<table>
<thead>
<tr>
<th>Title</th>
<th>Cardiovascular disease and functional ability in older adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Canavan, Michelle</td>
</tr>
<tr>
<td>Publication Date</td>
<td>2015-06-03</td>
</tr>
<tr>
<td>Item record</td>
<td><a href="http://hdl.handle.net/10379/5038">http://hdl.handle.net/10379/5038</a></td>
</tr>
</tbody>
</table>

Some rights reserved. For more information, please see the item record link above.
Cardiovascular Disease and Functional Ability in Older Adults

A thesis submitted for degree of Doctor of Philosophy to the School of Medicine, College of Medicine, Nursing and Health Sciences, National University of Ireland Galway

By

Dr Michelle Canavan, MB BCh BAO MRCPI

Department of Geriatric Medicine,
HRB Clinical Research Facility Galway,
National University of Ireland, Galway.

Research Supervisor:
Prof Martin O’Donnell

Date: June 2015
Contents

Abstract .......................................................................................................................... x
Declaration .................................................................................................................. xi
Acknowledgements ................................................................................................... xii
Dedications ................................................................................................................ xiii
List of Figures ............................................................................................................ xiv
List of Tables ............................................................................................................... xvi
List of Abbreviations ................................................................................................ xvii

Chapter 1 Introduction ............................................................................................... 1
Introduction: ................................................................................................................. 2
  1.1 Functional Impairment ....................................................................................... 2
  1.2 Definition of Cardiovascular Disease and Cardiovascular Risk Factors .......... 3
  1.3. Relationship between Cardiovascular Disease and Functional Impairment in Older People........................................................................................................... 3
  1.4. Relationship between Subclinical Vascular Disease and Functional Impairment in Older People........................................................................................................... 3
  1.5 Relationship between Cardiovascular and Other Risk Factors and Functional Impairment in Older People........................................................................................................... 6
  1.6 Relationship between Hypertension and Functional Impairment in Older Adults. .......................................................................................................................... 6
  1.7 The Multifactorial Nature of Functional Impairment ........................................ 7
  1.7 Overview of Thesis Objectives ........................................................................... 10

Chapter 2: Vascular Risk Factors, Cardiovascular Disease and Functional Impairment in Community-Dwelling Adults ............................................................. 11
  2.1 Introduction ....................................................................................................... 12
  2.2 Study Objectives ............................................................................................. 12
  2.3 Methods ........................................................................................................... 13
2.3.1 Population and Study Design ................................................................. 13
2.3.2 Data Collection ...................................................................................... 13
2.3.3 Definition of Variables......................................................................... 14
2.3.4 Statistical Analysis ............................................................................... 15
2.4 Results ........................................................................................................ 16
  2.4.1 Univariate analysis .............................................................................. 19
  2.4.2 Multivariable Logistic Regression Analysis ....................................... 19
  2.4.3 Subgroup Analysis ............................................................................. 23
2.5 Discussion .................................................................................................. 26
  2.5.1 Summary of Findings ........................................................................ 26
  2.5.2 Strengths ............................................................................................. 26
  2.5.3 Limitations .......................................................................................... 27
2.6 Conclusions ................................................................................................. 29

Chapter 3: Does Lowering Blood Pressure with Antihypertensive Therapy Preserve
Independence in Activities of Daily Living? A Systematic Review.......................... 30

  3.1 Introduction ............................................................................................. 31
  3.2 Study Objectives ..................................................................................... 31
  3.3 Methods .................................................................................................. 32
    3.3.1 Search Strategy and Information Sources ....................................... 32
    3.3.2 Eligibility and Study Selection ......................................................... 32
    3.3.3 Data Abstraction .............................................................................. 32
    3.3.4 Data Synthesis and Summary Measures .......................................... 35
  3.4 Results: .................................................................................................... 35
    3.4.1 Study Selection ................................................................................ 35
    3.4.2 Characteristics of Studies: ............................................................... 35
      3.4.2.1 Demographics ........................................................................... 35
      3.4.2.2 Treatment ................................................................................ 36
      3.4.2.3 Measurement of ADLs .............................................................. 36
5.1 Introduction .............................................................................................................. 77
5.2 Study Objective ....................................................................................................... 78
5.3 Methods ................................................................................................................... 78
  5.3.1 Description of SPHERE Trial ............................................................................. 78
    5.3.1.1 Trial Design .............................................................................................. 78
    5.3.1.2 Sphere Population ..................................................................................... 79
    5.3.1.3 Data Collection ......................................................................................... 79
5.4 Description of Cardiovascular Risk Prediction Scores .............................................. 80
5.5 Statistical Analysis ................................................................................................. 81
  5.5.1 Generation of Framingham and Omnibus Scores for SPHERE cohort ................. 81
  5.5.2 Use of Framingham and Omnibus Risk Scores as Primary Outcomes in the SPHERE cohort ............................................................................................................. 82
  5.5.3 Generation of SPHERE Specific Logistic Regression Model .............................. 82
  5.5.4 Missing Data ..................................................................................................... 83
5.6 Results ..................................................................................................................... 85
  5.6.1 Descriptive Analysis .......................................................................................... 85
  5.6.2 Univariate (Unadjusted) Analysis .................................................................... 85
  5.6.3 Multivariate (Adjusted) Analysis ..................................................................... 88
  5.6.4 Effect of Multicomponent Intervention on Risk of Cardiovascular Disease Composite Using SPHERE-Specific Model .............................................................. 88
5.7 Discussion .............................................................................................................. 90
  5.7.1 Summary of Findings ...................................................................................... 90
  5.7.2 Strengths .......................................................................................................... 90
  5.7.3 Limitations ....................................................................................................... 92
5.8 Conclusions ........................................................................................................... 94

Chapter 6: Systolic Target in Aging to Reduce Functional Impairment (STAR-FIT): A Cluster Randomised Trial ............................................................................................................. 95

  6.1 Background .......................................................................................................... 97
6.1.1 Summary of Rationale

6.1.2 Hypertension, Mortality and Major Cardiovascular Events

6.1.3 Hypertension and Functional Impairment

6.1.4 Treatment of Hypertension to Prevent Functional Impairment

6.1.5 Treatment of Hypertension to Prevent Major Cardiovascular Events in Older Adults

Evidence to Support BP Lowering in Older Adults with Severe and Moderate Hypertension

Evidence to Support BP Lowering in Older Adults with Mild Hypertension

Guideline Recommendations for Target BP in Older Adults

6.1.6 Clinical Equipoise/Uncertainty

6.1.7 Novel Aspects of this Trial

6.2 Study Objectives

6.2.1 Primary Research Question

6.2.2 Secondary Research Questions

6.3 Study Design

6.3.1 Population, Sampling Frame and Clinical Setting

6.3.2 Feasibility

6.4 Eligibility Criteria

6.4.1 Practice Inclusion Criteria

6.4.2 Practice Exclusion Criteria

6.4.3 Patient Inclusion Criteria

6.4.4 Patient Exclusion Criteria

6.5 Randomisation

6.5.1 Screening

6.5.1.1 Practice Identification

6.5.1.2 Patient Identification
6.5.1.3 Baseline GP Visit to Confirm Eligibility for Study ......................... 114
6.5.2 Cluster Randomisation ........................................................................ 114
6.5.3 Allocation Sequence Generation......................................................... 115
6.5.4 Allocation Concealment ...................................................................... 115
6.5.5 Blinding ............................................................................................... 115
6.6 Intervention and Usual Care .................................................................... 116
  6.6.1 Intervention and Usual Care for Both Target Groups ......................... 116
    6.6.1.1 Intervention for Staff in Participating Practices ............................ 116
    6.6.1.2 Interventions for Participants in Both Target Groups ................. 117
  6.6.2 Feasibility and Acceptability of the Intervention ............................... 118
6.7 Contamination .......................................................................................... 118
6.8 Baseline and Follow Up Visit Schedules .............................................. 120
  6.8.1 Standardisation of Intervention & Follow-Up ................................... 121
  6.8.2 Methods to Maximise Participant Adherence .................................... 121
6.9. Measurements ....................................................................................... 123
  6.9.1 Baseline GP Visit ............................................................................... 123
  6.9.2 Baseline Assessment HRB-CRFG Visit ............................................ 123
    Collection of Baseline Characteristics ..................................................... 123
    Functional Assessment ........................................................................... 124
    Cognitive Assessment ............................................................................ 125
  6.9.3 Measurements at GP Follow-Up Visits ............................................ 126
  6.9.4 Measurements at HRB-CRFG Phone Follow Up Visits .................... 126
  6.9.5 Measurements at Final Visit .............................................................. 127
  6.9.6 Confounding Variables ...................................................................... 128
6.10 Criteria for Permanent Withdrawal of Intervention ............................ 128
6.11 Study Outcomes ..................................................................................... 128
  6.11.1 Primary Outcome ............................................................................ 128
  6.11.2 Secondary Outcomes ...................................................................... 130
6.12 Statistical Considerations ................................................................. 130
  6.12.1 Sample Size Considerations.......................................................... 130
  6.12.2 Descriptive Statistics and Baseline Characteristics ...................... 131
  6.12.3 Statistical Analysis of Primary Outcome ..................................... 132
  6.12.4 Statistical Analysis of Secondary Outcomes ........................... 132
  6.12.5 Subgroup & Sensitivity Analyses ............................................. 132
  6.12.6 Enrolment and Disposition....................................................... 133
  6.12.7 Missing Data ......................................................................... 133
  6.12.8 Data Safety & Monitoring Board ............................................. 133
  6.13 Ethical Considerations .................................................................. 134
    6.13.1 Patient Confidentiality ....................................................... 134
    6.13.2 Risk-Benefit Ratio ................................................................. 135
  6.14 Limitations & Methods to Control Bias ........................................ 135
  6.15 Trial Administration ..................................................................... 139
    6.15.1 Site .................................................................................... 139
    6.15.2 Steering, Local Operations and Publication Committees ........ 139
    6.15.3 Study Monitoring ................................................................. 139
    6.15.4 Data Collection & Quality Control ...................................... 140
    6.15.5 Study Timeline .................................................................... 140
  6.16 Dissemination Strategy ................................................................. 141
  6.17 Protocol Amendments .................................................................... 141
  6.18 Ownership of Data and Use of Study Results ............................... 141
  6.19 Declaration of Interests ................................................................ 141
  6.20 Ancillary & Post-Trial Care ........................................................... 142

Chapter 7: Discussion and Conclusions ............................................... 143

Chapter 2 ......................................................................................... 144

Chapter 3 ......................................................................................... 145

Chapter 4 ......................................................................................... 146
Chapter 5 .................................................................................................................. 147

Chapter 6 .................................................................................................................. 148

Future Directions ...................................................................................................... 149

Appendix 1 Copyright Permission for Vascular Risk Factors, Cardiovascular Disease and Functional Impairment in Community Dwelling Adults ........................................ cl

Appendix 2 CLARITY Questionnaire ........................................................................ cliii

Appendix 3: Copyright Permission for Does Lowering Blood Pressure with Antihypertensive Therapy Preserve Independence in Activities of Daily Living ......clviii

Appendix 4: Research Ethics Committee Approval Letter for Survey..........................clx

Appendix 5: Research Ethics Committee Approval Participant Information Sheet ....clxi

Appendix 6: Survey on Importance of Functional Outcomes in Clinical Research ....clxii

Appendix 7: Framingham and Omnibus Risk Equations ............................................ clxv

Appendix 8: Standard Assessment of Global Activities in the Elderly (SAGE) Scale clxvii

Appendix 9: Timed Up and Go Test........................................................................... clxix

Appendix 10: Cognitive Tests ..................................................................................... clxx

Digital Symbol Substitution Test ........................................................................... clxx

Trail Making Test Part B ....................................................................................... clxxi

Montreal Cognitive Assessment .......................................................................... clxxii

Published Papers and Outputs Arising From This Work ........................................ clxxiii

Presentations ........................................................................................................... clxxiii

Publications ............................................................................................................ clxxiii

Papers Under Review .............................................................................................. clxxiii

References .............................................................................................................. clxxiv
Abstract

Preservation of functional independence is important to older adults. The consequences of functional impairment (increased dependence on others for activities of daily living and requirement for nursing home care) place a significant burden on older people, their families and health care systems. Prevention of functional impairment is of considerable importance, and requires the systematic identification of modifiable determinants of loss of independence in activities of daily living to develop interventions to prevent this loss. My thesis addresses the association of cardiovascular disease and cardiovascular risk factors with functional impairment in older adults, identifies the importance of functional outcome measures in cardiovascular research and proposes an approach to evaluating the effect of vascular risk factor modification on loss of function.

Employing a number of different methodological and statistical approaches (with a particular focus on hypertension), I report the association between vascular risk factors and functional impairment in community dwelling older adults in cohort studies and systematic review of clinical trials, I explore attitudes of individuals to the importance of measuring functional outcomes in trials of cardiovascular prevention, and evaluate different methodological approaches to estimating the effect of interventions with effects on multiple outcomes. Finally, I describe a protocol for a randomised controlled trial to determine whether lowering blood pressure in older adults with mild hypertension (without cardiovascular disease) reduces the risk of functional impairment.

Findings from my thesis emphasise the importance of modifiable vascular risk factors in the development (and prevention) of loss of independence for activities of daily living, mediated largely through clinical and covert cardiovascular disease. Despite this association, and the importance of functional outcome measures to the general public, cardiovascular prevention trials rarely report functional outcome measures. My thesis proposes a paradigm change in selecting outcome measures for cardiovascular prevention trials in older adults, to include functional outcomes.
Declaration

This thesis is submitted to the National University of Ireland, Galway in accordance with the requirements for Doctor of Philosophy (PhD) in the School of Medicine, Faculty of Health Sciences.

This thesis is a record of my own work and has not been submitted for any other academic award in this university or in any other academic institution.

Parts of this work have appeared in peer reviewed publications and presentations. All information sources have been fully referenced.

Michelle Canavan

June 2015
Acknowledgements
Firstly, I would like to thank my PhD supervisor Prof. Martin O’Donnell for his advice, guidance, endless patience and encouragement throughout my research and clinical training. I am extremely fortunate to have a supervisor and mentor of his calibre. His enthusiasm for clinical research and its translation into medical practice to improve patient care is truly inspiring.

A very special word of thanks to my fellow PhD student Dr Andrew Smyth for his support, encouragement, friendship and invaluable technical help and advice during this structured PhD.

Sincere thanks to everyone in the Department of Geriatric Medicine, UHG, particularly Prof. Eamon Mulkerrin who encouraged and facilitated me, while in the role of clinical tutor in the department, to pursue training in clinical research. Thanks also to my fellow Geriatric Medicine Specialist Registrar colleague Dr. Stephanie Robinson.

I would like to thank Dr. John Newell and Patricia Gunning from the Biostatistics Unit at the HRB-CRFG for their assistance in developing the statistical framework for some of the analysis in this thesis. Thanks also to Prof. Andrew Murphy and the WestREN group for allowing me access to their datasets (CLARITY and SPHERE) and for their advice and feedback in relation to the analysis.

I would like to acknowledge the support of research staff at the HRB Clinical Research Facility in Galway who have taught me a lot about the day to day administration of clinical trials and who helped me with distribution of surveys for my survey.

I would also like to thank colleagues in the Department of Endocrinology where I am working this year particularly Dr. Marcia Bell and Dr. Ruth Casey who have facilitated me in terms of finding time to complete the write up of my thesis.

A word of thanks to Dr Jackie Bosch for her support and advice particularly during my trip to Population Health Research Institute and McMaster University, Hamilton, Canada in 2013.

Finally, heartfelt thanks to my husband Donnchadh, my parents, sisters, in laws and friends for their unwavering support and encouragement, as always.
Dedications

I would like to dedicate this PhD thesis to my husband Donnchadh Glynn.
List of Figures

Figure 1.1 Impact of Subclinical Cardiovascular Disease on Function in Older People ...... 5
Figure 1.2 Multifactorial Relationship between Cardiovascular Risk Factors, Subclinical Vascular Disease, Cardiovascular Disease and Functional Impairment ......................... 9
Figure 2.1 Forest Plot of Risk of Functional Impairment Adjusted for Demographics, Vascular Risk Factors and Established Cardiovascular Disease .............................. 21
Figure 2.2 Forest Plot of Subgroup Analysis by Age for Risk of Functional Impairment According to Vascular Risk Factors ............................................................................. 24
Figure 3.1 PRISMA Flow Diagram Summarising Results from Database Searches ........ 37
Figure 3.2 Risk of Bias Graph ......................................................................................... 44
Figure 3.3 Summary of Risk of Bias for Included Studies ............................................. 44
Figure 3.4 Number and Proportions of RCTs Reporting Functional Outcomes .......... 46
Figure 3.5 Forest Plot of the Effect of Blood Pressure Lowering on Ability to Carry out ADLs for Antihypertensive Therapy and Control Groups ........................................ 47
Figure 3.6 Forest Plot of the Effect of Blood Pressure Lowering on Ability to Carry Out ADLs for Subgroups with and without Established Stroke or Cerebrovascular Disease ... 49
Figure 3.7 Forest Plot of the Effect of Blood Pressure Lowering on Ability to Carry Out ADLs by Subgroups: Mean age greater than 65 years versus Mean age less than 65 years ...................................................................................................................... 50
Figure 3.8 Forest Plot of the Effect of Blood Pressure Lowering on Ability to Carry Out ADLs by Subgroups: Established hypertension versus Prehypertension .................. 51
Figure 4.1 Comparison of Responses to Survey Questions between Younger and Older Adults ....................................................................................................................... 66
Figure 5.1 Comparison of Distribution of Baseline Framingham Scores Using Complete Data vs. Imputed Values ...................................................................................... 84
Figure 5.2 Comparison of Distribution of Baseline Omnibus Scores Using Complete Data vs. Imputed Values ................................................................. 84
Figure 5.3 Boxplots of (Unadjusted) Change in Framingham & Omnibus Scores at 18 Months Follow Up ............................................................................................................. 87
Figure 6.1 Schematic of Screening and Randomisation Process ...................................... 112
Figure 6.2 Algorithm for GP Practices for Initiation and Adjustment of Medications .... 119
Figure 6.3 Study Flow Diagram ..................................................................................... 122
List of Tables
Table 2.1 Baseline Characteristics According to Functional Impairment Status .......... 17
Table 2.2 Multivariable Logistic Regression Model for Risk of Functional Impairment
Adjusted for Demographics, Vascular Risk Factors and Established Disease .......... 22
Table 2.3 Multivariable Logistic Regression Model for Risk of Impairment in IADL and
BADL .................................................................................................................................... 25
Table 3.1 Example of Electronic Search Strategy for Medline ........................................ 34
Table 3.2 Description of Trials that included Function as a Primary or Secondary
Outcome .................................................................................................................................. 38
Table 3.3 Checklist for Preferred Reporting Items for Systematic Reviews & Meta-
Analyses (PRISMA) ............................................................................................................. 55
Table 4.1 Characteristics of Survey Participants .............................................................. 64
Table 4.2 Comparisons within Subgroups of Responses to Survey Questions .......... 69
Table 4.3 Multivariable Logistic Regression Analysis for Odds of Choosing a MACE
outcome vs. a Functional outcome .................................................................................... 72
Table 5.1 Baseline Characteristics in SPHERE Study ...................................................... 86
Table 5.2 Change in Risk Factors and Framingham and Omnibus scores for Intervention
and Control Groups from Baseline to Follow Up ............................................................. 89
Table 6.1 STAR-FIT Study Synopsis ................................................................................ 96
Table 6.2 Guideline Recommendations for Management of Hypertension ............... 105
Table 6.3 Check list for Standardised Protocol Items: Recommendations for
Interventional Trials (SPIRIT) ............................................................................................ 137
List of Abbreviations

ACE Inhibitors = Angiotensin Converting Enzyme Inhibitors

ADL(s) = Activities of Daily Living

AF = Atrial Fibrillation

AHA = American Heart Association

ARB = Angiotensin Receptor Blocker

APOLLO = Aliskiren in the Prevention of Major Cardiovascular Events in Elderly People

BADL(s) = Basic Activities of Daily Living

bd = Twice per day

BI = Barthel Index

BMI = Body Mass Index

BP = Blood Pressure

CABG = Coronary Artery Bypass Graft

CAD = Coronary Artery Disease

CARE Scale = Comprehensive Assessment and Referral Evaluation Scale

CHD = Coronary Heart Disease

CI = Confidence Intervals

CKD = Chronic Kidney Disease

CLARITY = Cardiovascular Multimorbidity in primary care study

CHF = Congestive Heart Failure

Co-PI = Co-Principal Investigators

CRF = Case report form

CV = Cardiovascular

CVD = Cardiovascular disease
DALYs = Disability-Adjusted Life-Years

DBP = Diastolic Blood Pressure

DM = Diabetes Mellitus

DSMB = Data Safety and Monitoring Board

DSS = Digital Symbol Substitution

e.g. = For example

eGFR = Estimated Glomerular Filtration Rate

EQ-5D = Euro Qual Health Questionnaire

GMS = General Medical Services

GP(s) = General Practitioner(s)

GUH = Galway University Hospital

HCTZ = Hydrochlorothiazide

HDL = High Density Lipoprotein

HF = Heart Failure

HRB-CRFG – Health Research Board Clinical Research Facility Galway

HYVET = Hypertension in the Very Elderly Trial

IADL(s) = Instrumental Activities of Daily Living

ICF = International Classification of Functioning, Disability and Health

ICGP = Irish College of General Practitioners

IHD = Ischemic Heart Disease

IQR = Interquartile Range

JATOS = Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients

LDL = Low Density Lipoprotein

MACE = Major Adverse Cardiovascular Event
MCS = Mental Component Summary
MDRD = Modification of Diet in Renal Disease
MI = Myocardial Infarction
mmHG = Millimetres of Mercury
MOCA = Montreal Cognitive Assessment
MRI = Magnetic Resonance Imaging
MRS = Modified Rankin Scale
NH = Nursing Home
NHS = National Health Service
NIH = National Institute of Health
NSTEMI = Non ST elevation myocardial infarction
NUIG = National University of Ireland Galway
od = Once per day
OR = Odds ratio (95% confidence interval)
PAD = Peripheral Arterial Disease
PCS = Physical Component Summary
PROBE = Prospective Randomised Open Blinded End-point
PVD = Peripheral Vascular Disease
QoL = Quality of Life
RCT(s) = Randomised Controlled Trial(s)
SAGE = Standardised Assessment of Global Activities in the Elderly
SBP = Systolic Blood Pressure
SCOPE = Study on Cognition and Prognosis in the Elderly
SD = Standard deviation
SF-36 = Rand Medical Outcomes Study Short Form
SHEP = Systolic Hypertension in the Elderly Program

SIP = Sickness Impact Profile

SLEPT = Sleep to lower elevated blood pressure

SPHERE = Secondary Prevention of Heart disease in general practice

STEMI = ST elevation Myocardial Infarction

TIA = Transient Ischemic Attack

TILDA = The Irish Longitudinal Study on Ageing

TUG = Timed Up and Go

US = United States

VALISH = Valsartan in eLderly Isolated Systolic Hypertension

vs. = Versus

WestREN = Western Research and Education Network

WHO = World Health Organisation

WHO-DAS = WHO Disability Schedule

WTE = Whole Time Equivalent

≥ = greater than or equal to

≤ = less than or equal to
Chapter 1

Chapter 1 Introduction


Chapter 1

Introduction:

1.1 Functional Impairment

Functional impairment is common among older adults, and many value maintaining independence above exceptional longevity and even death\(^1\)\(^3\). The World Health Organisation (WHO), International Classification of Functioning, Disability and Health (ICF) defines the term “functioning” as all body functions, activities and participation and the term “disability” as impairments, activity limitation and participation restriction\(^4\). In my thesis, functional impairment is defined as difficulty that interferes with or limits functioning in basic or instrumental activities of daily living (ADL). Basic Activities of Daily living (BADLs) are basic self-care tasks including dressing, eating, ambulation, toileting and hygiene while instrumental activities of daily living (IADLs), which are needed for independent living in the community, include shopping, housework, managing finances and medications, using telephone or other technology and using transportation\(^5\).

Functional impairment has an estimated prevalence of between 10-30% in community dwelling older adults worldwide and is one of the principal reasons for transition from the home to long term nursing home (NH) care\(^6\)\(^-\)\(^8\). Functional impairment is frequently associated with progressive cognitive impairment, and loss of independence is often the end result of severe cognitive deficits in diseases such as Alzheimer's and vascular dementia\(^9\),\(^10\).

The Global Burden of Disease Study reported that cardiovascular (CV) disease (atherosclerotic diseases including ischemic heart disease [IHD] and stroke) is one of the top ten causes of disability worldwide which predominantly affects older people\(^11\). Hypertension is the leading modifiable cardiovascular risk factor accounting for premature disability. It is estimated to be responsible for between 35-50% of the population attributable risk for stroke\(^12\),\(^13\) and its effects on functional ability are largely mediated through its association with stroke and other vascular disease, both clinical and subclinical\(^14\)\(^-\)\(^16\). In this introduction I will describe the relationship between cardiovascular disease, cardiovascular risk factors and functional impairment in older people.
1.2 Definition of Cardiovascular Disease and Cardiovascular Risk Factors

Cardiovascular disease (CVD) refers to any disease which affects the circulatory system and includes cardiac disease (coronary artery disease (CAD), heart failure (HF), arrhythmias and valvular disease), vascular diseases of brain (stroke) and kidney and peripheral vascular disease (PVD). Cardiovascular risk factors are conditions which are associated with increased risk of cardiovascular diseases including stroke and myocardial infarction (MI). These risk factors can be classified into modifiable and non-modifiable risk factors. Non-modifiable risk factors include age, gender, race, genetics and family history while modifiable risk factors include hypertension, smoking, increased cholesterol levels, diabetes mellitus (DM), physical inactivity, diet, atrial fibrillation (AF) and obesity.

1.3. Relationship between Cardiovascular Disease and Functional Impairment in Older People

Over two-thirds of cardiovascular related deaths in the US occur in those aged over 75 years and half of those who have CHD are aged over 65 years. The prevalence of stroke (a leading cause of acquired disability in adults) increases with age. For each successive decade over the age of 55 years the incidence of stroke more than doubles in both men and women. Although a reduced case-fatality has been observed over the last decade, there has been an increase in numbers living with stroke (and other CVD), the majority of whom do so into advanced older age living with the resultant functional impairment. Indeed, the most recent report on the global burden of disease study showed that the most striking increases in the number of stroke survivors (113%) and Disability-Adjusted Life-Years (DALYs) lost (31%) occurred in those aged over 75 years.

1.4. Relationship between Subclinical Vascular Disease and Functional Impairment in Older People

The contribution of covert or ‘subclinical’ vascular disease to functional impairment, mediated by vascular disease in a number of vascular beds, is an emerging research field, with growing recognition of its importance as a determinant of functional impairment and dependence in older people. There is evolving evidence that functional loss due to ‘overt’ major vascular events may merely represent the “tip of the iceberg” of vascular decline in ageing (Figure 1.1). More than one-third of patients aged 65 and over, in the Cardiovascular
Health study, had evidence of subclinical vascular disease at baseline. Subclinical vascular disease is associated with frailty\textsuperscript{23,24} and with a 20-30% increase in risk of self-reported physical impairment\textsuperscript{25} as well as a two-fold higher risk of a future major cardiovascular event\textsuperscript{16,26}. In addition, studies have shown that older adults with a low subclinical vascular disease burden have lower levels of functional disability, compared to those without vascular disease\textsuperscript{16,23,24,26}. Longitudinal studies have reported that subclinical white matter changes found on brain imaging are associated with cognitive decline\textsuperscript{27,28}, urinary disturbances\textsuperscript{29,30}, mood instability\textsuperscript{31,32}, swallowing disorders\textsuperscript{33,34} and gait disorders\textsuperscript{35-37} and that such changes are associated with demonstrably lower physical performance scores\textsuperscript{38,39}. Moreover, studies suggest that these white matter changes may be used to predict functional impairment in older non-disabled people\textsuperscript{38,40}. 
Chapter 1

Figure 1.1 Impact of Subclinical Cardiovascular Disease on Function in Older People

Major Vascular Events

Cognitive loss
Dementia
Depression
Frailty
Dependence
Institutionalization
Chapter 1

1.5 Relationship between Cardiovascular and Other Risk Factors and Functional Impairment in Older People

Cardiovascular risk factors including hypertension, smoking, diabetes and hyperlipidaemia are established risk factors for stroke and MI. The prevalence of cardiovascular disease increases with age, but optimal management of some cardiovascular risk factors in older age is uncertain, for example, the optimal blood pressure target for primary prevention. Recent epidemiological studies suggest that cardiovascular risk factors are associated with functional and cognitive impairment independent of major vascular events. In addition other risk factors and conditions common in older people (atrial fibrillation, alcohol intake, chronic kidney disease (CKD), obesity and physical inactivity) increase risk of both functional and cognitive impairment.

Frailty (a clinically recognizable state of increased vulnerability resulting from age-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with every day or acute stressors is comprised) is a construct which identifies those with an increased risk of substantial dependency for ADLs. The relationship between frailty and cardiovascular disease is bidirectional with many studies showing an association between frailty and increased risk of cardiovascular morbidity and mortality and also between frailty and poor outcomes from cardiovascular events. Sarcopenia (age-associated loss of skeletal muscle mass and strength) is a feature of frailty and a major contributor to functional impairment in older people, and recent research suggests that sarcopenia may have vascular etiologies. Physical frailty is also associated with metabolic risk factors (hypertension, diabetes, waist: hip ratio and smoking) and atherosclerosis independent of sarcopenia and cognitive function. Frailty and cognitive impairment are related but distinct concepts that frequently co-exist and cardiovascular disease and risk factors are implicated in the development of both.

1.6 Relationship between Hypertension and Functional Impairment in Older Adults.

Hypertension is a key modifiable risk factor for cardiovascular disease, but remains underdiagnosed and undertreated. It is estimated that only 13% of
people with hypertension worldwide have adequate blood pressure control (<140/90mmHg)\textsuperscript{73,74}. My thesis has a focus on hypertension because of its leading role as a potent risk factor for cardiovascular disease (especially cerebrovascular disease), and by implication, a leading risk factor for functional impairment.

Numerous longitudinal studies have evaluated the effect of hypertension on functional ability and have found an association between high blood pressure and difficulty carrying out ADLs\textsuperscript{75-77}. Those who have exceptional longevity or “age successfully” have low levels of hypertension and correspondingly low levels of functional impairment\textsuperscript{77-82}. The pattern of ADL decline associated with hypertension is largely mediated through brain white matter changes. It has a hierarchal pattern, initially affecting executive function (social and work activities, followed by loss of IADLS [shopping, laundry, cooking]) and finally loss of BADLs\textsuperscript{83-85}. In addition, hypertension is associated with development of cognitive impairment through stroke and increased risk of covert stroke which can have devastating functional consequences\textsuperscript{27,86}. Control of midlife hypertension has been postulated to reduce risk of dementia in later life\textsuperscript{87-91} but treatment of hypertension in older frailer people to prevent dementia has been less conclusive\textsuperscript{92,93}.

Despite the epidemiologic association between hypertension and functional impairment, the evidence supporting the contention that reducing blood pressure leads to a reduction in functional impairment is not based on consistent results of randomised controlled trials. No antihypertensive agent is indicated for preservation of function. However, logical inference would support that prevention of major vascular events through treatment of hypertension will result in lower rates of functional impairment. However, this may be offset by potential adverse effects of blood pressure lowering, especially in mild hypertension (e.g. orthostatic hypotension, falls etc.)\textsuperscript{92,93}.

1.7 The Multifactorial Nature of Functional Impairment

The relationship between functional impairment, cardiovascular risk factors, and overt and covert cardiovascular disease is complex and multidirectional (Figure 1.2). Functional impairment can be directly caused by cardiovascular disease (overt) particularly stroke but subclinical (covert) vascular disease and vascular risk factors are also associated with functional impairment.
Chapter 1

Cardiovascular risk factors such as hypertension lead to increased risk of vascular events including stroke and MI. Although these events can directly cause functional impairment the simple paradigm of a vascular risk factor leading to a vascular event does not fully explain the relationship between cardiovascular risk and functional impairment. Instead there are a number of alternative steps along the way, beginning with vascular risk factors which lead to different intermediate phenotypes including cognitive impairment, sarcopenia, gait instability and frailty. These intermediate phenotypes can directly result in impairment of function or a situation where cumulative deficits over time mean that impairment of function is inevitable.

Modification of multiple risk factors is expected to have a positive effect on functional ability by reducing the risk of many different conditions each of which contribute to functional impairment. Use of outcomes like function are therefore useful to describe the patient important effect of a multifactorial complex vascular process. An older person will not attend their doctor complaining that they have subclinical vascular disease but they will complain that they are unsteady on their feet or that they cannot manage their daily activities. Functional outcomes are regularly used in clinical practice to gauge the effect of a particular disease on a patient’s functional ability but despite this valuable utility in clinical practice they are rarely reported in cardiovascular prevention trials.
Figure 1.2 Multifactorial Relationship between Cardiovascular Risk Factors, Subclinical Vascular Disease, Cardiovascular Disease and Functional Impairment.
Chapter 1

1.7 Overview of Thesis Objectives

The overarching theme of this work is to: a) determine the association between modifiable vascular risk factors and functional impairment, with a particular focus on hypertension; b) explore individuals’ attitudes to functional outcomes in cardiovascular prevention trials; and c) evaluate methodological approaches to estimating the effect of interventions with expected effects on multiple outcomes.

In Chapter 2, I evaluate the association of vascular risk factors and cardiovascular disease with functional impairment, in a cross-sectional analysis of a large community-based cohort in the West of Ireland. In Chapter 3, I report the results of a systematic review and meta-analysis of blood pressure lowering in randomised controlled trials, which evaluated the effect of blood pressure lowering on functional outcomes. Chapter 4, details the findings of a survey which explores attitudes of older and younger adults to outcomes measured in cardiovascular prevention trials and compares the relative importance of traditional outcome measures in cardiovascular prevention trials (i.e. death, myocardial infarction and stroke) to functional-related outcomes.

In Chapter 5, I expand the theme of outcome measures in cardiovascular trials, and address the challenge of measuring composite outcomes, when evaluating multi-component interventions in cardiovascular trials, or when evaluating an intervention that may have an effect on multiple mechanisms. Specifically, I evaluate different approaches to estimating the effect of a multicomponent intervention on multiple modifiable vascular risk factors. The indirect relevance of this study to my overarching objective is that the association between vascular risk factors and functional impairment is mediated through a variety of mechanisms, and requires composite outcome approaches to measure the effect of interventions, particularly in Phase II trials.

The final chapter builds on my thesis work by detailing a protocol of a randomised controlled trial to determine whether lowering blood pressure in older adults (without cardiovascular disease) with mild hypertension compared to not lowering blood pressure, reduces the risk of developing functional impairment.
Chapter 2 : Vascular Risk Factors, Cardiovascular Disease and Functional Impairment in Community-Dwelling Adults


Reproduced with Permission (Appendix 1)
Chapter 2

2.1 Introduction

Preservation of functional independence is identified by older adults as an important domain in the construct of ‘successful ageing’\textsuperscript{24}. Cardiovascular diseases, and consequently their risk factors, are associated with cognitive and functional decline resulting in increased risk of dependence for routine ADLs\textsuperscript{16, 49, 94, 95}. Several prospective cohort studies have shown that avoidance of hypertension, smoking, obesity and hyperglycaemia is associated with better quality of life and functional ability in older age\textsuperscript{59, 77, 81, 88, 96}. In addition, there are known associations between atrial fibrillation and alcohol intake and functional impairment \textsuperscript{49, 50, 95}. However, the magnitude of the association between vascular risk factors and functional decline may have been underestimated in previous research for a number of reasons.

First, most research has focused on individual disease-specific associations between major cardiovascular disease and functional impairment such as the functional consequences of acute stroke, myocardial infarction and congestive heart failure. Second, and related, most studies have not considered the effect of both vascular risk factors and cardiovascular diseases together, which is required to determine the residual association between primary vascular risk factors and functional loss independent of established cardiovascular diseases. Third, the principal focus of previous studies, especially clinical trials, has been on cognitive testing with less of an emphasis on impairment of function or ability to carry out daily living activities\textsuperscript{83, 97}. Finally, measurement of functional impairment in some studies has focused on loss of basic ADL, and failed to measure loss of instrumental ADL, which is known to be preferentially lost with covert cerebrovascular disease.

2.2 Study Objectives

In this study, we focus on the association between both vascular risk factors and established cardiovascular diseases and impairment of IADLs and BADLs in a representative sample of community-dwelling adults attending General Practice (GP) in the West of Ireland. We hypothesize that a large proportion of functional impairment is associated with vascular risk factors independent of established cardiovascular disease.
Chapter 2

2.3 Methods

2.3.1 Population and Study Design

The Cardiovascular Multimorbidity in Primary Care (CLARITY) study is a cross-sectional study of people attending primary care practice in the West of Ireland. Patients were recruited from a university-affiliated primary care research network comprised of 71 practices, previously reported to be representative of Irish national general practice profile. Of 71 practices, 17 were invited (because these practices had the appropriate software to participate in the study) and 65% (n=11) participated in the study. Within each primary care centre, all patients aged ≥50 years with ≥2 consultations in the previous 24 months were considered eligible. Ethical approval was obtained from the Irish College of General Practitioners (ICGP).

2.3.2 Data Collection

We used a combination of data collection methods including extraction of written diagnoses, current medications, recent blood pressure (BP), and blood test results from the medical notes and self-reported responses to a questionnaire, which included measures of function and additional demographic information.

