated with oral hypoglycaemic therapy only, 2 were diet controlled and only one was on insulin therapy. Only 2 patients had a conventional pacemaker for bradyarrhythmia and there were no patients recruited in this cohort with implantable cardiac defibrillators or cardiac resynchronisation pacemakers.

67.2% of cardiac control patients stated they had a family history of premature coronary artery disease. 45 patients (74%) lived with a relative and 2 (3%) patients had regular employed carers to assist with activities of daily living.

5.2.4 Medication use

Patients were excluded from the healthy control cohort if they were prescribed any regular medication. Tables 5-3 to 5-5 present the number of cardiac control patients receiving the most commonly prescribed medications.

Over 98% of this population were prescribed some form of antiplatelet agent, 93% were on some form of lipid lowering therapy and no patients in this group were formally anticoagulated with warfarin or NOAC. Other non-cardiovascular medications prescribed included anxiolytics (n=2), antidepressants (n=1), incontinence medication (n=2) and bronchodilators (n=5).

Table 5-4: Commonly prescribed cardiovascular medications in cardiac control cohort

	CAD CONT (n=61)
Statin	59 (96.7)
Any lipid lowering drug	57 (93.4)
Beta Blocker	51 (83.6)
ACE Inhibitor	39 (63.9)
Nicorandil	12 (19.7)
Diuretics	12 (19.7)
Long-acting nitrates	11 (18.0)
Calcium channel-blocker	10 (16.4)
Diabetic medication	10 (16.4)
ARB	5 (8.2)
Ivabradine	2 (3.3)
Aldosterone Blocker	1 (1.6)
Digoxin	1 (1.6)

Data are presented as N (%). ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

Table 5-5: Antiplatelet and anticoagulant use in cardiac control cohort

	CAD CONT (n=61)
Any antiplatelet therapy	60 (98.4)
Aspirin	59 (96.7)
Clopidogrel	17 (27.9)
Any anticoagulant therapy	0
Warfarin	0
NOAC	0

Data are presented as N (%). NOAC, novel oral anticoagulant

Table 5-6: Other medication use in cardiac control cohort

	CAD control (n=61)
Anxiolytic	2 (3.3)
Antidepressant	1 (1.6)
Incontinence medication	2 (3.3)
Antihistamine	0
Bronchodilator	5 (8.2)

Data are presented as N (%).

5.2.5 Clinical examination findings

Routine physiological measurements were taken for each study participant at the initial screening visit and again at return visit 1. Table 5-4 lists the physiological measurements taken at return visit 1 for those recruited into wither the cardiac or healthy control cohort. According to the World Health Organisation (WHO) BMI classification, the mean BMI of participants in both control cohorts (28.4, 26.4) fell into the overweight range (>25). A full cardiovascular examination was also performed at this time. Participants recruited into these control cohorts had no clinical signs of heart failure. The presence of a cardiac murmur was recorded for 7% of the cardiac control cohort and otherwise cardiovascular examinations for participants in these cohorts were essentially normal.

Table 5-7: Physiological measurements taken at return visit 1

		CAD CONT (n=61)	HC (n=87)
Height (cm)	Median	168	172
	Mean (SD)	167.1 (8.8)	169.7 (11.0)
Weight (Kg)	Median	81	77
	Mean (SD)	82.4 (16.3)	78.0 (14.3)
BMI	Median	28.4	26.4
	Mean (SD)	29.4 (5.0)	27.0 (3.9)
Neck circumference males (cm)	Median	18.0	17.8
	Mean (SD)	18.5 (2.2)	17.5 (1.3)
Neck circumference females (cm)	Median	15.7	15.0
	Mean (SD)	15.4 (2.2)	15.2 (2.1)
Systolic BP (mmHg)	Median	133	137
	Mean (SD)	138.2 (24.3)	141.3 (20.6)
Diastolic BP (mmHg)	Median	76	79
	Mean (SD)	75.7 (11.5)	78.4 (10.2)
Heart rate (BPM)	Median	70	62
	Mean (SD)	72.1 (12)	64.3 (10.1)
SpO_2(%)	Median	97	97
	Mean (SD)	97.1 (1.4)	96.9 (1.4)
Respiratory rate (BPM)	Median	16	14
	Mean (SD)	15.2 (1.8)	14.9 (2.1)
Temperature(˚C)	Median	36.5	36.1
	Mean (SD)	36.5 (0.7)	36.0 (0.8)

Data are presented as means (SD) or median [Q1, Q3]. BP, blood pressure; BPM, beats per minute; cm, centimetres; Kg, kilogram; mmHg, millimetres of mercury

5.2.6 Electrocardiography

All patients recruited into cohorts 4 (cardiac control cohort) and 5 (healthy control cohort) were in normal sinus rhythm and this was confirmed on 12 lead ECG at their initial screening visit. The mean heart rates were 62 (10) beats per minute and 69 (10) beats per minute for cohorts 4 and 5 respectively. One patient in the cardiac control group had (left) bundle branch block on their ECG, all others had a QRS duration <120ms. 7 (11.5%) of cardiac patients had evidence of an old myocardial infarction on their ECG with pathological Q waves present. There were no acute ischaemic changes seen on any of the ECGs.

5.2.7 Echocardiography

The majority of cardiac control patients had already had transthoracic echocardiography performed within the past 6 months as part of routine clinical care. Healthy control participants underwent transthoracic echocardiography at time of enrolment by a

sonographer accredited by the British Society of Echocardiography. Study participants recruited into these control groups were required to have a LVEF >55% to fulfil the inclusion criteria. The mean calculated ejection fractions were 66% for those with ischaemic heart disease and 64% for the healthy control subjects. 16% of the cardiac control patients had evidence of concentric LVH in keeping with a prior history of hypertension. Otherwise, there were no significant echocardiographic findings and no other between group differences.

5.2.8 Biochemistry

Participants recruited into the 2 control cohorts had the same laboratory tests performed as those recruited into the HF cohorts. These included U&E, LFT, CRP, BNP, TFT, glucose, calcium, phosphate, urate and cholesterol. Bloods were taken from each participant at the initial screening visit and analysed at the Western Infirmary Glasgow within 4 hours of collection (with the exception of BNP which was batched and sent to the department of biochemistry at Gartnavel General Hospital in Glasgow for testing). There were a mixture of normally distributed and skewed data, therefore mean and median values are both presented in this section.

Current ESC HF guidelines recommend an optimum exclusion cut-off point of 35pg/mL for BNP in patients presenting in a non-acute way. In this cohort the median BNP concentration was 28pg/mL [15, 37] for healthy control participants and 62pg/mL [29, 106] for the cardiac control group. These values were considerably lower than the median BNP for the HF cohort (204.5pg/mL, [81, 401]). See table 5-5.

The mean sodium and potassium values were similar to the mean values in the HF cohort and were within normal limits. The mean urea and creatinine values were lower than those found in the HF cohorts (6.2mmol/l (2.8) vs. 8.9mmol/l (4.0) and 79.3µmol/l (27.9) vs. 104.4µmol/l (35.8) respectively). The distribution of eGFR by control cohort is illustrated in figure 5-2 with the majority of patients having normal renal function (eGFR>60ml/min/1.73m^2). See table 5-5.

Table 5-8: BNP and renal function results for control cohorts

	CAD CONT (n=61)	HC (n=87)	Reference range/ Units
Mean BNP	93.2 (96.4)	33.1 (26.7)	<35 pg/ml
Median BNP	62 [29, 106]	28 [15, 37]	<35 pg/ml
Mean sodium	138 (3)	139 (2)	133-146 mmol/l
Median sodium	139 [137, 140]	139 [137, 140]	133-146 mmol/l
Mean potassium	4.3 (0.4)	4.1 (0.3)	3.5-5.3 mmol/l
Median potassium	4.3 [4.1, 4.5]	4.1 [3.9, 4.3]	3.5-5.3 mmol/l
Mean urea	6.5 (4.3)	5.9 (1.3)	2.5-7.8 mmol/l
Median urea	5.5 [5.0, 6.6]	5.6 [5.0, 6.6]	2.5-7.8 mmol/l
Mean creatinine	83.8 (43.3)	74.8 (12.4)	40-130 µmol/l
Median creatinine	73 [67, 92]	74 [65, 84]	40-130 µmol/l
Mean eGFR	86.7 (23)	88.0 (15)	>60ml/min/1.73m^2
Median eGFR	85.6 [15, 180]	88.3 [60, 126]	>60ml/min/1.73m^2

Data are presented as means (SD) or median [Q1, Q3]. BNP, brain natriuretic peptide; eGRF, estimated glomerular filtration rate

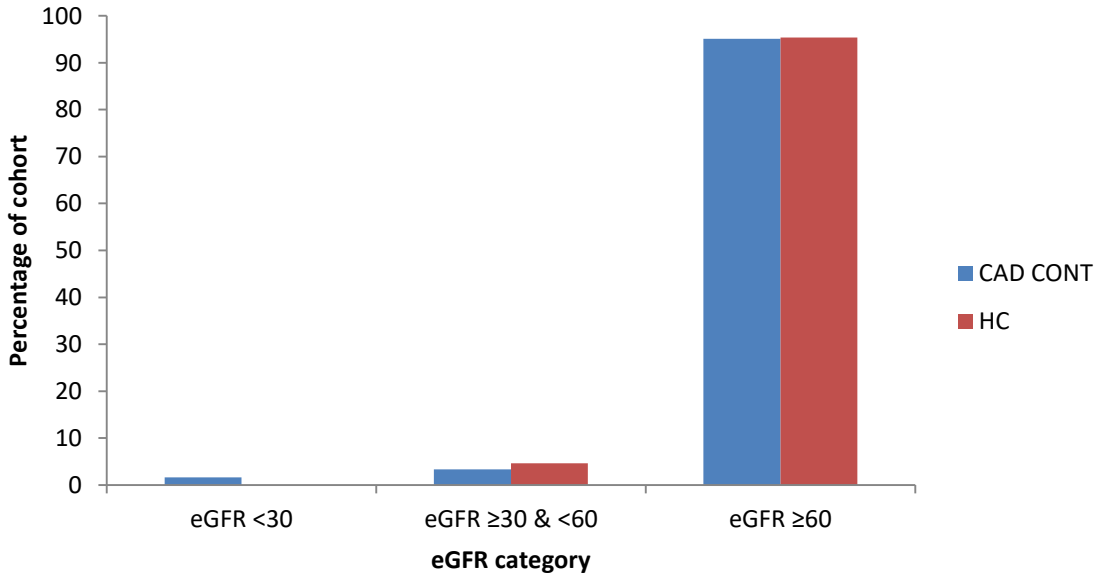


Figure 5-2: Distribution of eGFR by control cohort

Every study participant had LFTs checked at the initial screening visit (table 5-6). The mean bilirubin, AST, ALT, alkaline phosphatase and albumin concentrations were all within normal limits for both the cardiac control patients and healthy volunteers.

Table 5-9: Liver function test results for control cohorts

	CAD CONT (n=61)	HC (n=87)	Reference range/ Units
Mean bilirubin	11.0 (5.0)	11.9 (5.4)	<20 mmol/l
Median bilirubin	10 [8, 12]	10 [8, 13]	<20 mmol/l
Mean AST	22.7 (7.7)	22.5 (6.3)	<40 mmol/l
Median AST	22 [19, 26]	21 [18, 25]	<40 mmol/l
Mean ALT	25.6 (14.1)	23.4 (10.3)	<50 mmol/l
Median ALT	22 [17, 29]	21 [17, 27]	<50 mmol/l
Mean alkaline phosphatase	81 (24.3)	75 (18.6)	30-130 mmol/l
Median alkaline Phosphatase	80 [65, 94]	74 [61, 86]	30-130 mmol/l
Mean albumin	38.1 (2.8)	37.6 (2.4)	35-50 mmol/l
Median albumin	38 [37, 40]	37 [36, 39]	35-50 mmol/l

Data are presented as means (SD) or median [Q1, Q3]. ALT; alanine transaminase AST; aspartate transaminase

In addition to these biochemical tests TFTs, glucose, CRP, urate, calcium, phosphate and cholesterol were also measured. All participants recruited into either control cohort had normal thyroid function tests, urate levels and CRP.

No participants in the HC cohort were on lipid lowering therapy. Even when compared to those patients with ischaemic heart disease not on lipid lowering therapy, the HC population had higher mean cholesterol levels (5.3 versus 4.6). Median random glucose levels were within normal limits. Fasting blood glucose levels were not checked. These results are shown in table 5-7.

Table 5-10: Results of other biochemical tests measured in control cohorts

	CAD CONT (n=61)	HC (n=87)	Reference range/ Units
Mean TSH	1.9 (3.1)	1.8 (1.0)	0.35-5.0 mU/L
Median TSH	1.3 [1.0, 1.7]	1.6 [1.2, 2.3]	0.35-5.0 mU/l
Mean T4	13.3 (2.0)	13.3 (1.7)	9.0-21.0 pmol/l
Median T4	13.0 [12.1, 13.9]	13.0 [12.0, 14.0]	9.0-21.0 pmol/l
Mean urate	0.4 (0.1)	0.4 (0.1)	0.2-0.43 mmol/l
Median urate	0.4 [0.3, 0.4]	0.4 [0.3, 0.4]	0.2-0.43 mmol/l
Mean CRP	4.4 (5.6)	3.4 (10.0)	0-10 mg/l
Median CRP	3.0 [1.0, 5.0]	2.0 [1.0, 3.0]	0-10 mg/l
Mean glucose	6.4 (3.1)	5.4 (1.0)	3.5-6.0 mmol/l
Median glucose	5.5 [4.8, 6.8]	5.0 [4.7, 5.7]	3.5-6.0 mmol/l
Mean total cholesterol on lipid lowering therapy	4.0 (0.8)	N/A	<5.0 mmol/l
Mean total cholesterol not on lipid lowering therapy	4.6 (0.9)	5.3 (1.0)	<5.0 mmol/l
Median total cholesterol on lipid lowering therapy	3.9 [3.5, 4.4]	N/A	<5.0 mmol/l
Median total cholesterol not on lipid lowering therapy	4.5 [3.7, 5.1]	5.3 [4.7, 6.1]	<5.0 mmol/l

Data are presented as means (SD) or median [Q1, Q3]. CRP, C-reactive protein; TSH, thyroxine stimulating hormone

5.2.9 Haematology

Table 5-8 displays the full blood count results for the control cohorts. Data were normally distributed and so mean (SD) results are presented in this section. There were no significant differences between the 2 control cohorts and all mean haematological results were within the normal reference range.

Table 5-11: Full blood count results for control cohorts.

	CAD CONT (n=61)	HC (n=87)	Reference range/ Units
Mean WBC count	7.2 (1.8)	6.4 (1.5)	4.0 11.0 $x10^9$/l
Mean Hb	137.7 (11.9)	143.7 (12.7)	115-165 g/L
Mean RDW	13.3 (0.6)	13.3 (1.0)	11.6-14.6 %
Mean platelet count	238 (56.2)	235 (47.8)	150-400 $x10^9$/l
Mean lymphocyte count	2.0 (0.8)	1.9 (0.6)	1.5-4.0 $x10^9$/l
Mean ESR	7.2 (7.0)	7.6 (8.3)	1-12 mm/h

Data are presented as means (SD). ESR, erythrocyte sedimentation rate; Hb, haemoglobin; RDW, Red Cell Distribution Width; WBC, White Blood Cell

Patients in the CAD control group tended to have higher serum concentrations of vitamin B12 and folate when compared to the healthy controls, however, mean levels were within normal limits for both groups. Although healthy controls had higher mean levels of serum ferritin all mean levels were within reference range. See table 5-9.

Table 5-12: Haematinic results for control cohorts

	CAD CONT (n=61)	HC (n=87)	Reference range/ Units
Mean vitamin B12	410.5 (160.8)	347.2 (120.6)	200-900 pg/ml
Mean serum folate	7.0 (4.7)	6.3 (3.6)	3.1-20 µg/L
Mean serum ferritin	136.3 (129.3)	165.0 (141.9)	15-200 ng/mL

Data are presented as means (SD)

5.3 Summary

This chapter outlines in detail the process of recruitment into two control cohorts. A disease control cohort was included to allow comparison between patients with coronary artery disease with and without HF. This allows examination into whether HF *per se* is associated with certain cognitive outcomes rather than the atherosclerotic process that often underlies it. In our systematic review of the literature (see chapter 2) no prior studies were found that used this particular study design.

61 patients with CAD, no clinical HF and LVEF >55% were enrolled from cardiac rehabilitation clinics. They were relatively well matched to 87 healthy controls who had no previous diagnosis of any chronic illness, prescribed no regular medication and had LVEF >55%. These control participants underwent the same baseline investigations as those patients with HF and this chapter has described their results in detail.

Participant demographics were similar across each of the 5 study cohorts. Only 3 statistically significant differences were found when between group comparisons were made. Healthy control participants were on average younger, with longer years of total years of education and more likely to consume alcohol within recommended limits.

Patients with HF were more likely to have renal dysfunction, elevated red blood cell distribution width and ESR levels than either of the 2 control cohorts. Patients with HF had higher levels of plasma BNP, followed by patients with CAD and no HF. All cohorts had normal liver function and thyroid function. There was no documented anaemia nor iron, folate or vitamin B12 deficiency found.

CHAPTER SIX

REPEATABLE BATTERY FOR THE ASSESSMENT OF NEUROPSYCHOLOGICAL STATUS

6.1 Introduction

Each participant in this study underwent detailed neuropsychological testing using an extensive battery of cognitive assessment tools. These assessment tools were administered to each participant in the same order by either Sister Meyer or I. Both Sister Meyer and I were trained in their administration by Dr Niall Broomfield, consultant clinical neuropsychologist. The results from the neuropsychological assessment tools employed will be outlined in the following five chapters in the order in which they were administered to each study participant.

This chapter will describe in detail the results of the repeatable battery for the assessment of neuropsychological status (RBANS) for all study participants. This was the first cognitive test administered to each participant. This assessment tool has previously been described in chapter 3 and the RBANS scoring sheet is shown in appendix IX. The RBANS assesses the following individual domains of cognition: immediate memory, language, attention, visuospatial awareness and delayed memory.

Once individual subtests were scored, the raw scores were converted to index scores using normative tables provided in the RBANS stimulus booklet.[167] A total scale score was then derived from the index scores using the reference tables again provided in the RBANS manual. Following their administration, the RBANS booklets were blindly scored by Dr Rosalind Lees with a random 20% of the sample re-scored by 2 independent consultant neuropsychologists (Dr Niall Broomfield and Dr John Sharp) for quality assurance. Any disagreements in marking were referred to a third arbitrator (Professor Jonathan Evans).

In this chapter, the individual scores for each cognitive domain in addition to the total scale scores will be described. Difference in results between the 5 study cohorts will also be outlined. Significance testing was only performed for certain pre-specified variables. At the end of this chapter the results presented here will be compared to other published results in an attempt to put these results into context.

6.2 Results

6.2.1 RBANS total scale

6.2.1.1 RBANS total scale results

Table 6-1 presents the RBANS total scale results for each of the 5 study cohorts. Patients with HF and AF had the lowest (worst) mean RBANS total scale scores of 82.0± 16.2 followed by those with HF and CAD (86.3 ± 14.3). There were similar mean scores found in those with HF and no CAD (89.2 ± 14.6) and cardiac control patients (91.2 ± 15.9). Patients with HF were at increased risk of CI when compared to both the healthy control cohort (odds ratio, 12.73; 95% confidence interval [CI], 7.14 to 22.7; p<0.0001) and the cardiac control cohort (odds ratio, 2.05; 95% CI, 1.2 to 3.49; p=0.0081). The relationship between CI and HF persisted even after adjustment for potential confounding variables as shown in tables to 6-3 and 6-4.

Table 6-2 outlines the variables included in each of the models used in this analysis. In addition to age and sex (adjusted for in model 1) model 2 also adjusted for race, co-morbidity score, medication count and full scale IQ (derived from the Wechsler test of adult reading and used as a measure of education). Adjusting for these variables resulted in the largest difference in odds ratio (see tables 6-3 and 6-4) suggesting that co-morbid conditions and pre-morbid education are the variables which have the greatest impact on cognition.

There was no significant difference in RBANS total scale scores between HF patients with CAD and those without CAD (odds ratio, 0.83; 95% CI, 0.49 to 1.40; p=0.4849).

Table 6-1: Repeatable battery for the assessment of neuropsychological status total scale scores by cohort

	HF CAD (n=70)	HF no CAD (n=51)	HF AF (n=75)	CAD CONT (n=61)	HC (n=87)
Mean (SD)	86.3 (14.3)	89.2 (14.6)	82.0 (16.2)	91.2 (15.9)	106.9 (16.4)
Median	86.0	93.0	82.0	91.0	108.0
Range	51.0, 116.0	59.0, 117.0	53.0, 123.0	54.0, 127.0	64.0, 149.0

Data are presented as means (SD)

Table 6-2: Reference for model adjustment labels

Model label	Model text	Covariates
0	Unadjusted Model	N/A
1	Basic Model	Sex, Age
2	Demographic Adjusted Model	As for model 1, plus Co-Morbidity Score, Race, Wechsler Test of Adult Reading, Medication Count
3	Cognitive Adjusted Model	As for model 2, plus History of Depression, HADS depression score, History of Anxiety
4	Vascular Adjusted Model	As for model 3, plus Smoker, Systolic Blood Pressure, Diabetes Mellitus, BMI, Previous MI, Chronic Kidney Failure (defined as eGFR < 60), Hypertension

Table 6-3: Repeatable battery for the assessment of neuropsychological status total scale results for HF cohort versus healthy controls

Outcome	Model	Total N	OR.(95% CI)	p-value
All HF vs Healthy controls	0	283	12.73 (7.14, 22.7)	<0.0001
All HF vs Healthy controls	1	283	13.17 (7.36, 23.57)	<0.0001
All HF vs Healthy controls	2	283	4.98 (1.90, 13.07)	0.0011
All HF vs Healthy controls	3	271	5.47 (2, 14.97)	0.0009
All HF vs Healthy controls	4	268	4.19 (1.36, 12.87)	0.0124

Table 6-4: Repeatable battery for the assessment of neuropsychological status total scale results for HF cohort versus CAD controls

Outcome	Model	Total N	OR.(95% CI)	p-value
All HF vs CAD controls	0	257	2.05 (1.20, 3.49)	0.0081
All HF vs CAD controls	1	257	1.96 (1.13, 3.38)	0.0158
All HF vs CAD controls	2	257	1.92 (1.06, 3.47)	0.0316
All HF vs CAD controls	3	248	2.02 (1.1, 3.71)	0.0243
All HF vs CAD controls	4	244	2.20 (1.05, 4.61)	0.036

HF patients with AF were more likely to have CI than HF patients in sinus rhythm (odds ratio, 2.00; 95% CI, 1.18 to 3.37; p=0.0098). Patients with AF who were receiving formal anticoagulation (with either warfarin or a novel oral anticoagulant) had lower RBANS total scale scores compared to those who were not. This is demonstrated in figure 6-1. Although this may seem counterintuitive it is probably explained in part by the fact that those patients commenced on formal anticoagulation would be those patients identified as being at greatest risk of thromboembolic disease e.g. older with a history of vascular disease, hypertension or other cardiovascular risk factors. There are therefore more potential confounders present in these patients and this may in part explain why they had poorer cognitive scores documented by RBANS.

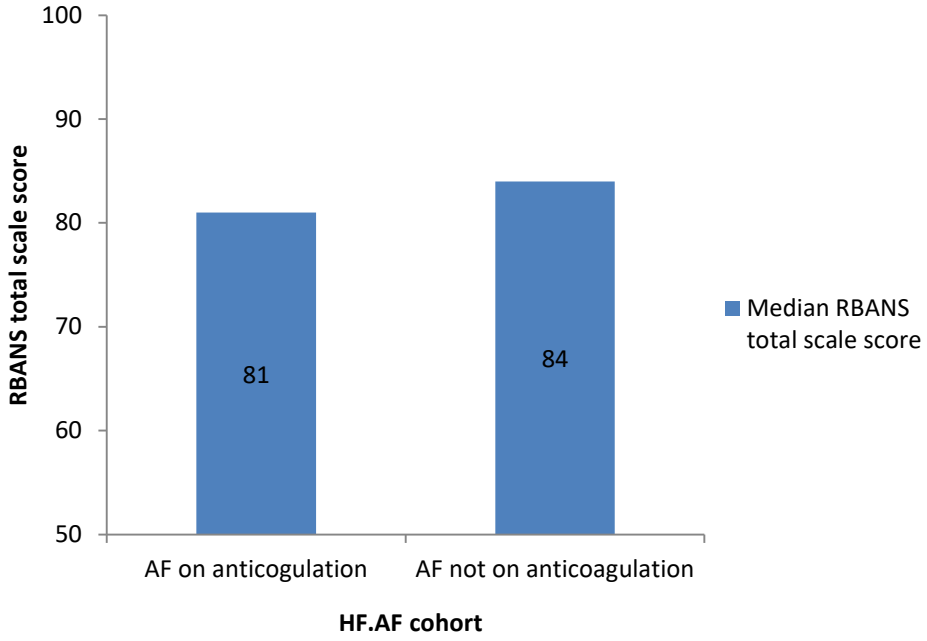


Figure 6-1: Repeatable battery for the assessment of neuropsychological status median total scale scores for the heart failure and atrial fibrillation cohort

6.2.1.2 RBANS total scale results: Binary analyses

Formal diagnosis of cognitive impairment requires evidence of abnormality on formal neuropsychological testing in at least one cognitive domain. Typically an abnormal result is taken as one which is ≥1.5 standard deviations below the age-standardised mean. Results from this study were therefore analysed using the following three RBANS total scale scores: 70 (≥2 SD below the mean), 80 (≥1.5 SD below the mean) and 90 (≥0.75 SD below the mean) to define impaired cognition. The proportion of participants categorised as having CI varied greatly depending on which RBANS cut-off value was used. The results from these binary analyses are shown in table 6-5.

A threshold value of <90 classified nearly 75% of patients with HF and AF as having abnormal cognition however only 25% of the same cohort were classified as cognitively impaired using the more conservative cut-off of <70.

Table 6-5: Repeatable battery for the assessment of neuropsychological status binary analyses

Variable	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
RBANS binary (<70 vs ≥70)					
Normal	61 (87.1%)	46 (90.2%)	56 (74.7%)	55 (90.2%)	86 (98.9%)
Abnormal	9 (12.9%)	5 (9.8%)	19 (25.3%)	9 (12.9%)	1(1.1%)
RBANS binary (<80 vs ≥80)					
Normal	48 (68.6%)	37 (72.5%)	46 (61.3%)	50 (82.0%)	83 (95.4%)
Abnormal	22 (31.4%)	14 (27.5%)	29 (38.7%)	11 (18.0%)	4 (4.6%)
RBANS binary (<90 vs ≥90)					
Normal	29 (41.4%)	27 (52.9%)	19 (25.3%)	33 (54.1%)	76 (87.4%)
Abnormal	41 (58.6%)	24 (47.1%)	56 (74.7%)	28 (45.9%)	11 (12.6%)

Data are presented as N(%)

6.2.1.3 Clinical severity classified by RBANS total scale

Qualitative descriptions of RBANS scores are provided in the RBANS manual. Depending on results of the total scale scores study subjects are classified into the following categories: very superior, superior, high average, average, low average, borderline and extremely low. The aim of this qualitative classification is to aid with the clinical interpretation of the RBANS scores.

Table 6-6 shows the proportion of participants categorised into each class. As expected, the majority (43.7%) of the healthy control population were categorised as average. Only healthy control participants were classified as "superior" or "very superior". More patients with HF and AF fell into the "borderline" and "extremely low" category compared to any of the other cohorts.

Table 6-6: Qualitative descriptions of repeatable battery for the assessment of neuropsychological status total scale scores

Variable	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
Very Superior ≥130	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (6.9%)
Superior ≥120 & ≤129	0 (0.0%)	0 (0.0%)	3 (4.0%)	4 (6.6%)	13 (14.9%)
High Average ≥110 & ≤119	3 (4.3%)	3 (5.9%)	1 (1.3%)	3 (4.9%)	19 (21.8%)
Average ≥90 & ≤110	26 (37.1%)	24 (41.7%)	15 (20.0%)	26 (42.6%)	38 (43.7%)
Low Average ≥80 & ≤89	19 (27.1%)	10 (19.6%)	27 (36.0%)	17 (27.9%)	7 (8.0%)
Borderline ≥70 & ≤79	13 (18.6%)	9 (17.6%)	10 (13.3%)	5 (8.2%)	3 (3.4%)
Extremely Low ≤69	9 (12.9%)	5 (9.8%)	19 (25.3%)	6 (9.8%)	1 (1.1%)

Data are presented as N (%)

6.2.2 RBANS assessment of immediate memory

Immediate memory is assessed using 2 subtests as part of the RBANS. These 2 subtests are described below:

1. ***List learning:*** A list of 10 semantically unrelated words is orally presented, and the examinee is asked to recall as many words as he or she can. This process is repeated over 4 learning trials.

2. ***Story memory:*** A short story is orally presented, and the examinee is asked to recall the story from memory. The same story is presented a second time and the examinee is again asked to retell the story from memory.

The two individual raw scores are then converted into an index score for that domain using previously published normative data.[167] The mean index scores for each cohort are shown in table 6-7.

Patients with both HF and AF had the lowest mean score (79.6 ± 18) in the domain of immediate memory followed by patients with non-ischaemic cardiomyopathy (84.9 ± 17.8) and then those with ischaemic cardiomyopathy (85.5 ± 15.8). Patients with HF had poorer immediate memory scores than either the CAD (87.8 ± 18) or the healthy control (100.3 ± 15.6) groups.

Table 6-7: Repeatable battery for the assessment of neuropsychological status immediate memory scores

	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
Mean (SD)	85.5 (15.8)	84.9 (17.8)	79.6 (18.0)	87.8 (18.0)	100.3 (15.6)
Median	85.0	85.0	78.0	87.0	103.0
Range	49.0, 120.0	44.0, 120.0	40.0, 123.0	53.0, 126.0	65.0, 136.0

6.2.3 RBANS assessment of language

Language is assessed as part of this neuropsychological battery by the two subtests outlined below:

1. ***Picture naming:*** The examinee is presented with a series of pictured objects and is asked to name each one. A semantic cue is provided only if an object is obviously misperceived.

2. ***Semantic fluency:*** The examinee is given one minute to name as many examples as possible from a given semantic category (fruits and vegetables).

The language index scores are presented in table 6-8. Patients with HF and AF had the lowest mean score (89.2 ± 11.5) followed by those with ischaemic cardiomyopathy (90 ± 10.7) and those with non-ischaemic cardiomyopathy (94.1 ± 10.5). Scores were similar between CAD control patients (92.2 ± 9.2) and those with ischaemic cardiomyopathy.

Table 6-8: Repeatable battery for the assessment of neuropsychological status language scores

	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
Mean (SD)	90.0 (10.7)	94.1 (10.5)	89.2 (11.5)	92.9 (9.2)	100.2 (10.9)
Median	92.0	96.0	90.0	92.0	101.0
Range	57.0, 110.0	75.0, 120.0	51.0, 117.0	60.0, 120.0	57.0, 134.0

6.2.4 RBANS assessment of attention

The domain of attention indicates the examinee's capacity to remember and manipulate both visually and orally presented information. Scores from the two subtests below contribute to this index score and the index scores are shown in table 6-9.

1. ***Digit span:*** The examiner reads a string of digits and asks the examinee to repeat the digits in the same order. The length of the digit string increases by one on each trial.

2. ***Coding:*** The examinee is presented a page filled with rows of boxes with a number from 1 to 9 above each box (in a random sequence), and a blank space below the number. At the top of the page is a key with a unique geometric shape beneath each of the numbers, 1 to 9. Using the key, the examinee is asked to fill in the number corresponding to each shape, for as many boxes as the examinee can complete in 90 seconds.

Poorest scores of attention were found in the HF and AF cohort followed by those with HF in sinus rhythm. The healthy control participants had the highest scores of attention.

Table 6-9: Repeatable battery for the assessment of neuropsychological status attention scores

	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
Mean (SD)	93.8 (14.9)	95.7 (15.3)	90.5 (19.6)	99.8 (18.7)	112.0 (16.4)
Median	97.0	97.0	91.0	100.0	109.0
Range	53.0, 122.0	60.0, 132.0	53.0, 150.0	60.0, 150.0	82.0, 150.0

6.2.5 RBANS assessment of visuospatial awareness

Visuospatial awareness is assessed based on the examinee's ability to perceive spatial relations and to construct a spatially accurate copy of a drawing. Scores from the figure copy and line orientation subtests contribute to this domains assessment.

1. ***Figure copy:*** The examinee is shown a geometric drawing and is asked to make an exact copy while the drawing remains on display.

2. ***Line orientation:*** The examinee is presented with a drawing that consists of thirteen equal lines radiating out from a single point to form a semi-circular fan-shaped pattern. All lines are numbered 1-13. Below this drawing are two lines that match two of the lines from the array above. The examinee is asked to identify which two lines they match. Ten trials are given, with different sets of test lines on each trial.

Table 6-10 shows the mean index scores for visuospatial awareness for each of the study cohorts. Healthy control participants had the highest mean score (108.8 ± 19.0) followed by patients with non-ischaemic cardiomyopathy (98.0 ± 18.2). Patients in the CAD control group had a mean score of 95.9 ± 20.0 and this was followed by those patients with ischaemic cardiomyopathy (90.8 ± 19.6). Patients with HF and AF had the lowest mean scores in visuospatial awareness (87.8 ± 20.7).

Table 6-10: Repeatable battery for the assessment of neuropsychological status visuospatial scores

	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
Mean (SD)	90.8 (19.6)	98.0 (18.2)	87.8 (20.7)	95.9 (20.2)	108.8 (19.0)
Median	89.0	100.0	89.0	92.0	112.0
Range	53.0, 131.0	56.0, 126.0	50.0, 136.0	53.0, 131.0	62.0, 131.0

6.2.6 RBANS assessment of delayed memory

Delayed memory indicates the examinee's anterograde memory capacity and is assessed by the four individual subtests described below.

1. ***List recall:*** The examinee is asked to recall the list of 10 words learned in the list learning subtest.

2. ***List recognition:*** The examinee is read 20 words (10 words from the list, 10 distractors) and asked to indicate whether each word was on the word list.

3. ***Story memory:*** The examinee is asked to retell the story they learned earlier.

4. ***Figure recall:*** The examinee is asked to draw the figure shown earlier from memory.

The lowest delayed memory scores were found in patients with HF and AF (84.4 ± 16.2). Overall, patients with HF had lower scores than either of the control cohorts. These results are shown in table 6-11.

Table 6-11: Repeatable battery for the assessment of neuropsychological status delayed memory scores

	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
Mean (SD)	88.0 (18.3)	86.4 (18.9)	84.4 (16.2)	90.5 (16.9)	101.9 (14.6)
Median	89.0	88.0	86.0	95.0	102.0
Range	40.0, 129.0	44.0, 123.0	40.0, 123.0	40, 122.0	56.0, 130.0

6.3 Summary

Chapter 6 has described the results of the repeatable battery for the assessment of neuropsychological status in patients with ischaemic and non-ischaemic cardiomyopathy both in sinus rhythm and AF, in patients with CAD without HF and in a cohort of age and sex matched healthy controls. The RBANS took approximately 40 minutes to administer and was well tolerated by study participants, with all study subjects completing the assessments.

Although many previously published studies have assessed cognition using the RBANS battery, less have used RBANS in the HF population with fewer still assessing cognition with RBANS in a defined group of patients with CAD in sinus rhythm with no HF.[193] In an attempt to put our results into context, the tables below outline the results found in this study compared to other published studies. Table 6-12 displays the key study characteristics and RBANS scores found in studies looking at healthy control populations alongside the results from the healthy control population in this study.[194;195] The results from each RBANS subtest looking at the individual domains of cognition were higher (better) for the healthy control population assessed in this study when compared to the other two. In keeping with this pattern, the mean total RBANS score from the healthy control population in this study was higher than those from the other studies which used RBANS in a healthy control population (106.9 versus 97.9 and 92.4).

The RBANS manual gives a mean value of 100 for the RBANS total scale score and for each individual cognitive domain in the general population.[196] Other studies (including the 2 shown below) have attempted to extend the original normative data by reporting on RBANS performances in community dwelling older adults. As illustrated in table 6-12, our healthy control cohort tended to have higher (better) mean results than the cohorts studies by Duff

and Gaita. The results from our healthy control cohort were therefore more in keeping with the original RBANS published normative values used in the RBANS manual.

Table 6-12: Repeatable battery for the assessment of neuropsychological status scores for healthy control populations

RBANS measure	Duff et al[194] (N=718)	Gaita et al[195] (N=90)	CIHF HC (N=87)
Age	73.3 (5.8)	59.7 (13.1)	70.3 (6.7)
Male sex (%)	300 (41.8)	68 (75.6)	55 (63.2)
Years of education	N/A	N/A	14.8 (3.6)
Immediate Memory	95.2 (18.0)	95.6 (17.5)	100.3 (15.6)
Visuospatial	102.7 (17.5)	93.8 (16.7)	108.8 (19.0)
Language	95.4 (11.2)	92.9 (11.4)	100.2 (10.9)
Attention	99.9 (16.1)	101.4 (21.2)	112.0 (16.4)
Delayed memory	98.9 (17.0)	93.5 (11.7)	101.9 (14.6)
Total scale score	97.9 (15.9)	92.4 (15.4)	106.9 (16.4)

Data are presented as mean (SD) or N (%)

Only 1 study was found which used RBANS in a cohort of patients with CAD and no HF and these results are compared to our cardiac control cohort in table 6-13.[193] That study looked at 82 patients with atherosclerotic vascular disease. Transthoracic echocardiography was not performed as part of the study inclusion criteria; however, these patients had no clinical history of HF. The mean age of study subjects were relatively well matched (68.0 versus 67.5). Our study included a higher proportion of males (70.5% versus 57.3%) who on average had fewer years of education (13.0 versus 14.5). With the exception of attention, our cardiac

control cohort had lower (poorer) results for each individual domain and total scale score (91.2 versus 97.0).

