Blood pressure, antihypertensive treatment and cognitive decline in older adults

Brian Kent Saxby

Submitted for Doctor of Philosophy

Newcastle University, Faculty of Medical Sciences

Date of submission 30th June 2008

ABSTRACT

Hypertension is prevalent in older adults and associated with impaired cognitive function compared to normotensive peers. The effect of antihypertensive therapy on preventing or reducing the rate of cognitive decline is unclear. The studies in this thesis examined the association of elevated blood pressure in older adults on changes in specific cognitive domains and tested the hypothesis that antihypertensive treatment reduces the rate of cognitive decline in older adults with mild hypertension. 507 older individuals (70-89 years) were recruited from a general practice population (250 normotensives, and 257 hypertensives who participated in an international, placebo-controlled trial of candesartan). Cognition was assessed annually for 3-5 years using a comprehensive computerised assessment battery and tests of executive function. Analysis of cognitive function at baseline showed hypertensive subjects performed worse than normotensives across a range of tasks (Chapter 3). Exploratory factor analyses were conducted on the baseline data to derive composite scores used to characterise five domains of cognition and reduce the number of statistical comparisons (Chapter 4). Regression analyses were performed for each participant to calculate individual slopes of decline on the five domains, to provide a sensitive method of analysing repeated assessment data with differential length of follow-up. The primary analysis showed that candesartan-based therapy reduced cognitive decline associated with hypertension on Attention and Episodic Memory, with a trend for Speed of Cognition; effect sizes were small-to-moderate. There were no effects on Working Memory or Executive Function (Chapter 6). The normotensive subjects showed less cognitive decline than the hypertensives (Chapter 7). These data suggest that the rate of cognitive decline associated with hypertension in older adults may be reduced by blood-pressure-lowering. Analysing individual slopes of decline on empirically-derived domains of cognition provides a sensitive and feasible methodology for assessing the effects.

Dedicated to the memory of Zeta May Perry

Acknowledgements

I would like to give my sincere thanks and appreciation to my supervisor Prof Gary Ford for his guidance and support during the research, and his unwavering belief and patience during the thesis writing process. Thanks to Prof Keith Wesnes for supporting the SCOPE substudy, and giving advice on the cognitive and factor analytical aspects. Advice from Prof Ian McKeith and Prof John Matthews on the study design and analysis approach is also appreciated. And I thank my examiners, Prof Anthony Passmore and Dr. Alan Thomas for their time and effort in assessing the quality of the work.

The cognitive data presented in this thesis represent one aspect of a research study that was very much a team effort, and thanks must go to those people whose contribution made my work possible: Frances Harrington, Rebecca Wiseman, Philip Simpson, Jenny Logan, John Davis, Anu Kulkarni, the ASCOT nurses, Helen Poppleton, and Teresa Thompson, for their various contributions to the running of the SCOPE study; Brenda, Carol, Colin and the Eye Man for somewhere to see the participants; the Astra Research Foundation UK for providing financial support for the Newcastle SCOPE substudies; Karen Fairbrother, Avril Mackay and Elisa Clarke from AstraZeneca for keeping us on our toes; Gareth Ayre, Nick Hargaden, Caroline Brookes and Tamsin Manktelow for being my ‘handlers’ at CDR Ltd; and most importantly, the participants themselves for their time and effort, and for making the data collection the most interesting and rewarding aspect of the research.

I would also like to express my gratitude to those people in my personal life who have supported and encouraged me throughout the various stages, or have simply been polite enough to feign interest in what I’ve been going on about for the last 10 years. In particular Mam, Dad, Dave, Heather and the kids, Mark, the FootieLads, Rachel, Becky and Julie. And last but not least, Caroline Hodgson who finally proved the theory that nagging works!

List of contents

LIST OF TABLES

LIST OF FIGURES

Publications and dissemination

Peer reviewed publications

Cognitive data

Cognitive data presented in this thesis have been published in the following peer-reviewed journal articles:

Saxby BK, Harrington F, McKeith IG, Wesnes K and Ford GA (2008). Candesartan and cognitive decline in older patients with hypertension: A substudy of the SCOPE trial. Neurology 70: 1858-1866.

Saxby BK, Harrington F, McKeith IG, Wesnes K and Ford GA (2003). Effects of hypertension on attention, memory and executive function in older adults. Health Psychology 22: 587-591.

O'Brien KK, **Saxby BK**, Ballard CG, Grace J, Harrington F, Ford GA, O'Brien JT, Swan AG, Fairbairn AF, Wesnes K, del Ser T, Edwardson JA, Morris CM and McKeith IG (2003). Regulation of attention and response to therapy in dementia by butyrylcholinesterase. Pharmacogenetics 13: 231-239.

O'Brien JT, Wiseman R, Burton EJ, Barber B, Wesnes K, **Saxby BK** and Ford GA (2002). Cognitive associations of subcortical white matter lesions in older people. Alzheimer's Disease: vascular etiology and pathology. Annals of the New York Academy of Sciences 977: 436-444.

Harrington F, **Saxby BK**, McKeith IG, Wesnes K and Ford GA (2000). Cognitive performance in hypertensive and normotensive older subjects. Hypertension 36: 1079-1082.

Blood pressure data

Blood pressure data from the Newcastle Cognitive Substudy have been published in conjunction with other measures not presented in this thesis, in the following peer-reviewed journal articles:

Firbank MJ, Wiseman RM, Burton EJ, **Saxby BK**, O' Brien JT and Ford GA (2007). Brain atrophy and white matter hyperintensity change in older adults and relationship to blood pressure. Journal of Neurology 254: 713-721.

Burn J, Sims AJ, Ford GA and Murray A (2006). Factors affecting the use of cumulative sums in the analysis of circadian blood pressure. Physiological Measurement 27: 529-538.

Wiseman RM, **Saxby BK**, Burton EJ, Barber R, Ford GA and O'Brien JT (2004). Hippocampal atrophy, whole brain volume, and white matter lesions in older hypertensive subjects. Neurology 63: 1892-1897.

Harrington F, Murray A and Ford GA (2000). Relationship of baroreflex sensitivity and blood pressure in an older population. Journal of Hypertension 18: 1629-1633.

Conference presentation abstracts

Data from the Newcastle Cognitive Substudy have been presented at the following meetings:

<u>Cognitive performance and hypertension</u>

Saxby BK, Harrington F, McKeith IG, Wesnes K, Ford GA. Effects of hypertension on attention, memory and executive function in older adults. Journal of Human Hypertension. 2002;16(Suppl.):11. Platform presentation by BKS at the British Hypertension Society Annual Scientific Meeting, Cambridge, September 2002: shortlisted for the Young Investigator Award

Saxby BK, Harrington F, McKeith IG, Wesnes K, Ford GA. A comparison of cognitive function in hypertensive and normotensive older subjects. Journal of Psychopharmacology. 2001;15(S3):A54. Poster presentation by BKS at the Summer Meeting of the British Association for Psychopharmamcology, Harrogate, July 2001

Saxby BK, Harrington F, McKeith IG, Wesnes K, Ford GA. A comparison of cognitive function in hypertensive and normotensive older subjects. Proceedings of the British Psychological Society: Centenary Annual Conference. 2001. Poster

presentation by BKS at the British Psychological Society Centenary Annual Conference, Glasgow, March 2001

Saxby BK, Harrington F, McKeith IG, Wesnes K, Ford GA. Factor analysis of the Cognitive Drug Research assessment battery in elderly hypertensives. Proceedings of the British Psychological Society: Psychobiology Section. 2000. Poster presentation by BKS at the Annual Scientific Meeting of the British Psychological Society Psychobiology Section, ODG Langdale, Lake District, September 2000

Saxby BK, Harrington F, McKeith IG, Wesnes K, Ford GA. Factor analysis of the Cognitive Drug Research assessment battery in elderly hypertensives. Journal of Psychopharmacology. 2000;14(supplement 3):A47. Poster presentation by BKS at the Summer Meeting of the British Association for Psychopharmamcology in Cambridge, July 2000

Harrington F, **Saxby BK**, Poppleton H, McKeith IG, James OFW, Wesnes K, Ford GA. Cognitive performance in normotensive and mildly hypertensive older subjects. Age and Ageing. 2000;29(Supplement 1):74. Platform presentation by FH at the British Geriatrics Society Meeting.

Saxby BK, Harrington F, Poppleton H, McKeith IG, James OFW, Wesnes K, Ford GA. Cognitive performance in normotensive and hypertensive older subjects. Proceedings of the British Psychological Society. 2000;8(2). Platform presentation by BKS at the Annual Scientific Meeting of the British Psychological Society Psychobiology Section, ODG Langdale, Lake District, September 1999

Saxby BK, Harrington F, Poppleton H, McKeith IG, James OFW, Wesnes K, Ford GA. Cognitive performance in normotensive and hypertensive older subjects. Journal of Psychopharmacology. 1999;13(supplement 3):A29. Poster presentation by BKS at the Summer Meeting of the British Association for Psychopharmamcology, Harrogate, July 1999

Harrington F, **Saxby BK**, Poppleton H, McKeith IG, James OFW, Wesnes K, Ford GA. Cognitive performance in normotensive and hypertensive older subjects. Journal

of Human Hypertension. 1999;13:894. Platform presentation by FH at the Annual Scientific Meeting of the British Hypertension Society, Glasgow, September 1999

Treatment of hypertension and cognition

Saxby BK, Harrington F, McKeith IG, Wesnes KA, Ford GA. The effect of candesartan on cognitive function in older adults with mild hypertension. Journal of Psychopharmacology. 2003;17(Suppl.):A65. Poster presentation by BKS at the Summer Meeting of the British Association for Psychopharmamcology, Cambridge, July 2003

Saxby BK, Harrington F, McKeith IG, Wesnes K, Ford GA. The effect of candesartan on cognitive function in older adults with mild hypertension. Journal of the Neurological Sciences. 2004;226(Suppl.):161. Poster presentation by BKS at the First Congress of the International Society for Vascular Behavioural and Cognitive Disorders (VAS-COG 2003), Goteborg, Sweden, August 2003

Saxby BK, Harrington F, McKeith IG, Wesnes K, Ford GA. The effect of candesartan cilexetil on cognitive function in older adults with mild hypertension. Journal of Hypertension. 2003;21(Suppl.):S18-S9. Platform presentation by BKS at the European Society for Hypertension, Milan, September 2003

Saxby BK, Harrington F, McKeith IG, Wesnes K, Ford GA. The effect of candesartan on cognitive function in older adults with mild hypertension. Journal of Human Hypertension. 2003;17:725. Platform presentation by BKS at the British Hypertension Society Annual Scientific Meeting, Cambridge, September 2003: shortlisted for the Young Investigator Award

Homocysteine

Narayan SK, **Saxby BK**, Firbank MJ, O'Brien JT, McKeith I, Gray JC and Ford G (2007). Plasma homocysteine level is independently associated with rates of cognitive decline. Poster presentation by SKN at the 15th Annual Conference of the Indian Academy of Neurology, Mumbai, India, October 2007

Saxby BK, Narayan S, Firbank MJ, Ford GA and O' Brien JT (2007). Elevated homocysteine concentrations are associated with cognitive decline and increased rates of brain atrophy on serial MR imaging in older people with hypertension. International Psychogeriatrics 19: FC14-4. Platform presentation by BKS in the Hot Topics section of International Psychogeriatrics Association conference, Osaka, Japan, October 2007

Saxby BK, Narayan S, Firbank MJ, Ford GA and O' Brien JT (2007). Elevated homocysteine concentrations are associated with cognitive decline and increased rates of brain atrophy on serial MR imaging in older people with hypertension. Platform presentation by BKS in key topic communications II - Biomarkers section of VAS-COG 2007, San Antonio, USA, July 2007

<u>24h Ambulatory Blood Pressure Monitoring and cognition</u>

Harrington F, **Saxby BK**, Wesnes KA, Ford GA. Increased variability in blood pressure in older subjects is related to cognitive impairment. Journal of Psychopharmacology. 2001;15(S3):A51. Poster presentation by BKS at the Summer Meeting of the British Association for Psychopharmamcology, Harrogate, July 2001

Harrington F, **Saxby BK**, Wesnes K, Ford GA. The effect of blood pressure variability on cognitive function in older subjects. Age and Ageing. 2001;30(Supplement 2):62. presentation by FH at the British Geriatrics Society Spring Meeting, Cardiff, April 2001

Harrington F, **Saxby BK**, Wesnes K, Ford GA. The effect of diurnal blood pressure differences on cognitive function in older hypertensives. Journal of the American Geriatrics Society. 2001;49(4):P86. Presented by FH at American Geriatrics Society, Chicago, 2001

<u>Imaging and cognition</u>

Wiseman RM, **Saxby BK**, Barber R, O'Brien J, Wesnes KA, Ford GA. The relationship between white matter lesions on magnetic resonance imaging and cognitive performance in hypertensive and normotensive older subjects. Journal of Psychopharmacology. 2001;15(S3):A54. Poster presentation by BKS at the Summer Meeting of the British Association for Psychopharmamcology, Harrogate, July 2001

Wiseman RM, **Saxby BK**, Barber R, O'Brien J, Wesnes KA, Ford GA. The relationship between white matter lesions on magnetic resonance imaging and cognitive performance in hypertensive and normotensive older subjects. Journal of Human Hypertension. 2001;5(12):18. Platform presentation by RMW at the British Hypertension Society Annual Scientific Meeting, Cambridge, September 2001

Genetics and cognition

Saxby BK, O'Brien KK, Morris CM, McKeith IG, Wesnes KA, Ford GA. Butyrylcholinesterase K and attention in hypertensive and normotensive older adults. Journal of Psychopharmacology. 2002;16(3):B15. Poster presentation by BKS at the Summer Meeting of the British Association for Psychopharmacology, Harrogate, July 2002

O'Brien KK, Morris CM, Edwardson JA, McKeith I, Ballard CG, Grace J, **Saxby B**, Ford G, Wesnes K, del Sur T. Regulation of attention and response to therapy in dementia by butyrylcholinesterase. Neurobiology of Aging. 2002;23(suppl 1):1685. Poster presentation by KO'B at the 8th International Conference on Alzheimer's Disease and Related Disorders; 2002 July 20-25, Stockholm, Sweden

Saxby BK, Morris CM, O'Brien KK, McKeith IG, Wesnes KA, Ford GA. Butyrylcholinesterase K and attention in older adults. 2001. Platform presentation by BKS at the joint meeting of the British Geriatric Society Drugs & Prescribing Section and the Cerebral Ageing & Mental Health Special Interest Group in London on the 17th October 2001

Imaging

Saxby BK, Firbank MJ, Wiseman RM, Burton EJ, O' Brien JT, Ford GA. Brain atrophy and white matter hyperintensity change in older adults and effects of candesartan. Proceedings of the 2nd Congress of the International Society for Vascular Behavioural and Cognitive Disorders (VAS-COG). 2005. Poster presentation by BKS at the 2nd Congress of the International Society for Vascular Behavioural and Cognitive Disorders (VAS-COG 2005), Florence, Italy, June 2005

Firbank MJ, Wiseman RM, Burton EJ, **Saxby BK**, O'Brien JT, Ford GA. Brain atrophy and white matter hyperintensity change in normo-and hyper-tensive older adults. Poster presentation by MJF at Annual Meeting of the European Society of Magnetic Resonance in Medicine and Biology. Basel, Switzerland, September 2005

Wiseman RM, Burton EJ, **Saxby BK**, O'Brien JT, Ford GA. Increased brain atrophy rate and white matter lesions in treated older hypertensive subjects: a longitudinal magnetic resonance imaging study. Journal of Human Hypertension. 2003;17:725. Platform presentation by RMW at the British Hypertension Society Annual Scientific Meeting, Cambridge, September 2003

Wiseman RM, Burton EJ, **Saxby BK**, O'Brien JT, Ford GA. Increased brain atrophy rate in older hypertensive subjects. Journal of Hypertension. 2003;21(Suppl.):S17-S8. Platform presentation by RMW at the European Society for Hypertension, Milan, September 2003

Wiseman RM, Barber R, O'Brien J, Ford GA. White matter lesions on magnetic resonance imaging in older hypertensives and normotensives. Journal of the American Geriatrics Society. 2001;49(4):P111. Platform presentation by RMW at the American Geriatrics Society, Chicago, 2001

<u>Recruitment</u>

Kulkarni A, Harrington F, Logan J, **Saxby BK**, Ford GA, James OFW. Recruitment of older subjects to a hypertension trial from primary care. Journal of Human Hypertension. 2001;15:361. Platform presentation by AK at the Annual Meeting of the Nurses Hypertension Association, Cambridge, September 2001

Kulkarni A, Harrington F, Davis J, Logan J, **Saxby BK**, Ford GA. Recruitment of older subjects into research studies from primary care. 2001. Platform presentation by AK at the Clinical Research Nurses' Association Annual Conference, Leicester, 2001

Harrington F, Kulkarni A, **Saxby BK**, Ford GA, James OFW. Recruitment of older subjects to a hypertension trial from primary care. Age and Ageing. 2001;30(Supplement 1):44. Poster presentation by FH at the British Geriatrics Society, 2001

Symbols, abbreviations and acronyms

♀	female
APOE	apolipoprotein E allele
ACE	angiotensin-converting-enzyme
AD	Alzheimer's Disease
ARB	angiotensin-receptor-blocker
BDAT	Boston Diagnostic Aphasia Test
BP	blood pressure
CDR	Cognitive Drug Research
CFQ	Cognitive Failures Questionnaire
CRF	Case Report Form
DBP	diastolic blood pressure
DSS	digit-symbol substitution subtest of the WAIS/ WAIS-R
DSM-III	Diagnostic and Statistical Manual of Mental Disorders (3rd Edition)
ECG	electrocardiogram
GDS	Geriatric Depression Scale
GP	general practitioner
HCTZ	hydrochlorothiazide
HOT	Hypertension Optimal Treatment study
ISH	isolated systolic hypertension

IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
LOCF	last observation carried forward
mmHg	millimetres of mercury
NART	New Adult Reading Test
MMSE	Mini-Mental State Examination
MRC	Medical Research Council
MRI	magnetic resonance imaging
PALT	Paired Associate Learning Test
PCA	Principal Components Analysis
RPM	Raven's Progressive Matrices
SBP	systolic blood pressure
SCOPE	Study on COgnition and Prognosis in the Elderly
SHEP	Systolic Hypertension in Elderly Prevention trial
Syst-Eur	Systolic Hypertension in Europe study
TMT	Trail-Making Test
VaD	Vascular Dementia
WAIS-(R)	Wechsler Adult Intelligence Sacle (Revised)
WCST	Wisconsin Card Sort Test
WMS	Wechsler Memory Scale

CHAPTER 1: INTRODUCTION

1.1 Epidemiological changes and the greying society

The population of the UK is ageing. The population has grown by 8 per cent over the last few decades, from 55.9 million in 1971 to 60.6 million in mid-2006, but this change has not occurred evenly across all age groups: the population aged over 65 grew by 31%, from 7.4 to 9.7 million. The largest percentage growth in population in the year to mid-2006 was at ages 85 and over (5.9%); the number of people aged 85+ grew by 69,000, reaching a record 1.2 million [1]. This large increase reflects improving survival and the post World War One baby boomers now reaching this age group. The trend towards a greying society is also reflected in other major Western societies.

As the population ages, diseases and morbidity associated with age will increase the social and healthcare burden of society. The challenge for researchers is to identify the conditions where morbidity can be treated or prevented. Hypertension and cognitive decline are two such areas worthy of investigation.

1.2 Cognitive function

1.2.1 Definition and description

The word cognition derives from the Latin *cognoscere*, 'to know'. The American Heritage Medical Dictionary defines it as, 'the mental faculty of knowing, which includes perceiving, recognizing, conceiving, judging, reasoning, and imagining' [2].

Cognitive function refers to the underlying mental processes we often take for granted that enable us to go about our conscious everyday activities. Although a number of inter-related processes can be involved in any particular task, such as reading, or driving a car, for the purpose of description and investigation it is useful to separate cognition into different functions. The level to which each function is broken down and the descriptive terminology used often varies depending on the interests, discipline and hypotheses of the researcher or clinician. The general domains include,

but are not limited to: attention, information processing, working memory, long-term or episodic memory, and executive function.

1.2.1.1 Attention

Attention refers to the focus of resources being brought to bear on the task at hand. It reflects the intensity of concentration at any particular moment and the ability to sustain concentration for the period of time required whilst ignoring distraction. By virtue of its moment-to-moment fleeting nature, attention can be difficult to measure. An example of attention is listening intently to the school register waiting for your name to be called.

1.2.1.2 Information processing

This refers to the ability to select information relevant to the task at hand, and reject extraneous information, to make simple but appropriate decisions quickly. Information processing is allied to attention to a large extent, as without paying due attention the information will not be available for processing. Measurement is often based on both the speed and the quality of the processing decisions made. An example is responding correctly with 'Yes Sir' and not 'Yes Miss' in response to your name being called in the school register, and responding before the teacher marks you as absent.

1.2.1.3 Working memory

Working memory is sometimes referred to as short-term memory, and relates to any information that is currently being held temporarily for manipulation or calculation. The two primary modes of information are images and sounds, held in the visuo-spatial scratchpad and auditory loop respectively (temporary information from other senses is dealt with by somatic memory, not usually considered a major part of cognitive function). Working memory provides a temporary store for information relevant to the task at hand. An example is holding the words from the beginning of a teacher's sentence until they get to the end, so you can make sense of the instruction to attend detention after school.

1.2.1.4 Episodic memory

Sometimes called long-term memory, the term episodic implies that a period of time has elapsed and refers to any information recalled or recognised after it is no longer being held in the temporary working memory store. This can be a matter of minutes, hours, days or years. The information may be verbal or visual, and is generally declarative so that the information can be described. An example is remembering to attend a detention session after school and recalling the misdemeanour from earlier that day that put you there.