The following data were abstracted from medical notes of consecutive patients in each general practice: age, gender, vascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia and atrial fibrillation), past cardiovascular history (including medication use), blood glucose levels, cholesterol levels, estimated glomerular filtration rates (eGFR) and blood pressure recordings.

All eligible patients were sent a standardized, self-reported health postal questionnaire to measure additional information including: age of person when leaving formal education, smoking status, marital status, employment status, alcohol use, falls within the preceding year, perceived health, well-being and functional status. IADL and BADL were measured using modified items from the well validated Lawton, Barthel and EQ-5D scales (Appendix 2). Mobility was categorized as independent or requiring assistance of a person, walking stick, walking frame or wheelchair. Self-care was categorized as independent or requiring assistance for washing and/or dressing.
Chapter 2

Of the entire cohort of 9698 patients, 2,212 patients were unable to participate (as they had died since study initiation), were ineligible (as they were deemed unsuitable by their primary care physician due to terminal illness or dementia) or their questionnaire was returned by postal services. The questionnaire was sent to 7,486 participants and was completed and returned by 47% (n=3,499). For the current analysis, we included participants who completed and returned the questionnaire. Compared to non-responders, patients who responded to the questionnaire were slightly older (mean age 66.2±10.3 vs. 65.2±10.6, p<0.001) and more likely to be female (36% of females responded vs. 34% of males, p=0.049). Rates of vascular risk factors between responders and non-responders were current or former smokers (15.3% vs. 16.8% p=0.21), diagnosis of hypertension (48.9% vs. 45.8%, p=0.003) and diabetes mellitus (11.8% vs. 11%, p=0.078).

2.3.3 Definition of Variables

To be consistent with the ICF definition of function in this study4, functional impairment was defined as self-reported difficulty that interfered with or limited functioning in basic or instrumental activities of daily living. The primary outcome measure was a composite of any impairment of IADL or BADL. BADL was defined as basic self-care tasks (washing, dressing) and mobility; IADL was defined as activities including shopping, cooking and doing laundry. In order to ask participants about difficulty with mobility, self-care or usual activities in the questionnaire we used questions from the EQ-5D quality of life instrument101.

Vascular risk factors which were collected in this study included known risk factors for cardiovascular disease (smoking, hypertension, diabetes, cholesterol, atrial fibrillation and alcohol intake). Smoking status was categorized as current, former or never smoker. Alcohol intake was categorized as current, former and never drinker. Participants were also asked about binge drinking (consuming over five units in a day at least once per month). Hypertension was defined as either documented hypertension or a systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg in the case files. Diabetes was defined as documented type 1 or 2 DM in case files or a documented fasting blood glucose of >7.0mmol/L. Atrial fibrillation was defined as documentation of atrial fibrillation in case files. LDL and HDL cholesterol values were extracted from the last documented total cholesterol blood test result and measured in mmol/L.
Established cardiovascular disease included; coronary heart disease, congestive heart failure, peripheral vascular disease and stroke. A prior history of coronary heart disease was defined as a history of angina, MI, percutaneous coronary intervention or coronary artery bypass graft (CABG). Congestive heart failure (CHF), peripheral vascular disease and stroke (either stroke or transient ischemic attack [TIA]) were defined as documentation of the diagnosis in case files. Diagnosis of CKD was also extracted from the case files and defined as either documented CKD or eGFR<60ml/min/1.73m².

2.3.4 Statistical Analysis
Continuous variables were reported as mean (SD) and compared using t-test or Kruskal-Wallis test where appropriate. Categorical variables were reported in proportions and compared using Chi-square test. Binary multivariable logistic regression analyses were used to determine the independent association between risk factors and functional impairment.

We generated three \textit{a priori} multivariable models. The first included vascular risk factors (smoking, hypertension, diabetes, LDL and HDL cholesterol levels, atrial fibrillation and alcohol intake) and covariates including age, sex and education-level. The second and principal model included evidence of established cardiovascular disease (history of stroke, coronary heart disease, congestive heart failure, peripheral vascular disease) and all variables in model 1. The third model included all variables in models 1 and 2 and diagnosis of CKD. All variables were entered and retained in all of the models. We completed subgroup analyses by age, sex and established cardiovascular disease for any functional impairment and for the individual outcome of impairment in IADL and BADL. We tested for interactions between individual risk factors and established cardiovascular disease. We also explored the relationship between binge drinking and functional impairment.

Odds ratios (OR) and confidence intervals (CI) were calculated for each variable. A 95% CI that did not include one, or a two-sided p-value <0.05 were considered statistically significant. We used SPSS for Windows V20 (Armonk, NY: IBM Corp) for analyses.
Chapter 2

2.4 Results
The mean age of the cohort was 66.2 years (SD 10.3) (52% of the population were aged over 65 years) and 45.6% were male. Some level of functional impairment was self-reported in 1413/3499 (40.4%) of participants. Of those who reported functional impairment, 843/1366 (61.7%) were aged greater than 65 years, while 523/1366 (38.3%) were aged less than 65 years (p=<0.001). Baseline characteristics are presented in Table 2.1. Overall, 1240/3499 (35.4%) reported some difficulty with IADL while 1029/3499 (29.4%) reported some difficulty with BADL. Impairment in IADL included impaired ability to do shopping [458/2922 (15.7%)], to cook and to do laundry [397/2846 (13.9%)]. Impairment in BADL included impaired mobility [1004/3499 (28.7%)] and impaired ability to provide self-care [344/3499 (9.8%)].
Table 2.1 Baseline Characteristics According to Functional Impairment Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=3499)</th>
<th>Functional Impairment* (n=1413, 40.4%)</th>
<th>No Functional Impairment (n=2086, 59.6%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Mean (SD)</td>
<td>66.2 (10.3)</td>
<td>69.0 (10.97)</td>
<td>64.3 (9.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male Gender (%)</td>
<td>1046/3390 (45.6%)</td>
<td>658/1366 (48.2%)</td>
<td>888/2024 (43.9%)</td>
<td>0.140</td>
</tr>
<tr>
<td>Race (White) (%)</td>
<td>3387/3390 (99.9%)</td>
<td>1366/1367 (99.9%)</td>
<td>2021/2023 (99.9%)</td>
<td>0.686</td>
</tr>
<tr>
<td>Age leaving Education, Mean in Years (SD)</td>
<td>17.3 (4.58)</td>
<td>16.6 (4.07)</td>
<td>17.76 (4.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker (%)</td>
<td>1600/3479 (46%)</td>
<td>588/1405 (41.9%)</td>
<td>1012/2074 (48.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>473/3479 (13.6%)</td>
<td>208/1405 (14.8%)</td>
<td>265/2074 (12.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Former Smoker (%)</td>
<td>1406/3479 (40.4%)</td>
<td>609/1405 (43.3%)</td>
<td>797/2074 (38.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension ** (%)</td>
<td>1712/3499 (48.9%)</td>
<td>760/1413 (53.8%)</td>
<td>952/2086 (45.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes Mellitus (%)</td>
<td>413/3382 (12.2%)</td>
<td>210/1359 (15.5%)</td>
<td>203/2023 (10.0%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Last recorded HDL, Mean (SD)</td>
<td>1.47 (0.46)</td>
<td>1.41 (0.45)</td>
<td>1.51 (0.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Last recorded LDL, Mean (SD)</td>
<td>2.9 (0.9)</td>
<td>2.8 (0.97)</td>
<td>3.01 (0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never used (%)</td>
<td>872/2920 (29.9%)</td>
<td>401/1157 (34.7%)</td>
<td>471/1763 (26.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current user (%)</td>
<td>1726/2920 (59.1%)</td>
<td>566/1157 (48.9%)</td>
<td>1160/1763 (65.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Former user (%)</td>
<td>319/2920 (10.9%)</td>
<td>190/1157 (16.42%)</td>
<td>129/1763 (7.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>122/3499 (3.5%)</td>
<td>72/1413 (5.1%)</td>
<td>50/2086 (2.4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Past Medical History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary Heart Disease *** (%)</td>
<td>398/3392 (11.7%)</td>
<td>213/1367(15.6%)</td>
<td>185/2025(9.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart Failure (%)</td>
<td>84/3390 (2.5%)</td>
<td>59/1366 (4.3%)</td>
<td>25/2024 (1.2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke/TIA (%)</td>
<td>163/3392 (4.8%)</td>
<td>103/1367 (7.5%)</td>
<td>60/2025 (3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral Vascular Disease (%)</td>
<td>104/3385 (3.1%)</td>
<td>66/1365 (4.8%)</td>
<td>38/2020 (1.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic Kidney Disease (%)</td>
<td>630/3499 (18%)</td>
<td>350/1413 (24.8%)</td>
<td>280/2086 (13.42%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular Disease**** (%)</td>
<td>551/3392 (16.2%)</td>
<td>313/1367 (22.9%)</td>
<td>238/2025 (11.8%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Functional Impairment = a composite of any impairment of IADL or BADL.
** Hypertension = composite of documented hypertension in case files or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.
*** Coronary Heart Disease = composite for angina, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft.
**** Cardiovascular Disease = composite for coronary heart disease, heart failure or stroke/TIA.
Table 2.1 (Continued) Baseline Characteristics According to Functional Impairment Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=3499)</th>
<th>Functional Impairment* (n=1413, 40.4%)</th>
<th>No Functional Impairment (n=2086, 59.6%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications, Mean No. (SD)</td>
<td>4.59 (4.4)</td>
<td>6.1 (4.8)</td>
<td>3.6 (3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antiplatelet therapy (%)</td>
<td>744/3499 (21.3%)</td>
<td>374/1413 (26.5%)</td>
<td>370/2086 (17.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Warfarin (%)</td>
<td>108/3499 (3.1%)</td>
<td>71/1413 (5%)</td>
<td>37/2086 (1.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid lowering (%)</td>
<td>1053/3499 (30.1%)</td>
<td>479/1413 (33.9%)</td>
<td>574/2086 (27.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Benzodiazepines (%)</td>
<td>20/1555 (1.3%)</td>
<td>16/587 (2.7%)</td>
<td>4/9680 (0.4%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Functional Impairment = a composite of any impairment of IADL or BADL.
** Hypertension = composite of documented hypertension in case files or systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.
*** Coronary Heart Disease = composite for angina, myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft.
**** Cardiovascular Disease = composite for coronary heart disease, heart failure or stroke/TIA.
Chapter 2

2.4.1 Univariate analysis

Age (OR 1.05 [1.04, 1.05]), male gender (OR 1.19 [1.04, 1.37]), current smoking versus never smoking (OR 1.35 [1.10, 1.66]), former smoking versus never smoking (OR 1.32 [1.14, 1.52]), hypertension (OR 1.39 [1.21, 1.59]), diabetes (OR 1.64 [1.33, 2.02]), atrial fibrillation (OR 2.19 [1.51, 3.16]) and former alcohol use versus no prior use (OR 1.74 [1.34, 2.26]) were significantly associated with a higher risk of functional impairment. Older age of leaving formal education (OR 0.93 [0.91, 0.95]), never using alcohol versus current use (OR 0.58 [0.49, 0.68]), and higher HDL cholesterol levels (OR 0.63 [0.53, 0.74]) were significantly associated with a decreased risk of functional impairment (Table 2.2).

2.4.2 Multivariable Logistic Regression Analysis

Model 1 (Vascular Risk Factors)

In this multivariable logistic regression model, older age, current and former smoking versus never smoking, atrial fibrillation and former alcohol use versus never using alcohol, were associated with increased risk of functional impairment. Older age of leaving formal education, never using alcohol versus current use and increased HDL levels were associated with reduced risk of functional impairment. Male gender, hypertension and diabetes mellitus were not associated with functional impairment on multivariable analysis. (Table 2.2)

Model 2 (Vascular Risk Factors, and Established Cardiovascular Disease)

In this multivariable logistic regression model, older age (OR 1.03 [1.02, 1.04]), current smoking versus never smoking (OR 1.43 [1.08, 1.89]), atrial fibrillation (OR 1.68 [1.07, 2.65]), former use of alcohol versus never using (OR 1.87 [1.36, 2.57] and prior stroke (OR 1.91 [1.24, 2.93]) were associated with an increased risk of functional impairment. Age of leaving formal education, never using alcohol versus current use and increased HDL cholesterol levels were associated with a reduced risk of functional impairment. A history of coronary heart disease, congestive heart failure and peripheral vascular disease were not significantly associated with functional impairment on multivariable analysis. (Figure 2.1)
Chapter 2

Model 3 (Vascular Risk factors, and Established Cardiovascular Disease and Chronic Kidney Disease)

The addition of chronic kidney disease to model 2 resulted in similar associations (increased risk of functional impairment with age, current smoking, atrial fibrillation, former alcohol use and prior stroke) and chronic kidney disease was also independently associated with increased risk of functional impairment in the fully adjusted model (OR 1.39 [1.06, 1.83]) (Table 2.2).
Figure 2.1 Forest Plot of Risk of Functional Impairment Adjusted for Demographics, Vascular Risk Factors and Established Cardiovascular Disease

Multivariable model adjusted for demographics (age, gender and years of education), vascular risk factors (smoking, hypertension, diabetes, HDL and LDL cholesterol, atrial fibrillation and alcohol use), and established cardiovascular disease (stroke, coronary heart disease, congestive heart failure and peripheral vascular disease) (Model 2). Odds Ratio for risk of functional impairment given for unit increase in continuous variables (HDL cholesterol, LDL cholesterol, years of education and age). Odds Ratio for risk of functional impairment given in the presence of categorical variables (male gender, hypertension, diabetes, atrial fibrillation, current and former smoking/ drinking [vs. the reference category of never], stroke, coronary Heart disease, congestive heart failure and peripheral vascular disease)
Table 2.2 Multivariable Logistic Regression Model for Risk of Functional Impairment Adjusted for Demographics, Vascular Risk Factors and Established Disease

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Univariate Model</th>
<th>p-value</th>
<th>Model 1*</th>
<th>p-value</th>
<th>Model 2**</th>
<th>p-value</th>
<th>Model 3***</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05 (1.04,1.05)</td>
<td>0.001</td>
<td>1.03 (1.02,1.04)</td>
<td>&lt;0.001</td>
<td>1.03 (1.02,1.04)</td>
<td>&lt;0.001</td>
<td>1.03 (1.02,1.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.19 (1.04,1.37)</td>
<td>0.014</td>
<td>1.01 (0.83,1.23)</td>
<td>0.913</td>
<td>0.99 (0.81,1.20)</td>
<td>0.900</td>
<td>1.01 (0.83,1.23)</td>
<td>0.931</td>
</tr>
<tr>
<td>Age leaving education (years)</td>
<td>0.93 (0.91,0.95)</td>
<td>&lt;0.001</td>
<td>0.96 (0.94,0.99)</td>
<td>0.002</td>
<td>0.96 (0.94,0.99)</td>
<td>0.002</td>
<td>0.97 (0.94,0.99)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Univariate Model</th>
<th>p-value</th>
<th>Model 1*</th>
<th>p-value</th>
<th>Model 2**</th>
<th>p-value</th>
<th>Model 3***</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never Smoking vs. Current Smoking</td>
<td>-</td>
<td>-</td>
<td>1.46 (1.10,1.92)</td>
<td>0.008</td>
<td>1.43 (1.08,1.89)</td>
<td>0.013</td>
<td>1.43 (1.08,1.89)</td>
<td>0.012</td>
</tr>
<tr>
<td>Former Smoking</td>
<td>1.32 (1.14,1.52)</td>
<td>&lt;0.001</td>
<td>1.22 (1.01,1.49)</td>
<td>0.046</td>
<td>1.22 (1.00,1.48)</td>
<td>0.054</td>
<td>1.22 (0.99,1.48)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.39 (1.21,1.59)</td>
<td>&lt;0.001</td>
<td>1.12 (0.93,1.34)</td>
<td>0.238</td>
<td>1.10 (0.91,1.33)</td>
<td>0.311</td>
<td>1.09 (0.90,1.31)</td>
<td>0.384</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.64 (1.33,2.02)</td>
<td>&lt;0.001</td>
<td>1.34 (0.99,1.79)</td>
<td>0.052</td>
<td>1.34 (1.00,1.80)</td>
<td>0.054</td>
<td>1.31 (0.98,1.77)</td>
<td>0.072</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>0.63 (0.53,0.74)</td>
<td>&lt;0.001</td>
<td>0.70 (0.56,0.87)</td>
<td>0.001</td>
<td>0.70 (0.56,0.88)</td>
<td>0.002</td>
<td>0.72 (0.57,0.90)</td>
<td>0.003</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>0.82 (0.76,0.89)</td>
<td>&lt;0.001</td>
<td>0.91 (0.82,1.01)</td>
<td>0.76</td>
<td>0.93 (0.84,1.04)</td>
<td>0.197</td>
<td>0.94 (0.85,1.04)</td>
<td>0.237</td>
</tr>
<tr>
<td>Never using Alcohol vs. Current user</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Former user</td>
<td>0.58 (0.49,0.68)</td>
<td>&lt;0.001</td>
<td>0.75 (0.61,0.93)</td>
<td>0.008</td>
<td>0.76 (0.61,0.93)</td>
<td>0.009</td>
<td>0.76 (0.61,0.93)</td>
<td>0.009</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>2.19 (1.51,3.16)</td>
<td>&lt;0.001</td>
<td>1.92 (1.24,2.98)</td>
<td>0.004</td>
<td>1.68 (1.07,2.65)</td>
<td>0.024</td>
<td>1.71 (1.09,2.70)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Established Disease</th>
<th>Univariate Model</th>
<th>p-value</th>
<th>Model 1*</th>
<th>p-value</th>
<th>Model 2**</th>
<th>p-value</th>
<th>Model 3***</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/TIA</td>
<td>2.67 (1.93,3.70)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td>1.91 (1.24,2.93)</td>
<td>0.003</td>
<td>1.87 (1.22,2.89)</td>
<td>0.004</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>1.84 (1.49,2.27)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td>0.95 (0.70,1.29)</td>
<td>0.729</td>
<td>0.93 (0.68,1.26)</td>
<td>0.627</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>3.61 (2.25,5.79)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td>1.71 (0.86,3.39)</td>
<td>0.126</td>
<td>1.55 (0.78,3.09)</td>
<td>0.214</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>2.65 (1.77,3.97)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td>1.55 (0.95,2.50)</td>
<td>0.083</td>
<td>1.57 (0.95,2.58)</td>
<td>0.076</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>2.12 (1.78,2.53)</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.39 (1.06,1.83)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

*Model 1 = OR (95% CI) for risk of functional impairment adjusted for demographics (age, gender, age leaving formal education) and vascular risk factors (smoking, hypertension, diabetes, HDL cholesterol, LDL cholesterol atrial fibrillation and alcohol intake). **Model 2 =OR (95% CI) for risk of functional impairment adjusted for demographics, vascular risk factors and established cardiovascular disease (stroke/TIA, coronary heart disease, congestive heart failure and peripheral vascular disease). ***Model 3 = OR (95% CI) for risk of functional impairment adjusted for demographics, vascular risk factors and established cardiovascular disease (stroke/TIA, coronary heart disease, congestive heart failure, peripheral vascular disease and chronic kidney disease).
2.4.3 Subgroup Analysis

On subgroup analysis neither age, (categorised by dividing the cohort into those over and under 65 years), gender nor presence of established cardiovascular disease modified the association between any of the risk factors (hypertension, diabetes, smoking, LDL or HDL cholesterol, atrial fibrillation or alcohol intake) and functional impairment. Tests for interaction were not significant. The subgroup analysis by age is presented in Figure 2.2.

We also analysed the results for impairment in IADL and BADL individually. We included demographics, vascular risk factors and established cardiovascular disease in this multivariable model (Table 2.3). Age, current smoking versus never smoking, former drinking alcohol versus never drinking, diabetes and stroke were associated with an increased risk of impairment of both IADL and BADL while education and HDL cholesterol were associated with a lower risk of impairment of both domains.

We explored current alcohol consumption further by categorizing into binge drinking-pattern (defined as more than five units on single occasion at least once per month) and non-binge-drinking pattern. Of current alcohol users, 533/1700 (31.4%) admitted to binge drinking at least once per month. On multivariate analysis (adjusted for demographics, vascular risk factors and established cardiovascular disease) never using alcohol was associated with reduced risk of functional impairment vs. non-binge drinking (OR 0.71 [0.57, 0.89]) however this association with reduced risk of impairment was not significant for binge drinkers (OR 0.82 [0.62, 1.09]).
Figure 2.2 Forest Plot of Subgroup Analysis by Age for Risk of Functional Impairment According to Vascular Risk Factors

Odds ratios (95% CI) given for risk of functional impairment for each vascular risk factor for those under and over 65 years of age. P value is given for interaction.
### Table 2.3 Multivariable Logistic Regression Model for Risk of Impairment in IADL and BADL

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Impairment in IADL (OR, 95% CI)</th>
<th>p-value</th>
<th>Impairment in BADL (OR, 95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02 (1.01, 1.03)</td>
<td>&lt;0.001</td>
<td>1.04 (1.03, 1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>1.04 (0.85, 1.27)</td>
<td>0.699</td>
<td>0.84 (0.67, 1.05)</td>
<td>0.104</td>
</tr>
<tr>
<td>Age in years leaving Education</td>
<td>0.96 (0.94, 0.98)</td>
<td>0.001</td>
<td>0.95 (0.92, 0.98)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Risk Factors**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Impairment in IADL (OR, 95% CI)</th>
<th>p-value</th>
<th>Impairment in BADL (OR, 95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never Smoking vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Smoking</td>
<td>1.43 (1.08, 1.90)</td>
<td>0.014</td>
<td>1.40 (1.03, 1.90)</td>
<td>0.032</td>
</tr>
<tr>
<td>Former Smoking</td>
<td>1.22 (1.00, 1.50)</td>
<td>0.053</td>
<td>1.20 (0.96, 1.49)</td>
<td>0.104</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.13 (0.93, 1.36)</td>
<td>0.226</td>
<td>1.02 (0.83, 1.25)</td>
<td>0.851</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.41 (1.05, 1.89)</td>
<td>0.024</td>
<td>1.72 (1.27, 2.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>0.72 (0.57, 0.91)</td>
<td>0.005</td>
<td>0.76 (0.59, 0.97)</td>
<td>0.027</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>0.98 (0.88, 1.09)</td>
<td>0.722</td>
<td>0.93 (0.83, 1.04)</td>
<td>0.195</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>1.51 (0.96, 2.35)</td>
<td>0.072</td>
<td>1.45 (0.92, 2.28)</td>
<td>0.110</td>
</tr>
<tr>
<td>Never Using Alcohol vs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current User</td>
<td>0.77 (0.62, 0.96)</td>
<td>0.019</td>
<td>0.89 (0.70, 1.12)</td>
<td>0.304</td>
</tr>
<tr>
<td>Former User</td>
<td>2.04 (1.49, 2.81)</td>
<td>&lt;0.001</td>
<td>1.82 (1.31, 2.53)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Established Cardiovascular Disease**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Impairment in IADL (OR, 95% CI)</th>
<th>p-value</th>
<th>Impairment in BADL (OR, 95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/TIA</td>
<td>1.97 (1.29, 2.99)</td>
<td>0.002</td>
<td>1.66 (1.09, 2.54)</td>
<td>0.018</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>0.93 (0.68, 1.27)</td>
<td>0.642</td>
<td>0.88 (0.63, 1.21)</td>
<td>0.429</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.74 (0.90, 3.35)</td>
<td>0.100</td>
<td>1.87 (0.98, 3.60)</td>
<td>0.060</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>1.41 (0.87, 2.30)</td>
<td>0.168</td>
<td>2.08 (1.27, 3.41)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Model adjusted for demographics, vascular risk factors, and established cardiovascular disease.

Instrumental Activities of Daily Living (IADL) and Basic Activities of Daily Living (BADL).
2.5 Discussion

2.5.1 Summary of Findings
We found an independent association between some vascular risk factors and functional impairment, after adjustment for established cardiovascular disease. Within established cardiovascular disease, a history of stroke had the strongest association with functional impairment.

2.5.2 Strengths
Vascular risk factors may increase the risk of functional disability, through a number of mechanisms. First, traditional vascular risk factors account for over 90% of the population attributable risk of myocardial infarction and stroke, for which an association between established cardiovascular disease and functional impairment is established, particularly for stroke. In our study, we found that stroke had the strongest association with functional impairment, and did not find a significant association between coronary heart disease and functional impairment. Second, vascular risk factors increase the risk of other chronic vascular conditions, usually mediated through small vessel disease. We found that chronic kidney disease and congestive heart failure were strongly associated with functional impairment on univariate analysis, which have been reported previously. In addition, both of these conditions are strongly correlated with cognitive impairment and covert stroke. Lastly, recent research has reported an association between some vascular risk factors (e.g. hypertension, diabetes mellitus, atrial fibrillation and alcohol intake) and sarcopenia, frailty and gait instability. Therefore, cardiovascular risk factors are expected to have a multi-organ impact on functional impairment.

While established cardiovascular disease is responsible for a considerable proportion of functional decline in older people, the true contribution of subclinical or covert vascular events to functional and cognitive impairment is not fully known and is an exciting area of research. Cohort studies have demonstrated the importance of vascular risk factor modification early in adulthood to prevent cognitive and functional impairment in later life but there have been few randomised trials. Most previous studies in this area have not considered the effect of both vascular risk factors and cardiovascular diseases together, which is required to determine the residual association between primary risk factors and functional loss independent of established cardiovascular...
diseases. We propose that this residual association may represent the contribution of subclinical cardiovascular disease to functional impairment in later life.

2.5.3 Limitations

An obvious limitation of our study is the lack of a physical measure of subclinical disease (carotid atherosclerosis, ankle brachial index or white matter changes on Magnetic Resonance Imaging [MRI] brain) which has been used in other studies\textsuperscript{16, 23, 39, 108-110}. We could not measure covert stroke, which requires MRI of brain or cognitive function testing. However, we propose that the residual association between cardiovascular risk factors and functional impairment, after adjustment for established cardiovascular disease, may represent a measure of subclinical stroke. Subclinical white matter changes are associated with cognitive decline and people with these changes on MRI of brain have demonstrably lower physical performance scores\textsuperscript{38, 39}.

We found that current smoking was associated with functional impairment, which is expected and due to the strong association of smoking with all cardiovascular diseases\textsuperscript{12, 102}. For alcohol consumption, we found that participants who currently consume alcohol were at the lowest risk of functional impairment, and those who had stopped consuming alcohol were at highest risk. Moderate alcohol intake has been suggested to be protective against cardiovascular disease and functional impairment\textsuperscript{50}. People with prior unhealthy patterns of alcohol consumption, a risk for CV diseases\textsuperscript{111}, may be over-represented in the former alcohol consumers, although this is speculative. In addition, this finding may be due to reverse causation, whereby patients who are functionally impaired are unable to attend social events or local bars. In this study, we did not measure the amount of alcohol consumed, and are therefore unable to determine the true nature of the association.

Given the known robust association between hypertension and stroke, dementia and cardiovascular disease, we had expected that hypertension would be the most important risk factor for functional impairment. However, while we report an association between hypertension and functional impairment on univariate analysis, the association was not significant on multivariable analyses. A number of factors may account for these findings, which have important implications for
the interpretation of our results. First, the lack of association between hypertension and functional impairment on multivariable analysis may be due to the inclusion of established cardiovascular diseases and other risk factors. For example, we found that atrial fibrillation had a strong association with functional impairment; however, hypertension is an important risk factor for atrial fibrillation. Second, it is plausible that patients with hypertension were well controlled on antihypertensive medications by their physician, which would diminish the association. Third, our study is cross-sectional and there may have been attrition of the vulnerable, given the strong association between hypertension and premature stroke and mortality. Finally, hypertension in mid-life has a stronger association with cognitive impairment in later-life than hypertension in later-life, which cannot be explored in our cross-sectional study.

There are a number of other limitations to our study. First, due to the cross-sectional design, our findings may be considered exploratory and hypothesis generating in nature, cannot establish causation, and need to be confirmed in a prospective cohort study. Second, the questionnaire was completed by only 47% of the eligible patients and responder bias may have occurred. We had no measure of the functional status of those who did not respond and although we found some differences in risk factor profile between responders and non-responders, these were modest and our cohort appeared to be generally representative of the entire cohort with respect to key demographics and risk factor burden. Third, the exclusion of patients for practical reasons is expected to introduce a selection bias and may have underestimated the prevalence of functional impairment. Conversely including only those who attended their GP (on at least two occasions) is expected to also introduce selection bias and perhaps overestimate the presence of functional impairment by excluding people who do not regularly attend medical services.

Finally, the proportion of people who reported any impairment in BADL or IADL in our study was higher than expected (40% overall, 35% IADL and 29% BADL). A recent analysis of the Health and Retirement Study (a cohort of over 30,000 people) reported a lower proportion of impairment of 26%. Worldwide estimated of levels of functional impairment in community dwelling older people range from 10-30%. Our study found a high level of self-reported mobility problems (28%), which accounted for the majority of BADL impairment. Mobility
was not included in categorization of ADL dependence in the aforementioned study.

2.6 Conclusions
In conclusion, there is an association between some vascular risk factors and functional impairment independent of established cardiovascular disease. The effect of risk factor modification on functional outcomes requires greater attention in clinical trials of interventions to prevent cardiovascular diseases.
Chapter 3: Does Lowering Blood Pressure with Antihypertensive Therapy Preserve Independence in Activities of Daily Living? A Systematic Review


Reproduced with Permission (Appendix 3)
3.1 Introduction

Functional impairment is often cited as a deciding factor in the transition from independent living to nursing home care and some older people prioritise preservation of functional independence over prevention of major vascular events. It is increasingly recognised that patient-important outcome measures like preservation of ADL in later life should be incorporated into clinical research, clinical practice and healthcare policy. However, this may not be commonly reflected in outcome measures reported in major cardiovascular trials of predominantly older populations with established cardiovascular risk factors or diseases.

Hypertension is responsible for a considerable proportion of the population attributable risk for major vascular diseases that can increase risk of functional decline, particularly stroke. The association between hypertension and functional impairment may also be mediated through subclinical cardiovascular disease independent of major vascular events. Hypertension has a role in covert stroke, which can manifest as cognitive decline, gait instability and frailty and lead to functional impairment. In addition hypertension is a risk factor for developing chronic kidney disease, and may be a risk factor for sarcopenia which are both associated with functional impairment. The effects of blood pressure lowering therapies on functional outcomes has not been quantified, with most clinical trials, and meta-analyses of these trials, focusing on major cardiovascular events, and secondarily on cognitive testing and self-reported quality of life.

3.2 Study Objectives

This review had two objectives. First, we wanted to determine the proportion of trials of antihypertensive therapies that included function (defined as ability to complete ADL) as an outcome measure. To compare reporting of ADL with reporting of other non-cardiovascular event based outcomes we secondarily determined the proportion of trials that included cognition and quality of life (QOL). Second, we aimed to calculate a summary estimate of the effect of blood pressure lowering on risk of functional impairment during follow-up for included studies.
3.3 Methods

3.3.1 Search Strategy and Information Sources

Electronic database searches of Medline, Embase, Psych Info, Cochrane Central Register of Controlled Trials and the Database of Abstracts of Reviews of Effects were conducted in December 2013 (Table 3.1). Reference lists of recent systematic reviews and guidelines on antihypertensive therapy were also searched for additional citations\textsuperscript{117-120}. The title and abstract for each reference identified by the literature search was screened by two independent reviewers for eligibility. A list of records for full text screening was compiled and screened for inclusion in the review. There were no restrictions on language or year of publication of citations.

3.3.2 Eligibility and Study Selection

We adopted a two-step approach to eligibility criteria. Step 1 involved determining the proportion of randomized controlled trials (RCTs) that reported ADL as an outcome measure. For step 1, eligible studies were RCTs comparing an anti-hypertensive medication to control in adults with hypertension (BP ≥ 140/90) or prehypertension (systolic [SBP] of 130-139 mmHg or a diastolic [DBP] BP of 85-89 mmHg), that had a follow up period of at least 1 year. This follow-up period was required because the benefit of blood pressure lowering on functional outcome is not expected to manifest in the short-term. The primary outcome measure was reporting of ADL as either a primary or secondary outcome. Other outcome measures of interest were reporting of cognition or quality of life, in order to provide a comparison between the reporting of functional outcomes and other non-cardiovascular event outcomes reported in trials. Step 2 involved determining the effect of antihypertensive therapy on ADL. For step 2, we included all trials from step 1 that reported ADL as an outcome measure.

3.3.3 Data Abstraction

Data was independently abstracted by two reviewers (MC and AS). Any disagreement regarding the inclusion of a study was resolved by consensus with a third reviewer (MO’D). Data extracted from each eligible trial included characteristics of trial participants, information about intervention and control treatments and outcomes listed above. We used the Cochrane Risk of Bias tool to assess eligible trials for adequacy of randomization and concealment of allocation;
Chapter 3

blinding of patients, health care providers, and outcome assessors; and the extent of loss to follow-up\textsuperscript{121}.
### Table 3.1 Example of Electronic Search Strategy for Medline

<table>
<thead>
<tr>
<th>Search Term</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 exp angiotensin receptor antagonist/ or angiotensin receptor antagonist.mp. or angiotensin receptor blocker.mp. or ARB.mp.</td>
<td>20703</td>
</tr>
<tr>
<td>2 (angiotensin converting enzyme inhibitor or ace inhibitors).mp. or exp Angiotensin-Converting Enzyme Inhibitors/ or exp dipeptidyl carboxypeptidase inhibitor/</td>
<td>45821</td>
</tr>
<tr>
<td>3 exp Diuretics, Osmotic/ or diuretics.mp. or exp Diuretics/ or exp Diuretics, Potassium Sparing/ or loop diuretics.mp. or thiazide diuretic.mp. or exp Sodium Chloride Sympporter Inhibitors/</td>
<td>79570</td>
</tr>
<tr>
<td>4 calcium channel blockers.mp. or exp Calcium Channel Blockers/ or calcium channel antagonists.mp.</td>
<td>76213</td>
</tr>
<tr>
<td>5 aldosterone antagonists.mp. or exp Mineralocorticoid Receptor Antagonists/</td>
<td>8009</td>
</tr>
<tr>
<td>6 (direct renin inhibitors or renin inhibitors).mp.</td>
<td>656</td>
</tr>
<tr>
<td>7 beta adrenergic blockers.mp. or exp Adrenergic beta-Antagonists/ or beta-blockers.mp. or beta blockers.mp.</td>
<td>85691</td>
</tr>
<tr>
<td>8 exp Adrenergic-Antagonists/ or alpha blockers.mp. or alpha-blockers.mp.</td>
<td>47531</td>
</tr>
<tr>
<td>9 vasodilators.mp. or exp Vasodilator Agents/</td>
<td>364572</td>
</tr>
<tr>
<td>10 sympathomimetics.mp. or exp Sympathomimetics/ or sympatholytics.mp. or exp Sympathomylitics/</td>
<td>272949</td>
</tr>
<tr>
<td>11 antihypertensive drugs.mp. or exp Antihypertensive Agents/ or anti-hypertensive drugs.mp. or antihypertensive drugs.mp.</td>
<td>231602</td>
</tr>
<tr>
<td>12 myocardial infarction.ab,ti. or exp Myocardial Infarction/</td>
<td>193264</td>
</tr>
<tr>
<td>13 stroke.ab,ti. or exp stroke/ or cerebrovascular accident.ab,ti.</td>
<td>172484</td>
</tr>
<tr>
<td>14 diabetes.ab,ti. or exp Diabetes Mellitus/</td>
<td>435374</td>
</tr>
<tr>
<td>15 smoking.ab,ti. or exp Smoking/</td>
<td>201074</td>
</tr>
<tr>
<td>16 exp Hypertension/ or hypertension.ab,ti. or hypertens*.ab,ti. or hyper-tens*.ab,ti. or blood pressure.ab,ti.</td>
<td>492904</td>
</tr>
<tr>
<td>17 cardiovascular disease.ab,ti. or exp Cardiovascular Diseases/ or cardio-vascular disease.ab,ti.</td>
<td>1886368</td>
</tr>
<tr>
<td>18 hyperlipidemia.ab,ti. or exp Hyperlipidemias/</td>
<td>63743</td>
</tr>
<tr>
<td>19 exp activities of daily living/ or activities of daily living.mp. or ADL.ab,ti.</td>
<td>59517</td>
</tr>
<tr>
<td>20 self care.ab,ti. or exp Self Care/</td>
<td>46031</td>
</tr>
<tr>
<td>21 quality of life.ab,ti. or exp &quot;Quality of Life&quot;/</td>
<td>191481</td>
</tr>
<tr>
<td>22 mobility.ab,ti. or exp Mobility Limitation/</td>
<td>94808</td>
</tr>
<tr>
<td>23 (dependency or disability).ab,ti.</td>
<td>117515</td>
</tr>
<tr>
<td>24 (randomized controlled trial or controlled clinical trial).pt.</td>
<td>467375</td>
</tr>
<tr>
<td>25 (randomized or randomised or placebo or randomly or trial or groups).ab.</td>
<td>1870860</td>
</tr>
<tr>
<td>26 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11</td>
<td>806618</td>
</tr>
<tr>
<td>27 12 or 13 or 14 or 15 or 16 or 17 or 18</td>
<td>2579284</td>
</tr>
<tr>
<td>28 19 or 20 or 21 or 22 or 23</td>
<td>463776</td>
</tr>
<tr>
<td>29 24 or 25</td>
<td>1990174</td>
</tr>
<tr>
<td>30 26 and 27 and 28 and 29</td>
<td>2104</td>
</tr>
<tr>
<td>31 limit 30 to (humans and &quot;all adult (19 plus years&quot;)</td>
<td>1434</td>
</tr>
</tbody>
</table>

*mp= Free text search for term including title (ti), abstract (ab), original title, name of substance word, subject heading word, keyword, heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier. exp= Explode search so that Medline will expand the search using broad or narrow headings*
3.3.4 Data Synthesis and Summary Measures

Step 1: We calculated the proportion of eligible RCTs which included (a) ability to carry out ADL as a primary outcome, (b) ability to carry out ADL as a secondary outcome and for comparative purposes the proportion of trials that included cognitive function and quality of life as an outcome.