The study population recruited by Moser et al was recruited from the University of Iowa. In the study manuscript there was no documentation of other vascular risk factors such as smoking history. Inherent heterogeneity in the two study populations may explain the differences in RBANS scores found.

Table 6-13: Repeatable battery for the assessment of neuropsychological status scores in patients with CAD compared to other studies

RBANS measure	Moser et al[193] (N=82)	CIHF CAD CONT (N=61)
Age	68.0 (7.7)	67.5 (6.3)
Male sex (%)	47.0 (57.3)	43.0 (70.5)
Years of education	14.5 (3.2)	13.0 (3.3)
Immediate Memory	99.5 (15.4)	87.8 (18.0)
Visuospatial	96.4 (15.1)	95.9 (20.2)
Language	99.7 (10.3)	92.9 (9.2)
Attention	95.7 (14.0)	99.8 (18.7)
Delayed memory	98.9 (13.0)	90.5 (16.9)
Total scale score	97.0 (11.4)	91.2 (15.9)

Data are presented as mean (SD) or N (%)

Table 6-14 compares the scores from the HF population in this study to results from other studies assessing cognition in HF patients using RBANS.[112;113;142] The other HF studies using RBANS to assess cognition did not divide the total HF cohorts into patients with AF, ischaemic cardiomyopathy and non-ischaemic cardiomyopathy as I did in this study. Table 6-14 therefore shows the scores for the individual HF cohorts as well as the total HF population.

Our HF population had fewer average years of education compared to the study cohorts assessed in the other 3 HF studies. HF patients recruited into this study had lower (poorer) scores in the domains of immediate memory, language, visuospatial and delayed memory when compared to the other 3 HF cohorts. Overall, the total HF cohort in this study had higher (better) scores in the domain of attention when compared to the other study populations. The mean total scale score for all HF patients was lower in our study compared to the others (85.4 versus 94.1, 90.1 and 106.4).

RBANS measure	Bauer et al (N=80)[113]	Bratzke - Bauer et al[112] (N=47)	Alosco et al[142] (N=52)	CIHF HF CAD (N=70)	CIHF HF no CAD (N=51)	CIHF HF AF (N=75)	CIHF All HF (N=196)
Age	72.0 (12.0)	74.7 (8.9)	65.7 (8.9)	71.0 (8.1)	69.4 (7.5)	71.0 (8.6)	70.6 (8.1)
Male sex (%)	51.0 (64.0)	37.0 (79.0)	21.0 (40.4)	49.0 (70.0)	32.0 (62.7)	56.0 (74.7)	137.0 (69.9)
Years of education	N/A	13.8 (3.1)	16.1 (2.6)	11.6 (3.4)	11.8 (3.7)	12.6 (4.0)	12.0 (3.7)
Immediate Memory	88.5 (16.11)	86.5 (17.8)	105.6 (13.5)	85.5 (15.8)	84.9 (17.8)	79.6 (18.0)	83.1 (17.3)
Language	94.1 (10.6)	93.3 (9.1)	103.8 (11.8)	90.0 (10.7)	94.1 (10.5)	89.2 (11.5)	90.8 (11.1)
Attention	89.5 (18.2)	90.2 (19.3)	105.1 (13.3)	93.8 (14.9)	95.7 (15.3)	90.5 (19.6)	93.0 (17.0)
Visuospatial	100.1 (16.7)	102.4 (18.0)	104.8 (11.8)	90.8 (19.6)	98.0 (18.2)	87.8 (20.7)	91.5 (20.0)
Delayed memory	94.2 (15.4)	91.1 (16.8)	103.4 (12.5)	88.0 (18.3)	86.4 (18.9)	84.4 (16.2)	86.2 (17.7)
Total scale score	94.1 (14.1)	90.1 (15.8)	106.4 (12.8)	86.3 (14.3)	89.2 (14.6)	82.0 (16.2)	85.4 (15.3)

Table 6-14: Repeatable battery for the assessment of neuropsychological status scores in patients with HF. Data are presented as means (SD)

A number of previous studies have suggested that dementias of differing aetiologies may have distinct neuropsychological profiles. The most common distinction made is between "cortical" dementias e.g. Alzheimer's disease and "subcortical" dementias e.g. vascular dementia. Typically, such studies report poor immediate memory in patients with cortical dementia compared to those with subcortical dementia being more impaired on tests of attention and executive function.[197] It is therefore clinically useful to be able to profile individual domains of cognition. The majority of previous studies comparing dementias of differing aetiologies on neuropsychological tests have employed experimental tests which often have a number of shortcomings including insensitivity of screening tests and lack of population based normative data. The repeatable battery for the assessment of neuropsychological status appears to have overcome these obstacles.

A striking finding was the impact of a co-morbid diagnosis of AF. Those patients with AF and HF had the poorest cognitive outcomes. Using the clinical qualitative descriptions of RBANS over half of patients with HF and AF were categorised as having cognitive impairment on RBANS testing. There is a substantial body of influence linking AF with an increased risk of CI with a recent meta-analysis of the literature showing that AF is associated with a higher risk of CI with or without a clinical history of stroke.[70;198-200] Results from this research support this (a clinical history of stroke being a reason for exclusion from this study). I am not aware of any other study that has particularly examined this relationship in a HF cohort, such as I have done.

Looking at the results of the individual cognitive domains in this study, there appeared to be less effect of AF on the domain of memory which perhaps suggests a subcortical rather than cortical pattern of CI in these patients. The adverse effect of AF on cognitive function seen in these results could in part be explained by the occurrence of subclinical thromboembolism or may simply be a marker of more extensive CVD. A sub-study of this research project using neuroimaging is currently underway to further investigate this hypothesis.

Even using the more conservative threshold value of <70 to define cognitive impairment I found that a substantial proportion of those with HF had evidence of impaired cognition on formal neuropsychological testing. Overall 19% of HF patients were categorised as having cognitive impairment in one or more cognitive domain. This relationship persisted even after adjustment for other potential confounding variables including age, sex, education level, co-morbidity score, medication count and mood disorder.

RBANS was only one of a number of neuropsychological assessment tools that were employed in this study. Over the next 3 chapters the results of the other cognitive assessment tools will be presented.

CHAPTER SEVEN

MONTREAL COGNITIVE ASSESSMENT TOOL

7.1 Introduction

The second neuropsychological assessment tool to be administered during the return study visit was the Montreal Cognitive Assessment Tool (MoCA). This assessment tool is outlined in chapter 3 and a copy of it is shown in appendix VIII. It was completed by every study subject and took approximately 15 minutes to administer.

The MoCA was initially designed as a cognitive screening tool to assist physicians in detection of subtle changes in cognition. It is a one page 30 point test providing scores for seven individual domains of cognition. The MoCA adds one point for those whose educational level is 12 years or less.

The individual MoCA items are as follows. The short term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 minutes. Visuospatial abilities are assessed using a clock drawing task (3 points) and a three-dimensional cube copy (1 point). Multiple aspects of executive functions are assessed using an alternation task adapted from the Trails making test part B (1 point), a phonemic fluency task (1 point), and a two item verbal abstraction task (2 points). Attention and concentration are evaluated using a tapping test (1 point), a serial subtraction task (3 points) and a forward and backward digit task (2 points). Language is assessed using a three-item naming task with animals (3 points), repetition of two sentences (2 points) and a fluency test. Finally orientation to time and place is assessed (6 points).

Following its administration, the MoCA assessment forms were blindly scored by Dr Rosalind Lees with a random 20% of the sample re-scored by two independent neuropsychologists (Dr Niall Broomfield and Dr John Sharp) for quality assurance. Any disagreements in marking were referred to a third arbitrator (Professor Jonathan Evans).

In this chapter, the individual scores for each cognitive domain as well as the total MoCA scores will be described for each study participant and any difference in results between the five study cohorts will be outlined. Significance testing was only performed for certain pre-specified variables. At the end of this chapter the results presented here will be compared to other published results in an attempt to put these results into context.

7.2 Results

7.2.1 MoCA total score

7.2.1.1 MoCA total score results

The Montreal Cognitive Assessment tool has a potential maximum score of 30. The mean (SD), median and range of total scores are presented in table 7-1. The healthy control participants had the highest mean score of 26.8 ± 2.4. This was followed by the CAD control group with a mean score of 24.1 ± 4.1. Of the three HF groups, those with HF and AF had the lowest mean score (22.6 ± 3.3) compared to patients with ischaemic cardiomyopathy in sinus rhythm (23.4 ± 3.7) and those with non-ischaemic cardiomyopathy in sinus rhythm (23.2 ± 4.2). The mean MoCA score for patients in AF receiving anticoagulation was lower than those who were treated with antiplatelet therapy only (22.4 ± 3.2 versus 23.2 ± 4.2). The distribution of total MoCA scores demonstrated by group is shown in figure 7-1.

Table 7-1: Montreal cognitive assessment tool total scores

	HF CAD (n=70)	**HF no CAD (n=51)**	**HF AF (n=75)**	**CAD CONT (n=61)**	**HC (n=87)**
Mean (SD)	23.4 (3.7)	23.2 (4.2)	22.6 (3.3)	24.1 (4.1)	26.8 (2.4)
Median	24.0	24.0	23.0	25.0	27.0
Range	(14.0, 30.0)	(12.0, 30.0)	(15.0, 29.0)	(5.0, 30.0)	(19.0, 30.0)

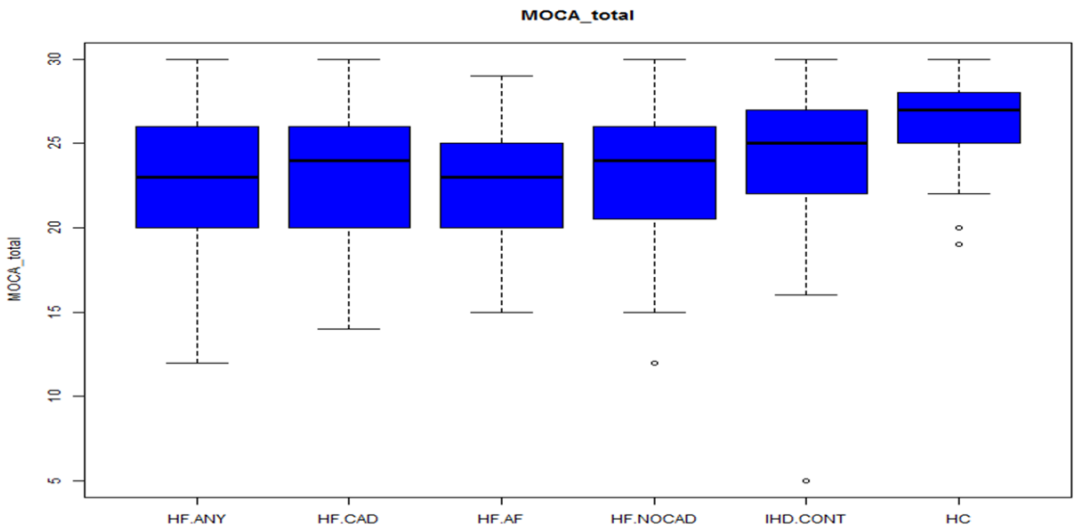


Figure 7-1: Montreal cognitive assessment tool total scores distributions by cohort

Patients with HF were at increased risk of CI when compared to both the healthy control cohort (effect estimate, -3.81; 95% confidence interval [CI], -4.66 to -2.96; p<0.0001) and the cardiac control cohort (effect estimate, -1.12; 95% CI, -2.25 to 0.01; p=0.0524). The same adjustment models were used as previously described in table 6-2. Tables 7-2 and 7-3 show the relationship between CI and HF after adjustment for potential confounding variables. Similarly to RBANS, the biggest difference in effect estimates was found between adjustment models 1 and 2 suggesting that the additional factors of co-morbid conditions and education level are important variables in the development of CI in HF.

Table 7-2: Montreal cognitive assessment tool total scores for HF cohort versus healthy controls

Outcome	Model	Total N	Effect estimate (95%CI)	p-value
All HF vs Healthy controls	0	254	-3.81 (-4.66, -2.96)	<0.0001
All HF vs Healthy controls	1	254	-3.85 (-4.69, -3.00)	<0.0001
All HF vs Healthy controls	2	254	-2.64 (-4.16, -1.11)	0.0008
All HF vs Healthy controls	3	242	-2.66 (-4.22, -1.10)	0.001
All HF vs Healthy controls	4	239	-2.36 (-4.1, -0.61)	0.0088

Table 7-3: Montreal cognitive assessment tool total scores for HF cohort versus CAD controls

Outcome	Model	Total N	Effect estimate (95%CI)	p-value
All HF vs CAD controls	0	225	-1.12 (-2.25, 0.01)	0.0524
All HF vs CAD controls	1	225	-0.99 (-2.13, 0.15)	0.0892
All HF vs CAD controls	2	225	-0.77 (-1.87, 0.34)	0.1763
All HF vs CAD controls	3	217	-0.75 (-1.88, 0.38)	0.1957
All HF vs CAD controls	4	213	-0.78 (-2.13, 0.58)	0.2614

7.2.1.2 MoCA total score results: Binary analyses

Depending on the population being studied, a variety of threshold values for MoCA have previously been used to define CI in prior studies.[201;202] We performed binary analyses using 3 threshold values to define CI: 25, 26 and 27 as these are the 3 most commonly used cut-off values used in clinical practice. The proportion of each cohort categorised as having CI for each of these threshold values are presented in table 7-4.

Table 7-4: Binary analyses of Montreal cognitive assessment tool total scores

Variable	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
MoCA binary (<25 vs ≥25)					
Normal	23 (41.8%)	13 (33.3%)	22 (30.1%)	31 (53.4%)	76 (87.4%)
Abnormal	32 (58.2%)	26 (66.7%)	51 (69.9%)	27 (46.6%)	11 (12.6%)
MoCA binary (<26 vs ≥26)					
Normal	18 (32.7%)	11 (28.2%)	16 (21.9%)	22 (37.9%)	64 (73.6%)
Abnormal	37 (67.3%)	28 (71.8%)	57 (78.1%)	36 (62.1%)	23 (26.4%)
MoCA binary (<27 vs ≥27)					
Normal	13 (23.6%)	8 (20.5%)	11 (15.1%)	16 (27.6%)	56 (64.4%)
Abnormal	42 (76.4%)	31 (79.5%)	62 (84.9%)	42 (72.4%)	31 (35.6%)

Data are presented as N (%)

Using a cut-off value of <25 to define CI, almost 70% of those patients with HF and AF were identified as having CI. Even when using this more conservative threshold value to represent CI, almost 13% of the healthy control cohort were categorised as having some degree of CI. This is in comparison to 85% of patients with HF and AF being described as cognitively impaired when using a threshold value of <27. Using this cut-off, over one third of the healthy control population were described as cognitively impaired.

Using the cut-off value of <25, patients with HF were at increased risk of CI when compared to both the healthy control cohort (odds ratio, 13.72; 95% confidence interval [CI], 6.67 to 28.23;

p<0.0001) and the cardiac control cohort (odds ratio, 2.32; 95% CI, 1.24 to 4.32; p=0.0084). Those with AF were more likely to have CI than those patients in sinus rhythm, however this difference was not statistically significant (odds ratio, 1.49; 95% CI, 0.77 to 2.88; p=0.2339).

7.2.2 MoCA individual domain scores

The MoCA questionnaire assesses six individual cognitive domains with the individual tests outlined above. Table 7-5 shows these individual domains of cognition (with the range of scores possible) and the mean scores for each cohort.

Table 7-5: Montreal cognitive assessment tool individual domain scores

	All HF (N=196)	**HF.CAD (N = 70)**	**HF.NOCAD (N = 51)**	**HF.AF (N = 75)**	**CAD.CONT (N = 61)**	**HC (N = 87)**
Visuospatial (Range 0-5)	3.7 (1.2)	3.6 (1.2)	3.8 (1.4)	3.6 (1.2)	4.2 (0.9)	4.4 (0.7)
Attention (Range 0-6)	4.9 (1.3)	4.9 (1.2)	4.9 (1.4)	4.9 (1.4)	5.2 (1.2)	5.7 (0.7)
Language (Range 0-6)	4.9 (1.3)	4.9 (1.4)	4.9 (1.5)	4.9 (1.4)	5.1 (1.2)	5.7 (0.7)
Executive function (Range 0-2)	1.2 (0.8)	1.1 (0.8)	1.4 (0.8)	1.3 (0.8)	1.3 (0.7)	1.7 (0.6)
Memory (0-5)	2.0 (1.5)	2.4 (1.3)	1.8 (1.5)	1.7 (1.4)	2.2 (1.6)	3.1 (1.2)
Orientation (0-6)	5.7 (0.5)	5.7 (0.5)	5.7 (0.7)	5.8 (0.5)	5.7 (0.9)	5.9 (0.5)

Data are presented as mean (SD)

Patients with HF had lower mean scores than the CAD or healthy control cohorts in all individual cognitive domains with the exception of orientation to time and place. Between the three HF cohorts similar scores were found for the domains of attention, language and orientation. The biggest difference between the three HF groups was found in the assessment of memory. Patients with HF and AF had the lowest mean score in this domain (1.7 ± 1.4) followed by patients with non-ischaemic cardiomyopathy (1.8 ± 1.5) and ischaemic cardiomyopathy (2.4 ± 1.3). Participants in the healthy control cohort had higher mean scores than any other group in all cognitive assessments.

7.3 Summary

The Montreal Cognitive Assessment tool was easy and quick to administer and was well tolerated by study participants. All participants recruited into this study completed the MoCA.

The MoCA was initially developed to try to identify those patients with mild CI that may have previously been missed by other global cognitive assessment tools and has been shown to be a sensitive measure of CI in previous studies.[161;203] When compared to RBANS, the MoCA failed to differentiate between the individual HF cohorts when assessing language and attention. Otherwise, a similar pattern was seen in the individual cognitive domains when assessed by MoCA and RBANS. Patients with HF and AF had the poorest results for visuospatial awareness and memory when assessed by both the RBANS assessment tool and MoCA. Those with cardiac disease (including HF and CAD) had poorer results than the healthy control cohort in all domains with less difference seen between the heart failure and cardiac control groups.

In this study, using the more conservative cut-off value of <25 in our binary analyses, the MoCA identified almost 65% of all patients with HF and 13% of healthy control participants as having some degree of CI. In an attempt to put these results into context, tables 7-6 to 7-8 compare total MoCA scores found in this study to other published studies which used MoCA to assess cognition.

The initial validation study by Nasreddine et al, included 90 healthy control volunteers with a mean age comparable to that of our healthy control cohort (72.8 versus 70.3).[160] A higher proportion of the initial validation cohort were female (40% versus 36.8%) with fewer average years of education (13.3 versus 14.8). Despite these differences in study population demographics the overall mean MoCA scores were the same in the 2 healthy control cohorts as shown in table 7-6.

Table 7-6: Total MoCA scores for healthy control populations

MoCA	Nasreddine et al[160] (N=90)	CIHF HC (N=87)
Age	72.8 (7.0)	70.3 (6.7)
Male sex (%)	36 (40.0)	55 (63.2)
Years of education	13.3 (3.4)	14.8 (3.6)
Total MoCA	26.9 (2.3)	26.8 (2.4)

Data are presented as mean (SD) or N(%)

Only 2 studies using MoCA as a cognitive assessment tool in patients with known CAD and no clinical HF were found.[161;204] The results from these studies are compared to results from this study in table 7-7 below. The MoCA was administered to 2,653 ethnically diverse subjects as part of a population based study of cardiovascular disease in Dallas, USA.[204] The majority of patients included in that study were African American (52%) with 33% Caucasian, 11% Hispanic and 2% classified as "other". Although variation in cognition cannot be attributed to ethnicity *per se* there may be other related variables such as quality of education and culture which would make it difficult to compare those results directly to the results from this study.

The second study by McLennan et al administered MoCA to 110 patients attending cardiology outpatient clinics in a large tertiary referral hospital in South Australia.[161] The patients recruited into that study had fewer mean years of total education compared to our cardiac control cohort (10.5 versus 13.0) and they had lower total MoCA scores compared to this study (22.8 versus 24.1).

Table 7-7: Total MoCA scores in patients with CAD compared to other studies

MoCA	Rossetti et al[204] (N=2,653)	McLennan et al[161] (N=110)	CIHF CAD CONT (N=61)
Age	50.3 (11.2)	67.9 (11.7)	67.5 (6.3)
Male sex (%)	1061 (40.0)	44 (40.0)	43 (70.5)
Years of education	13.4 (2.5)	10.5 (3.2)	13.0 (3.3)
Total MoCA	23.4 (4.0)	22.8 (3.8)	24.1 (4.1)

Data are presented as mean (SD) or N(%)

When MoCA results from this study were compared to MoCA results from other studies assessing cognition in HF patients the results were similar.[100;121;127] Table 7-8 describes the main demographic variables in 3 published HF studies which used the MoCA assessment tool and compares these to the HF patients recruited into this study. As the published studies did not divide HF cohorts into those patients with AF, ischaemic cardiomyopathy or non ischaemic cardiomyopathy I have included MoCA scores for the total HF population in addition to the individual HF cohorts. It can be seen that those patients with HF and AF had the lowest (worst) mean MoCA scores in this study - although this was still comparable with the total mean MoCA score found by Harkness et al.

Table7-8: Total MoCA scores in patients with HF compared to other studies

MoCA	Athilingham et al[121] (N=90)	Gallagher et al[127] (N=128)	Harkness et al[100] (N=100)	CIHF HF CAD (N=70)	CIHF HF no CAD (N=51)	CIHF HF AF (N=75)	CIHF All HF (N=196)
Age	62.2 (9.2)	80.7 (11.5)	72.4 (9.8)	71.0 (8.1)	69.4 (7.5)	71.0 (8.6)	70.6 (8.1)
Male sex (%)	59 (65.6)	71 (55.5)	68 (68)	49.0 (70.0)	32.0 (62.7)	56.0 (74.7)	137.0 (69.9)
Years of education	13.8 (2.8)	N/A	N/A	11.6 (3.4)	11.8 (3.7)	12.6 (4.0)	12.0 (3.7)
Total MoCA	24.9 (2.8)	24.6 (3.5)	22.2 (4.5)	23.4 (3.7)	23.2 (4.2)	22.6 (3.3)	23.0 (3.7)

Data are presented as mean (SD) or N(%)

CHAPTER EIGHT

MINI MENTAL STATE EXAMINATION

8.1 Introduction

The mini-mental state examination (MMSE) is a 30-point questionnaire that has been used extensively in clinical and research settings to measure cognitive impairment. The MMSE has been described previously in chapter 3 and a copy of the MMSE is shown in appendix VII.

The MMSE was the third neuropsychological assessment tool to be administered and took approximately 10 minutes for participants to complete. Although recognised as a measure of global cognition, the MMSE questionnaire does categorise tasks according to the particular cognitive domain being studied. Tasks within each individual domain are individually marked and then totalled to give a score for each domain. These scores are then combined to give a total score out of 30. The maximum possible scores for each category are shown in table 8-1. Upon completion, the MMSE scores for each domain were totalled to give the overall score by Dr Rosalind Lees. A random 20% of the sample was re-scored by 2 independent consultant neuropsychologists (Dr Niall Broomfield and Dr John Sharp) for quality assurance. Any disagreements in marking were referred to a third arbitrator (Professor Jonathan Evans).

In this chapter, the MMSE scores for each domain will be given in addition to the total scores for each study cohort. Any differences found between the five study cohorts will also be described. Significance testing was only performed for certain pre-specified variables. At the end of this chapter the results presented here will be compared to other published results in an attempt to put these results into context.

Table 8-1: Domains assessed by mini mental state examination

Category	Possible points
Orientation	10
Learning	6
Language	8
Attention and calculation	5
Concentration	1

8.2 Results

8.2.1 MMSE total score

8.2.1.1 MMSE total score results

The mean (SD), median and range of MMSE scores are shown in table 8-2 for each study cohort. The healthy control group had the highest mean score of 29.1 ± 1.3 out of a possible maximum score of 30. Patients with non-ischaemic cardiomyopathy, ischaemic cardiomyopathy and the CAD control cohort had similar mean scores (27.5 ± 3.1 versus 27.5 ± 2.2 versus 27.9 ± 2.5). Those with HF and AF had the lowest mean MMSE scores of 26.9 ± 2.8.

Table 8-2: Mini mental state examination total scores

	HF CAD (n=70)	**HF no CAD (n=51)**	**HF AF (n=75)**	**CAD CONT (n=61)**	**HC (n=87)**
Mean (SD)	27.5 (2.2)	27.5 (3.1)	26.9 (2.8)	27.9 (2.5)	29.1 (1.3)
Median	28.0	29.0	27.0	29.0	30.0
Range	(21.0, 30.0)	(16.0, 30.0)	(17.0, 30.0)	(20.0, 30.0)	(23.0, 30.0)

The same models were used in adjustment as described in table 6-2. Patients with HF had an increased risk of CI detected by MMSE when compared to healthy control participants (effect estimate, -1.82; 95% confidence interval [CI], -2.41 to -1.23; p<0.0001). This statistically significant relationship persisted even after adjustment for age and sex. When co-morbidity count and level of education were adjusted for, this statistical significance was lost (p=0.1057). Patients with HF were at increased risk of CI when compared to the cardiac control cohort (as detected by MMSE), however this association was not statistically significant (0.1002). These results are demonstrated in tables 8-3 and 8-4.

Table 8-3: Mini Mental State Examination total scores for HF cohort versus healthy controls

Outcome	Model	Total N	Effect estimate (95%CI)	p-value
All HF vs Healthy controls	0	283	-1.82 (-2.41, -1.23)	<0.0001
All HF vs Healthy controls	1	283	-1.79 (-2.39, -1.2)	<0.0001
All HF vs Healthy controls	2	283	-0.89 (-1.98, 0.19)	0.1057
All HF vs Healthy controls	3	271	-1.3 (-2.36, -0.24)	0.0173
All HF vs Healthy controls	4	268	-0.9 (-2.04, 0.24)	0.1214

Table 8-4: Mini Mental State Examination total scores for HF cohort versus CAD controls

Outcome	Model	Total N	Effect estimate (95% CI)	p-value
All HF vs CAD controls	0	257	-0.64 (-1.39, 0.12)	0.1002
All HF vs CAD controls	1	257	-0.51 (-1.27, 0.25)	0.1913
All HF vs CAD controls	2	257	-0.32 (-1.06, 0.43)	0.4066
All HF vs CAD controls	3	248	-0.48 (-1.21, 0.25)	0.1984
All HF vs CAD controls	4	244	-0.5 (-1.34, 0.34)	0.2474

The effect of anticoagulation on MMSE scores and the overall distribution of scores are shown in figures 8-1 and 8.2.

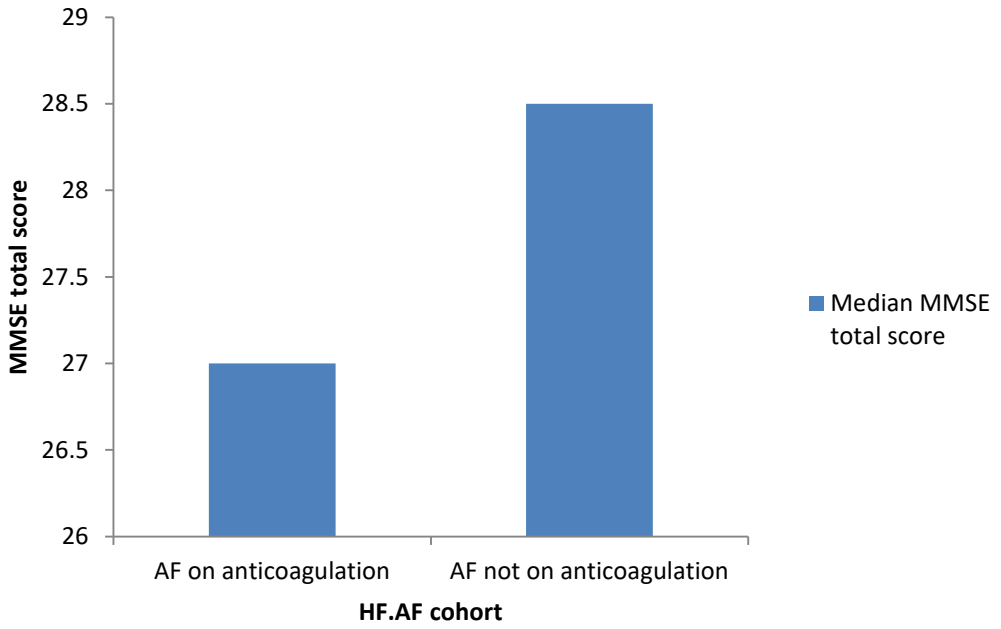


Figure 8-1: Mini mental state examination total scores for the heart failure and atrial fibrillation cohort

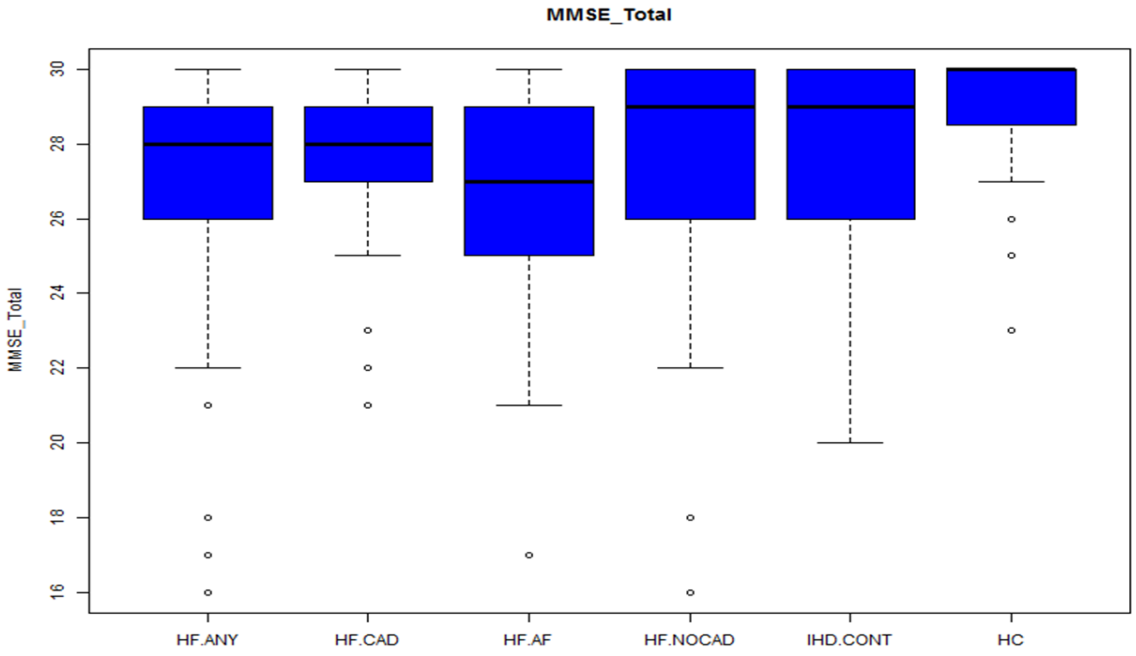


Figure 8-2: Mini mental state examination total scores distributions by cohort

8.2.1.2 MMSE total score results: Binary analyses

In addition to ordinal analysis, total MMSE scores were also analysed using the following three cut-off values taken to represent cognitive impairment: 26, 27 and 28 out of 30. These 3 cut-off values were chosen as they are the cut-off values most commonly used in clinical practice. The proportion of subjects identified as having impaired cognition varied significantly depending on which value was used. These results are shown in table 8-5.

When a threshold value of 28 was used, over half of those patients with HF and AF were categorised as having CI (53.3%) compared to a proportion of 29.3% classified as cognitively impaired when the lower cut-off of <26 was used. Using the cut-off value of <26, patients with HF were at increased risk of CI when compared to the healthy control cohort (odds ratio, 13.01; 95% confidence interval [CI], 3.08 to 55.03; p=0.0005). This cut-off score classified 2.3% of the healthy control cohort as having CI with a higher proportion of the CAD control group showing impairment of cognition (16.4%).

Table 8-5: Binary analyses of mini mental state examination total scores

Variable	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
MMSE binary (<26 vs ≥26)					
Normal	57 (81.4%)	39 (76.5%)	53 (70.7%)	51 (83.6%)	85 (97.7%)
Abnormal	13 (18.6%)	12 (23.5%)	22 (29.3%)	10 (16.4%)	2 (2.3%)
MMSE binary (<27 vs ≥27)					
Normal	53 (75.7%)	37 (72.5%)	46 (61.3%)	44 (72.1%)	83 (95.4%)
Abnormal	17 (24.3%)	14 (27.5%)	29 (38.7%)	17 (27.9%)	4 (4.6%)
MMSE binary (<28 vs ≥28)					
Normal	41 (58.6%)	33 (64.7%)	35 (46.7%)	42 (68.9%)	77 (88.5%)
Abnormal	29 (41.4%)	18 (35.3%)	40 (53.3%)	19 (31.1%)	10 (11.5%)

Data are presented as N (%)

8.2.2 MMSE individual domain scores

Patients with HF had the lowest mean scores in subtests assessing attention and calculation – particularly patients with both HF and AF (3.9 ± 1.4). Patients with CAD – either with or without HF also had reduced scores in this domain (4.2 ± 1.4), followed by those with non-ischaemic cardiomyopathy (4.4 ± 1.4). Similar scores were found in all domains between patients with CAD regardless of whether or not they had HF. Performance in orientation, concentration and language were similar across all five cohorts. These results are shown in table 8-6.

Table 8-6: Mini mental state examination individual domain scores

	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
Orientation (0-10)	9.6 (0.7)	9.5 (1.0)	9.6 (0.8)	9.6 (1.0)	9.9 (0.4)
Learning (0-6)	5.3 (0.9)	5.2 (1.2)	5.0 (1.1)	5.3 (0.9)	5.6 (0.8)
Language (0-8)	7.7 (0.6)	7.7 (0.8)	7.6 (0.8)	7.8 (0.5)	7.9 (0.4)
Attention and calculation (0-5)	4.2 (1.4)	4.4 (1.4)	3.9 (1.4)	4.2 (1.4)	4.7 (0.8)
Concentration (0-1)	0.8 (0.4)	0.8 (0.4)	0.8 (0.4)	0.9 (0.3)	1.0 (0.2)

Data are presented as mean (SD)

8.3 Summary

The MMSE defined lower proportions of participants as having mild CI compared to the other global cognitive assessment tools (RBANS and MoCA) – this is however affected by the cut-off values used in each cognitive assessment tool. This assessment tool was quick and easy to administer and was well tolerated by study subjects.

In an attempt to put these results into context, tables 8-7 to 8-9 compare the MMSE results from this study to MMSE results from other published studies.

The original study by Folstein et al in 1974 administered MMSE to 63 healthy control participants in addition to their disease cohorts.[155] This cohort was recruited from New York, USA and had a mean age of 73.9 years with the majority being female (57%). The mean total MMSE score from this cohort was lower than the mean MMSE for our healthy control cohort (27.6 versus 29.1) however no information was available regarding the education level of the population studied.

In an attempt to describe the population distribution of performance on the MMSE in a representative UK population, Huppert et al administered MMSE to 3,035 healthy participants.[205] The mean total MMSE in that cohort was 28.3 (1.4) – a value slightly lower than the mean MMSE result in our sample. Unfortunately however, no data were available on mean years of education for that sample for comparison.

Table 8-7: Total MMSE scores for healthy control populations

MMSE	Huppert et al[205] (N=3,035)	Folstein et al[155] (N=63)	CIHF HC (N=87)
Age	72.4	73.9	70.3 (6.7)
Male sex (%)	1328 (44)	27 (43)	55 (63.2)
Years of education	N/A	N/A	14.8 (3.6)
Total MMSE	28.3 (1.4)	27.6 (1.7)	29.1 (1.3)

Data are presented as mean (SD) or N(%)

Two cross sectional studies were found which assessed cognition in patients with CAD and no HF using the MMSE.[206;207] Similar total MMSE scores were seen in our cardiac control cohort as was found in these 2 studies as shown in table 8-8 below.