1.2.1.5 Executive function

This is a general term that covers a range of higher level complex abilities, often composed of a number of the more discrete functions such as attention and working memory. Planning, organisation, problem-solving and managing multiple tasks are typically involved. An example is finding the quickest method to complete the punishment of writing out the sentence 100 times, 'I must address my teacher with the correct gender-specific salutation'.

During everyday activities, cognitive function can go unnoticed if there are no problems and tasks can be completed satisfactorily. However, there are many factors that can have detrimental effects on performance, to lesser or greater degrees, including age, disease, effects of drugs, diet and sleep deprivation. When cognition is affected to the extent that task performance is disrupted, the cognitive deficits become apparent. However, even subtle deficits can be problematic and interfere with quality of life, or be early indicators of future declines. In order to detect such changes, measurement of cognitive function becomes an important issue.

1.2.2 Measurement

In the same way that individual researchers and clinicians have their own interests in specific areas of cognition, so there is a proliferation of tests to measure these functions. In recent decades the cognitive testing market has become a sizeable industry and there are a range of tests available from commercial and academic sources, both public domain and proprietary tools sold under copyright licence.

However, the wide range of tests used in research can make comparison between studies somewhat problematic. The main distinction between test types reflects the theoretical background of their development and original intentions for use.

1.2.2.1 Neuropsychological tests

Neuropsychological tests are designed specifically for detecting impairment in patient populations and often require trained administrators and qualified personnel for their interpretation. They are more likely to be paper-and-pencil measures and require 1-to-1 administration. As they are not usually designed for frequent repeated testing, they have limited or no parallel forms so may suffer from learning effects. That said, because they are designed for clinic use, the measures are usually sensitive and specific for detecting clinically-relevant impairments and in some cases, validated to contribute to the disease diagnosis.

1.2.2.2 Cognitive tests

Cognitive tests are designed to measure specific aspects of cognitive function, and as a result tend to be more sensitive to subtle changes. Computerised cognitive testing has become a niche market within the drug-development process in the pharmaceutical industry. This has fuelled the development of cognitive test batteries that cover a range of functions to comprehensively identify impairments and enhancements to cognition, designed specifically with repeated testing in mind. Because of the environment in which they are employed, cognitive test batteries are well-equipped for electronic data capture, automation and standardisation of test administration, and can sometimes be administered in groups. Training of participants is usually a requirement to reduce practice effects, and multiple parallel forms enable repeated testing without learning effects.

A similar distinction can be made between tests that provide a brief, global assessment of cognition to be used as screening measures, and more in-depth batteries designed to profile differential aspects of cognitive function. There are advantages and disadvantages to all measures of cognitive function as no one measure can be ideal in all situations. Therefore at the design stage of any research study the relative merits of

the available assessment methods need to be considered. In addition to the practicalities, the psychometric properties have to be considered.

1.2.2.3 Reliability

The reliability of an assessment tool refers to the level of consistency with which it provides the measurements. Test-retest reliability is the most important aspect as it gives an indication to what extent the same scores will be produced if the assessment is repeated, all other things being equal. Test-retest reliability is assessed using correlation methods, ranging from -1 to 1, where a value of 1 represents total concordance between two assessments. With psychometric data there are a number of extraneous factors beyond control that can add noise to repeated measurements, so test-retest values in the range of 0.9 are usually deemed acceptable.

1.2.2.4 Validity

The validity of an assessment tool refers to the extent to which it actually measures what it purports to measure. There are a number of methods for test validation, including comparison to established measures of the same concept, and testing the ability of the measure to distinguish between groups known to differ on the concept in question. Reliability and validity are related concepts, although it is possible to have a reliable measure that is not valid; any valid measure must be reliable if change is to be measured.

1.2.2.5 Utility

The utility of a measure refers to how practical and appropriate it is for assessing the population it is intended for. There are no specific metrics to determine utility as the factors that need to be taken into consideration vary according to the research intended. These can include method of administration, time taken, training or qualification requirements of staff, language availability, data handling and processing, ease of interpretation etc. Utility is an important consideration as it can impact on the quality of data collected and the amount of missing data in a study.

1.3 Cognitive function and ageing

1.3.1 Changes over time

It is generally accepted that cognitive function declines with age. This is borne out by the normative data from neuropsychological and cognitive tests. For example, data from the Cognitive Drug Research (CDR) computerised assessment battery normative database (v.3) show on the attention task Choice Reaction Time, the speed of response in making a simple decision becomes slower (i.e. higher response times) as age increases (Figure 1). Similar trends for decline are seen with published norms for neuropsychological tests such as the Trail-Making Test [3]. There is some debate as to whether a certain amount of decline is an inevitable part of the ageing process as the biological systems underpinning cognition accumulate damage and naturally degenerate. However, there are a number of conditions where distinct pathological processes are known to cause cognitive decline.

Figure 1: Normative data from the Cognitive Drug Research (CDR) system

Normative data in five-year age bands for the Choice Reaction Time task from the Cognitive Drug Research (CDR) computerised assessment system.

Data shown are mean and standard error.

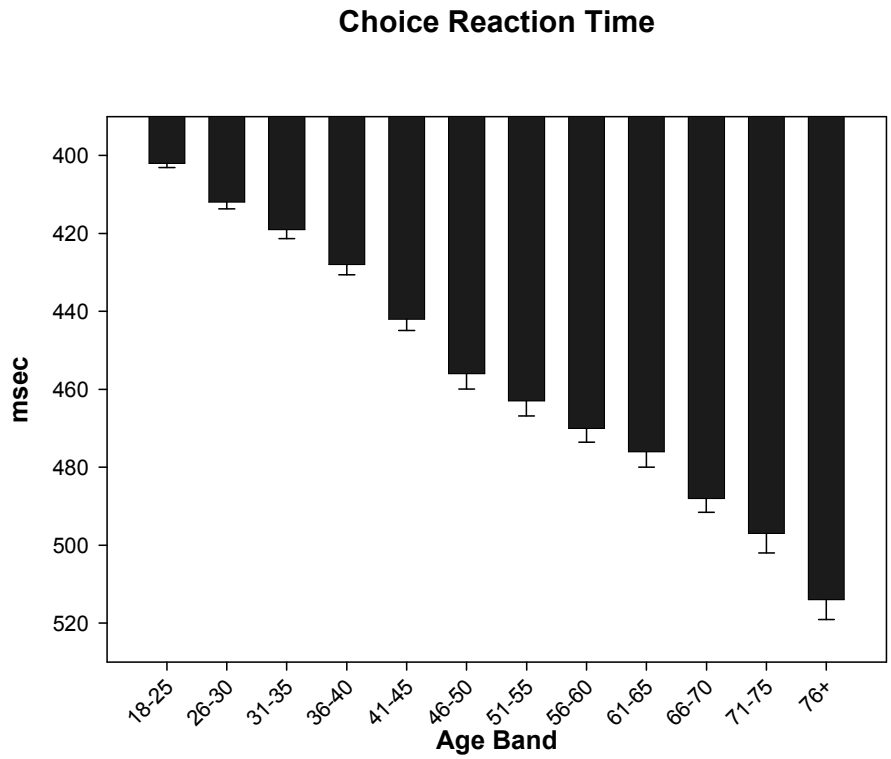
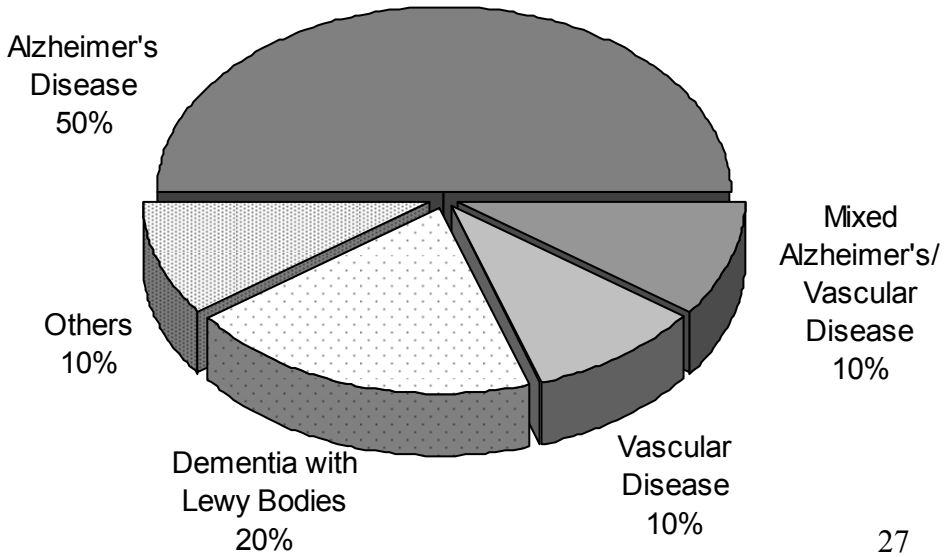


Figure 2: Distribution of the dementia subtypes



1.3.2 Dementia

Dementia refers to a group of conditions that gradually destroy brain cells and lead to progressive decline in mental function. Dementia affects a range of cognitive functions including memory, attention, the ability to learn, reason, make judgements, communicate and carry out daily activities. Personality changes are often evident and patients can suffer from anxiety, suspiciousness, agitation, delusions and hallucinations. There are a number of subtypes of dementia (distribution shown in Figure 2), the most common being Alzheimer's Disease (AD). Vascular Dementia (VaD) (including mixed dementia) accounts for approximately 20% of dementia cases. The diagnosis requires significant cerebrovascular disease to be present that is judged to be causally relevant to the cognitive impairment. As with AD, VaD requires histopathological confirmation and is a postmortem diagnosis. There are a number of risk factors for VaD that are currently incompletely understood. However, hypertension is a major risk factor and can be a targeted for intervention.

1.4 Blood pressure

1.4.1 Definition

The heart acts as a pump to force blood around the body through the circulatory system of arteries, veins and capillaries. As a pump, it works by generating pressure, and the level of blood pressure (BP) depends on a combination of two factors: how forcefully the heart pumps, and how narrowed or relaxed the arteries are. Blood pressure can be measured using a range of devices, but the traditional gold standard is the mercury sphygmomanometer, from which the unit of measurement, millimetres of mercury (mmHg), is derived. BP readings are written as two figures, for example 120/80 mmHg:

The first figure is the systolic blood pressure (SBP) - the maximum pressure in the arteries when the heart contracts and pushes blood out into the body

The second figure is the diastolic blood pressure (DBP) - the minimum pressure in the arteries between beats when the heart relaxes to fill with blood

1.4.2 Changes with age

Blood pressure (BP) increases with age through much of adult life, in particular SBP which continues to rise towards the end of life (whereas DBP may remain the same), and is thought to be associated with reduced arterial compliance. The results from the 7-year follow-up of the Healthy Old People in Edinburgh (HOPE) study showed that SBP continued to rise in participants who remained disease-free into their ninth decade [4]. It used to be thought that rising BP was an inevitable natural consequence of ageing and therefore did not require treatment. However, it has now become accepted that hypertension is a modifiable risk factor for vascular disease.

1.4.3 Hypertension

When resting blood pressure is consistently raised beyond certain limits, the risk of cardiovascular events increases. If this occurs in the absence of a known underlying cause (secondary hypertension), it is referred to as primary or essential hypertension. Essential hypertension accounts for approximately 90% of cases, and although there are a number of contributing lifestyle factors (smoking, diet, obesity, lack of exercise etc.), the exact etiology is unknown. Unless severe, hypertension itself has few symptoms and so can go undetected and therefore untreated for years. However, the complications associated by hypertension can be serious and include atherosclerosis, stroke, aneurysm, heart failure, myocardial infarction (MI), kidney failure and eye damage. The prevalence of hypertension varies depending on the diagnostic criteria used, however in developed countries between 35 and 50% of the over-65s are thought to be hypertensive [5].

1.4.3.1 Treatment

There are a number of antihypertensive medications available, and are categorised according to mechanism of action [6]:

ACE inhibitors - stop the production of the hormone angiotensin II that makes the blood vessels narrow. As a result, the vessels expand, improving blood flow. Tension in the circulation is also lowered by the kidneys filtering more fluid from the blood vessels into urine.

Angiotensin-II receptor antagonists – block the action of angiotensin II. This allows the blood vessels to expand, improving blood flow and reducing BP.

Beta-blockers - block the effect of adrenaline and the sympathetic nervous system on the body. This relaxes the heart so that it beats more slowly, lowering BP.

Alpha-blockers - cause the blood vessels to relax and widen. Combining them with beta-blockers has a greater effect on the resistance in the circulation.

Calcium-channel blockers - reduce muscle tension in the arteries, expanding them and creating more room for the blood flow. In addition, they slightly relax the heart muscle so it beats more slowly, reducing BP.

Diuretics - help the body get rid of excess salt and fluids via the kidneys. In certain cases, they relax blood vessels, reducing the strain on the circulation.

1.4.3.2 BP treatment target guidelines

The BP criteria for defining hypertension and the associated treatment guidelines have changed over time, in line with new evidence of the benefits of treatment in reducing the risk of cardiovascular events. At the time of the study inception, the 'Management guidelines in essential hypertension: report of the second working party of the British Hypertension Society' were current [7]. Evidence from the Systolic Hypertension in the Elderly (SHEP) study [8] and the Medical Research Council (MRC) treatment trial of hypertension [9] showed benefits to treatment in the over 60's at reducing cardiovascular events as well as stroke. However, there were insufficient data on the benefits of treating patients over 80 years of age. The recommendations were that treatment was indicated in the elderly for SBP>160 or DBP>90 mmHg.

1.5 Hypertension and cognitive function

1.5.1 Cross-sectional studies

Detailed characteristics of the cross-sectional studies are presented in Appendix I.

One of the earliest studies of hypertension and cognitive function compared twenty newly diagnosed hypertensive men (DBP > 105 mmHg) with twenty normotensive

controls [10]. Subjects were untreated, with an average age of 50 years. A neuropsychological test battery was used that included subtests of the Wechsler Adult Intelligence Scale (WAIS), simple reaction time, memory and visual-spatial ability. The results showed that hypertensives had slower reaction times and reduced digit spans compared to the normotensives. Although the sample size was small and the subjects were middle-aged males only, the study was among the first to recognise that the relationship between hypertension and cognition warranted further investigation.

A study reporting cross-sectional data from the Framingham Heart Study examined the relationship between neuropsychological test performance and concurrently measured blood pressure [11]. The analysis included over 2,000 subjects aged 55-89 years without history of stroke and controlled for age, sex, education, antihypertensive medication, smoking and alcohol consumption. There was no consistent relationship between blood pressure and cognitive function even when subjects receiving antihypertensive medication were excluded. However, the categorisation of subjects into groups on the basis of single BP readings pre- and post-testing has since been questioned [12].

A large community population study involving over 3,500 subjects aged 65 years or older, investigated the relationship between BP and cognitive function over the entire blood pressure range [13]. Cognitive function was assessed using a story retelling task to measure immediate and delayed memory, digit span to measure attention, and items from the Pfeiffer Mental Status Questionnaire to assess orientation. Despite a small but significant association between increased DBP and decreased digit span score, the results showed no consistent pattern of association across the tests.

Similarly, a population sample of over 900 healthy community-dwelling adults from the Maastricht Aging Study showed no linear relationship between blood pressure and various aspects of cognitive function [14]. The study included subjects unselected for blood pressure status, stratified for age (24-81 years), sex and occupational level. Additional analyses comparing a subgroup of hypertensives and matched normotensive controls showed impairment on a letter-copying task, but not on any other cognitive tests.

Conversely, in a community sample of approximately 600 healthy untreated subjects over 70 years of age, Mini Mental State Examination (MMSE) scores correlated negatively with systolic blood pressure but not DBP [15]. To investigate the possibility that the relationship followed a J-shaped curve, subjects were divided into low, medium and high BP groups. The effects of age and NART-predicted IQ were controlled for in multivariate analyses which found significant associations between low MMSE score and both high systolic and high diastolic blood pressure. Compared with the medium BP groups, MMSE scores were not significantly lower for the low systolic and diastolic groups, suggesting that a threshold may exist at which the risk of decline becomes significant.

Analysis of a population sample of over 1100 subjects aged 65-95 years showed that diastolic but not SBP predicted cognitive impairment (MMSE < 24) independently of sex, age, education, Geriatric Depression Scale score and antihypertensive medication, but only for subjects aged 75 years or over [16]. However, the sample was characterised by low educational levels (only 17.7% had over 5 years in education) compared to other population studies. As MMSE scores are influenced by education level [17], the degree of impairment in the study may be overestimated.

Cross-sectional data from the randomisation period of the European Trial in Elderly with Systolic Hypertension (Syst-Eur Vascular Dementia Project) showed that blood pressure contributed weakly to MMSE score compared with age and education level [18]. For women systolic blood pressure correlated negatively and independently with cognitive function; the lack of a significant correlation for men may be due to the lower proportion of males in the study. The analysis included 2225 subjects aged between sixty and 100 years old, without evidence of dementia based on DSM-III criteria where MMSE score was less than 24. The sample was characterised by a high level of cognitive functioning due to the selective recruitment of subjects, which may have led to a ceiling effect on the MMSE scores.

An extensive neuropsychological test battery, sensitive to mild cognitive impairment, was used in a small study (n = 44) of well-matched hypertensive and normotensive healthy elderly subjects [19]. Subjects were over 60 years old, with 3-10 years in education and MMSE scores over 23. In the hypertensive group, for those on

treatment (7 out of seventeen), antihypertensive medication was substituted for placebo for the two weeks prior to testing. The results showed that the hypertensives had lower levels of performance on the attention tasks of the battery compared with the normotensive group, but were not impaired on the memory or judgement tasks.

In a larger study of similar design, 90 matched pairs of hypertensives and normotensives were recruited from general practitioners' registers [20]. Subjects were stratified by 10-year age bands from 40-79 years. Hypertension was defined as DBP ≥ 100 mmHg or SBP ≥ 180 mmHg, or taking antihypertensive medication at the time of assessment; controls were defined as having DBP ≤ 90 mmHg and no record of hypertensive BP measurements or antihypertensive treatment in the preceding year. The hypertensives showed a consistent trend of impairment on the cognitive function tests, with significant differences on the Verbal Learning task (immediate recall, total recall after repetition, and change in recall after interference). As 89% of the hypertensive group were taking antihypertensive medication, it remains unclear whether the observed deficits were due to the effect of hypertension or the antihypertensive medication itself. In addition, allocation of subjects to groups was based on BP readings from one occasion only.

1.5.1.1 Summary

The evidence for a relationship between blood pressure and cognitive function from cross-sectional studies is equivocal. Large population and community-based epidemiological studies report associations with diastolic blood pressure [13, 16], systolic blood pressure [15, 18] or no association at all [11, 14]. Smaller studies comparing groups of hypertensive and normotensive subjects have generally found hypertensives to be impaired, but the nature of the impairment varies according to the measures of cognition used [10, 19, 20].

Interpretation of the results across studies is difficult as there are variations on a number of important criteria. Appendix I details the main characteristics of the studies described above. Perhaps most importantly, the definition of hypertension itself differs between studies. The lower SBP bound ranges from as low as ≥ 140 mmHg in some studies [13, 14] to ≥ 180 mmHg in another [20]. Definitions based on DBP also vary ranging

from ≥ 90 mmHg to ≥ 105 mmHg. Although the BP criteria for a diagnosis of hypertension have become lower historically, and the recommended cut-off levels increase with age [21], the differences between studies do not appear systematic. The implications of differing criteria become most apparent in studies that have defined hypertensive and control groups based on a single cut-off point. For example, the control group defined as SBP ≤ 165 and DBP ≤ 95 mmHg in the study by Palombo et al (1997) would have been classified as hypertensive in analyses performed by Scherr et al (1991).

Studies also differ in the number of BP measurements used to classify subjects. In particular the use of measurements from a single occasion has been criticised as BP is known to be affected in some individuals by virtue of the fact that it is being measured – white coat hypertension [22]. However in large community studies, time and resource constraints will often determine the number of BP readings that can be taken.

The inclusion of both treated and untreated hypertensives also makes interpretation difficult. From cross-sectional data it is not possible to delineate the effects of hypertension per se and the effects of the antihypertensive agents on cognition. Although the presence of treatment can be controlled for statistically, the mechanism by which the antihypertensive achieves its effect will vary according to the agent, and may have differential effects on cognitive function.

There is also wide variation in the age ranges of subjects across the various studies. The absence of a linear relationship between BP and cognition over the full adult age range [14] yet some significant differences between hypertensives and normotensives in older adults, suggests that the strength or nature of the relationship may change with age. However, even in those studies concentrating only on the 'elderly' there is variation in the age criteria used to define the samples.

A further complication relates to the tendency for BP to fall preceding the onset of dementia [23]. In studies that have not excluded subjects with possible dementia there is the likelihood that a relationship between raised BP and cognitive impairment will be weakened.

In addition to the specific problems of interpretation highlighted above, cross-sectional studies in general suffer from methodological limitations inherent in their design. In most cross-sectional studies, the temporal relationship of variables is not discernible as the data provide only a 'snapshot' of a particular point in time. Whilst associations between variables can be identified, it is not possible to determine cause-effect relationships. However, cross-sectional studies are of value in identifying relationships for further investigation and generating hypotheses. To investigate temporal relationships between hypertension and cognitive function, longitudinal studies are required.

1.5.2 Longitudinal studies

Studies investigating the relationship between hypertension and cognitive function over time can be divided into two groups according to whether the assessment of cognitive function was retrospective or prospective.

1.5.2.1 Retrospective studies

The retrospective studies have, in general, capitalised on large samples of subjects originally recruited to epidemiological studies of cardiovascular risk factors where repeated measures of blood pressure have been taken. Assessment of cognitive function has been added to the studies much later in the follow-up period. As a result, the retrospective studies provide an opportunity to investigate the relationship between blood pressure levels during middle-age and cognitive function in later life within the same subjects.