Step 2: We completed a meta-analysis and generated a summary odds ratio for the effect of antihypertensive therapy on ability to carry out ADL where available data permitted. However, we did not meta-analyse the effect of antihypertensive therapy on cognition and quality of life as these outcomes have been reported in previous reviews and meta-analyses.

For trials which reported physical performance scores within a QOL scale, we converted mean differences to log odds ratios and generated odds ratios for the treatment effect in each included trial. We used the generic inverse method from Review Manager Software (Version 5.2. The Cochrane Collaboration, 2012) for this analysis. We pre-specified that we would use a random effects model for meta-analysis and quantified heterogeneity using the $I^2$ statistic. We generated funnel plots to evaluate risk of publication bias.

For subgroup analysis we specified a priori that the summary effects could vary in relation to the presence of prevalent or incident stroke or cerebrovascular disease which is a common cause of functional impairment, in those who have established hypertension versus prehypertension and in those aged younger and older than 65 years.

3.4 Results:

3.4.1 Study Selection

The search of electronic databases retrieved 2924 citations. After title and abstract screening, 2740 were discarded. 184 full text articles were screened for further eligibility and 93 RCTs were eligible for inclusion. Reasons for exclusion at each stage of screening are outlined in Figure 3.1.

3.4.2 Characteristics of Studies:

3.4.2.1 Demographics

The characteristics of included trials are summarized in Table 3.2. Ten RCTs which reported a measure of ability to complete ADL as a primary or secondary outcome
were included in the qualitative analysis which involved 17,459 participants. Duration of follow up for included trials varied from one to four years and mean ages of participants ranged from 48-72 years. Participants were recruited predominantly from community or primary care facilities. Six trials were based in US, three in Europe and one was an international multi-centred trial. The proportion of participants with a history of cardiovascular disease at baseline (coronary artery disease, diabetes, stroke and chronic kidney disease) varied among studies and five of the included studies had little or no participants with a history of cardiovascular disease at baseline.

3.4.2.2 Treatment
Six of the included trials compared an anti-hypertensive drug to placebo, two trials compared two different antihypertensive drugs, one trial compared two different blood pressure targets and one trial evaluated multi-component cardiovascular intervention strategies. Types of antihypertensive agents used in these trials included: ACE Inhibitors, alpha blockers, angiotensin II receptor antagonists, beta- blockers, calcium channel blockers, diuretics and vasodilators.

3.4.2.3 Measurement of ADLs
Measurement of ADLs varied among included studies. Six studies measured ADL using dedicated validated scales including the Barthel Index, WHO Disability Schedule (WHO-DAS), Rapid Disability Rating scale, Katz Index of ADL, Guttman Health Scale for the Aged, Modified Rankin Scale (MRS) and Comprehensive Assessment and Referral Evaluation (CARE) scale. Four studies used quality of life scores which incorporated a physical functioning domain including Rand Medical Outcomes Study Short Form 36 and Sickness Impact Profile (SIP). One study included a simple question about whether or not the participant had difficulty with or was dependent for ADL in addition to a validated ADL scale.
Chapter 3

Figure 3.1 PRISMA Flow Diagram Summarising Results from Database Searches

- Records Identified through Database Searching (n=5,762)
- Additional Records Identified through Other Sources (n=102)

- Records after Duplicates removed (n=2,924)

- Records for Title and Abstract Screening (n=2,924)
- Records Excluded (n=2,740)
  - Did not meet Inclusion Criteria

- Full-text Articles Assessed for Eligibility (n=184)
- Full-text Articles Excluded (n=93)
  - Not RCT (n=2)
  - Protocol for RCT (n=1)
  - Not Trial of Antihypertensive Drug (n=38)
  - RCT with <1 year follow-up (n=50)

- No of RCTs Eligible for Inclusion (n=53)

- RCTs with Quality of Life as Outcome (n=29) 31%
- RCTs with ADL as Primary or Secondary Outcome (n=10) 11%
- RCTs with Cognition as Outcome (n=17) 18%

- Step 1

- RCTs with ADL as Secondary Outcome (n=9) 10%
- RCTs with ADL as Primary Outcome (n=1) 1%
Table 3.2 Description of Trials that included Function as a Primary or Secondary Outcome

<table>
<thead>
<tr>
<th>Trial Name and Author</th>
<th>Participants</th>
<th>Intervention/Comparator</th>
<th>Functional Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veterans Affairs Coop Study</td>
<td>690 Males with Hypertension, US Hospital patients 48% Black All ≥60 years Mean age 64.3 Follow up 1 year</td>
<td>Titration 1: High dose Hydrochlorothiazide (HCTZ) (50mg once per day [od]/twice per day [bd]) vs. Low dose HCTZ (25mg od/bd). Goal BP attained: continue maintenance. If Goal BP not Attained: continue HCTZ and proceed to titration 2. Titration 2: Daily Oral Hydralazine vs. Methylprednisolone vs. Metoprolol vs. Reserpine.</td>
<td>1. Difficulty with ADLs * 2. Depression 3. Deterioration of Cognitive function  *Comprehensive assessment and Referral Evaluation [CARE] scale used.</td>
<td>1. None of the ADL factors deteriorated over time in either the low dose or high dose HCTZ groups. 2. Some ADL factors showed improvement over time, including personal hygiene in the low dose HCTZ group, ambulation in both HCTZ groups, and alertness in the high dose HCTZ group. 3. When changes in problems with ADL factors were compared between the low and high dose HCTZ groups, no statistically significant differences were found.</td>
</tr>
<tr>
<td>Applegate 1994</td>
<td>4736 community based US adults with Hypertension. History of MI/Stroke excluded. 14% Black 43% Male Mean Age 71.6 Follow up 4 years</td>
<td>Chlorthalidone 12.5-25mg od and/or Atenolol 25-50mg od (or Reserpine 0.05 mg od added if Goal BP not reached) vs. Placebo.</td>
<td>1. Physical function* 2. Cognitive Function 3. Quality of Life 4. Leisure Activities  *Items from Katz Index of ADL scale and Gutman Health scale for the Aged used.</td>
<td>1. Overall at the end of study 51% in treatment group and 50% in placebo group had difficulty with any ADL (from basic to advanced) but this was not a significant difference. 2. Treatment group: significantly less deterioration (p&lt;0.05) for certain individual components although magnitude was small: (a) Personal grooming (3.4% V vs 4.7%) (b) Dressing (7.2% vs 9.3%), (c) Eating (2.1% vs 3.4%) (d) Using the toilet (3.5% vs 5.2%) (e) Walking up and down stairs (5.7% vs 7.7%) (f) Walking a half mile (10.3% vs 12.4%).</td>
</tr>
</tbody>
</table>
Table 3.2 (Continued) Description of Trials that included Function as a Primary or Secondary Outcome

<table>
<thead>
<tr>
<th>Trial Name and Author</th>
<th>Participants</th>
<th>Intervention/Comparator</th>
<th>Functional Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOMHS Grimm 1997125</td>
<td>902 US adults with Mild Hypertension (DBP) &lt;100 mmHg</td>
<td>Antihypertensive medication (n=668) and nutritional-hygienic intervention: Acebutolol 400 mg od, Amlodipine 5mg od, Chlorthalidone 15 mg od, Doxazosin 2 mg od, Enalapril 5 mg od vs. Placebo (n=234) Dose doubled if DBP &gt;95mmHg. Persistent DBP&gt;95 mmHg: addition of Chlorthalidone 15-30 mg od. If randomized to Chlorthalidone, then Enalapril (2.5 – 5mg od) added.</td>
<td>1. Quality of Life* (General Functioning index within QOL scale used) *Medical Outcomes Study RAND SF-36</td>
<td>1. Participants randomized to active treatment experienced more favourable changes in most QOL indexes compared with placebo: (a) Mental health (p=0.05) (b) General functioning (p=0.01) (c) Social functioning indexes (p=0.04) (d) Global statistic (p=0.007) 2. Comparisons of each drug with placebo showed acebutolol and chlorthalidone groups had significantly greater improvements than placebo for most indexes.</td>
</tr>
<tr>
<td>Frank 1999127</td>
<td>156 Spanish outpatients with a diagnosis of vascular dementia Age 55-80 (Mean 72) 94 (60%) had Hypertension at baseline.</td>
<td>Nicardipine 20mg vs. Placebo</td>
<td>1. Primary outcome was loss of 10% in basal score on MMSE 2. Secondary outcome was the effect on functional disability* *Rapid Disability Rating Scale used.</td>
<td>1. There were no statistically significant differences in scores on ADL scales for the active treatment group.</td>
</tr>
<tr>
<td>Trial Name and Author</td>
<td>Participants</td>
<td>Intervention/Comparator</td>
<td>Functional Outcomes</td>
<td>Results</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------</td>
<td>-------------------------</td>
<td>---------------------</td>
<td>---------</td>
</tr>
<tr>
<td>SYST-EUR Fletcher 2002&lt;sup&gt;129&lt;/sup&gt;</td>
<td>1348 European Adults with Hypertension</td>
<td>Nitrendipine (10–40 mg od combined, if necessary, with Enalapril (5–20 mg od) and hydrochlorothiazide 12.5–25 mg od to reach target BP vs. Placebo</td>
<td>1. Quality of Life* 2. Cognition 3. Depression</td>
<td>1. 7.8% in active group and 4.8% in placebo group reported problems with home-work, 9.4% and 8.9% reported problems with ambulation but there were no significant differences found. 2. More actively treated patients reported problems on the social interaction dimension at end of follow up which was felt to be related to side effects. 3. No overall treatment differences were observed for the SIP dimensions (physical functioning, ambulation and home work), or with problems with sleep, although there was some suggestion of an adverse treatment effect in the 4th year of follow-up for the dimension ‘home work’.</td>
</tr>
<tr>
<td>PROGRESS Fransen 2003&lt;sup&gt;14&lt;/sup&gt;</td>
<td>6105 Adults with Hypertension and History of Stroke/TIA in last 5 years</td>
<td>Single Drug Therapy Perindopril 4mg od vs. Single Placebo</td>
<td>1. Disability* 2. Dependency**</td>
<td>1. Overall 19% of the active group and 22% of the placebo group were disabled. (Adjusted odds ratio, 0.76; 95% Cl 0.65, 0.89; &lt;0.001). 2. 12% of the active group and 14% of the placebo group were dependent. (Adjusted odds ratio, 0.84; 95% Cl 0.71, 0.99; P=0.04). 3. Effects of treatment was mediated primarily through the prevention of disability and dependency associated with recurrent stroke. 4. Four-year treatment with the study drug would be expected to result in the avoidance of 1 case of long-term disability for every 30 (95% Cl 19,79) patients.</td>
</tr>
<tr>
<td>PROGRESS Fransen 2003&lt;sup&gt;14&lt;/sup&gt;</td>
<td>6105 Adults with Hypertension and History of Stroke/TIA in last 5 years</td>
<td>Combination Drug Therapy Perindopril 4mg od AND Indapamid 2.5mg od vs. Double Placebo</td>
<td>1. Disability* 2. Dependency**</td>
<td>1. Overall 19% of the active group and 22% of the placebo group were disabled. (Adjusted odds ratio, 0.76; 95% Cl 0.65, 0.89; &lt;0.001). 2. 12% of the active group and 14% of the placebo group were dependent. (Adjusted odds ratio, 0.84; 95% Cl 0.71, 0.99; P=0.04). 3. Effects of treatment was mediated primarily through the prevention of disability and dependency associated with recurrent stroke. 4. Four-year treatment with the study drug would be expected to result in the avoidance of 1 case of long-term disability for every 30 (95% Cl 19,79) patients.</td>
</tr>
</tbody>
</table>
Table 3.2 (Continued) Description of Trials that included Function as a Primary or Secondary Outcome

<table>
<thead>
<tr>
<th>Trial Name and Author</th>
<th>Participants</th>
<th>Intervention/Comparator</th>
<th>Functional Outcomes</th>
<th>Results</th>
</tr>
</thead>
</table>
| MOSES Schrader 2005\textsuperscript{126} | 1405 adults with hypertension and a cerebrovascular event (Stroke) in last 24 months.  
Mean Age 67.9  
Germany and Austria  
PROBE Trial Follow up 2.5 Years | Eprosartan or Nitrendipine for blood pressure lowering after a stroke. | 1. Functional capacity\*  
2. Mental function **  
*Barthel Index (BI) and Modified Rankin Scale  
**MMSE | 1. The mean values before and at the end of the study showed no significant differences in the scores of MMSE, BI, and MRS between treatment groups.  
2. Actual Values for theses scores were not reported in the paper. |
| AASK Lash 2006\textsuperscript{124} | 1094 African American adults with hypertension and hypertensive kidney disease.  
Aged 18-70  
61% male.  
Community based US study.  
Follow up 4 years. | Usual mean arterial pressure goal of 102 to 107 mmHg (n=540) vs.  
Lower mean arterial pressure goal of ≤92 mm Hg (n=554)  
AND  
Metoprolol 50-200mg od (n=441) vs.  
Ramipril 2.5-10 mg od (n=436) vs.  
Amlodipine 5-10 mg od (n=217) (2:2:1 randomization ratio for 3 drugs) | 1. Quality of Life\* (physical and mental health components of QOL scale used)  
*Medical Outcomes Study RAND SF-36 Instrument reported | 1. No significant differences in QOL were seen between the low- and usual-blood-pressure groups.  
2. Reported side effects also were similar between blood-pressure groups.  
3. The Mental Health Component of QOL had a slightly smaller decrease during the first 4 years in the ramipril group than amlodipine group. |
### Table 3.2 (Continued) Description of Trials that included Function as a Primary or Secondary Outcome

<table>
<thead>
<tr>
<th>Trial Name and Author</th>
<th>Participants</th>
<th>Intervention/Comparator</th>
<th>Functional Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>TROPHY Williams 2008[130]</td>
<td>809 US Adults with Prehypertension: SBP ≤139 and DBPs89 mmHg. 30-65 years (mean 48.7) 83% Caucasian Low level of CVD at baseline Follow up 4 years</td>
<td>Candesartan 16 mg od vs. Placebo</td>
<td>1. Quality of Life* (physical and mental health components within QOL scale used) *Medical Outcomes Study RAND SF-36 Instrument used.</td>
<td>1. At each follow up point scores for Physical component Summary (PCS) and Mental Component Summary (MCS) were relatively unchanged relative to baseline values in both treatment groups. 2. There were no differences between the candesartan and placebo groups for any of the individual physical or mental scales at any time point (P&gt;.05) 3. Health related QOL was maintained over the four years of trial with no difference between active and placebo groups.</td>
</tr>
<tr>
<td>Multi-Condition Collaborative Care Von Korff 2011[128]</td>
<td>214 US Adults with: 1. Diabetes or CHD, or both 2. BP&gt;140/90 mm Hg 3. LDL &gt;3.37 mmol/L 4. Hba1C ≥8.5% 5. PHQ-9 depression scores ≥10. Mean Age 56 Follow Up 1 year</td>
<td>12 month intervention: “Treat to target” programme which combined: 1. Self-management support, 2. Monitoring of disease control, and 3. Pharmacotherapy to control depression, hyperglycaemia, hypertension, and hyperlipidaemia. vs. Usual care</td>
<td>1. Social role disability* 2. Global quality of life rating 3. Disability assessment schedule** *Sheehan disability scale **WHODAS-2 used to measure disabilities in ADL (mobility, self-care, household maintenance).</td>
<td>1. Improvements from baseline on the Sheeehan disability scale (~0.9, 95% CI [-1.5, -0.2]; P=0.006) and global quality of life rating (0.7, [0.2, 1.2]; P=0.005) were significantly greater at six and 12 months in the intervention group. 2. There was a trend toward greater improvement in disabilities in ADL (~1.5, [-3.3, 0.4]; P=0.10) but this was not statistically significant.</td>
</tr>
</tbody>
</table>
3.4.3 Risk of Bias in Included Studies

A double blind RCT design was used in eight trials. Of those remaining, one used a prospective, randomized, open, blinded end point (PROBE) design\textsuperscript{126} while the other was a randomized controlled trial with no blinding\textsuperscript{128}. The latter trial evaluated a multi-component intervention and neither participants nor outcome assessors were blinded to intervention status or outcomes. Although randomization was adequate, this study was deemed to be at risk of performance and detection bias\textsuperscript{128}.

Four trials were deemed at risk of selection, performance and detection bias due to insufficient reporting of allocation concealment, random sequence generation, and blinding in the published papers\textsuperscript{123-125, 127}. Three of these RCTs (labelled as double blind) were designed and conducted prior to the publication of the CONSORT statement in 2001 which makes it likely that correct procedures were followed but not actually reported\textsuperscript{123, 125, 127}. Three studies were deemed at risk of attrition bias due to a substantial number of participants being lost to follow up\textsuperscript{122, 123, 129}. Pre-specified outcomes were reported in all the included trials. (Figure 3.2 and 3.3)
Chapter 3

Figure 3.2 Risk of Bias Graph

<table>
<thead>
<tr>
<th>Risk of Bias Item</th>
<th>Low risk of bias</th>
<th>Unclear risk of bias</th>
<th>High risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment (selection bias)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random sequence generation (selection bias)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3.3 Summary of Risk of Bias for Included Studies
3.4.4 Step 1 Results: Proportion of Clinical Trials Reporting ADL Outcomes

Of 93 eligible RCTs, one (1%) reported a measure of ADL as a primary outcome measure\(^{128}\) while nine (10%) included it as a secondary outcome measure\(^ {14, 122-127, 129, 130}\). Cognition was reported as an outcome in seventeen (18%) of these trials while twenty-nine (31%) reported QOL (Figure 3.4).

3.4.5 Step 2 Results: Effect of Antihypertensive Therapy on ADL

One study reported a significant benefit of anti-hypertensive therapy on ability to carry out ADL in those treated with antihypertensive drugs versus the control group\(^ {14}\). In another study, significant improvements were reported for individual elements of ADL (walking, dressing, eating and using stairs) for those randomized to antihypertensive therapy\(^ {122}\). Of the four studies that reported physical health component scores from QOL scores, there was only one which reported a significant improvement in functioning scores in favour of treatment\(^ {125}\).

Of 10 trials fulfilling eligibility criteria\(^ {14, 122-130}\), four were excluded from the meta-analysis because the trial compared the effects of multiple interventions not just anti-hypertensive therapy\(^ {128}\) or the trials did not report outcomes in a data format that facilitated meta-analysis\(^ {124, 126, 129}\).

We included six trials in the meta-analysis (n=12663). Overall, we found a significant reduction in risk of having difficulty with ADL on follow-up in those randomized to antihypertensive therapies OR 0.84 [95% CI 0.77, 0.92] compared to control (Figure 3.5). There was no evidence of statistical heterogeneity (I\(^2\)=0%, p=0.46) although there were only six trials included in the meta-analysis. There was no evidence of publication bias or selective reporting within included studies.
The number of trials (proportions reported in brackets) reporting functional outcomes as primary or secondary outcomes and the number of trials reporting cognition and quality of life (QOL) outcomes.
Figure 3.5 Forest Plot of the Effect of Blood Pressure Lowering on Ability to Carry out ADLs for Antihypertensive Therapy and Control Groups

Forest plot of the effect of blood pressure lowering on ability to carry out activities of daily living for antihypertensive therapy and control groups. Odds ratio (OR) and 95% confidence interval (CI) are shown for effect of antihypertensive therapy on ability to carry out activities of daily living for each included study and for the summary estimate of overall effect.
3.4.6 Subgroup Analysis

Subgroup analysis was limited by the small numbers of trials in the meta-analysis. Participants in two of the studies included in our meta-analysis had a history of previous stroke or cerebrovascular disease. On subgroup analysis the effect of blood pressure lowering on ability to carry out ADL was similar in those who had established stroke or cerebrovascular disease at baseline (OR 0.82 [0.72, 0.93] versus those who didn’t (OR 0.86 [0.72, 1.03]) and tests for subgroup differences were not significant ($I^2 = 0\%$, $p = 0.62$) (Figure 3.6).

For those trials where the mean age was less than 65 years blood pressure lowering decreased the risk of functional impairment OR 0.81 [0.72, 0.91]. We found that in trials where the mean age was over 65 years there was a trend towards a reduced risk of functional impairment with blood pressure lowering but this was not significant (OR 0.91 [0.78, 1.05]. However, it was difficult to separate the studies based on age as functional outcomes were not stratified by age in the papers. We crudely divided studies based on mean age of participants in each trial of greater or less than 65 years. Tests for subgroup differences were not significant ($I^2 = 32\%$, $p = 0.22$) (Figure 3.7).

For trials that included those with established hypertension, blood pressure lowering reduced the risk of functional impairment (OR 0.84 [0.77, 0.91]). Only one trial included those with “prehypertension” which showed a trend towards an increase in risk of functional impairment (OR 1.95 [0.66, 5.81]) but this was not statistically significant nor were tests for subgroup differences ($I^2 = 56\%$, $p = 0.13$) (Figure 3.8).

One trial (n=610) which we could not include in the meta-analysis provided an estimate for ability to carry out ADL for active and control groups in graphical format. We extrapolated estimates of the changes in ability to do “home-work” in active and control groups from the graph and included them in a sensitivity analysis. The estimate for the effect of blood pressure lowering on ability to carry out ADL for this study was OR 1.03 [0.71, 1.50]. When this estimate was included in the meta-analysis it did not affect the significance of the overall estimate (OR 0.87 [0.81, 0.93]).
**Chapter 3**

**Figure 3.6 Forest Plot of the Effect of Blood Pressure Lowering on Ability to Carry Out ADLs for Subgroups with and without Established Stroke or Cerebrovascular Disease**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROGRESS 2003</td>
<td>-0.2032</td>
<td>0.0637</td>
<td>48.9%</td>
<td>0.82 [0.72, 0.93]</td>
<td></td>
</tr>
<tr>
<td>Frank 1999</td>
<td>0.15</td>
<td>1.0197</td>
<td>0.1%</td>
<td>1.16 [0.99, 1.35]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>49.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.82 [0.72, 0.93]</strong></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00, Chi² = 0.07, df = 1 (P = 0.79), I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 3.18 (P = 0.001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOMHS 1997</td>
<td>-0.29</td>
<td>0.1166</td>
<td>14.6%</td>
<td>0.75 [0.60, 0.94]</td>
<td></td>
</tr>
<tr>
<td>SHEP 1994</td>
<td>-0.0866</td>
<td>0.0758</td>
<td>34.5%</td>
<td>0.91 [0.78, 1.05]</td>
<td></td>
</tr>
<tr>
<td>Goldstein 1990</td>
<td>-0.0924</td>
<td>0.1477</td>
<td>1.2%</td>
<td>0.91 [0.81, 1.03]</td>
<td></td>
</tr>
<tr>
<td>TROPHY 2009</td>
<td>0.07</td>
<td>0.0556</td>
<td>0.8%</td>
<td>1.07 [0.96, 1.21]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>51.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.86 [0.72, 1.03]</strong></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.01, Chi² = 4.12, df = 3 (P = 0.25), I² = 27%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.60 (P = 0.11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)** | **100.0%** | **0.84 [0.77, 0.92]** |
| Heterogeneity: Tau² = 0.00, Chi² = 4.84, df = 5 (P = 0.46), I² = 0% |
| Test for overall effect: Z = 3.65 (P = 0.0001) |
| Test for subgroups differences: Chi² = 0.24, df = 1 (P = 0.62), I² = 0% |
Chapter 3

Figure 3.7 Forest Plot of the Effect of Blood Pressure Lowering on Ability to Carry Out ADLs by Subgroups: Mean age greater than 65 years versus Mean age less than 65 years

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age Greater than 65 Years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHEEP 1994</td>
<td>-0.0968</td>
<td>0.0758</td>
<td>34.5%</td>
<td>0.91 [0.78, 1.05]</td>
<td></td>
</tr>
<tr>
<td>Frank 1999</td>
<td>0.15</td>
<td>1.3373</td>
<td>11%</td>
<td>1.11 [0.99, 1.25]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>34.7%</td>
<td>0.91 [0.78, 1.05]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.86); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.21 (P = 0.22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Mean Age Less than 65 Years |                 |     |        |                             |                             |
| Goldstein 1980           | -0.0904         | 0.4077 | 1.2%   | 0.91 [0.41, 2.03]           |                             |
| TOMHS 1977               | -0.29           | 0.1106 | 14.0%  | 0.75 [0.60, 0.94]           |                             |
| HKUHGES 2003             | -0.72           | 0.0825 | 41.9%  | 0.52 [0.36, 0.72]           |                             |
| TROPHY 2003              | 0.67            | 0.556  | 0.6%   | 1.95 [0.66, 5.81]           |                             |
| Subtotal (95% CI)        | 65.3%           | 0.8110 [0.72, 0.91] |        |                             |                             |
| Heterogeneity: Tau² = 0.00; Chi² = 3.07, df = 3 (P = 0.38); I² = 2% |
| Test for overall effect: Z = 3.66 (P = 0.0003) |

| Total (95% CI)           | 100.0%          | 0.84 [0.77, 0.92] |                             |                             |
| Heterogeneity: Tau² = 0.00; Chi² = 4.84, df = 5 (P = 0.46); I² = 0% |
| Test for overall effect: Z = 3.85 (P = 0.0001) |
| Test for subgroups differences: Chi² = 1.49, df = 1 (P = 0.22), I² = 32.8% |
Chapter 3

Figure 3.8 Forest Plot of the Effect of Blood Pressure Lowering on Ability to Carry Out ADLs by Subgroups: Established hypertension versus Prehypertension

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Established Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frank 1999</td>
<td>0.15</td>
<td>1.3323</td>
<td>0.1%</td>
<td>1.16 [0.09, 15.02]</td>
<td></td>
</tr>
<tr>
<td>Coldstein 1990</td>
<td>-0.0024</td>
<td>0.4077</td>
<td>1.7%</td>
<td>0.91 [0.41, 2.01]</td>
<td></td>
</tr>
<tr>
<td>PROGRESS 2003</td>
<td>-0.2032</td>
<td>0.0837</td>
<td>48.9%</td>
<td>0.82 [0.72, 0.92]</td>
<td></td>
</tr>
<tr>
<td>SHEP 1994</td>
<td>-0.0666</td>
<td>0.0758</td>
<td>34.5%</td>
<td>0.91 [0.76, 1.05]</td>
<td></td>
</tr>
<tr>
<td>IOMBS 1981</td>
<td>-0.20</td>
<td>0.1158</td>
<td>14.8%</td>
<td>0.51 [0.36, 0.71]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.84 [0.77, 0.91]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.00$, $Chi^2 = 7.34$, df = 4 ($P = 0.07$), $I^2 = 0$

Test for overall effect: $Z = 2.98$ ($P < 0.0001$)

| **Prehypertension** |
|---------------------|----------------|--------|-------------------|-------------------------------|
| TROPHY 2006         | 0.07           | 0.566  | 0.6%   | 1.05 [0.86, 1.28] |
| **Subtotal (95% CI)** |                |       |        | 1.05 [0.86, 1.28] |

Heterogeneity: Not applicable

Test for overall effect: $Z = 1.21$ ($P = 0.23$)

**Total (95% CI)** | 100.0% | 0.04 [0.77, 0.92] |

Heterogeneity: $I^2 = 0.00$, $Chi^2 = 1.81$, df = 5 ($P = 0.48$), $I^2 = 0$

Test for overall effect: $Z = 3.05$ ($P = 0.0001$)

Test for subminum difference: $Chi^2 = 2.31$, df = 1 ($P = 0.10$), $P = 56.6%$
3.5 Discussion

3.5.1 Summary of Findings
We found that reporting of ability to carry out ADL in RCTs of antihypertensive agents was uncommon, with only one in ninety-three trials including it as a primary outcome measure and nine in ninety-three including it as a secondary outcome. However, despite the low proportion of trials including ADL as an outcome measure, we found evidence that blood pressure lowering using antihypertensive drugs was associated with preservation in ability to carry out ADL (OR 0.84 [95% CI 0.77, 0.92]) in a meta-analysis of six trials. The methods used to measure ADL (either as primary or secondary outcomes) in included trials, were heterogeneous which hindered comparability across studies and reduced the number of studies included in the meta-analysis.

3.5.2 Strengths
The benefit of blood pressure lowering for primary and secondary prevention of stroke, myocardial infarction and cardiovascular death is established in many large RCTs of participants with hypertension. However, the benefits of lowering blood pressure for functional and cognitive outcomes have not been proven\textsuperscript{92}. Longitudinal observational studies have shown that there is an association between mid-life hypertension and both loss of ADL and subsequent development of dementia\textsuperscript{87,131} but systematic reviews evaluating the effect of blood pressure lowering on the development of dementia and cognitive impairment have been inconclusive\textsuperscript{90,92}. Few large clinical trials of antihypertensive therapy have evaluated the effect of blood pressure lowering on ability to carry out ADLs and therefore this knowledge gap can be explained in large part by absence of evidence, rather than evidence of absence.

Stroke is the leading cause of acquired disability worldwide so it is expected that studies reporting a high number of strokes will report a high level of difficulty with ADL. Those randomized to antihypertensive therapy in the two largest and most influential trials included in our meta-analysis had an overall stroke rate after four years of follow up of 10.06 \% (307/3051)\textsuperscript{14} and 4.36\% (103/2365)\textsuperscript{132} respectively. However, the total rate of loss of ADL in the antihypertensive therapy group was much higher in both studies (18.72\%\textsuperscript{14} and 18.63\%\textsuperscript{122}) respectively, suggesting that stroke was not the sole contributor to functional impairment in these studies,
that not all recurrent strokes were associated with ADL impairment and that other mechanisms of functional impairment had a contributory role. The proportion of disability reported in PROGRESS in the absence of recurrent stroke accounted for more than 80% of the overall disability reported \(^{14}\).

Loss of independence through disability is an important outcome for individuals, their families’ and communities’ and healthcare systems. Hypertension increases the risk of functional loss through major vascular events (stroke, MI, congestive cardiac failure) and through the development of subclinical vascular disease (covert stroke \(^ {16, 23}\) and CKD \(^ {52}\), therefore, a beneficial effect of blood pressure lowering on maintaining independence for ADL is expected. Ability to carry out ADL therefore may be considered an important cardiovascular-related outcome measure as it reflects the spectrum of clinical and subclinical vascular disease that may contribute to loss of function.

The underrepresentation of ADL as an outcome measure in hypertension trials to date might be explained by a number of factors. First, measurement of ADL is challenging, time consuming, unstandardized and trials that measure ADL may require longer follow up time for benefit in ADL to be observed which is costly. Second, there is uncertainty about whether hypertension treatment will preserve independence in ADL given the influence of other non-vascular factors (sarcopenia, macular degeneration, osteoarthritis and peripheral neuropathy) which are known to contribute to disability. Third, excessive lowering of blood pressure particularly in frail older patients, may be associated with adverse events such as syncope, falls and hip fractures and therefore it is possible that effects of hypotension, particularly orthostatic hypotension in this cohort could also lead to functional impairment \(^ {133-135}\). While there is a consistent positive association between blood pressure in mid-life and cognitive decline in later life, some observational studies report an inverse association between blood pressure and risk of cognitive decline and mortality in older adults, especially those who are frail \(^ {136, 137}\). Therefore, it is plausible, but unproven in clinical trials, that lowering blood pressure in some older adults with hypertension (e.g. frail older adults with mild hypertension) could have an adverse effect on independence in ADL. Lastly, most blood pressure trials have included people in mid-life where the rates of loss of independence of ADL may be low.
This review was conducted using a standardized, guideline-adherent approach to study identification and summarizing data, consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Table 3.3). All items of this internationally accepted guideline document for the reporting of systematic reviews and meta-analyses were considered. Although a structured summary (abstract) is not included in this PhD chapter, it is included in the published manuscript138.
## Table 3.3 Checklist for Preferred Reporting Items for Systematic Reviews & Meta-Analyses (PRISMA)

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>#</th>
<th>Checklist Item</th>
<th>Reported In</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TITLE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
<td>Title</td>
</tr>
<tr>
<td><strong>ABSTRACT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured summary</td>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
<td>See Publication</td>
</tr>
<tr>
<td><strong>INTRODUCTION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
<td>3.1</td>
</tr>
<tr>
<td>Objectives</td>
<td>4</td>
<td>Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>METHODS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
<td>Not Registered</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
<td>3.3.2</td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
<td>3.3.1</td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
<td>Table 3.1</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, and, if applicable, included in the meta-analysis).</td>
<td>3.3.2</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
<td>3.3.3</td>
</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List &amp; define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions/simplifications made.</td>
<td>3.3.3</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
<td>3.3.3</td>
</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
<td>3.3.4</td>
</tr>
</tbody>
</table>
Table 3.3 (Continued) Checklist for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

<table>
<thead>
<tr>
<th>METHODS (Continued)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis of results</td>
<td><strong>14</strong></td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td><strong>15</strong></td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
</tr>
<tr>
<td>Additional analyses</td>
<td><strong>16</strong></td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
</tr>
</tbody>
</table>

RESULT

| Study selection | **17** | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | Figure 3.1 |
| Study characteristics | **18** | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 3.4.2, Table 3.2 |
| Risk of bias within studies | **19** | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 3.4.3 |
| Results of individual studies | **20** | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates & confidence intervals, ideally with a forest plot. | 3.4.4, Figure 3.4 |
| Synthesis of results | **21** | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 3.4.5, Figure 3.5 |
| Risk of bias across studies | **22** | Present results of any assessment of risk of bias across studies (see Item 15). | Figure 3.2 & 3.3 |
| Additional analysis | **23** | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 3.4.6, Figure 3.6, 3.7 & 3.8 |

DISCUSSION

| Summary of evidence | **24** | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 3.5.1, 3.5.2 |
| Limitations | **25** | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 3.5.3 |
| Conclusions | **26** | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 3.6 |

FUNDING

| Funding | **27** | Describe sources of funding for the systematic review and other support (e.g., supply of data); | None |
3.5.3 Limitations

The absence of a standardized approach to measuring ADL in clinical trials is an important issue, and was one of the main limitations of this review in terms of conducting a more definitive meta-analysis. In 2008, a working group on functional outcome measures for older people, called for collaboration between pharmaceutical companies and researchers to establish guidelines for developing outcome measures in clinical trials of frail older people. In addition, there is growing recognition that insufficient attention has been paid to ensure standardization of patient-reported outcome measures used in clinical trials. The development and use of an agreed standardised collection of outcomes, known as a core outcome set, which should be measured and reported, as a minimum, in all trials for a specific clinical area is under development which will greatly improve the quality of future reviews.

A number of other limitations require review. First, the low number of eligible trials precluded definitive conclusions and limited valid subgroup analyses. It could be argued that these trials should not have been combined in a meta-analysis due to differences in measurement of ADL and, variations in established levels of cardiovascular disease and ages of participants, all of which could influence the estimate of effect. Second, longer term follow up may be required to detect change in lower cardiovascular risk populations where loss of ADL may be very low. Third, although we conducted a comprehensive search of electronic databases with no language restrictions, extensive searches of the grey literature were not done and may infer publication bias. Trials reporting positive results are more likely to be published and therefore we may have missed unpublished trials that showed a beneficial effect of antihypertensive drugs on ADL. This may be pertinent in particular for trials that reported ADL as a secondary outcome and had a negative primary outcome.

Lastly, cardiovascular outcomes were the primary endpoints of the majority of the included trials and the trials were terminated once benefits for the primary endpoints were seen. It is possible that the lag phase between blood pressure lowering and preventing decline in ADL is longer than the lag phase required for prevention of major vascular events, meaning that included trials may not have had adequate duration of follow-up to detect meaningful ADL change. Evidence to
support this contention comes from the Syst-Eur trial, which reported a reduction in the risk of dementia after eight years of extended follow-up\textsuperscript{143}.

### 3.6 Conclusions

Reporting of independence in ADL is uncommon in clinical trials of antihypertensive drugs. Of trials that did report ADL as an outcome measure, there was no standardized approach to measurement. Results of this review suggest that lowering blood pressure may significantly decrease the risk of difficulty with ADL. Functional outcomes are important to patients and a measure of ability to carry out ADL as a cardiovascular outcome measure should be reported in future hypertension trials.

Although our meta-analysis focused on hypertension trials, our findings have relevance to clinical trials of all cardiovascular prevention therapies, including cholesterol lowering, blood sugar lowering, smoking cessation and vitamin D replacement. An extended appreciation of the benefits of risk factor modification on outcomes other than major vascular events may increase awareness of risk factor modification and may increase adherence with therapies since preservation of independence is appreciated as a critical component of successful ageing.
Chapter 4: Attitudes to Outcomes Measured in Clinical Trials of Cardiovascular Prevention
Chapter 4

4.1 Introduction
Randomized controlled trials are the gold standard for evaluating the effectiveness of preventive cardiovascular therapies. Selection of outcome measures in these trials is based on a number of factors, including importance to patients and healthcare systems, ability to measure objectively, frequency of events and modifiability of risk factor with the intervention\textsuperscript{141, 142, 144}. Since most interventions are expected to have an effect on a number of related vascular outcomes, composite outcome measures are usually employed\textsuperscript{145, 146}. Commonly used outcomes in cardiovascular prevention trials include MI, heart failure and stroke which are associated with significant mortality and morbidity. However, there is a paucity of evidence on which outcomes are most relevant to patients. In particular, cognitive and functional impairment, which are often not reported in cardiovascular trials, may be of similar or greater importance to the participants as vascular-related outcomes\textsuperscript{138}.