Table 8-8: Total MMSE scores in patients with CAD compared to other studies

MMSE	Swardfager et al[207] (N=81)	Freiheit et al[206] (N=248)	CIHF CAD CONT (N=61)
Age	62.5 (11)	70.1 (5.8)	67.5 (6.3)
Male sex (%)	70 (86.4)	186 (75)	43 (70.5)
Years of education	16.5 (3.4)	13.2 (3.8)	13.0 (3.3)
Total MMSE	28.9 (1.7)	27.6 (0.25)	27.9 (2.5)

Data are presented as mean (SD) or N(%)

MMSE has been employed in several HF studies to date as a method of assessing cognition.[110;112;208] Table 8-9 shows results from some of these published studies and compares the total MMSE scores from those studies to the results found in this study. As previous studies have not looked at individual HF cohorts e.g. HF with AF, non ischaemic cardiomyopathy, ischaemic cardiomyopathy results are presented from our total HF population in addition to each of the separate HF cohorts. The mean MMSE from our total HF cohort was similar to the mean scores from 2 of these studies (27.2 versus 27.6)[110;112] with the third total mean MMSE score being more in keeping with the mean MMSE from our HF plus AF cohort (26.9).[208]

Table 8-9: Total MMSE scores in patients with HF compared to other studies

MMSE	Karlsson et al[208] (N=74)	Bratzke - Bauer et al[112] (N=47)	Pressler et al[110] (N=249)	CIHF HF CAD (N=70)	CIHF HF no CAD (N=51)	CIHF HF AF (N=75)	CIHF All HF (N=196)
Age	76.0 (7.0)	74.7 (8.9)	62.9 (14.6)	71.0 (8.1)	69.4 (7.5)	71.0 (8.6)	70.6 (8.1)
Male sex (%)	41 (55.0)	37.0 (79.0)	158 (63.0)	49.0 (70.0)	32.0 (62.7)	56.0 (74.7)	137.0 (69.9)
Years of education	N/A	13.8 (3.1)	12.9 (2.8)	11.6 (3.4)	11.8 (3.7)	12.6 (4.0)	12.0 (3.7)
Total MMSE	26.9 (3.0)	27.6 (1.9)	27.6 (2.2)	27.5 (2.2)	27.5 (3.1)	26.9 (2.8)	27.2 (2.7)

Data are presented as mean (SD) or N (%)

CHAPTER NINE

ADDITIONAL MEASURES OF EXECUTIVE FUNCTION

9.1 Introduction

The domain of "executive function" is an umbrella term for cognitive processes that regulate, control and manage other cognitive processes such as planning, problem solving, mental flexibility, and initiating and monitoring of actions.[52] Executive function is thought to be particularly important in patients with HF as this determines how a person can recognise novel situations and adapt to them appropriately. Neuropsychological assessments of executive function have been underused in studies of CI in HF to date. Although executive function is assessed as part of the RBANS, additional measures of executive function including trails making tests parts A & B, controlled oral word association, Wechsler letter number sequencing, animal naming test and frontal assessment battery were included in this study to attempt to address this gap.

The results from each of these additional measures of executive function are discussed in turn below. Results of each individual test are presented in the order in which they were administered at return visit 1. Statistical significance testing was only performed for certain pre-specified variables.

9.2 Results

9.2.1 Trails making test part A

Trails making test A is shown in appendix X. In this assessment of executive function, participants are asked to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. The exercise is timed and the final score is the amount of time taken to complete the task. This is the first of the additional "bolt-on" measures of executive function that each study subject was asked to complete.

Normative values for this assessment tool have previously been discussed in chapter 3. Following completion of the task, scores were compared with published normative data and participants were stratified into percentiles based on their performance. These results are shown in tables 9-1 and 9-2.

All participants included in this study completed Trails making test part A. There was a wide variation in the time taken to complete the test (ranging from 16 to 180 seconds). The healthy control cohort had the lowest mean time of completion (36.3 ± 13.9 seconds) followed by the CAD cohort (39.1 ± 17.7 seconds). Patients with HF took longer to complete this task. Of the three HF groups those with AF took the longest (58.5 ± 27.7 seconds) followed by those with CAD (55.4 ± 23.4 seconds). Patients with AF receiving formal anticoagulation (with either

warfarin or a NOAC) had a mean duration of 60.8 ± 28.7 seconds compared to 46.1 ± 17.9 seconds in patients not receiving anticoagulation. Patients with HF and no CAD had the shortest mean duration of the three HF groups (49.2 ± 21.2 seconds). The majority of patients with HF fell below the 50th percentile when compared to published normative data (table 9-2).

Table 9-1: Results for trails making test part A

	HF.CAD (N = 70)	**HF.NOCAD (N = 51)**	**HF.AF (N = 75)**	**CAD.CONT (N = 61)**	**HC (N = 87)**
Mean (SD)	55.4 (23.4)	49.2 (21.2)	58.5 (27.7)	39.1 (17.7)	36.3 (13.9)
Median	52	43	52	33	34
Range	24, 140	19, 110	19, 180	18, 90	16, 120

Data are presented in seconds.

Table 9-2: Trails making test part A results by percentile

	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
Percentile					
0-10	29 (41.4)	15 (29.4)	29 (39.2)	12 (20.0)	3 (3.4)
10-20	9 (12.9)	4 (7.8)	11 (14.9)	7 (11.7)	11 (12.6)
20-30	4 (5.7)	6 (11.8)	7 (9.5)	4 (6.7)	9 (10.3)
30-40	4 (5.7)	6 (11.8)	5 (6.8)	3 (5.0)	6 (6.9)
40-50	5 (7.1)	4 (7.8)	4 (5.4)	3 (5.0)	12 (13.8)
50-60	7 (10.0)	4 (7.8)	4 (5.4)	5 (8.3)	11 (12.6)
60-70	3 (4.3)	4 (7.8)	2 (2.7)	3 (5.0)	4 (4.6)
70-80	1 (1.4)	3 (5.9)	3 (4.1)	4 (6.7)	11 (12.6)
80-90	6 (8.6)	2 (3.9)	3 (4.1)	9 (15.0)	7 (8.0)
90-100	2 (2.9)	3 (5.9)	6 (8.1)	10 (16.7)	13 (14.9)

Data are presented as N (%)

9.2.2 Trails making test part B

Trails making test part B is similar to Trails making test part A, however they are separate cognitive assessment tools and can be used independently of each other. Trails making test part B involves drawing sequential lines alternating between numbers and letters and is shown in appendix X. The final score is the time taken to complete the test (seconds).

Participants were asked to complete Trails making test part B after they had completed part A. Only 2 participants did not complete this task - one patient with HF and AF and one patient with non-ischemic cardiomyopathy. These were both due to difficulties visualising the assessment form. The mean (SD), median and range of results are shown in table 9-3. Individual scores were then compared to published normative values and participants were classified into percentiles based on their performance.[172] The number of participants in each percentile is shown in table 9-4.

Patients with HF and AF on average took longer to complete this task than those participants in the other four cohorts. The average time taken to complete Trails B was 144.2 ± 67.7 seconds for those with HF and AF compared to 136.8 ± 67.7 seconds and 110.6 ± 57.6 seconds in patients with ischaemic cardiomyopathy and non-ischaemic cardiomyopathy, respectively. In patients with AF, those receiving anticoagulation with either warfarin or a NOAC had a longer mean time of completion (151.2 ±68.3 seconds) compared to those on antiplatelet therapy only (107.6 ± 52.7 seconds).

The healthy control cohort had the shortest average time of completion (77.9 ± 30.2 seconds) followed by the CAD control cohort (97.4 ± 56.2 seconds). A large proportion of patients with HF fell below the 10th percentile when compared with published normative data (table 9-4).

In summary, results for trail making test B followed the same pattern as those for trail making test A with patients with both HF and AF having the poorest performance in these tests of executive function.

Table 9-3: Results for trails making test part B

	HF.CAD (N = 70)	HF.NOCAD (N = 50)	HF.AF (N = 74)	CAD.CONT (N = 61)	HC (N = 87)
Mean (SD)	136.8 (67.7)	110.6 (57.6)	144.2 (67.7)	97.4 (56.2)	77.9 (30.2)
Median	120.0	101.0	125.5	79.0	73.0
Range	39, 320	41, 280	47, 296	37, 300	31, 180

Data are presented in seconds.

Table 9-4: Trails making test part B results by percentile

	HF.CAD (N = 70)	HF.NOCAD (N = 50)	HF.AF (N = 74)	CAD.CONT (N = 61)	HC (N = 87)
Percentile					
0-10	28 (40)	17 (34)	34 (47)	17 (28)	13 (15)
10-20	5 (7)	3 (6)	12 (16)	6 (10)	2 (2)
20-30	8 (11)	2 (4)	4 (6)	5 (8)	6 (7)
30-40	4 (6)	3 (6)	2 (3)	4 (7)	4 (5)
40-50	1 (1)	4 (8)	4 (6)	2 (3)	8 (9)
50-60	5 (7)	1 (2)	2 (3)	4 (7)	3 (3)
60-70	5 (7)	5 (10)	4 (6)	3 (5)	13 (15)
70-80	2 (3)	6 (12)	3 (4)	9 (15)	7 (8)
80-90	4 (6)	2 (4)	4 (6)	1 (2)	6 (7)
90-100	8 (11)	7 (14)	4 (6)	9 (15)	25 (29)

Data are presented as N (%)

Previous studies assessing CI in HF have also used trails making tests A and B as a measure of executive function. In an attempt to put our results into context, tables 9-5 and 9-6 compare results from trails making tests A & B from this study to other published studies.

Hoth et al performed the trails making test on 31 patients with CAD and no HF and 31 patients with HF (of any aetiology).[209] The group found those patients with CAD (and no HF) had faster (better) completion times than those with HF for both trails making tests A and B – this is consistent with our findings. Although the results from that study were similar to ours, patients recruited into our CAD control group had slightly longer (worse) results from Trails A and slightly faster (better) for Trails B.

Table 9-5: Results for Trails making tests A & B in CAD cohorts

Trails A & B	**Hoth et al[209] CAD group (N=31)**	**CIHF CAD CONT (N=61)**
Age	68.9 (8.5)	67.5 (6.3)
Male sex (%)	14 (45)	43 (70.5)
Years of education	13.1 (2.7)	13.0 (3.3)
Trails A (s)	34.7 (10.4)	39.1 (17.7)
Trails B (s)	99.7 (32.9)	97.4 (56.2)

Data are presented as mean (SD) or N (%)

A study by Bratzke-Bauer et al also used trails making test as a measure of executive function in HF patients.[112] These results are displayed in table 9-6. Although their results were similar to the results from this study, on average HF patients enrolled into this study took longer to complete trails A (worse) and a shorter time to complete trails B (better) compared to those in the Bratzke-Bauer study.

Table 9-6: Results for Trails making tests A & B in HF cohorts

Trails A & B	Bratzke -Bauer et al[112] (N=47)	Hoth et al[209] (N=31)	CIHF All HF (N=196)
Age	74.7 (8.9)	69.1 (8.5)	70.6 (8.1)
Male sex (%)	37.0 (79.0)	17.0 (54.0)	137.0 (69.9)
Years of education	13.8 (3.1)	12.9 (2.8)	12.0 (3.7)
Trails A (s)	52.5 (24.2)	45.9 (28.8)	55.0 (24.8)
Trails B (s)	134.0 (68.5)	143.2 (79.8)	132.9 (66.3)

Data are presented as mean (SD) or N (%)

9.2.3 Controlled oral word association test

The controlled oral word association test (COWA) is a test of phonemic verbal fluency and executive function. This assessment tool is outlined in chapter 3 and the record sheet is shown in appendix XII. The number of words beginning with the same designated letter said by the participant in one minute is recorded. The letters F, A and S were used in this study and the number of words for each letter were added together to give a total number of words given in 3 minutes. All study participants completed this task.

Table 9-7 shows the mean (SD), median and range of total number of words given in three minutes in each of the study cohorts. There was a large range in the number of words given in 3 minutes (ranging from 5 to 71). Patients with HF and AF had the lowest mean number of words (32 ± 12) and the healthy control participants had the highest (43 ± 12). Patients with AF on anticoagulation had the poorest performance with an overall average of 31 ± 11 words compared to an average of 40 ± 14 words for those patients on antiplatelet therapy only.

Table 9-7: Results of controlled oral word association test

	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
Mean (SD)	34 (11)	35 (12)	32 (12)	38 (14)	43 (12)
Median	32	34	31	37	43
Range	14, 60	13, 61	5, 64	8, 67	13, 71

Data are presented as number of words given in 3 minutes

On review of the current literature, 2 studies were found which used COWA in cognitive assessment of HF patients.[110;209] The results from these studies are shown in table 9-8 alongside results for the total HF cohort from this study for comparison. In these other published HF studies, the HF cohort was not divided according to underlying aetiology of HF nor presence of AF and so these results have been compared to the total HF cohort in this study. The total HF cohort in this study had a higher mean total number of words given in 3 minutes compared to the other studies suggesting an overall better performance on this assessment tool. This was despite having a higher mean age of participant with lower average years of education.

Table 9-8: Results of controlled oral word association test in this study compared to other published HF studies

COWA	Hoth et al[209] (N=31)	Pressler et al[110] (N=249)	CIHF All HF (N=196)
Age	69.1 (8.5)	62.9 (14.6)	70.6 (8.1)
Male sex (%)	17 (54.0)	158 (63.0)	137.0 (69.9)
Years of education	12.9 (2.8)	12.9 (2.8)	12.0 (3.7)
COWA	30.3 (13.1)	30.1 (11.9)	33.6 (11.8)

Data are presented in mean (SD) or N (%)

For each participant, the reference age and education band into which they appeared was determined using published normative values.[175] The total COWA scores for each individual were then compared to the relevant reference tables and the percentile into which they appeared was determined. The assigned percentiles were compared across all subjects and are shown in table 9-9.

Table 9-9: Controlled oral word association test results by percentile

	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
Percentile					
0-10	10 (15)	7 (14)	13 (18)	9 (15)	6 (7)
10-20	6 (9)	4 (8)	8 (11)	2 (3)	6 (7)
20-30	3 (4)	6 (12)	8 (11)	9 (15)	3 (4)
30-40	11 (16)	6 (12)	8 (11)	9 (15)	3 (4)
40-50	6 (9)	5 (10)	4 (6)	9 (15)	7 (8)
50-60	7 (10)	6 (12)	7 (10)	7 (12)	13 (15)
60-70	9 (13)	5 (10)	9 (13)	5 (8)	9 (11)
70-80	4 (6)	4 (8)	3 (4)	2 (3)	7 (8)
80-90	4 (6)	6 (12)	8 (11)	5 (8)	15 (18)
90-100	9 (13)	6 (12)	4 (6)	9 (15)	15 (18)

Data are presented as N (%)

9.2.4 Wechsler letter number sequencing

The Wechsler letter number sequencing test assesses attention and executive function. This is frequently used as part of the Wechsler Adult Intelligence Scale (WAIS) which is composed of 15 individual subtests. These individual subtests can then be totalled together to give an overall score. On review of current literature, no prior HF studies were found which used this test as a method to assess cognition.

In this test, examinees are read a series of numbers and letters and are asked to arrange these into numerical and alphabetical order before repeating them back to the examiner. A copy of the Wechsler letter number sequencing is shown in appendix VII. There is a maximum total score of 30.

Table 9-10 shows the mean (SD), median and range in results for each study cohort. There was a striking reduction in the mean and median results in patients with HF for this particular test compared to both the cardiac and healthy control cohorts. All study participants completed this assessment tool. Total scores ranged from 0 to 25 out of 30. The lowest mean scores were found in patient with HF and AF.

Table 9-10: Results of Wechsler letter number sequencing test

	HF.CAD (N = 70)	**HF.NOCAD (N = 51)**	**HF.AF (N = 75)**	**CAD.CONT (N = 61)**	**HC (N = 87)**
Mean (SD)	10.9 (6.1)	12.1 (6.7)	10.2 (6.3)	14.4 (5.9)	17.2 (5.1)
Median	12	13	10	17	18
Range	0, 22	0, 22	0, 22	1, 24	1, 25

9.2.5 Animal naming test

The animal naming test assesses executive function using verbal fluency. Individuals are asked to generate as many names as possible from a specified category in one minute. The category chosen in this study was animals. This assessment tool is discussed in more detail in chapter 3 and a copy of the scoring sheet is shown in appendix VII.

The minimum number of animal names given in one minute was 3 and the maximum was 30. Overall, the healthy control cohort had the highest mean score (19.2 ± 4.2) followed by the CAD control cohort (17.8 ± 4.6). There was a striking reduction in median scores of HF patients compared to the cardiac and healthy control cohorts in this particular test. Of the 3 HF cohorts, those with AF had the lowest mean score (14.4 ± 4.8), followed by those with ischaemic cardiomyopathy (14.9 ± 4.8) and non-ischaemic cardiomyopathy (15.1 ± 4.8). Individual scores were then compared to published normative data and participants were categorised into percentiles.[175] These results are shown in tables 9-11 and 9-12.

Table 9-11: Results of animal naming test

	HF.CAD (N = 70)	**HF.NOCAD (N = 51)**	**HF.AF (N = 75)**	**CAD.CONT (N = 61)**	**HC (N = 87)**
Mean (SD)	14.9 (4.8)	15.1 (4.8)	14.4 (4.8)	17.8 (4.6)	19.2 (4.2)
Median	15	14	14	19	20
Range	3, 30	7, 25	3, 25	9, 30	7, 29

Data are presented as number of animals given in 1 minute

Table 9-12: Animal naming test results by percentile

	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
Percentile					
0-10	14 (20)	12 (24)	22 (31)	7 (12)	5 (6)
10-25	13 (19)	5 (10)	15 (21)	7 (12)	10 (12)
25-50	14 (20)	15 (30)	7 (10)	9 (15)	12 (14)
50-75	16 (23)	6 (12)	14 (19)	17 (28)	18 (21)
75-90	6 (9)	8 (16)	9 (13)	16 (27)	27 (32)
90-100	6 (9)	4 (8)	5 (7)	4 (7)	13 (15)

Data are presented as N (%)

On review of current literature, one previous study was found that used the animal naming test in the cognitive assessment of HF patients.[210] The animal naming test results from that study are compared to the results from this study in table 9-13. The HF patients recruited into this study were on average older with fewer years of education compared to the cohort studied by Garcia et al. By comparison, the total HF cohort in this study had a lower mean number of animals (14.8 versus 19.9) suggesting a poorer performance on this assessment tool in our study cohort.

Table 9-13: Animal naming test results compared to other HF studies

Animal naming test	Garcia et al[210] (N=41)	CIHF All HF (N=196)
Age	68.3 (8.4)	70.6 (8.1)
Male sex (%)	27.0 (66.0)	137.0 (69.9)
Years of education	13.6 (3.0)	12.0 (3.7)
Number of animals	19.9 (4.99)	14.8 (4.8)

Data are presented as mean (SD) or N (%)

9.2.6 Frontal assessment battery

The frontal assessment battery (FAB) was the final additional measure of executive function that was given to study participants. It took approximately 10 minutes to administer and all study participants completed this assessment tool. The FAB is described in chapter 3 and a copy of the questionnaire is shown in appendix XII. The results of the raw scores are presented in table 9-14. There was a similar range in results found between all study cohorts with similar mean and median results between groups.

In addition to the ordinal analysis a binary analysis was also performed. A cut-off score of <12 was taken as being abnormal. This is based on previously published data.[176] Based on results from this analysis, 17% of those with patients with HF and AF were categorised as cognitively impaired compared to 3% of the healthy control cohort.

Table 9-14: Results of frontal assessment battery

	HF.CAD (N = 70)	HF.NOCAD (N = 51)	HF.AF (N = 75)	CAD.CONT (N = 61)	HC (N = 87)
Mean (SD)	15 (3)	16 (3)	15 (3)	16 (2)	17 (2)
Median	16	17	15	17	17
Range	6, 18	9, 18	6, 18	8, 18	7, 18
N (%) with score <12	9 (13)	4 (8)	13 (17)	3 (5)	3 (3)

On review of current literature, only one previous study was found that used the frontal assessment battery in the cognitive assessment of HF patients.[210] The results from that study are shown in table 9-15. Results from the HF cohort recruited into this study were similar to the FAB results from the study by Garcia et al (15.0 versus 15.9).

Table 9-15: Frontal assessment battery results compared to other HF studies

Frontal assessment battery	Garcia et al[210] (N=41)	CIHF All HF (N=196)
Age	68.3 (8.4)	70.6 (8.1)
Male sex (%)	27.0 (66.0)	137.0 (69.9)
Years of education	13.6 (3.0)	12.0 (3.7)
Frontal assessment battery score	15.9 (2.46)	15.0 (2.8)

Data are presented as mean (SD) or N (%)

9.3 Summary

This chapter described the main findings from the additional measures of executive function used in this study. In addition to the three global cognitive assessment tools, six additional measures of executive function were employed. These additional measures were added as executive function has been understudied in previous studies looking at cognitive impairment in heart failure. In general, these additional tests were well tolerated and completed by the majority of study participants.

The study of executive function is relevant to the clinical management of patients with HF. Central to the treatment of chronic heart failure is complex pharmacological therapy requiring careful monitoring in the community which often involves patient self-monitoring for signs indicative of clinical decline e.g. weight gain. It is important that patients can recognise a change in their clinical condition, process this information and react to it accordingly e.g. reduce their fluid intake. This ability may be jeopardised if patients have impaired executive function.

With the exception of the frontal assessment battery, the other 5 tests of executive function showed the same pattern in their results. . Patients with both HF and AF had the poorest overall results suggesting the greatest degree of executive dysfunction. Of the patients with AF, those on treatment with formal anticoagulation (either warfarin or a NOAC) had lower scores than those who were not. All patients included in this study who had a history of AF and who were not formally anticoagulated, were receiving treatment with an antiplatelet agent. . Patients with HF had poorer scores than either the ischaemic heart disease control cohort or the age and sex matched healthy control participants.

Of the other HF cohorts (ischaemic cardiomyopathy in sinus rhythm and non-ischaemic cardiomyopathy in sinus rhythm), those with a confirmed diagnosis of CAD had poorer performances in each of the six individual neuropsychological tests. Patients with no clinical history of HF and a preserved ejection fraction with a history of CAD had poorer performances in each of these tests than age and sex matched healthy controls but still had better results than patients with HF. Of the six tests employed, the animal naming test and the Wechsler letter number sequencing test showed the greatest difference in scores between patients with HF (poorer scores) and those with no HF.

The frontal assessment battery showed a different pattern of results. In this subtest, there was less of a difference seen between patients with HF and AF versus ischaemic cardiomyopathy. This test appeared to differentiate more between patients with ischaemic cardiomyopathy versus non ischaemic cardiomyopathy.

The results discussed in this chapter confirm that patients with HF have greater executive dysfunction compared to those patients without HF. Apart from one of the tests employed all of these cognitive assessment tools showed the same pattern of results with the combination of HF and AF resulting in the greatest degree of impairment compared to patients in sinus rhythm. This is clinically relevant as we know that executive function is the broad description of a set of processes involved in higher cortical function, particularly in goal formation, self-monitoring and planning – all of which are involved in a patients ability to recognise changes in their clinical conditions and react appropriately.

CHAPTER TEN

OTHER MEASURES

Chapter 10: Other measures

10.1 Introduction

In addition to the previously discussed measures of cognition, several other questionnaires were also given to study participants. These questionnaires were given at return study visit 1 and patients returned these by post once completed. Results from each of these are discussed in turn below.

10.2 Results

10.2.1 Kansas city cardiomyopathy questionnaire

The KCCQ is a commonly used disease specific health related quality of life questionnaire and so was only applicable to patients with HF included in this study. The KCCQ is described in more detail in chapter 3 and shown in appendix XVII.

Out of 196 patients with HF 177 completed and returned the KCCQ. The results of the overall KCCQ summary score, clinical summary score and their individual components are presented in table 10-1.

The overall summary score has a maximum score of 100 and assesses functional ability. A low score reflects poor self-reported levels of functioning. The clinical summary score assesses symptom burden and has a maximum value of 100. Low scores indicate a high burden of symptoms.

Patients with HF and CAD reported the highest burden of symptoms and poorest level of functioning, followed by those with HF and AF. Patients with non-ischaemic cardiomyopathy reported fewest symptoms and the best levels of functional ability. Patients reporting the highest symptom burden and poorest functional ability also reported most social limitation. Despite this however, patients with ischaemic cardiomyopathy had the highest scores for questions pertaining to quality of life and self-efficiency.

Table 10-1: Results of Kansas city cardiomyopathy questionnaire

	HF.CAD (N = 65)	HF.NOCAD (N = 45)	HF.AF (N = 67)
KCCQ physical (0-100)	54.9 (28.4)	57.8 (30.2)	55.1 (25.5)
KCCQ symptom (0-100)	67.6 (25.9)	70.3 (26.2)	70.6 (23.7)
KCCQ self-efficacy (0-100)	76.5 (21.9)	73.9 (22.3)	77.1 (23.2)
KCCQ quality of life (0-100)	60.9 (25.8)	59.6 (28.4)	58.1 (25.4)
KCCQ social limitation (0-100)	50.8 (27.4)	54.9 (32.7)	55.5 (31.9)
KCCQ clinical summary score (0-100)	61.3 (24.8)	64.3 (26.1)	63.2 (23.1)
KCCQ overall summary score (0-100)	58.7 (23.8)	61.0 (26.5)	59.8 (24.0)

Data are presented as mean (SD)

To help put our results from the disease specific quality of life questionnaire into context, table 10-2 presents KCCQ clinical and overall summary scores from other HF studies.[34;211-213] The heart failure cohort investigated in this study had similar results for both summary scores suggesting our sample population were fairly representative of the wider HF population.

Table10-2: Kansas city cardiomyopathy questionnaire summary scores from heart failure studies

	SHIFT[34]	RED-HF[212]	STICH[211]	Heart Mate II[213]	CIHF
Clinical Summary Score (Max. 100)	68	59	64	34	63
Overall Summary Score (Max. 100)	65	56	54	27	59

Data are presented as means. SHIFT, systolic heart failure treatment with the I_f inhibitor ivabradine trial; RED-HF, reduction of events with darbopoetin alfa in heart failure trial; STICH, surgical treatment for ischaemic heart failure; CIHF, cognitive impairment in heart failure

10.2.2 Self-care of heart failure index

The SCHFI was given to all patients with HF in this study and a copy of the questionnaire is shown in appendix XVIII. 173 out of 196 patients completed and returned this assessment form and the results are shown in table 10-3.

This questionnaire asks about symptom recognition and daily interventions that patients can employ to improve their clinical status. A score ≥70 is used as the cut-point to judge adequate self-care.

Patients with non-ischaemic cardiomyopathy had the lowest scores for questions assessing ability to adhere to lifestyle modifications for HF treatment (e.g. eating a low salt diet). They also had the poorest scores for self-management of HF however they had the highest scores of confidence in managing their condition. From the results below it appears that the HF cohort enrolled into this study had poor HF self-care.

Table 10-3: Results of the self-care of heart failure index

	HF.CAD (N = 62)	**HF.NOCAD (N = 45)**	**HF.AF (N = 66)**
SCHFI maintenance (0-100)	53.3 (14.9)	51.6 (13.9)	56.6 (14.7)
SCHFI management (0-100)	47.7 (19.9)	42.0 (24.1)	46.0 (22.0)
SCHFI confidence (0-100)	53.6 (20.8)	55.5 (23.5)	52.9 (23.3)

Data are presented as mean (SD)

10.2.3 EuroQol five dimensions questionnaire

The EQ-5D is a standardised instrument for use as a measure of health outcome and was given to all study participants. A copy of the EQ-5D is shown in appendix XVII. A total of 328 participants completed and returned this assessment form. A single index value is given as a measure of health status (with a maximum score of 1) and a visual analogue scale records the respondents self-rated health status from 0-100. Similar results were found across the 3 HF cohorts with a mean of 65 out of 100 on the visual analogue scale for both patients with ischaemic and non-ischaemic cardiomyopathy. Of the 3 HF cohorts, patients with AF reported the poorest health status on the visual scale. The results of the EQ-5D for each cohort are presented in table 10-3.

Table 10-3: Results of EuroQol five dimensions questionnaire

	HF.CAD (N = 67)	HF.NOCAD (N = 45)	HF.AF (N = 75)	CAD.CONT (N =58)	HC (N = 83)
EQ-5D utility (0-1)	0.62 (0.32)	0.69 (0.26)	0.66 (0.27)	0.73 (0.25)	0.89 (0.13)
EQ-5D visual scale (0-100)	65 (17)	65 (20)	62 (20)	74 (19)	88 (8.8)

Data are presented as mean (SD)

10.2.4 Hospital anxiety and depression scale

The mood assessment tool used in this study was the HADS questionnaire. This was given to each study participant at return study visit 1. The questionnaire was completed at home and returned by 330 participants. A copy of the questionnaire is shown in appendix XVII and the results are presented in tables 10-4 and 10-5. In clinical practice, a score of 0-7 out of a maximum score of 21 is normal. A score of 8-10 out of 21 represents mild mood disorder. A score of 11-14 defines moderate mood disorder and 15-21 defines severe mood disorder.

Patients with HF had the highest scores for both the anxiety and depression subscale of HADS. Patients with non-ischaemic cardiomyopathy had the highest mean score on the anxiety scale while patients with ischaemic cardiomyopathy had the highest mean depression score. Overall 19% of HF patients were categorised as significantly anxious (defined as scores >10 out of 21) and 13% of HF patients were categorised as significantly depressed (defined as scores >10 out of 21) on binary analyses – these results are shown in table 10-6.

Table 10-4: Results of hospital anxiety and depression scale *anxiety* subscale (Range 0-21)

	HF.CAD (N = 70)	HF.NOCAD (N = 46)	HF.AF (N = 73)	CAD.CONT (N =59)	HC (N = 82)
Mean	6.5 (5.2)	6.7 (4.4)	5.1 (3.7)	5.6 (4.6)	3.9 (3.1)
Median	5.0	6.0	4.0	4.5	3.0
Range	0, 20	0, 15	0, 16	0, 17	0, 18

Table 10-5: Results of hospital anxiety and depression scale *depression* subscale (Range 0-21)

	HF.CAD (N = 70)	HF.NOCAD (N = 46)	HF.AF (N = 73)	CAD.CONT (N =59)	HC (N = 82)
Mean	5.7 (3.9)	5.6 (4.1)	5.0 (3.2)	4.4 (4.3)	2.3 (2.1)
Median	5.0	5.0	4.0	3.0	2.0
Range	0, 15	0, 15	1, 15	0, 17	0, 10

Table 10-6: Results from binary analyses of the hospital anxiety and depression questionnaire

	HF.CAD (N = 70)	HF.NOCAD (N = 46)	HF.AF (N = 73)	CAD.CONT (N =59)	HC (N = 82)
Non-anxiety	51 (72.9%)	37 (80.4%)	65 (89%)	50 (84.5%)	79 (96.3%)
Anxiety	19 (27.1%)	9 (19.6%)	8 (11%)	9 (15.5%)	3 (3.7%)
Non-depressed	60 (85.7%)	38 (82.6%)	66 (90.4%)	54 (91.5%)	82 (100%)
Depressed	10 (14.3%)	8 (17.4%)	7 (9.6%)	5 (8.5%)	0 (0%)

Data are presented as N (%). Cut-off defined as >10 out of 21 representing anxiety / depression

10.2.5 Zarit burden interview

The Zarit burden interview was administered to family members or friends of all enrolled participants. This questionnaire was used as a measure of care giver strain and was given at return visit 1. The questionnaire was completed by a relative of the participant at home and returned by post. A copy of the questionnaire is shown in appendix XIX.

146 questionnaires were returned by relatives caring for patients with HF. 53 forms were completed for the relatives of those in the cardiac control group and 80 for the healthy volunteers. Lowest scores (reflecting less burden) were given regarding the healthy control group followed by the cardiac control group and non-ischaemic cardiomyopathy group. Relatives of patients with HF and AF gave the highest scores with 7.3% reporting moderate to severe levels of strain. No completed questionnaires gave a total score falling into the "severe strain" category. These results are shown in tables 10-7 and 10-8. The cut-off values used in the binary analyses were taken from recently published guidelines.[214]

Table 10-7: Results of the Zarit burden interview (Range 0-88)

	HF.CAD (N =50)	HF.NOCAD (N =41)	HF.AF (N =55)	CAD.CONT (N =53)	HC (N =80)
Mean	13.5 (11.4)	12.1 (12.9)	14.1 (13.1)	11.4 (12.7)	3.6 (5.3)
Median	10.5	8.0	11.0	8.0	2.0
Range	0, 46	0, 60	0, 45	0, 46	0, 24

Table 10-8: Binary analysis of Zarit burden interview results

	HF.CAD (N=50)	HF.NOCAD (N=41)	HF.AF (N=55)	CAD.CONT (N=53)	HC (N=80)
No- little burden (0-21)	37 (74)	33 (80.5)	43 (78.2)	43 (81.1)	78 (97.5)
Mild-moderate burden (21-40)	12 (24)	6 (14.6)	8 (14.5)	6 (11.3)	2 (2.5)
Moderate – severe burden (41-60)	1 (2)	2 (4.9)	4 (7.3)	4 (7.5)	0 (0)
Severe burden (61-88)	0 (0)	0 (0)	0 (0)	0 (0)	0(0)

Data are presented as N (%)

10.2.6 Informant questionnaire on cognitive decline in the elderly

This questionnaire uses informant reports as an alternative way to measure cognitive decline from a pre-morbid level. A copy of the IQCODE is shown in appendix XVI and the questionnaire is described in more detail in chapter 3. In this questionnaire the informant is asked to comment on any perceived change in cognition over the past 10 years. A copy of the questionnaire was given at return visit 1, completed at home and returned by post. This questionnaire has a range of scores of 1-5 with scores 0-3 representing "no change", a score of 4 representing "a bit worse" and 5 representing "much worse".

The largest perceived change in cognition was reported for patients with HF and AF with 16.4% of participants reporting cognitive decline in their relative. Only one relative of a healthy volunteer reported that they saw a change in the cognitive function of their relative.

Table 10-8: Results of the informant questionnaire on cognitive decline in the elderly (Range 1-5)

	HF.CAD (N =58)	**HF.NOCAD (N =42)**	**HF.AF (N =61)**	**CAD.CONT (N =56)**	**HC (N =80)**
Mean	3.1 (0.5)	3.1 (0.4)	3.2 (0.4)	3.1 (0.5)	3.1 (0.3)
Median	3.0	3.0	3.1	3.1	3.0
Range	1.1, 4.2	1.6, 4.3	1.1, 4.2	1.0, 3.9	1.0, 3.8
Normal N (%)	53 (91.4%)	38 (90.5%)	51 (83.6%)	50 (89.3%)	79 (98.8%)
Abnormal N (%)	5 (8.6%)	4 (9.5%)	10 (16.4%)	6 (10.7%)	1 (1.2%)

10.3 Summary

This chapter has shown results from questionnaires assessing disease specific quality of life, disease self-management and mood. The results from two questionnaires given to participants' relatives assessing care giver strain and perceived cognitive changes are also presented for each study cohort.

The results presented from the KCCQ confirm that the HF population recruited into this study are representative of the wider HF population by comparing their summary scores to those from other clinical HF trials. Despite having low scores in the self-care of HF index (suggesting poor levels of self-care) patients with HF were confident in managing their condition.

Patients with HF had the lowest scores for self-reported health outcomes. Healthy control participants had the best results for self-reported health outcomes. HF patients reporting the highest burden of symptoms (those with HF are coronary artery disease) also reported the poorest levels of daily functional ability. Almost one fifth of the HF population had scores indicative of clinically relevant anxiety with a lower proportion (13%) reporting clinically relevant depressive symptoms.

Overall there was a low level of care giver burden reported. Relatives of patients with HF and AF reported the highest level of care giver strain but none of these fell into the "serious" category. Of relatives who reported care giver strain, most was classified as mild. In addition to reporting care giver strain, relatives of those patients with AF also reported the highest perceived level of cognitive decline.

In summary, the HF patients recruited into this study had a relatively high symptom burden and reduced functional ability but despite this reported confidence in the management of their condition and continued reasonable quality of life. In general, anxiety was more common than depression and overall there was not a huge burden of mood disorder. Despite relatives and caregivers being aware of cognitive decline in these patients there were low overall levels of caregiver strain reported.

CHAPTER ELEVEN

CONCLUSIONS

11.1 Discussion and main findings of the study

It is estimated that 1-2% of the adult population in developed countries have HF with the prevalence increasing to ≥10% among patients aged over 70 years. HF admissions account for 5% of all medical admissions (making it the commonest cause of unscheduled admissions in older adults). Societal and demographic changes, including ageing of the general population and improved survival from heart disease will increase the prevalence of HF with a potential doubling in HF prevalence within the next 40 years.

The estimated prevalence of CI / dementia in the UK in adults over the age of 65 years old is 7.1% (based on 2013 data). For the reasons outlined above the total number of people living with dementia in the UK is also forecast to increase to over 1 million by 2025 and over 2 million by 2051 if age-specific prevalence remains stable. Figure 11-1 shows the rising incidence of HF and rising prevalence of dementia in two community based populations.

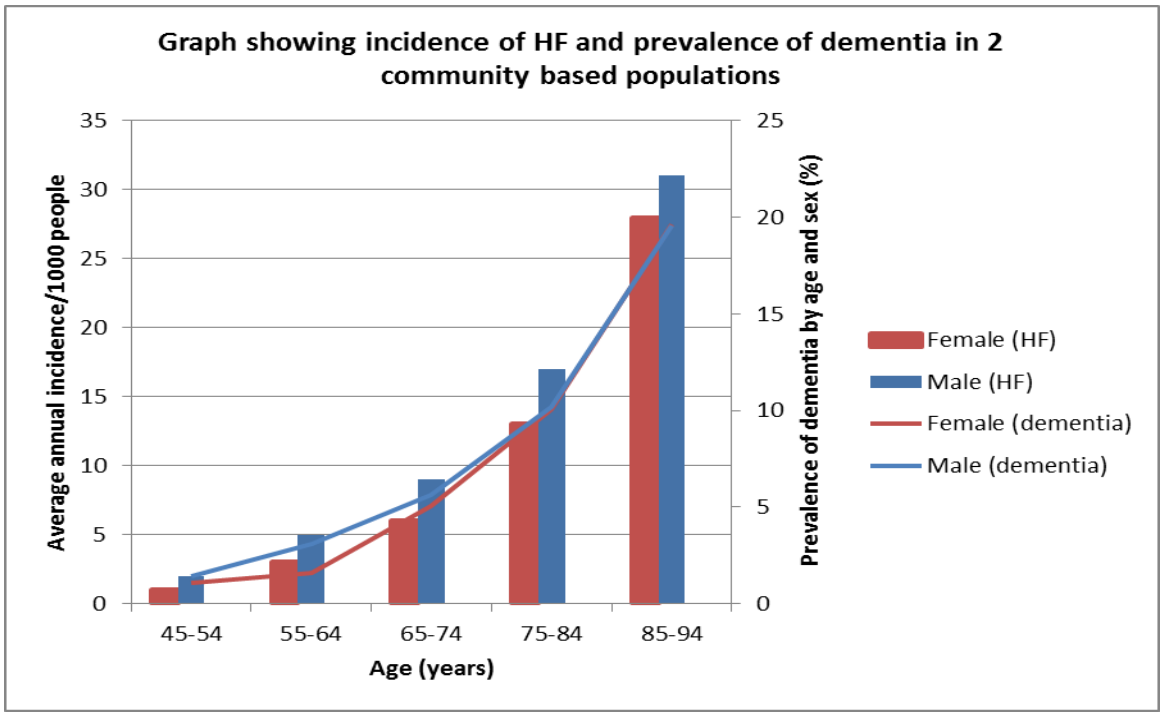


Figure 11-1: Incidence of heart failure within the Framingham cohort and prevalence of dementia by age and sex (pooled from 5 centres of the Medical Research Council cognitive function and ageing study). Reproduced with permission.[215]

The term "cardiogenic dementia" was first coined in an editorial published in the Lancet in 1977 and so the co-existence of HF and "brain failure" has been recognised for decades. Although the idea of concomitant CI and HF will be familiar to most clinicians the topic has received relatively little research interest compared with other aspects of cardiac disease.