The previous analysis of cross-sectional data from the Framingham Heart Study failed to show a consistent relationship between cognitive function and BP measured concurrently [11]. Due to concerns over the validity of grouping subjects on the basis of BP readings from a single occasion, the authors examined the relationship between the cognitive data and blood pressure measurements averaged over the 26 years up to, and including, the cognitive testing phase [12]. The analyses controlled for demographic variables and were stratified by use of antihypertensives in the two years prior to testing. The results showed that for subjects taking antihypertensive medication at follow-up, there was no association between cognitive function and blood pressure.

However, for subjects not on medication at assessment, both chronicity of hypertension and average systolic and DBP were inversely related to cognitive performance. For subjects that had previously been taking antihypertensive medication, there was a relationship between cognitive impairment and the probability of not being on medication at the time of testing.

In order to minimise the confounding effects of antihypertensive therapy, the data were re-analysed including only those subjects who were untreated during an 8-year BP measurement phase [24]. The time window of the BP phase was selected in order to maximise the number of untreated subjects and as a result, reduced the follow-up period between the end of the BP phase and cognitive testing to 14 years. For analysis, the full sample was also divided into two groups: subjects who were untreated during the BP measurement phase only; and subjects who remained untreated throughout the study. The results showed that average BP levels and chronicity of hypertension were inversely related to both a composite score of cognition, and individual tests of memory and attention measured 14 years later. This was the case for the full sample, for the subsample untreated during the BP phase only, and for the subsample who remained untreated throughout.

The data were re-examined further in two studies to investigate the interaction effects of age with BP level and chronicity of hypertension [25, 26]. Age, ranging from 55 to 88 years, was analysed both as a continuous variable and stratified into ten-year age bands. Multiple linear regression and binary logistic regression analyses produced very similar results: the interaction effects of age with BP were trivial or non-significant; the independent associations between BP and cognition remained; age was inversely associated with performance and increased the odds of performing poorly more than the BP variables.

The relationship between midlife BP and late-life cognitive function was also examined in a large population sample of Japanese-American men [27]. Participants in the Honolulu Heart Program were examined for factors relating to coronary heart disease and stroke then followed up as part of the Honolulu-Asia Aging Study over a 25-year period. Cognitive function was measured at the final follow-up using the Cognitive Abilities Screening Instrument (CASI), a composite of the Hasegawa

Dementia Scale, Mini-Mental State Examination, and the Modified Mini-Mental State Examination. Subjects were categorised into low, normal, borderline and high groups according to their systolic and diastolic BP, and into good, intermediate and poor according to CASI scores. Approximately 58% of the sample had never been treated with antihypertensive medication, and treatment status was not associated with impaired cognitive function. After adjustment for age and education, the results showed that the risk for intermediate and poor cognitive performance increased with the level of midlife systolic blood pressure category. Every 10 mmHg increase in systolic BP was associated with 7% increased risk of intermediate and 9% increased risk of poor cognitive function. When prevalent cerebrovascular accident, coronary heart disease and subclinical atherosclerosis were taken into consideration, the increased risk of poor cognition was 5%. There was no association with midlife diastolic BP.

Conversely, high midlife diastolic blood pressure but not SBP predicted impaired cognitive function 20 years later in the Uppsala community study of Swedish men [28]. Cognitive function was analysed as a continuous variable and dichotomised at the lowest quintile, using a composite score derived from transformed MMSE scores and the Trail-Making Test forms A & B. The multivariate model adjusted for age, education, previous occupation, stroke diagnosis and medications affecting blood pressure. Subjects were split into five categories according to baseline diastolic BP, measured to the nearest 5 mmHg. A statistically significant trend indicated that cognitive performance at follow-up was highest for those with the lowest DBP at baseline; those with high DBP had the poorest performance. In addition, cross-sectional data at follow-up showed that high systolic and DBP levels from 24-hour ambulatory blood pressure monitoring (ABPM), non-dipping, insulin resistance and diabetes were associated with low cognitive function.

Individual changes in systolic blood pressure over time were studied in healthy males from the Western Collaborative Group Study [29]. Based on numerous BP readings over a 25-30 year follow-up period, subjects were classified by SBP as: trackers – high in midlife and at follow-up; normals – consistently low/ medium, or increasing over the follow-up period; decreasers – high/ medium in midlife decreasing to medium/ low at follow-up. Cognitive function was assessed at follow-up using a number of

neuropsychological tests, reduced to the three factors of verbal memory, psychomotor speed and verbal fluency that emerged from a principal components analysis. After adjustment for age, education, depression, stroke and antihypertensive medication, the results showed that high SBP trackers performed worse than normals on the verbal memory factor, decreasers performed worse than normals on psychomotor speed, but there were no differences between the groups on verbal fluency.

A much shorter follow-up period was employed in an analysis of data from the Healthy Old People in Edinburgh (HOPE) study [30]. Subjects were aged between 70 and 88 years at baseline, with no reported health problems or prescription medication. Raven's Progressive Matrices (RPM) and subtests of the Wechsler Memory Scale were administered four years later to assess fluid intelligence and memory respectively. The results showed that for subjects who remained healthy throughout the follow-up period, demographic variables, pre-morbid IQ and BP accounted for 39% of the variance in RPM scores but only 12% of the memory variance. Subjects with high baseline diastolic BP performed worse on the RPM than those with medium or low DBP. In addition, subjects diagnosed as hypertensive by their family doctor during the follow-up period had significantly lower RPM scores than healthy subjects with medium or low DBP; healthy subjects with high DBP scored between the two groups. Whether or not the poor performance of the diagnosed hypertensives is due to sustained hypertension is difficult to ascertain, as although they are likely to have a greater duration of hypertension, they are also more likely to be treated with antihypertensive medication.

Cognitive decline was the focus of study in a subgroup of males from the National Heart, Lung, and Blood Institute (NHBLI) Twin Study [31]. Subjects were categorised as low, normal, high or mixed according to SBP measurements taken on three occasions over a 15-year period. Cognitive function was assessed on two occasions in the following 10-year period using the MMSE, digit-symbol substitution (DSS) subtest of the WAIS, Benton Visual Retention Test (BVRT) and verbal fluency. For all midlife SBP groups, there was significant decline on the DSS with the high SBP group declining most and the low SBP group declining least. The low SBP group showed no significant decline in MMSE scores; all other groups declined, with the mixed group showing the greatest change. There was a tendency for verbal fluency to increase over

time, but no differences between the groups. Similarly, there were no differences on the BVRT.

1.5.2.2 Summary

The retrospective studies often involve large numbers of subjects as, in many cases, the samples have been taken from epidemiological studies. The main characteristics of the studies described above are presented in Appendix II. Overall, they suggest an association between blood pressure levels in middle-age and cognitive function in later life. The variables used as measures of blood pressure, such as SBP, DBP, average BP readings over follow-up period, and chronicity of hypertension vary between studies, as do the measures of cognitive function. However, the general nature of the relationship appears consistent: higher blood pressure levels in midlife are associated with poorer cognitive function in later life.

Despite the large numbers of subjects involved, there are some issues regarding the generalisability of the findings. In particular, only two of the six reported studies (excluding reanalyses) included female subjects [12, 30], representing 17.1% of the total number of subjects studied. This is due to the original epidemiological studies of cardiovascular risk factors concentrating on males. Although the two studies that did include female subjects found no sex differences, it nevertheless warrants caution when applying the overall conclusions to the population as a whole.

In general, the design of longitudinal studies provides an opportunity to examine the temporal relationship between variables. However, the retrospective longitudinal studies do not necessarily allow conclusions to be drawn regarding cause and effect. As the measurements of blood pressure are taken many years before the measures of cognition, there is a tendency to infer that raised blood pressure in midlife causes poor cognitive function in later life. However, as cognitive function was not measured in midlife, the possibility that poor cognition already existed in subjects with raised BP cannot be ruled out. To address this issue, prospective longitudinal studies are required.

1.5.2.3 Prospective studies

In contrast to measurements from a single timepoint used in the majority of retrospective studies, prospective studies involve the assessment of cognitive function on successive occasions. This enables investigation of the relationship between hypertension and cognitive function over time. As subjects act as their own controls, the study design allows the effects of blood pressure on changes in cognitive function within the individual to be assessed.

In a population sample of dementia-free subjects over 75 years of age from the Kingsholmen Project in Sweden, overall decline in MMSE scores over the mean follow-up period of 3.4 years was minor (0.4 MMSE points per annum) [32]. Approximately a quarter of the sample declined more than 10%, with the greatest declines exhibited by subjects over 85 years of age or with stroke. Analyses showed that age, lower education and stroke predicted decline for women; lower education and stroke, but not age predicted decline for men. The sex differences may be due to lower numbers of males in the study. Although baseline BP did not predict decline, in women there was a significant correlation between reduction in systolic blood pressure and decline, independent of cardiovascular disease and antihypertensive medication use. As the sample included subjects unselected for BP status, it is unclear whether the results identify low blood pressure as a risk factor for decline, or whether the blood pressure reduction is itself a result of the early dementing process.

Blood pressure variables also failed to predict decline on the Paired Associate Learning Test (PALT) in the Medical Research Council (MRC) Elderly Hypertension Trial [33]. Hypertensive subjects, untreated and free from serious cardiovascular and cerebrovascular disease at baseline were followed up for 4.5 years. Decline was calculated for each subject as the slope of the regression line of PALT scores on time. Decline was associated with age, male gender, rural residence, depression and low intelligence. There were no associations for the cardiovascular variables including baseline systolic and diastolic blood pressure, mean SBP over the follow-up period, or trial therapy. There were also no associations within the placebo group between untreated BP levels and later decline.

A further follow-up of a subsample of subjects from the MRC trial was performed nine to 12 years after baseline [34]. The MMSE was used as the outcome measure after log-transformation, and all analyses accounted for baseline cognitive function using a factor derived from a principal components analysis of the baseline PALT, Trail-Making Test (TMT) and Raven's Progressive Matrices (RPM) scores. Analyses also adjusted for apolipoprotein-E allelic status, alcohol, education, diet, lifetime smoking, social class and 'history of dementia' loading. The results showed that poor cognition at follow-up was associated with greater history of dementia loading, older age, abstinence from alcohol before the age of 60, and less decline in systolic BP over the trial period. However, the effect of SBP decline became non-significant when 41 cases of dementia were excluded from the analysis.

Decline on the MMSE was also used as the outcome measure in the Epidemiology of Vascular Ageing (EVA) population study [35]. The analyses adjusted for age, gender, education, income, alcohol consumption, depressive symptomology, APOE and baseline cognitive function, after excluding subjects with stroke during the four year follow-up period. Hypertension was defined as SBP ≥ 160 mmHg and/or DBP ≥ 95 mmHg or taking antihypertensive medication. The results showed that the risk of decline of 4 or more MMSE points was 2.8 times greater for the hypertensive group compared to the normotensives. The association remained even when the threshold for hypertension was reduced to SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. In addition, compared to subjects who remained normotensive at baseline and 2 years, subjects with chronic high blood pressure were at greater risk of decline. In relation to the use of antihypertensive medication, there was no overall association between treatment at baseline and decline at 4 years. However, when compared to subjects receiving treatment at either baseline or 2 years, those hypertensives that remained untreated were more likely to show decline at 4 years.

Decline on the MMSE over a four year period was also examined in the Healthy Old People in Edinburgh (HOPE) study [36], in addition to the retrospective study of fluid intelligence and memory reported previously [30]. As before, all subjects were aged between 70 and 88 years, with no reported health problems or prescription medication at baseline. The analysis accounted for baseline MMSE performance, and detected

both ceiling effects and regression to the mean effects on MMSE scores. The magnitude of decline was relatively small with a mean drop of 0.44 MMSE points over four years. The main multiple regression model indicated that older people declined faster, higher NART-IQ scores conferred protection against decline, and high systolic blood pressure increased risk of decline. There were no significant differences in the models predicting decline between subjects who had started medication and those who remained untreated, although for those who remained both disease and medication-free, systolic BP became marginally non-significant as a predictor.

The relationship between blood pressure and both cognitive performance and cognitive decline was investigated in a large sample of non-institutionalised elderly subjects from the Hypertension Detection and Follow-up Program (HDFP) in Boston [37]. The Pfeiffer Mental Status Questionnaire and the East Boston Memory Test were used to measure cognitive function at baseline, three and six years. Blood pressure was measured at baseline and, for the majority of subjects, BP readings were also available from nine years previous. After controlling for age, gender, education and time of evaluation, the analyses showed that overall there was no strong linear association between BP and cognition. For the analysis of change over time, there was little evidence of an effect of BP on either test. However, in terms of the level of cognition, subjects with high systolic or diastolic blood pressure either at baseline or 9 years prior, made significantly more errors on the Mental Status Questionnaire than subjects in the medium BP group. There was a suggestion of a U-shaped relationship as subjects in the low systolic and diastolic BP groups also had higher error scores than those with medium BP. The use of antihypertensive medication did not appear to alter the relationship between BP and cognition.

The possibility of a U-shaped relationship was also examined in the Atherosclerosis Risk in Communities (ARIC) study, a very large multiethnic, multi-centre investigation of cardiovascular risk factors [38]. Although primarily a study of middle-aged subjects, over 4,800 subjects were aged between 64 and 76 years at the 6-year follow-up stage, representing approximately half of the study sample. For the analyses hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or taking antihypertensive medication at baseline. Decline was measured as change in scores on the delayed word recall test, digit-symbol substitution (DSS) subtest of the WAIS-R,

and word fluency. After controlling for demographic variables and medication, the presence of diabetes at baseline was associated with decline on the DSS test and word fluency, and hypertension was associated with greater decline on the DSS test. There was no evidence of a U-shaped relationship using the same cut-off points as the HDFP study [37], as the low BP group showed the least cognitive decline on the digit-symbol substitution and word fluency tests.

1.5.2.4 Summary

The prospective studies permit the investigation of the relationship between blood pressure and cognitive decline over time. The measurement of cognitive function at multiple time points enables subjects to act as their own controls. As such, the natural variation that exists in cognitive function test scores within the study population is controlled for. The results of the prospective studies however are somewhat mixed, with three studies finding no association between blood pressure variables and decline [32-34], three studies indicating a relationship does exist [35, 36, 38], and one study finding a relationship between blood pressure and cognitive performance, but not decline [37]. The main characteristics of the studies are presented in Appendix III.

Across the studies the overall level of decline throughout the follow-up period is relatively minor. When the studies reporting negative and positive results are compared, the studies indicating no relationship tend to have smaller subject numbers. It is possible that a combination of fewer subjects and small effect sizes have led the negative studies to be under-powered to detect a relationship. However, there are two notable exceptions: the MRC trial involved over 2,500 subjects and found no relationship between blood pressure variables and decline [33], whereas the HOPE study included less than 400 subjects and found raised systolic BP to be a predictor of relatively minor levels of decline [36].

The combination of negative and positive findings does not appear to be related to the measures of cognitive function used, as two studies in each category have used the same measure: the MMSE. However, the MMSE was originally designed as a screening tool and is known to have reduced sensitivity when cognitive impairment is mild [39]. Therefore, if the negative studies were inadequately powered, it is possible

that a relationship would have been detected had a more sensitive measure of cognitive function been employed. In addition, the MMSE only provides a global measure of functioning. As there is evidence that some aspects of cognitive function deteriorate before others [40], it is possible that more comprehensive or more specific measures of cognition would have detected a relationship.

A further complication for interpreting prospective observational studies is the previous and concurrent use of antihypertensive medication, as this is not controlled by the investigators but tends to rely on standard clinical practice. It cannot be assumed that this practice is the same between countries, or indeed sites within a country as the extent to which BP treatment guidelines are adhered to is known to vary. Given the known cardiovascular benefits of antihypertensive treatment, observational studies of untreated hypertensive patients are now regarded as unethical.

Although the relationship between blood pressure and decline was not found in all studies, among the positive studies the relationship is consistent: higher blood pressure increases the risk of cognitive decline. The possibility of a U-shaped relationship was suggested [37] but refuted [38]. Due to the prospective nature of the studies where cognition is monitored over time, the relationship between hypertension and cognitive decline would appear to be causal. However, as the mechanism by which hypertension affects cognitive function is not yet known, it must be borne in mind that hypertension and cognition may both be influenced by a third factor.

Alongside the investigations of blood pressure, evidence from both the negative and positive studies associated decline with increasing age, lower educational achievement and co-morbidity; higher IQ was found to be protective. Of the risk factors identified, blood pressure lends itself more readily to intervention. However, the existence of a relationship between blood pressure and cognitive function does not necessarily imply that treatment with antihypertensive medication will reverse or halt subsequent decline. Therefore the effect of antihypertensive treatment on cognitive function is of great interest.

1.6 RCTs of antihypertensive treatment and cognitive function

Randomised controlled trials (RCT) provide the strongest methodology for determining the effect of antihypertensive treatment on cognition. Detailed characteristics of the RCTs are presented in Appendix IV.

1.6.1 Systolic Hypertension in the Elderly Program (SHEP)

The SHEP study provided the earliest data from a large multicentre RCT looking at cognitive outcomes [41]. Community-screened participants with isolated systolic hypertension were randomised to receive a diuretic and/or a beta-blocker versus placebo, and assessed annually with a battery of paper-and-pencil neuropsychological tests. Despite a large sample size of 4736, the last observation carried forward (LOCF) analysis showed no difference between the treatment and placebo groups on cognitive outcomes over the average 5 year follow-up period, with cognitive function being well-maintained in both groups. However, it has since been suggested that differential loss to follow-up could have biased the study towards a null finding of a treatment effect [42], and the use of LOCF would contribute to this.

1.6.2 Medical Research Council (MRC) hypertension treatment trial

The MRC hypertension treatment trial was a single-blind, randomised, placebo-controlled trial of a diuretic versus the beta-blocker atenolol in approximately 2500 hypertensives aged 65-74 years [43]. BP was reduced in both treatment groups compared to placebo at 9 months, but there were no significant differences between groups on a range of neuropsychological tests.

Similar results were found when followed-up over 4.5 years [44]. Using a calculation of decline based on the regression of the test score on time, there were no significant differences between groups on the cognitive outcomes, either for the Intention-to-Treat (ITT) analysis or per-protocol analysis.

1.6.3 The Hypertension Old People in Edinburgh (HOPE) study

The HOPE study was a single-centre, randomised, double-blind trial of captopril versus bendrofluazide treatment in community-dwelling hypertensives between 70

and 85 years of age and an MMSE of 20-28 at baseline [45]. A range of neuropsychological tests was used including the Paired Associates Learning Test (PALT) and Trail-Making Test used in the MRC study, with testing taking place in participants' homes. There were no differences between treatment groups on cognitive tests at any timepoints (0, 4, 12 & 24 weeks) using a repeated measures ANOVA, although participants with the greatest DBP reductions showed improvement on the PALT compared to those with the smallest DBP changes. There were no effects of SBP. The study is notable as participants were selected with MMSE scores in a range that was designed to avoid ceiling effects.

1.6.4 The Systolic Hypertension in Europe (Syst-Eur) trial

In the international, multicentre Syst-Eur trial, participants over 60 years old were randomised to treatment for isolated systolic hypertension with the calcium-channel blocker nitrendipine, with the addition of enalapril/hydrochorothiazide (HCTZ) or both if required, versus placebo. Cognition was assessed annually using the MMSE, and patients with scores of 23 or less were examined for dementia. The median follow-up period was 2 years in the double-blind study, as the trial was concluded earlier than planned when a pre-specified interim analysis showed that the primary outcome had been met. The study reported a 50% reduction in the risk of dementia with active treatment and a mean between-group BP difference of 8/4 mmHg [46]. However, there was little change in the mean MMSE scores in either group. The dementia findings were reinforced when follow-up was extended for a further 2 years as an open-label study [47].

However, the robustness of the findings has since been questioned as the actual number of dementia endpoints was low (n=32) and the confidence intervals of relative risk were wide, ranging from no effect to a 76% reduction [48].

1.6.5 Early phase studies

In addition to the large RCTs, a number of smaller studies have been reported but suffer from methodological problems such as being open-label [49], small sample size (n=13) [50], or inadequate reporting. In sixty-nine participants aged 30 to 73 years with mild to moderate hypertension, improvements were seen in MMSE scores in

participants randomised to losartan treatment (23±3 to 27±3, p<0.001) compared to hydrochlorothiazide (24±3 to 25±2.7, non-significant) from baseline to study close at 26 months [51]. Although the MMSE changes scores appear impressive, the study did not adequately report the direct treatment comparisons. From the data presented it appears that between-group conclusions were based on differences between the p values of the within-group statistics.

1.6.5.1 Summary

The evidence from the treatment studies is the strongest to date, but as yet is far from convincing. The Syst-Eur study gives the most encouragement that treatment of hypertension may be effective for the prevention of dementia, but clearly the finding needs to be replicated. The lack of association of treatment with MMSE scores could potentially be due to the limitations of the measure itself, and suggests that more sensitive methods of assessing cognition need to be incorporated into clinical trials where cognitive outcomes are considered.

1.7 Rationale and hypothesis

There is a large amount of literature surrounding the relationship of BP, antihypertensive treatment and cognition, and despite methodological issues between studies, it suggests that hypertension could be a potential target for intervention to prevent cognitive decline. Randomised controlled trials are the gold-standard for determining treatment efficacy. However, the results are mixed, and the Syst-Eur study provides the strongest indication that antihypertensive treatment could be effective at reducing the risk of dementia. To date, cognitive decline has been a secondary outcome in studies that have used global assessment tools, not designed specifically for clinical trial use. Therefore, investigating the effect of antihypertensive treatment on cognition with sensitive cognitive assessments was clearly warranted. The Study on Cognition and Prognosis in the Elderly (SCOPE) provided an opportunity to test the hypothesis that in older adults with mild hypertension, compared to placebo, candesartan-based antihypertensive treatment would reduce the rate of cognitive decline.