The inclusion of outcome measures that are most relevant to patients has obvious advantages, both in ability to recruit and retain participants in clinical trials, but also for adherence with effective preventative therapies\textsuperscript{139, 147-149}. If the evidence base for recommending a medication is not based on a treatment effect that is of immediate and appreciable importance to patients, adherence with the intervention is more likely to be compromised\textsuperscript{147, 148, 150-152}. Moreover, a better appreciation of the potential for preventive therapies to reduce the burden of key contributors to healthcare costs (such as dementia and disability), would provide a greater incentive to fund national and global preventive programmes using such therapies\textsuperscript{11, 153}.

The CONSORT statement stipulates that the primary outcomes of trials should be the outcome considered to be of greatest importance to relevant stakeholders and lists patients before policy makers, clinicians and funders\textsuperscript{154}. However, incorporating outcomes relevant to patients have been relatively underused when compared with traditional clinical outcomes particularly major adverse cardiac events (MACE) in the design of cardiovascular prevention trials\textsuperscript{155}.

4.2 Study Objectives
In this study, we explored what outcomes in clinical trials of cardiovascular prevention would be viewed as important by groups of adults in the West of
Ireland. We also explored whether attitudes varied among younger and older adults within the cohort.

### 4.3 Methods

#### 4.3.1 Participants

This study was approved by the Ethics Committee at Galway University Hospital (GUH) (Appendix 4). Three convenience groups were studied: (1) adult outpatients attending cardiology clinics at GUH or secondary cardiovascular prevention programmes at CROI (a West of Ireland cardiac charity); (2) community dwelling older adults who were attending active retirement groups in the Galway city area and (3) 3rd year medical students rotating through clinical attachments at GUH. The medical student group was used as an internal control group. Medical students were approached after a lecture and asked to participate while outpatients were approached and asked to participate in the waiting room while waiting for their clinic consultation. For those recruited at the active retirement group meetings, each part of the survey was presented in a series of slides by the researcher and participants were then asked to complete the survey. Participants were provided with a participant information sheet which explained the study, their rights as participants and contact details of the lead investigator. (Appendix 5). Of 367 people approached, 280 (76%) agreed to participate and 261 surveys were suitable for analysis. We conducted the survey between January and April 2014.

#### 4.3.2 Description of Survey

The first part of this anonymised cross-sectional survey asked participants about basic demographics (age, gender, nationality and living arrangements) and current status with respect to ADLs. Participants were asked if they had difficulty with any of the following ADLs: (dressing, bathing, going up stairs, doing household chores, shopping or dealing with finances). They were also asked whether they could mobilise independently, required an aide or were chair or bed bound.

Participants were then asked to indicate if they had any cardiovascular risk factors (current smoking, diabetes, hypertension or hypercholesterolaemia) and whether they had established cardiovascular disease (history of myocardial infarction (MI), angina, heart failure, stroke or transient ischemic attack [TIA]).
In the second part, participants were asked to rank in order of importance and relevance a number of outcome measures which may be included in a cardiovascular prevention clinical trial concentrating on three areas: (1) outcomes that should be measured in clinical trials (2) outcomes related to successful ageing and (3) outcomes which would concern them most when considering the future.

The questions asked to participants were: (1) What do you rank as the most important outcome in a trial of a new blood pressure drug? (2) What do you rank as most important regarding successful ageing? and (3) What is your greatest concern about the future? (Appendix 6)

4.3.3 Statistical Analysis

We divided the participants into two groups: by age (<65s [n=157] and ≥65s [n=104]) and compared differences between the two groups. Continuous variables were reported as median (IQR) and differences were compared using Kruskal Wallis test. Categorical variables were reported in proportions and compared using Chi square and Fisher’s Exact test. We hypothesised that answers may differ between <65s excluding medical students and <65s including medical students, therefore differences between these two groups were compared. In addition we conducted subgroup comparisons within the <65 group looking for differences between non-medical students and medical students and between these individual groups and ≥65s.

For each of the three questions, we categorised answers into either a functional outcome (dementia, dependence, NH care, good family/social life and contributing to society) or as a MACE or medical outcome (death, MI, stroke cancer). Multivariable binary logistic regression analyses were used to determine association between predictors (age, gender, hypertension, established cardiovascular disease and being a medical student) and choice of functional or MACE outcome. We generated two models, the first included the whole cohort and the second excluded medical students. We wanted to evaluate the effect of being a medical student on the outcome selected therefore we used this variable instead of age in the first model and included age in the second model. Analysis was done using SPSS for Windows V20 (Armonk, NY: IBM Corp).
Chapter 4

4.4 Results
Overall, the median [Interquartile Range (IQR)] age was 55 (49). Median age in those <65 years was 23 (25) and 73 (9) in ≥65s. The ages of participants in the study ranged from 19-91 years. 36% (n=100) were male. The majority (96%) were independently mobile and 12% (n=31) required assistance with at least one ADL. Previous history of established CVD was noted in a fifth of participants and risk factors for cardiovascular disease among participants included hypercholesterolaemia (31.4%), hypertension (30.4%), diabetes (6.1%) and current smoking (3.6%) (Table 4.1).

Those aged ≥65 years were significantly more likely to live alone (34.6% vs. 8.9%, p <0.001), to require assistance with ADLs (17.3% vs. 8.3%, p=0.033) and assistance with mobility (9.6% vs. 0%, p<0.001). Looking specifically at each group, there was no statistically significant difference between those in the outpatient group and those in the active retirement groups regarding needing help with ADLs (14.4% vs. 18.7%, p = 0.461). Of the medical student group 6.5% reported needing assistance with ADLs (they mostly answered yes to requiring assistance with financial affairs).

4.4.1 Overall Responses to Survey Questions
When asked what outcomes were most important to measure in clinical trials respondents reported: dying (31.6%) stroke (28.5%), dementia (26.9%), MI (7.9%) and requiring NH care (5.1%). When asked which outcomes were most relevant to the construct of successful ageing respondents reported; maintaining independence (32.4%), avoiding major illness (24.3%), having a good family/social life (23.6%), living as long as possible (15.8%), avoiding NH care (3.1%) and contributing to society (0.8%). Finally, when asked what concerns them most about the future, respondents selected dementia (32.6%), dependence on others (30.4%), dying (12.8%), stroke (12.5%), cancer (6.2%), requiring NH care (4.8%) and MI (0.7%).
### Table 4.1 Characteristics of Survey Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All</th>
<th>Aged &lt;65 years</th>
<th>Aged ≥65 years</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Age (IQR)</td>
<td>55 (49)</td>
<td>23 (25)</td>
<td>73 (9)</td>
<td>&lt;0.001$</td>
</tr>
<tr>
<td>Male Gender (%)</td>
<td>100/276 (36.2)</td>
<td>58/157 (36.9)</td>
<td>35/104 (33.7)</td>
<td>0.600*</td>
</tr>
<tr>
<td><strong>Social Situation and ADLs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lives Alone (%)</td>
<td>57/280 (20.4)</td>
<td>14/157 (8.9)</td>
<td>36/104 (34.6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Lives with Spouse/Partner (%)</td>
<td>98/280 (35)</td>
<td>33/157 (21)</td>
<td>55/104 (52.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Requires Assistance with ≥ 1 ADL (%)</td>
<td>35/280 (12.5)</td>
<td>13/157 (8.3)</td>
<td>18/104 (17.3)</td>
<td>0.0326*</td>
</tr>
<tr>
<td>Independently Mobile (%)</td>
<td>268/280 (95.7)</td>
<td>157/157 (100)</td>
<td>94/104 (90.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Risk Factors and Established Cardiovascular Disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>85/280 (30.4)</td>
<td>22/157 (14)</td>
<td>51/104 (49)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Current Smoker (%)</td>
<td>10/280 (3.6)</td>
<td>6/157 (3.8)</td>
<td>3/104 (2.9)</td>
<td>1.000^</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>17/280 (6.1)</td>
<td>7/157 (4.5)</td>
<td>10/104 (9.6)</td>
<td>0.125*</td>
</tr>
<tr>
<td>Hypercholesterolaemia (%)</td>
<td>88/280 (31.4)</td>
<td>24/157 (15.3)</td>
<td>58/104 (55.8)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>MI/Angina (%)</td>
<td>34/280 (12.1)</td>
<td>6/157 (3.8)</td>
<td>27/104 (26)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Stroke/TIA (%)</td>
<td>29/280 (10.4)</td>
<td>10/157 (6.4)</td>
<td>17/104 (16.3)</td>
<td>0.015*</td>
</tr>
<tr>
<td>Heart Failure (%)</td>
<td>8/280 (2.9)</td>
<td>1/157 (0.6%)</td>
<td>6/104 (5.8)</td>
<td>0.017^</td>
</tr>
<tr>
<td>≥ 1 Risk Factor for CVD</td>
<td>129/280 (46.1)</td>
<td>42/157 (26.8)</td>
<td>73/104 (70.2)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Established CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(MI/Angina or Stroke/TIA or HF)</td>
<td>58/280 (20.7)</td>
<td>16/157 (10.2)</td>
<td>39/104 (37.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Comparisons between <65s and ≥65s are shown. For categorical variables Chi Square* and Fisher’s Exact^ tests were used. For comparisons between continuous variables Kruskal-Wallis ² test was used.
4.4.2 Comparison of Responses to Survey between Younger and Older Adults

The differences between the younger and older cohort are illustrated in Figure 4.1. Regarding outcomes most important to measure in clinical trials there were no significant differences between groups but more ≥65s felt that stroke and dementia were most important outcomes compared to <65s. Regarding outcomes relevant to the construct of successful ageing both older and younger age groups chose maintenance of independence as most important (31.2% vs. 34.2%, p=0.623). Living as long as possible was more important for ≥65s (23.7% vs. 9.2%, p=0.004) while having a good family life was more important for <65s (30.9% vs. 14%, p=0.001). There were no significant differences between groups regarding concerns about the future with both groups most concerned about dependence on others and dementia.
Comparison between answers from <65s and ≥65s using Chi Square test of two proportions. Two significant differences were reported: *More <65s reported having a good family/social life was most important compared to ≥65s. (30.9% vs. 14%, p=0.001). **More ≥65s reported that living as long as possible was most important compared to <65s. (23.7% vs. 9.2%, p=0.004).
4.4.3 Comparisons between Subgroups

In addition to comparing answers between those aged <65 years and those aged ≥65 years we made the following subgroup comparisons which are illustrated in Table 4.2.

(1) Within <65 group (non-medical students [n=49] vs. medical students [n=108])

Regarding outcomes most important to measure in clinical trials more medical students ranked dementia as most important compared to non-medical students (32.4% vs. 11.4%, p=0.008). Attitudes to successful ageing differed among medical and non-medical students with more non-medical students ranking living as long as possible (24.4% vs. 2.8%, p=0.001) and avoiding major illness (35.6% vs. 15%, p=0.009) as most important. More medical students ranked maintaining independence (40.2% vs. 20%, p=0.008) and having a good family/social life (37.4 vs. 15.6%, p=0.002) as most important compared to non-medical students.

(2) ≥65s (n=104) vs. Non-medical students (n=49)

More ≥65s ranked dementia as the most important outcome in a trial of a new blood pressure drug compared to those aged <65 who were non-medical students (29.2% vs. 11.4%, p=0.028).

(3) ≥65s (n=104) vs. Medical students (n=108).

Regarding successful ageing medical students ranked having a good family/social life as more important than ≥65s (37.4% vs. 14%, p=0.001). More ≥65s ranked living as long as possible (23.7% vs. 2.8%, p=0.001) and avoiding major illness (28% vs. 15%, p=0.025) as most important compared to the medical student group. Regarding concerns about the future more ≥65s were concerned about stroke (17.8% vs. 6.5%, p=0.011) and requiring NH care (7.9% vs. 0.9%, p=0.016) than the medical student group.

(4) All <65s (n=157) vs. Non-medical students (n=49)

Regarding outcomes most important to measure in clinical trials more of All <65s group chose dementia as the most important outcome compared to the non-medical student group (26.2% vs. 11.4%, p=0.042). Regarding successful ageing, living as long as possible was more important for the non-medical student group (24.4% vs. 9.2%, p=0.026) while maintenance of independence was more
important for All <65s group (34.2% vs. 20%, p=0.045). There were no significant differences between groups regarding concerns about the future except the All <65s group were more concerned about dementia than the non-medical student group (32.5% vs. 17.4%, p=0.025).
### Table 4.2 Comparisons within Subgroups of Responses to Survey Questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Within &lt;65s</th>
<th>Non-Medical Students (NMS)</th>
<th>Medical Students (MS)</th>
<th>≥65s vs. NMS</th>
<th>NMS (n=49)</th>
<th>P value</th>
<th>≥65s vs. MS</th>
<th>MS (n=108)</th>
<th>P value</th>
<th>All &lt;65s vs. NMS</th>
<th>NMS (n=49)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most Important Count (%)</strong></td>
<td>NMS (n=49)</td>
<td>MS (n=108)</td>
<td></td>
<td></td>
<td>≥65s (n=104)</td>
<td>P value</td>
<td>≥65s (n=104)</td>
<td>MS (n=108)</td>
<td>P value</td>
<td>≥65s (n=157)</td>
<td>NMS (n=49)</td>
<td>P value</td>
</tr>
<tr>
<td><strong>What do you rank as the most important outcome in a trial of a new blood pressure drug?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dying</td>
<td>17/44 (38.6)</td>
<td>37/105 (35.2)</td>
<td>0.696*</td>
<td></td>
<td>22/89 (24.7)</td>
<td>0.108*</td>
<td>37/105 (35.2)</td>
<td>0.107*</td>
<td>54/149 (36.2)</td>
<td>0.774*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>14/44 (31.8)</td>
<td>24/105 (22.9)</td>
<td>0.270*</td>
<td></td>
<td>28/89 (31.5)</td>
<td>0.967*</td>
<td>24/105 (22.9)</td>
<td>0.179*</td>
<td>38/149 (25.5)</td>
<td>0.423*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>5/44 (11.4)</td>
<td>9/105 (8.6)</td>
<td>0.556^</td>
<td></td>
<td>5/89 (5.6)</td>
<td>0.298^</td>
<td>9/105 (8.6)</td>
<td>0.580*</td>
<td>14/149 (9.4)</td>
<td>0.744^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>5/44 (11.4)</td>
<td>34/105 (32.4)</td>
<td>0.008^</td>
<td></td>
<td>26/89 (29.2)</td>
<td>0.028^</td>
<td>34/105 (32.4)</td>
<td>0.633*</td>
<td>39/149 (26.2)</td>
<td>0.042^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Requiring NH Care</td>
<td>3/44 (6.8)</td>
<td>1/105 (1)</td>
<td>0.077^</td>
<td></td>
<td>8/89 (9.0)</td>
<td>1.000^</td>
<td>8/89 (9.0)</td>
<td>0.112^</td>
<td>4/149 (2.7)</td>
<td>0.196^</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>What do you rank as most important regarding successful ageing?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Living as long as possible</td>
<td>11/45 (24.4)</td>
<td>3/107 (2.8)</td>
<td>0.001^</td>
<td></td>
<td>22/93 (23.7)</td>
<td>0.919*</td>
<td>3/107 (2.8)</td>
<td>0.001^</td>
<td>14/152 (9.2)</td>
<td>0.026*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoiding Major Illness</td>
<td>16/45 (35.6)</td>
<td>16/107 (15)</td>
<td>0.009*</td>
<td></td>
<td>26/93 (28)</td>
<td>0.372*</td>
<td>16/107 (15)</td>
<td>0.025*</td>
<td>32/152 (21.1)</td>
<td>0.65*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintaining Independence</td>
<td>9/45 (20)</td>
<td>43/107 (42.0)</td>
<td>0.008*</td>
<td></td>
<td>29/93 (31.2)</td>
<td>0.144*</td>
<td>43/107 (40.2)</td>
<td>0.182*</td>
<td>52/152 (34.2)</td>
<td>0.045*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Having good family/social life</td>
<td>7/45 (15.6)</td>
<td>40/107 (37.4)</td>
<td>0.002*</td>
<td></td>
<td>13/93 (14)</td>
<td>0.808*</td>
<td>140/107 (37.4)</td>
<td>0.001^</td>
<td>74/152 (30.9)</td>
<td>0.019*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contributing to society</td>
<td>0/45 (0)</td>
<td>2/107 (1.9)</td>
<td>1.00^</td>
<td></td>
<td>0/93 (0)</td>
<td>1.00^</td>
<td>0/107 (1.9)</td>
<td>0.500^</td>
<td>2/152 (1.3)</td>
<td>1.00^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoiding NH care</td>
<td>2/45 (4.4)</td>
<td>3/107 (2.8)</td>
<td>0.633^</td>
<td></td>
<td>3/93 (3.1)</td>
<td>0.661^</td>
<td>3/107 (2.8)</td>
<td>1.00^</td>
<td>5/152 (3.3)</td>
<td>0.66^</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Chi Square test for two proportions, ^Fishers Exact Test for two proportions
Table 4.2 (Continued) Comparisons within Subgroups of Responses to Survey Questions

<table>
<thead>
<tr>
<th>Question</th>
<th>Within &lt;65s Non-Medical Students (NMS) vs. Medical Students (MS)</th>
<th>≥65s vs. NMS</th>
<th>≥65s vs. MS</th>
<th>All &lt;65s vs. NMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dying</td>
<td>NMS (n=49)</td>
<td>MS (n=108)</td>
<td>P value</td>
<td>NMS (n=49)</td>
</tr>
<tr>
<td>What is your greatest concern about the future?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dying</td>
<td>8/46 (17.4)</td>
<td>14/108 (13)</td>
<td>0.493*</td>
<td>10/101 (9.9)</td>
</tr>
<tr>
<td>Dementia</td>
<td>8/46 (17.4)</td>
<td>42/108 (38.9)</td>
<td>0.003*</td>
<td>31/101 (30.7)</td>
</tr>
<tr>
<td>Dependence on others</td>
<td>15/46 (32.6)</td>
<td>35/108 (32.4)</td>
<td>0.981*</td>
<td>28/101 (27.8)</td>
</tr>
<tr>
<td>Requiring NH Care</td>
<td>4/46 (8.7)</td>
<td>1/108 (0.9)</td>
<td>0.028^</td>
<td>8/101 (7.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>7/46 (15.2)</td>
<td>7/108 (6.5)</td>
<td>0.132*</td>
<td>18/101 (17.8)</td>
</tr>
<tr>
<td>MI</td>
<td>0/46 (0)</td>
<td>2/108 (1.9)</td>
<td>1.00^</td>
<td>0/101 (0)</td>
</tr>
<tr>
<td>Cancer</td>
<td>4/46 (8.7)</td>
<td>7/108 (6.5)</td>
<td>0.734^</td>
<td>6/101 (5.9)</td>
</tr>
</tbody>
</table>

*Chi Square test for two proportions, ^Fishers Exact Test for two proportions
4.4.4 Multivariable Logistic Regression

On multivariable logistic regression analysis (Table 4.3), which included the whole cohort, being a medical student was associated with a significantly lower odds of choosing a MACE outcome for the question on successful ageing [OR 0.22 (0.11, 0.44)], but this was not significant for the other two questions. There was no association between gender, hypertension or established cardiovascular disease and odds of choosing a MACE outcome in any of the three questions. In a second model that excluded medical students, increasing age was associated with a significantly lower odds of choosing a MACE outcome in the question on what outcomes are important to measure in a new clinical trial, [OR 0.97 (0.92, 0.99)] per year increase in age. Hypertension was associated with significantly higher odds of choosing a MACE outcome in the question on what outcomes are important for successful ageing [OR 2.44 (1.20, 4.98)] but not for the other two questions. Tests for interaction were not significant between age and being a medical student when this was added to the multivariable models.
Table 4.3 Multivariable Logistic Regression Analysis for Odds of Choosing a MACE outcome vs. a Functional outcome

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Important outcomes in trial of new BP drug</th>
<th>Important outcomes regarding successful ageing</th>
<th>Outcomes of greatest concern for the future</th>
<th>Important outcomes in trial of new BP drug</th>
<th>Important outcomes regarding successful ageing</th>
<th>Outcomes of greatest concern for the future</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.97 (0.92, 0.99)</td>
<td>0.98 (0.95, 1.01)</td>
<td>0.98 (0.95, 1.01)</td>
</tr>
<tr>
<td>Male Gender</td>
<td>1.14 (0.64, 2.03)</td>
<td>0.79 (0.43, 1.44)</td>
<td>1.47 (0.85, 2.54)</td>
<td>1.14 (0.49, 2.68)</td>
<td>0.74 (0.34, 1.63)</td>
<td>0.97 (0.45, 2.08)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.68 (0.34, 1.37)</td>
<td>1.79 (0.93, 3.44)</td>
<td>1.46 (0.76, 2.78)</td>
<td>0.62 (0.29, 1.34)</td>
<td>2.44 (1.20, 4.98)</td>
<td>1.35 (0.68, 2.71)</td>
</tr>
<tr>
<td>Established CVD</td>
<td>0.69 (0.33, 1.46)</td>
<td>0.99 (0.49, 2.03)</td>
<td>0.98 (0.49, 1.10)</td>
<td>0.65 (0.28, 1.51)</td>
<td>1.06 (0.49, 2.32)</td>
<td>1.12 (0.52, 2.39)</td>
</tr>
<tr>
<td>Medical Students</td>
<td>0.68 (0.34, 1.36)</td>
<td>0.22 (0.11, 0.44)</td>
<td>0.84 (0.44, 1.62)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

1 Multivariable Binary Logistic Regression Model using the whole cohort. Odds ratio for choosing a Major Cardiovascular Event outcome (MACE) versus a functional outcome. Model adjusted for gender, hypertension, established cardiovascular disease and medical students.

4.5 Discussion

4.5.1 Summary of Findings

In this exploratory cross-sectional survey of adults in the west of Ireland, we found that stroke and dementia were viewed as the most important outcomes for trials of cardiovascular drugs with less emphasis placed on MI. When considering the construct of successful ageing maintenance of independence and avoiding major illnesses with a good family/social life were viewed as most important. The majority of adults surveyed were most concerned about being dependent on others in the future and about getting dementia.

4.5.2 Strengths

Trials of drugs for cardiovascular diseases have traditionally focused on “hard” outcomes that are unambiguous and easy to measure objectively including death, MI, stroke or combined cardiovascular endpoints. Our study highlights a discrepancy in terms of commonly measured ‘modifiable’ outcomes and what people deem important which has also been observed in other studies. MACE outcomes are commonly used as composite outcomes in clinical trials and can include conditions ranging from cardiac death, MI, heart failure and revascularisation to arrhythmias and valvular disorders. Our findings suggest that reporting these types of outcomes as composite outcomes may require greater attention to ‘weighting’ of individual components of the composite, because these outcomes may not be of similar importance to individuals. Selection of suitable outcome measures also requires evidence of an association between risk factor and outcome and a large body of evidence implicates modifiable vascular risk factors in the development of cognitive and functional impairment. Moreover, there is evidence that modification of some risk factors, particularly hypertension, reduces the risk of functional impairment.

We found that MI, which is often measured as an outcome in clinical trials of cardiovascular drugs, was not deemed as important as stroke, dementia or dying as an outcome and was not as concerning to respondents when considering the future. This may relate to perceptions of the differing consequences of MI compared to stroke, or awareness of advances in treatment of MI and improvements in survival post MI. The fact that the functional consequences of dementia and stroke are much more devastating than those of MI may also

73
explain this finding and the reason that they are prioritised in terms of prevention by patients\textsuperscript{6, 158}. Awareness of associations between risk factor and vascular outcomes may also be relevant to our finding that history of hypertension increased the odds of endorsing MACE outcome as most important, compared to those without hypertension\textsuperscript{75}(Table 3.4).

4.5.3 Limitations

This study had a number of limitations. First, due to the cross-sectional design and convenience sampling used in this study our findings may be considered exploratory and hypothesis generating in nature only. Second, although we had a good response to the survey (76%) we could not analyse in detail those that refused to participate and responder bias may have occurred. Although 280 agreed to participate we could only analyse 261 surveys, which may also introduce bias. We asked people to fill out the survey independent of the researcher to avoid social desirability bias, which may have occurred if the survey had been led by a researcher, but this approach can be associated with incomplete data collection. Third, participants who were members of active retirement groups or completed the survey before attending a secondary cardiovascular prevention classes may be more likely to have positive attitudes to ageing and to prevention of cardiovascular disease which may result in selection bias. Similarly, members of active retirement groups may not be representative of the older frailer adult category who may not be able to or choose not to attend group meetings due to functional or cognitive deficits. Fourth, this survey of west of Ireland adults is generalizable to Ireland but different countries with different cultural beliefs may have different attitudes to successful ageing and outcomes measured in clinical trials\textsuperscript{159-161}. Further larger, more representative studies in other regions are required, and our findings highlight the need for such studies to be completed. Lastly, medical students accounted for the majority of younger adults surveyed and they may not be representative of younger adults in general. We found that medical students were more concerned about the need to measure dementia as an outcome in clinical trials and about getting dementia in the future than the All <65s group or the non-medical student group. Younger people in general may not think as much about their mortality or becoming dependent for activities of daily living as older people, as for most it is not directly imminent but this view may be influenced by personal experiences of contact
with an older person or education about the ageing process. Medical students have greater exposure to people with dementia during their training and have a greater awareness of the extent of disability associated with it than may be found in the general public which may have influenced their responses.

This exploratory study highlights the fact that outcomes traditionally measured in cardiovascular prevention trials are not necessarily the outcomes that trial participants deem most important. This raises two important questions which will inform future studies in this area. Firstly, responses may differ depending on the focus of the question. For example, perspective on outcomes important for studies of successful ageing may be different to those deemed important to measure in clinical trials which could have biased answers given by participants. It would be interesting to explore this in greater detail drawing attention to the fact that outcomes may have to be individualised depending on what population is being studied. Secondly, we used slightly different outcomes in the question on outcomes deemed important to measure in clinical trials than in the other question. This was an attempt to capture attitudes to outcomes currently measured in clinical trials but it may not have placed enough importance on functional outcomes particularly maintenance of independence. However, the fact that traditional outcomes such as MI did not rank as important as stroke and dementia in this study can be used to inform future studies in this area.

4.6 Conclusions
In conclusion, our findings suggest that cognitive and functional outcomes are important patient relevant outcomes in trials of cardiovascular disease prevention, in some cases more important than major vascular events, of which stroke was deemed most important. Incorporating these outcomes into trials may encourage patient participation and adherence to treatment regimens in clinical trials. More research is required to further elicit preferences of older people in particular, regarding outcomes that may encourage participation in clinical trials of this often neglected group.
Chapter 5: Measuring the Composite Effect of Multicomponent Interventions
Chapter 5

5.1 Introduction
A substantial proportion of the reduction in age-adjusted rates of CV events observed between the 1970s-1990s relates to changes in modifiable risk factors, most notably for hypertension, smoking and dyslipidemia\textsuperscript{12, 19, 41, 153}. A combination of small changes in multiple risk factors can have considerable additive changes on incidence of cardiovascular disease in populations\textsuperscript{170-173}.

Identifying effective interventions to reduce cardiovascular risk usually requires evaluation of risk factor modification in clinical trials. For evaluation of individual risk factor modification (e.g. blood pressure), phase II trials are undertaken to demonstrate that an intervention favourably modifies a surrogate outcome, before undertaking Phase III trials to demonstrate an effect on CV events. Such an approach involves measuring a single outcome measure in Phase II trials, such as blood pressure, cholesterol or glucose etc. For multicomponent interventions, which often target numerous risk factors\textsuperscript{174, 175}, evaluation in Phase II trials poses a methodological challenge in selecting an appropriate outcome measure. While the most obvious approach is to evaluate the effect of the multicomponent intervention on change in each risk factor individually, such an approach increases the probability of type 1 error, due to multiple testing\textsuperscript{174, 176, 177}. Against that consideration, selection of a single risk factor outcome measures increases the risk of missing an important clinically meaningful effect of the intervention (Type 2 error) on other risk factors expected to be modified by the intervention.

Another approach is to use a composite outcome measure that represents a measure of all modifiable CV risk factors, an approach that is consistent with the use of composite of CV events in Phase 3 trials. However, there is no consensus on the best approach to composite outcomes for multiple vascular risk factors to reflect the effect of a multicomponent intervention. One potential approach is use of existing cardiovascular risk prediction tools. Validated risk prediction scores include the Framingham risk score, ASSIGN, Q-Risk-2, Procam, Reynolds Risk Score and SCORE\textsuperscript{178-183}, and their use has been explored in clinical trials, as an adjunct to reporting effects on individual risk factors\textsuperscript{184-189}. Common to each of these scores is inclusion of modifiable cardiovascular risk factors including blood pressure, smoking, diabetes and cholesterol and non-modifiable risk factors, age and sex. Differences among risk prediction scoring systems are variable inclusion of other
Chapter 5

risk factors including, body mass index, social deprivation score, high sensitivity CRP, a history of CKD, history of atrial fibrillation and rheumatoid arthritis.\textsuperscript{178-183}

5.2 Study Objective
In this study, we evaluated the use of validated cardiovascular risk prediction rules as outcome measures in a previously reported clinical trial (SPHERE\textsuperscript{190}) of a multicomponent intervention to reduce CV risk among patients with established CVD\textsuperscript{190, 191}. In addition, we explored use of a study-specific regression equation score as a composite measure of change in modifiable risk factors. Overall, we speculated that use of composite methods to measure change in risk factor burden may detect an important treatment benefit, which may not be detected when evaluating individual risk factor changes alone.

5.3 Methods
5.3.1 Description of SPHERE Trial
5.3.1.1 Trial Design
The SPHERE trial (Secondary Prevention of Heart disease in general practice) investigators conducted a trial which evaluated a tailored practice and personal care plan intervention to improve control of vascular risk factors and cardiovascular outcomes for patients with established coronary heart disease in general practice\textsuperscript{191}. It was a cluster randomised controlled trial, with practice-level randomisation to intervention and control groups which recruited 960 patients from 48 practices in three study centres on the island of Ireland (Belfast, Dublin and Galway).

The multicomponent intervention arm included (a) tailored care plans for practices (practised based training in prescribing and behaviour change, administrative support and quarterly newsletter) and (b) tailored care plans for participants (motivational interviewing, goal identification and target setting for lifestyle change). Specific risk factors were targeted within the tailored care plans for participants including optimal blood pressure control (<140/90mmHg), reduction of total cholesterol levels (<5mmol/L), Body Mass Index (BMI) <25, smoking cessation, exercise (30 minutes of exercise at least 5 times per week), diet (avoidance of saturated fats, five portions of fruit and vegetables per day) and stress avoidance.
Participants in the control arm received usual care which, at that time, was usually opportunistic in the Republic of Ireland and lacked targeted education of practice staff on secondary prevention measures, individualised goal setting or motivational interviewing methods. In Northern Ireland, usual care consisted of a system for annual review of blood pressure, cholesterol concentration, smoking status, and prescribed drugs, in accordance with the criteria specified within the National Health Service (NHS) GP contract for management of coronary heart disease.

Primary outcomes were assessed at 18 month follow up for all participants. The principal outcome measures for the SPHERE study were (a) the proportions of patients at 18 month follow up who were above target levels for blood pressure (SBP <140mmHg, DBP <90mmHg) and total cholesterol concentration (<5mmol/L) (b) hospital admissions and (c) changes in physical and mental health status using Short Form-12 Health Survey.

5.3.1.2 Sphere Population

SPHERE included 903 participants with established coronary heart disease registered with participating GP practices. Potential participants from each practice were randomly selected at a remote site and sent an invitation to participate. Patients were invited in sequence from lists in random order, until 20 in each practice had agreed to participate. Established cardiovascular disease for inclusion in the study was defined as documented MI, CABG, angioplasty, or angina (confirmed by exercise stress test, isotope test, or coronary angiogram). Participants who had major mental or physical illness that was likely to impair their capacity to change lifestyle behaviour or assimilate new information were excluded.

5.3.1.3 Data Collection

Data collection for this study consisted of three components (questionnaire, physical assessment/consultation and chart search). A questionnaire was sent to all participants which included items on quality of life, exercise, lifestyle and dietary habits. Demographic data collected included age, gender, highest educational level attained, type of GP practice attended and health service usage in the preceding 12 months. Baseline and subsequent measurements of blood pressure, serum cholesterol levels [total, HDL and LDL], height, weight, BMI and
current medications were recorded by study nurses. GP records were also searched for patient diagnoses, (including diabetes, previous history of MI, stroke/TIA, angina, previous coronary interventions) and health service usage (visits to GP and hospitalisations in the previous 12 months).

5.4 Description of Cardiovascular Risk Prediction Scores

For this analysis of the SPHERE cohort, we aimed to estimate the effect of the multicomponent intervention used in SPHERE on two cardiovascular risk prediction scores (Framingham Risk Score and Omnibus Risk Score). Therefore, the principal outcome measure for this analysis was the change in risk score over the period of the intervention (from baseline to 18 months).

The Framingham score was developed by D'Agostino et al for use in primary care settings and is available online (www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php). It was developed to predict 10 year CVD risk in people aged between 30-74 years of age without cardiovascular disease. For this risk score, cardiovascular disease is defined as coronary death, MI, coronary insufficiency, angina, ischemic stroke, haemorrhagic stroke, TIA, peripheral artery disease or heart failure. The model predicts 10-year risk of a CVD event based on risk factors including (age, gender, diabetes, smoking, systolic blood pressure, hypertension (treated or untreated) total cholesterol and HDL cholesterol).

The Omnibus or Atherosclerotic Cardiovascular Disease (ASCVD) risk calculator predicts 10 year ASCVD event risk in people aged 49-79 years without prior history of ASCVD. For the purposes of this paper, it will be referred to as the Omnibus score. An ASCVD event is defined as a nonfatal MI, coronary heart disease death, or stroke. This score is also available online (static.heart.org/ahamah/risk/OmnibusRiskEstimator.xls). The model predicts 10-year risk of ASCVD event based on the following risk factors: age, gender, smoking, diabetes, systolic blood pressure, hypertension (treated or untreated), total and HDL cholesterol and ethnicity (white or African American).

We used the Framingham score because it is a widely known score and was applicable to the SPHERE cohort. We also included the Omnibus score as it has been recently advocated by the American Heart Association (AHA) for assessment
Chapter 5

of cardiovascular risk. It has been proposed as a replacement for the Framingham risk prediction score because it is thought to be more representative of the general population than the original Framingham population. This is because it was developed using pooled data from 5 large National Institute of Health (NIH)-funded cohorts that included men and women of both white and African American ethnicities. Regarding differences between scores, the original Framingham equations estimate risk in those aged 30 to ≤ 74 years of age only while the Omnibus calculator has a cut off of 49 to ≤79 years and neither of the scores recognise very low levels of certain risk factors.

5.5 Statistical Analysis

Descriptive statistics were used to present baseline demographics and risk factors for intervention and control groups. Continuous variables were reported as mean (SD) and compared using t-test. Categorical variables were reported in proportions and compared using Chi-square test. Framingham and Omnibus scores were generated for SPHERE participants (Section 5.5.1). These scores were then used as primary outcomes in the adjusted analysis to test for the effect of the multicomponent intervention used in SPHERE (Section 5.5.2). We then used outcome events within the SPHERE study to generate a SPHERE specific risk prediction model for cardiovascular events (Section 5.5.3). Finally we describe multiple imputation methods used to deal with missing data in the SPHERE database (Section 5.5.4).

5.5.1 Generation of Framingham and Omnibus Scores for SPHERE cohort

We used the reported regression coefficients to calculate Framingham\(^{179}\) and Omnibus\(^{195,\,197}\) risk scores for all participants in SPHERE at baseline and 18 months. The Framingham Risk Score equation generates a score representing an estimated 10 year risk of CVD using a single multivariable risk function (D’Agostino et al, 2008)\(^{179}\). This involves using a Cox proportional-hazards regression model to relate risk factors to the incidence of a first CVD event during a maximum follow-up period of 12 years. We generated CVD risk functions from these models to estimate 10-year absolute CVD risk in the SPHERE population (Appendix 7). Covariates included in Cox models included: sex, age (between 30 and 74 years), systolic blood pressure (between 90 and 200 mmHg), antihypertensive medication use, current smoking, diabetes, HDL cholesterol (between 10 and 100 mg/dl) and total cholesterol (between 100 and 405 mg/dl). Values for age, systolic blood
pressure, high-density lipoprotein or total cholesterol outside the specified range were scaled upwards or downwards as appropriate. Our calculations generate the actual 10 year risk score as a percentage, e.g. 15% risk of developing a CVD event over 10 years. The original D’Agostino calculator has a maximum value for 10 year CVD risk of 30%.

We used the reported regression coefficients to calculate the Omnibus Risk Score, an equation to predict the 10 year risk of ASCVD. We used Cox proportional hazards regression models to relate risk factors to the incidence of a first ASCVD event during 10 years of follow up. We then generated ASCVD risk functions from these equations to calculate the estimated 10 year absolute ASCVD risk as a percentage in the SPHERE population (Appendix 7). Covariates included in this Cox model included sex, age (between 49 and 79 years), systolic blood pressure (90-200mmHg), antihypertensive medication use, current smoking, diabetes, HDL cholesterol (20-100 mg/dL)and total cholesterol (130-320 mg/dL) and ethnicity (white or African American).