The systematic literature review presented in chapter 2 found disparate and inconsistent literature, characterised by small sample sizes, heterogeneity and multiple potential biases. This heterogeneity resulted from differences in study designs, case mix and cognitive assessments employed.

This study has provided a comprehensive evaluation of cognition in a well-defined population of patients with HF, ischaemic heart disease and age- and sex- matched healthy controls. The tolerability of performing these cognitive assessment tools has been demonstrated. Differences in the prevalence of CI identified with the various cognitive assessment tools have been demonstrated. This study has therefore achieved its main aims.

Of the 817 potential participants screened, 344 were included in this study. The study cohort included 196 patients with HF, 61 patients with ischaemic heart disease and no HF and 87 healthy control participants. The HF cohort consisted of 70 patients with HF and coronary artery disease in sinus rhythm, 51 patients with no coronary artery disease in sinus rhythm and 75 patients with HF and atrial fibrillation.

All patients with HF had evidence of HF-REF with a LVEF <45% on transthoracic echocardiography. The majority of the cohort was male and elderly. HF patients with AF were more likely to have multiple co-morbidities. Despite this the majority lived independently at home and were stable, community-dwelling HF patients who had not been recently discharged from hospital.

Patients recruited from cardiac rehabilitation clinics had proven coronary artery disease, no clinical HF and a LVEF >55%. The ischaemic heart disease group were relatively well matched to healthy controls who had no previous diagnosis of any chronic illness, prescribed no regular medication and also had a LVEF >55%. All participants underwent the same baseline investigations and there were no obvious differences in baseline demographics between each of the cohorts.

Many potential confounding variables are relevant to cognition assessment in these cohorts of participants. Our stringent exclusion criteria along with baseline investigations including detailed biochemical and haematological laboratory testing, urinalysis, electrocardiography and echocardiography aimed to reduce the possibility of confounding from other pathological processes. To minimise the chance of any change in clinical condition of the participant, the return visit for neuropsychological assessment was held within 10 days of the initial screening visit.

The majority of participants completed all cognitive assessment tools (with the exception of 2 participants who did not complete trails making test part B). This detailed cognitive assessment took approximately 90 minutes to perform and was generally well tolerated. The instruments used to assess cognition were administered in the same order to each participant and additional questionnaires assessing quality of life, self-care of HF and mood were completed at home by participants and their carers and returned by post.

Nine individual tests of cognition were administered to 344 study participants. In addition to the nine direct cognitive tests, an informant based interview was also performed to assess perceived change in cognitive function over time. Three questionnaires were used to assess quality of life, one assessment tool to assess mood and one questionnaire to assess caregiver strain.

The prevalence of CI in this sample of stable HF outpatients varied from 20-80% depending on the cognitive assessment tool and threshold value used. The most commonly used cognitive screening test in clinical practice is the MMSE. Using a recognised threshold of <26 out of 30, 24% of HF patients were categorised as cognitively impaired compared to 44% when a higher threshold value of <28 was used. The second global assessment tool used was the MoCA. This reported a prevalence of CI of 65% in the HF cohort when a threshold of <25 was used compared to 80% using the higher threshold of <27. The RBANS categorised 19% of HF patients as cognitively impaired using a threshold of <70 and 70% when a threshold of <90 was used.

Using the more conservative cut-off scores outlined above, the MoCA detected most cognitive changes, followed by the MMSE and then RBANS. This is in keeping with the clinical applications of these neuropsychological assessment tools. MoCA and MMSE being designed as global screening tools whereas RBANS being a more specific domain specific cognitive assessment tool.

Regardless of the cognitive assessment tool used or the cut-off value taken to define CI the results always followed the same pattern. Patients with a combination of HF and AF (either permanent or paroxysmal) had poorer cognition than those with HF and no history of AF. Patients with cardiac disease (either HF or ischaemic heart disease and no HF) always had poorer scores than the age- and sex- matched healthy control population and less of a difference was seen between the HF and ischaemic heart disease control group.

At the start of this study, we made the following three hypotheses:

1. Patients with a combination of HF and AF (either permanent or paroxysmal) will have poorer cognition than those with HF and no history of AF.

2. HF patients will attain lower cognitive scores than age and sex matched cardiac control participants.

3. Patients with HF will attain lower cognitive scores than the age- and sex- matched healthy control participants.

The results generated from this study support hypothesis 1 and 3 but do not support hypothesis 2.

11.2 Strengths of the study

The major strength of this study is the inclusion of a cardiac control cohort which has been missing from previous other studies as outlined in chapter 2. The inclusion of a cohort of patients with confirmed ischaemic heart disease and preserved left ventricular ejection fraction with no clinical HF allows us to make an assessment of whether HF *per se* is associated with CI, rather than the underlying atherosclerotic risk factors.

The second major strength of this study is the extensive battery of neuropsychological tests employed. Routine screening for CI in patients with HF is not recommended in current HF guidelines and this is in part due to a lack of standardised assessment tools. By using a comprehensive battery of tests I not only thoroughly investigated cognition (and its individual domains) but was also able to compare global assessment tools and their ability to detect subtle changes in cognition.

All enrolled patients have consented to re-contact for future study visits to further investigate the potential mechanistic basis that may underlie CI in HF. All patients have also consented to be "flagged" with the Information Services Division of the Scottish Health Service. This will allow accurate mortality data to be obtained by linking the study database to information on deaths, held by the General Registrar's Office for Scotland.

I employed several techniques to ensure that all data collected and processed in this study were robust. Data collected from the neuropsychological tests used were marked by a blinded independent reviewer trained in neuropsychology (Dr Rosalind Lees). A random 20% of the study booklets were then re-marked by two consultant neuropsychologists (Dr John Sharp and Dr Niall Broomfield), with any discrepancy in marking referred to a third Professor of

neuropsychology (Professor Jonathan Evans). The creation of an electronic database held at the Robertson Centre for Biostatistics at the University of Glasgow ensured quality control of the data processed. Although data were manually entered into this database, these were independently checked by two database managers. At completion, this study was randomly selected for an independent audit by the NHS Greater Glasgow and Clyde Research and Development Governance Team (appendix XX). The positive outcome from this rigorous audit process also confirms the robust nature of the data gathered.

11.3 Limitations of the study

This was a cross-sectional design study which aimed to look at the prevalence of CI in HF. I therefore do not have any serial measures of cognition which would allow me to have some assessment of the incidence of CI in HF and the rate of cognitive decline. To answer this question, prospective follow up of a cohort of HF patients free from CI at inception would be required. Few studies to date have utilised this study design.

Reports published in 2001 noted that the visuospatial/constructional and delayed memory indexes of RBANS tend to over classify deficits in healthy older adults.[217] Common to the assessment of these two domains is the figure copy sub-test of RBANS which involves participants copying a complex geometric drawing (shown in appendix XXI). At the end of the RBANS assessment the participant is then asked to draw the same shape from memory as an assessment of delayed memory. An examination of a subsample of these tests showed that strict adherence to the scoring criteria presented in the RBANS manual resulted in lower than expected raw scores in these two subtests (figure copy and figure copy recall).[217] Following suggestions from the RBANS developer the scoring criteria for figure copy and figure copy recall were then modified to reflect less stringent adherence to the manual's scoring criteria.[196] Examples of these modifications included: less exact measurements, emphasising the majority of correct elements and discouraging the use of a ruler for measuring. These minor modifications led to scores that more closely approximated that of the original standardisation sample.[167] Despite these modifications and clear scoring guidelines there does remain some subjectivity in the scoring of these two subtests of the RBANS.

In this study I aimed to control for AF by having patients with HF in both sinus rhythm and AF. I did not however include a cohort of patients with AF free from HF. Although patients in the HF in sinus rhythm cohort had no clinical history of AF and no previous objective documentation of AF, I did not routinely perform ambulatory cardiac monitoring to look for occult AF.

11.4 Future research relating to this study

Additional funding has been secured to allow continuation of this existing body of work. The first additional exploratory study is using neuroimaging to describe the pathophysiology of cognitive decline in HF. I aim to compare the ordinal and quantitative markers of cerebral small vessel disease across the individual study cohorts. Although this study shows that CI is prevalent in patients with HF the underlying mechanism of this association is poorly understood.

Through investigator initiated funding I have performed cerebral MRIs on patients with HF and AF (N=25) and healthy controls (N=16). Additional funding recently secured will now allow me to add neuroimaging of a third comparator group – HF with limited concomitant cardiovascular disease (non-ischaemic cardiomyopathy).

The neuropathological processes of interest have specific neuroimaging signatures, these are - stroke: focal flair lesions; small vessel disease: white matter disease and microbleeds; Alzheimer's disease: focal and hippocampal atrophy. Neuroimaging sequences include: T1, T2, FLAIR, DWI, SWI MRI spectroscopy [two regions of interest per hemisphere] and diffusion tractography. Assessments will use both ordinal assessments scales (Fazekas, Scheltens) and quantitative measures of regions/lesions of interest. The primary analyses will assess the relationship of differing neuroimaging findings to participant group, using Kruskal-Wallis testing to test ordinal and quantitative data for potential between group differences. Other potential differences between groups will be explored with univariate and multivariate models.

The second additional study relating to the work contained in this thesis aims to assess if cognitive screening measures can predict non-compliance with medication in HF. Stored urine samples for each study participant are being analysed for metabolites of commonly used HF medications (as a means of identifying whether these medications have been ingested by the patient). By identifying a subgroup of patients with HF and CI and linking this to poorer medication adherence I would highlight the need for better supportive strategies in the community (e.g. nursing and pharmacy assistance) to improve adherence and this may in turn help improve patient outcomes. This additional study will allow us to tie together the demographic, echocardiographic and neuropsychological data with the "real-life" clinical implications of CI in HF.

The third additional area of interest arising from this original study is regarding the potential relationship between plasma immune/inflammatory markers and CI. A major strength of this study is the extensive phenotyping of all enrolled participants allowing comparisons of the

clinical characteristics between groups. There is literature indicating a role for immune/inflammatory markers in CI and so I have stored stored EDTA and SST samples for each study participant to allow immunophenotyping of those patients who display CI versus those who do not.[216] One possible "real life" consequence of CI is non-compliance with medication. As a measure of medication adherence I am also performing urinalysis to look for metabolites of common HF medications and comparing any differences between those with CI and those without.

11.5 Conclusion

CI was common in this cohort of stable, community dwelling patients with chronic HF. Up to 80% of those patients with HF and AF showed some degree of mild CI on formal neuropsychological testing and this association persisted after adjustment for vascular comorbidities common to both conditions. Patients with both HF and AF have poorer cognition than those with HF only. Patients with cardiac disease (including HF or ischaemic heart disease with no HF) have poorer cognition than age and sex matched healthy adults. There is less difference in cognition between patients with HF versus those with proven coronary artery disease and no HF.

Appendix I

NHS Greater Glasgow and Clyde Health Board
Glasgow Royal Infirmary & Western Infirmary Glasgow
Cardiology Department

Enquiries to Dr Jane Cannon
Telephone: 0141 330 2237

Cognitive Impairment in Heart Failure

Patient Information Sheet

We would like to invite you to take part in a research study looking at the link between heart problems and difficulty with memory/thinking skills. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

Who is conducting the research?

The research is being carried out by Dr Jane Cannon, Professor John JV McMurray, Professor Matthew Walters and Dr Karen Hogg from the Department of Cardiology and Cardiovascular Research at the University of Glasgow.

What is the purpose of the study?

Heart failure is a debilitating condition which occurs when the heart muscle becomes damaged and its ability to pump blood around the body becomes reduced. There is evidence that this is linked to poorer thinking skills (cognitive impairment) in some people. Cognitive impairment usually presents as memory difficulties and these people appear to be at increased risk of dementia in later life. We aim to study patients with and without heart failure, and compare them with healthy volunteers, to see if the patients with heart failure show an increased risk of cognitive impairment compared to those without. If we identify that this is the case then we will investigate the possible causes behind this. Cognitive impairment in heart failure is an important predictor of disability, poor quality of life, increased hospital admissions and death. By highlighting groups of people who are more likely to be at risk of cognitive impairment, it may be possible to intervene and provide extra support to these types of patients and so improve their quality of life. This study does not involve taking any extra tablets or new medication.

Why have I been invited?

We are recruiting 5 groups of people:

- Group 1: Patients with heart failure caused by coronary artery disease
- Group 2: Patients with coronary artery disease but no signs of heart failure
- Group 3: Patients with heart failure ***not*** caused by coronary artery disease
- Group 4: Healthy control participants with no history of heart failure, coronary artery disease, or any other chronic inflammatory disease
- Group 5: Patients with heart failure of any cause and atrial fibrillation

You have been invited to consider taking part in this study as you fall into one of the groups described above.

Do I have to take part?

It is up to you to decide. We will describe the study and go through this information sheet, which we will then give to you. You will be asked to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving reason. This would not affect the standard of care you receive or your future treatment.

What does taking part involve?

If you are interested in taking part in the study a member of the research team will go through this information sheet with you and, if you decide to take part, you will be asked to sign a consent form in the presence of the research doctor. There are two stages to this study, and you will only be asked to participate in stage 2 providing the results of the blood tests (taken in stage 1) are satisfactory.

Stage 1

The first part of this study will last approximately 30 minutes and will be held at the Clinical Research Unit at the British Heart Foundation Glasgow Cardiovascular Research Centre (GCRC) which is located at the Western Infirmary. This meeting will involve the following:

- Medical History and Examination: Speaking to a doctor about any symptoms/previous illnesses. You will be examined for any signs of heart failure.
- We will seek your permission to view your medical notes. Any information gathered is only available to the doctors running the study.
- A blood sample: 20mls of blood (four teaspoons) will be taken to check for any signs of infection/inflammation, thyroid function, kidney function, liver function, glucose, vitamin B12, folate and a special blood test to check for any signs of heart failure (BNP). Having blood taken can be uncomfortable and some people may feel faint. There is a small risk of bleeding or bruising at the puncture site following the blood

being taken. This blood sample will be taken in exactly the same way as other blood samples you would have had taken before.

- Electrocardiograph: This is a commonly used, noninvasive procedure for recording electrical changes in the heart. The record, which is called an electrocardiogram (ECG), shows the series of waves that relate to the electrical impulses which occur during each beat of the heart. The results are printed on paper. You will be asked to disrobe from the waist up, and electrodes (tiny wires in adhesive pads) are applied to specific sites on the arms, legs, and chest. It takes approximately 10 minutes and no complications have been observed from this procedure.

If the results of these tests meet the criteria required for inclusion in the study, a further appointment to take part in the second stage of the study will then be arranged with you (see stage 2 below).

If any of the results of these tests exclude you from taking part in the second stage of the study then we would like to thank you for taking the time to read about and take part in this study.

Stage 2

If you remain agreeable to participating in the study, you will be asked to attend a further visit lasting up to 60 minutes. This will be to the British Heart Foundation Glasgow Cardiovascular Research Centre (GCRC) which is located at the Western Infirmary.

The visit will involve:

- Hospital Anxiety and Depression Scale: This is a brief 14 question self rating scale which can detect the presence and severity of mild degrees of mood disorder, anxiety and depression.
- Geriatric Depression Scale: This is a 15 point questionnaire comprising of yes/no answers which is used as a screening test for depression. It is quick and easy to complete.
- Kansas City Cardiomyopathy Questionnaire: This questionnaire will be completed only by patients with heart failure. This aims to show the ways that heart failure and its treatments can affect key physical, emotional, social and mental dimensions of a persons' life.
- Neuropsychological Testing: These are scoring tests/questionnaires which allow us to assess short and long term memory, language, attention and IQ among other aspects of cognition.

A taxi to and from these appointments will be provided free of charge if needed.

We may also decide to look in the near future at the cause of Cognitive Impairment using Magnetic Resonance Imaging (MRI) of your heart and head, and ask for your permission to contact you to invite you to take part in this.

What happens to the information?

Your identity and personal information will be completely confidential and known only to the researcher. The information obtained will remain confidential. The data is held in accordance with the Data Protection Act, which means that we keep it safely and cannot reveal it to other people, without your permission.

What are the possible benefits of taking part?

It is hoped that by taking part in this research, you will be providing valuable information regarding the link between these two common medical conditions (heart failure and cognitive impairment). Heart failure is one of the leading causes of hospital admissions and death in Western countries. Due to the aging population the number of cases of heart failure is set to rise. We aim to identify if there is a link between heart failure and cognitive impairment which may make these individuals at increased risk of dementia in later life. If we identify a link then we will investigate the reasons behind this and so allow for early detection and intervention in the future. The aim is to improve the treatment of these patients by improving our understanding of the conditions and the link between the two. We will keep the blood samples for future ethically approved research, or in case future tests become available to perform which would help with our research topic.

If the research doctor discovers during the study that you have another medical condition of which you were previously unaware, you will be referred to the appropriate doctor for the treatment of this condition.

Who has reviewed the study?

This study has been reviewed by one of the committees of the West of Scotland Research Service (WoSRES).

If you have any further questions?

We will give you a copy of the information sheet and signed consent form to keep. If you would like more information about the study and wish to speak to someone **not** closely linked to the study, please contact Professor Scott Muir.

Professor Scott Muir
Consultant Physician & Clinical Director ECMS West Glasgow
Western Infirmary
Glasgow
G11 6NT

Telephone: 0141 211 2575.

Email: Scott.Muir@glasgow.ac.uk

If you have a complaint about any aspect of the study?

If you are unhappy about any aspect of the study and wish to make a complaint, please contact the researcher in the first instance but the normal NHS complaint mechanisms is also available to you.

Thank-you for your time and co-operation

Appendix II

Department of Cardiovascular Research
British Heart Foundation
Glasgow Cardiovascular Research Centre
106 University Place
Glasgow
G12 8TA

Enquiries to Dr Jane Cannon
Telephone: 0141 330 2237

Cognitive Impairment in Heart Failure

Participant Information Sheet

We would like to invite you to take part in a research study looking at the link between heart problems and difficulty with memory/thinking skills. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

Who is conducting the research?

The research is being carried out by Dr Jane Cannon, Professor John JV McMurray, Professor Matthew Walters and Dr Karen Hogg from the Department of Cardiology and Cardiovascular Research at the University of Glasgow.

What is the purpose of the study?

Heart failure is a debilitating condition which occurs when the heart muscle becomes damaged and its ability to pump blood around the body becomes reduced. There is evidence that this is linked to poorer thinking skills (cognitive impairment) in some people. Cognitive impairment usually presents as memory difficulties and these people appear to be at increased risk of dementia in later life. We aim to study patients with and without heart failure, and compare them with healthy volunteers, to see if the patients with heart failure show an increased risk of cognitive impairment compared to those without. If we identify that this is the case then we will investigate the possible causes behind this. Cognitive impairment in heart failure is an important predictor of disability, poorer quality of life, increased hospital admissions and death. By highlighting groups of people who are more likely to be at risk of cognitive impairment, it may be possible to intervene and provide extra support to these patients and so improve their quality of life. This study does not involve taking any extra tablets or new medication.

Why have I been invited?

We are recruiting 5 groups of people:

- Group 1: Patients with heart failure caused by coronary artery disease
- Group 2: Patients with coronary artery disease but no signs of heart failure
- Group 3: Patients with heart failure ***not*** caused by coronary artery disease
- Group 4: Healthy control participants with no history of heart failure, coronary Artery disease, or any other chronic inflammatory disease
- Group 5: Patients with heart failure of any cause and atrial fibrillation

You have been invited to consider taking part in this study as you fall into group 4.

Do I have to take part?

It is up to you to decide. We will describe the study and go through this information sheet, which we will then give to you. You will be asked to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving reason.

What does taking part involve?

If you are interested in taking part in the study, a member of the research team will go through this information sheet with you and, if you decide to take part, you will be asked to sign a consent form in the presence of the research doctor. There are two stages to this study, and you will only be asked to participate in stage 2 providing the results of blood tests (taken in stage 1) are satisfactory.

Stage 1

The first part of this study will last approximately 30 minutes and will be held at the Clinical Research Unit at the British Heart Foundation Glasgow Cardiovascular Research Centre (GCRC) which is located at the Western Infirmary Glasgow. This meeting will involve the following:

- Medical History and Examination: Speaking to a doctor about any symptoms/previous illnesses. You will be examined for any signs of heart failure.
- We will seek your permission to view your medical notes. Any information gathered is only available to the doctors running the study.
- A blood Sample: 20mls of blood (four teaspoons) will be taken to check for signs of infection/inflammation, thyroid function, kidney function, liver function, glucose, vitamin B12, folate and a special blood test to check for any signs of heart failure (BNP). Having blood taken can be uncomfortable and some people may feel faint. There is a small risk of bleeding or bruising at the puncture site following the blood being taken.
- Electrocardiograph: This is a commonly used, noninvasive procedure for recording electrical changes in the heart. The record, which is called an electrocardiogram (ECG), shows the series of waves that relate to the electrical impulses which occur

during each beat of the heart. The results are printed on paper. You will be asked to disrobe from the waist up, and electrodes (tiny wires in adhesive pads) are applied to specific sites on the arms, legs, and chest. It takes approximately 10 minutes and no complications have been observed from this procedure.

If the results of these tests meet the criteria required for inclusion in the study, a further appointment to take part in the second stage of the study will then be arranged with you (see stage 2 below).
If any of the results exclude you from taking part in the second stage of the study, then we would like to thank you for taking the time to read about and take part in this study.

Stage 2

If you remain agreeable to participating in the study you will be asked to attend a further visit lasting 60 minutes. This will be to the Clinical Research Unit at the British Heart Foundation Glasgow Cardiovascular Research Centre (GCRC) which is located at the Western Infirmary Glasgow. The visit will involve:

- Hospital Anxiety and Depression Scale: This is a brief 14 question self rating scale which can detect the presence and severity of mild degrees of mood disorder, anxiety and depression.
- Geriatric Depression Scale: This is a 15 point questionnaire comprising of yes/no answers which is used as a screening test for depression. It is quick and easy to complete.
- Neuropsychological Testing: These are scoring tests/questionnaires which allow us to assess short and long term memory, language, attention and IQ among other aspects of cognition. These may be similar to previous cognitive assessments carried out through Generation Scotland.

A taxi to and from these appointments will be provided free of charge if needed.

We may also decide to look in the near future at the cause of cognitive impairment using Magnetic Resonance Imaging (MRI) of your heart and head, and ask for your permission to contact you to invite you to take part in this.

What happens to the information?

Your identity and personal information will be completely confidential and known only to the researcher. The information obtained will remain confidential. The data is held in accordance with the Data Protection Act, which means that we keep it safely and cannot reveal it to other people, without your permission. This study data can be linked to the Generation Scotland Data anonymously for future research proposals. All potential proposals will be reviewed by the existing Generation Scotland Access Committee.

What are the possible benefits of taking part?

It is hoped that by taking part in this research, you will be providing valuable information regarding the link between these two common medical conditions (heart failure and cognitive impairment). Heart failure is one of the leading causes of hospital admissions and death in Western countries. Due to the aging population the number of cases of heart failure is set to rise. We aim to identify if there is a link between heart failure and cognitive impairment which may make these individuals at increased risk of dementia in later life. If we identify a link then we will investigate the reasons behind this and so allow for early detection and intervention in the future. The aim is to improve the treatment of these patients by improving our understanding of the conditions and the link between the two. We will keep the blood samples for future ethically approved research, or in case future tests become available to perform which would help with our research topic. If the research doctor discovers during the study that you have a medical condition of which you were previously unaware, you will be referred to the appropriate doctor for the treatment of this condition.

Who has reviewed the study?

This study has been reviewed by one of the committees of the West of Scotland Research Service (WoSRES).

If you have any further questions?

We will give you a copy of the information sheet and signed consent form to keep. If you would like more information about the study and wish to speak to someone **not** closely linked to the study, please contact Professor Scott Muir.

Professor Scott Muir
Consultant Physician & Clinical Director ECMS West Glasgow
Western Infirmary
Glasgow
G11 6NT
Telephone: 0141 211 2575.
Email: Scott.Muir@glasgow.ac.uk

If you have a complaint about any aspect of the study?

If you are unhappy about any aspect of the study and wish to make a complaint, please contact the researcher in the first instance but the normal NHS complaint mechanisms is also available to you.

Thank-you for your time and co-operation

Appendix III

Cognitive Impairment in Heart Failure

British Heart Foundation Cardiovascular Research Centre
126 University Place
University of Glasgow
Glasgow
G12 8TA

Dear .....

Thank you for agreeing to take part in this Heart Failure Study.
An appointment has been made for you at the BHF Glasgow Cardiovascular Research Centre on:

..... at .....

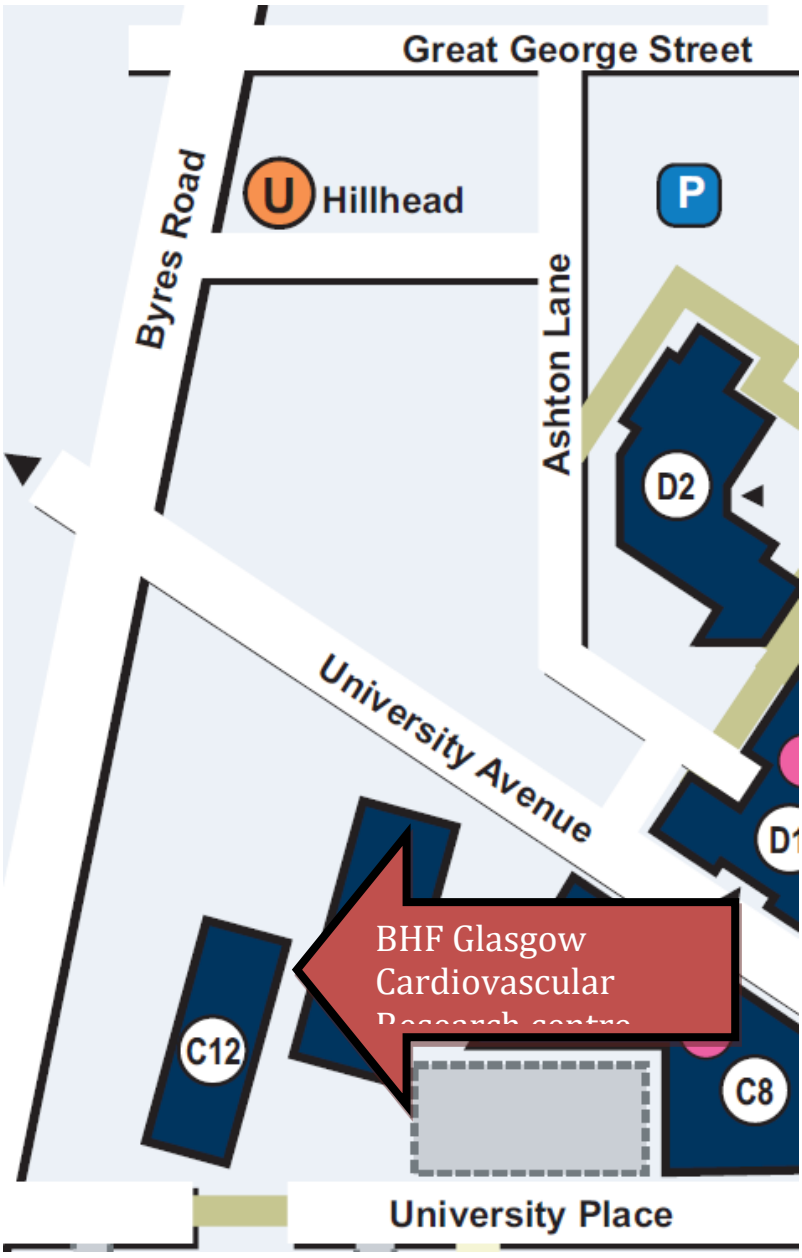
Transport will / will not be organised by us. If you are arriving with your own transport please see the map for directions.

When you arrive please report to the reception and someone will take you through to the clinic area. The visit should last no more than 45 minutes.

Please bring your medicines with you.

Kind regards,
Dr Jane Cannon

For appointment queries or to change the date or time, please contact a member of the research team on 0141 330 2237


Great George Street
Byres Road
U
Hillhead
P
Ashton Lane
D2
University Avenue
D1
BHF Glasgow
Cardiovascular
C12
C8
University Place

British Heart Foundation Cardiovascular Research Centre
126 University Place
University of Glasgow
Glasgow
G12 8TA

Appendix IV

Department of Cardiovascular Research
British Heart Foundation
Glasgow Cardiovascular Research Centre
106 University Place
Glasgow
G12 8TA

Cognitive Impairment in Heart Failure Consent Form **Please inital boxes**

I confirm that I have read and understand the information sheet dated 21/01/2013 for the above study and have had the opportunity to ask questions ☐

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

I understand that sections of my medical notes may be looked at by the research team where it is relevant to my taking part in the research. I give my permission for the research team to have access to my records. ☐

I agree to my details being entered into the database at Information Services Division of NHS Scotland for use during this study and future ethically approved research. ☐

I agree to take part in the above study ☐

	YES	NO
I agree to be contacted within the next 12 months regarding taking part in further research related to this study.	☐	☐

| --- | --- | --- |
| Name of Patient | Date | Signature |

| --- | --- | --- |
| Name of Researcher | Date | Signature |

1 copy to the patient, 1 copy to the researcher, 1 original for the patients' notes

Appendix V

Department of Cardiovascular Research
British Heart Foundation
Glasgow Cardiovascular Research Centre
106 University Place
Glasgow
G12 8TA

Cognitive Impairment in Heart Failure Consent Form

Please initial boxes

I confirm that I have read and understand the information sheet dated 21/01/2013 for the above study and have had the opportunity to ask questions	☐
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
I understand that sections of my medical notes may be looked at by the research team where it is relevant to my taking part in the research. I give my permission for the research team to have access to my records.	☐
I agree to anonymous linkage of this data to the data already held by Generation Scotland	☐
I agree to take part in the above study	☐

	YES	NO
I agree to be contacted within the next 12 months regarding taking part in further research related to this study.	☐	☐

| --- | --- | --- |
| Name of Participant | Date | Signature |

| --- | --- | --- |
| Name of Researcher | Date | Signature |

1 copy to the participant, 1 copy to the researcher, 1 original for the patients' notes

Appendix VI

Cognitive Impairment in HF Study — **Patient Identification and Contact Information**

Version 1.1 (14 Oct 2013)

Patient ID. ___-___ (01) Initials ___ (02) Date of Completion D D M M Y Y Y Y (03)

* ***PLEASE FILE - do NOT send to Data Centre*** *

1. Gender Male ☐1 Female ☐2 (04)
2. Patient's base hospital: WIG ☐1 GRI ☐2 Other ☐3 (05)
   If Other, specify _____ (06)
3. Site of screening visit1: WIG ☐1 GRI ☐2 BHF ☐34 (07)
4. Date of Recruitment D D M M Y Y Y Y (08)
5. Surname _____ (09)
6. Forename(s) _____ (10)
7. Hospital Number (11)
8. CHI Number (12)
9. Date of Birth D D M M Y Y Y Y (13)
10. Address _____ (14)
    Postcode _____ (15)
11. Home phone Number (16)
12. Mobile phone Number (17)
13. Work phone Number (18)
14. Holiday home phone No. (19)
15. Next of kin (or friend /carer) _____ (20)
16. Relationship _____ (21)
17. Next of kin phone number (22)
18. Next of kin address _____ (23)
    Postcode _____ (24)

19. GP Name _____ (25)
20. GP Address _____ (26)
    Postcode _____ (27)
21. GP phone number (28)

Checklist

Old casenotes OR clinical letters reviewed ☐ (29)
Letter to GP sent ☐ (30)
Date of Study Visit issued to patient ☐ (31)
Follow up site ☐GRI ☐WIG ☐BHF (32)

Other useful info

1. Recruitment Site
   ☐ Cardiology OPC
   ☐ Cardiac Rehab OPC
   ☐ SFHS
   ☐ HFLS
   ☐ Other (33)
   If Other, specify _____ (34)

Produced by Robertson Centre for Biostatistics, University of Glasgow

Cognitive Impairment in HF Study

Screening Visit, Page 1
Inclusion Criteria

Version 1.1 (14 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

Group 1

	Yes	No
1. Chronic Heart Failure	1	2 04
2. Ejection fraction ≤45%	1	2 05
3. Known coronary artery disease (Previous MI or CAD on cor angio)	1	2 06
If Yes, for CAD then....		
a. Previous MI	1	2 07
b. Coronary Artery Disease on coronary angiography (≥50% stenosis in ≥ 1 vessel)	1	2 08

Group 2

	Yes	No
1. Chronic Heart Failure	1	2 09
2. Ejection fraction ≤45%	1	2 10
3. Absence of coronary artery disease:	1	2 11
If Yes, then....		
a. Excluded on invasive coronary angiography	1	2 12
b. Excluded on stress echo	1	2 13
c. Excluded SPECT/PET	1	2 14
d. Excluded on CMRI	1	2 15
e. Excluded on CT coronary angiography	1	2 16
4. Absence of history of MI		2 17

Group 3

	Yes	No
1. Known coronary artery disease	1	2 18
If Yes, to known CAD then....		
a) Previous MI	1	2 19
b) Coronary Artery Disease on coronary angiography (>50% stenosis in ≥ 1 vessel)	1	2 20
2. Absence of clinical heart failure	1	2 21
3. Ejection fraction >55%	1	2 22

Group 4

	Yes	No
1. Absence of coronary artery disease	1	2 23
2. Absence of clinical heart failure	1	2 24
3. Ejection fraction >55%	1	2 25
4. Absence of chronic disease	1	2 26
5. No regular medication	1	2 27

Group 5

	Yes	No
1. Chronic Heart Failure (of any aetiology)	1	2 28
2. Ejection fraction ≤45%	1	2 29
3. Atrial Fibrilation		2 30

PATIENTS MUST FULFIL ALL CRITERIA IN ONE GROUP TO CONTINUE

Produced by Robertson Centre for Biostatistics, University of Glasgow

Cognitive Impairment in HF Study

Screening Visit, Page 2
Exclusion Criteria

Version 1.1 (14 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

Group 1, 2 ,3 and 4

	Yes	No
1. Hospital admission within past 3 months	1	2 04
2. History of alcohol excess (i.e. >21units/week for men and >14 units/week for females)	1	2 05
3. History of stroke	1	2 06
4. Previous cardiac arrest	1	2 07
5. Significant hearing/visual impairment or language barrier preventing completion of study assessments	1	2 08
6. AF on 12 lead ECG or a history of paroxysmal AF	1	2 09
7. Participants younger than 60 years of age	1	2 10
8. Depression as defined by HADS Score >10 or clinically evident depression/anxiety	1	2 11
9. Known neurodegenerative disease including known dementia	1	2 12
10. Inability to provide informed consent	1	2 13

Group 5

	Yes	No
1. Hospital admission within past 3 months	1	2 14
2. History of alcohol excess (i.e. >21units/week for men and >14 units/week for females)	1	2 15
3. History of stroke	1	2 16
4. Previous cardiac arrest	1	2 17
5. Significant hearing/visual impairment or language barrier preventing completion of study assessments	1	2 18
6. Participants younger than 60 years of age	1	2 19
7. Depression as defined by HADS Score >10 or clinically evident depression/anxiety	1	2 20
8. Known neurodegenerative disease including known dementia	1	2 21
9. Inability to provide informed consent	1	2 22

PATIENTS MUST FULFIL ALL CRITERIA IN ONE GROUP TO CONTINUE

Cognitive Impairment in HF Study

Screening Visit, Page 3
Demographics and Heart Failure Symtoms

Version 1.1 (14 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

A. DEMOGRAPHICS

1. Date of Birth D D M M Y Y Y Y 04

2. Gender Male 1 Female 2 05

3. Race

- White 1
- Black 2 (Caribean / African)
- South Asian 3 (India, Pakistan, Sri Lanka, Nepal, Bangladesh, Maldives)
- Arab/Middle East 4 (Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Palestinian territories, Oman, Qatar, Saudi Arabia, Sudan, Syrian Arab Republic, United Arab Emirates and Yemen)
- Oriental 5 (Japanese, Chinese)
- Malay 6 (Malaysia, Philippines, Indonesia)
- Other 7 06

If Other, specify _____ 07

4. Education Years
   School Years ___ 08
   Higher Education Years ___ 09

5. Date of Recruitment D D M M Y Y Y Y 10

6. Date of last Admission D D M M Y Y Y Y 11

B. SCREENING CHECK

	Yes	No
1. Has screening sheet been completed?	1	2 12
2. Has patient fulfilled all inclusion/exclusion criteria and is eligible to take part in the study?	1	2 13
3. Has Patient signed informed consent?	1	2 14

Answers must all be YES for inclusion in study.