CHAPTER 2: METHODS

2.1 The SCOPE Study

The Study on Cognition and Prognosis in the Elderly (SCOPE) was an international, multicentre, prospective, randomised, double-blind, placebo-controlled trial investigating the effects of candesartan cilexetil on major cardiovascular events and cognition in the elderly. The SCOPE trial was sponsored by AstraZeneca.

2.1.1 Rationale

At the time of study inception, the lower threshold of DBP below which the risk of stroke is not continuously reduced, had not been determined. The Hypertension Optimal Treatment (HOT) Study showed that the lowest risk of fatal and non-fatal stroke was at a DBP < 85 mmHg in patients with a mean age of 62 years and an initial mean DBP of 105 mmHg [52]. The question remained unanswered as to whether antihypertensive therapy provided protection against stroke in elderly individuals with DBP in the range 90-99 mmHg.

With regard to cognitive function, the Syst-Eur Study showed that treatment of isolated systolic hypertension with the calcium-channel blocker nitrendipine reduced the incidence of dementia and AD by 50% over the two years of follow-up [46]. Taken alongside the cross-sectional and prospective longitudinal evidence showing an association between hypertension and cognitive function, a clinical trial of the effects of antihypertensive therapy on cognition in elderly patients with mild hypertension was clearly warranted. The SCOPE trial included cognition as a secondary outcome to investigate this.

2.1.2 Candesartan

Candesartan cilexetil is an angiotensin II type I (AT_1) receptor blocker, the newest class of antihypertensive drugs available for clinical use. Angiotensin receptor blockers have a good tolerability profile, particularly the absence of the dry cough associated with ACE-inhibitors. Candesartan cilexetil provides a dose-related antihypertensive effect up to 16mg [53] and shows a smooth profile of BP reduction that persists over the 24-hour dosing period. The lack of significant orthostatic effects is

especially important in elderly patients to avoid injuries from falls [54]. There is also evidence from animal studies that angiotensin II impairs learning and memory performance [55] and that AT_1-receptor blockade may improve performance [56]. The combination of suitability for the treatment of hypertension in the elderly and the plausibility of possible cognitive effects made candesartan an ideal candidate drug around which the SCOPE trial was designed.

2.1.3 Objectives of the main SCOPE study

The main objective was to assess the effect of candesartan on major cardiovascular events (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) in elderly patients with mild hypertension. Secondary objectives were to assess the effect of candesartan on: the incidence of dementia according to modified ICD-10 criteria; change in cognitive function as measured by the MMSE; significant cognitive decline defined as a reduction in MMSE score ≥ 4 points from baseline score on two consecutive occasions; total mortality; cardiovascular mortality; fatal and non-fatal myocardial infarction; fatal and non-fatal stroke; impaired renal function; hospitalisation; quality of life; and health economics.

2.1.4 Participants

Individuals were recruited from participating centres in 15 countries in Europe, Israel and North America between March 1997 and January 1999. The target population was males and females, aged 70-89 years, with an MMSE score ≥ 24 and treated or untreated hypertension (defined as a sitting SBP 160-179 mmHg and /or DBP 90-99 mmHg) on two consecutive visits separated by a minimum of 14 days. The requirement to meet criteria on consecutive occasions beyond the screening visit was designed to exclude participants with initial high BP readings that subsequently returned to lower levels of their own accord i.e. participants with ‘white coat’ hypertension. Treated patients were standardised to hydrochlorothiazide 12.5 mg once daily before randomisation. Exclusion criteria are shown in Table 1.

2.1.5 Study design

2.1.5.1 Initial screening / enrolment visit

At this initial visit, eligibility and exclusion criteria were checked. Written, informed consent was obtained and blood pressure, heart rate and MMSE assessments were performed. Individuals receiving treatment for hypertension were switched to treatment with hydrochlorothiazide.

2.1.5.2 First qualifying visit

Eligible individuals returned after a period of at least 14 days to receive repeat BP, heart rate and MMSE assessments. In cases where the BP and MMSE criteria were met, this constituted their first qualifying visit. All individuals, whether fulfilling the inclusion criteria or not, were invited to return in a further 14 days, and at 14-day intervals thereafter until the BP and MMSE inclusion were met on two consecutive visits.

Table 1: Exclusion criteria for the SCOPE study

General exclusion criteria
Stroke or myocardial infarction within 6 months prior to randomisation
Decompensated congestive heart failure
Other serious concomitant diseases considered by the investigator to affect survival during the next 3-4 years
Alcoholism, drug abuse or any other problems which may compromise patients' compliance
Currently participating in other clinical study
Clinically significant impaired renal function (S-creatinine > 180 μmol/l for males and > 140 μmol/l for females)
S-ASAT or S-ALAT more than three times the upper normal limit for the laboratory.
Blood pressure-related exclusion criteria
Need of antihypertensive treatment other than hydrochlorothiazide
Standing systolic BP <140 mmHg after 2 minutes, or a history of symptomatic orthostatic hypotension
Sitting SBP > 180 mmHg or DBP > 100 mmHg
Secondary hypertension
Known hypersensitivity to the study drug
Known contraindications to HCTZ

Table 1 continued: Exclusion criteria for the SCOPE study

Cognitive exclusion criteria
Obvious dementia, even if MMSE score remains above 23
Current treatment with antidementia drugs
Conditions which preclude MMSE e.g. illiteracy, poor vision or hearing, paralysis, aphasia or other speech disorder
Vitamin B12 deficiency, untreated or treated less than 12 months
Hypothyroidism, untreated or treated less than 12 months
Neurosyphilis or AIDS
Severe brain disorder that may interfere with cognitive function
Severe depression within the last 12 months or psychotic disorder
Psychopharmacological treatment instituted within the last 6 months

2.1.5.3 Second qualifying visit / randomisation / baseline visit

If the BP and MMSE inclusion criteria were met at the second consecutive visit, a medical history was taken and individuals underwent a physical examination, 12-lead ECG, laboratory analysis, and the documentation of any adverse events. Data were faxed to the SCOPE Coordinating Centre at Sahlgrenska University Hospital/Östra, Göteburg, Sweden. Individuals fulfilling all of the inclusion and none of the exclusion criteria were randomised using a version of the Pocock-Simon procedure [57] with the prognostic factors shown in Table 2 to guarantee balance between the candesartan and placebo groups. Investigators were informed of the treatment allocation using numeric patient identifiers by return fax to ensure double-blind status. Participants were randomised to receive either 8 mg candesartan cilexetil or placebo once daily.

2.1.5.4 Treatment schedule

Figure 3 shows the study design. After randomisation to 8 mg candesartan or placebo once daily, participants with SBP > 160 mmHg or a reduction in SBP < 10 mmHg

from baseline, or DBP > 85 mmHg, had treatment doubled to two study tablets (16 mg candesartan or placebo once daily). If SBP remained ≥ 160 mmHg or DBP ≥ 90 mmHg, open label HCTZ 12.5 mg once daily was added. To further achieve the target BP additional antihypertensive medications, excluding other AT_1-receptor blockers or ACE-inhibitors, were permitted at the discretion of the investigator.

Table 2: Prognostic factors used in randomisation procedure

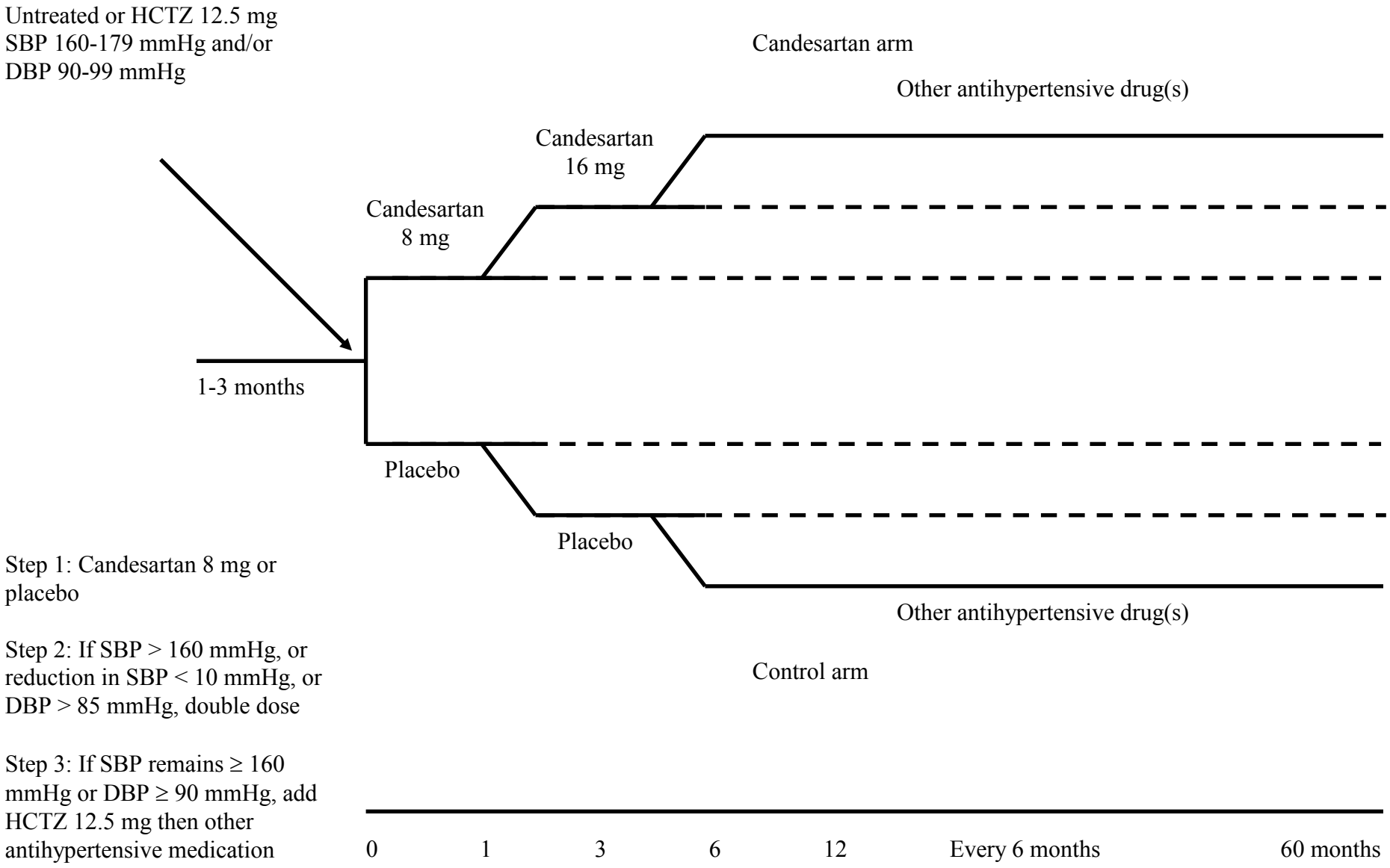
Prognostic factor
age
gender
previous myocardial infarction
atrial fibrillation
previous stroke
treatment with non-steroid anti-inflammatory agents including aspirin
MMSE score
level of education (number of years in formal education)
body mass index
treatment with lipid-lowering drugs
chronic treatment with psychopharmacological therapy
previously treated with antihypertensive drugs
smoking
language area

2.1.5.5 Study visits

Participants returned for scheduled study visits at 1 month (± 7 days) from the randomisation visit, 3 months (± 7 days), then every 6 months (± 1 month) until study

close. Blood pressure and heart rate were recorded at every visit; MMSE was assessed every 6 months; physical examination, ECG and laboratory analysis were repeated at 1, 12 and 24 months. Additional study visits were permitted at the investigators' discretion according to medical need. Participants were free to withdraw from the study at any time but were encouraged to attend follow-up visits for observation if study medication ceased.

Figure 3: Main SCOPE trial study design



2.1.5.6 Study closeout visit

At the end of the follow-up period, all participants, current and withdrawn, were invited back for a final study visit to reduce loss to follow-up. Blood pressure, heart rate, MMSE, physical examination, ECG, and laboratory analyses were performed. Participants taking study medication were instructed to cease at this visit; replacement scripts for bendrofluazide were provided for participants taking HCTZ prescribed under the study protocol. Blood pressure was monitored on three occasions in the following 6 weeks (± 7 days) before responsibility for BP care was handed back to participants' general practitioners.

2.1.6 Protocol amendments

Based on data from the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) [58] and a predicted event rate of approximately 40 major cardiovascular events per 1000 patient years, randomised participants were scheduled to be followed-up for a minimum of 24 months. As the event rate was lower than expected, follow-up was extended to a minimum of 36 months, provision for which was made in the original study protocol [59], resulting in a follow-up range of 3-5 years.

The BP target in the original protocol was <160/90 mmHg based on accepted international guidelines current at the time of study design [60]. However, new British Hypertension Society guidelines were released in September 1999 when the study was ongoing that recommended a lower target of <150/90 mmHg and ideally <140/85 mmHg applicable to patients in the study population. As such it would have been unethical to maintain the higher BP target, therefore in Newcastle the BP target of <150/90 mmHg was instituted at participants' next scheduled study visit.

2.2 Newcastle Cognitive Substudy

2.2.1 Introduction

Newcastle was one of the UK centres participating in the SCOPE trial, and the Newcastle Cognitive Substudy ran concurrently with the main trial at this centre.

2.2.2 Rationale

One of the secondary objectives of the SCOPE trial was to assess the effect of candesartan on cognitive function assessed using the MMSE. The MMSE and other similar brief global measures have been widely used in studies of hypertension and cognition. Such measures have distinct advantages when used in large multi-centre trials: they involve short administration time; little training is needed to administer them; they are available in different languages; and they have good inter-site reliability. However, the sensitivity of a particular measure affects the power of a study to detect relationships between variables. Although the utility of the MMSE as a screening tool for dementia is well established, it has been found to be relatively insensitive to mild dementia, suffers from well-recognised ceiling and practice effects, and provides little information about the profile of cognitive function [39]. There is evidence that some cognitive domains are more susceptible to and exhibit decline earlier than others [40] hence the assessment of a range of domains is necessary to investigate the full nature of the relationship between hypertension and cognition.

The Newcastle Cognitive Substudy was designed to extend the assessment of cognitive function beyond the MMSE, using a comprehensive computerised assessment battery and traditional neuropsychological tests of executive function, at one centre participating in the SCOPE trial.

2.2.2.1 Hypothesis

Compared to placebo, candesartan-based antihypertensive treatment will reduce the rate of cognitive decline in older adults with mild hypertension.

2.2.3 Normotensive comparison group

The comparison of the candesartan and placebo groups was designed to determine the effect of candesartan on cognitive decline in hypertensives. Previous studies have generally found hypertensive patients to have mild cognitive deficits compared to their normotensive counterparts. In order to place the magnitude of any study effects in the context of normal ageing and decline, the Newcastle Cognitive Substudy also included a parallel, non-intervention, observational normotensive comparison group. The assessment schedule for the normotensive group followed that of the main SCOPE trial with the following exceptions: blood pressure was not measured at 1 and 3 months as these assessments were included in the SCOPE study participants to assess acute drug effects; no further physical examinations, ECG or laboratory analyses were performed beyond the baseline visit. At the follow-up visits, if BP was raised and confirmed by a repeat BP check after a minimum of 14 days, a letter was sent to the participant's general practitioner informing them of the readings and suggesting monitoring. As the normotensive group was for observation only, no restrictions could be placed on the prescription of concomitant medications, including antihypertensive therapy.

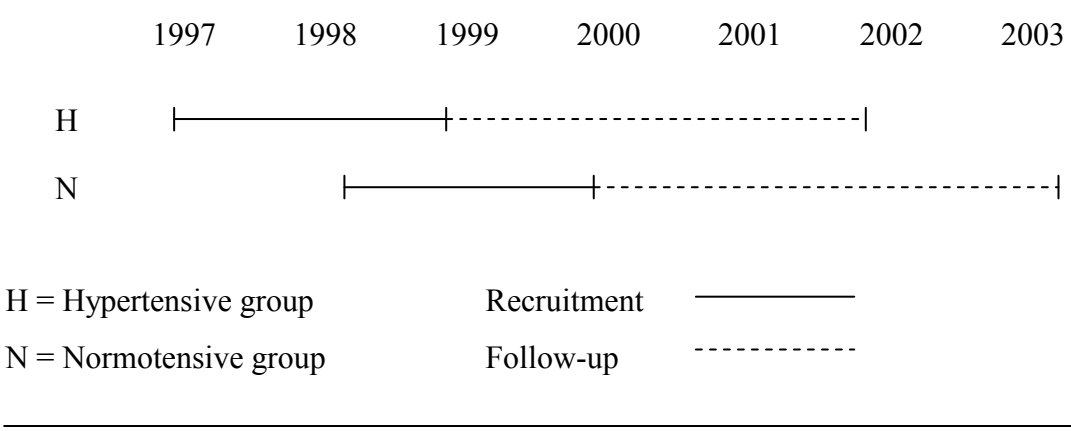
2.2.4 Recruitment

Primary care medical notes were screened by research nurses attending 10 general practice surgeries in the Newcastle and North Tyneside area of the UK. Potentially eligible individuals were invited to participate by a letter from their general practitioner. Appointments for interested individuals were arranged by the research team via telephone to attend the research clinic at the Freeman Hospital for an initial screening / enrolment visit.

As the success of the Newcastle Cognitive Substudy depended to a large extent on successful recruitment to the main SCOPE trial, efforts concentrated on the recruitment of hypertensive participants initially. Individuals identified by case note screening who were potentially eligible for the main SCOPE trial were contacted in the first instance. Potentially eligible individuals for the normotensive control group who were identified through the hypertensive screening process were contacted

toward the end of the hypertensive recruitment period. At this time, a second wave of case note screening was initiated to screen for further normotensive individuals. This led to overlapping recruitment and follow-up periods: hypertensives were recruited between March 1997 and January 1999, and followed up until March 2002; normotensives were recruited between June 1998 and March 2000, and followed up until June 2003 (Figure 4).

Figure 4: Newcastle Cognitive Substudy timelines



2.2.5 Participants

Participants were males and females, aged 70-89 years, with an MMSE score ≥ 24 on two consecutive visits separated by a minimum of 14 days. The exclusion criteria were the same as those for the main SCOPE trial (see Table 1), and identical for both hypertensive and normotensive groups except in regard to blood pressure-related criteria. Based on criteria current at the time of recruitment [7] participants were defined as:

Hypertensive: SBP 160-179 mmHg and/or DBP 90-99 mmHg untreated or HCTZ treated, as per SCOPE protocol

Normotensive: BP < 150/90 mmHg untreated

In accordance with the main SCOPE study protocol, individuals with possible dementia as defined by an MMSE score <24 and/or reported significant decline in cognitive function assessed using the Clinical Dementia Rating scale [61] and IQCODE informant questionnaire [62] were not eligible, although no potential participants were actually excluded by this criteria. Ethical approval was granted by the Newcastle Joint Ethics Committee. Hypertensive participants were recruited to the main SCOPE trial in the first instance and gave informed, written consent; participation in the Newcastle Cognitive Substudy was optional and required participants to sign a substudy consent form. Normotensive participants were recruited to the substudy only and gave informed, written consent. Participants were not paid for their participation in either the main SCOPE study or the Newcastle Cognitive Substudy, although travel expenses were reimbursed on request. GP surgeries received a gratuity for each participant randomised in the main SCOPE study.

2.2.6 Blood pressure measurement

All BP measurements were taken by a doctor or trained research nurse using a manual sphygmomanometer with a cuff of appropriate size in relation to the participant's arm circumference. The diastolic pressure was taken as the pressure at which the Korotkoff sounds disappeared (phase V) [22]. On each occasion, three readings were taken in the seated position after five minutes rest, with the mean of the second and third readings used.

2.2.7 Cognitive assessment

2.2.7.1 Measures

Cognitive function was assessed using the Cognitive Drug Research computerised assessment battery [63] and traditional neuropsychological tests of executive function, the Trail-Making Tests A and B [64] and Verbal Fluency for letters F, A, S and category of Animals [3]. The subtests, in order of presentation, are described in Table 3. The battery took approximately 40 minutes to complete. At the baseline visit only, the New Adult Reading Test (NART) was administered as an estimate of pre-morbid intelligence [65]. Participants were also given two self-report questionnaires to be completed at home and returned by post: the Cognitive Failures Questionnaire (CFQ)

[66] to assess cognitive slips and errors; and the Geriatric Depression Scale (GDS) [67] to assess depressive symptomatology.

The CDR battery was chosen as the main assessment for cognitive function as it was specifically designed for use in clinical trials and has been used extensively in this field [68]. The CDR system demonstrates good test-retest reliability and validity [63], and has been shown to be sensitive to detecting change over time in elderly populations [69]. The system also has multiple parallel forms for each subtest meaning to ensure that the same stimuli are not presented at more than one test session per participant, and the order of stimuli is randomised on the simple attention tasks to prevent learning of stimuli sequences. CDR Ltd also provided ongoing technical support for the duration of the study. The traditional test of executive function were chosen because they were the most commonly-used measures in the public domain, and have been used previously to supplement the CDR battery.

2.2.7.2 Equipment

The CDR battery was presented on a Viglen Dossier CDP laptop computer with a 12.1" TFT colour screen, and participants responded with 'YES' and 'NO' buttons on a proprietary two-button response box (Figure 5) using the index finger from each hand. The Trail-Making Test and Verbal Fluency tests were administered according to the recommended standard task instructions (Appendix V and VI); participants completed the Trail-Making Test in ballpoint pen on photocopies of standard A4 test sheets with the time taken for completion recorded by the administrator; participants' responses to the Verbal Fluency tests were recorded verbatim by the administrator on standard A4 forms.