5.5.2 Use of Framingham and Omnibus Risk Scores as Primary Outcomes in the SPHERE cohort

We conducted univariate and multivariate linear mixed model analysis using change in Framingham and Omnibus scores (from baseline to follow-up) as primary outcomes in the models. The following variables were included in the multivariable model; baseline Framingham/Omnibus score, age, gender, education, smoking, previous MI, total and HDL cholesterol, systolic blood pressure [treated and untreated] and diabetes and a random effect was incorporated to adjust for heterogeneity within each GP cluster.

5.5.3 Generation of SPHERE Specific Logistic Regression Model

We also generated a logistic regression model to predict future risk of cardiovascular events at 18 months follow-up, using actual data from the SPHERE cohort, to generate a population-specific prediction model for cardiovascular events. We generated a binary composite outcome for composite of MI, stroke or TIA from baseline to 18 months. We used a non-linear mixed model to model the odds of having the composite at 18 months adjusting for baseline characteristics and clustering. The following variables were included in the model: age, gender, education, smoking, previous MI, total and HDL cholesterol, systolic blood
Chapter 5

pressure and diabetes. We generated a probability for each participant at baseline and follow-up, and compared change in ‘probability score’ from baseline to trial end, between intervention and control groups.

All statistical analysis was done using Minitab Version 16 and R statistical software programme (version 2.9.0).

5.5.4 Missing Data

We reviewed the extent of missing data in the data set. There were no missing values for age, gender or previous MI. The proportions of missing values within remaining predictor variables for the total cohort (n=903) were as follows: educational level (3.3%), smoking status (3.4%), diabetes (0.2%), systolic blood pressure (1.1%), total cholesterol (4.8%), HDL cholesterol (37.9%). Missing data can limit precision of regression models. For example a Framingham score was unavailable for 369/903 participants due to missing data on variables required to calculate the score. To address this, multiple imputation (using random forests) was used to impute missing data for these variables. This method calculates a value for the missing variable based on the other available baseline values. To test this method we compared the distribution of Framingham/Omnibus scores using complete available data and those where multiple imputation was used. The distribution of Framingham and Omnibus scores were comparable for those with complete data and those where multiple imputation was used. This is illustrated in Figures 5.1 and 5.2.
Chapter 5

Figure 5.1 Comparison of Distribution of Baseline Framingham Scores Using Complete Data vs. Imputed Values

Figure 5.2 Comparison of Distribution of Baseline Omnibus Scores Using Complete Data vs. Imputed Values
5.6 Results

5.6.1 Descriptive Analysis

Baseline characteristics for intervention (n= 444) and control groups (n=459) in the original SPHERE study are presented in Table 5.1. The mean age of the cohort was 67.5 (SD 9.6), 633 (70%) were male and 453 (50%) had a previous MI. Almost two thirds of participants attended a large GP practice (defined as >2 Whole Time Equivalents [WTE]) and 324 (37%) had completed secondary level education. Participants in the intervention group were older (68.5 v 66.5, p=0.002), had completed secondary education (40.3% v 31.6, p=0.006) and had a lower HDL cholesterol (1.27 v 1.23, p=0.02) than those in the control group. There were no significant differences between intervention and control groups for other baseline risk factors (systolic blood pressure, diabetes, total cholesterol level, smoking status). Mean baseline Framingham and Omnibus scores were significantly higher in the intervention group which may reflect the older age and lower HDL cholesterol at baseline in this group. As this is a cluster randomised controlled trial, participants may not be perfectly balanced at baseline and all analysis in this study is adjusted for the effect of clustering.

5.6.2 Univariate (Unadjusted) Analysis

The unadjusted changes in Framingham and Omnibus scores from baseline to 18 months are illustrated in Figure 5.3.
## Table 5.1 Baseline Characteristics in SPHERE Study

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>All</th>
<th>Intervention</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>903</td>
<td>444 (49.2%)</td>
<td>459 (50.8%)</td>
<td>-</td>
</tr>
</tbody>
</table>

### Demographics

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Intervention</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males (%)</td>
<td>633/903 (70)</td>
<td>311/444 (70)</td>
<td>322/459 (70)</td>
<td>0.91</td>
</tr>
<tr>
<td>Completed Secondary Education (%)</td>
<td>324/873 (37.1)</td>
<td>179/430 (41.6)</td>
<td>145/443 (32.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>Larger Practice Size (WTE&gt;2) (%)</td>
<td>540/903 (59.8)</td>
<td>280/444(63.1)</td>
<td>260/459 (56.7)</td>
<td>0.057</td>
</tr>
<tr>
<td>Mean (SD) Age</td>
<td>67.48 (9.6)</td>
<td>68.5 (9.3)</td>
<td>66.5 (9.9)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

### Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>All</th>
<th>Intervention</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Systolic Blood Pressure (SD)</td>
<td>136.54 (21.7)</td>
<td>136.3 (22.2)</td>
<td>136.8 (21.2)</td>
<td>0.72</td>
</tr>
<tr>
<td>Mean Diastolic Blood Pressure (SD)</td>
<td>78.92 (11.6)</td>
<td>78.4 (11.9)</td>
<td>79.4 (11.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean Total Cholesterol (SD)</td>
<td>4.4 (0.9)</td>
<td>4.4 (0.9)</td>
<td>4.34 (0.91)</td>
<td>0.31</td>
</tr>
<tr>
<td>Mean HDL Cholesterol (SD)</td>
<td>1.27 (0.4)</td>
<td>1.23 (0.33)</td>
<td>1.3 (0.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>160/901 (17.8)</td>
<td>78/443 (17.6)</td>
<td>82/458 (17.9)</td>
<td>0.93</td>
</tr>
<tr>
<td>Current Smokers</td>
<td>130/872 (14.4)</td>
<td>59/430 (13.7)</td>
<td>71/442 (16.1)</td>
<td>0.33</td>
</tr>
<tr>
<td>Never Smokers</td>
<td>248/872 (27.5)</td>
<td>118/430 (27.4)</td>
<td>130/442 (29.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>Former Smokers</td>
<td>494/872 (54.7)</td>
<td>253/430 (58.8)</td>
<td>241/442 (54.5)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

### Established Cardiovascular Disease

<table>
<thead>
<tr>
<th>Established Cardiovascular Disease</th>
<th>All</th>
<th>Intervention</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous Myocardial Infarction</td>
<td>453/903 (50)</td>
<td>220/444 (50)</td>
<td>233/459 (51)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

### Baseline Risk Scores

<table>
<thead>
<tr>
<th>Baseline Risk Scores</th>
<th>All</th>
<th>Intervention</th>
<th>Control</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Framingham Score (SD)*</td>
<td>34.6 (20.2)</td>
<td>37.1 (21.3)</td>
<td>32.7 (19.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Omnibus Score (SD)*</td>
<td>25.6 (15.6)</td>
<td>27.8 (15.9)</td>
<td>23.9 (15.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Framingham Imputed Score (SD)**</td>
<td>33.6 (19.7)</td>
<td>35.1 (20.3)</td>
<td>32.3 (19.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean Omnibus Imputed Score (SD)**</td>
<td>25.1 (15.3)</td>
<td>26.4 (15.3)</td>
<td>23.9 (15.3)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Mean Framingham and Omnibus scores are given as score calculated using our risk functions.

**Mean Imputed Framingham and Omnibus Scores.
Chapter 5

Figure 5.3 Boxplots of (Unadjusted) Change in Framingham & Omnibus Scores at 18 Months Follow Up
5.6.3 Multivariate (Adjusted) Analysis

Between-Group Comparison of Change in Individual Risk Factors (Baseline to 18 Months)

Between-group comparison of change in individual risk factors from baseline to 18 months follow-up are reported in Table 5.2. For individual risk factors, there were no significant differences in mean change between treatment groups for blood pressure, cholesterol, exercise scores, dietary scores, BMI or smoking between baseline and follow up.

Between-Group Comparison of Mean Change in Framingham and Omnibus Scores (Baseline to 18 Months)

Baseline and 18 month follow-up mean Framingham scores in intervention and control groups are reported in Table 5.2. Mean change in Framingham score was significantly reduced in the intervention group (mean change -2.7%) compared to the control group (mean change +0.4%). Between-group adjusted mean difference in score was -2.7% (95% CI -5.24, -0.18, p=0.037). An analysis using imputation for missing variables did not materially alter findings (between-group adjusted mean difference in score of -2.6% (95% CI -4.48, -0.76, p=0.007).

Baseline and 18 month follow-up mean Omnibus scores in intervention and control groups are also reported in Table 5.2. Mean change in score in the intervention group was -0.5 compared to a mean change in the control group of +1.5. Between-group adjusted mean difference in score was -1.55% (95% CI 3.13, -0.03, p=0.05). An analysis using imputation was consistent, but was statistically significant (between-group adjusted mean difference in score of -1.7% (95% CI -2.99, -0.51, p=0.007).

5.6.4 Effect of Multicomponent Intervention on Risk of Cardiovascular Disease Composite Using SPHERE-Specific Model

Using the SPHERE-specific non-linear mixed multivariable logistic regression model to generate a probability score, we found no difference between intervention and control groups (p=0.15).
Table 5.2 Change in Risk Factors and Framingham and Omnibus scores for Intervention and Control Groups from Baseline to Follow Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Follow Up (18 mths)</th>
<th>Between Group Mean Difference (Baseline to 18 mths) (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td>Systolic Blood Pressure [mean (SD)]</td>
<td>136.3 (22.2)</td>
<td>136.8 (21.2)</td>
<td>133.8 (17.0)</td>
<td>137.9 (19.3)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>78.4 (11.9)</td>
<td>79.4 (11.3)</td>
<td>77.4 (10.1)</td>
<td>78.6 (10.4)</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>4.4 (0.9)</td>
<td>4.3 (0.9)</td>
<td>4.2 (0.9)</td>
<td>4.2 (0.9)</td>
</tr>
<tr>
<td>BMI</td>
<td>28.7 (5.2)</td>
<td>28.8 (4.7)</td>
<td>28.4 (5.0)</td>
<td>28.7 (4.8)</td>
</tr>
<tr>
<td>Godin’s exercise score</td>
<td>22.6 (20.7)</td>
<td>18.9 (17.2)</td>
<td>23.9 (23.7)</td>
<td>21.1 (21.7)</td>
</tr>
<tr>
<td>DINE² Diet Score Fibre</td>
<td>36.5 (12.4)</td>
<td>34.7 (12.1)</td>
<td>33.5 (12.0)</td>
<td>33.5 (13.4)</td>
</tr>
<tr>
<td>DINE² Diet Score Fat</td>
<td>31.2 (10.2)</td>
<td>30.7 (10.1)</td>
<td>27.8 (9.6)</td>
<td>27.4 (9.6)</td>
</tr>
<tr>
<td>DINE² Diet Score Unsaturated Fat</td>
<td>9.2 (1.5)</td>
<td>9.4 (1.8)</td>
<td>9.1 (1.9)</td>
<td>9.1 (1.9)</td>
</tr>
<tr>
<td>Self-reported smoker [N (%)]</td>
<td>13.5 (57)</td>
<td>16.2 (71)</td>
<td>11.4 (40)</td>
<td>13.8 (52)</td>
</tr>
<tr>
<td>Framingham Score</td>
<td>37.1 (21.3)</td>
<td>32.7 (19.0)</td>
<td>34.4 (19.9)</td>
<td>33.1 (18.4)</td>
</tr>
<tr>
<td>Omnibus Score</td>
<td>27.8 (15.9)</td>
<td>23.9 (15.2)</td>
<td>27.3 (14.5)</td>
<td>25.4 (15.1)</td>
</tr>
<tr>
<td>Imputed Framingham Score</td>
<td>35.1 (20.3)</td>
<td>32.3 (19.1)</td>
<td>33.9 (18.5)</td>
<td>33.3 (18.3)</td>
</tr>
<tr>
<td>Imputed Omnibus Score</td>
<td>26.4 (15.3)</td>
<td>23.9 (15.3)</td>
<td>26.9 (13.8)</td>
<td>25.8 (15.2)</td>
</tr>
</tbody>
</table>

Analysis adjusted for clustering, baseline differences, and prespecified covariates including: age, sex, education, occupation, years since diagnosis, angina, MI, CABG, percutaneous transluminal coronary angioplasty, diabetes, region, practice size. Smoking status was also considered for all measurements of blood pressure. * Scores for change in risk factors extracted from original SPHERE analysis. + Scores range from zero upwards (no upper limit); score of ≥24 represents active, <24 represents insufficiently active. ‡Scores for dietary instrument for nutrition education range from 1-132 (fibre), 7-122 (fat), and 3-12 (unsaturated fat); higher scores represent more fibre, fat, or unsaturated fat. Values are means (standard deviations) unless stated otherwise.
Chapter 5

5.7 Discussion

5.7.1 Summary of Findings

The original SPHERE study reported no significant effect of the multicomponent intervention on individual risk factors (blood pressure and cholesterol levels that were at or below target levels)\textsuperscript{190}. In this post-hoc secondary analysis of a cluster randomised trial of a multicomponent intervention versus usual care to reduce CV risk, we found evidence suggesting a potential treatment effect with the intervention compared to control, when the Framingham and Omnibus Scores were used as outcome measures rather than changes in individual risk factors.

5.7.2 Strengths

The magnitude of change in scores from baseline to 18 months was modest. For the Framingham score, we report a difference of 2.7\% in 10-year CVD risk, which means that the SPHERE intervention may result in about 3 fewer CVD events per year for every 1,000 patients included in a programme that included a primary prevention population, compared to usual care. Although the number needed to treat is large, the intervention is simple, generalizable and amenable to implementation at a population-level. However, our findings should be interpreted with caution, as our analyses are post-hoc and exploratory in nature. In addition, we used the Framingham score (developed and validated in a primary prevention population) on a secondary prevention population. The intervention’s ability to modify risk factors would be expected to be greater in a primary prevention population given that greater attention is currently given to risk factor modification in secondary prevention populations\textsuperscript{193}.

Although widely used in clinical practice, the Framingham risk score (or other validated CV risk prediction scores) has been rarely employed as an outcome measure in RCTs of cardiovascular interventions. In my review of the literature, 1 published RCT employed its use as primary outcome measure\textsuperscript{186}, and 4 other trials reported Framingham score as a secondary outcome measure\textsuperscript{185, 187, 188, 199}. Its use has also been employed in observational research studies, including those evaluating the effect of multicomponent interventions within prospective cohort studies\textsuperscript{200}. Some of these studies reported significant improvement in Framingham scores with intervention, compared to control, despite no statistically significant improvement in individual risk factors, which is consistent with our findings\textsuperscript{185, 188}. Evaluating the effect of multicomponent interventions, or
modification of risk factors expected to have effect on a number of risk factors (e.g. weight reduction, physical activity), presents challenges. Evaluating the effect of multicomponent interventions on a single risk factor increases the probability of type II error, in that other important changes may be missed or the true cardiovascular benefits of the intervention may be underestimated. Against this, including a number of risk factors increases the risk of type I error due to multiple testing. Therefore, an approach that enables representation of all modifiable risk factors, but confines analysis to a single primary composite outcome has appeal in this type of research study. Moreover, as such studies may be considered Phase II in nature (as the outcome is surrogate rather than using a clinical endpoint) it enables improved guidance on sample size calculation for a larger Phase III trial, or projection of the anticipated benefits if an intervention is implemented.

Measuring the composite of change in all risk factors with a validated clinical risk prediction score reflects the overall risk of a CVD event based on all modifiable risk factors rather than the effect of the intervention on each modifiable risk factor alone. Use of CV risk prediction tools is advantageous in that the majority of key cardiovascular risk factors are included in most scores\textsuperscript{179-181, 183, 193, 196, 197, 201.} Another key utility in using CV risk prediction tools as primary outcomes, is that they are readily transferrable to patients in terms of helping them to appreciate their cardiovascular risk and the effect of a multicomponent intervention on both risk factor change and change in estimated future risk of CVD. There is evidence to suggest that knowledge of global CHD risk improves accuracy of risk perception and may increase intent to initiate CHD prevention among individuals at risk\textsuperscript{202, 203.}

There are also advantages of this approach to the healthcare professional, who instead of trying to translate the odds ratio for the effect of an intervention on each risk factor into something the patient can understand, has a ready-made estimate of how the intervention will impact on patient care\textsuperscript{304.} Therefore adopting a risk prediction score as a composite outcome may be a more practical and translatable way of explaining the benefits of multicomponent interventions to patients and may uncover underappreciated benefits potentially missed in the past by the focus on individual target risk factor levels\textsuperscript{188.}

For our analyses, we selected the Framingham and Omnibus scores for a number of reasons. First, both scores contained a set of predictor variables which were
most applicable to our dataset (SPHERE study). Second, their regression equations and coefficients were available online which enabled more precise calculation of these scores using values from participants in our cohort. Lastly, the Framingham score has been the most widely used cardiovascular risk prediction score used in clinical practice, until its recent recommended replacement with the Omnibus score\textsuperscript{194}. The Omnibus score is now recommended for estimation of ASCVD risk, and is reported to be superior to the Framingham score\textsuperscript{205}. Further work is required to determine which validated prediction score might be most useful in clinical trials. A key item is variables included in the scoring system. None of the prediction rules include all modifiable risk factors known to be causally associated with CVD. In our study, for example, diet, physical activity and psychosocial stress were measured, but not included in the Framingham or Omnibus scores, and therefore changes in these risk factors are not captured. Other scores, such as the INTERHEART score, which focus on modifiable risk factors, could not be used because the SPHERE trial did not capture all variables included in that score.

5.7.3 Limitations

Use of CV risk prediction scores as composite outcomes to measure the effect of multicomponent interventions is not without limitations. However, there are alternative approaches that warrant consideration. One approach is to determine population-specific risk probability scores, which we explored in our analyses. As such, this allowed us to measure change in risk probability in the population included in the trial. Although an attractive approach, a number of factors worked against this method. First, our sample size was small, and number of outcome events were low, which limited our ability to detect significant association. Ideally, we would have used the control group only, as modification of risk factors in the intervention group would further mitigate probability of finding associations. Second, our population included patients with established CHD who already had aggressive risk factor modification, which is expected to distort the true association between vascular risk factors and CV events. Nonetheless, our analyses serve as an example of an alternative approach, which may be more appropriately used in a primary prevention cohort. Another approach might be to use known relative CV risk, ideally from meta-analyses to estimate relative risk reductions associated with unit change in each risk factor. For example, a 2 mmHg reduction in systolic blood pressure is associated with a 7% decrease in risk of
Chapter 5

mortality due to ischemic heart disease and a 10% decrease in risk of stroke mortality\textsuperscript{171, 172}. Similarly a 1 mmol/L decrease in serum total cholesterol concentration is associated with a 20-50% reduction in ischemic heart disease mortality depending on the age group of the patient\textsuperscript{170, 172}. However, a number of factors limit the validity of this approach, such as the assumption of linearity between risk factor and outcome, variations in methodological quality of studies used to determine treatments effects (e.g. blood pressure is based on randomized controlled trials, while exercise is based on epidemiologic studies), and lack of estimates for some risk factors (e.g. BMI, psychosocial stress).

Our study has a number of other limitations. First, each score includes non-modifiable risk factors in the CV risk prediction scores such as age and gender as well as modifiable risk factors. This reduces the ability to detect changes in modifiable risk factors within a scoring system that uses both modifiable and non-modifiable risk factors. Development and validation of a scoring system that exclusively includes “modifiable” risk factors may overcome this issue, such as the INTERHEART score for AMI\textsuperscript{206}. Second, the Framingham score has been reported to overestimate cardiovascular risk and may not be applicable to different ethnicities as the scores were calculated originally using a cohort of Caucasian North Americans\textsuperscript{207, 208}. Use of the Omnibus score is proposed to be associated with less biased estimates in diverse populations. In our study, if these scores overestimated risk, it would have been distributed randomly between treatment groups, and not influence the relative risk estimates, but would bias absolute risk estimates. It is difficult to have a one size fits all approach to risk factor modification. The relationship of some risk factors with future cardiovascular events may not be linear and advocating stringent control may actually cause harm which would not be reflected in use of risk prediction scores as primary outcomes\textsuperscript{136, 209, 210}. Third, the Framingham and Omnibus risk scores have been used as baseline predictors of future CV risk, but the responsiveness of change in score to predict change in CV risk has not been validated, although it would seem intuitive that it would\textsuperscript{211}. In addition, the Framingham and Omnibus risk scores we used are designed to predict a first CVD or ASCVD event only and have not been validated to predict risks of subsequent events.

Fourth, both scores used were developed to predict risk in patients who were free from CVD at baseline and therefore may not be applicable to the SPHERE
population which was a secondary prevention population\textsuperscript{179, 194, 212}. Of note, the Framingham tool we used was developed for use in primary care. Fifth, missing data in the SPHERE study (baseline demographics and risk factors) may have affected the validity of scores obtained. We used imputation to try to minimise the effect of missing data but this may have affected the overall estimates. Missing data is a key issue for use of risk prediction scores, as these scores are generated from numerous variables, and a single missing value will require imputation of a score. Sixth, in our analyses, certain variables between intervention and control groups were unbalanced at baseline, given the cluster randomised control design. Participants in the intervention group were more likely to be older and to have completed secondary education than those in the control group which may have influenced the findings. However, we used mixed linear regression models to adjust for baseline imbalances. Lastly, our analyses are exploratory, and not apriori analysis, and therefore, should not be interpreted as evidence that the intervention is superior to control in this trial, but rather provides a framework to consider various approaches to evaluating multicomponent interventions that target multiple vascular risk factors.

5.8 Conclusions

Use of validated cardiovascular prediction scores should be considered for selection of primary outcomes in clinical trials evaluating the effect of a multicomponent interventions affecting multiple risk factors and may identify an effect not seen by reporting effects on individual risk factors. More research is required to identify which validated score is most appropriate in this setting, and perhaps to further refine existing scores to focus on modifiable risk factors, that are responsive to change over time.
<table>
<thead>
<tr>
<th>Table 6.1 STAR-FIT Study Synopsis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
</tr>
<tr>
<td><strong>Version</strong></td>
</tr>
<tr>
<td><strong>Trial Registration</strong></td>
</tr>
<tr>
<td><strong>Funding Sources</strong></td>
</tr>
<tr>
<td><strong>Study Sponsor</strong></td>
</tr>
<tr>
<td><strong>Public Queries</strong></td>
</tr>
<tr>
<td><strong>Scientific Queries</strong></td>
</tr>
<tr>
<td><strong>Public Title</strong></td>
</tr>
<tr>
<td><strong>Countries involved</strong></td>
</tr>
<tr>
<td><strong>Health Condition</strong></td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Key Patient Inclusion Criteria</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Key Patient Exclusion Criteria</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Study Type</strong></td>
</tr>
<tr>
<td><strong>Enrolment</strong></td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Primary Outcome</strong></td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
</tr>
<tr>
<td><strong>Protocol Contributors</strong></td>
</tr>
</tbody>
</table>

Based on the World Health Organisation Trial Registration Data Set (Version 1.2.1)\textsuperscript{213}
6.1 Background

6.1.1 Summary of Rationale
There is considerable uncertainty about the optimal target of blood pressure lowering in older adults with hypertension for primary prevention of CV events. While there is some evidence to support a target of <140/90mmHg, the evidence is not robust and a target of <150/90mmHg may be preferred (and recommended by numerous guidelines), where evidence to support blood pressure lowering is based on definitive randomised controlled trials. The uncertainty is due largely to the absence of definitive randomized controlled trials comparing a target of <140/90mmHg to a target of <150/90mmHg in older adults without a history of cardiovascular disease.

Preservation of functional independence is important to all people but particularly to older adults where the prevalence of functional impairment is high. While functional impairment is often viewed as an inevitable, unpreventable consequence of ageing, a solid and emerging body of research shows an association between hypertension and risk of developing functional impairment. Therefore, hypertension is an important modifiable determinant of functional impairment, mediated through increasing the risk of CV events and subclinical vascular disease. Moreover, we have reported that older adults value preservation of functional independence to be as important, or in some cases more important, than prevention of major vascular events (See Chapter 4).

There is an unmet clinical need to determine whether a target blood pressure of <140/90mmHg is superior to a target of <150/90mmHg in older adults with hypertension for prevention of major vascular events and major functional impairment, both of which are important patient-focused outcomes, which may be modifiable with blood pressure lowering.

6.1.2 Hypertension, Mortality and Major Cardiovascular Events
Hypertension is a leading modifiable risk factor for premature death and disability and it accounts for 7% of global DALYs, based on estimates from the Global Burden of Disease study 2010. The economic burden of hypertension is estimated at US$370 billion worldwide comprising 10% of global healthcare expenditures which is predicted to rise in the coming years. The prevalence of hypertension in the general European population is estimated to be between 30-
40%[^214]. Prevalence increases sharply with ageing and varies between countries and geographical regions with a high prevalence in low to middle income countries[^20, 74, 217-219]. The Irish Longitudinal Study on Ageing (TILDA) reports that prevalence of hypertension in Ireland is 29.2% in the youngest age group (52-64 years) rising to 50.3% in the oldest age group (≥75 years)[^220]. Hypertension is traditionally defined as having blood pressure values of >140 mmHg SBP and/or >90 mmHg DBP[^214].

There is a strong curvilinear association between increasing blood pressure and mortality in epidemiologic studies. For blood pressure over 115/70mmHg an increase in SBP of 20 mmHg is associated with a two-fold increase in risk of death and cardiovascular disease (CVD)[^171], and lowering blood pressure reduces an older person’s lifetime risk for cardiovascular and stroke death by 25% to 40%, for those with blood pressures >150/90mmHg[^221]. Hypertension is common, and therefore responsible for a considerable proportion of the population attributable risk for major CVD including stroke, MI, HF, peripheral vascular disease and CKD worldwide[^12, 20, 41, 218, 222-224]. In addition, hypertension is a risk factor for subclinical vascular disease (including covert stroke and vascular cognitive impairment)[^225], frailty and gait instability which are each associated with increased risk of morbidity and mortality especially in older people[^226].

### 6.1.3 Hypertension and Functional Impairment

Hypertension is responsible for a large proportion of acquired functional impairment, mediated through increasing the risk of major vascular events and through development of subclinical vascular disease (most notably covert stroke). The risk of functional impairment is also increased with angina, peripheral vascular disease and CKD, for which hypertension is a key risk factor[^52, 227-233].

Hypertension is estimated to be responsible for almost 50% of the population attributable risk (PAR) for stroke, which is a leading cause of disability and dependence[^12, 20, 41]. Hypertension increases the risk of intermediate vascular phenotypes (including atherosclerosis and small vessel disease) and intermediate risk factors for stroke (most importantly atrial fibrillation[^234]), meaning that the true contribution of hypertension to clinical and covert stroke risk may be larger than reported in epidemiological studies[^235].
Chapter 6

Hypertension is also an important risk factor for subclinical (more appropriately termed ‘covert’) cerebrovascular disease, which may manifest as covert infarction, white matter hyperintensities, microbleeds or brain atrophy. Increasing burden of these findings on neuroimaging is associated with cognitive decline, gait instability and frailty and can lead to functional impairment\(^{16, 23, 24, 34}\). In particular, the presence and severity of white matter hyperintensities is associated with impairments in executive function which can manifest first as loss of key IADLS and finally as loss of BADLs\(^{83-85}\).

A number of studies have also reported an independent association between increased blood pressure and functional impairment, even after controlling for cardiovascular events and measures of subclinical cardiovascular disease (although this observation may be due to residual confounding)\(^{15, 75-77}\). Other ecological observations to support the importance of blood pressure in preservation of functional independence include studies reporting that populations with exceptional longevity or those who “age successfully” have a very low prevalence of hypertension\(^{77, 82}\). Elevations in systolic blood pressure (>140mmHg) were associated with decline in three measures of disability in community-dwelling elderly patients without previous stroke (OR 1.3; 95%CI 1.0-1.7) in the Charleston Heart Study\(^{236}\).

6.1.4 Treatment of Hypertension to Prevent Functional Impairment

In Chapter 3, I report the results of a meta-analysis of randomised controlled trials of antihypertensive therapy for prevention of functional impairment, in which reducing blood pressure in older adults with blood pressure >160/90mmHg was associated with a 16% relative risk reduction in loss of ability to carry out ADLs\(^{14, 122, 129, 138}\). However, these trials included differing patient populations, different baseline levels of blood pressure, and only two clinical trials which were conducted in middle-aged adults, included those with mild hypertension\(^{125, 130}\). Whether lowering blood pressure in older adults with mild hypertension will result in lower rates of functional impairment is not known. While there is a convincing rationale to support this contention, there is also evidence to suggest that lowering blood pressure in older adults with mild hypertension may have adverse effects on function. First, there is an increased risk of orthostatic hypotension, which may increase the risk of falls, a common cause of functional impairment. Orthostatic hypotension is associated with syncope, increased risk of
falls and hip fractures which has major implications not only for mortality and morbidity in this population\textsuperscript{93, 134, 135, 237, 238} but also on functional ability\textsuperscript{134, 237}.

Second, stringent lowering of blood pressure in older adults may impact negatively on cognitive function. One of the potential benefits of blood pressure lowering to prevent functional decline is prevention of cognitive impairment, (for which hypertension is a key risk factor) however, the relationship between blood pressure and cognitive function in later life is complex. While there is a positive association between increasing blood pressure in mid-life and dementia in later life\textsuperscript{87–91}, some studies reported an inverse association between later-life blood pressure and risk of cognitive impairment and dementia, suggesting that the association between blood pressure and cognition may vary by age groups\textsuperscript{92, 93}. In addition, some observational studies have demonstrated an association between low systolic blood pressure (and orthostatic hypotension) and worsening physical and cognitive function in frailer older adults\textsuperscript{136, 239–241}. It is hypothesised that excessive lowering of blood pressure may cause hypo-perfusion which can affect functional and cognitive ability\textsuperscript{242}. In addition, a recent Cochrane review of blood pressure trials evaluating the effect of blood pressure lowering on incidence of dementia failed to report a beneficial effect\textsuperscript{92}.

Further uncertainty about the merits of targeting restrictive blood pressure targets in older adults relates to increased requirement for multiple antihypertensive agents, making it an important source of polypharmacy. Polypharmacy (taking more than four medicines concurrently) is associated with an increase in mortality and falls in older people, while taking five or more medications is associated with increased risk of disability and frailty\textsuperscript{243}. The adverse effects of polypharmacy can negatively impact on the quality of life and functional ability of older adults\textsuperscript{244, 245}.

To summarise, not all older adults may benefit from aggressive reduction in blood pressure and trials to date that adopted a stringent systolic blood pressure target of <140mmHg included participants that were relatively healthy and free from CVD at baseline\textsuperscript{246–248}. A randomised controlled trial is required to demonstrate whether net benefits outweigh risks.
6.1.5 Treatment of Hypertension to Prevent Major Cardiovascular Events in Older Adults

Evidence to Support BP Lowering in Older Adults with Severe and Moderate Hypertension

Several meta-analyses or randomised controlled trials have reported that lowering blood pressure in adults with moderate and severe hypertension (BP 160/90 mmHg and higher) lowers the risk of CV events, particularly stroke\textsuperscript{117, 171, 221, 249, 250}. The biggest relative risk reductions in the rate of stroke in these studies were observed in older people. In clinical trials that specifically recruited older populations, significant reductions in mortality and cardiovascular events have been observed. These studies included primary prevention populations where participants had marked elevations in systolic blood pressure ranging from 160-240 mmHg at baseline and achieved systolic blood pressures ranging from 148-158 mmHg by the end of follow up (in intervention groups)\textsuperscript{132, 251-253}. The Systolic Hypertension in the Elderly Program (SHEP) trial (mean age of participants 72 years) reported a relative risk reduction of 36% in incidence of stroke and a 32% relative risk reduction in major CV events in those in the intervention group\textsuperscript{132}. Similarly, The Hypertension in the Very Elderly Trial (HYVET) (which recruited participants aged ≥ 80 years) also reported that lowering blood pressure to <150/80 mmHg significantly reduced mortality and major CV events in those with and without a history of CVD\textsuperscript{254}. By end of follow up in SHEP\textsuperscript{132} and HYVET\textsuperscript{254, 255} the majority of participants had managed to attain a systolic blood pressure of 140-150 mmHg which was well tolerated and associated with reduced mortality and stroke risk.

While there is a strong evidence base to support blood pressure lowering in older adults with blood pressure > 160/90, results of trials in primary prevention populations of older adults with mild to moderate hypertension have met with more inconsistent results. Two trials including participants with mild to moderate hypertension attempted to further evaluate the effects of blood pressure lowering on older populations in particular. The Aliskiren in the Prevention of Major Cardiovascular Events in Elderly People (APOLLO) trial assigned older adults (mean age of participants 72 years) with SBP 130-159 mmHg to an aliskiren-based drug regimen versus usual antihypertensive medications\textsuperscript{248} while the Study on Cognition and Prognosis in the Elderly (SCOPE) trial assigned older adults (mean
age of participants 76 years) with SBP 160-179 mmHg to candesartan versus placebo\textsuperscript{83}. Although both of these trials concluded that sizeable blood pressure reductions were well tolerated in this population using a combination of antihypertensive drugs, neither of them reported significantly lower risks of major CVD or cognitive or functional impairment (although in the case of APOLLO the trial was terminated before potential benefits in the latter outcomes could be appreciated)\textsuperscript{248}. Interpretation of the SCOPE trial is challenging as blood pressure control was improved in both the active and control groups, and the difference between groups was 3mmHg of systolic blood pressure.

Therefore, it has been assumed that further reductions in blood pressure may have benefits in this population. The minimum threshold to which blood pressure should be controlled in hypertensive older adults is not known and trials that attempted to achieve lower target levels while promising in younger adults but have not been evaluated in older populations\textsuperscript{256, 257}.

**Evidence to Support BP Lowering in Older Adults with Mild Hypertension**

There is some evidence in favour of lowering of systolic blood pressure to <140 mmHg in older primary prevention populations. First, targeting systolic blood pressure <140/90mmHg in a primary prevention population of adults (mean age of participants 63.5 years) with mild hypertension (140-159/90 mmHg) was reported to significantly reduce risk of CV death and CV events in a recent meta-analysis\textsuperscript{258}. Second, in a post-hoc analysis of a secondary prevention trial (INternational VErapamil SR Trandolapril Study (INVEST)), participants were categorised into three blood pressure target groups: <140mmHg, 140-150mmHg and >150mmHg. In this predominantly older population (mean age of participants 71 years), over 4,500 (57%) of participants achieved a systolic blood pressure below 140 mmHg which was associated with significantly fewer strokes and less cardiovascular mortality than those achieving a target of <150mmHg\textsuperscript{259}. Lastly, a subgroup analysis of older adults (n=3179, mean age 70), in the Felodipine Event Reduction (FEVER) trial\textsuperscript{260}, reported that lowering of mean systolic blood pressure by felodipine to below 140 mmHg significantly reduced stroke, CV events, cardiac events and all-cause death\textsuperscript{246}. 

102
Evidence Against BP lowering in Older Adults with Mild Hypertension

In contrast, two large randomised controlled trials; Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS)\textsuperscript{261} (mean age of participants 73 years, n = 4418) and Valsartan in eLderly Isolated Systolic Hypertension (VALISH)\textsuperscript{262} (mean age of participants 76 years, n = 3260), concluded that setting a blood pressure target of <140/80mmHg conferred no additional benefit than higher targets in terms of prevention of CVD. However, both of these trials reported that systolic blood pressure levels of <140mmHg were well tolerated in older adults and reported no difference in adverse events between those assigned to systolic target levels <140mmHg versus those assigned to systolic target levels <150mmHg or <160mmHg. These trials have been cited as evidence for the change in systolic blood pressure target to <150mmHg for people aged >60 years in recent hypertension guidelines, despite criticism that the trials were underpowered to definitively determine the optimal blood pressure target in this population\textsuperscript{120, 263}.

Guideline Recommendations for Target BP in Older Adults

Guideline recommendations on blood pressure targets for older adults have changed in recent years\textsuperscript{263, 264}. Prior to 2013, guidelines uniformly advocated achieving a blood pressure of <140/90mmHg (and lower if tolerated), in all hypertensive patients\textsuperscript{265-267}. However, recent European hypertension guidelines (2013) recommend a target systolic blood pressure <150mmHg in those aged <80 years of age, following re-appraisal of evidence\textsuperscript{214}. US guidelines (2014) recommend that adults aged >60 should aim to achieve a blood pressure <150/90mmHg\textsuperscript{120}. Canadian and UK NICE guidelines recommend a target systolic blood pressure <140mmHg in all those aged <80 years and favour a target of <150mmHg only in those aged over 80 years (Table 6.2).

Current guidelines recommend blood pressure lowering for older adults with blood pressure above 150/90mmHg, but are inconsistent about whether blood pressure lowering should be recommended when systolic blood pressure lies between 140-150mmHg. A recent epidemiological study in the West of Ireland (Cardiovascular Multimorbidity in Primary Care [CLARITY]) reported that 30% of the people aged over 70 years in the study had a systolic blood pressure between 140-150 mmHg\textsuperscript{44, 52}. The optimal target blood pressure in this population is therefore a very clinically important question encountered by practising clinicians.
in primary care every day. Recent changes to guideline recommendations have been controversial for a number of reasons. First, there is no consensus on the age cut-offs used among guidelines, with US guidelines using 60 years as the cut off and European, Canadian and NICE guidelines choosing 80 years. Second, the guidelines appear to ignore the inherent increase in cardiovascular risk associated with increasing age. For example, healthy men aged >70 years with no history of CVD and blood pressure <150/90 mmHg still have a 20% risk of a CV event based on standard cardiovascular risk prediction tools194. Second, the definition of what constitutes a “frail” versus a “fit” older person is not very clear from guidelines and recommendations for the frailer category are most often based on expert opinion rather than high quality evidence214.