C. HEART FAILURE SYMPTOM STATUS

1. NYHA I 1 II 2 III 3 IV 4 15

I = No limitation of daily activities
II = mild limitation of activity
III = marked limitation of activity
IV = symptoms at rest

	Yes	No
2. Orthopnea	1	2 16
3. Paroxysmal Nocturnal Dyspnoea	1	2 17
4. Ankle swelling	1	2 18
5. Wheeze	1	2 19
6. Palpitations	1	2 20

D. CHF

	Yes	No
1. Diagnosed Chronic Heart Failure	1	21
If Yes, diagnosis over 2 years ago	1	2 22

If Yes, which healthcare professionals are involved:

	Yes	No
a. GP only	1	2 23
b. General physician	1	2 24
c. Cardiologist	1	2 25
d. HF specialist	1	2 26
e. HF liaison nurse	1	2 27
If Yes, previous admission with decompensated heart failure	1	2 28

Cognitive Impairment in HF Study

Screening Visit, Page 4
Aetiology of Heart Failure

Version 1.1 (14 Oct 2013)

Patient ID. ☐☐ - ☐☐☐☐☐☐ 01 Initials ☐☐☐ 02 Date of Completion D D M M Y Y Y Y 03

A. Primary Aetiology

1. Ischaemic — Yes ☐1 No ☐2 Unknown ☐3 04

If Yes, must have:

a. Definite previous MI ☐1

OR

b. Angio. CHD (>50% stenosis in ≥1 vessel) ☐2 05

If No (and all other causes excluded)

a. Idiopathic DCM ☐1

b. Hypertension ☐2

c. Alcohol Cardiomyopathy ☐3

d. Valvular ☐4

e. Other ☐5 06

If other, specify _____ 07

2. Unknown Aetiology — Yes ☐1 No ☐2 08

B. Contributing Aetiologies

1. Valvular Heart Disease — Yes ☐1 No ☐2 09

If Yes,

a. AS ☐ 10

b. AR ☐ 11

c. MS ☐ 12

d. MR ☐ 13

e. TR ☐ 14

	Yes	No	
2. Diabetes Mellitus	☐1	☐2	15
3. Atrial Fibrillation	☐1	☐2	16
4. Hypertension	☐1	☐2	17
5. Alcohol Cardiomyopathy	☐1	☐2	18
6. Other	☐1	☐2	19

If Other, specify _____ 20

C. Previous EHO

1. Previous Echo — Yes ☐1 No ☐2 21

If Yes,

a. Date of most recent D D M M Y Y Y Y 22

2. Analysis of Echo

a. LVEDD ☐☐.☐ cm 23

	Yes	No	
b. Dilated LV	☐1	☐2	24
c. LVH	☐1	☐2	25
d. Left Ventricular Systolic Dysfunction	☐1	☐2	26

If Yes,

Mild ☐1 Mild-Mod ☐2 Moderate ☐3 Mod-Severe ☐4 Severe ☐5 27

e. Valvular heart disease ☐1 ☐2 28

If Yes,

	Mild	Mild-Mod	Moderate	Mod-Severe	Severe	
a. AS	severity...: ☐1	☐2	☐3	☐4	☐5	29
b. AR	severity...: ☐1	☐2	☐3	☐4	☐5	30
c. MS	severity...: ☐1	☐2	☐3	☐4	☐5	31
d. MR	severity...: ☐1	☐2	☐3	☐4	☐5	32
e. TR	severity...: ☐1	☐2	☐3	☐4	☐5	33
f. Other	severity...: ☐1	☐2	☐3	☐4	☐5	34

specify _____ 35

g. LVEF (Simpson's)

a. Preserved (> 55%) ☐1

b. Reduced (≤ 45%) ☐2 → Value ☐☐ % 37

c. Borderline (46%-55%) ☐3

d. LVEF incalculable ☐4 36

If incalculable,

- Estimated preserved ☐1
- Estimated reduced ☐2 38

h. Other Relevant echo findings

_____

_____

_____

_____ 39

Produced by Robertson Centre for Biostatistics, University of Glasgow

Cognitive Impairment in HF Study

Screening Visit, Page 5
Medical History

Version 1.1 (14 Oct 2013)

Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊_____⌋ 02 Date of Completion ⌊D D M M Y Y Y Y⌋ 03

A. MEDICAL HISTORY

1. Myocardial Infarction — Yes 1 / No 2 (04)
2. History of Angina — Yes 1 / No 2 (05)
   - **If Yes**, current — Yes 1 / No 2 (06)
     - **If Current**, stable — Yes 1 / No 2 (07)
3. Coronary Angiography — Yes 1 / No 2 (08)
   - **If Yes,**
     - Year ⌊Y Y Y Y⌋ 09
     - **Result**
       - Normal (10)
       - Plaque only (11)
       - Significant CHD (>50% Stenosis in ≥ 1 vessel) (12) → No. of vessels involved ⌊__⌋ 13
       - Unknown (14)
4. Percutaneous Coronary Intervention (PCI) — Yes 1 / No 2 (15)
5. Coronary Artery Bypass Graft (CABG) — Yes 1 / No 2 (16)
6. Treated Hypertension — Yes 1 / No 2 (17)
7. Hypercholesterolaemia — Yes 1 / No 2 (18)
8. Cerebrovascular disease (CVA/TIA) — Yes 1 / No 2 (19)
9. Atrial Fibrillation/Flutter — Yes 1 / No 2 (20)
   - **If Yes,**
     - a. past (1)
     - b. paroxysmal (2)
     - c. persistent (potential restoration SR) (3)
     - d. permanent (4)
     - (21)
10. Valvular Heart Disease — Yes 1 / No 2 (22)
    - **If Yes,**
      - a. AS (23)
      - b. AR (24)
      - c. MS (25)
      - d. MR (26)
      - e. TR (27)
11. Rheumatic Valvular Heart Disease — Yes 1 / No 2 (28)
12. History of Rheumatic Fever — Yes 1 / No 2 (29)
13. Valve replacement — Yes 1 / No 2 (30)
14. Pacemaker — Yes 1 / No 2 (31)
    - **If Yes,**
      - a. Conventional (1)
      - b. CRT-P (2)
      - c. CRT-D (3)
      - (32)
15. Primary Prevention ICD — Yes 1 / No 2 (33)
16. Syncope (brief loss of consciousness) — Yes 1 / No 2 (34)
    - **If Yes,** how many episodes ⌊__⌋ 35
17. Prior arrythmia — Yes 1 / No 2 (36)
    - **If Yes,**
      - a. SVT (37)
      - b. Ventricular tachycardia (38)
        - 1. Sustained (39)
        - 2. Nonsustained (40)
      - c. SSS (41)
      - d. AV block (42)
        - 1. 1st degree (1)
        - 2. 2nd degree (2)
        - 3. 3rd degree (3)
        - (43)

Group 5 Only

18. CHADS2VASC Score ⌊__⌋ 44

Cognitive Impairment in HF Study

Screening Visit, Page 6
Medical History continued...

Version 1.1 (14 Oct 2013)

Patient ID. ☐☐ - ☐☐☐☐☐☐ 01 Initials ☐☐☐ 02 Date of Completion ☐☐ ☐☐ ☐☐ ☐☐ ☐☐☐☐ 03
(D D M M Y Y Y Y)

19. Diabetes Mellitus — Yes ☐1 No ☐2 04
If Yes,
a. Diet Controlled ☐1
b. Oral Hypoglycaemic ☐2
c. Insulin ☐3 05

20. Involuntary weight loss (>5% in 6 months) — Yes ☐1 No ☐2 06

21. Depression — Yes ☐1 No ☐2 07
If Yes, Current — Yes ☐1 No ☐2 08

22. Cancer — Yes ☐1 No ☐2 09
If Yes,
a. Current ☐1 b. Previous ☐2 10
Site _____ 11

23. COPD — Yes ☐1 No ☐2 12

24. Peripheral Vascular Disease — Yes ☐1 No ☐2 13

25. Asthma — Yes ☐1 No ☐2 14

26. Neuropathy — Yes ☐1 No ☐2 15

27. Hypothyroidism — Yes ☐1 No ☐2 16

28. Hyperthyroidism — Yes ☐1 No ☐2 17

29. Rheumatoid Arthritis — Yes ☐1 No ☐2 18

30. Connective tissue disease — Yes ☐1 No ☐2 19

31. Osteoarthritis — Yes ☐1 No ☐2 20

32. Anaemia — Yes ☐1 No ☐2 21

33. Urinary incontinence — Yes ☐1 No ☐2 22

34. Smoker — Yes ☐1 No ☐2 23
If Yes,
a. Current ☐1
b. Ex (<12 months) ☐2
c. Ex (≥12 months) ☐3 24

35. Alcohol — Yes ☐1 No ☐2 25
If Yes, (Excess: Male > 21units/wk Female > 14 units/wk)
a. Excess ☐1
b. Previous Excess ☐2
c. Within recommended limits ☐3 26

36. Family history heart disease — Yes ☐1 No ☐2 27
If Yes,
a. Coronary heart disease — Yes ☐1 No ☐2 28
b. Cardiomyopathy — Yes ☐1 No ☐2 29
c. Unknown — Yes ☐1 No ☐2 30
d. Other — Yes ☐1 No ☐2 31
(specify) _____ 32

37. Social History
a. Lives Alone — Yes ☐1 No ☐2 33
If No,
i. Lives with carer — Yes ☐1 No ☐2 34
ii. Lives with relative — Yes ☐1 No ☐2 35
iii. Lives with friend — Yes ☐1 No ☐2 36
iv. Other — Yes ☐1 No ☐2 37
(specify) _____ 38

b. Employed Carers — Yes ☐1 No ☐2 39
If Yes, number of times per day ☐☐ 40

c. Independent with Activities of Daily Living — Yes ☐1 No ☐2 41

38. Any other significant medical history — Yes ☐1 No ☐2 42
If Yes, specify
1. _____ 43
2. _____ 44
3. _____ 45
4. _____ 46
5. _____ 47
6. _____ 48
7. _____ 49
8. _____ 50

Produced by Robertson Centre for Biostatistics, University of Glasgow

Cognitive Impairment in HF Study

Screening Visit, Page 7
Medications

Version 1.1 (14 Oct 2013)

Patient ID. ___ - ___ (01) Initials ___ (02) Date of Completion D D M M Y Y Y Y (03)

A. CARDIOVASCULAR MEDICATION

1. ACE-Inhibitor — Yes (1) No (2) (04)

(i) **If Yes**, specify type and dose

	Yes	No		
a. Captopril	1	2 (05)	(06)	mg
b. Enalapril	1	2 (07)	(08)	mg
c. Fosinopril	1	2 (09)	(10)	mg
d. Lisinopril	1	2 (11)	(12)	mg
e. Perindopril	1	2 (13)	(14)	mg
f. Quinapril	1	2 (15)	(16)	mg
g. Ramipril	1	2 (17)	(18)	mg
h. Trandolapril	1	2 (19)	(20)	mg
i. Other	1	2 (21)		
Specify (22)			(23)	mg

	Yes	No
(ii) Previous intolerance	1	2 (24)
(iii) Intolerant of higher dose than current	1	2 (25)
(iv) Patient on optimal dose	1	2 (26)
(v) If No, Patient on optimal tolerated dose	1	2 (27)

2. Hydralazine — Yes (1) No (2) (28)

If Yes, specify dose (29) mg

	Yes	No
(ii) Previous intolerance	1	2 (30)
(iii) Intolerant of higher dose than current	1	2 (31)
(iv) Patient on optimal dose	1	2 (32)
(v) If No, Patient on optimal tolerated dose	1	2 (33)

3. Beta-blocker — Yes (1) No (2) (34)

(i) **If Yes**, specify type and dose

	Yes	No		
a. Atenolol	1	2 (35)		mg
b. Bisoprolol	1	2 (36)		mg
c. Carvedilol	1	2 (37)		mg
d. Metoprolol	1	2 (38)		mg
e. Nebivolol	1	2 (39)		mg
f. Propanolol	1	2 (40)		mg
g. Other	1	2 (41)		
Specify (42)			(43)	mg

	Yes	No
(ii) Previous intolerance	1	2 (44)
(iii) Intolerant of higher dose than current	1	2 (45)
(iv) Patient on optimal dose	1	2 (46)
(v) If No, Patient on optimal tolerated dose	1	2 (47)

4. Aldosterone Blocker — Yes (1) No (2) (48)

(i) **If Yes**, specify type and dose

	Yes	No		
a. Spironolactone	1	2 (49)	(50)	mg
b. Eplerenone	1	2 (51)	(52)	mg

	Yes	No
(ii) Previous intolerance	1	2 (53)
(iii) Intolerant of higher dose than current	1	2 (54)
(iv) Patient on optimal dose	1	2 (55)
(v) If No, Patient on optimal tolerated dose	1	2 (56)

Cognitive Impairment in HF Study

Screening Visit, Page 8
Medications continued...

Version 1.1 (14 Oct 2013)

Patient ID. ☐☐-☐☐☐ 01 Initials ☐☐ 02 Date of Completion ☐☐/☐☐/☐☐☐☐ (D D M M Y Y Y Y) 03

5. ARB — Yes ☐1 No ☐2 04

(i) **If Yes**, specify type and dose

	Yes	No		
a. Candesartan	☐1	☐2 05	____ 06	mg
b. Irbesartan	☐1	☐2 07	____ 08	mg
c. Losartan	☐1	☐2 09	____ 10	mg
d. Olmesartan	☐1	☐2 11	____ 12	mg
e. Telmisartan	☐1	☐2 13	____ 14	mg
f. Valsartan	☐1	☐2 15	____ 16	mg
g. Other	☐1	☐2 17		

Specify ____ 18 ____ 19 mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 20
(iii) Intolerant of higher dose than current	☐1	☐2 21
(iv) Patient on optimal dose	☐1	☐2 22
(v) If No, Patient on optimal tolerated dose	☐1	☐2 23

6. Ivabradine — Yes ☐1 No ☐2 24

If Yes, specify dose ____ 25 mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 26
(iii) Intolerant of higher dose than current	☐1	☐2 27
(iv) Patient on optimal dose	☐1	☐2 28
(v) If No, Patient on optimal tolerated dose	☐1	☐2 29

7. Anti-arrhythmic — Yes ☐1 No ☐2 30

If Yes, specify type

	Yes	No
a. Amiodarone	☐1	☐2 31
b. Other	☐1	☐2 32

Specify ____ 33

8. Calcium channel-blocker — Yes ☐1 No ☐2 34

If Yes, specify type

	Yes	No
a. Amlodipine	☐1	☐2 35
b. Diltiazem	☐1	☐2 36
c. Felodipine	☐1	☐2 37
d. Nifedipine	☐1	☐2 38
e. Verapamil	☐1	☐2 39
f. Other	☐1	☐2 40

Specify ____ 41

9. Long-acting nitrates (not s/c or short acting GTN) — Yes ☐1 No ☐2 42

If Yes, specify type

	Yes	No
a. ISDN	☐1	☐2 43
b. ISMN	☐1	☐2 44
c. GTN patch	☐1	☐2 45
d. Other	☐1	☐2 46

Specify ____ 47

10. Statin — Yes ☐1 No ☐2 48

If Yes, specify type

	Yes	No
a. Atorvastatin	☐1	☐2 49
b. Pravastatin	☐1	☐2 50
c. Rosuvastatin	☐1	☐2 51
d. Simvastatin	☐1	☐2 52
e. Other	☐1	☐2 53

Specify ____ 54

11. Other lipid-lowering drug — Yes ☐1 No ☐2 55

Cognitive Impairment in HF Study

Screening Visit, Page 9
Medications continued...

Version 1.1 (14 Oct 2013)

Patient ID. ☐☐ - ☐☐☐☐ 01 Initials ☐☐☐ 02 Date of Completion ☐☐☐☐☐☐☐☐ D D M M Y Y Y Y 03

12. Diabetic Meds — Yes ☐1 No ☐2 04

If Yes, specify type

	Yes	No	
a. Insulin	☐1	☐2	05
b. Sulphonylurea (eg gliclazide)	☐1	☐2	06
c. Biguanide (eg metformin)	☐1	☐2	07
d. Glitazone	☐1	☐2	08
e. Other	☐1	☐2	09

Specify _____ 10

13. Diuretics — Yes ☐1 No ☐2 11

If Yes, specify type and dose where relevant

	Yes	No		
a. Furosemide	☐1	☐2	12	_____ 13 mg
b. Other loop	☐1	☐2	14	
c. Spironolactone	☐1	☐2	15	
d. Other K+ sparing	☐1	☐2	16	
e. Thiazide	☐1	☐2	17	
f. Bumetanide	☐1	☐2	18	_____ 19 mg
g. Other	☐1	☐2	20	

Specify _____ 21

	Yes	No	
14. Digoxin	☐1	☐2	22
15. Aspirin	☐1	☐2	23
16. **Clopidogrel**	☐1	☐2	24
17. Warfarin	☐1	☐2	25
18. **Nicorandil**	☐1	☐2	26

19. List Other Cardiovascular medications in addition to above prior to admission (state indication)

a. Name _____ 27
Indication _____ 28

b. Name _____ 29
Indication _____ 30

c. Name _____ 31
Indication _____ 32

d. Name _____ 33
Indication _____ 34

e. Name _____ 35
Indication _____ 36

f. Name _____ 37
Indication _____ 38

B. ASSESSMENT OF THERAPY

1.	Optimally tolerated HF therapy	☐1 ☐2 39
2.	Optimal HF therapy	☐1 ☐2 40

Cognitive Impairment in HF Study

Screening Visit, Page 10
Medications continued...

Version 1.1 (14 Oct 2013)

Patient ID. ___ - ___ 01 | Initials ___ 02 | Date of Completion D D M M Y Y Y Y 03

C. NON-CARDIOVASCULAR MEDICATION

	Yes	No
1. Bronchodilator	1	2 (04)

If Yes, specify type

	Yes	No
a. Beta-agonist tablets	1	2 (05)
b. Steroid tablets	1	2 (06)
c. Beta-agonist inhalers	1	2 (07)
d. Anti-cholinergic inhalers	1	2 (08)
e. Steroid inhalers	1	2 (09)

	Yes	No
2. Antidepressants	1	2 (10)

If Yes, specify type

	Yes	No
a. SSRI	1	2 (11)
b. TCA	1	2 (12)
c. MAOI	1	2 (13)
d. Other	1	2 (14)

Specify ___ 15

	Yes	No
3. NSAIDs	1	2 (16)
4. Vitamins	1	2 (17)
5. Incontinence meds	1	2 (18)
6. Antihistamines	1	2 (19)

7. List any prescribed medications in addition to above prior to admission (state indication

a. Name ___ 20
Indication ___ 21

b. Name ___ 22
Indication ___ 23

c. Name ___ 24
Indication ___ 25

d. Name ___ 26
Indication ___ 27

e. Name ___ 28
Indication ___ 29

f. Name ___ 30
Indication ___ 31

g. Name ___ 32
Indication ___ 33

Cognitive Impairment in HF Study

Screening Visit, Page 11
Examination

Version 1.1 (14 Oct 2013)

Patient ID. ___-___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

A. VITAL SIGNS

1. Height ___ cm 04
2. Weight ___.___ kg 05
3. Neck circumference ___.___ cm 06
4. SpO2 ___ % 07 Air ___ or O_2 ___ 08
5. Blood pressure systolic ___ mmHg 09
   diastolic ___ mmHg 10
6. Heart rate ___ bpm 11
7. Temperature ___.___ °C 12
8. Respiratory rate ___ bpm 13

B. CARDIOVASCULAR EXAMINATION

	Yes	No	Not Seen
1. Elevated JVP (>4cm)	1	2	3 (14)
2. Palpable Apex	1	2 (15)	
If Yes, Displaced Apex	1	2 (16)	
3. Third Heart Sound	1	2 (17)	
4. Murmur	1	2 (18)	
If Yes, a. AS	1	2 (19)	
b. AR	1	2 (20)	
c. MR	1	2 (21)	
d. MS	1	2 (22)	
e. TR	1	2 (23)	
5. Pulmonary crackles	1	2 (24)	
If Yes, a. Basal	1	2 (25)	
b. Middle	1	2 (26)	
c. Apex	1	2 (27)	

	Yes	No
6. Pleural effusion	1	2 (28)
If Yes, a. Right	1	2 (29)
b. Left	1	2 (30)
c. Bilateral	1	2 (31)
7. Peripheral Oedema	1	2 (32)
If Yes, a. Ankle	1	2 (33)
b. Knee	1	2 (34)
c. Thigh	1	2 (35)
d. Sacrum	1	2 (36)
e. Abdomen	1	2 (37)
8.		
9. Ascites	1	2 (38)
Carotid Bruit	1	2 (39)

If Yes, specify: Right 1 Left 2 Bilateral 3 (40)

10. Killip Class I 1 II 2 III 3 IV 4 (41)

I = No clinical signs heart failure
II = lung crackles / gallop rhythm / S3
III = frank pulmonary oedema
IV = cardiogenic shock

Cognitive Impairment in HF Study

Screening Visit, Page 12
Baseline Blood Results

Version 1.1 (14 Oct 2013)

Patient ID. ___ - ___ 01 | Initials ___ 02 | Date of Completion ___ D D M M Y Y Y Y 03

1. Blood sample taken — Yes ☐1 No ☐2 04

If Yes,

a. Time blood taken ___ : ___ H H M M 24HRs 05

a. Time patient last ate previous to blood being taken ___ : ___ H H M M 24HRs 06

A: Biochemistry

1. BNP level ___ pg/ml 07
2. Tn_I ___ . ___ µg/l 08
3. Sodium ___ mmol/l 09
4. Potassium ___ . ___ mmol/l 10
5. Chloride ___ mmol/l 11
6. Urea ___ . ___ mmol/l 12
7. Creatinine ___ µmol/l 13
8. eGFR ___ ml/min 14
9. Bilirubin ___ mmol/l 15
10. AST ___ mmol/l 16
11. ALT ___ mmol/l 17
12. Alk Phos ___ mmol/l 18
13. Albumin ___ mmol/l 19
14. TSH ___ . ___ mUl/l 20
15. T4 ___ . ___ pmol/L 21
16. Urate ___ . ___ mmol/l 22
17. Phosphate ___ . ___ mmol/l 23
18. Glucose ___ . ___ mmol/l 24
19. CRP ___ mg/L 25
20. Calcium ___ . ___ mmol/L 26

B: Coagulation Screen

1. PT ___ seconds 27
2. PTT ___ seconds 28
3. INR ___ : ___ 29

C: Lipid Profile

Fasting ☐1 Non-Fasting ☐2 30

1. Chol (total) ___ . ___ mmol/l 31
2. C/HDL ___ . ___ mmol/l 32
3. LDL ___ . ___ mmol/l 33
4. HDL ___ . ___ mmol/l 34
5. Triglycerides ___ . ___ mmol/l 35

D: Haematology

1. WCC ___ . ___ x10 9/l 36
2. Haemoglobin ___ g/L 37
3. MCV ___ . ___ fl 38
4. RDW ___ . ___ % 39
5. Platelets ___ x10 -/9 40
6. Lymphocytes ___ . ___ x10 9/l 41
7. Haematocrit ___ . ___ L/L 42

E: Haematinics

1. Vitamin B12 ___ . ___ pg/ml 43
2. Serum Folate ___ . ___ µg/L 44
3. Red Cell Folate ___ nmol/l 45
4. Serum Ferritin ___ ng/mL 46
5. Serum Iron ___ µg/dL 47

F: ESR

1. ESR ___ . ___ x10-/l 48

G: Urine Sample

Urine sample taken — Yes ☐1 No ☐2 49

If Yes,

	- ive	trace	+	+ +	+ + +
a. Protein	☐1	☐2	☐3	☐4	☐5 50
b. Glucose	☐1	☐2	☐3	☐4	☐5 51
c. Ketones	☐1	☐2	☐3	☐4	☐5 52
d. Nitrites	☐1	☐2	☐3	☐4	☐5 53
e. Leucocytes	☐1	☐2	☐3	☐4	☐5 54

Produced by Robertson Centre for Biostatistics, University of Glasgow

Cognitive Impairment in HF Study

Screening Visit, Page 13
Investigations: ECG & Checklist

Version 1.1 (14 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

A. ECG

1. ECG Analysis

a. Rate ___ beats/min 04

b. SR ☐ 05

c. AF/flutter ☐ 06

d. BBB ☐ 07

specify... Right ☐ 1 Left ☐ 2 08

e. Paced ☐ 09

f. Pathological Q waves ☐ 10

g. LVH ☐ 11

h. Ischaemic ST depression ☐ 12

i. QRS duration ___ ms 13

j. QTc duration ___ ms 14

k. Other ☐ 15

specify ___ 16

CHECKLIST

Please ensure that:

1. Medical history is taken
2. Physical examination is completed
3. Blood samples are taken
4. Urine sample is taken
5. ECG is performed
6. Inclusion/Exclusion criteria are met

Appendix VII

Cognitive Impairment in HF Study

Return Visit 1, Page 1
Study Visit Details

Version 1.2 (14 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

A. STUDY VISIT DETAILS

1. Attended Yes ☐ 1 No ☐ 2 04

If Yes,

Date of study visit D D M M Y Y Y Y 05

Complete all subsequent pages

Location
- ☐ GRI
- ☐ WIG
- ☐ BHF
- ☐ Home Visit 06

If No, give reason

a. Failed to attend ☐ 1
b. Refused to attend ☐ 2
c. Due to deteriorating health ☐ 3
d. Deceased ☐ 4 07

If deceased or withdrawn from the study please complete a 'Withdrawl/End of Study' form for the patient.

If No, was patient eligible to continue Yes ☐ 1 No ☐ 2 08

B. Checklist

Please ensure that:

1. IQCODE is given to the patient/relative.
2. Zarit Burden Interview is given to the patient/relative.
3. Self Care for HF Index is given to the patient.

Produced by Robertson Centre for Biostatistics, University of Glasgow

Cognitive Impairment in HF Study

Return Visit 1, Page 2
Changes in Medical Condition

Version 1.2 (14 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

A. CHANGES IN MEDICAL CONDITION

	Yes	No
1. Re-admission to hospital with decompensated heart failure since recruitment?	☐ 1	☐ 2 (04)

PATIENT MUST ANSWER NO TO CONTINUE

2. Deterioration in heart failure symptoms since last review?	☐ 1	☐ 2 (05)

3. NYHA I ☐ 1 II ☐ 2 III ☐ 3 IV ☐ 4 (06)

I = No limitation of daily activities
II = mild limitation of activity
III = marked limitation of activity
IV = symptoms at rest

	Yes	No
4. Orthopnea	☐ 1	☐ 2 (07)
5. Paroxysmal Nocturnal Dyspnoea	☐ 1	☐ 2 (08)
6. Ankle swelling	☐ 1	☐ 2 (09)
7. Wheeze	☐ 1	☐ 2 (10)
8. Palpitations	☐ 1	☐ 2 (11)

	Yes	No
9. Myocardial infarction during or since last review?	☐ 1	☐ 2 (12)
10. New arrhythmia?	☐ 1	☐ 2 (13)

If Yes,

a. SVT ☐ (14)

b. Ventricular tachycardia ☐ (15)

1. Sustained ☐ (16)
2. Nonsustained ☐ (17)

c. SSS ☐ (18)

d. AV block ☐ (19)

1. 1st degree ☐ 1
2. 2nd degree ☐ 2
3. 3rd degree ☐ 3 (20)

e. AF (paroxysmal or permanent) ☐ (21)

	Yes	No
11. New medical condition?	☐ 1	☐ 2 (22)

If Yes, specify

a. _____ (23)

b. _____ (24)

c. _____ (25)

d. _____ (26)

	Yes	No
12. Coronary Angiography since recruitment	☐ 1	☐ 2 (27)

If Yes, Result

Normal ☐ (28)

Plaque only ☐ (29)

Significant CHD (>50% Stenosis in ≥ 1 vessel) ☐ (30) → No. of vessels involved ___ (31)

Unknown ☐ (32)

Cognitive Impairment in HF Study

Return Visit 1, Page 3
Medications

Version 1.2 (14 Oct 2013)

Patient ID. ___ - ___ (01) Initials ___ (02) Date of Completion D D M M Y Y Y Y (03)

A. CARDIOVASCULAR MEDICATION

1. ACE-Inhibitor — Yes (1) No (2) (04)

(i) **If Yes**, specify type and dose

	Yes	No		
a. Captopril	(1)	(2) (05)	(06)	mg
b. Enalapril	(1)	(2) (07)	(08)	mg
c. Fosinopril	(1)	(2) (09)	(10)	mg
d. Lisinopril	(1)	(2) (11)	(12)	mg
e. Perindopril	(1)	(2) (13)	(14)	mg
f. Quinapril	(1)	(2) (15)	(16)	mg
g. Ramipril	(1)	(2) (17)	(18)	mg
h. Trandolapril	(1)	(2) (19)	(20)	mg
i. Other	(1)	(2) (21)		
Specify (22)			(23)	mg

	Yes	No
(ii) Previous intolerance	(1)	(2) (24)
(iii) Intolerant of higher dose than current	(1)	(2) (25)
(iv) Patient on optimal dose	(1)	(2) (26)
(v) If No, Patient on optimal tolerated dose	(1)	(2) (27)

2. Hydralazine — Yes (1) No (2) (28)

If Yes, specify dose ___ (29) mg

	Yes	No
(ii) Previous intolerance	(1)	(2) (30)
(iii) Intolerant of higher dose than current	(1)	(2) (31)
(iv) Patient on optimal dose	(1)	(2) (32)
(v) If No, Patient on optimal tolerated dose	(1)	(2) (33)

3. Beta-blocker — Yes (1) No (2) (34)

(i) **If Yes**, specify type and dose

	Yes	No		
a. Atenolol	(1)	(2) (35)	(36)	mg
b. Bisoprolol	(1)	(2) (37)	(38)	mg
c. Carvedilol	(1)	(2) (39)	(40)	mg
d. Metoprolol	(1)	(2) (41)	(42)	mg
e. Nebivolol	(1)	(2) (43)	(44)	mg
f. Propanolol	(1)	(2) (45)	(46)	mg
g. Other	(1)	(2) (47)		
Specify (48)			(49)	mg

	Yes	No
(ii) Previous intolerance	(1)	(2) (50)
(iii) Intolerant of higher dose than current	(1)	(2) (51)
(iv) Patient on optimal dose	(1)	(2) (52)
(v) If No, Patient on optimal tolerated dose	(1)	(2) (53)

4. Aldosterone Blocker — Yes (1) No (2) (54)

(i) **If Yes**, specify type and dose

	Yes	No		
a. Spironolactone	(1)	(2) (55)	(56)	mg
b. Eplerenone	(1)	(2) (57)	(58)	mg

	Yes	No
(ii) Previous intolerance	(1)	(2) (59)
(iii) Intolerant of higher dose than current	(1)	(2) (60)
(iv) Patient on optimal dose	(1)	(2) (61)
(v) If No, Patient on optimal tolerated dose	(1)	(2) (62)

Produced by Robertson Centre for Biostatistics, University of Glasgow

Cognitive Impairment in HF Study

Return Visit 1, Page 4
Medications continued...

Version 1.2 (14 Oct 2013)

Patient ID. ☐☐ - ☐☐☐☐ (01) Initials ☐☐ (02) Date of Completion ☐☐☐☐☐☐☐☐ (D D M M Y Y Y Y 03)

5. ARB — Yes ☐1 No ☐2 (04)

(i) **If Yes**, specify type and dose

	Yes	No		
a. Candesartan	☐1	☐2 (05)	____ (06)	mg
b. Irbesartan	☐1	☐2 (07)	____ (08)	mg
c. Losartan	☐1	☐2 (09)	____ (10)	mg
d. Olmesartan	☐1	☐2 (11)	____ (12)	mg
e. Telmisartan	☐1	☐2 (13)	____ (14)	mg
f. Valsartan	☐1	☐2 (15)	____ (16)	mg
g. Other	☐1	☐2 (17)		

Specify ____ (18) ____ (19) mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 (20)
(iii) Intolerant of higher dose than current	☐1	☐2 (21)
(iv) Patient on optimal dose	☐1	☐2 (22)
(v) If No, Patient on optimal tolerated dose	☐1	☐2 (23)

6. Ivabradine — Yes ☐1 No ☐2 (24)

If Yes, specify dose ____ (25) mg

	Yes	No
(ii) Previous intolerance	☐1	☐2 (26)
(iii) Intolerant of higher dose than current	☐1	☐2 (27)
(iv) Patient on optimal dose	☐1	☐2 (28)
(v) If No, Patient on optimal tolerated dose	☐1	☐2 (29)

7. Anti-arrhythmic — Yes ☐1 No ☐2 (30)

If Yes, specify type

	Yes	No
a. Amiodarone	☐1	☐2 (31)
b. Other	☐1	☐2 (32)

Specify ____ (33)

8. Calcium channel-blocker — Yes ☐1 No ☐2 (34)

If Yes, specify type

	Yes	No
a. Amlodipine	☐1	☐2 (35)
b. Diltiazem	☐1	☐2 (36)
c. Felodipine	☐1	☐2 (37)
d. Nifedipine	☐1	☐2 (38)
e. Verapamil	☐1	☐2 (39)
f. Other	☐1	☐2 (40)

Specify ____ (41)

9. Long-acting nitrates (not s/c or short acting GTN) — Yes ☐1 No ☐2 (42)

If Yes, specify type

	Yes	No
a. ISDN	☐1	☐2 (43)
b. ISMN	☐1	☐2 (44)
c. GTN patch	☐1	☐2 (45)
d. Other	☐1	☐2 (46)

Specify ____ (47)

10. Statin — Yes ☐1 No ☐2 (48)

If Yes, specify type

	Yes	No
a. Atorvastatin	☐1	☐2 (49)
b. Pravastatin	☐1	☐2 (50)
c. Rosuvastatin	☐1	☐2 (51)
d. Simvastatin	☐1	☐2 (52)
e. Other	☐1	☐2 (53)

Specify ____ (54)

11. Other lipid-lowering drug — Yes ☐1 No ☐2 (55)

Produced by Robertson Centre for Biostatistics, University of Glasgow

Cognitive Impairment in HF Study

Return Visit 1, Page 5
Medications continuted...

Version 1.2 (14 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

12. Diabetic Meds — Yes ☐1 No ☐2 04

If Yes, specify type

	Yes	No
a. Insulin	☐1	☐2 05
b. Sulphonylurea (eg gliclazide)	☐1	☐2 06
c. Biguanide (eg metformin)	☐1	☐2 07
d. Glitazone	☐1	☐2 08
e. Other	☐1	☐2 09

Specify ___ 10

13. Diuretics — Yes ☐1 No ☐2 11

If Yes, specify type and dose where relevant

	Yes	No	
a. Furosemide	☐1	☐2 12	___ 13 mg
b. Other loop	☐1	☐2 14	
c. Spironolactone	☐1	☐2 15	
d. Other K+ sparing	☐1	☐2 16	
e. Thiazide	☐1	☐2 17	
f. Bumetanide	☐1	☐2 18	___ 19 mg
g. Other	☐1	☐2 20	

Specify ___ 21

	Yes	No
14. Digoxin	☐1	☐2 22
15. Aspirin	☐1	☐2 23
16. **Clopidogrel**	☐1	☐2 24
17. Warfarin	☐1	☐2 25
18. **Nicorandil**	☐1	☐2 26

19. List Other Cardiovascular medications in addition to above prior to admission (state indication)

a. Name ___ 27
Indication ___ 28

b. Name ___ 29
Indication ___ 30

c. Name ___ 31
Indication ___ 32

d. Name ___ 33
Indication ___ 34

e. Name ___ 35
Indication ___ 36

f. Name ___ 37
Indication ___ 38

B. ASSESSMENT OF THERAPY

1.	Optimally tolerated HF therapy	☐1 ☐2 39
2.	Optimal HF therapy	☐1 ☐2 40

Cognitive Impairment in HF Study

Return Visit 1, Page 6
Medications continued...