Figure 5: Equipment used for computerised cognitive testing

Table 3: Description of the subtests from the cognitive battery

CDR subtest	Description
immediate word recall	number of stimuli recalled orally from 12 visually-presented words
immediate word recognition	speed and accuracy of discrimination of 12 novel and 12 previously presented words
simple reaction time	speed of detection of a simple repeated stimulus (the word 'YES')
number vigilance	speed and accuracy of response to a single target digit in a rapidly presented series of digits
choice reaction time	speed and accuracy of discrimination between the words 'YES' and 'NO'
spatial memory	storage and retrieval of visuospatial information in working memory using a house with dark and lit windows as the stimulus
numeric working memory	discrimination of three target digits from a digit sequence using the articulatory loop of working memory
delayed word recall	number of stimuli recalled orally from 12 previously presented words after a delay
delayed word recognition	speed and accuracy of discrimination of 12 previously presented words from 12 further novel words
picture recognition	speed and accuracy of discrimination of 14 previously presented pictures from 14 novel pictures after a delay
Traditional neuropsychological tests	
Trail-Making Test form A	timed task in which participant joins with a ballpoint pen, in numeric order, the encircled numbers 1 to 25 randomly arranged on a page
Trail-Making Test form B	contains encircled numbers and letters to be joined in alternating order
Verbal Fluency for letters (F, A, S)	participant produces orally in 60 seconds as many words beginning with a given letter, avoiding proper nouns, variations and repetitions
Verbal Fluency for category (animals)	as above, with words belonging to the category of animals and beginning with no specific letter

2.2.7.3 Testing environment

Cognitive assessments were performed at the Freeman Hospital, in any one of three similar examination rooms located in the Melville Day Hospital, depending on availability. Participants were seated at a desk with an adjustable chair to allow for a comfortable writing position. The CDR laptop was placed so that the button box was within easy reach with relaxed arms, with forearms resting on the desk, and a viewing distance to the screen of approximately 50 centimetres. Background noise was kept to a minimum. Room temperature and lighting were adjusted as necessary to maintain normal office conditions. To reduce missing data, home visits were permitted to assess cognitive function where it was not possible for participants to attend the hospital clinics. Efforts were made to keep the testing environment as close to the clinic conditions as possible.

2.2.7.4 Procedure

Standardised task instructions were given verbally by the administrator, present throughout each testing session (see Appendix VII). Where it was obvious the participant had not understood the task correctly, the instructions were repeated and/or reworded. All tests could be restarted or repeated if it was clear from the participant or their performance that they had misunderstood the task. Tests were not restarted or repeated however if the participant had understood the instructions but performance was poor. If a participant was agitated in any way by the testing i.e. by being unable to understand the task despite repeated explanations or distressed by their performance, the task could be omitted or aborted at the discretion of the administrator. However, participants were encouraged to complete as much of each testing session as possible and reassured of the confidentiality of the testing. A written log was kept for each session documenting the suitability of the data on each subtest, and the reason for any missing data.

2.2.7.5 Assessment schedule

A training session on the CDR battery was performed at the first qualifying visit to familiarise participants with the computerised tests. If an individual met all of the inclusion criteria and none of the exclusion criteria at the second qualifying visit, full

cognitive assessment was performed constituting the baseline assessment. Further assessments were made annually to coincide with, and performed after, the scheduled blood pressure visits until study close. An additional CDR assessment was performed at 1 month to assess acute effects. Parallel forms of the CDR battery were used at each visit to reduce learning effects. The traditional neuropsychological tests were not performed at the first qualifying visit or 1 month visits as equivalent forms of the test are not available, and short-term repeated testing with the same stimuli would produce a sizeable learning effect.

2.2.8 Study organisation

2.2.8.1 Personnel

The Newcastle Cognitive Substudy was undertaken by a multi-disciplinary team, supervised by Professor Gary A. Ford, consisting of the following: a Clinical Research Associate responsible for physical examinations, medical history taking, ECG interpretation and clinical decision-making; research nurses responsible for screening primary care medical notes, undertaking BP, heart rate and ECG measurements, adverse event monitoring and study drug administration; an assistant psychologist / Junior Research Associate responsible for performing cognitive assessments and database management; and an administrative assistant for data entry and general study administration. A representative from AstraZeneca attended regularly to monitor the Case Report Forms (CRF) of participants to fulfil the regulatory requirements of the main SCOPE trial.

2.2.8.2 Role of candidate in the study

The candidate joined the Newcastle Cognitive Substudy as an assistant psychologist/ Junior Research Associate in July 1998 after recruitment of the hypertensive cohort had already begun, and performed the majority of the cognitive assessments after this date, with the exception of a small number of post-closeout assessments in the hypertensive cohort (Table 30) and closeout visits in the normotensive group (Table 50). The candidate had significant input into the design of the normotensive arm of the study, the assessment schedule after the study extension, and the protocol for study closeout. The candidate created the relational database and was responsible for the

management of all data from the Newcastle Cognitive Substudy and other related substudies at the Newcastle site. The candidate performed and interpreted the factor analyses. In consultation with Prof. Gary Ford and Prof. John Matthews, the plan for statistical analysis was devised and all analyses carried out and reported by the candidate. The candidate disseminated the study findings at regional, national and international meetings. The candidate led the development of first-authored manuscripts for submission to peer-reviewed journals, including analysis and interpretation. Where co-author, the candidate provided datasets from the relational database for analysis, and contributed significantly to the interpretation and intellectual content of the manuscripts.

2.2.8.3 Data management

All data from the Newcastle Cognitive Substudy were entered into an in-house relational database created using Microsoft Access v.2.0, subsequently updated to Access 2000. Data from the CRFs of the main SCOPE trial relevant to the substudy (e.g. BP measurements) were entered independently by members of the substudy research team after the CRFs had been monitored by AstraZeneca.

Two methods were used to verify the integrity of the data and reduce transcription errors: exploratory data analysis and double data entry [70]. Range checks were performed on the data fields of physiological variables to ensure that all values were clinically plausible. All outliers were verified/corrected by referring to the CRF and handwritten clinic source notes. Two-person double data entry was performed by creating a dummy database into which all data for a 10% random sample were entered. Numeric data fields were compared between the master and dummy databases using an automated procedure to highlight discrepancies. Text fields were compared manually as judgement was needed to determine whether discrepancies were meaningful (e.g. mistyping hypertensive instead of hypotensive) or ignorable (i.e. differences in punctuation, use of abbreviations). Subsequent 10% samples were entered until a 'clean' iteration was achieved where no transcription errors were detected in any fields involved in the statistical analyses. This was achieved at the second iteration.

2.2.8.4 Randomisation code break

All data relating to the hypertensive groups were entered and checked, and the database locked before the randomisation codes were received from the AstraZeneca Coordinating Centre. Due to the overlapping follow-up period, data collection was ongoing for the normotensive group at the time of the code break. The normotensive database was locked before the statistical analyses involving the data were performed.

2.3 Variable reduction

2.3.1 Rationale

The battery of tests used to assess cognitive function in the substudy was designed to be as comprehensive as possible. However, as the majority of subtests produced both an accuracy and a speed score, this resulted in 22 variables as possible outcome measures. Analysis of a large number of outcome variables with repeated statistical testing presented the problem of an increased risk of making Type I errors – accepting statistically significant differences that have occurred by chance which do not actually exist in the population. A number of methods were considered to avoid such errors.

One option was to select a small number of subtests for analysis based on *a priori* hypotheses. However, the substudy was designed to be as comprehensive as possible in the range of cognitive function assessed. In particular the profile of cognitive function was of interest, as some areas of cognition are known to be more susceptible and show decline earlier than others, allowing differential effects of treatment on cognition to be examined. The wide variation in measures used in previous studies made it difficult to determine which subtests were more likely to show an effect. Even if this were possible, the selection of only those subtests most likely to show significant effects would not have been desirable as the areas of cognition *not* affected by treatment were also of interest. Also, as subtests from the CDR battery are timed, the analysis of reaction times and accuracy scores from the same test would enable speed/accuracy trade-offs to be ruled out as the cause of any effect.

A second option was to use the Bonferroni adjustment to the statistical tests which applies more stringent criteria for statistical significance than $p<0.05$ based on the

number of statistical anlyses performed. Although this would decrease the risk of Type I errors, such a procedure has a corollary of the inevitable increase in the risk of a Type II error, accepting the null hypothesis when differences do actually exist. The consequences of both types of error need to be considered. There is also some debate as to the applicability of Bonferroni adjustments to research data with the suggestion that it is most appropriate for repeated analyses on the same data [71], as opposed to repeated analyses using the same statistical test on different data [72]. The question as to what extent the family-wide adjustment should be made has also been raised, with the recommendation that statistical significant alone not be relied upon, but that the magnitude of effects and quality of the research also be taken into consideration [73].

The use of factor analytic techniques has been proposed as a means to produce a smaller number of cognitive domains for analyses of data with respect to cognitive functioning and hypertension [74]. Previous studies have demonstrated the utility of the approach with neuropsychological measures alone [29], and in combination with information-processing paradigms [75, 76]. Using data from the Framingham Heart Study, Elias and colleagues explored the factor structure of the Kaplan-Albert Battery supporting the reduction of variables into two factors [26]. The factor structure of the CDR system has previously been demonstrated in a large sample of healthy middle-aged volunteers [77]. Thus factor analysis provided a method for reducing the number of outcome variables in a meaningful way to reduce the risk of Type I error.

2.3.2 Factor analysis

2.3.2.1 Theoretical basis

Factor analysis refers to a number of statistical techniques that provide a method of simplifying complex datasets. By examining the correlation coefficients between the variables in a correlation matrix, the interrelationships are condensed into a simplified and more understandable form. Factor analysis is particularly useful where there is a good *a priori* reason to believe that variables will be correlated. With the cognitive data in the Newcastle Cognitive Substudy, such correlations were likely. Although speed of response on a memory task may be independent of speed on an attention task to some extent, a certain amount of common variance would be expected i.e. due to

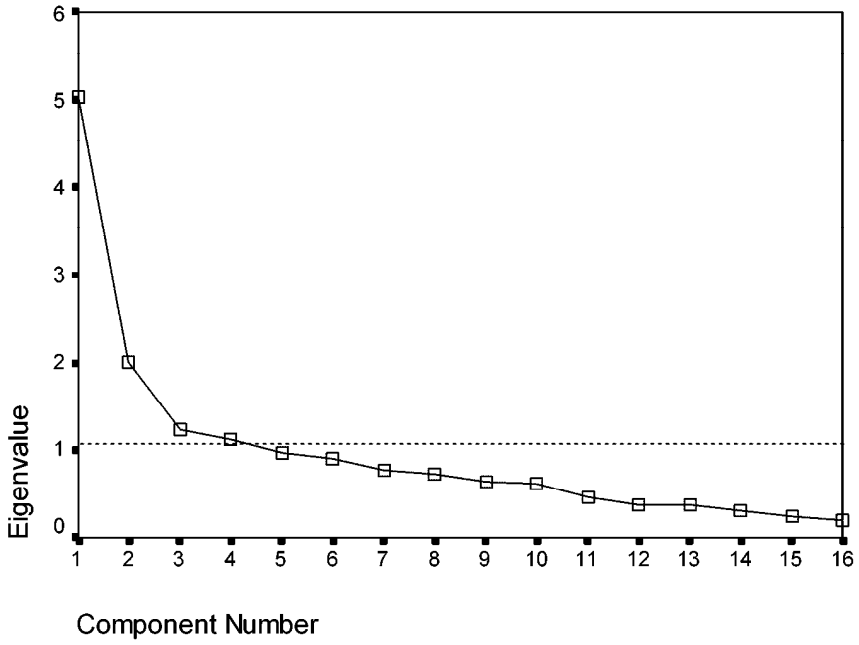
the shared physiological processes involved in responding quickly. The 22 variables produced from the cognitive tests resulted in a matrix of 242 unique correlations which would be impossible to interpret fully without some form of simplification. Factor analysis often reveals that a large number of correlations can be accounted for by a smaller number of factors. Each factor is a construct which represents the relationships between a set of variables. The meaning of the factor must then be interpreted or deduced from the factor loadings – the correlations of the variables with the factors – in essence, the factor is defined by the variables that make up that factor.

2.3.2.2 Principal components analysis (PCA)

Principal components analysis is a specific method of factor analysis that maximises the amount of variance accounted for by the factors. No other method of extracting factors yields a solution that explains more variance; it is possible with PCA to continue extracting components until all of the variance in the matrix is accounted for. However, as the purpose of the analysis is variable reduction, it is common to extract the fewest factors that explain the majority of the variance. The PCA method extracts factors in order of the variance explained which means the last few components are small and contribute very little. Deciding on the number of factors to accept in the solution is somewhat subjective, although it is common to use the Kaiser technique. This involves examining the eigenvalues, as these indicate the proportion of the variance explained by each component, and excluding components with eigenvalues less than one. The scree plot, a line plot of eigenvalues versus components, is also used as a visual guide to select the number of components up to the point that the slope begins to flatten (example scree plot Figure 6). Both methods are used as a guide but the most important criteria is that the factor solution makes sense in terms of the factors that emerge. It is common to examine solutions with more or less factors to find the one with the ‘best fit’ to the data in question after factor rotation.

Figure 6: Example scree plot

Dashed line indicates cut-off guideline of an eigenvalue of 1



2.3.2.3 Factor rotation

It is an artefact of the algebra of PCA that the first factor to emerge is a general factor followed by a series of bipolar factors. The first factor will have many large loadings that will be difficult to interpret and merely reflect the mathematics by which they were computed. Before the factors can be interpreted, the factor solution must be rotated.

The relationship of variables to factors can be represented geometrically in Euclidean space. Figure 7 represents the factor loadings of two variables on two factors. Variable A loads 0.5 on Factor 1 and 0.5 on Factor 2; variable B loads 0.6 on Factor 1 and 0.6 on Factor 2. By rotating the axes through 30°, as shown in Figure 8, variable A now loads 0.68 on the new Factor 1 and 0.19 on new Factor 2, and variable B loads 0.81 and 0.23 on the same factors.

The proportion of variance explained by a factor for a particular variable can be calculated by the sum of the squared factor loadings for that variable. Table 4 shows the loadings and variance explained by the unrotated and rotated factors for variables A and B (the values in the table are approximate as they are taken manually from the figures and subject to rounding errors). Both solutions account for the same amount of variance but the rotated solution is simpler and easier to interpret.

Figure 7: Diagrammatic representation of factor loadings

Figure shows two variables (A and B) on two factors in Euclidean space

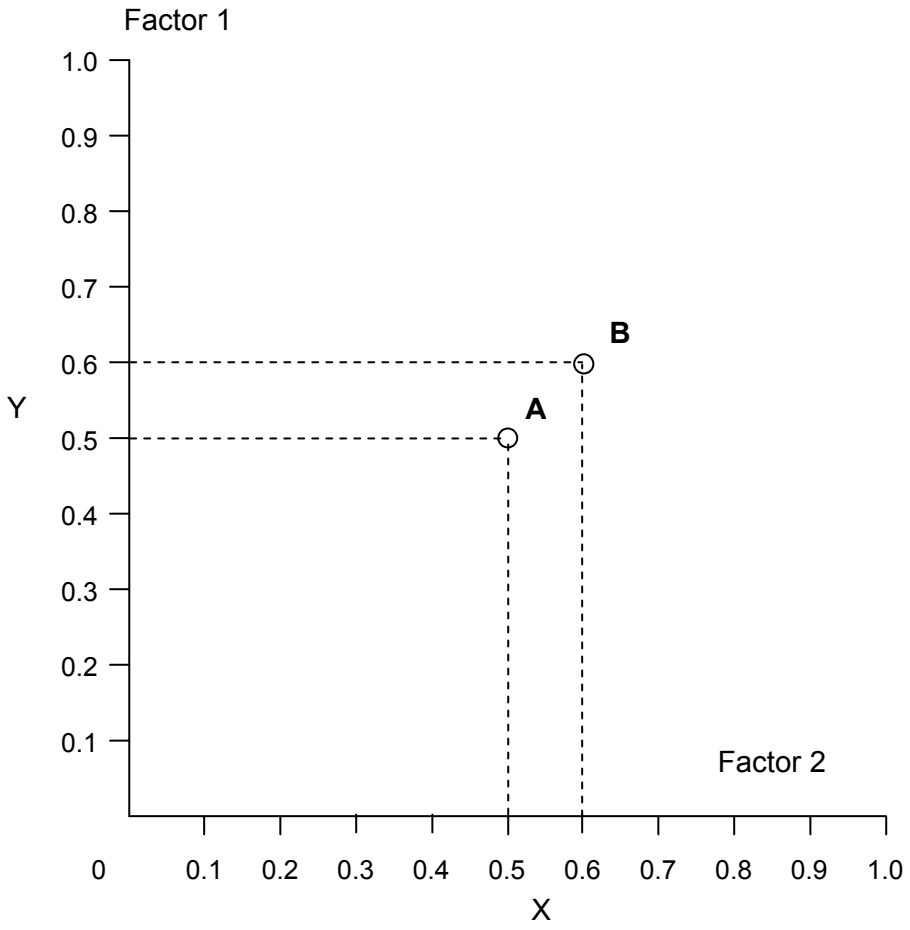


Figure 8: Diagrammatic representation of factor rotation

Figure shows loadings of two variables (A and B) on two factors, with axes rotated through 30°

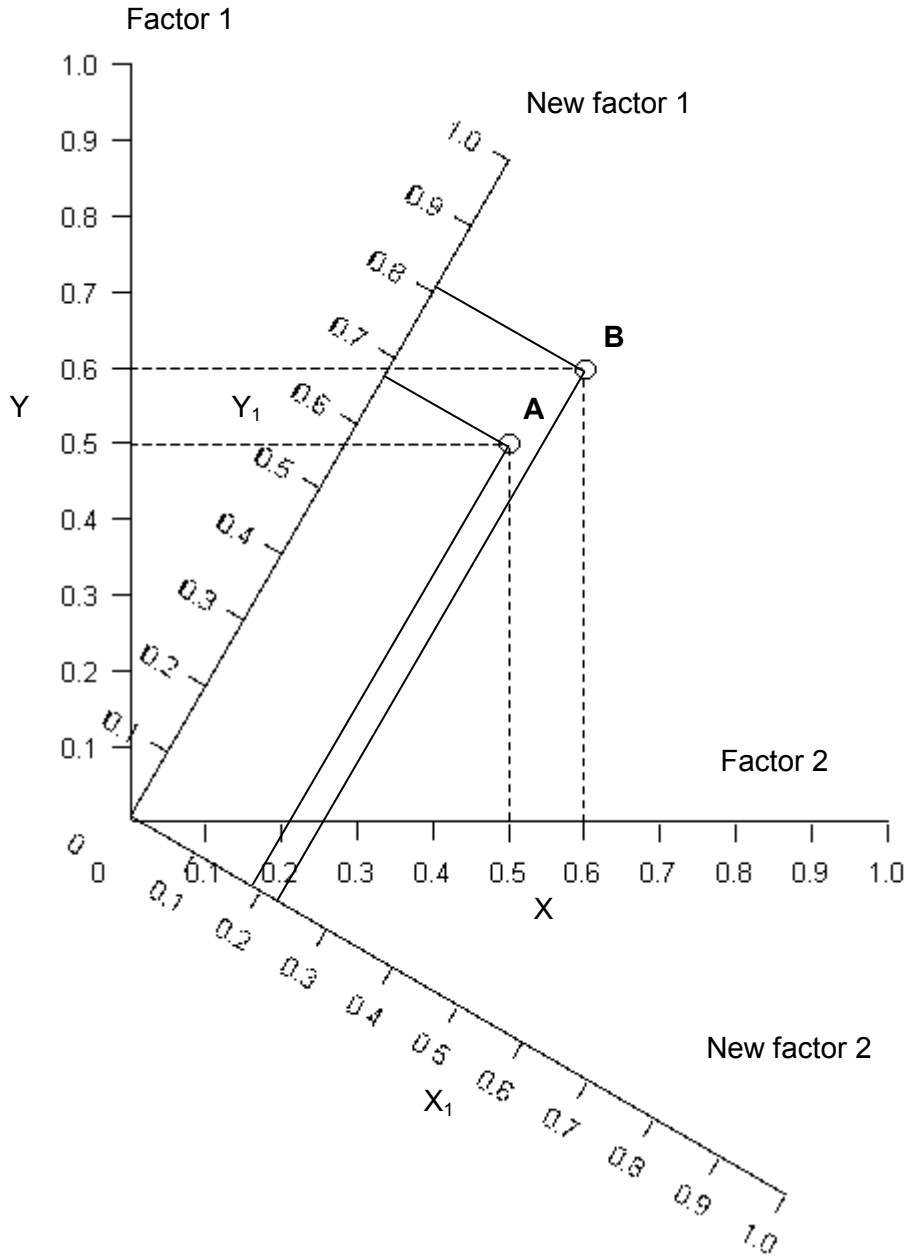


Table 4: Factor loadings and variance explained by unrotated and rotated factors

Variable		Factor 1	Factor 2	Variance (Σ of squared loadings)	% Variance explained
A	unrotated	0.5	0.5	0.25 + 0.25	50
	rotated	0.68	0.19	0.45 + 0.04	49
B	unrotated	0.6	0.6	0.36 + 0.36	72
	rotated	0.81	0.23	0.66 + 0.05	71

There are two distinct methods of factor rotation with different theoretical underpinnings: orthogonal and oblique. With orthogonal rotation, the factors are rotated at right angles maintaining the axes at 90° to each other, meaning the factors remain uncorrelated. With oblique rotation, the factor axes can be placed in any position in factor space, the angle between the axes indicating the correlation between them. Oblique rotation has been used in psychology in the search for the underlying determinants of personality where it has been argued that factors are likely to be correlated due to shared genetic and environmental factors [78]. However, as the purpose of the factor analysis in this study was simplification and variable reduction, orthogonal rotation was chosen such that within a factor the variables (cognitive subtests) would be as highly correlated as possible, but the factors (cognitive domains) themselves would be as uncorrelated as possible.