Lastly, it is argued that increasing the recommended target for older people to <150/90mmHg will lead to a decrease in the intensity of blood pressure lowering at a population level, in a cohort which is at high risk of CVD events. National Health and Nutrition Examination Survey (NHANES) 2001-08 data show that adults aged ≥60 years with treated hypertension had a median systolic blood pressure of 136mmHg whereas those with untreated hypertension had a median value of 163mmHg263, 268. Systolic blood pressure in this age group has been decreasing over the last fifty years with antihypertensive treatment, therefore there is a concern that a target blood pressure of <150/90 mmHg may lead to an increase in mean blood pressure in the population of older people with treated hypertension263.

It is clear that a well-designed clinical trial which randomises older people with mild hypertension to one of the two disputed targets is required to determine the optimal target blood pressure in this primary prevention population.
### Table 6.2 Guideline Recommendations for Management of Hypertension

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Population</th>
<th>Goal BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eighth Joint National Committee (JNC 8) Hypertension Guidelines 2014&lt;sup&gt;120&lt;/sup&gt;</td>
<td>Aged &lt;60 years</td>
<td>&lt;140/90mmHg</td>
</tr>
<tr>
<td></td>
<td>Aged ≥60 years</td>
<td>&lt;150/90mmHg</td>
</tr>
<tr>
<td></td>
<td>Aged ≥60 years</td>
<td>If treatment results in BP &lt;140/90mmHg and is tolerated – no need to adjust treatment</td>
</tr>
<tr>
<td>European Society of Hypertension (ESH)/European Society of Cardiology (ESC) Guidelines for management of Arterial Hypertension 2013&lt;sup&gt;214&lt;/sup&gt;</td>
<td>General Non-Elderly</td>
<td>&lt;140/90mmHg</td>
</tr>
<tr>
<td></td>
<td>Aged &lt;80 years and fit</td>
<td>&lt;140/90mmHg if tolerated</td>
</tr>
<tr>
<td></td>
<td>Aged over 80 and fit</td>
<td>&lt;150/90mmHg</td>
</tr>
<tr>
<td></td>
<td>Aged over 80 and frail</td>
<td>Physician decision on optimal target</td>
</tr>
<tr>
<td>Canadian Hypertension Education Program (CHEP) Guidelines 2013&lt;sup&gt;269&lt;/sup&gt;</td>
<td>Aged &lt;80 years</td>
<td>&lt;140/90mmHg</td>
</tr>
<tr>
<td></td>
<td>Aged ≥80 years</td>
<td>&lt;150/90mmHg</td>
</tr>
<tr>
<td>National Institute for Clinical Excellence (NICE) Guidelines 2011&lt;sup&gt;270&lt;/sup&gt;</td>
<td>Aged &lt;80 years</td>
<td>&lt;140/90mmHg</td>
</tr>
<tr>
<td></td>
<td>Aged ≥80 years</td>
<td>&lt;150/90mmHg</td>
</tr>
<tr>
<td>American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Expert Consensus Document on Hypertension in the Elderly, 2011&lt;sup&gt;271&lt;/sup&gt;</td>
<td>Aged ≥65 years</td>
<td>&lt;140/90mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>It is unclear whether target SBP should be the same in patients aged 65-79 years as in patients aged &gt;80 years</td>
</tr>
</tbody>
</table>
6.1.6 Clinical Equipoise/Uncertainty

The uncertainty about optimal target for blood pressure lowering in older adults, reflected in variations in guideline recommendations, is an important unresolved clinical issue. Evidence from clinical trials of patients with established CVD, and primary prevention trials in younger populations, support a blood pressure target of <140/90mmHg. However, definitive clinical trials are lacking and findings from available clinical trials have been inconsistent, with observational studies suggesting potential harm from lowering blood pressure from mild hypertensive levels. If lowering blood pressure below 140/90mmHg is associated with a lower risk of CVD and functional impairment, current guideline recommendations will need to be revised. If our trial fails to report a benefit, older adults will require a less intensive approach to blood pressure management and lower use of antihypertensive drugs which will have a significant impact on healthcare costs and incidence of adverse effects. Finally, there is uncertainty about whether lowering blood pressure to treat mild hypertension reduces the risk of major functional impairment, a key outcome for older adults.

6.1.7 Novel Aspects of this Trial

The STAR-FIT trial has a number of novel features. First, we include the composite of major loss of independence for ADLs and major cardiovascular events, which has not been an outcome measure in any previous clinical trial of blood pressure lowering. In fact, very few blood pressure trials included any measures of function as outcomes, although cognition and quality of life are often reported as secondary outcomes138 (See Chapter 3). The main advantage of the composite outcome is that it addresses the key patient-reported outcomes for older adults, and provides a better measure of the ‘net’ clinical effects of different blood pressure targets. Functional impairment may result from CV events, or from adverse effects of aggressive blood pressure lowering (fall with injury). Inclusion of major functional impairment in the composite is appropriate, based on criteria proposed by Montori et al for a valid composite outcome272. In Chapter 4, I report the comparative importance of major functional impairment as an outcome with major vascular events, and in Chapter 3, I report that the relative risk reduction of blood pressure lowering for prevention of independent functional loss is consistent with the anticipated risk reduction for major vascular events. Therefore, the component parts of the proposed composite for this trial (major
loss of independence for ADLs and major CVD [CV death, non-fatal stroke, non-fatal MI or hospital admission due to HF]] are of similar importance to patients and both occur with relatively similar frequency in this population\textsuperscript{272}. Use of this composite outcome measure may help to capture the multifactorial nature of functional impairment as direct and indirect adverse vascular effects of hypertension (Chapter 5).

Second, the majority of previous trials of blood pressure lowering randomised participants to specific antihypertensive agents versus placebo at a selected baseline blood pressure threshold, rather than randomising participants to blood pressure range targets. This has contributed to the controversy, and such an approach is less consistent with routine clinical practice where a blood pressure range is targeted. Our trial specifically addresses the issue of optimal blood pressure target, which is most relevant to clinicians.

Finally, the perspective of our trial is at a general practice level, where primary cardiovascular prevention is based. Targeting a lower blood pressure range has important implications on resource utilisation, opportunity cost and practice variations. Our research question relates to whether assuming a practice-wide approach to comparing two blood pressure intensities is effective in reducing CVD and major functional impairment. Moreover, individual-level randomisation in general practice presents key challenges (e.g. contamination) which we try to overcome in this trial by using a cluster randomise design.

6.2 Study Objectives

6.2.1 Primary Research Question

In older adults (those aged $\geq$70 years), without a history of CVD or diabetes, is general practice-level targeting of blood pressure $<140/90$mmHg associated with a lower risk of major loss of independence for ADLs and major CVD events compared to a target of $<150/90$ mmHg over 5 years of follow up?

6.2.2 Secondary Research Questions

Does a target blood pressure of $<140/90$mm Hg, compared to a target of $<150/90$mmHg, in older adults without CVD or diabetes, result in:

1. A lower rate of major loss of independence for ADLs?
Chapter 6

2. A lower rate of major CVD (CV death, non-fatal stroke, non-fatal MI or hospital admission due to HF)?

3. A lower rate of all-cause mortality?

4. A lower rate of cognitive decline?

5. A higher rate of major falls (associated with death, hospitalization or major disability)?

6.3 Study Design
A phase III cluster randomised controlled trial with general practice-level randomisation to target blood pressure <140/90mm Hg vs. target blood pressure <150/90mmHg.

6.3.1 Population, Sampling Frame and Clinical Setting
The sampling frame is General Practice (GP) or primary care centres in the Western Research and Education Network (WestREN). This network is a partnership between 71 GP practices (>170 GPs) and the Department of General Practice at National University of Ireland, (NUI) Galway. It covers a population of over 500,000 people in Ireland which extends geographically from Donegal to Cork. WestRen practices have been shown in previous studies to be largely representative of the national profile of GP practices in Ireland. GP practices who agree to participate will screen all their patients aged 70 and over without a history of established CVD and diabetes and patients meeting the eligibility criteria will be invited to participate in the trial. Informed consent will be obtained at the GP practice. Participants will then invited to the Health Research Board-Clinical Research Facility (HRB-CRFG) at NUI Galway, for blinded baseline (and end of follow-up) assessments of function (dependence for ADL measured using Standard Assessment of Global Activities in the Elderly (SAGE) scale) and cognition. They will receive yearly follow-up phone calls during which they will be asked to complete the SAGE scale and answer standardised questions on whether they have had interval cardiovascular events or hospitalisations. Using a cluster randomised approach which has previously been successful in this cohort of GP practices, centres will be randomised to a target blood pressure of ≤140/90 or a target of <150/90. Prior to initiation of the definitive clinical trial, we will complete a vanguard phase to determine whether blood pressure targets can be achieved in 8 randomised general practices.
6.3.2 Feasibility

GP practices in the West of Ireland have been involved in many recent epidemiological studies and RCTs of cardiovascular risk factor modification (CLARITY 44, SPHERE [Effect of tailored practice and patient care plans on secondary prevention of heart disease in general practice: a cluster randomised controlled trial]190, SLEPT [Sleep to lower elevated blood pressure: a randomised controlled trial]274 and COMPASS [A randomized controlled trial of rivaroxaban for the prevention of major cardiovascular events in patients with coronary or peripheral artery disease]275) in collaboration with the HRB-CRFG. The HRB-CRFG is a collaboration between GUH and NUI Galway which acts as a support to researchers in terms of clinical trial administration and development.

In the CLARITY study (which included 11 GP practices), 32.4% of the cohort were aged ≥70 years old (n=3143)44,52. Of these, 39% (n=1218), had a systolic blood pressure of ≥140mmHg. This figure is similar to national estimates for the prevalence of hypertension reported by TILDA which reported an overall prevalence of 37%, increasing to 50% in those aged over 75 years220,276. Based on these numbers, 90-120 individuals from each practice are expected to be eligible for inclusion in STAR-FIT (i.e. excluding those with prior CVD or diabetes). Of those in the CLARITY cohort aged ≥70 years, 16% had a history of diabetes, 8.8% had a history of angina, 6% had a history of MI and 5% had a history of stroke, further supporting the feasibility of our proposed primary prevention trial in this population with low baseline levels of established cardiovascular disease.

6.4 Eligibility Criteria

6.4.1 Practice Inclusion Criteria

Included practices must have:

1. A practice nurse involved in general patient care.
2. A minimum General Medical Services (GMS) list size of 200 patients aged ≥70 years.
3. An electronic patient record system.

6.4.2 Practice Exclusion Criteria

Participation in other hypertension or cardiovascular prevention trials, or another clinical research study that precludes participation.
Chapter 6

6.4.3 Patient Inclusion Criteria

1. Adults aged ≥70 years.
2. Last recorded blood pressure reading at the GP practice >140/90 mmHg and blood pressure confirmed >140/90 mmHg (mean of 3 readings) at time of GP baseline visit.
3. Written informed consent.

6.4.4 Patient Exclusion Criteria

Any indication for a target blood pressure of <140/90 mmHg, including prior history of:

1. CAD (defined as previous history of MI, coronary artery revascularisation, CABG, unstable angina or HF).
2. Stroke (defined as previous history of a clinically apparent focal neurological deficit lasting more than 24 hours of presumed vascular origin) or TIA (defined as previous history of a clinically apparent focal neurological deficit lasting less than 24 hours of presumed vascular origin with recovery of function).
3. Peripheral arterial disease (PAD) (defined as history of acute lower limb ischemia, lower limb revascularisation or bypass).
4. CKD stage 4 or 5, defined by eGFR <30 ml/min/1.73 m² (MDRD²⁷⁷).
5. Diabetes mellitus (defined as previous history of diabetes or HbA1c >48).
6. Other indication for blood pressure target of <140/90 mmHg or <150/90 mmHg, in the opinion of the clinician.
7. Dependence for the following BADLs (defined as requiring help of another person) for bathing, dressing, mobility and toileting.
8. Known diagnosis of dementia, or inability to provide informed consent due to cognitive impairment in the opinion of the investigator.
9. Unable to follow medication advice in the opinion of the clinician.
10. Diagnosis of symptomatic orthostatic hypotension.
6.5 Randomisation
We will use a cluster randomised approach where we randomise GP practices to one of two blood pressure targets rather than individual patient level randomisation. This will be a three step process. First, suitable practices are identified and approached, then practices who are willing to participate will compile lists of potentially suitable patients and lastly, individual practices will be randomised to either target blood pressure group (Figure 6.1). We selected this approach for two practical reasons. First, it would be difficult for GPs to have patients within the same practice randomised to different targets which might lead to contamination. Second, this approach has been used successfully in a recent cluster randomised controlled trial of WestREN GP practices. We adopted the cluster randomised methods used by investigators of that trial to develop the protocol for this trial\textsuperscript{190, 191}. Moreover, we are comparing two blood pressure targets that may be considered usual care, as major guidelines recommend $<150/90\text{mmHg}$, while others suggest a target of $<140/90\text{mmHg}$ in non-frail older adults.
Figure 6.1 Schematic of Screening and Randomisation Process

1. Practice Identification

Practice Eligibility
Practice Nurse
GMS List ≥ 200 patients aged ≥70yrs
Electronic Patient Record System

2. Patient Identification

Patient Eligibility
Adults aged ≥70 years
Last recorded blood pressure reading at the GP practice >140/90 mmHg

3. Baseline GP Visit to Confirm Eligibility

Blood pressure confirmed >140/90 mmHg (mean of 3 readings)
Patient doesn’t meet any exclusion criteria

Informed Consent Obtained

Baseline Visit to HRB-CRFG
(for baseline data collection and functional/cognitive assessments)

Cluster Randomisation at Practice Level

Target Blood Pressure <140/90 mmHg

Target Blood Pressure <150/90 mmHg
Chapter 6

6.5.1 Screening

6.5.1.1 Practice Identification

A list of all practices within the sampling frame will be compiled by the research coordinator. Centres meeting the practice inclusion criteria (6.4.1) will be included on the list and each practice will be allocated a number. An individual independent of the research team (at HRB-CRFG) will assign practices to a random number using computer generated random numbers and a list in random order will be provided back to the research team. The research coordinator will then contact each practice manager/lead GP on the list by phone to determine their interest in receiving information about the trial. If a practice demonstrates interest, information about the trial is posted to the practice and arrangements made for a member of the research team to visit the practice to discuss the trial. During this meeting the trial is explained to practice staff and a commitment to participate will be obtained from the lead GP in the practice. A practice implementation plan will be completed and approved by practice staff at this stage.

For practices that decline to participate or confirm that they do not meet the eligibility criteria, the next practice on the list is approached. Details of practices which declined to participate will be recorded including; the number of WTE practitioners, patient list sizes and reason for not participating.

6.5.1.2 Patient Identification

Practices that have agreed to participate will compile a list of all eligible patients from their practice meeting the patient inclusion criteria (6.4.3). They will allocate a number to each patient on the list from 1-X where X is the total number of eligible patients. They will then contact the research team who will provide them with a list of computer generated random numbers. The patient list will then be arranged in random order and held at HRB-CRFG until the practice’s patients have had their numbers allocated. Patients are invited to take part in this study according to this list. If an invited patient does not agree to take part, the patient corresponding to the next number on the random numbers list will be invited until the quota of 50 participating patients per practice is reached (see section 6.12.1). Patient confidentiality and the practice’s usual ethical procedures will be agreed between research team and practice staff.
Selected patients will be posted an invitation letter, information sheet and a reply slip. If they do not respond within 2 weeks the practice nurse will phone them to determine whether they are interested or not. Patients who agree to participate will be invited to attend the practice for a baseline consultation. If selected patients do not confirm that they fulfil eligibility criteria or decline to participate, the next patient on the random generated list of numbers will be selected until the quota is reached. Basic demographics (age, gender) and diagnostic inclusion criteria for those who do not participate will be recorded.

6.5.1.3 Baseline GP Visit to Confirm Eligibility for Study

During this consultation, the GP/practice nurse will confirm patient eligibility for the trial (i.e. blood pressure <140/90mmHg). This will involve recording blood pressure three times. A mean of three blood pressure readings will be calculated and patients with mean blood pressure >140/90 mmHg will included in the trial. Patients will also be asked to confirm that they don’t meet any of the exclusion criteria. If they are eligible and willing to participate after the trial has been explained to them they will sign the informed consent form.

After consent has been obtained, patients will be invited to HRB-CRFG for baseline data collection which will occur prior to practice randomisation to minimize potential bias introduced by researchers and practitioners being aware of their allocation to either of the blood pressure target groups.

6.5.2 Cluster Randomisation

Once 64 practices are recruited (32 clusters in each arm) (see section 6.12.1 for sample size calculation) and relevant baseline data is collected an individual independent of the research team will use computer generated random numbers to allocate practices to one of two usual care target blood pressure groups (Target BP <140/90mmHg) and (Target BP <150/90mmHg). Our selection of timing of randomisation after selection of study participants within practices is designed to reduce the risk of selection bias (i.e. difference between practices in patient selection when they have knowledge of treatment group).

In addition, practices will be stratified according to (1) numbers of WTE practitioners in each practice (<2 and ≥2), and (2) geographic location of practice
(urban and rural). This will be done using a process of minimisation by an individual independent of the research team.  

6.5.3 Allocation Sequence Generation
For both patient and practice identification, random number lists will be generated by an individual who is independent of the research study using computer generated random numbers (www.random.org). This is to ensure practices and patients are selected for inclusion in random order. An allocation sequence will then be generated using the same process at randomisation to allocate practices to one of two target blood pressure groups.

6.5.4 Allocation Concealment
An individual independent of the study team and GP practices will be responsible for generating lists of random numbers and for the stratification sequence.

6.5.5 Blinding
This study is open-label as blinding of participants and participating GPs is not possible. Both target blood pressure groups are aiming to achieve a blood pressure target, therefore participants, GPs, and practice nurses will be aware of treatment assignment. This method was chosen as it is most reflective of clinical practice. However, partial blinding will be employed as per Prospective Randomised Open Blinded Endpoint (PROBE) guidelines. The management of BP and attaining target levels will occur in GP practices but outcome measure assessment will be done at the HRB-CRFG where experienced research coordinators who will be blinded to blood pressure target allocation, will carry out baseline and end of follow up cognitive and functional assessments as well as standardised annual phone follow up in the intervening period. The study investigators will be blinded for the purposes of outcome assessment and the statistician completing the final analyses will also be blinded to treatment allocation. Independent blinded adjudication of major cardiovascular events will be performed by an independent committee, who are unaware of treatment allocation.
6.6 Intervention and Usual Care
6.6.1 Intervention and Usual Care for Both Target Groups

6.6.1.1 Intervention for Staff in Participating Practices

Staff in GP practices involved in the trial will have standardised training on risk factor management and on maximising blood pressure control in order to achieve target blood pressure. This will take the form of a 2 hour meeting which will take place in the practice with staff involved in the study. It will be led by a research coordinator from the HRB-CRFG and will take place before practices are randomised to their target blood pressure group.

This will involve:

- A summary of the current recommendations regarding modification of lifestyle as per current hypertension guidelines and will focus on the need to educate the patient on weight control, increasing physical activity, smoking cessation, alcohol moderation, increasing fruit and veg and low fat intake and reducing sodium intake as recommended by current hypertension guidelines\(^{19,282,214,271,282}\).
- A summary of the changes to recent hypertension guidelines and a discussion around the uncertainty within expert groups about optimal blood pressure target in this cohort of older patients. Many GPs will be familiar with targeting blood pressure <140/90 and may find it difficult to justify why a higher target level is acceptable practice.
- Review of medications that may be used in the trial to achieve blood pressure target including but not limited to Angiotensin Converting Enzyme (ACE) Inhibitors, calcium channel blockers, thiazide diuretics, Angiotensin Receptor Blockers (ARBs), beta and alpha blockers and the evidence around their efficacy both alone or in combination.
- Suggested approaches to tailoring therapy, awareness of common side effects, dose adjustment and emphasising the importance of follow up in order to achieve and maintain target blood pressure will be outlined (Figure 6.2).
- Suggested approaches to maximise patient adherence will be outlined including use of combination drugs to simplify the drug regimen, reminders, involvement of local pharmacist and engagement of
partner/family member in the education process particularly if they are involved in provision of medications.

- Training in standardised measurement of blood pressure. Each GP practice participating in the study will receive an automated, OMRON blood pressure cuff which practice staff will be trained to use in order to reduce potential measurement error within clusters.

As this is a pragmatic trial that is closely aligned to usual GP care, there will be some flexibility regarding the timing of follow up visits, medication choices and combinations which will be at the discretion of the GP. In addition, if a patient in a practice allocated to the <150/90mmHg target achieves a target <140/90 it will be left at the discretion of the GP whether alteration of medications is clinically indicated. A suggested timetable of visits will be provided to each GP recommending regular monthly follow up initially to achieve blood pressure target and moving to 6 monthly follow up when blood pressure is at target level (Figure 6.2).

6.6.1.2 Interventions for Participants in Both Target Groups

- For all participants, usual care will include treatment of underlying co-morbidities and modification of lifestyle and other cardiovascular risk factors as per usual primary care practice. No restriction on routine clinical care, including possible co-interventions, will be enforced during the trial. The groups will differ only with regards to their target blood pressure level.

- At each GP visit throughout the trial the GP or practice nurse will measure the patient’s blood pressure which will be followed by a discussion between the health care provider and patient regarding adherence to prescribed medication, need for adjustment or titration and any side effects from their prescribed medications.
6.6.2 Feasibility and Acceptability of the Intervention

A key threat to the validity of this trial is whether we can achieve separation of blood pressures between groups. The treating GP will have a crucial role in this when assessing whether patients are at target blood pressure. It is essential that GPs are familiar with the evidence underlying both target blood pressure groups and why either is acceptable as usual care depending on what guidelines are followed. An important aspect will be the delivery of the educational session around the uncertainty with recent hypertension guidelines and previous relevant trials before their practice is randomised.

We have designed the clinical trial to be embedded within routine clinical care in general practice (other than baseline and final follow-up assessment in HBR-CRFG and phone follow-up), so that participants have a low burden of follow-up visits. This schedule should not be overly onerous on this population which may have difficulty attending regular appointments away from their homes.

6.7 Contamination

Contamination will be a potential threat to the validity of this trial. Accordingly, it is essential for study participants to play a key role in maintaining blood pressure targets to which they are assigned. Patients will be provided with a trial card that specifies they are enrolled in a clinical trial. This card will detail their blood pressure target and current medications and will be updated at every GP visit. This will help in situations where patients attend outpatient appointments or are admitted to hospital for other reasons which may involve review of blood pressure control and medications. All participants are requested to inform their GP if they have had changes made to their blood pressure medications. Patients who have a CVD event or hospital admission for HF will be categorised as an event and will be managed as per usual care for that event.
Figure 6.2 Algorithm for GP Practices for Initiation and Adjustment of Medications

Algorithm for Achieving Target Blood Pressure (BP)

Aged ≥ 70 years and Blood Pressure > 140/90

Yes

Randomisation

Target BP < 140/90

Select a drug treatment titration strategy
1. At the discretion of individual GP
2. GP may also adopt strategies below:
   - Maximize 1st medication before adding 2nd or
   - Add 2nd medication before reaching maximum dose of 1st or
   - Start with 2 medication classes separately or as fixed-dose combination.

Review monthly

At Goal BP?

Yes

If Target < 140/90 achieved in this group, dose reduction or change in medications is at the discretion of the GP depending on the clinical context

NO

Target BP < 150/90

Initiate thiazide, ACE-I/ARB, CCB alone or in combination. Choice of agent at discretion of GP.

Review again in 1 month

At Goal BP?

NO

Reinforce medication and lifestyle advice.
Addition of medication class not previously selected.
Titrate doses of initial medications to a maximum. Avoid combined use of ACEI and ARB.

Review again in 1 month

YES

Continue Current Treatment and Review every 6 months

At Goal BP?

Reinforce medication and lifestyle adherence. Up titrate to maximum dosage.
Add additional medication class (e.g., β-blocker, aldosterone antagonist, or others) and/or refer to physician with expertise in hypertension management.

Review again in 1 month.

Adapted from JNC8 Guidelines on Hypertension Management 2014 and ESC/ESH European Guidelines 2013.
6.8 Baseline and Follow Up Visit Schedules

Patients will attend their GP for a baseline visit (T_2) where their eligibility for the trial will be confirmed and informed consent obtained. (Section 6.5.1.3). Once patients are deemed eligible and have given informed consent, they will be invited to attend the HRB-CRFG (T_1) prior to practice randomisation to have a baseline assessment of functional and cognitive status and for collection of data for baseline study characteristics. For individual practices, allocation of blood pressure target will be concealed until all participants have completed baseline assessment at the HRB-CRFG.

Once GP practices have been randomised, patients will be seen by their GP within a month (T1), which will require scheduling approximately 12 patients per week over a one-month period (each practice will receive a research nurse support for the baseline and 1-month follow-up assessments). The GP will arrange to see patients at monthly intervals until their blood pressure is at target range, depending on which blood pressure target the practice have been randomized to. Once blood pressure is at target range, patients will be reviewed every 6 months by their GP, although other visits may be required as part of their usual medical care. (Figure 6.3). Participants who are attending GP practices randomized to target blood pressure <150/90mmHg, and have readings between 140-149mmHg at baseline will attend their GP, and have their blood pressure measurement repeated (but will not be prescribed additional antihypertensive therapy if blood pressure remains <150/90mmHg).

As all baseline assessments will be completed by HRB-CRFG, and all baseline visits are completed before GP centre is aware of which treatment group they have been randomised, we expect to ‘activate’ 2 GP centres per month, which will require 100 baseline visits per month. We would expect to have completed baseline recruitment (and final follow-up assessment) in a 16-18 month period. The rationale for our approach is to; a) reduce the risk of selection bias (e.g. knowledge of group allocation prior to patient selection and baseline assessment may introduce a selection bias), and b) ensure that baseline assessment is completed before differential management of BP targets between groups.
6.8.1 Standardisation of Intervention & Follow-Up

It is likely that patients in the practices assigned to a blood pressure target of <140/90mmHg will require more GP visits in order to achieve target blood pressure than the higher target group. This will have an impact on GP time and practice resources. There are defined research study visit timelines set out for this trial but usual clinical GP care may dictate that a patient requires more frequent GP visits outside of study visits or in addition to these visits. Both target groups will have a schedule of predefined visits to HRB-CRFG at baseline and end of follow up and phone follow up in between these visits (Figure 6.3).

6.8.2 Methods to Maximise Participant Adherence

To maximise patient adherence with trial interventions, in addition to face-to-face sessions with their GP/practice nurse, patients will receive written information about their medications. This will apply to both target groups. All follow-up appointments with the GP practice will be scheduled at a convenient time for the patient. CRFG appointments will be also scheduled at the patient’s convenience.

To reduce loss to follow-up, patients who fail to return for a follow-up visit will be contacted by phone and/or mail to arrange an alternative convenient appointment. Patients will be asked to provide contact details for two nominated close relatives/acquaintances to act as additional contact persons, if necessary. This will be particularly important in this age group which has a potentially high rate of attrition due to mortality in order to minimise loss to follow up.

Reimbursement for transport costs will be available for patients for baseline and end of follow up assessments at the CRFG. If patients are unable to make the final follow-up visit to the CRFG, a home visit will be arranged, where possible, to obtain final outcome data. If the patient refuses or is unable to attend for follow-up visits, every effort will be made to establish the reason for nonattendance.
Figure 6.3 Study Flow Diagram

**Study Flow Diagram**

- Baseline GP Visit T1-2
  - Blood Pressure (BP) confirmed >140/90 mmHg
  - Informed Consent obtained

- HRB-CRF Baseline Visit T1-1
  - Functional and Cognitive Assessment, Baseline Bloods and Measurements

- Randomisation T0
  - Intervention: Target BP <140/90 mmHg
  - Control: Target BP <150/90 mmHg

- GP Visit T1 (1 mth)

- NO

- Review monthly until Target BP achieved.

- YES

- GP Visit T2 (6 mths)

- GP Visit T3 (12 mths)

- HRB-CRF Phone Follow Up T3 (12 mths)
  - To assess functional status and record CVD events.

- GP Visit T4 (18 mths)

- GP Visit T5 (24 mths)

- HRB-CRF Phone Follow Up T5 (24 mths)
  - To assess functional status and record CVD events.

- GP Visit T6 (30 mths)

- GP Visit T7 (36 mths)

- HRB-CRF Phone Follow Up T7 (36 mths)
  - To assess functional status and record CVD events.

- GP Visit T8 (42 mths)

- GP Visit T9 (48 mths)

- HRB-CRF Phone Follow Up T9 (48 mths)
  - To assess functional status and record CVD events.

- GP Visit T10 (54 mths)

- GP Visit T11 (60 mths)

- HRB-CRF Final Visit T11 (60 mths)
Chapter 6

6.9. Measurements
6.9.1 Baseline GP Visit
During this consultation the GP/practice nurse will confirm blood pressure eligibility criteria. This will involve recording blood pressure three times while the patient is sitting quietly using a standardised methodology (an automated, OMRON blood pressure cuff which will be provided to the GP practice). A mean of three blood pressure readings will be calculated and patients with mean blood pressure >140/90 mmHg will included in the trial.

6.9.2 Baseline Assessment HRB-CRFG Visit

Collection of Baseline Characteristics
The following baseline characteristics will be collected and entered onto an electronic case report form (CRF):

1. Demographics:
   - Age
   - Gender
   - Ethnicity
   - Highest educational level achieved [primary, secondary or third level]

2. Cardiovascular risk factors:
   - Current smoking status (never vs. former vs. current smoker [within last six months], number of cigarettes smoked per day)
   - Alcohol intake (no of units [half pint of beer, standard measure of spirits or wine = 1 unit] consumed per week)
   - Physical activity (does the patient get at least 30 minutes of exercise five times per week?)
   - Anthropometrics including height (using a wall-mounted non-stretchable standard tape measure) and weight (using a standard automated weighing scale) which will be used to calculate body mass index (BMI).
   - Diet (does the patient eat five portions of fruit and vegetables per day?)

3. Bloods will be collected for:
   - Glycated Haemoglobin (HbA1c)
Chapter 6

- Total, HDL and LDL cholesterol
- Urea and electrolytes, MDRD eGFR. Many of the medications used for lowering blood pressure can affect renal function which may already be compromised in this population therefore assessment of renal function at baseline is essential.

4. Current Medications will be recorded including but not exclusive to antihypertensive drugs, lipid lowering therapies, antiplatelet and anticoagulant drugs, analgesic drugs and others. The number of antihypertensive drugs a patient is taking will also be recorded.

5. Any co-morbid conditions will be recorded:
   - Musculoskeletal (osteoarthritis, osteoporosis, fractures, joint replacements)
   - Cancer (history of any cancer)
   - Other medical or surgical conditions.

**Functional Assessment**

This will involve detailed assessment of functional status using standardised questionnaires and tests (scores for each test will be recorded on an electronic CRF) including:

- The Standard Assessment of Global Activities in the Elderly (SAGE) scale (Appendix 8). This scale can be administered in person or over the phone and asks participants a number of questions about their level of difficulty in carrying out various IADLs and BADLs. This scale will be used to determine the patient’s level of independence for ADLs for the composite outcome (which is defined in detail in section 6.12.1). In terms of the functional part of the composite outcome, a negative response to all of the following questions from the SAGE scale will indicate independence for ADLs:
  i. Over the past month did you require the help of an aide or another person to walk?
  ii. Over the past month did you require the help of another person to dress yourself?
iii. Over the past month did you require the help of another person to use the toilet or bathe/shower?

iv. Over the past month did you have difficulty preparing a meal or doing laundry?

v. Over the past month did you have difficulty managing your own finances or shopping?

- Timed Up and Go Test (TUG). This involves timing the patient rise from a chair, walk three metres, turn around, walk back to the chair, and sit down again (Appendix 9). This test will be used to assess mobility\textsuperscript{283} and as a proxy for assessing frailty\textsuperscript{284}.

**Cognitive Assessment**

This will involve detailed assessment of cognitive status using multiple standardised cognitive tests (Appendix 10) including:

- Digit symbol substitution test (DSS)\textsuperscript{285}. Participants are shown numbers in a list from 1-9. Each number has a specific symbol underneath it. Participants are initially asked to copy the symbols for each digit using a sample list of numbers in random order. They are then asked to continue this for as many as lines of numbers as they can in two minutes. They are scored based on the number of correct boxes completed within the time period. This test will be used to assess the participant’s attention and psychomotor speed\textsuperscript{286}.

- Montreal Cognitive Assessment (MoCA)\textsuperscript{287}. This is a detailed assessment which evaluates the participant’s abilities in the following domains: visuospatial/executive function, language (fluency and naming), memory and recall, abstraction and orientation\textsuperscript{9}.

- Trail making test part B\textsuperscript{288}. This test involves asking the participant to make a trail between 25 digits and corresponding letters on a page (e.g. 1-A, 2-B) as quickly as possible. Time taken to complete the trail is recorded. This test will be used to assess the participant’s attention, psychomotor speed, abstraction, ability to
execute and modify a plan of action, and ability to maintain two trains of thought simultaneously.  

6.9.3 Measurements at GP Follow-Up Visits

GP follow up visits will include the following:

- Measurement of office blood pressure
- Review of level of adherence by patient to blood pressure medications
- Adjustment of blood pressure medications as required
- Recording of concomitant medications, any interval changes to medications and numbers of blood pressure medications the patient is taking
- Recording of adverse events
- Recording of outcome events of interest (GP will be responsible for event notification)
- Recording of deaths (GP will be responsible for death notification)

6.9.4 Measurements at HRB-CRFG Phone Follow Up Visits

Patients will be contacted by phone by HRB-CRFG research co-ordinators at yearly intervals (12, 24, 36 and 48 months) to ascertain if there has been any interval change in independence for ADLs or any cardiovascular events in the preceding period as well as other outcome events of interest. The HRB-CRFG will be responsible for monitoring all hospitalisations therefore patients will be also be asked about interval hospitalisation for any cause. These conversations will be standardised and patients will be asked the following questions about the preceding year:

1. Function:
   - The SAGE questionnaire will be re-administered to patients

2. CV Events:
   - Have you had a heart attack?
   - Have you had a stroke?
   - Have you been hospitalised for heart failure?

3. Other Outcomes:
   - Have you had a fall, syncope or collapse?
   - Have you been diagnosed with symptomatic orthostatic hypotension?
   - Have you had a fracture?
• Have you had a fall requiring hospital admission?
• Have you been hospitalised for any other reason?
• How often on average have you been taking your blood pressure medications? (100% of the time, 75% of the time, 50% of the time, <25% of the time?)

6.9.5 Measurements at Final Visit

The final study visit which will be five years after randomisation, will occur at the HRB-CRFG. The following end of study characteristics will be collected and entered onto a CRF:

1. Demographics:
   • Age at end of study

2. Cardiovascular risk factors:
   • Current smoking status (never vs. former vs. current smoker [within last six months], number of cigarettes smoked per day)
   • Alcohol intake (no of units consumed per week)
   • Physical activity (does the patient get at least 30 minutes of exercise five times per week?)
   • Anthropometrics including height and weight to calculate BMI.
   • Diet (does the patient eat five portions of fruit and vegetables per day?)

3. Blood samples will be collected for:
   • HbA1c
   • Total, HDL and LDL cholesterol
   • Urea and electrolytes, MDRD eGFR

4. Record of current medications and number of anti-hypertensive medications the patient is taking at close of study will be updated and any new co-morbid conditions will be recorded.

5. Other Assessments:
   • Functional and Cognitive assessments will be repeated at this visit including SAGE and TUG test
   • DSS test, MOCA and Trail making test B

127
6.9.6 Confounding Variables
A cluster randomised design may result in baseline imbalances in covariates between treatment groups. Potential confounding variables will be measured and controlled for in the analysis including sex, educational status, number of follow up visits with GP (as this may vary during the study), smoking, BMI, physical activity and diet.

6.10 Criteria for Permanent Withdrawal of Intervention
Criteria for withdrawal or changing the blood pressure target include:

- Severe symptomatic orthostatic hypotension or hypotension resulting in serious injury. Symptomatic orthostatic hypotension will be defined as dizziness on standing, blurring of vision, weakness or syncope in the presence of SBP≤100mmHg.
- Cardiovascular event, or new diagnosis of diabetes, that requires a blood pressure target of <140/90mmHg
- Clinical issue that in the opinion of the local clinician should change blood pressure targets.

6.11 Study Outcomes
6.11.1 Primary Outcome
The primary outcome is the proportion of patients experiencing either a major new loss of independence for ADLs or a CVD event from baseline to 5 years follow-up.

Definitions of Composite:

1. **Major new loss of independence for ADLs:**

   This will be defined as positive response to any of the following questions (based on the SAGE scale) which lasted for greater than three months during the five years of follow up:

   - Did you require the help of an aide (walking stick, rollator frame etc.) or help from another person to walk?
   - Did you require help from another person to dress yourself?
   - Did you require help from another person to use the toilet?
   - Did you require help from another person to bathe or shower?
Chapter 6

- Did you require help from another person to prepare a meal (this includes meals on wheels)?
- Did you require help from another person to do laundry?
- Did you require help from another person to manage your own basic finances?
- Did you require help from another person to complete shopping for groceries?
  (Note: it is accepted that some participants will not be completing these tasks independently at baseline, or may have never completed certain tasks, e.g. laundry. Our outcome measure relates to ‘new’ loss of ADL.)