Version 1.2 (14 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

C. NON-CARDIOVASCULAR MEDICATION

	Yes	No
1. Bronchodilator	1	2 (04)
If Yes, specify type		
a. Beta-agonist tablets	1	2 (05)
b. Steroid tablets	1	2 (06)
c. Beta-agonist inhalers	1	2 (07)
d. Anti-cholinergic inhalers	1	2 (08)
e. Steroid inhalers	1	2 (09)
2. Antidepressants	1	2 (10)
If Yes, specify type		
a. SSRI	1	2 (11)
b. TCA	1	2 (12)
c. MAOI	1	2 (13)
d. Other	1	2 (14)
Specify ___ (15)		
3. NSAIDs	1	2 (16)
4. Vitamins	1	2 (17)
5. Incontinence meds	1	2 (18)
6. Antihistamines	1	2 (19)

7. List any prescribed medications in addition to above prior to admission (state indication

a. Name ___ (20)
Indication ___ (21)

b. Name ___ (22)
Indication ___ (23)

c. Name ___ (24)
Indication ___ (25)

d. Name ___ (26)
Indication ___ (27)

e. Name ___ (28)
Indication ___ (29)

f. Name ___ (30)
Indication ___ (31)

g. Name ___ (32)
Indication ___ (33)

Cognitive Impairment in HF Study

Return Visit 1, Page 7
Physical Examination

Version 1.2 (14 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

A. VITAL SIGNS

1. Weight ___ . ___ kg 04
2. SpO2 ___ % 05 Air ___ or O_2 ___ 06
3. Blood pressure systolic ___ mmHg 07
   diastolic ___ mmHg 08
4. Heart rate ___ bpm 09
5. Temperature ___ . ___ °C 10
6. Respiratory rate ___ bpm 11

B. CARDIOVASCULAR EXAMINATION

	Yes	No	Not Seen
1. Elevated JVP (>4cm)	1	2	3 (12)
2. Palpable Apex	1	2 (13)	
If Yes, Displaced Apex	1	2 (14)	
3. Third Heart Sound	1	2 (15)	
4. Murmur	1	2 (16)	
If Yes, a. AS	1	2 (17)	
b. AR	1	2 (18)	
c. MR	1	2 (19)	
d. MS	1	2 (20)	
e. TR	1	2 (21)	
5. Pulmonary crackles	1	2 (22)	
If Yes, a.Basal	1	2 (23)	
b.Middle	1	2 (24)	
c. Apex	1	2 (25)	
6. Pleural effusion	1	2 (26)	
If Yes, a. Right	1	2 (27)	
b. Left	1	2 (28)	
c. Bilateral	1	2 (29)	

	Yes	No
7. Peripheral Oedema	1	2 (30)
If Yes, a. Ankle	1	2 (31)
b. Knee	1	2 (32)
c. Thigh	1	2 (33)
d. Sacrum	1	2 (34)
e. Abdomen	1	2 (35)
8. Ascites	1	2 (36)
9. Carotid Bruit	1	2 (37)

If Yes, specify: Right 1 Left 2 Bilateral 3 (38)

10. Killip Class I 1 II 2 III 3 IV 4 (39)

I = No clinical signs heart failure
II = lung crackles / gallop rhythm / S3
III = frank pulmonary oedema
IV = cardiogenic shock

Produced by Robertson Centre for Biostatistics, University of Glasgow

Cognitive Impairment in HF Study

Return Visit 1, Page 8
Mini Mental State Examination (MMSE)

Version 1.2 (14 Oct 2013)

Patient ID. __ - ____ 01 Initials ____ 02 Date of Completion D D M M Y Y Y Y 03

Time of Completion H H : M M 04

I am going to ask you a few questions to find out about your memory function. Some of them are very simple, while others are more difficult. You must try your best to answer the questions.

ORIENTATION

What is today's full date? D D M M Y Y Y Y

If the reply is incorrect or incomplete, ask the questions which have not been answered, in the following order:

1. What is the current Year? Incorrect ☐ 1 Correct ☐ 2
2. What is the Season? Incorrect ☐ 1 Correct ☐ 2
3. What is the month? Incorrect ☐ 1 Correct ☐ 2
4. What is the date of the month? Incorrect ☐ 1 Correct ☐ 2
5. What is the day of the week? **Incorrect** ☐ 1 **Correct** ☐ 2

Now I am going to ask you a few questions about the place we are in:

6. What is the name of the building we are in? Incorrect ☐ 1 Correct ☐ 2
7. Which town/city is it in? Incorrect ☐ 1 Correct ☐ 2
8. What is the name of the area in which this town is located? Incorrect ☐ 1 Correct ☐ 2
9. In which county or region is this department located? Incorrect ☐ 1 Correct ☐ 2
10. What Floor are we on? Incorrect ☐ 1 Correct ☐ 2

LEARNING SKILLS

I am going to say 3 words to you; I would like you to repeat them to me and try to remember them as I am going to ask you them again in a moment.

11. Cigar or Lemon Incorrect ☐ 1 Correct ☐ 2
12. Flower or Key Incorrect ☐ 1 Correct ☐ 2
13. Door or Ball Incorrect ☐ 1 Correct ☐ 2

Repeat the 3 words

ATTENTION AND CALCULATION

Can you count down from 100 by subtracting 7 each time?

14. 93 Incorrect ☐ 1 Correct ☐ 2
15. 86 Incorrect ☐ 1 Correct ☐ 2
16. 79 Incorrect ☐ 1 Correct ☐ 2
17. 72 Incorrect ☐ 1 Correct ☐ 2
18. 65 Incorrect ☐ 1 Correct ☐ 2

OR Can you spell the word WORLD backwards:

DLROW Score ☐

REMINDER

Can you tell me the 3 words I asked you to repeat and remember just before?

19. Cigar or Lemon Incorrect ☐ 1 Correct ☐ 2
20. Flower or Key Incorrect ☐ 1 Correct ☐ 2
21. Door or Ball Incorrect ☐ 1 Correct ☐ 2

Produced by Robertson Centre for Biostatistics, University of Glasgow

Cognitive Impairment in HF Study

Return Visit 1, Page 9
Mini Mental State Examination (MMSE)
Continued

Version 1.2 (14 Oct 2013)

Patient ID. ___-___ 01 Initials ___ 02 Date of Completion ___ D D M M Y Y Y Y 03

Time of Completion ___ : ___ H H M M 04

LANGUAGE

22. Show the patient a pencil
What is the name of this object? Incorrect ☐ 1 Correct ☐ 2

23. Show the patient your watch
What is the name of this object? Incorrect ☐ 1 Correct ☐ 2

24. Listen carefully and repeat after me:
"NO BUTS, "YESES", OR "ANDS" Incorrect ☐ 1 Correct ☐ 2

25.* Put a sheet of paper on the desk, show it to the patient, saying:
"listen carefully and do as I tell you:
pick up this sheet of paper in your right hand, Incorrect ☐ 1 Correct ☐ 2

26. fold it in two Incorrect ☐ 1 Correct ☐ 2

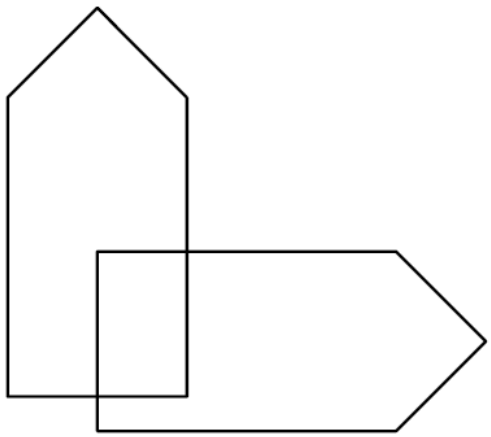
27. and throw it onto the floor. Incorrect ☐ 1 Correct ☐ 2

28.* Hand the patient a sheet of paper on which the following words are written in large letters:
"CLOSE YOUR EYES" and say to the patient: "carry out the instructions written on the paper". Incorrect ☐ Correct ☐ 2

29.* Hand the patient a sheet of paper and a pen, saying:
"please write down a sentence for me, anything you like, as long as it is a complete sentence" Incorrect ☐ 1 Correct ☐ 2

CONSTRUCTIVE PRACTICAL EXERCISE

30. Hand the patient a sheet of paper and ask him:
"can you copy this drawing"



Incorrect ☐ 1 Correct ☐ 2

SCORING

		Score
1	Orientation	___ 05 / 10
2	Learning	___ 06 / 6
3	Attention and Calculation	___ 07 / 5
4	Language	___ 08 / 8
5	Constructive Practical Exercise	___ 09 / 1
6	Total Score	___ 10 / 30

Produced by Robertson Centre for Biostatistics, University of Glasgow

Cognitive Impairment in HF Study

Return Visit 1, Page 10
Montreal Cognitive Assessment (MoCA)

Version 1.2 (14 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion ___ D D M M Y Y Y Y 03

Time of Completion ___ : ___ H H M M 04

		Score
1	Visuospatial / Executive	___ 05 / 5
2	Naming	___ 06 / 3
3	Attention	___ 07 / 6
4	Language	___ 08 / 3
5	Abstraction	___ 09 / 2
6	Delayed Recall	___ 10 / 5
7	Orientation	___ 11 / 6
8	Total Score	___ 12 / 30

Cognitive Impairment in HF Study

Return Visit 1, Page 11
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

Version 1.2 (14 Oct 2013)

Patient ID. __ - ___ 01 Initials ___ 02 Date of Completion ___ D D M M Y Y Y Y 03

Time of Completion ___ : ___ H H M M 04

Record Form A

	Immediate Memory	Visuospatial / Constructional	Language	Attention	Delayed Memory	Total Scale
Index Score	___ 05	___ 06	___ 07	___ 08	___ 09	___ 10
Confidence Interval ____% (range)	___ to ___ 11	___ to ___ 12	___ to ___ 13	___ to ___ 14	___ to ___ 15	___ to ___ 16
Percentile	__ . __ 17	__ . __ 18	__ . __ 19	__ . __ 20	__ . __ 21	__ . __ 22

Cognitive Impairment in HF Study

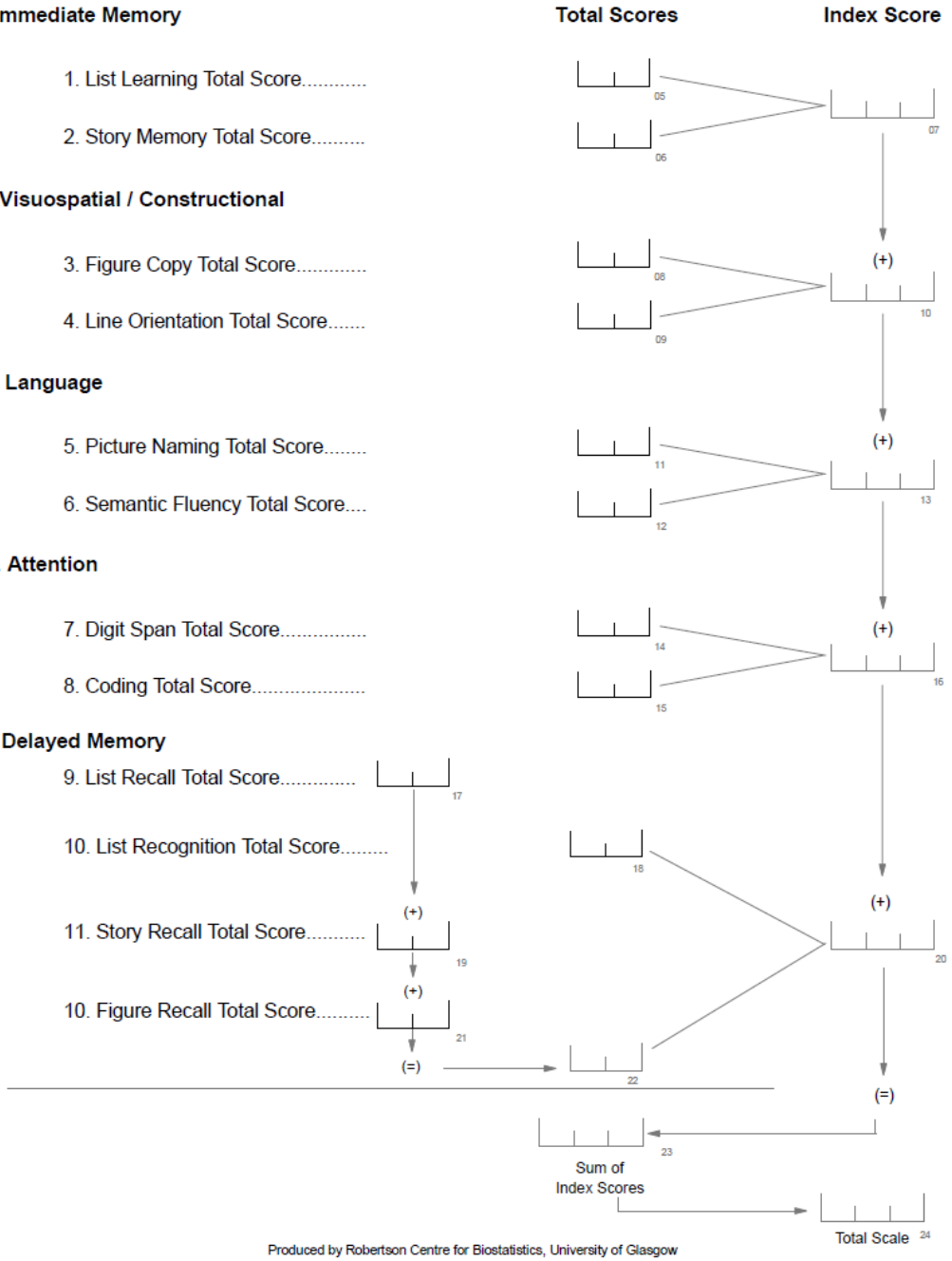
Return Visit 1, Page 12
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Continued

Version 1.2 (14 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

Time of Completion H H : M M 04

B. Score Conversion Page



Produced by Robertson Centre for Biostatistics, University of Glasgow

Cognitive Impairment in HF Study

Return Visit 1, Page 13
Trail Making Tests

Version 1.2 (14 Oct 2013)

Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊___⌋ 02 Date of Completion ⌊D D M M Y Y Y Y⌋ 03

Time of Completion ⌊H H⌋:⌊M M⌋ 04

A. Trail Making Test Part A

1. Time taken to complete task ⌊_____⌋ 05 seconds

B. Trail Making Test Part B

1. Time taken to complete task ⌊_____⌋ 06 seconds

Cognitive Impairment in HF Study

Return Visit 1, Page 14
Controlled Oral Word Association Task (COWAT)
Letter F

Version 1.2 (14 Oct 2013)

Patient ID. __ - ____ 01 Initials ____ 02 Date of Completion D D M M Y Y Y Y 03

Time of Completion H H : M M 04

A. Controlled Oral Word Association Task

LETTER F

Time Begun H H : M M 05

	Word	Valid		Word	Valid
1			13		
2			14		
3			15		
4			16		
5			17		
6			18		
7			19		
8			20		
9			21		
10			22		
11			23		
12			24		
Total				____ 06	

Time Ended H H : M M 07

Cognitive Impairment in HF Study

Return Visit 1, Page 15
Controlled Oral Word Association Task (COWAT)
Letter A

Version 1.2 (14 Oct 2013)

Patient ID. _ - _ 01 Initials _ _ 02 Date of Completion _ _ _ _ _ _ _ _ 03 (D D M M Y Y Y Y)

Time of Completion _ _ : _ _ 04 (H H : M M)

A. Controlled Oral Word Association Task

LETTER A

Time Begun _ _ : _ _ 05 (H H : M M)

	Word	Valid		Word	Valid
1			13		
2			14		
3			15		
4			16		
5			17		
6			18		
7			19		
8			20		
9			21		
10			22		
11			23		
12			24		
Total				_ _ 06	

Time Ended _ _ : _ _ 07 (H H : M M)

Cognitive Impairment in HF Study

Return Visit 1, Page 16
Controlled Oral Word Association Task (COWAT)
Letter S

Version 1.2 (14 Oct 2013)

Patient ID. _ - _ 01 Initials _ _ 02 Date of Completion _ _ _ _ _ _ _ _ 03 (D D M M Y Y Y Y)

Time of Completion _ _ : _ _ 04 (H H : M M)

A. Controlled Oral Word Association Task

LETTER S

Time Begun _ _ : _ _ 05 (H H : M M)

	Word	Valid		Word	Valid
1			13		
2			14		
3			15		
4			16		
5			17		
6			18		
7			19		
8			20		
9			21		
10			22		
11			23		
12			24		
Total				_ _ 06	

Time Ended _ _ : _ _ 07 (H H : M M)

Cognitive Impairment in HF Study

Return Visit 1, Page 17
Wechsler Test of Adult Reading (WTAR)

Version 1.2 (14 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

Time of Completion H H : M M 04

	Score (0,1)		Score (0,1)
1.		26.	
2.		27.	
3.		28.	
4.		29.	
5.		30.	
6.		31.	
7.		32.	
8.		33.	
9.		34.	
10.		35.	
11.		36.	
12.		37.	
13.		38.	
14.		39.	
15.		40.	
16.		41.	
17.		42.	
18.		43.	
19.		44.	
20.		45.	
21.		46.	
22.		47.	
23.		48.	
24.		49.	
25.		50.	

WTAR Raw Score ☐☐ 05 WTAR Standard Score ☐☐ 06

Cognitive Impairment in HF Study

Return Visit 1, Page 18
Wechsler Test of Adult Reading (WTAR)

Version 1.2 (14 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

Time of Completion H H : M M 04

WTAR Scores Predicted - Actual Comparision	
Standard Score (Appendix A)	05
Demographics - Predicted Score (Appendix B)	06
Prediction Interval ☐ 1 90% ☐ 2 95% 07	to 08
Actual Predicted Difference	☐ 1 -ive ☐ 2 +ive 09 10

Cumulative Percentage (Table I.1)	
> 50%	☐ 1
25% - 49%	☐ 1
10% - 24%	☐ 1
5% - 9%	☐ 1
2% - 4%	☐ 1
1%	☐ 1 11

Predicted full scale IQ / WAIS III Score ___ 12

Cognitive Impairment in HF Study

Return Visit 1, Page 19
Wechsler Letter Number Sequencing

Version 1.2 (14 Oct 2013)

Patient ID. ⌊__⌋-⌊____⌋ 01 Initials ⌊____⌋ 02 Date of Completion ⌊D D M M Y Y Y Y⌋ 03

Time of Completion ⌊H H⌋:⌊M M⌋ 04

	Trial	Correct Responses		Response	Trial Score (0 or 1)	Item Score (0, 1,2 or 3)
1	2 - B	2 - B				
	D - 1	1 - D				
	4 - C	4 - C				
2	E - 5	5 - E				
	3 - A	3 - A				
	C - 1	1 - C				
3	5 - C - A	5 - A - C	A - C - 5			
	F - E - 1	1 - E - F	E - F - 1			
	3 - 2 - A	2 - 3 - A	A - 2 - 3			
4	1 - G - 7	1 - 7 - G	G - 1 - 7			
	H - 9 - 4	4 - 9 - H	H - 4 - 9			
	3 - Q - 7	3 - 7 - Q	Q - 3 - 7			
5	Z - 8 - N	8 - N - Z	N - Z - 8			
	M - 6 - U	6 - M - U	M - U - 6			
	P - 2 - N	2 - N - P	N - P - 2			
6	V - 1 - J - 5	1 - 5 - J - V	J - V - 1 - 5			
	7 - X - 4 - G	4 - 7 - G - X	G - X - 4 - 7			
	S - 9 - T - 6	6 - 9 - S - T	S - T - 6 - 9			
7	8 - E - 6 - F - 1	1 - 6 - 8 - E - F	E - F - 1 - 6 - 8			
	K - 4 - C - 2 - S	2 - 4 - C - K - S	C - K - S - 2 - 4			
	5 - Q - 3 - H - 6	3 - 5 - 6 - H - Q	H - Q - 3 - 5 - 6			
8	M - 4 - P - 7 - R - 2	2 - 4 - 7 - M - P - R	M - P - R - 2 - 4 - 7			
	6 - N - 9 - J - 2 - S	2 - 6 - 9 - J - N - S	J - N - S - 2 - 6 - 9			
	U - 6 - H - 5 - F - 3	3 - 5 - 6 - F - H - U	F - H - U - 3 - 5 - 6			
9	R - 7 - V - 4 - Y - 8 - F	4 - 7 - 8 - F - R - V - Y	F - R - V - Y - 4 - 7 - 8			
	9 - X - 2 - J - 3 - N - 7	2 - 3 - 7 - 9 - J - N - X	J - N - X - 2 - 3 - 7 - 9			
	M - 1 - Q - 8 - R - 4 - D	1 - 4 - 8 - D - M - Q - R	D - M - Q - R - 1 - 4 - 8			
10	6 - P - 7 - S - 2 - N - 9 - A	2 - 6 - 7 - 9 - A - N - P - S	A - N - P - S - 2 - 6 - 7 - 9			
	U - 1 - R - 9 - X - 4 - K - 3	1 - 3 - 4 - 9 - K - R - U - X	K - R - U - X - 1 - 3 - 4 - 9			
	7 - M - 2 - T - 6 - F - 9 - A	2 - 6 - 7 - 9 - A - F - M - T	A - F - M - T - 2 - 6 - 7 - 9			

Total Raw Score (maximum = 30)	⌊____⌋ 05

Produced by Robertson Centre for Biostatistics, University of Glasgow

Cognitive Impairment in HF Study

Return Visit 1, Page 20
Animal Naming Test

Version 1.2 (14 Oct 2013)

Patient ID. _ - _ 01 Initials _ _ 02 Date of Completion _ _ _ _ _ _ _ _ D D M M Y Y Y Y 03

Time of Completion _ _ : _ _ H H M M 04

	Word	Valid		Word	Valid
1			12		
2			13		
3			14		
4			15		
5			16		
6			17		
7			18		
8			19		
9			20		
10			21		
11			22		
			Total _ _ 05		

Cognitive Impairment in HF Study

Return Visit 1, Page 21
Frontal Assessment Battery

Version 1.2 (14 Oct 2013)

Patient ID. __ - ____ 01 Initials ____ 02 Date of Completion __ __ M M Y Y Y Y 03

Time of Completion __ __ : __ __ 04

		Score
1	Similarities (conceptualization)	
2	Lexical fluency (mental flexibility)	
3	Motor series "Luria" test (programming)	
4	Conflicting instructions(sensitivity to interference)	
5	Go-No Go (inhibitory control)	
6	Prehension behaviour (environmental autonomy)	
	Total	____ 05

Cognitive Impairment in HF Study

Return Visit 1, Page 22
Epworth Sleepiness Scale

Version 1.2 (14 Oct 2013)

Patient ID. __ - ____ 01 Initials ____ 02 Date of Completion D D M M Y Y Y Y 03

Time of Completion H H : M M 04

SITUATION	CHANCE OF DOZING			
	would never doze	slight chance of dozing	moderate chance of dozing	high chance of dozing
Sitting and Reading	0	1	2	3
Watching Television	0	1	2	3
Sitiing inactive in a public place (theatre/meeting)	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3
Lying down to rest in the afternoon	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after lunch (with no alcohol)	0	1	2	3
In a car while stopped in traffic	0	1	2	3

Total Score	____ 05

Cognitive Impairment in HF Study

Return Visit 1, Page 23
Checklist

Version 1.2 (14 Oct 2013)

Patient ID. ⌊__⌋ - ⌊_____⌋ 01 Initials ⌊___⌋ 02 Date of Completion ⌊D D M M Y Y Y Y⌋ 03

CHECKLIST

Patient Group
- ☐ Group 1
- ☐ Group 2
- ☐ Group 3
- ☐ Group 4
- ☐ Group 5 04

Please ensure that for **Group 1, 2 and 5** Patients:

1. History and physical examiniations are completed
2. HADS is administered
3. KCCQ is administered
4. MMSE is completed
5. Neuropsychological assessments are completed
6. IQCODE is issued to the carer
7. Zarit Burden Interview is issued to the carer
8. Self Care for HF Index is issued to the patient

Please ensure that for **Group 3** Patients:

1. History and physical examiniations are completed
2. HADS is administered
3. MMSE is completed
4. Neuropsychological assessments are completed
5. IQCODE is issued to the carer
6. Zarit Burden Interview is issued to the carer

Please ensure that for **Group 4** Patients:

1. History and physical examiniations are completed
2. HADS is administered
3. MMSE is completed
4. Neuropsychological assessments are completed
5. IQCODE is issued to the carer

Produced by Robertson Centre for Biostatistics, University of Glasgow

Appendix VIII

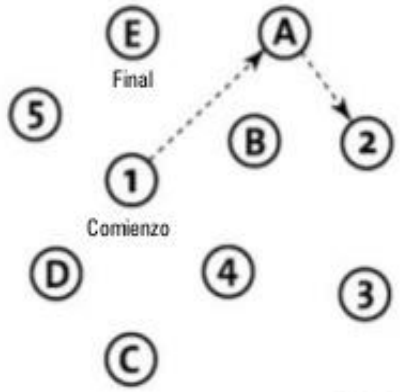
MONTREAL COGNITIVE ASSESSMENT (MOCA)

(EVALUACIÓN COGNITIVA MONTREAL)

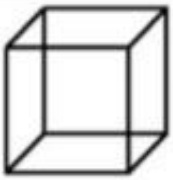
NOMBRE:
Nivel de estudios:
Sexo:

Fecha de nacimiento:
FECHA:

VISUOESPACIAL / EJECUTIVA



Copiar el cubo



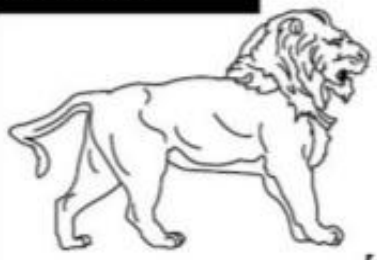
[ ] [ ]

Dibujar un reloj (Once y diez)
(3 puntos)

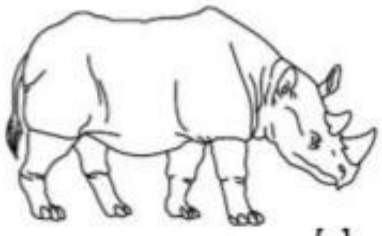
[ ] Contorno [ ] Números [ ] Agujas

Puntos ___/5

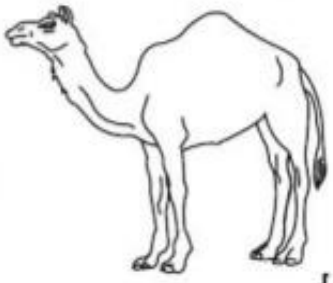
IDENTIFICACIÓN



[ ]



[ ]



[ ]

___/3

MEMORIA

Lea la lista de palabras, el paciente debe repetirlas. Haga dos intentos. Recuérdeselas 5 minutos más tarde.

	ROSTRO	SEDA	IGLESIA	CLAVEL	ROJO
1er intento					
2º intento					

Sin puntos

ATENCIÓN

Lea la serie de números (1 número/seg.) El paciente debe repetirla. [ ] 2 1 8 5 4

El paciente debe repetirla a la inversa. [ ] 7 4 2

___/2

Lea la serie de letras. El paciente debe dar un golpecito con la mano cada vez que se diga la letra A. No se asignan puntos si ≥ 2 errores.

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Restar de 7 en 7 empezando desde 100. [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 o 5 sustracciones correctas: **3 puntos**, 2 o 3 correctas: **2 puntos**, 1 correcta: **1 punto**, 0 correctas: **0 puntos**.

___/3

LENGUAJE

Repetir: El gato se esconde bajo el sofá cuando los perros entran en la sala. [ ] Espero que él le entregue el mensaje una vez que ella se lo pida. [ ]

___/2

Fluidez del lenguaje. Decir el mayor número posible de palabras que comiencen por la letra "P" en 1 min. [ ] ____ (N ≥ 11 palabras)

___/1

ABSTRACCIÓN

Similitud entre p. ej. manzana-naranja = fruta [ ] tren-bicicleta [ ] reloj-regla

___/2

RECUERDO DIFERIDO

	Debe acordarse de las palabras SIN PISTAS	ROSTRO [ ]	SEDA [ ]	IGLESIA [ ]	CLAVEL [ ]	ROJO [ ]	Puntos por recuerdos SIN PISTAS únicamente
Optativo	Pista de categoría						
	Pista elección múltiple						

___/5

ORIENTACIÓN

[ ] Día del mes (fecha) [ ] Mes [ ] Año [ ] Día de la semana [ ] Lugar [ ] Localidad

___/6

 Versión 07 noviembre 2004

www.mocatest.org

Normal ≥ 26 / 30

TOTAL ___/30

Añadir 1 punto si tiene ≤ 12 años de estudios

Appendix IX

RBANS™
Repeatable Battery for the Assessment of Neuropsychological Status
Christopher Randolph

UK Adaptation
Record Form A

Name _____ Age _____ Sex _____ Education Level _____

Examiner _____ Date of Testing _____ Ethnicity _____

Observations: _____

_____

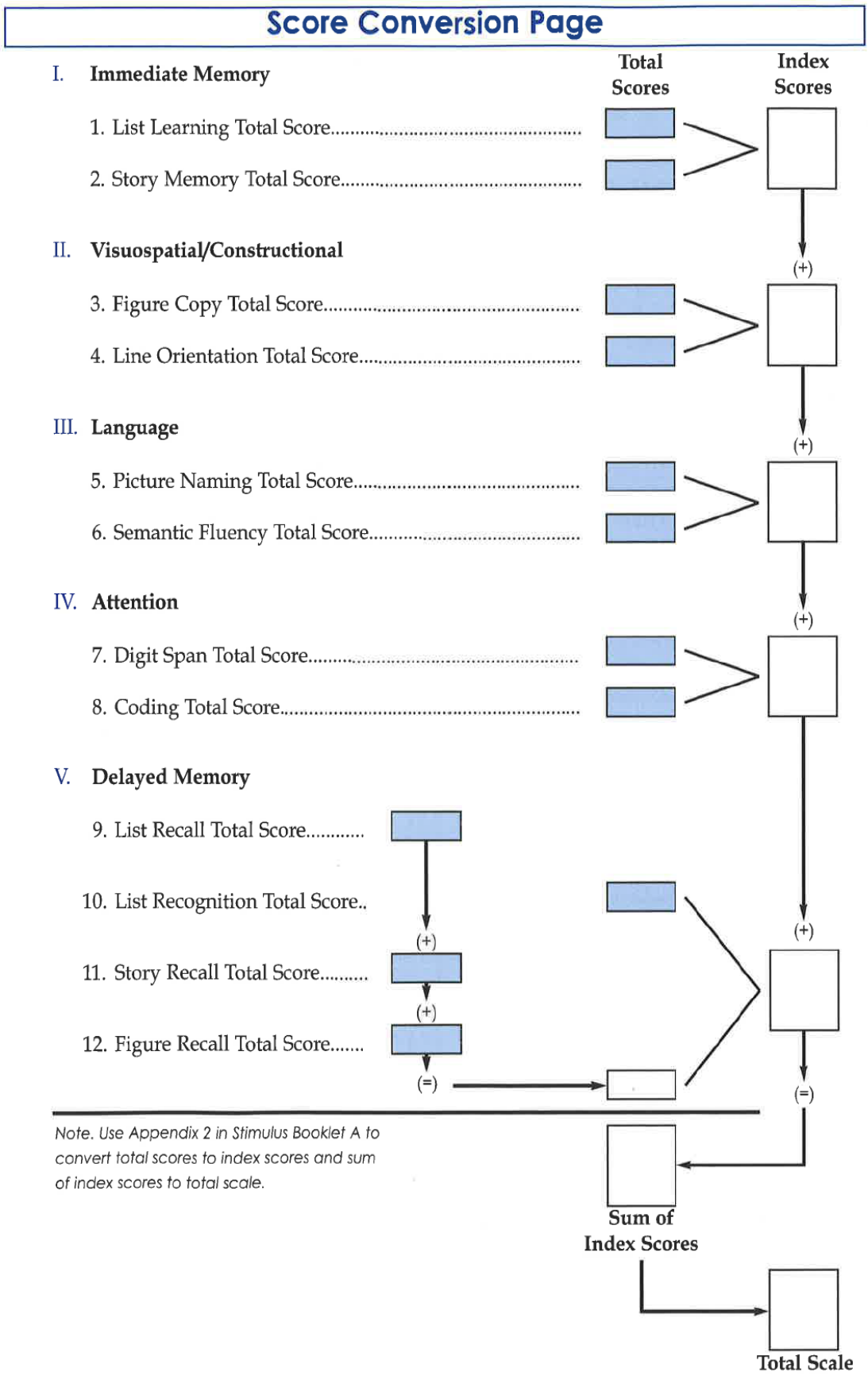
_____

	Immediate Memory	Visuospatial/ Constructional	Language	Attention	Delayed Memory	Total Scale
Index Score						
Confidence Interval ____%						
Percentile						

Index Score	Percentile Rank	Total Scale Index Score
160	>99.9	160
155	>99.9	155
150	>99.9	150
145	99.9	145
140	99.6	140
135	99	135
130	98	130
125	95	125
120	91	120
115	84	115
110	75	110
105	63	105
100	50	100
95	37	95
90	25	90
85	16	85
80	9	80
75	5	75
70	2	70
65	1	65
60	0.4	60
55	0.1	55
50	<0.1	50
45	<0.1	45
40	<0.1	40

PEARSON

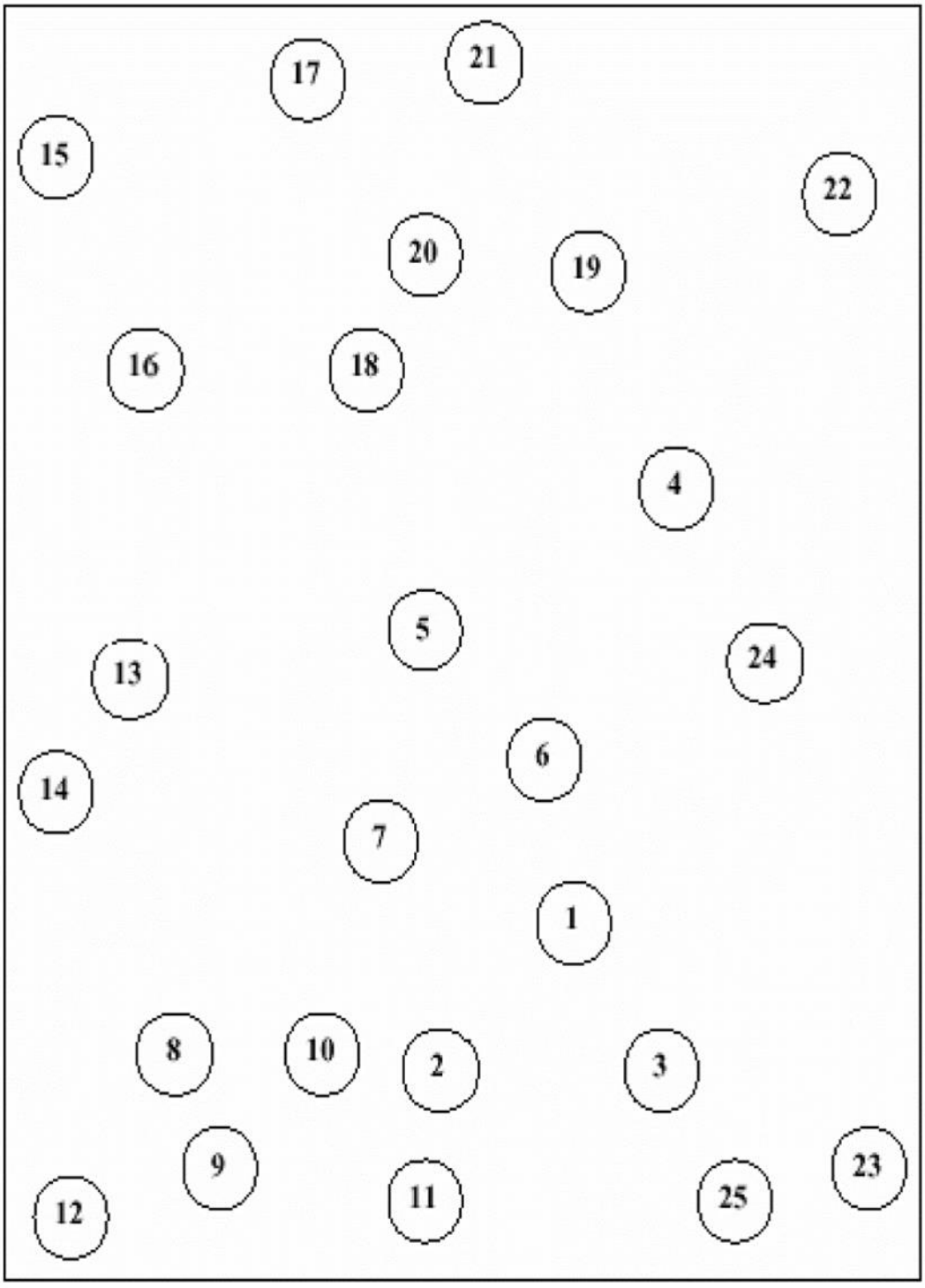
ISBN 978 0 749123 47 5


Score Conversion Page
I. Immediate Memory
Total Scores
Index Scores
1. List Learning Total Score.....
2. Story Memory Total Score.....
II. Visuospatial/Constructional
(+)
3. Figure Copy Total Score.....
4. Line Orientation Total Score.....
III. Language
(+)
5. Picture Naming Total Score.....
6. Semantic Fluency Total Score.....
IV. Attention
(+)
7. Digit Span Total Score.....
8. Coding Total Score.....
V. Delayed Memory
9. List Recall Total Score.....
10. List Recognition Total Score..
(+)
11. Story Recall Total Score.....
(+)
12. Figure Recall Total Score.....
(=)
(+)
(=)
Note. Use Appendix 2 in Stimulus Booklet A to convert total scores to index scores and sum of index scores to total scale.
Sum of Index Scores
Total Scale