2.3.2.4 Simple structure

There is an almost limitless number of possible rotated solutions as every factor can be rotated in relation to each of the others, with each new position giving different loadings. The solutions are mathematically equivalent, giving no mathematical reason

to choose one over another. As all solutions can be seen as possible explanations for the observed correlations, Occam's razor dictates that the most parsimonious solution be accepted. Therefore the objective of factor rotation is to rotate to simple structure.

The following criteria for simple structure were proposed by Thurstone (1947) [79]:

1. Each row of the loading matrix should contain at least one zero
2. Each column should contain as least as many zeros as there are factors
3. For each pair of factors there should be variables with high loadings on one and zero loadings on the other
4. For each pair of factors a large number of loadings should be zero
5. For each pair of factors few variables should have high loadings on both factors

In practice, the criteria are very strict and hard to obtain, although the aim of achieving simple structure remains. The main importance is that each factor has a few high loadings with the remaining loadings being as close to zero as possible. The closer to simple structure a solution is the better, as this will make it easier to interpret and replicable. The lack of reproduceability of solutions is a criticism of factor analysis that can be countered when robust simple structure solutions are produced.

2.3.2.5 Varimax rotation

Factor rotation can be performed graphically by hand and to do so is useful for understanding the data and the process involved. However, it is time-consuming to select the simplest solution and quickly becomes complicated when more than two factors are involved. Common statistical packages include analytic routines that perform the calculations. The Varimax procedure with Kaiser normalization is an orthogonal rotation method that aims at achieving simple structure, maintaining the uncorrelated status between factors. It is generally recognised as the most efficient procedure and is often used in conjunction with PCA.

2.3.2.6 Summary

In order to identify statistically independent domains of cognitive function, PCA with Varimax rotation was chosen as the appropriate factor analytic method, with the aim of achieving simple structure by examining various factor solutions. The analyses were performed using SPSS v.10.

2.3.3 Factor analysis dataset

Cognitive data from the baseline assessments of the hypertensive and normotensive cohorts were used as the basis for the factor analysis. Speed and accuracy scores from the CDR subtests provided a total of 18 variables for analysis, and the 4 traditional neuropsychological tests each provided a further variable. The characteristics of the cognitive variables are detailed in Appendix VIII. PCA with varimax rotation was performed on the 22 variables from 506 participants, giving a participant to variable ratio of 23:1. The recommended minimum in the literature is a 5:1 ratio and a sample size of at least 100, although it is generally accepted that a ratio of 10:1 and a sample of 200 is more satisfactory [80].

2.3.4 Composite factor scores

Following the results of the factor analysis (described in chapter 4), the individual subtest scores were combined into composite factor scores. The composite scores were calculated by summing unweighted subtest scores with primary loadings on each factor [81], with two exceptions: picture recognition accuracy was included in the Episodic Memory factor; spatial memory accuracy was included in the Working Memory factor to maintain a theoretically meaningful basis to the composite scores. To enable the addition of timed and numerical data, the subtests contributing to the Executive Function factor were first transformed into z scores. As the Speed of Cognition factor consisted of reaction times, scores were transformed by multiplying by –1 to provide consistency with the other factors based on accuracy scores, such that a higher score indicated better performance in all cases.

2.4 Measure of cognitive decline

2.4.1 Rationale

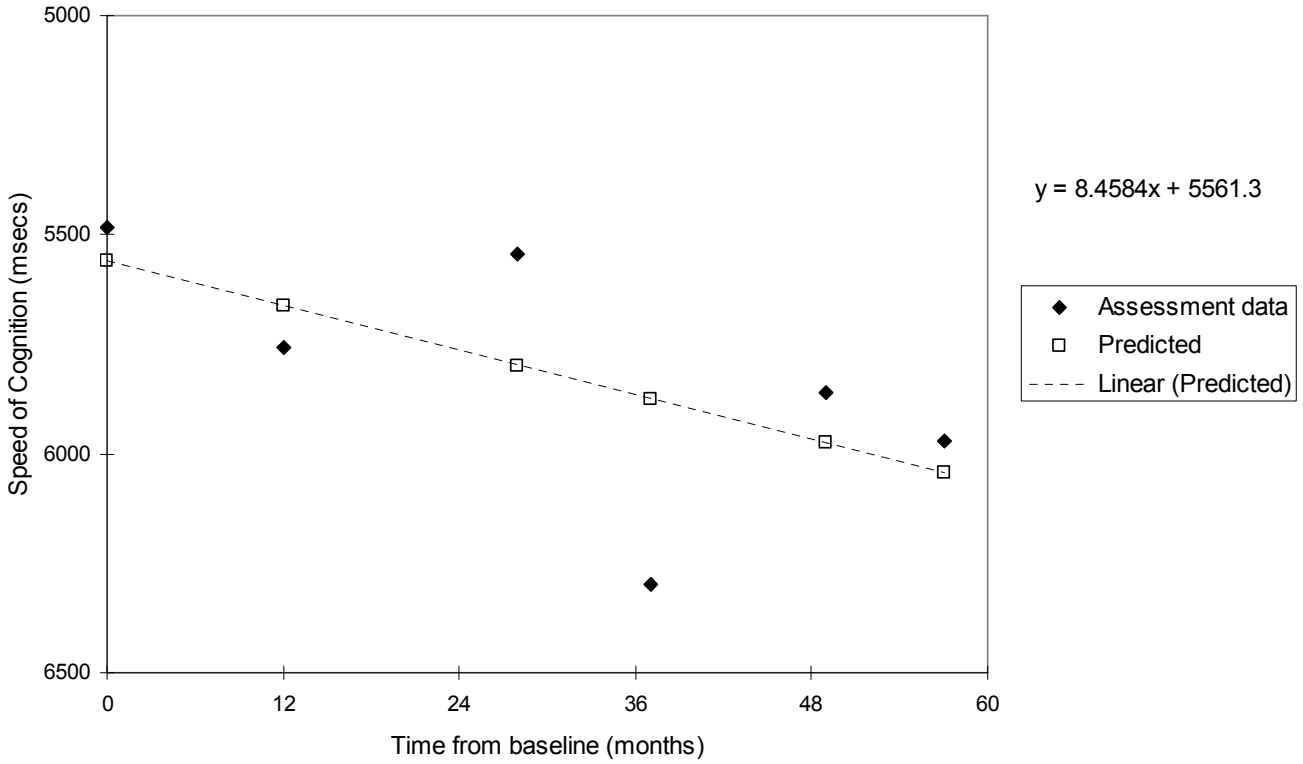
Cognitive decline represents the change in cognitive function over time and was subject to serial assessment. As such, the cognitive data could be thought of as representing a growth curve with the rate of decline being the variable of interest. Analysis of the data based simply on a pre-post comparison would not utilise the wealth of data provided by the serial measurements. Likewise, the common technique of analysing sequential measurements at each time point was also inappropriate as it would fail to take account of the fact that the measurements at each visit were related to the same participant and therefore highly correlated. Thus, the analysis could show at one time point the difference between groups as non-significant, but at the next time point indicate a significant effect, the distinction being somewhat artificial. These problems were overcome by calculating summary measures of decline using the method proposed by Matthews and colleagues [82], and employed in the MRC Hypertension Trial [44]. The slope of the regression line fitted to an individual's data was used to give a suitable estimate of decline over time. The method is particularly useful for dealing with missing data points as the slope can be estimated by the data points either side, and when the exact timing of assessments is variable, such as the variation in follow-up length due to the duration of the recruitment period. An example is shown in Figure 9.

2.4.2 Derivation of summary measures

The summary measures were calculated as the slope of the regression line derived by regressing composite factor scores at each visit on time of assessment (months since baseline) for each participant on each of the five cognitive factors. The resultant coefficients of decline were used as the main outcome variables of cognitive change. Regression values were calculated in all cases where data from 2 or more assessments were available a minimum of 12 months apart. As the 1 month and 6-weeks post-closeout cognitive assessments were performed primarily to assess acute drug effects and did not involve the traditional neuropsychological tests, data from these visits were not included in the regression calculations.

Figure 9: Example regression plot

Example regression plot of Speed of Cognition regressed against time of assessment (months from baseline). Higher values indicate worse performance.



2.5 Statistical analyses

The plan for analysis was developed and finalised before the study randomisation code was broken to ensure impartiality. All analyses were performed using SPSS v 10.0 for Windows. Significance was set at $p<0.05$.

2.5.1 Practice effects

A subset of hypertensive participants performed the CDR battery twice before their baseline visit to assess the influence of practice effects on the baseline data. Repeated measure general linear models were used to compare performance between 3 consecutive test sessions to determine the optimum number of training sessions required.

2.5.2 Tests of equivalence

Independent samples t-tests and chi-squared tests were used for interval and categorical data respectively.

The baseline characteristics of the hypertensive participants in the Newcastle Cognitive Substudy were compared to those reported by the main SCOPE trial [83] to demonstrate how representative the substudy sample was.

The candesartan and placebo groups were compared on the following variables at baseline to confirm the adequacy of the randomisation procedure: age; gender; NART errors (as an estimate of pre-morbid IQ); years in education; MMSE score; systolic and diastolic blood pressure; smoking status; and antihypertensive medication status (taking HCTZ at baseline or not).

The hypertensive and normotensive participants in the Newcastle Cognitive Substudy were compared to demonstrate how well matched the two groups were on characteristics other than BP.

2.5.3 Primary analysis

The primary analysis compared the rate of cognitive decline between the candesartan and placebo groups. Analysis was performed on an intent-to-treat basis; all available data from all randomised participants were included. The univariate general linear model procedure was used to compare decline on each factor between the two groups, controlling for age, estimated pre-morbid IQ and baseline cognitive function as covariates. In the event that the groups differed as a result of the tests of equivalence, the variable in question was entered as a covariate.

2.5.3.1 Effect sizes

Effect sizes of the primary analysis of candesartan over placebo were calculated as Cohen's D using the pooled standard deviation according to the formula:

D = (mean1-mean2)/(pooled SD)
where the pooled SD = $\sqrt{((SD1^2 + SD2^2) / 2)}$

Cohen's D is the standardised difference between groups and can be conceptualised as the number of standard deviations separating the two groups when the pooled SD is used. For interpretation, the generally-accepted conventions of effect size were used: 0.2 = small effect; 0.5 = medium effect; 0.8 = large effect. Effect sizes were computed so that negative values represented relative decline and positive values represented relative improvement.

2.5.4 Secondary analyses

2.5.4.1 Efficacy analysis

An efficacy (on treatment) analysis was performed. Data from participants who continued with the study medication until the end of the study constituted the evaluable subset. The statistical methods were the same as those for the primary analysis.

2.5.4.2 Efficacy subset versus the remainder ITT participants

Unplanned post-hoc analyses were performed to compare the characteristics of the efficacy subset with the remainder of the participants with calculable coefficients of decline.

2.5.4.3 Loss to follow-up

T-tests and chi-squared tests were used to compare the baseline characteristics of participants included in the primary analysis and participants lost to follow-up. The chi-squared test was used to check for any systematic differences in the distribution of loss to follow-up between the candesartan and placebo groups.

2.5.4.4 Excluding participants suffering stroke

As stroke is known to adversely affect cognitive function, the primary analysis was repeated excluding participants suffering a stroke during the study. Comparison of the baseline characteristics of participants suffering stroke versus participants remaining stroke-free was made using t-tests and chi-squared tests.

2.5.4.5 Excluding participants taking beta-blockers

As there is evidence to suggest that beta-blockers can adversely affect cognitive function, the primary analysis was repeated excluding participants taking beta-blockers at any time after randomisation. Comparison of the baseline characteristics of participants receiving beta-blockers versus participants remaining free of beta-blockers was made using t-tests and chi-squared tests.

2.5.4.6 Acute drug effects

Assessment of cognitive function was performed at the 1 month visit using the CDR computerised battery; tests of executive function were not administered because of anticipated learning effects. Data from this visit were used to examine acute effects of the study medication on cognition. Comparison between the candesartan and placebo groups on the change from baseline scores was made using independent t-tests.

2.5.5 Normotensive comparison

The primary analysis was repeated with the inclusion of data from the normotensive group to place the magnitude of any treatment effects in the context of normal ageing and decline. The univariate general linear model procedure was used to compare decline on each factor between the three groups, controlling for age, estimated pre-morbid IQ and baseline cognitive function as covariates. Where the F test was significant at the .05 level, pairwise comparisons were made using the Least Squared Difference (equivalent to no adjustment for multiple comparisons).

2.5.5.1 Effect sizes

Effect sizes for candesartan and placebo in comparison to the normative control group were calculated as Glass's Delta using the standard deviation of the normotensive group according to the formula:

D = (mean1-mean2)/(normotensive group SD)

Glass's Delta can be conceptualised as the number of standard deviations separating the treatment group from the normative reference group. For interpretation, the generally-accepted conventions of effect size were used: 0.2 = small effect; 0.5 = medium effect; 0.8 = large effect. Effect sizes were computed so that negative values represented relative decline and positive values represented relative improvement.

2.5.6 Exploratory analyses: blood pressure as a continuous variable

Due to the lowering of the BP treatment target to <150/90 mmHg according to British Hypertension Society guidelines released during the study, the expected SBP gap of approximately 10 mmHg between the hypertensive and normotensive groups was no longer maintained. Therefore, although there were differences in the group means, there was overlap between groups in the distribution of average SBP over the course of the study. As such, BP could be considered a continuous variable regardless of the original group allocation. The association between average BP over the course of the study and rate of cognitive decline was assessed using partial correlations, performed on the hypertensive and normotensive data combined, controlling for factors known to affect cognitive function (age, estimated pre-morbid IQ and baseline cognitive

function). Pearson correlations were used, with two-tailed significance tested at the 0.05 level.

CHAPTER 3: RESULTS – BASELINE DATA

This chapter presents the baseline data from the Newcastle Cognitive Substudy, for the hypertensive group in comparison to the main SCOPE cohort, and in comparison to the normotensive controls. The baseline equivalence of the candesartan and placebo groups is detailed. The analysis of practice effects is also presented.

3.1 Recruitment

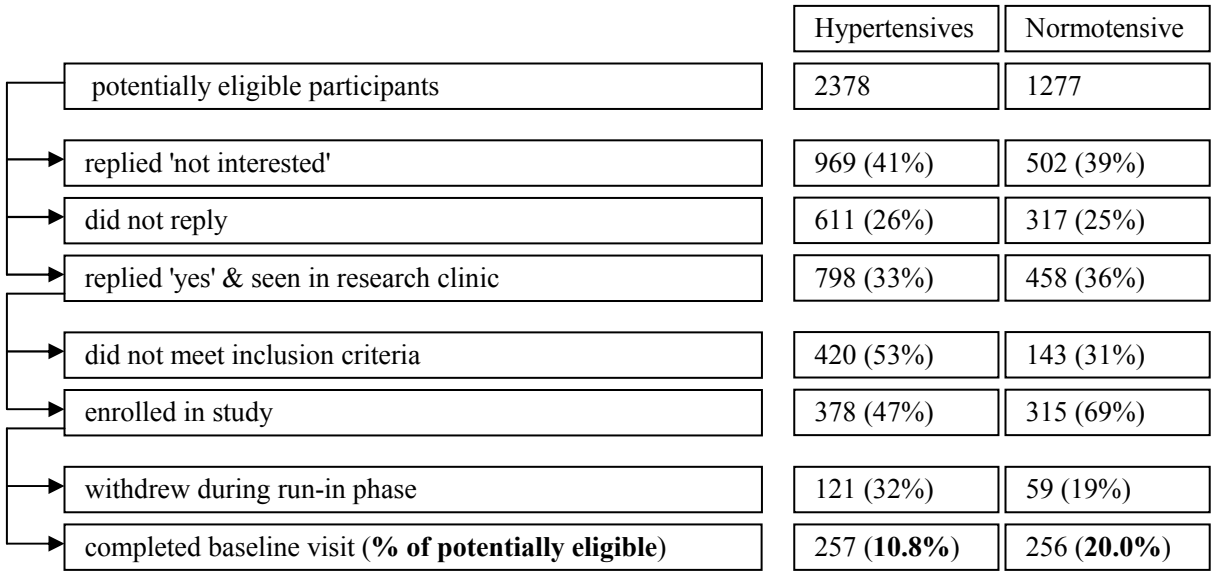
A total of 8593 patient records were screened by study research nurses to identify potentially eligible individuals for the main SCOPE trial. A further 1143 patient records were screened in the second wave of case note screening to identify potentially eligible normotensive individuals. The flow of participants through the recruitment process is shown in Figure 10. Of the 1256 individuals that attended the research clinic for the initial screening visit, 563 did not meet the inclusion criteria. Data regarding the characteristics of the ineligible individuals were not available as informed consent, and therefore permission to use such data, was only obtained at the initial screening visit when the criteria for enrolment were met. Of the 378 enrolled hypertensive participants, 121 were withdrawn before randomisation primarily because study BP criteria were not met. Other reasons for withdrawal after enrolment included concerns about study side-effects, reluctance to change current antihypertensive therapy to HCTZ, and the long-term commitment required. As the consent form stated that participants were free to withdraw from the study at any time without giving an explanation, reasons for withdrawal were not formally recorded.

The proportion of potentially eligible participants indicating an interest in the study and attending the screening clinic was approximately a third for both the hypertensive and normotensive groups. As expected, the proportion that failed to meet the inclusion criteria at the initial screening visit was greater for the hypertensive group than the normotensive group (53% vs. 31%), due to the more restrictive hypertensive BP criteria. Similarly, a lower proportion of normotensive individuals withdrew between the enrolment and baseline/ randomisation visits. As a reason for withdrawal was not required, the cause of differential dropout rates between the groups is not known

although the exclusion of hypertensive individuals with white-coat hypertension could account for a higher rate in this group. In addition, it is possible that in individuals meeting the study criteria, voluntary withdrawal was lower for normotensive participants due to the non-intervention nature of the observational control group.

Of the 257 hypertensives recruited to the main SCOPE study, 4 participants declined to enter the Newcastle Cognitive Substudy. Three participants agreed to participate but were unable to attend the baseline cognitive assessment portion of the randomisation visit due to personal time commitments, and were therefore withdrawn from the substudy. As normotensive individuals were recruited to the substudy only, all 256 participants were included.

Figure 10: Recruitment to the SCOPE trial and Newcastle Cognitive Substudy



3.2 Hypertensive participants

The baseline characteristics of the hypertensive participants in the Newcastle Cognitive Substudy are shown in Table 5. The Newcastle sample represents 29% of the 883 participants recruited in the UK, and 5% of all participants in the SCOPE trial. All participants were Caucasian.

3.2.1 Comparison with the SCOPE cohort

Comparison with the baseline characteristics of the main SCOPE cohort [83] in Table 5 shows that the Newcastle cohort was similar in terms of mean age, BP levels, MMSE score and the prevalence of previous stroke and atrial fibrillation. The mean age of 76 years reflects the predominance of participants in the younger age group of 70-79 years, with one in five participants aged 80 or over in both the Newcastle Cognitive Substudy (Figure 11) and the main SCOPE cohort (Figure 12). The distributions of SBP, DBP and MMSE score at randomisation were also similar (Figures 13-16).

Table 5: Baseline characteristics of hypertensive participants

Data shown are means or percentages.

	Newcastle Cognitive Substudy hypertensives	SCOPE trial participants
	n=250	n=4964
Age, years	76	76
Females	53%	64%
MMSE score	29	28
SBP mmHg	165	166
DBP mmHg	88	90
Smokers	15%	9%
Treated at enrolment with:		
HCTZ	27%	52%
NSAIDs / aspirin	32%	22%
Psychotropic drugs	14%	8%
Previous MI	8%	4%
Previous stroke	4%	4%
Atrial fibrillation	4%	4%

MMSE = Mini-Mental State Examination; SBP = systolic blood pressure; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; NSAIDs = non-steroidal anti-inflammatory drugs; MI = myocardial infarction.