**Criteria for ADL Outcome:**

To be included in the composite outcome, the following criteria need to be met; a) participant was completing ADL activity independently at baseline and; b) participant reports new dependence to complete ADL activity for longer than a 3 month duration (or reported at final follow-up). While we will measure the factors that resulted in loss of independence in ADL (e.g. stroke, cognitive decline, fall etc.), we will not restrict to loss for independence for ADL due to vascular causes, as our intention is to measure the net effect of intervention and loss of ADL is frequently multifactorial and can be difficult to attribute to a single cause only.

2. **Cardiovascular Disease Event (CVD event)**

This will be will be defined as:

- Death from cardiovascular disease including: (MI, HF, Cardiac Arrest, PVD, Stroke)
  or
- Non-fatal stroke (clinically apparent focal neurological deficit lasting more than 24 hours of presumed vascular origin survived by patient)
  or
- Non-fatal MI (ST elevation MI (STEMI), non STEMI, unstable angina)
  or
- First hospitalisation for Heart Failure (Note: participants with heart failure at baseline will be excluded).
6.11.2 Secondary Outcomes

- Proportions of patients reporting major loss of independence for ADLS from baseline to 5 years as per primary outcome criteria
- Mean change in SAGE scale from baseline to 5 years
- Proportions of patients with a change in cognition from baseline to 5 years
- Mean change in MOCA, DSS and Trail Making Scores from baseline to 5 years
- Proportions of patients with a change in mobility from baseline to 5 years
- Mean change in TUG score from baseline to 5 years
- Numbers of strokes from baseline to 5 years
- Numbers of MIs from baseline to 5 years
- Numbers of CV deaths from baseline to 5 years
- All-cause mortality from baseline to 5 years
- Proportions of patients with documented symptomatic orthostatic hypotension from baseline to 5 years
- Numbers of falls, syncope or collapse from baseline to 5 years
- Numbers of fractures from baseline to 5 years
- Number of falls requiring admission to hospital from baseline to 5 years
- Number of hospital admissions from baseline to 5 years

6.12 Statistical Considerations

6.12.1 Sample Size Considerations

The primary outcome is the proportion of patients experiencing a new major loss of independence for ADL or a CVD event from baseline to 5 years. The rate of composite events in this population is estimated at 24% over five years, based on the results of trials in primary prevention populations\textsuperscript{83, 97, 132, 248 290} and event rates from trials in secondary prevention populations\textsuperscript{14, 291}.

To calculate the number of subjects required when comparing the differences in two proportions (i.e. a binary outcome) in a cluster randomised trial the following formula will be used and calculated using R package version 0.4\textsuperscript{292}.
where \( n \) is the sample size needed for a comparison of two proportions when randomisation is at the individual level, \( \bar{m} \) is the average cluster size and \( \rho \) is the estimated Intracluster Correlation Coefficient (ICC). Note that \( \left\{ 1 + (\bar{m} - 1) \rho \right\} \) is often referred to as the Design Effect (sample size multiplier to account for within cluster similarities).293,294.

For this trial we assume that the proportion with the outcome of interest (composite of major new loss of independence for ADLs or CVD event) is 24% in the population of controls and a required minimally important relative risk reduction is 20% (i.e. rate of 19% in <140/90 group). Although we are targeting a 10mmHg difference between groups, we expect a 6-8mmHg difference in the actual trial. Based on findings from the APOLLO trial, a 6-8mmHg reduction in systolic blood pressure was associated with a non-significant 55% relative risk reduction in major CVD (trial stopped prematurely)248. We selected a 20% relative risk reduction as a minimally important difference, as treatment effects above this level have been assumed into clinical practice for CV prevention (e.g. antiplatelet therapy, statin therapy) and this a threshold that is consistent with other CV prevention trials in the field.193,194,295,296 Based on a two-sided alpha of 0.05 and power of 80%, a sample size of 3200 (1600 in each arm) is required for an assumed between cluster ICC of 0.01, an average cluster size of 50 and a minimum of 32 clusters in each arm. Assuming a dropout or cross-over rate of 10% and a loss to follow up rate of 5% up a sample size of 3980 would be preferable.

6.12.2 Descriptive Statistics and Baseline Characteristics

Descriptive statistics will be used to describe the baseline characteristics of the study population, the flow of trial participants and the level of missing data for both predictor and outcome variables. All losses to follow-up and dropouts will be accounted for and reasons documented. Categorical variables will be described using frequencies and percentages.

For continuous variables, the mean and standard deviation will be reported and if not normally distributed, the median and interquartile range will be reported.
Histograms and boxplots will be used to evaluate the distribution of continuous variables and to identify any outliers or potential errors in the data, with follow-up verification from CRFs. All tests of significance will be two-sided and conducted at an alpha of 0.05 for statistical significance. A secondary per-protocol analysis will also be carried out for all outcomes to account for post randomization exclusions due to ineligibility, non-compliance, loss to follow-up and missing data.

6.12.3 Statistical Analysis of Primary Outcome
The composite outcome will be categorised as a binary outcome (yes or no) and reported as percentage of patients experiencing the composite during the trial. We will use linear mixed effects regression models for all analyses to control for clustering (where each practice will be incorporated as a random effect), randomisation stratifiers, and prespecified variables (age, sex, education, region, practice size, smoking, BMI, diet and physical activity).

6.12.4 Statistical Analysis of Secondary Outcomes
For continuous variables (functional and cognitive scores) a two sample paired t-test will be used to compare changes from baseline to 5 years. For categorical outcomes (strokes, CV death, MI, all-cause mortality, falls, hospital admissions due to falls, symptomatic postural hypotension etc.) a Chi square test or Fisher’s exact test will be used.

6.12.5 Subgroup & Sensitivity Analyses
The primary outcome will be analysed by subgroups based on:

- Age (<80 years vs. ≥80 years)
- Sex
- Hypertension treated or untreated at baseline
- Number of antihypertensive medications used to achieve target blood pressure
- Adherence to medications
- Frailty (based on TUG scores at baseline and end of follow up)

Statistical tests of interaction (Wald) will be performed for all subgroup analyses.
6.12.6 Enrolment and Disposition

All subjects screened, randomized and followed up will be presented as will the level of missing data for predictor and outcome variables.

6.12.7 Missing Data

Missing data can compromise inferences from randomised controlled clinical trials. Every effort will be made to optimise study design and standardise data collection to minimise the amount of missing data. We will do this in a number of ways. First, regular visits to the GP on a sixth monthly basis, where the importance of adherence with medications are emphasised at every visit will increase likelihood of adherence with medications as well as enhancing the engagement of patients in the study. Second, conducting this trial in the patient’s local GP practice and only two visits to HRB-CRFG at baseline and end of follow up will reduce dropout. Third, standardised phone follow up in between GP visits from research coordinators at the HRB-CRFG will ensure independent collection of outcome events to corroborate what is reported from individual practices. Fourth, obtaining informed consent at the GP baseline eligibility visit will allow follow up of those patients who withdraw from the study. Lastly, due to the high likelihood of major loss of independence for ADL or CVD events in this population, a complete dataset for covariates is anticipated as well as outcome data for 95% of participants which will preserve the ability to analyse endpoints using the intention-to-treat approach.

It will be assumed that missing data are missing at random and therefore accounted for in the mixed model. If participants drop out, the reason(s) for withdrawal will be sought and used to test the assumption that data is missing at random. This assumption will also be investigated by looking at patterns of missing data as well as modelling the probability of missing data based on the explanatory variables available. A sensitivity analysis using multiple imputation will also be carried out if there is >10% missing data for covariates, to assess the robustness of findings to plausible alternative assumptions concerning missing data. The sample size was also increased to adjust for potential drop outs.

6.12.8 Data Safety & Monitoring Board

The Data Safety & Monitoring Board (DSMB) will be chaired by a clinician scientist with experience in clinical trials in the area of cardiovascular prevention and
functional impairment in older people. The remainder of the DSMB (additional 4 members) will consist of a statistician (with expertise in clinical trials), an ethicist and clinical experts in the content area of the clinical trial. All members of the DSMB will provide written declarations of freedom from conflicts of interest.

The DSMB will be blinded and will monitor the study for safety. The DSMB will meet at 6 months after trial initiation, and after 50%, 75% and 100% of participants are randomised and at 6 monthly intervals thereafter (or sooner if required or recommended by DMSB). For efficacy the primary outcome will be monitored using the Haybittle-Peto approach which has been successfully used in other cardiovascular prevention trials. This approach states that if an interim analysis shows a probability of <0.001 (or more than 3 times its standard error) that there is less primary outcomes in the intervention group than the control group then the trial should be terminated early. The advantage of this approach is that the same threshold is used at every DSMB analysis and the final analysis can still be evaluated at 0.05 level of significance. In terms of stopping the trial for safety reasons, no formal boundaries have been set but the following principles regarding stopping will apply: (1) if there is clear persistent evidence of net harm outweighing any benefit of lowering blood pressure to <140/90 mmHg and (2) if there is new external information that definitively answers the primary research question or raises serious safety issues with either blood pressure target groups.

It should be noted that our two treatment groups are managed according to routine clinical care (i.e. both BP targets are recommended by different guideline recommendations).

6.13 Ethical Considerations
This study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH-GCP) and the requirements of the research ethics committee from whom ethical approval will be sought prior to study initiation. Informed consent forms, patient information leaflets and other study documentation will be developed prior to submission to the research ethics committee.

6.13.1 Patient Confidentiality
There is a risk to patient confidentiality with this study on two levels, the GP practice and at the HRB-CRFG. Breach of confidentiality could result in distress to
involved participants. At each participating GP practice an agreement to follow the GP practice’s usual ethical procedures regarding patient confidentiality will be agreed between research team and practice staff. All information obtained in this study will be handled with strict privacy and electronic data security standards at practice level and at the CRFG in accordance with the Data Protection Act 1988 (section 16(1)), Regulations 2007). Unique subject identifiers will be assigned to each participant to prevent unauthorised identification of research participants outside of the GP practice. In addition, all primary data will be stored in a database devoid of any personal information or identifiers. All computers and laptops used to store the data will have password protection and encryption software in place.

6.13.2 Risk-Benefit Ratio

This trial will randomise GP practices to two different blood pressure targets, both of which are recommended by current international hypertension guidelines. While the trial is not without risk, the risk is anticipated to be low and the risk is associated with ‘usual’ care as both blood pressure targets are recommended by different guidelines. The overall risk benefit ratio is therefore favourable. This will be guided by the DSMB which will recommend discontinuation of the study if the risk benefit ratio changes.

6.14 Limitations & Methods to Control Bias

There are a number of potential limitations to this study. First this trial is open-label as we are using blood pressure targets which will be known to both patients and GPs. Partial blinding of study staff (data collection and entry), outcome assessment by the investigator and blinding of the statistician will be performed, as previously described, to reduce bias on outcome assessment. Second, during selection of patients for inclusion in the study, volunteer bias may occur where individuals who participate in studies are healthier than those who chose not to give informed consent or are incapable of giving informed consent. In addition, those who agree to participate may be more likely to attend their GP regularly than those who don’t agree. Therefore the sample of individuals included in the trial may not be representative of the relevant population which may limit generalisability of the study.
Chapter 6

Third, the effect of blood pressure lowering may have different relative risk reductions on different components of the composite which may either exaggerate or underestimate the effect. However current evidence would suggest a relative risk reduction of between 15-30% for each component of the composite\(^{14,122,248,291}\). Fourth, there is a risk of non-adherence with blood pressure medications which may limit the number of participants achieving their target blood pressure. However, a number of methods to maximise adherence have already been outlined and a sensitivity analysis will also be performed to determine the influence of non-adherence to medications on the estimated treatment effect. Fifth, the use of major loss of independence for ADLs as part of the composite outcome requires that a person has difficulty with carrying out either BADLS or IADLs for at least three months. This time-frame was chosen to ensure that there was some level of permanent disability but this may overestimate the prevalence of functional impairment by including disability which may be temporary including disability post hip replacement or other surgeries. Sixth, given the population of interest in this study, stratification by frailty would be a consideration, however this is not possible in a cluster randomised controlled trial (but can be adjusted for in analyses). To address this we are using the TUG test at baseline and end of follow up to measure frailty in the patient cohort. We have pre-specified inclusion of frailty as an \textit{a priori} subgroup analysis. The TUG score has been reported in previous studies as a sensitive and specific measure of frailty\(^{284,301,302}\). To maximize study quality, all components of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)\(^{303}\) statement were considered during the drafting of this protocol.
### Table 6.3 Check list for Standardised Protocol Items: Recommendations for Interventional Trials (SPIRIT)

<table>
<thead>
<tr>
<th>Checklist Item</th>
<th>Description</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial Administration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>Descriptive title identifying study design, population, interventions and trial acronym</td>
<td>Title Page</td>
</tr>
<tr>
<td>Trial registration</td>
<td>Trial identifier and registry name</td>
<td></td>
</tr>
<tr>
<td>Protocol version</td>
<td>All items from the WHO Trial Registration Data Set</td>
<td>Table 6.1</td>
</tr>
<tr>
<td>Funding</td>
<td>Sources and types of financial, material support</td>
<td></td>
</tr>
<tr>
<td>Roles and responsibilities</td>
<td>Role of study sponsor and funders in data management, analysis, interpretation or writing</td>
<td>6.16</td>
</tr>
<tr>
<td>Composition, roles and responsibilities of the coordinating centre, steering, adjudication and data management committees</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Background and rationale</td>
<td>Description of research question and justification for the trial</td>
<td>6.1, 6.2</td>
</tr>
<tr>
<td>Objectives</td>
<td>Specific objectives or hypotheses</td>
<td>6.2</td>
</tr>
<tr>
<td>Trial design</td>
<td>Description including type of trial, allocation ratio and trial framework</td>
<td>6.3, 6.11, Fig 6.1</td>
</tr>
<tr>
<td><strong>Methods: Participants, interventions, and outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study setting</td>
<td>Description of study settings</td>
<td>6.3.1</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>Inclusion and exclusion criteria for participants and study centres</td>
<td>6.4</td>
</tr>
<tr>
<td>Interventions</td>
<td>Interventions for each group with detail to allow replication</td>
<td>6.6</td>
</tr>
<tr>
<td>Criteria for discontinuing or modifying allocated interventions</td>
<td>6.6, 6.10, Fig 6.2</td>
<td></td>
</tr>
<tr>
<td>Strategies to improve adherence to intervention protocols</td>
<td>6.8.2</td>
<td></td>
</tr>
<tr>
<td>Relevant concomitant care and interventions</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary, secondary, and other outcomes including the measurement variable, analysis metric and time point</td>
<td>6.8, 6.9, 6.15, Fig 6.3</td>
</tr>
<tr>
<td>Timeline</td>
<td>Time schedule of enrolment, interventions assessments, and visits for participants</td>
<td>6.12.1</td>
</tr>
<tr>
<td>Sample size</td>
<td>Estimated number of participants needed to achieve study objectives, how it was determined, and sample size calculations</td>
<td></td>
</tr>
<tr>
<td>Recruitment</td>
<td>Strategies for achieving adequate participant enrolment to reach target sample size</td>
<td>6.5.1</td>
</tr>
<tr>
<td><strong>Methods: Assignment of interventions (Allocation and Blinding)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequence generation</td>
<td>Method of generating the allocation sequence</td>
<td>6.5, 6.5.3</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Mechanism of implementing the allocation sequence</td>
<td>6.5.4</td>
</tr>
<tr>
<td>Implementation</td>
<td>Who will generate allocation sequence, enrol participants, and assign participants to interventions</td>
<td>6.5.3</td>
</tr>
<tr>
<td>Blinding</td>
<td>Who will be blinded and how</td>
<td>6.5.5</td>
</tr>
</tbody>
</table>
Table 6.3 (Continued). Check list for Standardised Protocol Items: Recommendations for Interventional Trials (SPIRIT)

<table>
<thead>
<tr>
<th>Methods: Data Collection, Management and Analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Data collection</td>
<td>Plans for assessment and collection of outcome, baseline, and other data</td>
</tr>
<tr>
<td></td>
<td>Plans to promote participant retention and complete follow-up</td>
</tr>
<tr>
<td>Data management</td>
<td>Plans for data entry, coding, security, and storage, and processes to promote data quality</td>
</tr>
<tr>
<td>Statistical Methods</td>
<td>Analysis of primary and secondary outcomes</td>
</tr>
<tr>
<td></td>
<td>Additional analyses including subgroup analyses</td>
</tr>
<tr>
<td></td>
<td>Analysis of population relating to non-adherence, statistical methods to handle missing data</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methods: Monitoring</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Data monitoring</td>
<td>Data monitoring committee and processes</td>
</tr>
<tr>
<td></td>
<td>Description of any interim analyses and stopping guidelines</td>
</tr>
<tr>
<td>Harms</td>
<td>Plans for collecting, assessing, reporting, and managing reported adverse events</td>
</tr>
<tr>
<td>Auditing</td>
<td>Frequency and procedures for auditing trial conduct</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethics and dissemination</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Research ethics approval</td>
<td>Plans for seeking research ethics committee approval</td>
</tr>
<tr>
<td>Protocol amendments</td>
<td>Plans for communicating important protocol modifications</td>
</tr>
<tr>
<td>Consent or assent</td>
<td>Who will obtain informed consent/assent from trial participants and how</td>
</tr>
<tr>
<td>Confidentiality</td>
<td>How will personal information about participants be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial</td>
</tr>
<tr>
<td>Declaration of interests</td>
<td>Financial and other competing interests for PI</td>
</tr>
<tr>
<td>Access to data</td>
<td>Statement of who will have access to final trial dataset</td>
</tr>
<tr>
<td>Ancillary and post-trial care</td>
<td>Provisions, if any, for ancillary and post-trial care</td>
</tr>
<tr>
<td>Dissemination policy</td>
<td>Plans to communicate trial results to participants, healthcare professionals, the public and other relevant groups</td>
</tr>
<tr>
<td></td>
<td>Authorship eligibility guidelines and any intended use of professional writers</td>
</tr>
<tr>
<td></td>
<td>Plans, for granting public access to the protocol, dataset &amp; statistical code</td>
</tr>
</tbody>
</table>
6.15 Trial Administration

6.15.1 Site
This study will be conducted on multiple sites/GP practices and the co-ordinating centre will be the HRB-CRFG. Completed CRFs and other paperwork relating to the trial, including the trial master file, will be held at the coordinating centre (HRB-CRFG).

6.15.2 Steering, Local Operations and Publication Committees
The steering committee will consist of Dr. Michelle Canavan and Prof. Martin O’Donnell (Co-Principal Investigators [Co-PIs]), a lead research coordinator from the CRFG (to be appointed), Prof. Eamon Mulkerrin and Prof. Shaun O’Keeffe (Consultant Geriatricians at GUH), Dr. John Newell (Biostatistician) and Prof. Andrew Murphy, Department of GP at NUI Galway, who has considerable experience in running a cluster randomised controlled trial and conducting research within the WestRen network. The committee will also include a number of GPs as co-investigators and representatives of the many geographical locations of the GP practices involved in the trial. This committee will be responsible for publications arising from the trial.

The steering committee will meet every three months to review progress of the clinical trial, identify problems and implement solutions. The local operations committee will meet every month to review progress, recruitment, quality of data, etc. and will include the research coordinator, research assistant, Prof. O’Donnell and Dr. Canavan. Specifically, in the first year the committee will closely review recruitment to ensure that all study participants are randomised by a specific date in order complete five-years of follow-up by study end. In years three and four, the committee will focus on reviewing progress with patient follow-up and ensuring that the highest possible rate of follow-up is achieved. This process strives to minimise missing data.

6.15.3 Study Monitoring
Members of the steering committee will be responsible for the overall conduct and on-site monitoring of the study and for ensuring that all study procedures are compliant with ICH-GCP. Progress meetings will be held to monitor: (a) recruitment and adherence to procedures for informed consent; (b) adherence to the protocol and any protocol amendments by reviewing a random subsample of
patient consent forms and CRFs; (c) adherence to follow-up visits; (d) quality of the data collected; (e) verification that the data collected is valid and consistent on import into the study database. Ongoing training will occur to ensure that a good understanding of the protocol and of standardised operating procedures (for measuring blood pressure and for conducting functional and cognitive assessments) is maintained both at GP practice level and at the HRB-CRFG, to resolve problems and to promote staff commitment and enthusiasm for the study. Random audits by the Quality and Regulatory Affairs Manager from the HRB-CRFG will be performed in a number of GP practices during the trial.

6.15.4 Data Collection & Quality Control

All data collection and study outcome measurements collected locally at GP practices will be entered into electronic CRFs by the GP practice nurse or GP and then transferred into the study database by trial staff at HRB-CRFG. Data collected at HRB-CRFG visits will be entered directly into the study database.

To minimise errors, two staff members will enter data independently and any discrepancies will be highlighted and followed up with checks of the CRF to determine validity. Data to be extracted from CRFs will include: participant identification numbers, verification of eligibility criteria and written informed consent, relevant participant demographic and clinical characteristics, current medications, physical parameters, adherence with follow-up, patient reported adherence with medications and outcome events including major loss of independence for ADLs and major CVD events. Laboratory results will be electronically imported into the trial database. Trial staff entering data will be blinded to study group assignment which will help to avoid differential measurement bias or biased data entry. They will remain blinded until all data has been collated and entered into the database. To ensure high quality data is collected, staff will receive training on completing CRFs, extracting data from CRFs and entering this data into the study database. Practice nurses and GPs will receive training on standardised entry of study data at the initial training meeting.

6.15.5 Study Timeline

All baseline assessments are conducted in the HRB-CRFG before randomisation. We plan to activate at least 2 GP practices per month which will involve 100 patients attending the HRB-CRFG per month for baseline assessment. Once GP
practices have been randomised, participating patients should be seen by their GP within a month. It is expected that approximately 12 patients will be reviewed by the GP every week and that all patients in the cluster will be seen within a month of randomisation. This process will take up to 18 months for completion at the beginning and the end of follow up.

6.16 Dissemination Strategy
This research may demonstrate the benefits or harms of blood pressure lowering below 140/90 mmHg in older adults with mild hypertension. Study results will be presented at local, national and international meetings by the study investigators. The primary results will be submitted for publication in peer reviewed journals with an interest in hypertension, cardiovascular prevention and function in older people. The database created at HRB-CRFG will be available for further research studies.

6.17 Protocol Amendments
Any deviation from or changes of the trial protocol must be approved by the Research Ethics Committee (REC) except to eliminate an immediate danger to a trial participant. Changes will be recorded in writing, signed by the principal investigator and filed with the protocol. Approval from the REC must be received prior to implementation of changes.

6.18 Ownership of Data and Use of Study Results
The Co-PIs and HRB-CRFG have the ownership of all data and results collected during the trial including rights to publication on data from this study, without restriction. They must also approve any requests for access to the database which will be maintained at the HRB-CRFG. For all publications and presentations from this work, authors will be required to make substantial contributions to the design/writing of the manuscript, analysis of data, and giving final approval of the version to be published.

6.19 Declaration of Interests
The Co-PIs, collaborators and other protocol contributors have no financial or other competing interests to declare.
6.20 Ancillary & Post-Trial Care
Patients who meet the eligibility criteria and are included in this trial all have a diagnosis of hypertension and will continue to receive standard care at their GP practices on study completion.
Chapter 7 : Discussion and Conclusions
Chapter 7

Life expectancy has increased in most countries in the world, and mortality related to major cardiovascular disease has reduced markedly in Western Europe and North America. However, increased life expectancy may result in a larger proportion of older adults living with disability due to physical and cognitive (e.g. dementia) consequences of non-fatal chronic disease, especially cardiovascular disease\textsuperscript{215, 305}. Prevention of disability and dependence due to chronic disease, in addition to mortality, has emerged as a public health priority for the coming decades\textsuperscript{215, 306}.

In this thesis, I examined the association of cardiovascular risk factors and disease with risk of functional impairment, reporting an overall positive association. Within risk factors, my systematic review and meta-analysis of the literature identified preliminary evidence to suggest that lowering blood pressure reduces the risk of loss of independence, and provides evidence to support a randomised controlled trial to determine whether lowering blood pressure in older adults with mild hypertension reduces the risk of functional loss (and cardiovascular events). Use of a composite outcome measure of major vascular events and major loss of independence is supported by my survey exploring the attitudes of younger and older people to the comparative importance of loss of independence in ADL and major vascular events, suggesting that both constructs are of considerable importance. While my thesis specifically targets modifying blood pressure, prevention of major functional loss will likely require modification of numerous vascular risk factors (and other non-vascular determinants). Therefore, I explored various approaches to evaluating the effect of multicomponent interventions on the composite outcomes for cardiovascular risk factors, which is expected to be important and applicable to future research in this field.

Chapter 2
I completed a cross-sectional analysis of 3500 community dwelling older adults in the West of Ireland to explore the association between both vascular risk factors and established cardiovascular diseases and impairment of IADLs and BADLs. For this chapter I had access to an existing database and from there I developed the research question, designed the analysis plan and conducted the statistical analysis. I also collated and interpreted the results and wrote the manuscript. My hypothesis was that a large proportion of functional impairment may be attributable to vascular risk factors independent of established cardiovascular
disease. In multivariable logistic regression analysis, current smoking, atrial fibrillation, former alcohol use, chronic kidney disease and prior stroke were associated with impairment in ability to perform activities of daily living. Hypertension, diabetes and LDL cholesterol were all observed to be associated with functional impairment on univariate analysis, but were not significant on multivariable analysis. I had hypothesised that hypertension would be an important risk factor for functional impairment, but our observed null association may be due to the inclusion of other factors along the causal pathway (e.g. atrial fibrillation, coronary heart disease and stroke), and confounding by treatment indication (i.e. those with vascular conditions related to functional impairment may have more aggressive management of blood pressure). The findings of this study were limited by the cross-sectional design. However they highlight the need for further studies which focus on the effect of vascular risk factors on functional loss and add to the uncertainty about whether lowering blood pressure in older adults without cardiovascular disease will result in lower risk of functional impairment.

Chapter 3
To further explore the association between blood pressure and loss of independence in ADL, I conducted a systematic review and meta-analysis of hypertension trials that measured independence in function as an outcome measure. For this chapter I developed the research question in conjunction with collaborators. I designed the electronic search strategies, the data abstraction sheets and the statistical analysis plan. I carried out title and abstract searching as well as full text reviews, in conjunction with collaborators, of included articles and then extracted relevant data. I collated the results, conducted risk of bias assessments and the meta-analysis and wrote the manuscript.

This systematic review had two objectives (1) to determine the proportion of randomised controlled trials that included function (defined as ability to carry out ADL) as an outcome measure and (2) to calculate a summary estimate of the effect of blood pressure lowering on ability to carry out ADLs during follow up for included trials. Of 93 eligible trials only 1 included function as primary outcome measure, while 9 included it as a secondary outcome measure. The meta-analysis demonstrated that the odds of functional impairment were significantly reduced
Chapter 7

by 16% with blood pressure lowering therapy compared to control (OR 0.84 [0.77, 0.92]).

The rate of reporting functional outcomes in clinical trials of blood pressure lowering therapy is low which both highlights the deficit in our knowledge, and limited the number of studies included in the meta-analysis. However despite this, I found evidence to support lowering of blood pressure to decrease risk of functional impairment which from a patient’s perspective may help promote adherence to drug regimens as function is a patient important outcome. My systematic review also identified a lack of standardised outcome measures used across trials, which hindered my ability to reliably meta-analyse results among studies. Inclusion of functional outcomes in future clinical trials is important to patients, clinicians, healthcare systems and health policy makers. The development of a standardised core set of outcome measures that validly and reliably capture loss of function in diverse populations is required.

Chapter 4
Before one may propose including loss of ADL as an outcome measure in cardiovascular prevention trials, it is necessary to determine whether such outcomes are of importance to people, including potential participants in clinical trials. Remarkably, there has been little research examining attitudes of populations towards outcome measures in cardiovascular prevention trials, and primary outcome measures included in such trials have been usually confined to major vascular events (vascular death, myocardial infarction, stroke and heart failure). I conducted a cross-sectional survey of West of Ireland adults to ascertain their views on the relative importance of functional, cognitive and cardiovascular event outcome measures. The survey questions focused on what outcomes may be important in clinical trials of cardiovascular prevention, what outcomes they fear the most in the future and what outcomes are important with regard to “successful ageing”.

For this study, I designed the protocol, survey questionnaire, participant information form, selected the sampling frame and applied to the local ethics committee for study approval which was granted. I carried out the study over four months and during that time I distributed and collected questionnaires, cleaned
Chapter 7

and collated the data, conducted the statistical analysis and wrote the manuscript.

In each population studied, maintenance of independence, avoiding major illness and good family/social life were viewed as important constructs of successful ageing. The majority of participants feared dependence on others and dementia more than other outcomes (e.g. myocardial infarction), when specifically asked about concerns for the future. This study had a number of limitations including the cross-sectional design and the convenience sample in a geographically defined sampling frame, however it highlights the need for further study on attitudes of older people in particular to outcomes measured in clinical trials. My initial observations suggest that while traditional cardiovascular outcomes are deemed important there was more emphasis placed on outcomes like stroke which have more devastating functional consequences.

Chapter 5
At the outset of my thesis, I had anticipated that effective approaches to prevent functional impairment would require multicomponent interventions targeting multiple risk factors (e.g. polypill, multicomponent lifestyle interventions etc.). I identified that a key challenge in evaluating multicomponent interventions (to modify a number of vascular risk factors) was measuring the composite effect of the intervention on all relevant vascular risk factors, which is especially relevant in Phase II clinical trials. However, as my thesis evolved, the resultant evidence led me to more specifically target blood pressure, rendering the current chapter less relevant to the specific focus of my thesis, but remains relevant to this field of research, and will be an important area of my future research.

In this chapter, I conducted a post-hoc analysis of a completed cluster randomised controlled trial (SPHERE) of a multicomponent intervention designed to improve vascular risk factor control in patients with established coronary heart disease. My hypothesis was that using a risk prediction score (Framingham/Omnibus) would capture the effect of the multicomponent intervention which might be missed by focusing on individual risk factors. For this chapter I designed the research question and wrote the manuscript. I collaborated with colleagues in the Department of Biostatistics, Clinical Research Facility, Galway (Dr John Newell and Patricia Gunning) in developing the statistical analysis plan which involved
applying regression equations from the Framingham and Omnibus scores to the SPHERE cohort to generate risk prediction scores, and application of a SPHERE-specific generated logistic regression equation to determine the effect of the multicomponent intervention on composite risk factor score.

The original SPHERE study reported no significant effect of the multicomponent intervention on individual risk factors (e.g. patients at or below target for blood pressure and cholesterol). In this post-hoc analysis of SPHERE we found evidence of a potential treatment effect of the multicomponent intervention when using the Framingham or Omnibus score as outcome measures rather than change in individual risk factors (2.7% decrease in 10 year risk of CVD for Framingham score). Our analysis was post hoc and exploratory in nature and therefore should be interpreted with caution. However, although the magnitude of reduction of 10 year CVD risk was modest and large numbers would be needed to treat to show benefit in a primary prevention population, this analysis highlights the potential of an inexpensive multicomponent intervention to decrease numbers of cardiovascular events at primary prevention population level.

Chapter 6

Building on my work in previous chapters, and the emerging uncertainty in guidelines about whether older adults with mild hypertension should receive antihypertensive therapy for primary prevention, my final chapter is a protocol for a randomised controlled trial to evaluate the effect of blood pressure lowering on the composite of major loss of independence for ADLs and major vascular events in adults aged ≥70 with mild hypertension and without known cardiovascular disease. Key contributions from my thesis included, 1) meta-analytic evidence that lowering blood pressure may reduce the risk of functional impairment (even independent of major vascular events), and was associated with a relative risk reduction that is comparable to the relative risk reduction reported for major vascular events; 2) demonstrating that preservation of functional independence is important to older adults, and at least as important as prevention of major vascular events. My findings address the criteria reported by Montori et al for a valid composite outcome measure in clinical trials. During the course of my thesis, a controversy emerged regarding the optimal blood pressure target for older adults without cardiovascular disease, and
guidelines reported different recommendations in this population. To address this important unanswered clinical research question (whether to treat mild hypertension in older adults), I designed a randomised controlled trial that included some novel methodologic factors, namely; 1) use of a cluster randomised controlled trial that compared blood pressure targets between general practices (rather than individual level randomisation); and 2) use of a composite outcome measure of major loss of independence for ADLs and major vascular events, to represent a better measure of patient-important outcomes.

For this chapter, I drafted the trial protocol which included a review of hypertension guidelines, the trial rationale (uncertainty principle) and outlined the practical and statistical methods and approaches necessary to complete the trial. I collaborated with colleagues Dr. John Newell and Prof. Andrew Murphy regarding the cluster randomise trial design and sample size calculations.

**Future Directions**

In conclusion, cardiovascular risk factors, including hypertension, are important determinants of functional ability in older people. Functional outcomes are important to older people and use of these outcomes in trials of cardiovascular prevention is essential to assess the true impact of modification of multiple risk factors. Blood pressure lowering, in particular, has the potential to reduce the global burden of functional impairment in older people. Whether treating mild hypertension in older adults without cardiovascular disease is justified requires rigorous evaluation in a large definitive randomised controlled trial. My proposed clinical trial will provide valuable insight into the effect of lowering blood pressure below 140mm/90Hg in older people on both functional and cardiovascular event outcomes.
Appendix 1 Copyright Permission for Vascular Risk Factors, Cardiovascular Disease and Functional Impairment in Community Dwelling Adults

**KARGER PUBLISHERS LICENSE TERMS AND CONDITIONS**

<table>
<thead>
<tr>
<th>License Number</th>
<th>3603870176066</th>
</tr>
</thead>
<tbody>
<tr>
<td>License date</td>
<td>Apr 07, 2015</td>
</tr>
<tr>
<td>Licensed Content Publisher</td>
<td>Karger Publishers</td>
</tr>
<tr>
<td>Licensed Content Publication</td>
<td>Gerontology</td>
</tr>
<tr>
<td>Licensed Content Title</td>
<td>Vascular Risk Factors, Cardiovascular Disease and Functional Impairment in Community-Dwelling Adults</td>
</tr>
<tr>
<td>Licensed copyright line</td>
<td>Copyright © 2014, Karger Publishers</td>
</tr>
<tr>
<td>Licensed Content Author</td>
<td>Canavan Michelle, Glynn Liam G., Smyth Andrew, et al</td>
</tr>
<tr>
<td>Licensed Content Date</td>
<td>Jan 17, 2014</td>
</tr>
<tr>
<td>Licensed Content Volume Number</td>
<td>60</td>
</tr>
<tr>
<td>Licensed Content Issue Number</td>
<td>3</td>
</tr>
<tr>
<td>Special issue or supplement</td>
<td>None</td>
</tr>
<tr>
<td>Type of Use</td>
<td>Thesis/Dissertation</td>
</tr>
<tr>
<td>Requestor type</td>
<td>author of requested content</td>
</tr>
<tr>
<td>Format</td>
<td>Print, Electronic</td>
</tr>
<tr>
<td>Portion</td>
<td>full article</td>
</tr>
<tr>
<td>Rights for</td>
<td>Main product</td>
</tr>
<tr>
<td>Duration of use</td>
<td>Life of current edition/presentation</td>
</tr>
<tr>
<td>Creation of copies for the disabled</td>
<td>no</td>
</tr>
<tr>
<td>For distribution to</td>
<td>Worldwide</td>
</tr>
<tr>
<td>The lifetime unit quantity of new product</td>
<td>1</td>
</tr>
<tr>
<td>The requesting person/organization is:</td>
<td>Dr Michelle Canavan, Galway University Hospital Newcastle Road</td>
</tr>
<tr>
<td>Order reference number</td>
<td>None</td>
</tr>
<tr>
<td>Title of your thesis / dissertation</td>
<td>Cardiovascular Disease and Functional Ability in Older Adults.</td>
</tr>
<tr>
<td>Expected completion date</td>
<td>May 2015</td>
</tr>
</tbody>
</table>
Appendices

Appendix 1 (Continued).

STANDARD TERMS AND CONDITIONS FOR REPRODUCTION OF MATERIAL

Introduction

The Publisher for this copyrighted material is Karger Publishers. By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the Billing and Payment terms and conditions established by Copyright Clearance Center, Inc. ("CCC"), at the time that you opened your CCC account and that are available at any time at http://myaccount.copyright.com.

Limited License

Publisher hereby grants to you a non-exclusive license to use this material. Licenses are for one-time use only with a maximum distribution equal to the number that you identified in the licensing process. It is explicitly forbidden to reuse and/or translate a complete book or journal issue by separately obtaining permission for each book chapter or journal article. Any further use, edition, translation or distribution, either in print or electronically requires written permission again and may be subject to another permission fee. This permission applies only to copyrighted content that Karger Publishers owns, and not to copyrighted content from other sources. If any material in our work appears with credit to another source, you must also obtain permission from the original source cited in our work. All content reproduced from copyrighted material owned by Karger Publishers remains the sole and exclusive property of Karger Publishers. The right to grant permission to a third party is reserved solely by Karger Publishers.

Geographic Rights

Licenses may be exercised anywhere in the world with particular exceptions in China.

Altering/Modifying Material

• You may not alter or modify the material in any manner (except that you may use, within the scope of the license granted, one or more excerpts from the copyrighted material, provided that the process of excerpting does not alter the meaning of the material or in any way reflect negatively on the Publisher or any writer of the material), nor may you translate the material into another language, unless your license specifically grants translation rights.
• Other minor editing modifications are allowed when reusing figures/tables and illustrations (e.g. redesigning, reformation, coloring/recoloring) and can be made at the Licensee's discretion.