Appendix X

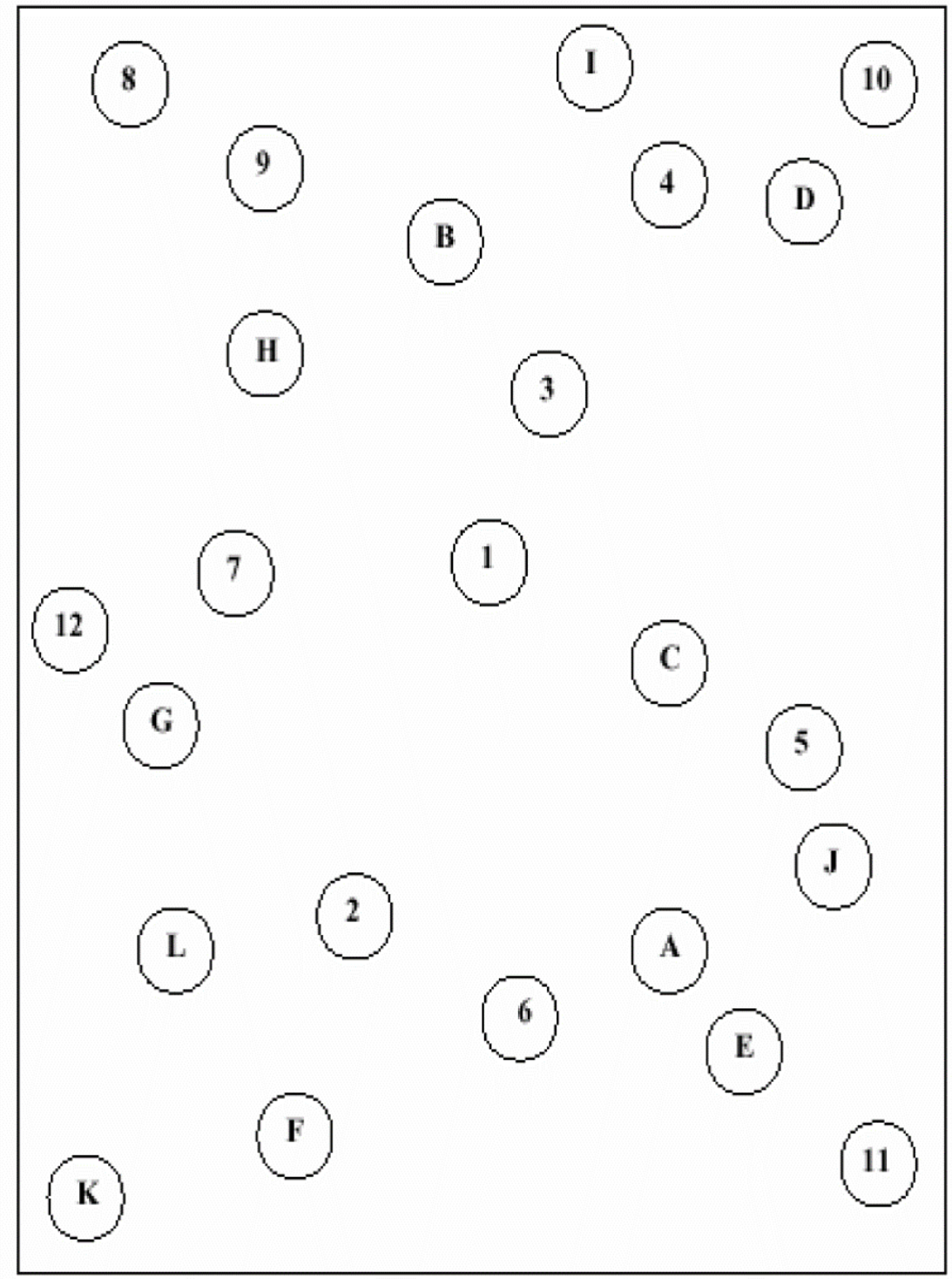
Trail Making Test Part A

Patient's Name: _____ Date: _____



Trail Making Test Part B

Patient's Name: _____ Date: _____



Appendix XI

Table 3 (*Continued*)

Age group 60–64

	Education 0–12 years ($n = 55$)		Education 12+ years ($n = 31$)		Total ($n = 86$)	
	Trail A	Trail B	Trail A	Trail B	Trail A	Trail B
90	21	56	22	45	22	48
80	24	58	25	48	24	56
70	26	62	26	53	26	59
60	30	67	27	59	29	62
50	33	72	31	60	32	68
40	37	75	33	66	34	72
30	40	79	35	71	37	77
20	43	92	37	77	42	84
10	45	96	43	87	45	96

Age group 65–69

	Education 0–12 years ($n = 65$)		Education 12+ years ($n = 32$)		Total ($n = 97$)	
	Trail A	Trail B	Trail A	Trail B	Trail A	Trail B
90	24	60	26	52	25	56
80	30	71	28	57	29	62
70	32	74	30	63	31	70
60	36	81	31	67	32	73
50	39	86	32	68	37	76
40	40	93	34	71	39	83
30	44	103	39	73	42	91
20	47	110	40	75	45	104
10	56	137	45	77	53	121

Age group 70–74

	Education 0–12 years ($n = 76$)		Education 12+ years ($n = 30$)		Total ($n = 106$)	
	Trail A	Trail B	Trail A	Trail B	Trail A	Trail B
90	25	70	26	59	26	64
80	30	79	29	63	30	76
70	35	83	31	68	34	81
60	37	95	33	80	36	85
50	38	101	36	84	38	97
40	42	112	41	85	41	105
30	46	124	42	103	45	112
20	52	146	46	109	49	138
10	57	172	71	112	61	159

Table 3 (*Continued*)

Age group 75–79

	Education 0–12 years ($n = 74$)		Education 12+ years ($n = 34$)		Total ($n = 108$)	
	Trail A	Trail B	Trail A	Trail B	Trail A	Trail B
90	30	78	22	57	27	65
80	37	92	27	59	34	79
70	39	96	34	66	38	88
60	45	107	37	73	40	98
50	50	120	40	87	46	115
40	53	140	43	105	50	128
30	56	156	46	126	54	148
20	61	167	58	141	58	163
10	72	189	66	178	70	185

Age group 80–84

	Education 0–12 years ($n = 84$)		Education 12+ years ($n = 34$)		Total ($n = 118$)	
	Trail A	Trail B	Trail A	Trail B	Trail A	Trail B
90	31	72	37	89	31	84
80	39	101	38	100	39	101
70	43	112	41	111	42	111
60	49	119	46	113	47	116
50	53	140	48	128	52	133
40	59	154	56	131	58	144
30	66	176	58	139	63	159
20	78	204	64	151	75	193
10	90	259	101	227	93	241

Age group 85–89

	Education 0–12 years ($n = 16$)		Education 12+ years ($n = 13$)		Total ($n = 29$)	
	Trail A	Trail B	Trail A	Trail B	Trail A	Trail B
90	37	89	35	70	36	81
80	39	95	42	81	39	87
70	43	112	49	87	47	95
60	47	132	52	90	51	121
50	55	143	53	121	54	138
40	56	188	60	143	56	150
30	63	194	67	156	65	194
20	72	214	78	212	68	199
10	94	317	125	290	120	296

Appendix XII

Frontal Assessment Battery

Purpose
The FAB is a brief tool that can be used at the bedside or in a clinic setting to assist in discriminating between dementias with a frontal dysexecutive phenotype and Dementia of Alzheimer's Type (DAT). The FAB has validity in distinguishing Fronto-temporal type dementia from DAT in mildly demented patients (MMSE > 24). Total score is from a maximum of 18, higher scores indicating better performance.

1. Similarities (conceptualization)
"In what way are they alike?"

- A banana and an orange

(In the event of total failure: "they are not alike" or partial failure: "both have peel," help the patient by saying: "both a banana and an orange are fruit"; but credit 0 for the item; do not help the patient for the two following items)

- A table and a chair
- A tulip, a rose and a daisy

Score (only category responses [fruits, furniture, flowers] are considered correct)

Three correct: 3 Two correct: 2 One correct: 1 None correct: 0

2. Lexical fluency (mental flexibility)
"Say as many words as you can beginning with the letter 'S,' any words except surnames or proper nouns."

If the patient gives no response during the first 5 seconds, say: "for instance, snake." If the patient pauses 10 seconds, stimulate him by saying: "any word beginning with the letter 'S.' The time allowed is 60 seconds.

Score (word repetitions or variations [shoe, shoemaker], surnames, or proper nouns are not counted as correct responses)

> 9 words: 3 6 -9 words: 2 3 -5 words: 1 < 3 words: 0

3. Motor series "Luria" test (programming)
"Look carefully at what I'm doing."

The examiner, seated in front of the patient, performs alone three times with his left hand the series of "fist–edge–palm."
"Now, with your right hand do the same series, first with me, then alone."
The examiner performs the series three times with the patient, then says to him/her:
"Now, do it on your own."

Score

Patient performs six correct consecutive series alone: 3
Patient performs at least three correct consecutive series alone: 2
Patient fails alone, but performs three correct consecutive series with the examiner: 1
Patient cannot perform three correct consecutive series even with the examiner: 0

4. Conflicting instructions (sensitivity to interference)
"Tap twice when I tap once."
To ensure that the patient has understood the instruction, a series of 3 trials is run: 1-1-1.

"Tap once when I tap twice."
To ensure that the patient has understood the instruction, a series of 3 trials is run: 2-2-2.

The examiner then performs the following series: 1-1-2-1-2-2-2-1-1-2.

Score No errors: 3 1 -2 errors: 2 > 2 errors: 1
Patient taps like the examiner at least four consecutive times: 0

5. Go–No Go (inhibitory control)
"Tap once when I tap once."
To ensure that the patient has understood the instruction, a series of 3 trials is run: 1-1-1.

"Do not tap when I tap twice."
To ensure that the patient has understood the instruction, a series of 3 trials is run: 2-2-2.

The examiner then performs the following series: 1-1-2-1-2-2-2-1-1-2.

Score No errors: 3 1 -2 errors: 2 > 2 errors: 1
Patient taps like the examiner at least four consecutive times: 0

6. Prehension behaviour (environmental autonomy)

"Do not take my hands."

The examiner is seated in front of the patient. Place the patient's hands palm up on his knees (or holds palms out in front). Without saying anything or looking at the patient, the examiner brings his own hands close to the patient's hands and touches (or strokes) the palms of both the patient's hands, to see if he will spontaneously take them. If the patient takes the examiner's hands, try again after asking the patient: "Now, do not take my hands."

Score

Patient does not take the examiner's hands: 3
Patient hesitates and asks what he/she has to do: 2
Patient takes the hands without hesitation: 1
Patient takes the examiner's hand even after he/she has been told not to do so: 0

Appendix XIII

wtar™ UK WORD CARD

WECHSLER® TEST OF ADULT READING™

1. again
2. address
3. cough
4. preview
5. although
6. most
7. excitement
8. know
9. plumb
10. decorate
11. fierce
12. knead
13. aisle
14. vengeance
15. prestigious
16. wreathe
17. gnat
18. amphitheatre
19. lieu
20. grotesque
21. iridescent
22. ballet
23. equestrian
24. porpoise
25. aesthetic
26. conscientious
27. homily
28. malady
29. subtle
30. fecund
31. palatable
32. menagerie
33. obfuscate
34. liaison
35. exigency
36. xenophobia
37. ogre
38. scurrilous
39. ethereal
40. paradigm
41. perspicuity
42. plethora
43. lugubrious
44. treatise
45. dilettante
46. vertiginous
47. ubiquitous
48. hyperbole
49. insouciant
50. hegemony

Harcourt Assessment

Printed in England. ISBN 0 7491 1597 1
B C D E F 7 8 9 10

Appendix XIV

WTAR Word List - UK pronunciation guide

Say, **I will show you some words that I will ask you to pronounce.** Place the WTAR Word Card in front of the examinee. As you point to the card, say, **Beginning with the first word on the list, pronounce each word aloud. Start with this word** (point to item 1), **and go down this column, one after the other, without skipping any. When you finish this column, go to the next column** (point to the second column). **Pronounce each word even if you are unsure. Do you understand?** When you are sure that the examinee understands the task, say, **Ready? Begin.**

	Item	Pronunciation	Score (0, 1)		Item	Pronunciation	Score (0, 1)
1.	again	ah-GEHN ah-GAIN *or* uh-GEHN or uh-GAIN		26.	conscientious	con-shee-EN-shss	
2.	address	ah-DRESS *or* uh-DRESS		27.	homily	HOM-ih-lay *or* HOM-ih-lee	
3.	cough	kawf *or* kof		28.	malady	MAL-uh-day *or* MAL-uh-dee	
4.	preview	PREE-vyue		29.	subtle	SUH-tl	
5.	although	awl-THO		30.	fecund	FE-cund *or* FEE-cund	
6.	most	mohst		31.	palatable	PAL-ah-tuh-bul *or* PAL-uh-tuh-bul	
7.	excitement	eck-SITE-munt *or* ik-SITE-munt		32.	menagerie	meh-NA-juh-ree	
8.	know	noh *or* no		33.	obfuscate	OB-fuh-skate	
9.	plumb	plum		34.	liaison	lee-AY-zon *or* lee-AY-zn	
10	decorate	DEK-oh-rate *or* DEK-uh-rate		35.	exigency	eks-IH-jen-say *or* eks-IH-jen-see	
11.	fierce	fee-us *or* feersa		36.	xenophobia	zen-oh-FO-bee-uh	
12.	knead	need		37.	ogre	OH-gur	
13.	aisle	iyle		38.	scurrilous	SKUR-ih-lus *or* SKUR-uh-lus	
14.	vengeance	VEN-jnss		39.	ethereal	ih-THEE-ree-ul *or* ih-THEER-ee-ul	
15.	prestigious	pre-STIJ-us *or* pre-STEEJ-us		40.	paradigm	PAH-rah-dime	
16.	wreathe	reeTH *or* REEEth		41.	perspicuity	per-spuh-KYEW-uh-tee	
17.	gnat	nat		42.	plethora	PLETH-oh rah *or* PLETH-eh-rah	
18.	amphitheatre	AM-fih-thee-uh-ter		43.	lugubrious	loo-GOOB-ree-uss *or* loo-GOO-bree-uss	
19.	lieu	loo *or* l(y)oo		44.	treatise	TREE-tiz *or* TREET-iz	
20.	grotesque	gro-TESK		45.	dilettante	DILL-ih-tan-tay *or* DILL-uh-tahnt	
21.	iridescent	ihr-ih-DESS-unt *or* ihr-uh-DESS-unt		46.	vertiginous	ver-TIDJ-in-iss	
22.	ballet	BA-lay or ba-LAY *or* bal-ay		47.	ubiquitous	you-BIC-wuh-tiss *or* you-BIC-wuh-tus	
23.	equestrian	eh-KWESS-tree-un or ih- KWESS-tree-un		48.	hyperbole	hy-PER-bul-lay or hy PUR-bul-lay	
24.	porpoise	PAW-pss or POR-poyz (Scots)		49.	insouciant	in-SOO-see-yunt	
25.	aesthetic	ess-THET-ik *or* ees-THET-ik		50.	hegemony	heh-GEM-o-nee *or* heh-JEM-o-nee or HEH-geh-mon-ee	

WTAR Raw Score

WTAR Standard Score

Appendix XV

Table A.2. Standard Score Equivalents of WTAR Raw Scores

WTAR Raw Score	16–24	25–44	45–64	65–79	80–89	Reference Group
0	50	50	50	50	50	50
1	50	50	50	50	50	50
2	50	50	50	50	50	50
3	50	50	50	50	50	50
4	50	50	50	50	50	50
5	50	50	50	50	50	50
6	51	50	50	50	50	50
7	53	50	50	50	50	50
8	55	50	50	50	50	50
9	57	51	50	50	50	50
10	59	53	50	50	52	51
11	60	55	51	52	54	53
12	62	57	53	54	56	55
13	64	59	55	56	58	57
14	66	60	57	58	60	59
15	67	62	59	60	62	61
16	69	64	60	62	63	63
17	71	66	62	63	65	64
18	73	67	64	65	67	66
19	74	69	66	67	69	68
20	76	71	67	69	71	70
21	78	73	69	71	73	72
22	80	74	71	73	75	74
23	81	76	73	75	77	76
24	83	78	74	77	78	78
25	85	80	76	78	80	79
26	87	81	78	80	82	81
27	89	83	80	82	84	83
28	90	85	81	84	86	85
29	92	87	83	86	88	87
30	94	89	85	88	90	89
31	96	90	87	90	92	91
32	97	92	89	92	93	93
33	99	94	90	93	95	94
34	101	96	92	95	97	96
35	103	97	94	97	99	98
36	104	99	96	99	101	100
37	106	101	97	101	103	102
38	108	103	99	103	105	104
39	110	104	101	105	107	106
40	111	106	103	107	108	108
41	113	108	104	108	110	109
42	115	110	106	110	112	111
43	117	111	108	112	114	113
44	119	113	110	114	116	115
45	120	115	111	116	118	117
46	122	117	113	118	120	119
47	124	119	115	120	122	121
48	126	120	117	122	123	123
49	127	122	119	123	125	124
50	129	124	120	125	127	126

U.K. Standardization Sample All Ages

Table B.3. Demographics-Predicted WTAR Scores

Education Level	Predicted WTAR Score	90% Prediction Interval	95% Prediction Interval
None	96	74–118	70–122
Other	99	77–121	73–125
GSCE	103	91–125	87–129
A-Level	106	84–128	80–132
Diploma	110	88–132	84–136
Degree	113	91–135	87–139

Appendix XVI

Cognitive Impairment in HF Study

Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE)
Page 1

Version 1.0 (29 April 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion ___ D D M M Y Y Y Y 03

Relative/friend/carer to complete - please return at next study visit.

Now we want you to remember what your friend or relative was like 10 years ago and to compare it with what he/she is like now. 10 years ago was 2003. Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same or got worse in that situation over the past 10 years. Note the importance of comparing his/her present performance with 10 years ago. So if 10 years ago this person always forgot where he/she had left things, and he/she still does, then this would be considered "Hasn't changed much". Please indicate the changes you have observed by ticking the appropriate box.

Compared with 10 years ago how is this person at:

	Much improved	A bit improved	Not much change	A bit worse	Much worse	
1. Remembering things about family and friends e.g. occupations, birthdays, addresses	☐0	☐1	☐2	☐3	☐4	04
2. Remembering things that have happened recently	☐0	☐1	☐2	☐3	☐4	05
3. Recalling conversations a few days later	☐0	☐1	☐2	☐3	☐4	06
4. Remembering his/her address and telephone number	☐0	☐1	☐2	☐3	☐4	07
5. Remembering what day and month it is	☐0	☐1	☐2	☐3	☐4	08
6. Remembering where things are usually kept	☐0	☐1	☐2	☐3	☐4	09
7. Remembering where to find things which have been put in a different place from usual	☐0	☐1	☐2	☐3	☐4	10
8. Knowing how to work familiar machines around the house	☐0	☐1	☐2	☐3	☐4	11

Cognitive Impairment in HF Study

Short Form of the Informant Questionnaire on Cognitive Decline in the Elderly (Short IQCODE)
Page 2

Version 1.0 (29 April 2013)

Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊____⌋ 02 Date of Completion ⌊_____⌋ D D M M Y Y Y Y 03

	Much improved	A bit improved	Not much change	A bit worse	Much worse	
9. Learning to use a new gadget or machine around the house	☐0	☐1	☐2	☐3	☐4	04
10. Learning new things in general	☐0	☐1	☐2	☐3	☐4	05
11. Following a story in a book or on TV	☐0	☐1	☐2	☐3	☐4	06
12. Making decisions on everyday matters	☐0	☐1	☐2	☐3	☐4	07
13. Handling money for shopping	☐0	☐1	☐2	☐3	☐4	08
14. Handling financial matters e.g. the pension, dealing with the bank	☐0	☐1	☐2	☐3	☐4	09
15. Handling other everyday arithmetic problems e.g. knowing how much food to buy, knowing how long between visits from family or friends	☐0	☐1	☐2	☐3	☐4	10
16. Using his/her intelligence to understand what's going on and to reason things through	☐0	☐1	☐2	☐3	☐4	11

Appendix XVII

Cognitive Impairment in HF Study

Return Visit 1: Group 1, 2 or 5, Page 1
Hospital Anxiety and Depression Scale

Version 1.1 (24 Oct 2013)

Patient ID. [01] Initials [02] Date of Completion [03] (D D M M Y Y Y Y)

This questionnaire helps your physician to know how you are feeling. Read every sentence. Place an "X" in the box that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important.

I feel tense or 'wound up': [A]
- Most of the time 3
- A lot of the time 2
- From time to time, occasionally 1
- Not at all 0

[04]

I still enjoy the things I used to enjoy: [D]
- Definitely as much 0
- Not quite so much 1
- Only a little 2
- Not at all 3

[05]

I get a sort of frightened feeling as if something awful is about to happen: [A]
- Very definitely and quite badly 3
- Yes, but not too badly 2
- A little, but it doesn't worry me 1
- Not at all 0

[06]

I can laugh and see the funny side of things: [D]
- As much as I always could 0
- Not quite so much now 1
- Definately not so much now 2
- Not at all 3

[07]

Worrying thoughts go through my mind: [A]
- A great deal of the time 3
- A lot of the time 2
- From time to time but not too often 1
- Only occasionally 0

[08]

I feel cheerful: [D]
- Not at all 3
- Not often 2
- Sometimes 1
- Most of the time 0

[09]

I can sit at ease and feel relaxed: [A]
- Definitely 0
- Usually 1
- Not often 2
- Not at all 3

[10]

I feel as if I am slowed down: [D]
- Nearly all of the time 3
- Very often 2
- Sometimes 1
- Not at all 0

[11]

I get a sort of frightened feeling like 'butterflies in the stomach': [A]
- Not at all 0
- Occasionally 1
- Quite often 2
- Very often 3

[12]

I have lost interest in my appearance: [D]
- Definitely 3
- I don't take as much care as I should 2
- I may not take quite as much care 1
- I take just as much care as ever 0

[13]

I feel restless as if I have to be on the move: [A]
- Very much indeed 3
- Quite a lot 2
- Not very much 1
- Not at all 0

[14]

I look forward with enjoyment to things: [D]
- As much as I ever did 0
- Rather less than I used to 1
- Definitely less than I used to 2
- Hardly at all 3

[15]

I get sudden feelings of panic: [A]
- Very often indeed 3
- Quite often 2
- Not very often 1
- Not at all 0

[16]

I can enjoy a good book or radio or TV programme: [D]
- Often 0
- Sometimes 1
- Not often 2
- Very seldom 3

[17]

Cognitive Impairment in HF Study

Return Visit 1: Group 1, 2 or 5, Page 2
Kansas City Cardiomyopathy Questionnaire (KCCQ)

Version 1.1 (24 Oct 2013)

Patient ID. ☐☐ - ☐☐☐☐ 01 Initials ☐☐☐ 02 Date of Completion ☐☐ ☐☐ ☐☐ ☐☐ 03
D D M M Y Y Y Y

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some may mainly feel shortness of breath while others mainly fatigue. Please indicate how limited you have been by heart failure (for example, shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Please put an X in one box on each line

Activity	Extremely limited	Quite a bit limited	Moderately limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
1. Dressing yourself	☐0	☐1	☐2	☐3	☐4	☐5 04
2. Showering or having a bath	☐0	☐1	☐2	☐3	☐4	☐5 05
3. Walking 100 yards on level ground	☐0	☐1	☐2	☐3	☐4	☐5 06
4. Doing gardening, housework or carrying groceries	☐0	☐1	☐2	☐3	☐4	☐5 07
5. Climbing a flight of stairs without stopping ..	☐0	☐1	☐2	☐3	☐4	☐5 08
6. Jogging or hurrying (as if to catch a bus).....	☐0	☐1	☐2	☐3	☐4	☐5 09

2. Compared with 2 weeks ago, have your symptoms of heart failure (for example, shortness of breath, fatigue, or ankle swelling) changed?

	Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
My symptoms of heart failure are now....	☐0	☐1	☐2	☐3	☐4	☐5 10

3. Over the past 2 weeks, how many times have you had swelling in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐0	☐1	☐2	☐3	☐4 11

4. Over the past 2 weeks, how much has swelling in your feet, ankles or legs bothered you?

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no swelling
☐0	☐1	☐2	☐3	☐4	☐5 12

5. Over the past 2 weeks, on average, how many times has fatigue limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐0	☐1	☐2	☐3	☐4	☐5	☐6 13

Cognitive Impairment in HF Study

Return Visit 1: Group 1, 2 or 5, Page 3
Kansas City Cardiomyopathy Questionnaire (KCCQ) (continued)

Version 1.1 (24 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion ___ 03 (D D M M Y Y Y Y)

6. Over the past 2 weeks, how much has your fatigue bothered you?

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no fatigue
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5 04

7. Over the past 2 weeks, on average, how many times has shortness of breath limited your ability to do what you wanted?

All of the time	Several times a day	At least once a day	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6 05

8. Over the past 2 weeks, how much has your shortness of breath bothered you?

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no shortness of breath
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5 06

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of shortness of breath?

Every night	3 or more times a week but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4 07

10. Heart failure symptoms can worsen for a number of reasons. How sure are you Ihat you know what to do, or whom to call, if your heart failure gets worse?

Not at all sure	Not very sure	Somewhat sure	Mostly sure	Completely sure
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4 08

11. How well do you understand what things you are able to do to keep your heart failure symptoms from getting worse (for example, regularly weighing yourself, eating a low salt diet etc.)?

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4 09

12. Over the past 2 weeks, how much has your heart failure limited your enjoyment of life?

It has extremely limited my enjoyment of life	It has limited my enjoyment of life	It has moderately limited my enjoyment of life	It has slighty limited my enjoyment of life	It has not limited my enjoyment of life
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4 10

Cognitive Impairment in HF Study

Return Visit 1: Group 1, 2 or 5, Page 4
Kansas City Cardiomyopathy Questionnaire (KCCQ)
(continued)

Version 1.1 (24 Oct 2013)

Patient ID. ___-___ 01 Initials ___ 02 Date of Completion ___ 03 (D D M M Y Y Y Y)

13. If you had to spend the rest of your life with your heart failure the way it is right now, how would you feel about this?

Completely dissatisfied	Mostly dissatisfied	Somewhat dissatisfied	Mostly satisfied	Completely satisfied
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4 04

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your heart failure?

I have felt that way all of the time	I have felt that way most of the time	I have occasionall felt that way	I have rarely felt that way	I have never felt that way
☐ 0	☐ 1	☐ 2	☐ 3	☐ 4 05

15. How much does your heart failure affect your lifestyle? Please indicate how your heart failure may have limited your participation in the following activities over the past 2 weeks.

Please put an **X** in one box on each line.

Activity	Extremely limited	Quite a bit limited	Moderately limited	Slightly limited	Not at all limited	Limited for other reasons or did not do the activity
1. Hobbies, recreational activities	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5 06
2. Working or doing household chores	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5 07
3. Visiting family or friends	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5 08
4. Intimate or sexual relationships	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5 09

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion ___ 03 (D D M M Y Y Y Y)

A. EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐ 04

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐ 05

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐ 06

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐ 07

Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐ 08

Cognitive Impairment in HF Study

Return Visit 1: Group 1, 2 or 5, Page 6
EQ-5D (continued)

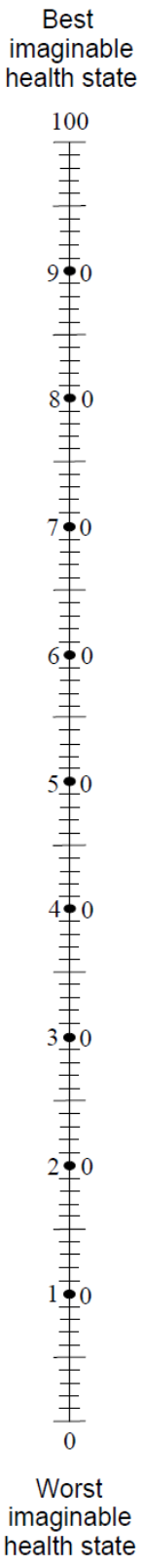
Version 1.1 (24 Oct 2013)

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today
04



Produced by Robertson Centre for Biostatistics, University of Glasgow

Appendix XVIII

Cognitive Impairment in HF Study **Self-Care of Heart Failure Index**
Page 1

Draf t 06

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

All answers are confidential.

Think about how you have been feeling in the last month or since we last spoke as you complete these items.

SECTION A:

Listed below are common instructions given to persons with heart failure. How routinely do you do the following?

	Never or rarely	Sometimes	Frequently	Always or daily	
1. Weigh yourself?	☐1	☐2	☐3	☐4	04
2. Check your ankles for swelling?	☐1	☐2	☐3	☐4	05
3. Try to avoid getting sick (e.g., flu shot, avoid ill people)?	☐1	☐2	☐3	☐4	06
4. Do some physical activity?	☐1	☐2	☐3	☐4	07
5. Keep doctor or nurse appointments?	☐1	☐2	☐3	☐4	08
6. Eat a low salt diet?	☐1	☐2	☐3	☐4	09
7. Exercise for 30 minutes?	☐1	☐2	☐3	☐4	10
8. Forget to take one of your medications?	☐1	☐2	☐3	☐4	11
9. Ask for low salt items when eating out or visitng others?	☐1	☐2	☐3	☐4	12
10. Use a system (pill box, reminders) to help you remember your medicines?	☐1	☐2	☐3	☐4	13

SECTION B:

Many patients have symptoms due to their heart failure. Trouble breathing and ankle swelling are common symptoms of heart failure.

In the past month, have you had trouble breathing or ankle swelling? Tick one.

No ☐0

Yes ☐1 14

Cognitive Impairment in HF Study **Self-Care of Heart Failure Index**
Page 2

Draf t 06

Patient ID. ___ - ___ 01 Initials ___ 02 Date of Completion D D M M Y Y Y Y 03

11. If you had trouble breathing or ankle swelling in the past month…

(tick **one** box)

	Have not had these	I did not recognise it	Not Quickly	Somewhat Quickly	Quickly	Very Quickly
How quickly did you recognize it as a symptom of heart failure?	N/A	☐0	☐1	☐2	☐3	☐4 04

Listed below are remedies that people with heart failure use. If you have trouble breathing or ankle swelling, how likely are you to try one of these remedies?

(tick **one** box for each remedy)

	Not Likely	Somewhat Likely	Likely	Very Likely
12. Reduce the salt in your diet	☐1	☐2	☐3	☐4 05
13. Reduce your fluid intake	☐1	☐2	☐3	☐4 06
14. Take an extra water pill	☐1	☐2	☐3	☐4 07
15. Call your doctor or nurse for guidance	☐1	☐2	☐3	☐4 08

16. Think of a remedy you tried the last time you had trouble breathing or ankle swelling.

(tick **one** box)

	I did not try anything	Not Sure	Somewhat Sure	Sure	Very Sure
How sure were you that the remedy helped or did not help?	☐0	☐1	☐2	☐3	☐4 09

Cognitive Impairment in HF Study **Self-Care of Heart Failure Index**
Page 3

Draf t 06

Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊_____⌋ 02 Date of Completion ⌊_____⌋ D D M M Y Y Y Y 03

SECTION C:

In general, how confident are you that you can:

	Not Confident	Somewhat Confident	Very Confident	Extremely Confident
17. Keep yourself free of heart failure symptoms?	☐1	☐2	☐3	☐4 04
18. Follow the treatment advice you have been given?	☐1	☐2	☐3	☐4 05
19. Evaluate the importance of your symptoms?	☐1	☐2	☐3	☐4 06
20. Recognize changes in your health if they occur?	☐1	☐2	☐3	☐4 07
21. Do something that will relieve your symptoms?	☐1	☐2	☐3	☐4 08
22. Evaluate how well a remedy works?	☐1	☐2	☐3	☐4 09

Appendix XIX

Cognitive Impairment in HF Study

The Zarit Burden Interview
Page 1

Version 1.0 (29 April 2013)

Patient ID. ⌊__⌋-⌊_____⌋ 01 Initials ⌊___⌋ 02 Date of Completion ⌊_____⌋ D D M M Y Y Y Y 03

Relative/friend/carer to complete - please return at next study visit.

Please tick the response that best describes how you feel.

	Never	Rarely	Sometimes	Quite Frequently	Nearly Always
1. Do you feel that your relative asks for more help than he/she needs?	☐0	☐1	☐2	☐3	☐4 04
2. Do you feel that because of the time you spend with your relative that you don't have enough time for yourself?	☐0	☐1	☐2	☐3	☐4 05
3. Do you feel stressed between caring for your relative and trying to meet other responsibilities for your family or work?	☐0	☐1	☐2	☐3	☐4 06
4. Do you feel embarrassed over your relative's behaviour?	☐0	☐1	☐2	☐3	☐4 07
5. Do you feel angry when you are around your relative?	☐0	☐1	☐2	☐3	☐4 08
6. Do you feel that your relative currently affects your relationships with other family members or friends in a negative way?	☐0	☐1	☐2	☐3	☐4 09
7. Are you afraid what the future holds for your relative?	☐0	☐1	☐2	☐3	☐4 10
8. Do you feel your relative is dependent on you?	☐0	☐1	☐2	☐3	☐4 11
9. Do you feel strained when you are around your relative?	☐0	☐1	☐2	☐3	☐4 12
10. Do you feel your health has suffered because of your involvement with your relative?	☐0	☐1	☐2	☐3	☐4 13
11. Do you feel that you don't have as much privacy as you would like because of your relative?	☐0	☐1	☐2	☐3	☐4 14
12. Do you feel that your social life has suffered because you are caring for your relative?	☐0	☐1	☐2	☐3	☐4 15
13. Do you feel uncomfortable about having friends over because of your relative?	☐0	☐1	☐2	☐3	☐4 16
14. Do you feel that your relative seems to expect you to take care of him/her as if you were the only one he/she could depend on?	☐0	☐1	☐2	☐3	☐4 17
15. Do you feel that you don't have enough money to take care of your relative in addition to the rest of your expenses?	☐0	☐1	☐2	☐3	☐4 18

Cognitive Impairment in HF Study

The Zarit Burden Interview continued ...
Page 2

Version 1.0 (29 April 2013)

Patient ID. __ - ____ 01 Initials ____ 02 Date of Completion __ __ __ __ __ __ __ __ D D M M Y Y Y Y 03

Please tick the response that best describes how you feel.

	Never	Rarely	Sometimes	Quite Frequently	Nearly Always
16. Do you feel that you will be unable to take care of your relative much longer?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4 04
17. Do you feel you have lost control of your life since your relative's illness?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4 05
18. Do you wish you could leave the care of your relative to someone else?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4 06
19. Do you feel uncertain about what to do about your relative?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4 07
20. Do you feel you should be doing more for your relative?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4 08
21. Do you feel you could do a better job in caring for your relative?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4 09
22. Overall, how burdened do you feel in caring for your relative?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4 10

Appendix XX

NHS Greater Glasgow & Clyde
Research & Development Department

Research and Development Department
NHS Greater Glasgow and Clyde

38 Church Street
Tennent Institute
R&D Management Offices
Western Infirmary
Glasgow
G11 6NT

Dr Jane Cannon University of Glasgow 126 University Place Glasgow jane.cannon@glasgow.ac.uk	Enquiries to: Extension: Direct Line: Date:	Ms Eileen McCafferty, Auditor Eileen.McCafferty2@ggc.scot.nhs.uk Mrs Jane Alexander, Co-ord Assistant Jane.Alexander@ggc.scot.nhs.uk 5 2207 0141 211 2207 or 0141 211 8550 23.06.2015

Investigator:	**Dr Jane Cannon**
Site:	**Glasgow Royal Infirmary**
Subject:	**Audit of: Non Commercial (Academic) Study**
Sponsor:	**NHS Greater Glasgow & Clyde**
Title:	**Cognitive Impairment in Heart Failure**
Acronym:	**n/a**
R&D Reference:	**GN12CA384**

Dear Dr Cannon

In order to comply with the Research Governance Framework for Health and Community Care 2006 (as amended) http://www.cso.scot.nhs.uk/nrs/research-governance/, NHS Greater Glasgow & Clyde is obliged to have oversight of all research conducted on NHS premises.

Part of this process includes systematic audit of Investigator site files. The above study is registered on our Research and Development (R&D) database and has been selected for internal audit by the R&D Governance Team.

The aim of the audit will be to review essential documentation within your site file(s). I anticipate the audit will take a few hours to conduct.

I would therefore be grateful if you could:

1. **Confirm a suitable date from below for me to conduct the audit**

   - **13 July – 31 July 2015**

If these dates are unsuitable, please indicate an alternative date. Please also advise a time which is convenient for you.

2. Confirm site to visit is as shown above.

3. Ensure the site file(s), which includes data collection forms and consent forms, are available for audit and there is dedicated space available for the audit to be undertaken. *Please note, casenotes and x-rays will not be required.*

4. Ensure either you or a member of your study team is available at the start and end of the audit.

In the meantime, please do not hesitate to contact me prior to the audit if I can be of any assistance.

Kind regards

Eileen McCafferty

Eileen McCafferty
Research Audit Facilitator

Appendix XXI

3 Figure Copy

Time Limit: 4 minutes

Fold this page back and present the Figure Copy Drawing Page along with the stimulus. Ask the examinee to make an exact copy of the figure. Tell the examinee that he or she is being timed, but that the score is based on the exactness of his or her copy.

Say: *In front of you is a figure. I want you to make an exact copy, but, before you begin, I need to tell you I will be timing you. It is important that you make an exact copy of the figure. To let me know you understand can you tell me what I have asked?* (Correct as necessary and re-enforce exactness of copy)

Scoring: 1 point for correctness and completeness (drawing), and 1 point for proper placement. See Appendix 1 in Stimulus Booklet A for complete scoring criteria and scoring examples.

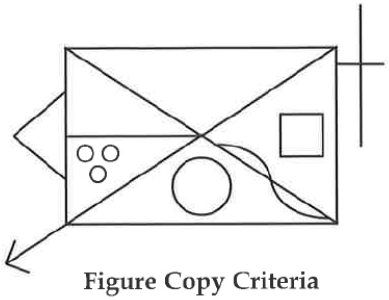


Figure Copy Criteria
(Fold back for use.)