Figure 11: Age distribution at baseline: NCS

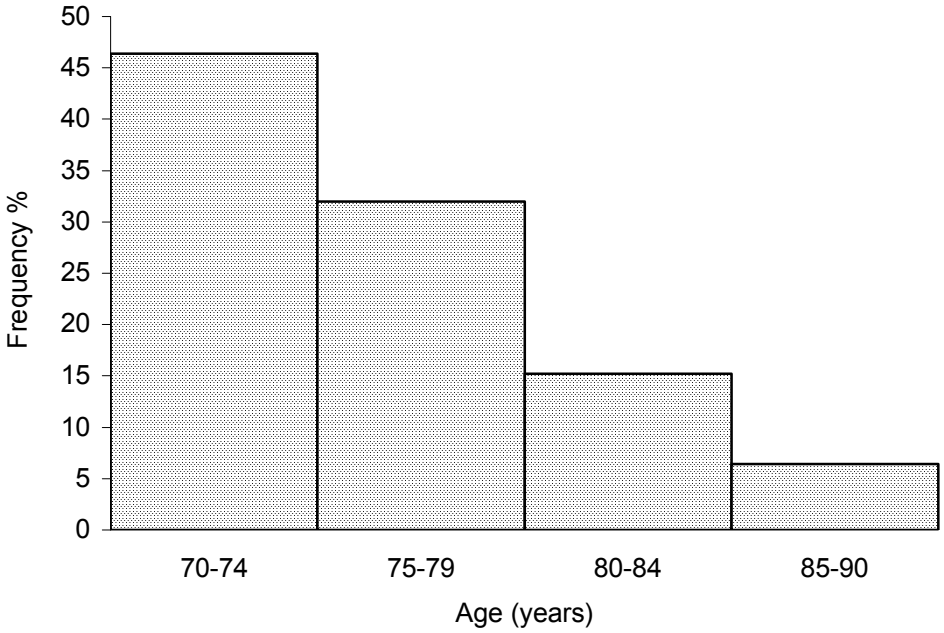


Figure 12: Age distribution at baseline: main SCOPE study

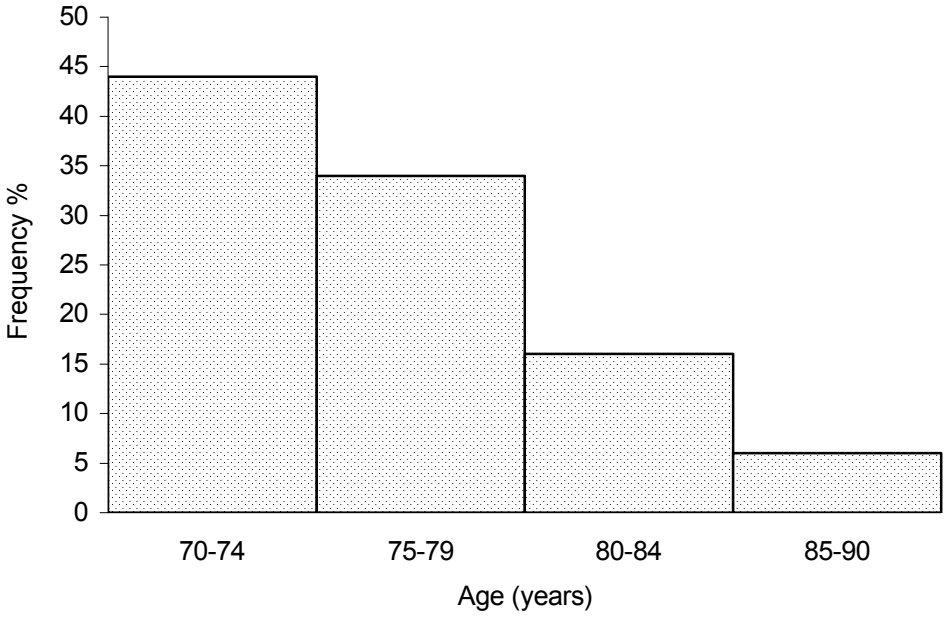


Figure 13: Distribution of SBP at baseline: NCS

Distribution of baseline systolic blood pressure (SBP) at baseline of participants in the Newcastle Cognitive Substudy (n=250)

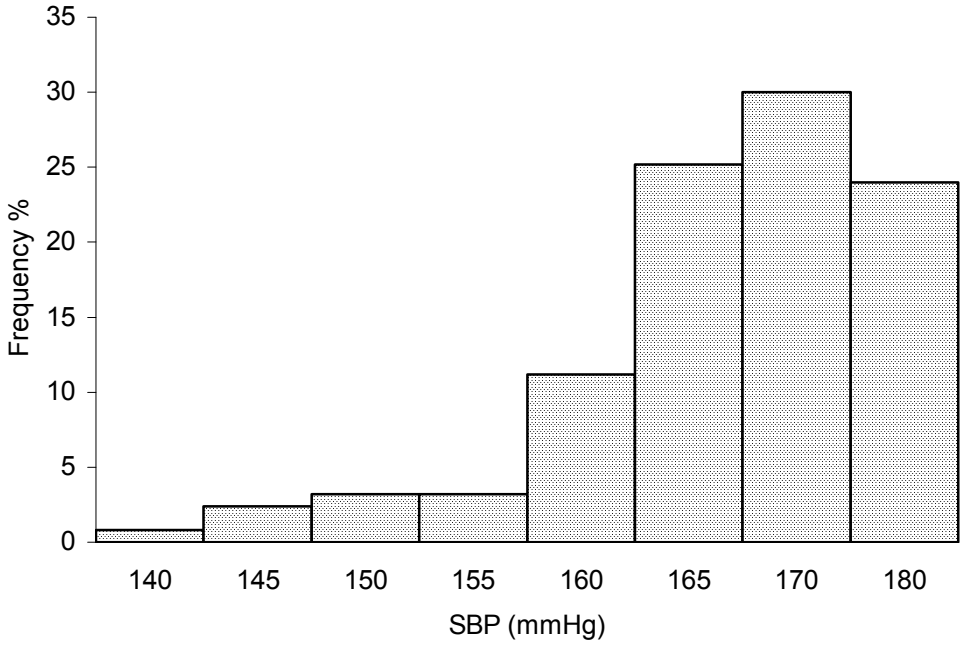


Figure 14: Distribution of SBP at baseline: main SCOPE study

Distribution of systolic blood pressure (SBP) at baseline of participants in the main SCOPE study (n=4964)

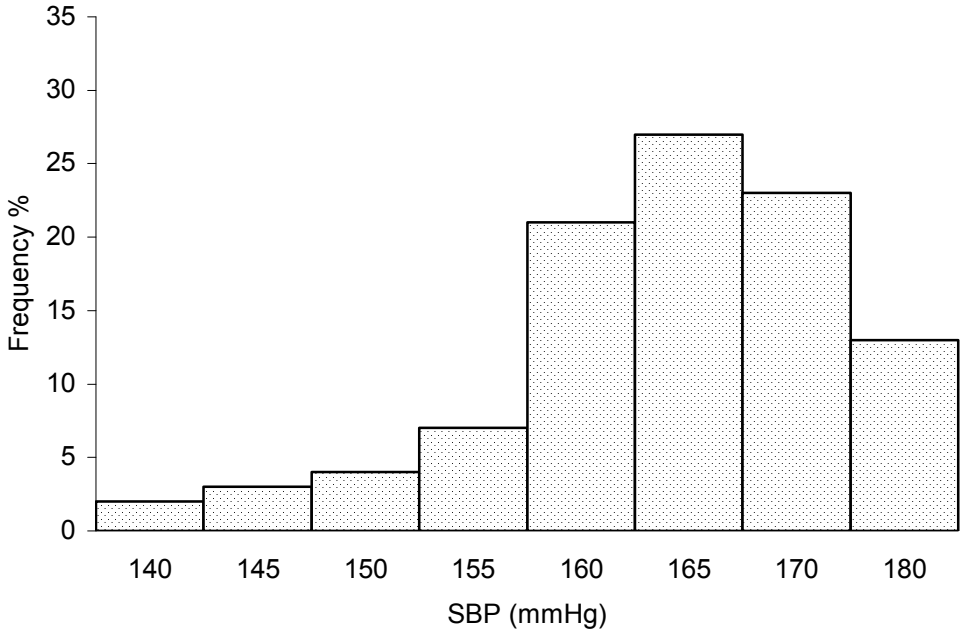


Figure 15: Distribution of DBP at baseline: NCS

Distribution of diastolic blood pressure (DBP) at baseline of participants in the Newcastle Cognitive Substudy (n=250)

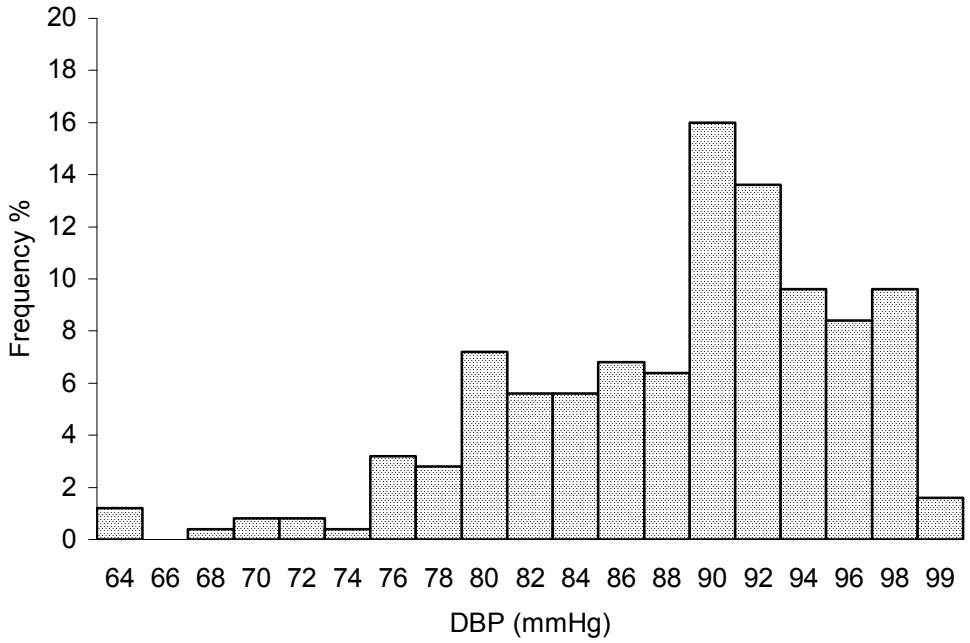


Figure 16: Distribution of DBP at baseline: main SCOPE study

Distribution of diastolic blood pressure (DBP) at baseline of participants in the main SCOPE study (n=4964)

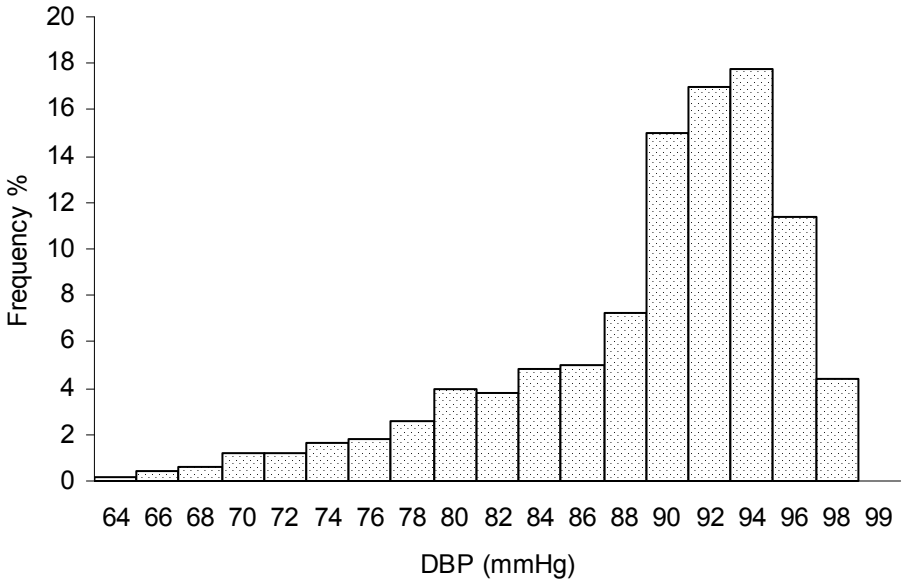


Figure 17: Distribution of MMSE at baseline: NCS

Distribution of Mini-Mental State Examination score (MMSE) at baseline of participants in the Newcastle Cognitive Substudy (n=250)

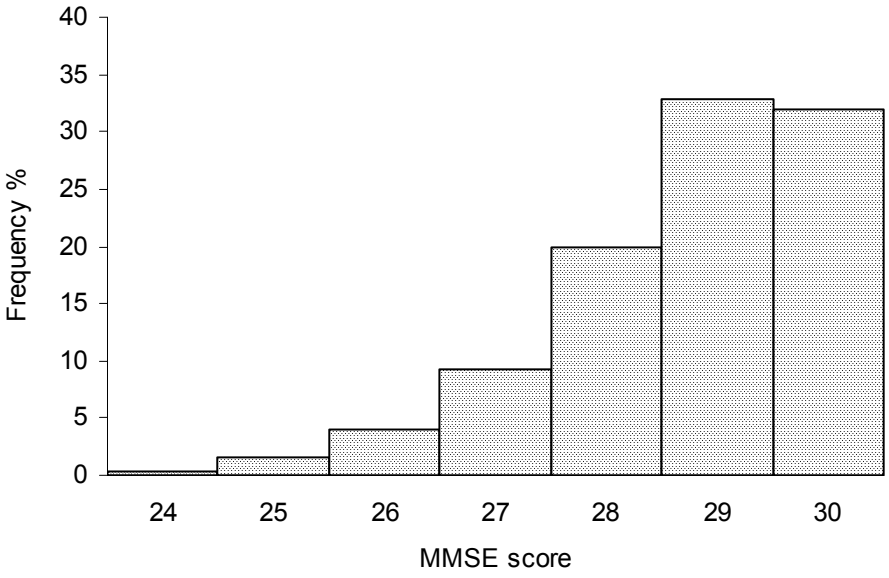
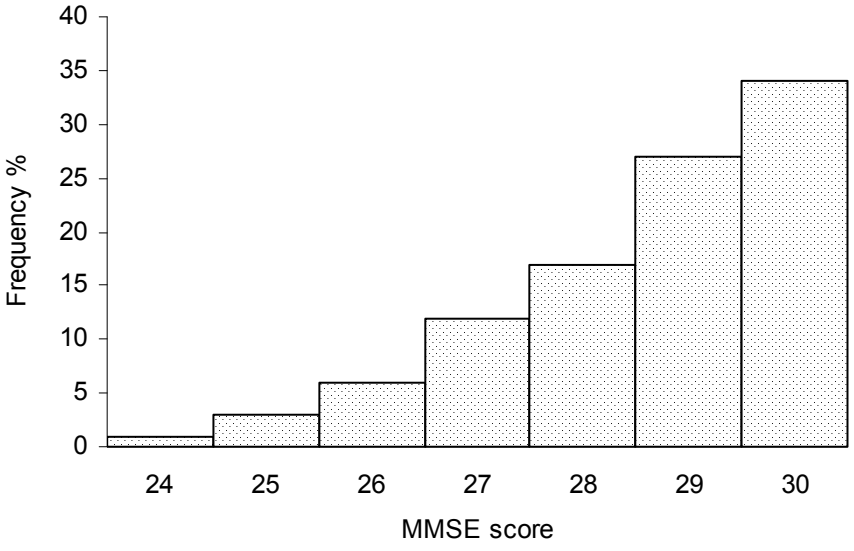


Figure 18: Distribution of MMSE at baseline: main SCOPE study

Distribution of Mini-Mental State Examination score (MMSE) at baseline of participants in the main SCOPE study (n=4964



The 1:1 ratio of males to females in the Newcastle sample was significantly higher than the ratio of approximately 1:2 in the main SCOPE cohort ($\chi^2 = 13.33$; df =1; p<.001). The proportion of smokers (15% vs. 9%; $\chi^2 = 8.80$; df =1; p<.01) and participants with a history of myocardial infarction (8% vs. 4%; $\chi^2 = 8.04$; df =1; p<.01) was higher, and the percentage receiving antihypertensive therapy (27% vs. 52%; $\chi^2 = 72.42$; df =1; p<.001) was significantly lower in the Newcastle cohort compared to the SCOPE cohort. As the raw data from the main SCOPE trial were unavailable, more detailed statistical analysis was not possible. Comparison with the rest of the UK sample would have indicated whether the differences were attributable to some aspect of recruitment at the Newcastle centre, or whether they reflected the characteristics of the UK population as a whole.

3.3 Normotensive participants

The baseline characteristics of the normotensive participants in the Newcastle Cognitive Substudy are shown in Table 6. All participants were Caucasian.

3.3.1 Comparison with hypertensive participants

Comparison of the hypertensive and normotensive cohorts in Table 6 shows that the groups were well matched for demographic characteristics known to affect cognitive function such as age, years in education and MMSE score. Within groups there was an approximate 1:1 ratio of males to females, although comparison between groups showed that the proportion of males was slightly higher in the normotensive group. The prevalence of previous MI and stroke was higher in the hypertensive group as expected, given the established relationship between hypertension and cardiovascular disease. The use of NSAIDS/aspirin was also higher; the prescription of aspirin in particular may have been associated with participants' hypertensive status and medical history. Psychotropic medication use was also higher in the hypertensive group, although the reason for this is not clear. However, the inclusion criteria for both groups stated that any pharmacological treatment could not have been initiated within the preceding six months to baseline, ensuring that participants were stable on their medication before entry into the study.

Table 6: Baseline demographic characteristics of the normotensive participants

Data shown are mean and (SD), or percentages.

	Hypertensive	Normotensive	p
	n=250	n=256	
Age, years	76 (4)	76 (5)	.82
Females	53%	44%	.04
Education, years	10 (2)	10 (2)	.73
MMSE score	29 (1)	29 (1)	.59
SBP mmHg	165 (8)	131 (11)	<.001
DBP mmHg	88 (7)	73 (7)	<.001
Smokers	15%	16%	.64
Treated at enrolment with:			
HCTZ	27%	n/a	n/a
NSAIDs / aspirin	32%	16%	<.001
Psychotropic drugs	14%	6%	<.01
Previous MI	8%	4%	.05
Previous stroke	4%	1%	.04
Atrial fibrillation	4%	2%	.18

MMSE = Mini-Mental State Examination; SBP = systolic blood pressure; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; NSAIDs = non-steroidal anti-inflammatory drugs; MI = myocardial infarction.

Cognitive function subtests: hypertensive vs. normotensives

Comparison of baseline cognitive function between the hypertensive and normotensive groups on the subtests of the CDR battery and traditional neuropsychological tests of executive function is shown in Table 7. The hypertensive participants performed significantly worse than the normotensives on the majority of subtests from the cognitive battery, with the exception of immediate word recognition, number vigilance reaction time, choice reaction time accuracy and numeric working memory accuracy. The differences existed despite the groups being well-matched on baseline demographic characteristics. However, the hypertensive group had a higher prevalence of previous cardiovascular and cerebrovascular disease, as well as a higher rate of psychotropic medication and prior BP-lowering medication use, which may have accounted for the differences in cognitive function between the groups.

3.3.2 Excluding factors that may affect cognition

Previous work undertaken by Dr. Frances Harrington had already focussed on group differences in the baseline data from the Newcastle Cognitive Substudy [84]. The analysis compared hypertensive and normotensive participants, excluding those with clinical evidence or history of cardiovascular/ cerebrovascular disease, or taking BP-lowering or psychotropic medication, to provide a sample that differed only in relation to BP level. A very similar pattern of subtle deficits was found with hypertensives performing worse than normotensives on the majority of subtests reported. Thus it was possible to exclude the influence of psychotropic medication, BP-lowering medication, and medical history variables as the cause of the observed group differences at baseline.

The group differences in cognitive function were expected as previous cross-sectional studies of well-matched groups have generally shown hypertensives to exhibit subtle deficits on a variety of cognitive measures. As baseline cognition has also been shown to be predictive of future performance and subsequent cognitive decline, the presence of subtle deficits in the hypertensive group supported the *a priori* inclusion of baseline cognition as a covariate in the general linear model used to analyse the effects of treatment (as detailed in section 2.5.2).

Table 7: Comparison of baseline performance on the cognitive subtests

Accuracy (acc) scores shown are %, where a higher score indicates better performance; reaction times (RT) shown are milliseconds, where a lower score indicates better performance.

Data shown are mean and (SD)

Subtest	Hypertensive		Normotensive		t	p
	n=250		n=256			
Immediate word recognition acc	88.5	(11.8)	89.1	(9.9)	-.56	.57
Immediate word recognition RT	950	(227)	904	(198)	2.4	.02
Simple reaction time RT	358	(113)	322	(60)	4.5	<.001
Number vigilance acc	99.1	(2.7)	99.8	(1.2)	-3.8	<.001
Number vigilance RT	460	(58)	454	(55)	1.2	.25
Choice reaction time acc	96.2	(3.7)	96.0	(3.8)	.59	.55
Choice reaction time RT	520	(82)	503	(75)	2.3	.02
Spatial memory acc	63.7	(31.5)	75.6	(23.7)	-4.8	<.001
Spatial memory RT	1434	(487)	1302	(468)	3.1	.002
Numeric working memory acc	94.3	(11.7)	95.8	(7.7)	-1.7	.10
Numeric working memory RT	875	(319)	812	(192)	2.7	.007
Delayed word recognition acc	82.6	(16.5)	86.8	(10.6)	-3.3	.001
Delayed word recognition RT	933	(229)	880	(207)	2.7	.007
Delayed picture recognition acc	86.0	(14.3)	88.8	(10.9)	-2.5	.012
Delayed picture recognition RT	983	(207)	912	(166)	4.3	<.001
Immediate word recall #	4.8	(1.7)	5.1	(1.7)	-2.1	.03
Delayed word recall #	2.9	(2.2)	3.3	(2.2)	-2.0	.03
Trail-Making Test form A (secs)	53	(22)	47	(18)	3.2	.001
Trail-Making Test form B (secs)	147	(70)	127	(62)	3.6	.001
Verbal fluency (animals) #	15	(5)	16	(4)	-2.4	.02
Verbal fluency (FAS) #	35	(12)	40	(13)	-4.7	<.001

3.4 Tests of equivalence: candesartan group vs placebo group

3.5.1 Demographics and medical history

The baseline demographic characteristics of hypertensive participants in the Newcastle Cognitive Substudy randomised to the candesartan group and placebo group are shown in Table 8. The groups were very closely matched on all variables both in terms of means and standard deviations, with no significant differences on any variables, confirming the adequacy of the randomisation procedure performed by the SCOPE Coordinating Centre as part of the main SCOPE trial.

3.5.2 Baseline cognitive function – subtests

The candesartan and placebo groups were also compared on baseline cognitive performance on the subtests of the CDR battery and traditional tests of executive function, as shown in Table 9. The randomisation procedure (described in section 2.1.5.3) was determined by the main SCOPE protocol, and as the detailed cognitive assessments were only undertaken in the Newcastle Cognitive Substudy, performance on the cognitive function subtests was not included as a prognostic factor in the randomised procedure. However, there was very little difference in the performance of the candesartan and placebo groups, with only the immediate word recall subtest reaching the significance level of $p<.05$. As baseline cognitive performance was entered into the general linear model as a covariate, small differences on individual subtests at baseline were unlikely to affect the comparison between the groups on rates of decline over time.

Table 8: Baseline demographics of candesartan versus placebo groups

Data shown are mean and (SD), or percentages.

	Candesartan	Placebo	p
	n=124	n=126	
Age, years	76 (5)	76 (5)	.46
Females	53%	53%	.99
Education, years	10 (2)	10 (2)	.72
MMSE score	29 (1)	29 (1)	.23
SBP mmHg	165 (8)	165 (9)	.92
DBP mmHg	88 (7)	88 (7)	.20
Smokers	13%	16%	.50
Treated at enrolment with:			
HCTZ	27%	27%	.94
NSAIDs / aspirin	31%	33%	.75
Psychotropic drugs	13%	14%	.89
Previous MI	11%	5%	.09
Previous stroke	5%	2%	.30
Atrial fibrillation	3%	6%	.37

MMSE = Mini-Mental State Examination; SBP = systolic blood pressure; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; NSAIDs = non-steroidal anti-inflammatory drugs; MI = myocardial infarction.