Reservation of Rights

All rights reserved. Publisher hereby grants to you a non-exclusive license to use this material. Licenses are for one-time use exclusively. No part of this publication may be translated into other languages, reproduced or utilized in any form or by any means, electronically or mechanically, including photocopying, recording, micro-copying, or by ny information storage and retrieval system, without permission in writing from the Publisher.

License Contingent on Payment

While you may exercise the rights licensed immediately upon issuance of the license at the end of the licensing process for the transaction, provided that you have disclosed complete and accurate details of your proposed use, no license is finally effective unless and until full payment is received from you (either by Publisher or by CCC) as provided in CCC's Billing and Payment terms and conditions. If full payment is not received on a timely basis, then any license preliminarily granted shall be deemed automatically revoked and shall be void as if never granted. Further, in the event that you breach any of these terms and conditions or any of CCC's Billing and Payment terms and conditions, the license is automatically revoked and shall be void as if never granted. Use of materials as described in a revoked license, as well as any use of the materials beyond the scope of an unrevoked license, may constitute copyright infringement and Publisher reserves the right to take any and all action to protect its copyright in the materials.

Copyright Notice

You must give full credit to the original source of the article/book chapter and include the following copyright notice in connection with any reproduction of the licensed material: “Copyright © 2012 (or other relevant year) Karger Publishers, Basel, Switzerland.” In case of translations you must additionally include the following disclaimer: “The article/book chapter printed herein has been translated into (relevant language) from the original by (Name of Licensee). KARGER PUBLISHERS CANNOT BE HELD RESPONSIBLE FOR ANY ERRORS OR INACCURACIES THAT MAY HAVE OCCURRED DURING TRANSLATION. THIS ARTICLE/BOOK CHAPTER IS COPYRIGHT PROTECTED AND ANY FURTHER DISTRIBUTION REQUIRES A WRITTEN CONSENT FROM KARGER PUBLISHERS.
Appendices

Appendix 1 (Continued).

Warranties
Publisher makes no representations or warranties with respect to the licensed material and adopts on its own behalf the limitations and disclaimers established by CCC on its behalf in its Billing and Payment terms and conditions for this licensing transaction.

Indemnity
You hereby indemnify and agree to hold harmless Publisher and CCC, and their respective officers, directors, employees and agents, from and against any and all claims arising out of your use of the licensed material other than as specifically authorized pursuant to this license.

No Transfer of License
This license is personal to you and may not be sublicensed, assigned, or transferred by you to any other person without Publisher's written permission.

No Amendment Except in Writing
This license may not be amended except in a writing signed by both parties (or, in the case of Publisher, by CCC on Publisher's behalf).

Objection to Contrary Terms
Publisher hereby objects to any terms contained in any purchase order, acknowledgment, check endorsement or other writing prepared by you, which terms are inconsistent with these terms and conditions or CCC's Billing and Payment terms and conditions. These terms and conditions, together with CCC's Billing and Payment terms and conditions (which are incorporated herein), comprise the entire agreement between you and Publisher (and CCC) concerning this licensing transaction. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall control.

Content Delivery
• Content Delivery Requested content such as a figure/table/cover or PDF of a full article will be provided to you by the Publisher directly via e-mail in high resolution quality.
• Delivery will be processed within five (5) working days from the date of your purchase.
• Subsequent cancellations of content delivery orders cannot be considered and will not be refunded.

Excluded Grants
• Exclusivity.
• Reuse/Translation of a complete book or journal issue.
• Reuse in another or in a future Edition.
• Reuse beyond the limitations within the license's scope, such as e.g. beyond the granted number of copies, beyond the granted format, beyond the chosen foreign language.
• Reuse of contents copyrighted by a third party without obtaining permission from the third party.
• Make any data available and authorize others to reuse the materials.
Appendix 2 CLARITY Questionnaire

The Clarity Study Patient Questionnaire

This questionnaire will take about 5 minutes to complete. Please answer all questions if possible.

If you have difficulty reading or understanding the questions, please ask a family member, friend or carer to assist you.

The information that you provide is confidential and will only be viewed by the researcher. You don’t have to write your name on the questionnaire.

When you have completed the questionnaire, please return it in the stamped, addressed envelope.

Thank you very much for your help.
Appendix 2 (Continued) CLARITY Questionnaire

SECTION A: YOUR OWN HEALTH STATE TODAY

By placing a tick (√) in one box in each group below, please indicate which statements best describe your own health today.

A1. Mobility
   - I have no problems in walking about
   - I have some problems in walking about
   - I am confined to bed

A2. 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

A3. 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

A4. Pain/Discomfort
   - I have no pain or discomfort
   - I have moderate pain or discomfort
   - I have extreme pain or discomfort

A5. Anxiety/Depression
   - I am not anxious or depressed
   - I am moderately anxious or depressed
   - I am extremely anxious or depressed

---

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 place an X on this scale to show how good or bad your own health is today, in your opinion.
Appendix 2 (Continued) CLARITY Questionnaire

**SECTION B: WELL-BEING**

Choose one response from the four given below to describe your current feelings. Please give your immediate response and do not think too long about your answers.

<table>
<thead>
<tr>
<th>B1. I still enjoy the things I used to enjoy</th>
<th>(Please tick (✓) one answer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely as much</td>
<td></td>
</tr>
<tr>
<td>Not quite so much</td>
<td></td>
</tr>
<tr>
<td>Only a little</td>
<td></td>
</tr>
<tr>
<td>Hardly at all</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B2. I can laugh and see the funny side of things</th>
<th>(Please tick (✓) one answer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>As much as I always could</td>
<td></td>
</tr>
<tr>
<td>Not quite so much now</td>
<td></td>
</tr>
<tr>
<td>Definitely not so much now</td>
<td></td>
</tr>
<tr>
<td>Not at all</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B3. I feel cheerful</th>
<th>(Please tick (✓) one answer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td></td>
</tr>
<tr>
<td>Not often</td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td></td>
</tr>
<tr>
<td>Most of the time</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B4. I feel as if I am slowed down</th>
<th>(Please tick (✓) one answer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nearly all the time</td>
<td></td>
</tr>
<tr>
<td>Very often</td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td></td>
</tr>
<tr>
<td>Not at all</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B5. I have lost interest in my appearance</th>
<th>(Please tick (✓) one answer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely</td>
<td></td>
</tr>
<tr>
<td>I don't take quite as much care as I should</td>
<td></td>
</tr>
<tr>
<td>I may not take quite as much care</td>
<td></td>
</tr>
<tr>
<td>I take as much care as ever</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B6. I look forward with enjoyment to things</th>
<th>(Please tick (✓) one answer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>As much as I ever did</td>
<td></td>
</tr>
<tr>
<td>Rather less than I used to</td>
<td></td>
</tr>
<tr>
<td>Definitely less than I used to</td>
<td></td>
</tr>
<tr>
<td>Hardly at all</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B7. I can enjoy a good book or radio or television programme</th>
<th>(Please tick (✓) one answer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often</td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td></td>
</tr>
<tr>
<td>Not Often</td>
<td></td>
</tr>
<tr>
<td>Very seldom</td>
<td></td>
</tr>
</tbody>
</table>
Appendices

Appendix 2 (Continued) CLARITY Questionnaire

SECTION C: YOUR VIEWS ABOUT MANAGING ANY ILLNESS IN YOUR LIFE

We would like to know how confident you are in doing certain activities when you are feeling unwell. For each of the following questions, please circle the number that corresponds to your confidence level.

For example, in question D1, if you want to say that you are totally confident that you can keep the tiredness caused by illness from interfering with the things you want to do, you would circle the number 10.

C1. How confident are you that you can keep any tiredness caused by illness from interfering with the things you want to do? (Please circle one number only)

Not at all confident 1 2 3 4 5 6 7 8 9 10 Totally confident

C2. How confident are you that you can keep any physical discomfort or pain caused by illness from interfering with the things you want to do? (Please circle one number only)

Not at all confident 1 2 3 4 5 6 7 8 9 10 Totally confident

C3. How confident are you that you can keep any emotional distress caused by illness from interfering with the things you want to do? (Please circle one number only)

Not at all confident 1 2 3 4 5 6 7 8 9 10 Totally confident

C4. How confident are you that you can keep any other symptoms or health problems you have from interfering with the things you want to do? (Please circle one number only)

Not at all confident 1 2 3 4 5 6 7 8 9 10 Totally confident

C5. How confident are you that you can do the different things needed to manage your health so as to reduce your need to see a doctor? (Please circle one number only)

Not at all confident 1 2 3 4 5 6 7 8 9 10 Totally confident

C6. How confident are you that you can do things other than just taking medication to reduce how much illness affects your everyday life? (Please circle one number only)

Not at all confident 1 2 3 4 5 6 7 8 9 10 Totally confident
Appendix 2 (Continued) CLARITY Questionnaire

SECTION D: GENERAL INFORMATION

This part of the survey asks for your views about your general health. If you are unsure about how to answer a question, please give the best answer you can.

D1. Which best describes you?  
(Please tick (✓) one box)
I smoke every day
I smoke occasionally (less than once a day)
I used to smoke but I quit
I do not smoke but am exposed to other people’s smoke on most days
I have never smoked

D2. What age were you when you left formal education?  
[_____] years

D3. What is your present marital status?  
(Please tick (✓) one box)
Single/Never married
Married/Living with partner
Separated/Divorced
Widowed

D4. What is your present employment status?  
(Please tick (✓) one box)
Employed
Working in the home
Unemployed
Retired
Receiving disability allowance

D5a. Which best describes your use of alcohol?  
(Please tick (✓) one box)
Never
Former (used to drink but stopped)
Currently use alcohol

D5b. At least once per month, I drink 5 or more drinks in a single day.  
(Please answer Yes or No)
Yes   ☐   No   ☐

D6. Social support  
(Please answer Yes or No to each question)
Do you live alone?  
Yes   ☐   No   ☐
Do you drive a car?  
Yes   ☐   No   ☐

D7. Do you require help from another person for any of the following?  
(Please answer Yes or No to each question)
Shopping?  
Yes   ☐   No   ☐
Laundry or preparing a meal?  
Yes   ☐   No   ☐
Walking?  
Yes   ☐   No   ☐
Dressing?  
Yes   ☐   No   ☐

D8. Do you use any of the following every day?  
(Please answer Yes or No to each question)
Walking stick?  
Yes   ☐   No   ☐
Walking frame?  
Yes   ☐   No   ☐
Wheelchair?  
Yes   ☐   No   ☐

D9. Have you had a fall in the last 12 months?  
If yes did this result in an overnight stay in hospital?  
Yes   ☐   No   ☐
Appendix 3: Copyright Permission for Does Lowering Blood Pressure with Antihypertensive Therapy Preserve Independence in Activities of Daily Living

OXFORD UNIVERSITY PRESS LICENSE
TERMS AND CONDITIONS

Apr 07, 2015

This is a License Agreement between Michelle Canavan ("You") and Oxford University Press ("Oxford University Press") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by Oxford University Press, and the payment terms and conditions.

| License Number | 3603860945713 |
| License date    | Apr 07, 2015  |
| Licensed content publisher | Oxford University Press |
| Licensed content publication | American Journal of Hypertension |
| Licensed content title | Does Lowering Blood Pressure With Antihypertensive Therapy Preserve Independence in Activities of Daily Living? A Systematic Review |
| Licensed content author | Michelle Canavan, Andrew Smyth, Jackie Bosch, Mette Jensen, Emer R. McGrath, Eamon C. Mulkerrin, Martin J. O’Donnell |
| Licensed content date | February 1, 2015 |
| Type of Use | Thesis/Dissertation |
| Institution name | None |
| Title of your work | Cardiovascular Disease and Functional Ability in Older Adults. |
| Publisher of your work | n/a |
| Expected publication date | May 2015 |
| Permissions cost | 0.00 EUR |
| Value added tax | 0.00 EUR |
| Total | 0.00 EUR |
| Total | 0.00 EUR |

Terms and Conditions
Appendices

Appendix 3 (Continued)

STANDARD TERMS AND CONDITIONS FOR REPRODUCTION OF MATERIAL FROM AN OXFORD UNIVERSITY PRESS JOURNAL

1. Use of the material is restricted to the type of use specified in your order details.

2. This permission covers the use of the material in the English language in the following territory: world. If you have requested additional permission to translate this material, the terms and conditions of this reuse will be set out in clause 12.

3. This permission is limited to the particular use authorized in (1) above and does not allow you to sanction its use elsewhere in any other format other than specified above, nor does it apply to quotations, images, artistic works etc that have been reproduced from other sources which may be part of the material to be used.

4. No alteration, omission or addition is made to the material without our written consent. Permission must be re-cleared with Oxford University Press if/when you decide to reprint.

5. The following credit line appears wherever the material is used: author, title, journal, year, volume, issue number, pagination, by permission of Oxford University Press or the sponsoring society if the journal is a society journal. Where a journal is being published on behalf of a learned society, the details of that society must be included in the credit line.

6. For the reproduction of a full article from an Oxford University Press journal for whatever purpose, the corresponding author of the material concerned should be informed of the proposed use. Contact details for the corresponding authors of all Oxford University Press journal contact can be found alongside either the abstract or full text of the article concerned, accessible from www.oxfordjournals.org. Should there be a problem clearing these rights, please contact journals.permissions@oup.com

7. If the credit line or acknowledgement in our publication indicates that any of the figures, images or photos was reproduced, drawn or modified from an earlier source it will be necessary for you to clear this permission with the original publisher as well. If this permission has not been obtained, please note that this material cannot be included in your publication/photocopies.

8. While you may exercise the rights licensed immediately upon issuance of the license at the end of the licensing process for the transaction, provided that you have disclosed complete and accurate details of your proposed use, no license is finally effective unless and until full payment is received from you (either by Oxford University Press or by Copyright Clearance Center (CCC)) as provided in CCC’s Billing and Payment terms and conditions. If full payment is not received on a timely basis, then any license preliminarily granted shall be deemed automatically revoked and shall be void as if never granted. Further, in the event that you breach any of these terms and conditions or any of CCC’s Billing and Payment terms and conditions, the license is automatically revoked and shall be void as if never granted. Use of materials as described in a revoked license, as well as any use of the materials beyond the scope of an unrevoked license, may constitute copyright infringement and Oxford University Press reserves the right to take any and all action to protect its copyright in the materials.

9. This license is personal to you and may not be sublicensed, assigned or transferred by you to any other person without Oxford University Press’s written permission.

10. Oxford University Press reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC’s Billing and Payment terms and conditions.

11. You hereby indemnify and agree to hold harmless Oxford University Press and CCC, and their respective officers, directors, employes and agents, from and against any and all claims arising out of your use of the licensed material other than as specifically authorized pursuant to this license.

12. Other Terms and Conditions:
Appendices

Appendix 4: Research Ethics Committee Approval Letter for Survey

Merlin Park University Hospital
Ospidéal na h-Ollscoile, Páirc Mheirlinne
GALWAY UNIVERSITY HOSPITALS

Clinical Research Ethics Committee
Main Administration Building
Merlin Park Hospital
Galway.


Dr. Michelle Caravan
Specialist Registrar in Geriatric Medicine
Department of Geriatric Medicine
University College Hospital
Galway.

Ref: C.A. 1007 – Pilot study of attitudes of younger and older people to outcome measures collected in clinical trials of cardiovascular drugs. What are the patient-important measures?

Dear Dr. Caravan,

I have considered the above project, and I wish to grant Chairman’s approval to proceed.

Yours sincerely,

[Signature]

Dr. Shaun T. O’Keeffe
Chairman Clinical Research Ethics Committee.
Appendix 5: Research Ethics Committee Approval Participant Information Sheet

Dear Participant,

You are invited to take part in a research study which aims to find out what outcomes are important to younger and older adults when reporting results of clinical trials of drugs used to prevent heart attacks and strokes. This study is part of my PhD Thesis at National University of Ireland, Galway.

Please take time to read the following information and you can keep this information sheet.

- It is up to you to decide whether or not to take part.
- Your response will be treated confidentially and all information is completely anonymous.
- No research participant will be identifiable from data collected or any publications.
- You have been chosen to complete this study for one of two reasons:
  - A. You are a patient who attends outpatient cardiology, stroke or healthy heart clinics at University Hospital Galway (UHG) or CROI
  - B. You are a medical student or doctor who is undergoing clinical training in UHG
- The standard of care you receive as a patient will not change whether or not you decide to participate in this study nor will it affect your training as a medical student/doctor.
- Filling out the survey should take approximately 10 minutes of your time.
- The information gained from this survey will be used to help researchers to find out what outcomes are important to patients and can inform the design of clinical trials in the future. Our results may be published in peer reviewed journals and conference presentations.
- This study has been reviewed and approved by the Research Ethics Committee at Galway University Hospital.

What is the study about?

- We want to find out what outcomes are important to report in results of clinical trials of drugs which are designed to prevent these heart disease and stroke.
- Most clinical research in this area focuses on prevention of major cardiac diseases by recording whether or not the person taking part in the trial develops a medical outcome like death, heart attack or stroke which is obviously very important.
- Although patients identify ability to walk, care for themselves and living at home as important outcomes after a major heart attack or stroke these outcomes are rarely measured or reported in trials of drugs that may prevent these events from happening.
- The purpose of the survey/questionnaire is to find out what outcomes are important to you and to ask your opinion on the outcomes which are currently collected in clinical trials of this nature.

Please do not hesitate to contact me if you need further information

Dr Michelle Canavan, 091 494367 or email michelle.canavan@nuigalway.ie
Appendices

Appendix 6: Survey on Importance of Functional Outcomes in Clinical Research

1. Please Enter your AGE and GENDER in the box below eg 56 years old, Male

2. Who do you live with? Please tick the box that applies

<table>
<thead>
<tr>
<th>Option</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I live alone</td>
<td></td>
</tr>
<tr>
<td>I live with a spouse/partner</td>
<td></td>
</tr>
<tr>
<td>I live with another family member daughter/son/niece/nephew</td>
<td></td>
</tr>
<tr>
<td>I live with a house mate/ non related person</td>
<td></td>
</tr>
<tr>
<td>I live in a nursing home</td>
<td></td>
</tr>
<tr>
<td>Other (Please Describe below)</td>
<td></td>
</tr>
</tbody>
</table>

3. Regarding your activities of Daily Living. Do you require assistance of another person for any of the following? Please tick all that apply

<table>
<thead>
<tr>
<th>Activity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dressing</td>
<td></td>
</tr>
<tr>
<td>Bathing</td>
<td></td>
</tr>
<tr>
<td>Going up stairs</td>
<td></td>
</tr>
<tr>
<td>Doing household chores (eg Cooking, Laundry, Ironing, Cleaning)</td>
<td></td>
</tr>
<tr>
<td>Shopping</td>
<td></td>
</tr>
<tr>
<td>Dealing with financial Matters (eg paying bills, pensions, banks)</td>
<td></td>
</tr>
<tr>
<td>I don’t need assistance with any of the activities listed above</td>
<td></td>
</tr>
</tbody>
</table>
Appendices

Appendix 6 (Continued) Survey on Importance of Functional Outcomes in Clinical Research

4. Regarding your mobility. Please tick the box that applies

<table>
<thead>
<tr>
<th>Option</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I can walk independently</td>
<td></td>
</tr>
<tr>
<td>I can walk with assistance of stick/frame</td>
<td></td>
</tr>
<tr>
<td>I am unable to walk unaided (I need wheelchair or I am bedbound)</td>
<td></td>
</tr>
</tbody>
</table>

5. Which of the following applies to you. Please tick ALL boxes that apply

<table>
<thead>
<tr>
<th>Condition</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I have High Blood Pressure OR take tablets for High Blood Pressure</td>
<td></td>
</tr>
<tr>
<td>I am a Current Smoker</td>
<td></td>
</tr>
<tr>
<td>I have Diabetes</td>
<td></td>
</tr>
<tr>
<td>I have High Cholesterol or take tablets for High Cholesterol</td>
<td></td>
</tr>
<tr>
<td>I have had a Heart Attack or Angina in the past</td>
<td></td>
</tr>
<tr>
<td>I have had a Stroke or Mini-Stroke in the past</td>
<td></td>
</tr>
<tr>
<td>I have Heart Failure</td>
<td></td>
</tr>
</tbody>
</table>

6. Which statement regarding successful or healthy ageing is the most important in your opinion? Please number the statements in order of their importance from 1-6 with 1 being MOST important and 6 being LEAST important.

<table>
<thead>
<tr>
<th>Statement</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Living as long as you can</td>
<td></td>
</tr>
<tr>
<td>Avoiding major illnesses including strokes, heart attacks and cancers</td>
<td></td>
</tr>
<tr>
<td>Maintaining your physical and mental independence</td>
<td></td>
</tr>
<tr>
<td>Having a good family and social life and interacting with people</td>
<td></td>
</tr>
<tr>
<td>Continuing to contribute to your local community and society (working, involved in clubs/societies, charity work etc.)</td>
<td></td>
</tr>
<tr>
<td>Avoiding the Nursing Home</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 6 (Continued) Survey on Importance of Functional Outcomes in Clinical Research

7. If you were taking part in a clinical trial for a new tablet that controls blood pressure which of the following would be most important things for the trial to find out? Please number the statements in order of their importance from 1-5 with 1 being most important and 5 being least important.

<table>
<thead>
<tr>
<th>If the new drug reduces my chances of dying</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>If the new drug reduces my chances of having a stroke</td>
<td></td>
</tr>
<tr>
<td>If the new drug reduces my chances of having a heart attack</td>
<td></td>
</tr>
<tr>
<td>If the new drug prevented dementia</td>
<td></td>
</tr>
<tr>
<td>If the new drug prevented me from needing to go into a Nursing Home</td>
<td></td>
</tr>
</tbody>
</table>

8. When you consider the future which of the following is of greatest concern to you? Please tick ONE statement that concerns you the most.

<table>
<thead>
<tr>
<th>Dying</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Getting Dementia</td>
<td></td>
</tr>
<tr>
<td>Being Dependent on Other People</td>
<td></td>
</tr>
<tr>
<td>Requiring a Nursing Home</td>
<td></td>
</tr>
<tr>
<td>Getting a Stroke</td>
<td></td>
</tr>
<tr>
<td>Getting a Heart Attack</td>
<td></td>
</tr>
<tr>
<td>Getting Cancer</td>
<td></td>
</tr>
</tbody>
</table>

Thank you for completing this survey.
Appendices

Appendix 7: Framingham and Omnibus Risk Equations

Framingham Risk Equations

For females not treated for hypertension

\[
femaleNoHypertensionTrt = \sum_{i=1}^{P} \beta_i X_i = 2.32888 \times \log(\text{age}) + 1.20904 \times \log(\text{total cholesterol}) - 0.70833 \times \log(\text{HDL}) + 2.76157 \times \log(\text{SBP}) + 0.52873 \times \text{smoker} + 0.69154 \times \text{diabetes}
\]

\[1 - (0.950121^{\exp(femaleNoHypertensionTrt-26.1931)})\]

For females treated for hypertension

\[
femaleHypertensionTrt = \sum_{i=1}^{P} \beta_i X_i = 2.32888 \times \log(\text{age}) + 1.20904 \times \log(\text{total cholesterol}) - 0.70833 \times \log(\text{HDL}) + 2.82263 \times \log(\text{SBP}) + 0.52873 \times \text{smoker} + 0.69154 \times \text{diabetes}
\]

\[1 - (0.950121^{\exp(femaleHypertensionTrt-26.1931)})\]

For males not treated for hypertension

\[
malesNoHypertensionTrt = \sum_{i=1}^{P} \beta_i X_i = 3.06117 \times \log(\text{age}) + 1.1237 \times \log(\text{total cholesterol}) - 0.93263 \times \log(\text{HDL}) + 1.93303 \times \log(\text{SBP}) + 0.65451 \times \text{smoker} + 0.57367 \times \text{diabetes}
\]

\[1 - (0.88936^{\exp(malesNoHypertensionTrt-23.9802)})\]

For males treated for hypertension

\[
malesHypertensionTrt = \sum_{i=1}^{P} \beta_i X_i = 3.06117 \times \log(\text{age}) + 1.1237 \times \log(\text{total cholesterol}) - 0.93263 \times \log(\text{HDL}) + 1.99881 \times \log(\text{SBP}) + 0.65451 \times \text{smoker} + 0.57367 \times \text{diabetes}
\]

\[1 - (0.88936^{\exp(malesHypertensionTrt-23.9802)})\]

Omnibus Risk Equations

For white females taking antihypertensive medication

\[
whiteFemalesHypertensionTrt = \sum_{i=1}^{P} \beta_i X_i = -29.799 \times \log(\text{age}) + 4.884 \times p_i = 1(\log(\text{age})) \times 2 + 13.54 \times \log(\text{total cholesterol}) - 3.114 \times \log(\text{age}) \times \log(\text{total cholesterol}) - 13.578 \times \log(\text{HDL}) + 3.149 \times \log(\text{age}) \times \log(\text{HDL}) + 2.019 \times \log(\text{SBP}) + (7.574 - 1.665 \times \log(\text{age})) \times \text{smoker} + 0.661 \times \text{diabetes}
\]

\[1 - (0.9665^{\exp(whiteFemalesHypertensionTrt-29.18)})\]

For white females not taking antihypertensive medication

\[
whiteFemalesNoHypertensionTrt = \sum_{i=1}^{P} \beta_i X_i = -29.799 \times \log(\text{age}) + 4.884 \times p_i = 1(\log(\text{age})) \times 2 + 13.54 \times \log(\text{total cholesterol}) - 3.114 \times \log(\text{age}) \times \log(\text{total cholesterol}) - 13.578 \times \log(\text{HDL}) + 3.149 \times \log(\text{age}) \times \log(\text{HDL}) + 1.957 \times \log(\text{SBP}) + (7.574 - 1.665 \times \log(\text{age})) \times \text{smoker} + 0.661 \times \text{diabetes}
\]

\[1 - (0.9665^{\exp(whiteFemalesNoHypertensionTrt-29.18)})\]
Appendix 7 (Continued) Framingham and Omnibus Risk Equations

For black females taking antihypertensive medication
blackFemalesHypertensionTrt = ΣβiXi = 17.114*log(age) + 0.94*pi = 1log(total cholesterol) – 18.92*log(HDLC) + 4.475*log(age)*log(HDLC) + 29.291*log(SBP) – (6.432*log(SBP)*log(age)) + 0.691*smoker + 0.874*diabetes

1 – (0.9533*exp(blackFemalesHypertensionTrt – 86.61))

For black females not taking antihypertensive medication
blackFemalesNoHypertensionTrt = ΣβiXi = 17.114*log(age) + 0.94*pi = 1log(total cholesterol) – 18.92*log(HDLC) + 4.475*log(age)*log(HDLC) + 27.82*log(SBP) – (6.087*log(SBP)*log(age)) + 0.691*smoker + 0.874*diabetes

1 – (0.9533*exp(blackFemalesNoHypertensionTrt – 86.61))

For white males taking antihypertensive medication
whiteMalesHypertensionTrt = ΣβiXi = 12.344*log(age) + 11.853*pi = 1log(total cholesterol) – 2.664*log(age)*log (total cholesterol) – 7.99*log(HDLC) + 1.769*log(age)*log(HDLC) + 1.797*log(SBP) + (7.837 – 1.795*log(age))*smoker + 0.658*diabetes

1 – (0.9144*exp(whiteMalesHypertensionTrt – 61.18))

For white males not taking antihypertensive medication
whiteMalesNoHypertensionTrt = ΣβiXi = 12.344*log(age) + 11.853*pi = 1log(total cholesterol) – 2.664*log(age)*log (total cholesterol) – 7.99*log(HDLC) + 1.769*log(age)*log(HDLC) + 1.764*log(SBP) + (7.837 – 1.795*log(age))*smoker + 0.658*diabetes

1 – (0.9144*exp(whiteMalesNoHypertensionTrt – 61.18))

For black males taking antihypertensive medication
blackMalesHypertensionTrt = ΣβiXi = 2.469*log(age) + 0.302*log(total cholesterol) – 0.307*log(HDLC) – 11.916*log(SBP) + 0.549*smoker + 0.645*diabetes

1 – (0.8954*exp(blackMalesHypertensionTrt – 19.54))

For black males not taking antihypertensive medication
blackMalesNoHypertensionTrt = ΣβiXi = 2.469*log(age) + 0.302*pi = 1log(total cholesterol) – 0.307*log(HDLC) + 1.809*log(SBP) + 0.549*smoker + 0.645*diabetes

1 – (0.8954*exp(blackMalesNoHypertensionTrt – 19.54))
Appendix 8: Standard Assessment of Global Activities in the Elderly (SAGE) Scale
Section 1: Instrumental Activities of Daily Living

Over the past month, did you have any difficulties with the following:

1. Keeping your attention or ‘train of thought’ during a conversation? □ None □ Some □ How much difficulty?

2. Remembering things that happened a few days before? (e.g., conversation, people visiting) □ None □ Some □ How much difficulty?

3. Ability to switch between things that are happening at the same time? (e.g., making tea and talking to someone) □ None □ Some □ How much difficulty?

Over the past month, did you perform any of the following activities:

4. Playing a game or reading a book that requires concentration? (e.g., games: crosswords, checkers, chess) □ No □ Yes □ Difficulty?

5. Finding your way around a new building? (e.g., hospital/clinic) □ No □ Yes □ Difficulty?

6. Organizing a trip or social activities? (e.g., vacation or family occasion) (score the activity that the person finds to be the more difficult of the two) □ No □ Yes □ Difficulty?

7. Doing your own finances or shopping? (score the activity that the person finds to be the more difficult of the two) □ No □ Yes □ Difficulty?

8. Organizing and taking your medications? □ No □ Yes □ Difficulty?

9. Preparing a meal and/or doing laundry? (score the activity that the person finds to be the more difficult of the two) □ No □ Yes □ Difficulty?

10. a) Driving? □ Do not drive (go to 10b) □ No □ Yes □ Difficulty?

b) Using public transportation? □ Do not use (go to 11) □ No □ Yes □ Difficulty?
Appendix 8 (Continued) Standard Assessment of Global Activities in the Elderly (SAGE) Scale

Section 2: Basic Activities of Daily Living

Over the past month, did you perform any of the following activities:

11. Using stairs? (one flight)  □ No  □ Yes  Difficulty?  □ None  □ Mild  □ Moderate  □ Severe
   ➝ Did you require help?  □ No  □ Yes  □ Walking stick
   ➝ Elevator/lift
   ➝ Another person
   ➝ Other:________________

12. Walking? (approx. 10m or 32ft or 14 steps)  □ No  □ Yes  Difficulty?  □ None  □ Mild  □ Moderate  □ Severe
   ➝ Did you require help?  □ No  □ Yes  □ Walking stick/rollator
   ➝ Another person
   ➝ Other:________________

13. Dressing?  □ No  □ Yes  Difficulty?  □ None  □ Mild  □ Moderate  □ Severe
   ➝ Did you require help?  □ No  □ Yes

14. Transfer from bed to chair?  □ No  □ Yes  Difficulty?  □ None  □ Mild  □ Moderate  □ Severe
   ➝ Did you require help?  □ No  □ Yes  □ Walking stick/rollator
   ➝ Another person
   ➝ Other:________________

15. Bathing or toileting?  □ No  □ Yes  Difficulty?  □ None  □ Mild  □ Moderate  □ Severe
   ➝ Did you require help?  □ No  □ Yes

If the participant reports difficulty with any of the items in questions 6-15, please ask:

16. Have any of the following problems limited your ability to perform activities? (check all that apply)
   □ Memory problems □ Physical injury (e.g. fracture) □ Loss of vision □ Not sure
   □ Arthritis □ Stroke or TIA □ Unsteadiness □ Other:________________
   □ Shortness of breath □ Chronic pain □ Other:________________
   □ Chest pain □ Heart failure □ None of the above

clxxviii
Appendices

Appendix 9: Timed Up and Go Test

Timed Up and Go Test (TUG)

1. Begin Timing

2. Patient Instructed to rise from standard chair

3. Walk 3 metres to a line on the floor

4. Turn around at the line

5. Walk back towards the chair

6. Sit back down on the chair

7. End Timing

Timing begins when patient’s bottom leaves the chair. Patients may use walking aide/stick.

Appendix 10: Cognitive Tests

Digital Symbol Substitution Test

Sample Items

<table>
<thead>
<tr>
<th>2</th>
<th>1</th>
<th>3</th>
<th>7</th>
<th>2</th>
<th>4</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>9</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>9</td>
<td>4</td>
<td>8</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>6</td>
<td>8</td>
<td>5</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

| 2 | 1 | 3 | 7 | 2 | 4 | 8 | 2 | 1 | 3 | 2 | 1 | 4 | 2 | 3 | 5 | 2 | 3 | 1 | 4 |
| 5 | 6 | 3 | 1 | 4 | 1 | 5 | 4 | 2 | 7 | 6 | 3 | 5 | 7 | 2 | 8 | 5 | 4 | 6 | 3 |
| 7 | 2 | 8 | 1 | 9 | 5 | 8 | 4 | 7 | 3 | 6 | 2 | 5 | 1 | 9 | 2 | 8 | 3 | 7 | 4 |
| 6 | 5 | 9 | 4 | 8 | 3 | 7 | 2 | 6 | 1 | 5 | 4 | 6 | 3 | 7 | 9 | 2 | 8 | 1 | 7 |
| 9 | 4 | 6 | 8 | 5 | 9 | 7 | 1 | 8 | 5 | 2 | 9 | 4 | 8 | 6 | 3 | 7 | 9 | 8 | 6 |
| 2 | 7 | 3 | 6 | 5 | 1 | 9 | 8 | 4 | 5 | 7 | 3 | 1 | 4 | 8 | 7 | 9 | 1 | 4 | 5 |
| 7 | 1 | 8 | 2 | 9 | 3 | 6 | 7 | 2 | 8 | 5 | 2 | 3 | 1 | 4 | 8 | 4 | 2 | 7 | 6 |
Appendices

Appendix 10 (Continued) Cognitive Tests

Trail Making Test Part B

Participant to be instructed to draw lines to connect the 25 circles in an ascending pattern, alternating between the numbers and the letters (i.e. 1-A-2-B-C), as quickly as possible without lifting the pen/pencil from the paper and without skipping any circles. The time taken for the patient to connect the complete trail is recorded.
Appendix 10 (Continued) Cognitive Tests

Montreal Cognitive Assessment

[Image of Montreal Cognitive Assessment test with various sections including Visuospatial/Executive, Naming, Memory, Attention, Language, Abstraction, Delayed Recall, Optional, and Orientation.]

© Z. Nasreddine MD  www.mocatest.org  Normal ±26 /30
Administered by: __________________________

TOTAL __/30

Add 1 point if ≤ 12 yr educ
Dissemination of Work

Published Papers and Outputs Arising From This Work

Presentations
1. Canavan M, Smyth A, Mcgrath E, Glynn LG, Murphy AW, Mulkerrin EC, O’Donnell MJ. Vascular Risk Factors and Functional Impairment in Community Dwelling Older Adults in the West of Ireland. **Poster presentation at the 60th Annual and Scientific Meeting of the Irish Gerontological Society (IGS), Cork 2012. Awarded President’s Prize for best poster.**

2. Canavan M, Smyth A, Jenson M, Robinson S, Mulkerrin EC, O’Donnell MJ. Effect of Blood Pressure Lowering Using Antihypertensive Drugs on Ability to Carry out Activities of Daily Living in Participants with Hypertension or Pre-Hypertension: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. **Oral Presentation at the 61st Annual and Scientific Meeting of the IGS, Dublin 2013**

3. Canavan M, Smyth A, Robinson S, Gibson I, Mulkerrin EC, O’Donnell MJ. Attitudes to Importance of Outcome Measures in Cardiovascular Prevention Trials. **Poster presentation at the 62nd Annual and Scientific Meeting of the IGS, Galway 2014**

4. Canavan M, Robinson S, Gibson, Costello C, Bosch J, Rahman H, Walsh T, O’Keeffe ST, Mulkerrin EC, O’Donnell MJ. Attitudes to Ageing and Importance of Outcome Measures in Cardiovascular Prevention Trials. Do they differ between younger and older adults? **Poster presentation at the International Association of Gerontology and Geriatrics, European Region (IAGG-ER) 8th Congress, Dublin April, 2015.**

Publications


Papers Under Review
References


References


References


References


References


76. Bayliss EA, Bayliss MS, Ware JE, Jr., Steiner JF. Predicting declines in physical function in persons with multiple chronic medical conditions: what we can learn from the medical problem list. *Health and quality of life outcomes*. 2004;2:47.


clxxxi
References


References


References


References


clxxxv
References


References


References


147. Watts G. Why the exclusion of older people from clinical research must stop. BMJ. 2012;344:e3445.


References


clxxxix
References


References


191. Murphy AW, Cupples ME, Smith SM, Byrne M, Leathem C, Byrne MC. The SPHERE Study. Secondary prevention of heart disease in general practice: protocol of a randomised controlled trial of tailored practice and patient...


References


210. Patel A. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes


References


230. Boyd CM, Xue QL, Guralnik JM, Fried LP. Hospitalization and development of dependence in activities of daily living in a cohort of disabled older...
References


240. Nilsson SE, Read S, Berg S, Johansson B, Melander A, Lindblad U. Low systolic blood pressure is associated with impaired cognitive function in the


References


cxcix
References


263. Wright JT, Jr., Fine LJ, Lackland DT, Ogedegbe G, Dennison Himmelfarb CR. Evidence supporting a systolic blood pressure goal of less than 150 mm Hg in patients aged 60 years or older: the minority view. Ann Intern Med. 2014;160(7):499-503.


References


References


References