Item	Drawing (0 or 1)	Placement (0 or 1)	Score (0, 1, or 2)	Scoring Critetria
1. **rectangle**				**Drawing:** lines unbroken and relatively straight; it appears a rectangle. **Placement:** not rotated more than 15 degrees.
2. **diagonal cross**				**Drawing:** lines are unbroken, relatively straight and approximately bisect each other. **Placement:** ends of lines should meet corners without significant overlap or significant distance from the corners.
3. **horizontal line**				**Drawing:** line is unbroken and relatively straight; should not exceed approximately 1/2 of the width. **Placement:** from approximately the centre of the left side and intersect at approximately the diagonal cross.
4. **circle**				**Drawing:** relatively round, unbroken, and relatively closed; diameter should be approximately 1/4 - 1/3 height of triangle. **Placement:** placed in appropriate segment; not touching any other figure.
5. **3 small circles**				**Drawing:** relatively round, unbroken and relatively closed; approximately equal in size; approximate triangular arrangement; not touching each other. **Placement:** in appropriate segment; not touching figure; triangle formed not rotated more than approximately 15 degrees.
6. **square**				**Drawing:** relatively closed; appears to be a square; lines relatively straight and unbroken; height is approximately 1/4 - 1/3 of triangle. **Placement:** in appropriate segment; not touching any other part of figure; not rotated more than approximately 15 degrees.
7. **curving line**				**Drawing:** 2 curved segments; approximately equal in appearance; correct direction of curves. **Placement:** ends of lines approximately touch diagonal; do not touch very corner of rectangle or diagonal intersection.
8. **outside cross**				**Drawing:** vertical line is relatively parallel to side of rectangle; horizontal line crosses the vertical at approximately 90 degrees and is between 20-50% of length of vertical line. **Placement:** horizontal line touches rectangle higher than 2/3 height of rectangle, but below top; it approximately touches the rectangle; vertical line stretches above the height of the rectangle and down to approximately the mid-point of the rectangle.
9. **triangle**				**Drawing:** angle formed by two sides is between approximately 60-100 degrees; sides are relatively straight, unbroken and meet in a point; distance on vertical side of triangle subsumed is approximately 50% of the height of vertical side. **Placement:** approximately at top of rectangle.
10. **arrow**				**Drawing:** relatively straight and unbroken; lines forming arrow are approximately equal in length. **Placement:** protrudes from appropriate corner of rectangle; it appears an approximate continuation of diagonal staff.
		Total Score Range=0-20		

Reference List

(1) Peterson A, Lantz MS. Is it Alzheimer's? Neuropsychological testing helps to clarify diagnostic puzzle. *Geriatrics* 2001;56:58, 61.

(2) McMurray JJ, Adamopoulos S, Anker SD et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;33:1787-1847.

(3) McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med* 1971;285:1441-1446.

(4) Curtis LH, Whellan DJ, Hammill BG et al. Incidence and prevalence of heart failure in elderly persons, 1994-2003. *Arch Intern Med* 2008;168:418-424.

(5) Jhund PS, MacIntyre K, Simpson CR et al. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation* 2009;119:515-523.

(6) Murphy NF, Simpson CR, McAlister FA et al. National survey of the prevalence, incidence, primary care burden, and treatment of heart failure in Scotland *Heart* 2004;90:1129-1136.

(7) Cowie MR, Wood DA, Coats AJ et al. Incidence and aetiology of heart failure; a population-based study *Eur Heart J* 1999;20:421-428.

(8) Remes J, Reunanen A, Aromaa A, Pyorala K. Incidence of heart failure in eastern Finland: a population-based surveillance study *Eur Heart J* 1992;13:588-593.

(9) Senni M, Tribouilloy CM, Rodeheffer RJ et al. Congestive heart failure in the community: trends in incidence and survival in a 10-year period. *Arch Intern Med* 1999;159:29-34.

(10) Elliott P, Andersson B, Arbustini E et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008;29:270-276.

(11) Fox KF, Cowie MR, Wood DA et al. Coronary artery disease as the cause of incident heart failure in the population *Eur Heart J* 2001;22:228-236.

(12) Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis *J Am Coll Cardiol* 2004;43:317-327.

(13) Petrie MC, Hogg K, Caruana L, McMurray JJ. Poor concordance of commonly used echocardiographic measures of left ventricular diastolic function in patients with suspected heart failure but preserved systolic function: is there a reliable echocardiographic measure of diastolic dysfunction? *Heart* 2004;90:511-517.

(14) McMurray JJ, Pfeffer MA. Heart failure. *Lancet* 2005;365:1877-1889.

(15) Frank O. Zur Dynamik des Herzmuskels. Ztschr.Biol. 32[370]. 2015. Ref Type: Generic

(16) Patterson SW, Starling EH. On the mechanical factors which determine the output of the ventricles *J Physiol* 1914;48:357-379.

(17) Starling EH. The Linacre Lecture of the Law of the Heart. Cambridge 1915. 2015. New York: Longmans, Green & Co., 1918. Ref Type: Generic

(18) Katz AM. The descending limb of the Starling curve and the failing heart. *Circulation* 1965;32:871-875.

(19) Harlan WR, Oberman A, Grimm R, Rosati RA. Chronic congestive heart failure in coronary artery disease: clinical criteria *Ann Intern Med* 1977;86:133-138.

(20) SIGN 147. Management of chronic heart failure 2016. 2015. Ref Type: Generic

(21) Mant J, Doust J, Roalfe A et al. Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care *Health Technol Assess* 2009;13:1-207, iii.

(22) Davie AP, Francis CM, Love MP et al. Value of the electrocardiogram in identifying heart failure due to left ventricular systolic dysfunction *BMJ* 1996;312:222.

(23) McDonagh TA, Cunningham AD, Morrison CE et al. Left ventricular dysfunction, natriuretic peptides, and mortality in an urban population*Heart* 2001;86:21-26.

(24) Tsutamoto T, Wada A, Maeda K et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction*Circulation* 1997;96:509-516.

(25) Francis CM, Caruana L, Kearney P et al. Open access echocardiography in management of heart failure in the community *BMJ* 1995;310:634-636.

(26) The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N.Engl.J.Med. 316 (23), 1429-1435. 2015.
Ref Type: Generic

(27) The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N.Engl.J.Med. 325 (5), 293-302. 2015.
Ref Type: Generic

(28) Granger CB, McMurray JJ, Yusuf S et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial*Lancet* 2003;362:772-776.

(29) Packer M, Fowler MB, Roecker EB et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study *Circulation* 2002;106:2194-2199.

(30) Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 353 (9169), 2001-2007. 2015.
Ref Type: Generic

(31) CIBIS-II Investigators. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. Lancet 353 (9146), 9-13. 2015.
Ref Type: Generic

(32) Pitt B, Zannad F, Remme WJ et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators *N Engl J Med* 1999;341:709-717.

(33) Zannad F, McMurray JJ, Krum H et al. Eplerenone in patients with systolic heart failure and mild symptoms*N Engl J Med* 2011;364:11-21.

(34) Swedberg K, Komajda M, Bohm M et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study*Lancet* 2010;376:875-885.

(35) The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N.Engl.J.Med. 336, 525-533. 2015.
Ref Type: Generic

(36) Cohn JN, Archibald DG, Ziesche S et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study*N Engl J Med* 1986;314:1547-1552.

(37) Bardy GH, Lee KL, Mark DB et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure*N Engl J Med* 2005;352:225-237.

(38) Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators *N Engl J Med* 1999;341:1882-1890.

(39) Moss AJ, Hall WJ, Cannom DS et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators*N Engl J Med* 1996;335:1933-1940.

(40) Moss AJ, Zareba W, Hall WJ et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-883.

(41) Cleland JG, Daubert JC, Erdmann E et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure *N Engl J Med* 2005;352:1539-1549.

(42) Moss AJ, Hall WJ, Cannom DS et al. Cardiac-resynchronization therapy for the prevention of heart-failure events*N Engl J Med* 2009;361:1329-1338.

(43) Tang AS, Wells GA, Talajic M et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure*N Engl J Med* 2010;363:2385-2395.

(44) Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study*Eur Heart J* 2006;27:2338-2345.

(45) Massie BM, Carson PE, McMurray JJ et al. Irbesartan in patients with heart failure and preserved ejection fraction *N Engl J Med* 2008;359:2456-2467.

(46) Yusuf S, Pfeffer MA, Swedberg K et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial*Lancet* 2003;362:777-781.

(47) Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK*Eur J Heart Fail* 2002;4:361-371.

(48) Cowie MR, Fox KF, Wood DA et al. Hospitalization of patients with heart failure: a population-based study*Eur Heart J* 2002;23:877-885.

(49) Roger VL, Weston SA, Redfield MM et al. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004;292:344-350.

(50) Solomon SD, Dobson J, Pocock S et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure*Circulation* 2007;116:1482-1487.

(51) Pocock SJ, Ariti CA, McMurray JJ et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies *Eur Heart J* 2013;34:1404-1413.

(52) EK Miller. Executive function and higher order cognition: Definition and Neural Substrate. Encyclopedia of Neuroscience 2009 [4], 99-104.

(53) Bottino CM, Zevallos-Bustamante SE, Lopes MA et al. Combined instruments for the screening of dementia in older people with low education*Arq Neuropsiquiatr* 2009;67:185-190.

(54) Mathuranath PS, Nestor PJ, Berrios GE, Rakowicz W, Hodges JR. A brief cognitive test battery to differentiate Alzheimer's disease and frontotemporal dementia. *Neurology* 2000;55:1613-1620.

(55) Bauer L, Pozehl B, Hertzog M, Johnson J, Zimmerman L, Filipi M. A brief neuropsychological battery for use in the chronic heart failure population*Eur J Cardiovasc Nurs* 2012;11:223-230.

(56) Harrison JK, Fearon P, Noel-Storr AH, McShane R, Stott DJ, Quinn TJ. Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) for the diagnosis of dementia within a general practice (primary care) setting*Cochrane Database Syst Rev* 2014;7:CD010771.

(57) Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation *Psychol Med* 1994;24:145-153.

(58) San Antonia T. The Psychological Corporation (2001). *Wechsler Test of Adult Reading*. 2015.

(59) Brand N, Jolles J. Information processing in depression and anxiety*Psychol Med* 1987;17:145-153.

(60) Ilsley JE, Moffoot AP, O'Carroll RE. An analysis of memory dysfunction in major depression*J Affect Disord* 1995;35:1-9.

(61) Sax KW, Strakowski SM, McElroy SL, Keck PE, Jr., West SA. Attention and formal thought disorder in mixed and pure mania *Biol Psychiatry* 1995;37:420-423.

(62) Marvel CL, Paradiso S. Cognitive and neurological impairment in mood disorders*Psychiatr Clin North Am* 2004;27:19-viii.

(63) Wilson RS, Barnes LL, Mendes de Leon CF et al. Depressive symptoms, cognitive decline, and risk of AD in older persons*Neurology* 2002;59:364-370.

(64) Zigmond AS, Snaith RP. The hospital anxiety and depression scale *Acta Psychiatr Scand* 1983;67:361-370.

(65) Crawford JR, Henry JD, Crombie C, Taylor EP. Normative data for the HADS from a large non-clinical sample*Br J Clin Psychol* 2001;40:429-434.

(66) World Health Organisation. The ICD-10 Classification of Mental and Behavioural Disorders. 2015.

(67) Jicha GA, Parisi JE, Dickson DW et al. Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia. *Arch Neurol* 2006;63:674-681.

(68) Georgiadis D, Sievert M, Cencetti S et al. Cerebrovascular reactivity is impaired in patients with cardiac failure. *Eur Heart J* 2000;21:407-413.

(69) Vogels RL, Oosterman JM, van HB et al. Profile of cognitive impairment in chronic heart failure. *J Am Geriatr Soc* 2007;55:1764-1770.

(70) Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a meta-analysis *Ann Intern Med* 2013;158:338-346.

(71) Yang H, Niu W, Zang X, Lin M, Zhao Y. The association between atrial fibrillation and cognitive function in patients with heart failure*Eur J Cardiovasc Nurs* 2016.

(72) Neuberger HR, Mewis C, van Veldhuisen DJ et al. Management of atrial fibrillation in patients with heart failure. *Eur Heart J* 2007;28:2568-2577.

(73) Feola M, Rosso GL, Peano M et al. Correlation between cognitive impairment and prognostic parameters in patients with congestive heart failure. *Arch Med Res* 2007;38:234-239.

(74) Debette S, Bauters C, Leys D, Lamblin N, Pasquier F, de GP. Prevalence and determinants of cognitive impairment in chronic heart failure patients. *Congestive Heart Failure* 2007;13:205-208.

(75) Kindermann I, Fischer D, Karbach J et al. Cognitive function in patients with decompensated heart failure: the Cognitive Impairment in Heart Failure (CogImpair-HF) study. *Eur J Heart Fail* 2012;14:404-413.

(76) Schmidt R, Fazekas F, Offenbacher H, Dusleag J, Lechner H. Brain magnetic resonance imaging and neuropsychologic evaluation of

patients with idiopathic dilated cardiomyopathy. *Stroke* 1991;22:195-199.

(77) Caplan LR. Translating what is known about neurological complications of coronary artery bypass graft surgery into action. *Arch Neurol* 2009;66:1062-1064.

(78) Kahlert P, Knipp SC, Schlamann M et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation* 2010;121:870-878.

(79) Diez-Quevedo C, Lupon J, Gonzalez B et al. Depression, antidepressants, and long-term mortality in heart failure. *Int J Cardiol* 2013;167:1217-1225.

(80) Willis MS, Patterson C. Proteotoxicity and cardiac dysfunction--Alzheimer's disease of the heart? *N Engl J Med* 2013;368:455-464.

(81) Athilingam P, Moynihan J, Chen L, D'Aoust R, Groer M, Kip K. Elevated Levels of Interleukin 6 and C-Reactive Protein Associated With Cognitive Impairment in Heart Failure. *Congest Heart Fail* 2012.

(82) Tchistiakova E, Anderson ND, Greenwood CE, MacIntosh BJ. Combined effects of type 2 diabetes and hypertension associated with cortical thinning and impaired cerebrovascular reactivity relative to hypertension alone in older adults. *Neuroimage Clin* 2014;5:36-41.

(83) Conti JB, Sears SF. Cardiac resynchronization therapy: can we make our heart failure patients smarter? *Trans Am Clin Climatol Assoc* 2007;118:153-164.

(84) Gruhn N, Larsen FS, Boesgaard S et al. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke* 2001;32:2530-2533.

(85) Koide H, Kobayashi S, Kitani M, Tsunematsu T, Nakazawa Y. Improvement of cerebral blood flow and cognitive function following pacemaker implantation in patients with bradycardia. *Gerontology* 1994;40:279-285.

(86) Kalaria VG, Passannante MR, Shah T, Modi K, Weisse AB. Effect of mitral regurgitation on left ventricular thrombus formation in dilated cardiomyopathy. *Am Heart J* 1998;135:215-220.

(87) Al-Khadra AS, Salem DN, Rand WM, Udelson JE, Smith JJ, Konstam MA. Antiplatelet agents and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction (SOLVD) trial. *J Am Coll Cardiol* 1998;31:419-425.

(88) Freudenberger RS, Hellkamp AS, Halperin JL et al. Risk of thromboembolism in heart failure: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation* 2007;115:2637-2641.

(89) Braunwald E. Heart Disease. Textbook of Cardiovascular Medicine . WB Saunders.

(90) Quinn TJ, Gallacher J, Deary IJ, Lowe GD, Fenton C, Stott DJ. Association between circulating hemostatic measures and dementia or cognitive impairment: systematic review and meta-analyzes. *J Thromb Haemost* 2011;9:1475-1482.

(91) Huijts M, van Oostenbrugge RJ, Duits A et al. Cognitive impairment in heart failure: results from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) randomized trial. *Eur J Heart Fail* 2013.

(92) Sink KM, Leng X, Williamson J et al. Angiotensin-converting enzyme inhibitors and cognitive decline in older adults with hypertension: results from the Cardiovascular Health Study. *Arch Intern Med* 2009;169:1195-1202.

(93) Solfrizzi V, Scafato E, Frisardi V et al. Angiotensin-converting enzyme inhibitors and incidence of mild cognitive impairment. The Italian Longitudinal Study on Aging. *Age (Dordr)* 2013;35:441-453.

(94) Levi MN, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. *J Hypertens* 2013;31:1073-1082.

(95) Korte SM, Korte-Bouws GA, Koob GF, De Kloet ER, Bohus B. Mineralocorticoid and glucocorticoid receptor antagonists in animal models of anxiety. *Pharmacol Biochem Behav* 1996;54:261-267.

(96) Packer M, Califf RM, Konstam MA et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). *Circulation* 2002;106:920-926.

(97) McMurray JJ, Packer M, Desai AS et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.

(98) Madani R, Poirier R, Wolfer DP et al. Lack of neprilysin suffices to generate murine amyloid-like deposits in the brain and behavioral deficit in vivo. *J Neurosci Res* 2006;84:1871-1878.

(99) Kubo T, Sato T, Noguchi T et al. Influences of donepezil on cardiovascular system--possible therapeutic benefits for heart failure--donepezil cardiac test registry (DOCTER) study. *J Cardiovasc Pharmacol* 2012;60:310-314.

(100) Harkness K. Cognitive Function and Self-Care Management in Older Patients with Heart Failure. European Journal of Cardiovascular Nursing 2013 12. 2013.

(101) van DD, Keizer AM, Diephuis JC, Durand C, Vos LJ, Hijman R. Neurocognitive dysfunction after coronary artery bypass surgery: a systematic review. *J Thorac Cardiovasc Surg* 2000;120:632-639.

(102) Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: the Framingham Study. *Am J Epidemiol* 1993;138:353-364.

(103) Kilander L, Andren B, Nyman H, Lind L, Boberg M, Lithell H. Atrial fibrillation is an independent determinant of low cognitive function: a cross-sectional study in elderly men. *Stroke* 1998;29:1816-1820.

(104) Stewart S, MacIntyre K, Capewell S, McMurray JJ. Heart failure and the aging population: an increasing burden in the 21st century? *Heart* 2003;89:49-53.

(105) Critical Appraisal Skills Programme 2014. 2016.

(106) PROSPERO International Prospective Register of Systematic Reviews. 2016.

(107) Callegari S, Majani G, Giardini A et al. Relationship between cognitive impairment and clinical status in chronic heart failure patients. *Monaldi Arch Chest Dis* 2002;58:19-25.

(108) Sauve MJ, Lewis WR, Blankenbiller M, Rickabaugh B, Pressler SJ. Cognitive impairments in chronic heart failure: a case controlled study. *J Card Fail* 2009;15:1-10.

(109) Trojano L, Antonelli Inc, Acanfora D, Picone C, Mecocci P, Rengo F. Cognitive impairment: a key feature of congestive heart failure in the elderly. *J Neurol* 2003;250:1456-1463.

(110) Pressler S. Cognitive deficits and health-related quality of life in chronic heart failure. Journal of Cardiovascular Nursing 2010 25, 189-198. 2013.

(111) Festa JR, Jia X, Cheung K et al. Association of low ejection fraction with impaired verbal memory in older patients with heart failure. *Arch Neurol* 2011;68:1021-1026.

(112) Bratzke-Bauer L. Neuropsychological patterns differ by type of left ventricular dysfunction in heart failure. Pozehl B, editor. Archives of Clinical Neuropsychology 2013 28, 114-124. 2013.

(113) Bauer L, Pozehl B, Hertzog M, Johnson J, Zimmerman L, Filipi M. A brief neuropsychological battery for use in the chronic heart failure population. *Eur J Cardiovasc Nurs* 2012;11:223-230.

(114) Alosco ML, Spitznagel MB, Cohen R et al. Reduced cognitive function predicts functional decline in patients with heart failure over 12 months. *European Journal of Cardiovascular Nursing*13:2014.

(115) Alosco ML, Spitznagel MB, Raz N et al. Executive dysfunction is independently associated with reduced functional independence in heart failure. *Journal of Clinical Nursing* 2014;23:829-836.

(116) Alosco ML, Gunstad J, Jerskey BA et al. The adverse effects of reduced cerebral perfusion on cognition and brain structure in older adults with cardiovascular disease. *Brain and Behavior*3:November.

(117) Alosco ML, Spitznagel MB, Raz N et al. Cognitive reserve moderates the association between heart failure and cognitive impairment. *J Clin Exp Neuropsychol* 2012;34:1-10.

(118) Miller LA, Spitznagel MB, Alosco ML et al. Cognitive profiles in heart failure: a cluster analytic approach. *J Clin Exp Neuropsychol* 2012;34:509-520.

(119) Antonelli Inc, Trojano L, Acanfora D et al. Verbal memory impairment in congestive heart failure. *J Clin Exp Neuropsychol* 2003;25:14-23.

(120) Arslanian-Engoren C, Giordani BJ, Algase D, Schuh A, Lee C, Moser DK. Cognitive dysfunction in older adults hospitalized for acute heart failure. *Journal of Cardiac Failure* 2014;20:669-678.

(121) Athilingam P, King KB, Burgin SW, Ackerman M, Cushman LA, Chen L. Montreal Cognitive Assessment and Mini-Mental Status Examination compared as cognitive screening tools in heart failure. *Heart Lung* 2011;40:521-529.

(122) Baldasseroni S, Mossello E, Romboli B et al. Relationship between cognitive function and 6-minute walking test in older outpatients with chronic heart failure. *Aging-Clinical & Experimental Research* 2010;22:308-313.

(123) Cacciatore F, Abete P, Ferrara N et al. Congestive heart failure and cognitive impairment in an older population. Osservatorio Geriatrico Campano Study Group. *Journal of the American Geriatrics Society* 1998;46:1343-1348.

(124) Cameron J. Does Cognitive Impairment Predict Poor Self-Care in Patients with Heart Failure. Worrall-Carter L, editor. European Journal of Heart Failure 2010 12, 508-515. 2013.

(125) Dodson J. Cognitive Impairment in Older Adults with Heart Failure: Prevalence, Documentation, and Impact on Outcomes. Truong T, editor. The American Journal of Medicine 2013 126, 120-126. 2013.

(126) Feola M, Garnero S, Vallauri P et al. Relationship between Cognitive Function, Depression/Anxiety and Functional Parameters in Patients Admitted for Congestive Heart Failure*The Open Cardiovascular Medicine Journal* 2013;7:54-60.

(127) Gallagher R, Sullivan A, Burke R et al. Mild cognitive impairment, screening, and patient perceptions in heart failure patients. *Journal of Cardiac Failure* 2013;19:641-646.

(128) Garcia S, Spitznagel MB, Cohen R et al. Depression is associated with cognitive dysfunction in older adults with heart failure. *Cardiovascular Psychiatry and Neurology , 2011 Article Number: 368324 Date of Publication: 2011*:368324.

(129) Ghanbari A, Moaddab F, Salari A, Kazemnezhad LE, Sedghi SM, Paryad E. The study of cognitive function and related factors in patients with heart failure. *Nursing & Midwifery Studies* 2013;2:34-38.

(130) Hajduk AM, Lemon SC, McManus DD et al. Cognitive impairment and self-care in heart failure. *Clinical Epidemiology* 2013;5:407-416.

(131) Hawkins LA, Kilian S, Firek A, Kashner TM, Firek CJ, Silvet H. Cognitive impairment and medication adherence in outpatients with heart failure. *Heart & Lung* 2012;41:572-582.

(132) Hawkins MA, Gunstad J, Dolansky MA et al. Greater body mass index is associated with poorer cognitive functioning in male heart failure patients. *Journal of Cardiac Failure* 2014;20:199-206.

(133) Hjelm C, Stromberg A, Arestedt K, Brostrom A. Association between sleep-disordered breathing, sleep-wake pattern, and cognitive impairment among patients with chronic heart failure. *European Journal of Heart Failure* 2013;15:496-504.

(134) Jesus PA, Vieira-de-Melo RM, Reis FJ et al. Cognitive dysfunction in congestive heart failure: transcranial Doppler evidence of microembolic etiology. *Arquivos de Neuro-Psiquiatria* 2006;64:207-210.

(135) Steinberg G, Lossnitzer N, Schellberg D et al. Peak oxygen uptake and left ventricular ejection fraction, but not depressive symptoms, are associated with cognitive impairment in patients with chronic heart failure. *Int J Gen Med* 2011;4:879-887.

(136) Vogels RL, Oosterman JM, van HB et al. Neuroimaging and correlates of cognitive function among patients with heart failure. *Dementia & Geriatric Cognitive Disorders* 2007;24:418-423.

(137) Almeida OP, Beer C, Lautenschlager NT, Arnolda L, Alfonso H, Flicker L. Two-year course of cognitive function and mood in adults with congestive heart failure and coronary artery disease: the Heart-Mind Study. *International Psychogeriatrics* 2012;24:38-47.

(138) Hjelm C, Dahl A, Brostrom A, Martensson J, Johansson B, Stromberg A. The influence of heart failure on longitudinal changes in cognition among individuals 80 years of age and older. *J Clin Nurs* 2012;21:994-1003.

(139) Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study
Arch Intern Med 2006;166:1003-1008.

(140) Riegel B, Lee CS, Glaser D, Moelter ST. Patterns of Change in Cognitive Function over Six Months in Adults with Chronic Heart Failure*Cardiol Res Pract* 2012;2012:631075.

(141) Riegel B, Lee CS, Glaser D, Moelter ST. Patterns of Change in Cognitive Function over Six Months in Adults with Chronic Heart Failure. *Cardiol Res Pract* 2012;2012:631075.

(142) Alosco ML, Gunstad J, Jerskey BA et al. The adverse effects of reduced cerebral perfusion on cognition and brain structure in older adults with cardiovascular disease*Brain Behav* 2013;3:626-636.

(143) Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail* 2007;9:440-449.

(144) Udompanich S, Lip GY, Apostolakis S, Lane DA. Atrial fibrillation as a risk factor for cognitive impairment: a semi-systematic review. *QJM* 2013;106:795-802.

(145) Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol* 2009;8:1006-1018.

(146) Eggermont LH, de BK, Muller M, Jaschke AC, Kamp O, Scherder EJ. Cardiac disease and cognitive impairment: a systematic review. *Heart* 2012;98:1334-1340.

(147) McCusker J, Cole M, Dendukuri N, Han L, Belzile E. The course of delirium in older medical inpatients: a prospective study *J Gen Intern Med* 2003;18:696-704.

(148) World Health Organisation. The ICD-10 classification of mental and behavioural disorders. 2015.

(149) Killip T, III, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients *Am J Cardiol* 1967;20:457-464.

(150) Mathieu A, Mazza S, Decary A et al. Effects of obstructive sleep apnea on cognitive function: a comparison between younger and older OSAS patients *Sleep Med* 2008;9:112-120.

(151) Knopman DS, DeKosky ST, Cummings JL et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology*Neurology* 2001;56:1143-1153.

(152) McDonagh TA, Gardner R, Clark A, Dargie H. Oxford textbook of heart failure. Oxford textbooks . 2015.

(153) Andreasen N, Hesse C, Davidsson P et al. Cerebrospinal fluid beta-amyloid(1-42) in Alzheimer disease: differences between early- and late-onset Alzheimer disease and stability during the course of disease *Arch Neurol* 1999;56:673-680.

(154) Arai H, Higuchi S, Sasaki H. Apolipoprotein E genotyping and cerebrospinal fluid tau protein: implications for the clinical diagnosis of Alzheimer's disease. *Gerontology* 1997;43 Suppl 1:2-10.

(155) Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189-198.

(156) Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level *JAMA* 1993;269:2386-2391.

(157) Stuss DT, Meiran N, Guzman DA, Lafleche G, Willmer J. Do long tests yield a more accurate diagnosis of dementia than short tests? A comparison of 5 neuropsychological tests*Arch Neurol* 1996;53:1033-1039.

(158) Nelson A, Fogel BS, Faust D. Bedside cognitive screening instruments. A critical assessment *J Nerv Ment Dis* 1986;174:73-83.

(159) Simard M, van RR. Memory assessment in studies of cognition-enhancing drugs for Alzheimer's disease *Drugs Aging* 1999;14:197-230.

(160) Nasreddine ZS, Phillips NA, Bedirian V et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695-699.

(161) McLennan SN, Mathias JL, Brennan LC, Stewart S. Validity of the montreal cognitive assessment (MoCA) as a screening test for mild

cognitive impairment (MCI) in a cardiovascular population*J Geriatr Psychiatry Neurol* 2011;24:33-38.

(162) Davis KK, Allen JK. Identifying cognitive impairment in heart failure: a review of screening measures*Heart Lung* 2013;42:92-97.

(163) Harkness K, Demers C, Heckman GA, McKelvie RS. Screening for cognitive deficits using the Montreal cognitive assessment tool in outpatients >/=65 years of age with heart failure. *Am J Cardiol* 2011;107:1203-1207.

(164) Lees R, Corbet S, Johnston C, Moffitt E, Shaw G, Quinn TJ. Test accuracy of short screening tests for diagnosis of delirium or cognitive impairment in an acute stroke unit setting*Stroke* 2013;44:3078-3083.

(165) Zadikoff C, Fox SH, Tang-Wai DF et al. A comparison of the mini mental state exam to the Montreal cognitive assessment in identifying cognitive deficits in Parkinson's disease*Mov Disord* 2008;23:297-299.

(166) Cameron J, Worrall-Carter L, Page K, Stewart S, Ski CF. Screening for mild cognitive impairment in patients with heart failure: Montreal cognitive assessment versus mini mental state exam *Eur J Cardiovasc Nurs* 2013;12:252-260.

(167) Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): preliminary clinical validity*J Clin Exp Neuropsychol* 1998;20:310-319.

(168) Duff K, Patton D, Schoenberg MR, Mold J, Scott JG, Adams RL. Age- and education-corrected independent normative data for the RBANS in a community dwelling elderly sample*Clin Neuropsychol* 2003;17:351-366.

(169) Kaufman, Alan S. Assessing adolescent and adult intelligence 3rd edition. 2015.

(170) 4th Edition from Pearson. Wechsler Adult Intelligence Scale. 2015.

(171) The Psychological corporation. Manual for the Wechsler adult intelligence scale-revised (WAIS-R). 2015.

(172) Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education *Arch Clin Neuropsychol* 2004;19:203-214.

(173) Spreen. Neurosensory Centre Comprehensive Examination for Aphasia. Benton, editor. 2015.

(174) Ruff RM, Light RH, Parker SB, Levin HS. Benton Controlled Oral Word Association Test: reliability and updated norms *Arch Clin Neuropsychol* 1996;11:329-338.

(175) Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming*Arch Clin Neuropsychol* 1999;14:167-177.

(176) Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology* 2000;55:1621-1626.

(177) Strauss E. A compendium of neuropsychological tests: Administration, norms and commentary. 2016.

(178) Jorm AF, Korten AE. Assessment of cognitive decline in the elderly by informant interview*Br J Psychiatry* 1988;152:209-213.

(179) Jorm AF. The Informant Questionnaire on cognitive decline in the elderly (IQCODE): a review. *Int Psychogeriatr* 2004;16:275-293.

(180) Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure *J Am Coll Cardiol* 2000;35:1245-1255.

(181) Riegel B, Lee CS, Dickson VV, Carlson B. An update on the self-care of heart failure index *J Cardiovasc Nurs* 2009;24:485-497.

(182) Riegel B, Carlson B, Moser DK, Sebern M, Hicks FD, Roland V. Psychometric testing of the self-care of heart failure index*J Card Fail* 2004;10:350-360.

(183) Rankin ED, Haut MW, Keefover RW, Franzen MD. The establishment of clinical cutoffs in measuring caregiver burden in dementia*Gerontologist* 1994;34:828-832.

(184) Zarit SH, Todd PA, Zarit JM. Subjective burden of husbands and wives as caregivers: a longitudinal study*Gerontologist* 1986;26:260-266.

(185) Anthony-Bergstone CR, Zarit SH, Gatz M. Symptoms of psychological distress among caregivers of dementia patients *Psychol Aging* 1988;3:245-248.

(186) Konstam V, Moser DK, De Jong MJ. Depression and anxiety in heart failure*J Card Fail* 2005;11:455-463.

(187) Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes*J Am Coll Cardiol* 2006;48:1527-1537.

(188) Jiang W, Alexander J, Christopher E et al. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure*Arch Intern Med* 2001;161:1849-1856.

(189) Barber M, Tait RC, Scott J, Rumley A, Lowe GD, Stott DJ. Dementia in subjects with atrial fibrillation: hemostatic function and the role of anticoagulation. *J Thromb Haemost* 2004;2:1873-1878.

(190) Mavaddat N, Roalfe A, Fletcher K et al. Warfarin versus aspirin for prevention of cognitive decline in atrial fibrillation: randomized controlled trial (Birmingham Atrial Fibrillation Treatment of the Aged Study)S*troke* 2014;45:1381-1386.

(191) Kay GG. The effects of antihistamines on cognition and performance *J Allergy Clin Immunol* 2000;105:S622-S627.

(192) Jewart RD, Green J, Lu CJ, Cellar J, Tune LE. Cognitive, behavioral, and physiological changes in Alzheimer disease patients as a function of incontinence medications*Am J Geriatr Psychiatry* 2005;13:324-328.

(193) Moser DJ, Robinson RG, Hynes SM et al. Neuropsychological performance is associated with vascular function in patients with atherosclerotic vascular disease. *Arterioscler Thromb Vasc Biol* 2007;27:141-146.

(194) Duff K, Patton D, Schoenberg MR, Mold J, Scott JG, Adams RL. Age- and education-corrected independent normative data for the RBANS in a community dwelling elderly sample *Clin Neuropsychol* 2003;17:351-366.

(195) Gaita F, Corsinovi L, Anselmino M et al. Prevalence of silent cerebral ischemia in paroxysmal and persistent atrial fibrillation and correlation with cognitive function*J Am Coll Cardiol* 2013;62:1990-1997.

(196) Randolph C. Repeatable Battery for the Assessment of Neuropsychological Status Manual. San Antonio, TX: The Psychological Corporation . 2016.

(197) Brown RG, Marsden CD. 'Subcortical dementia': the neuropsychological evidence*Neuroscience* 1988;25:363-387.

(198) Bunch TJ, Weiss JP, Crandall BG et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia*Heart Rhythm* 2010;7:433-437.

(199) Dublin S, Anderson ML, Haneuse SJ et al. Atrial fibrillation and risk of dementia: a prospective cohort study. *J Am Geriatr Soc* 2011;59:1369-1375.

(200) Elias MF, Sullivan LM, Elias PK et al. Atrial fibrillation is associated with lower cognitive performance in the Framingham offspring men *J Stroke Cerebrovasc Dis* 2006;15:214-222.

(201) Damian AM, Jacobson SA, Hentz JG et al. The Montreal Cognitive Assessment and the mini-mental state examination as screening instruments for cognitive impairment: item analyses and threshold scores*Dement Geriatr Cogn Disord* 2011;31:126-131.

(202) Trzepacz PT, Hochstetler H, Wang S, Walker B, Saykin AJ. Relationship between the Montreal Cognitive Assessment and Mini-mental State Examination for assessment of mild cognitive impairment in older adults*BMC Geriatr* 2015;15:107.

(203) Popovic IM, Seric V, Demarin V. Mild cognitive impairment in symptomatic and asymptomatic cerebrovascular disease*J Neurol Sci* 2007;257:185-193.

(204) Rossetti HC, Lacritz LH, Cullum CM, Weiner MF. Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample*Neurology* 2011;77:1272-1275.

(205) Huppert FA, Cabelli ST, Matthews FE. Brief cognitive assessment in a UK population sample -- distributional properties and the relationship between the MMSE and an extended mental state examination*BMC Geriatr* 2005;5:7.

(206) Freiheit EA, Hogan DB, Eliasziw M et al. A dynamic view of depressive symptoms and neurocognitive change among patients with coronary artery disease*Arch Gen Psychiatry* 2012;69:244-255.

(207) Swardfager W, Herrmann N, Marzolini S et al. Cardiopulmonary fitness is associated with cognitive performance in patients with coronary artery disease*J Am Geriatr Soc* 2010;58:1519-1525.

(208) Karlsson M. A nurse-based management program in heart failure patients affects females and persons with cognitive dysfunction most. Patient Education and Counseling 2005 58, 146-153. 2013.

(209) Hoth KF, Poppas A, Moser DJ, Paul RH, Cohen RA. Cardiac dysfunction and cognition in older adults with heart failure. *Cogn Behav Neurol* 2008;21:65-72.

(210) Garcia S, Alosco ML, Spitznagel MB et al. Cardiovascular fitness associated with cognitive performance in heart failure patients enrolled in cardiac rehabilitation*BMC Cardiovasc Disord* 2013;13:29.

(211) Carson P, Wertheimer J, Miller A et al. The STICH trial (Surgical Treatment for Ischemic Heart Failure): mode-of-death results *JACC Heart Fail* 2013;1:400-408.

(212) McMurray JJ, Anand IS, Diaz R et al. Baseline characteristics of patients in the Reduction of Events with Darbepoetin alfa in Heart Failure trial (RED-HF)*Eur J Heart Fail* 2013;15:334-341.

(213) Slaughter MS, Rogers JG, Milano CA et al. Advanced heart failure treated with continuous-flow left ventricular assist device*N Engl J Med* 2009;361:2241-2251.

(214) Stagg B. Zarit Burden Interview: Pragmatic study in a dedicated cognition function clinic. Progress in neurology and psychiatry , 23-27. 2016.

(215) Cannon JA, McMurray JJ, Quinn TJ. 'Hearts and minds': association, causation and implication of cognitive impairment in heart failure*Alzheimers Res Ther* 2015;7:22

.

(216) Magaki S, Yellon SM, Mueller C, Kirsch WM. Immunophenotypes in the circulation of patients with mild cognitive impairment *J Psychiatr Res* 2008;42:240-246.

(217) Lineweaver TT. Using the RBANS with older adults: Are age corrections enough? Journal of the International Neuropsychological Society 7. 2016.