Table 9: Baseline cognitive performance: candesartan vs placebo groups.

Accuracy (acc) scores shown are %, where a higher score indicates better performance; reaction times (RT) shown are milliseconds, where a lower score indicates better performance.

Data shown are mean and (SD)

Subtest	Candesartan		Placebo		t	p
	n=124		n=126			
Immediate word recognition acc	88.6	(10.5)	88.5	(13.0)	.09	.93
Immediate word recognition RT	944	(207)	956	(245)	-.44	.66
Simple reaction time RT	346	(74)	370	(141)	-1.7	.10
Number vigilance acc	99.1	(2.6)	99.2	(2.8)	-.20	.84
Number vigilance RT	460	(61)	459	(56)	.25	.80
Choice reaction time acc	95.8	(3.8)	96.7	(3.6)	-2.0	.05
Choice reaction time RT	512	(68)	527	(94)	-1.5	.14
Spatial memory acc	62.4	(30.2)	65.0	(32.8)	-.65	.52
Spatial memory RT	1443	(524)	1426	(449)	.27	.78
Numeric working memory acc	93.0	(12.6)	95.6	(9.8)	-1.9	.06
Numeric working memory RT	902	(402)	848	(206)	1.3	.18
Delayed word recognition acc	83.0	(15.5)	82.3	(17.5)	.30	.77
Delayed word recognition RT	926	(192)	941	(260)	-.51	.61
Delayed picture recognition acc	86.1	(14.6)	85.8	(14.0)	.17	.86
Delayed picture recognition RT	982	(212)	983	(202)	-.03	.98
Immediate word recall #	4.5	(1.6)	5.1	(1.8)	-2.5	.01
Delayed word recall #	2.5	(2.2)	3.2	(2.2)	-2.0	.05
Trail-Making Test form A (secs)	53	(20)	52	(23)	.10	.92
Trail-Making Test form B (secs)	152	(74)	143	(66)	.94	.35
Verbal fluency (animals) #	15	(4)	15	(5)	-.51	.61
Verbal fluency (FAS) #	34	(13)	36	(12)	-.98	.33

3.5.3 Baseline cognitive function – composite factor scores

The factor analyses (described in chapter 4) were designed to reduce the number of possible outcome variables, and the results produced a method of combining the cognitive subtest scores into composite factor scores in a meaningful way. As decline on the composite factor scores was the primary outcome measure, cognitive performance defined by the factor scores was compared between the randomised groups to test for equivalence at baseline, as shown in Table 10. As there was very little difference between the groups on the individual subtests that contributed to the composite factor scores, as expected the results showed no significant differences in baseline cognitive function defined by the composite factor scores.

Table 10: Baseline composite cognitive factors: candesartan vs placebo groups

A higher score indicates better performance except for Speed of Cognition, where a lower score indicates better performance.

Data shown are mean and (SD)

Factor	Candesartan		Placebo		t	p
	n=124		n=126			
Speed of Cognition	6515	(1404)	6510	(1235)	.03	.98
Continuity of Attention	92.0	(2.7)	92.5	(2.9)	-1.4	.17
Episodic Memory	217	(51)	230	(53)	-1.7	.09
Working Memory	1.55	(0.34)	1.61	(0.36)	-1.2	.23
Executive Function	1.06	(2.99)	1.41	(3.28)	-.86	.39

3.5 Practice effects

To determine the optimum number of training sessions required to reduce practice effects within the study, performance on the CDR composite scores between training session 1 and 2, and baseline were compared in a subset (n=49) of hypertensives who underwent two training sessions before their baseline assessment (Table 11). The results of training were most pronounced for Speed of Cognition (Figure 19), showing an improvement in reaction time scores between training session 1 and training session 2. Significant improvement did not occur between training session 2 and baseline, indicating that one training session was sufficient to reduce the effects of training in the study.

Table 11: Practice effects between training and baseline

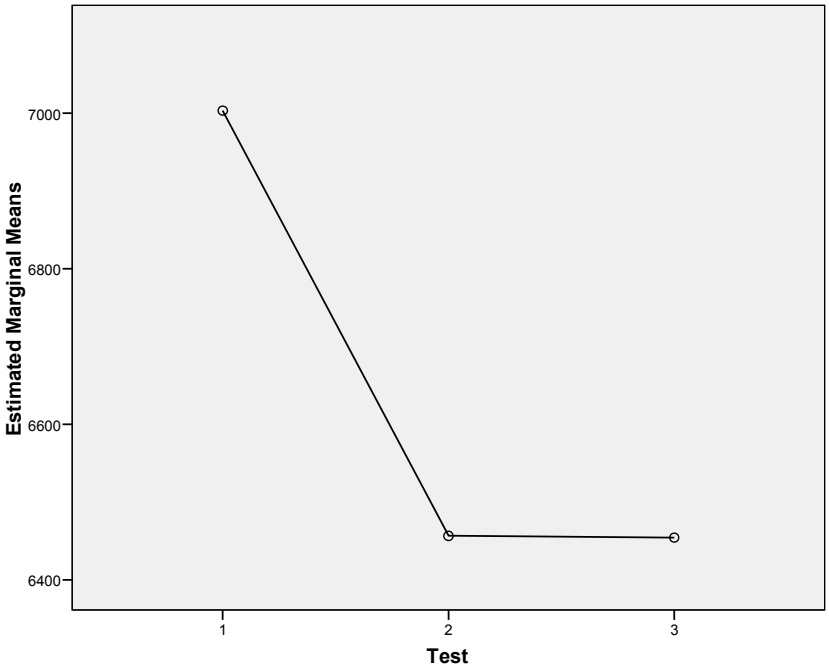
Difference scores between training session 1, 2 and baseline assessment in hypertensive participants who underwent two training sessions (n=49). A higher score indicates better performance except for Speed of Cognition, where a lower score indicates better performance.

Data shown are mean difference and standard error

Factor	Difference: training 2 minus training 1		p	Difference: baseline minus training 2		p
Speed of Cognition	-547	(112)	<.001	-2	(93)	.98
Continuity of Attention	0.55	(0.41)	.19	0.39	(0.40)	.33
Episodic Memory	5.5	(3.5)	.13	-6.8	(3.5)	.06
Working Memory	-0.02	(0.05)	.63	0.05	(0.05)	.32

Figure 19: Effects of practice on Speed of Cognition

Speed of Cognition scores across 3 consecutive test sessions (representing training sessions 1, 2 and baseline assessments) in hypertensive participants who underwent two training sessions (n=49). A higher score indicates worse performance; a lower score indicates better performance.



CHAPTER 4: RESULTS - FACTOR ANALYSIS

This chapter presents the results of the factor analytical methods used to investigate the inter-correlations of the variables from the cognitive test battery used in the Newcastle Cognitive Substudy, with the aim of producing a method of combining subtest variables into composite scores in a meaningful way.

4.1 Principal Components Analysis (PCA)

Baseline cognitive data from the hypertensive and normotensive participants were used as the basis for the factor analyses.

4.1.1 Solution 1: all baseline data

In the first instance, all cognitive variables (see Appendix VIII) from the hypertensive and normotensive groups combined were entered into the analysis. The correlation matrix is shown in Table 12.

4.1.1.1 Statistical output

The eigenvalues and variance explained by the extracted components after performing PCA are shown in Table 13; five components had eigenvalues greater than unity explaining approximately 58% of the variance. Examination of the scree plot (Figure 20) showed that the slope began to flatten at the third component, accounting for approximately 47% of the variance. The scree plot and eigenvalues suggested that the number of components selected for rotation should be no less than three and no more than five, respectively. As the inclusion of components four and five accounted for an additional 11% of the variance, five components were selected for rotation to maximise the variance explained in the first solution. The unrotated component matrix is shown in Table 14. Varimax rotation with Kaiser normalization produced a rotated solution that converged after 8 iterations. The rotated five factor solution is shown in Table 15; for ease of interpretation, variable names are listed in full.

Table 12: Correlation matrix of baseline cognitive data. For variable definitions, see Appendix VIII

	DRE1SI	DRE1RT	SRT	VIGACC	VIGRT	VIGFA	CRT2ACC	CRT2	SPMSI	SPMRT	MSSI	MSRT	DRE2SI	DRE2RT	DPICSI	DPICRT	IRECALL	DRECALL	TMTA	TMTB	VF_Animals	VF_FAS
DRE1SI	1.00																					
DRE1RT	-.23	1.00																				
SRT	-.14	.47	1.00																			
VIGACC	.06	-.20	-.25	1.00																		
VIGRT	-.14	.48	.57	-.26	1.00																	
VIGFA	-.03	.04	-.01	-.21	.00	1.00																
CRT2ACC	.09	.02	.16	.10	-.02	-.16	1.00															
CRT2	-.17	.57	.68	-.26	.59	.14	.03	1.00														
SPMSI	.15	-.20	-.24	.19	-.18	-.10	.12	-.25	1.00													
SPMRT	-.06	.45	.36	-.24	.38	.06	.00	.47	-.30	1.00												
MSSI	.10	-.01	-.04	.01	-.05	-.02	.11	.03	.11	-.02	1.00											
MSRT	-.15	.66	.45	-.15	.45	.12	-.01	.59	-.24	.54	-.22	1.00										
DRE2SI	.54	-.17	-.08	.17	-.11	-.05	.18	-.10	.15	-.03	.08	-.05	1.00									
DRE2RT	-.34	.76	.44	-.17	.42	.04	-.02	.54	-.22	.42	-.01	.59	-.26	1.00								
DPICSI	.27	-.17	-.09	.10	-.14	-.18	.19	-.19	.18	-.15	.15	-.23	.29	-.22	1.00							
DPICRT	-.21	.72	.54	-.20	.44	.13	.02	.65	-.23	.53	.05	.61	-.14	.69	-.19	1.00						
IRECALL	.34	-.28	-.25	.14	-.27	-.16	.11	-.26	.31	-.24	.15	-.25	.37	-.39	.33	-.28	1.00					
DRECALL	.40	-.29	-.23	.16	-.25	-.18	.18	-.23	.25	-.22	.14	-.30	.43	-.44	.33	-.31	.64	1.00				
TMTA	-.12	.43	.34	-.21	.38	.09	-.13	.44	-.24	.31	-.07	.44	-.15	.38	-.24	.41	-.27	-.29	1.00			
TMTB	-.15	.52	.44	-.20	.41	.13	-.12	.54	-.30	.43	-.12	.56	-.17	.48	-.32	.50	-.40	-.40	.66	1.00		
VF_Animals	.16	-.39	-.38	.18	-.40	-.09	.08	-.42	.22	-.25	.12	-.33	.17	-.36	.20	-.34	.34	.35	-.32	-.39	1.00	
VF_FAS	.19	-.28	-.29	.12	-.33	-.05	.11	-.30	.18	-.21	.14	-.29	.22	-.30	.27	-.24	.30	.36	-.35	-.36	.43	1.00

Table 13: Eigenvalue and variance of components: solution 1

hypertensives and normotensives using all cognitive variables

Component	Initial Eigenvalues		
	Total	% of Variance	Cumulative %
1	7.079	32.177	32.177
2	2.075	9.433	41.610
3	1.291	5.870	47.481
4	1.229	5.588	53.069
5	1.060	4.817	57.886
6	.988	4.493	62.379
7	.927	4.214	66.592
8	.888	4.036	70.629
9	.776	3.527	74.156
10	.715	3.250	77.406
11	.679	3.086	80.492
12	.644	2.929	83.421
13	.548	2.489	85.910
14	.526	2.392	88.302
15	.471	2.140	90.442
16	.389	1.769	92.211
17	.364	1.654	93.865
18	.330	1.499	95.364
19	.318	1.445	96.810
20	.258	1.174	97.984
21	.239	1.086	99.070
22	.205	.930	100.000

Extraction Method: Principal Component Analysis.

Figure 20: Scree plot from PCA for solution 1

Hypertensives and normotensives using all cognitive variables

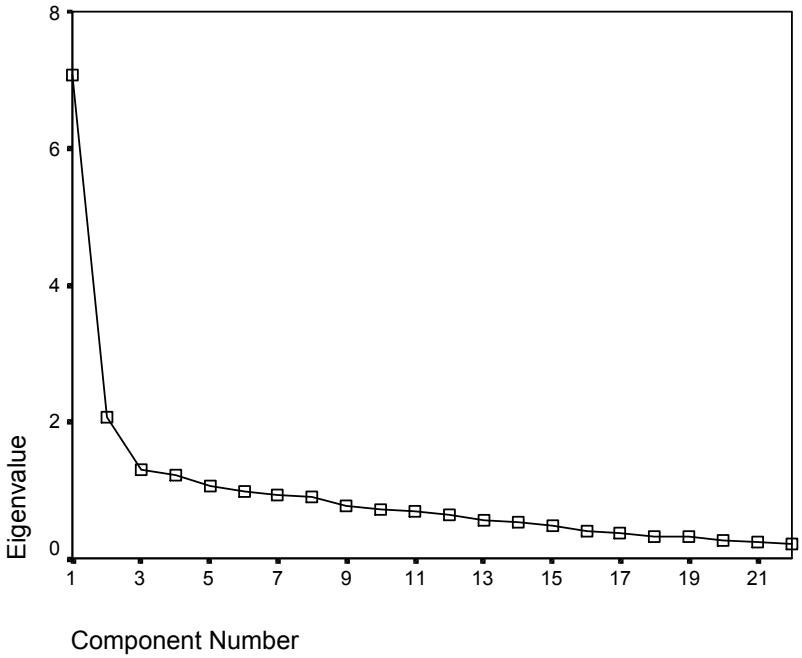


Table 14: Unrotated component matrix for solution 1. For variable definitions, see Appendix VIII

	Component				
	1	2	3	4	5
CRT2	.78	.34	.02	.01	.06
DPICRT	.78	.28	-.03	.23	.03
DRE2RT	.76	.12	-.28	.13	.08
DRE1RT	.76	.27	-.17	.14	.07
MSRT	.71	.23	.19	.19	-.32
TMTB	.67	-.01	.19	-.29	.24
VIGRT	.67	.25	-.04	-.10	-.04
SPMRT	.63	.25	.20	.19	-.12
TMTA	.62	.01	.23	-.27	.26
SRT	.62	.33	-.19	-.07	-.07
VF_Animals	-.58	.06	-.03	.40	.05
DRECALL	-.55	.53	.11	.04	-.02
VF_FAS	-.54	.17	.04	.45	.04
IRECALL	-.53	.49	.09	.08	.00
DPICSI	-.41	.37	-.05	.16	-.17
SPMSI	-.39	.23	-.26	.05	.07
DRE2SI	-.43	.49	.38	-.32	.04
DRE1SI	-.42	.46	.44	-.25	.10
CRT2ACC	-.11	.46	-.32	-.08	-.20
VIGFA	.18	-.22	.52	.39	.19
VIGACC	-.38	.09	-.34	-.39	.01
MSSI	-.16	.23	-.25	.15	.82

Extraction Method: Principal Component Analysis.

Table 15: Rotated component matrix for solution 1

	Component				
	1	2	3	4	5
Picture recognition RT - DPICRT	.81	-.14	-.17	-.15	.04
Choice reaction time - CRT2	.79	-.29	-.03	-.07	.03
Immediate word recognition RT - DRE1RT	.78	-.18	-.22	-.01	.10
Numeric working memory RT -MSRT	.74	-.10	-.07	-.22	-.35
Delayed word recognition RT - DRE2RT	.70	-.21	-.38	.03	.13
Simple reaction time - SRT	.68	-.20	-.09	.19	-.02
Spatial memory RT - SPMRT	.67	-.11	-.01	-.25	-.16
Number vigilance RT - VIGRT	.64	-.31	-.06	.05	-.06
Trail-making test B (time) - TMTB	.42	-.65	-.01	-.16	.08
Verbal fluency for letters - VF_FAS	-.22	.64	.18	-.13	.16
Trail-making test A (time) TMTA	.39	-.62	.03	-.19	.09
Verbal fluency for animals - VF_Animals	-.33	.60	.09	-.08	.16
Delayed picture recognition acc - DPICSI	-.05	.49	.29	.18	-.03
Spatial memory accuracy - SPMSI	-.14	.34	.13	.29	.21
Delayed word recognition acc - DRE2SI	-.15	.05	.79	.11	.01
Immediate word recognition acc - DRE1SI	-.15	.06	.79	.01	.05
Delayed word recall accuracy - DRECALL	-.11	.45	.58	.17	.08
Immediate word recall accuracy - IRECALL	-.11	.46	.53	.14	.11
Number vigilance false alarms - VIGFA	.05	-.02	-.02	-.73	.02
Number vigilance accuracy - VIGACC	-.30	-.01	.12	.55	.10
Choice reaction time accuracy - CRT2ACC	.21	.25	.16	.49	-.03
Numeric working memory accuracy - MSSI	.01	.10	.08	.03	.90

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.

4.1.1.2 Simple structure

Examination of the rotated component matrix shows that the factor solution is close to achieving simple structure, according to the Thurstone criteria (described in section 2.3.2.4). Each row of the matrix contains at least one loading close to zero (<.09) except for three variables (verbal fluency for letters, spatial memory accuracy, immediate word recall accuracy) where the lowest loadings are ≤.13. Each column contains at least as many loadings close to zero as there are factors, with the exception of Factor 1 that has three loadings less than .09. In general, each factor has a few high loadings with the other loadings being low or close to zero, and the majority of variables load primarily on one factor with low loadings on other factors.

4.1.1.3 Interpretation

Factors were interpreted by examining the primary loading of each variable. Factor 1 consisted of the reaction time scores from the subtests of the CDR assessment battery. As the subtests are designed to measure the range of cognitive functions of attention, episodic memory and working memory, and the reaction time scores from these subtests loaded together, Factor 1 appeared to represent the time taken for an individual to formulate a response, labelled Speed of Cognition.

Factor 2 consisted of the four variables from the traditional neuropsychological tests of executive function, with a lower loading from the delayed picture recognition accuracy. The loading of the traditional neuropsychological tests together suggests that the tests measure an aspect of cognition not covered by the CDR battery, and provides support for the construct validity of the tests. Therefore Factor 2 was labelled Executive Function.

Factor 3 had primary loadings from the accuracy scores of the CDR subtests. This factor, labelled Episodic Memory, appeared to reflect the ability to recognise and recall information from memory independent of the time taken to do so. Interestingly, the immediate and delayed word recall subtests that contributed to Factor 3 also had secondary loadings on Factor 2, in contrast to near-zero loadings from the immediate and delayed word recognition tasks. As the direction of the secondary loadings were the same as that for the verbal fluency tests on Factor 2, the loadings perhaps represent some aspect of the verbalising response common to the subtests.

Factor 4 consisted of the accuracy variables from the number vigilance and choice reaction time tasks that represent the ability to concentrate on the task at hand without making errors, thus labelled Continuity of Attention.

Factor 5 consisted of the numeric working memory accuracy variable alone, with the highest loading of the rotated matrix at .90. The only other variables with notable loadings on Factor 5 were a secondary loading of -.35 from numeric working memory reaction time, showing the dissociation between speed and accuracy, and a loading of .21 from spatial memory accuracy. The spatial memory accuracy variable loaded weakly across all five factors; given the nature of the task and its demands on working

memory, the loading on Factor 5 would be expected to be higher. Despite having only one primary loading, the magnitude of the loading from numeric working memory accuracy suggested that Factor 5 was a valid factor, and thus labelled Working Memory.

4.1.1.4 Comparison with Wesnes et al.'s (2000) solution

The factor structure of the CDR system has previously been demonstrated in a sample of 272 healthy middle-aged participants [77]. PCA with Varimax rotation was performed on 17 variables from the CDR assessment battery. The variables entered in the Wesnes et al. study differ slightly to those employed here: traditional neuropsychological tests of executive function were not administered in the Wesnes et al. study and data were therefore not available; data from the immediate word recognition subtest were not available as it is not routinely included with the CDR battery for middle-aged volunteers; an additional joystick tracking task was included in the battery by Wesnes et al. as a further measure of attention (tracking error); the number of stimuli was greater for the majority of subtests in the CDR battery for middle-aged participants than the battery used in the Newcastle Cognitive Substudy designed for elderly participants (e.g. word recognition, 15 vs. 12 words respectively).

Table 16: Factor structure from Wesnes et al. (2000)

	Component				
	1	2	3	4	5
Picture recognition RT - DPICRT	.80	-.16	.17	.05	.09
Word recognition RT - DRE2RT	.77	-.30	.02	.09	.14
Numeric working memory RT - MSRT	.74	-.10	.31	-.17	-.13
Spatial memory RT - SPMRT	.67	.10	.16	-.23	-.37
Immediate word recall accuracy - IRECALL	-.12	.84	.01	.11	.11
Delayed word recall accuracy - DRECALL	-.17	.83	.04	-.02	.07
Delayed word recognition acc - DRE2SI	-.13	.69	.13	.03	-.06
Delayed picture recognition acc - DPICSI	.09	.50	-.19	.33	.10
Simple reaction time - SRT	.10	-.30	.81	.10	.20
Choice reaction time - CRT2	.39	-.20	.68	-.16	-.11
Number vigilance detection RT - VIGRT	.31	.15	.65	-.24	-.08
Number vigilance detection acc - VIGACC	-.08	.04	-.06	.76	.06
Choice reaction time accuracy - CRT2ACC	.14	.16	.28	.47	.27
Number vigilance false alarms - VIGFA	.10	.06	-.45	-.53	-.16
Tracking error	.09	.07	.26	-.62	.04
Numeric working memory acc - MSSI	-.14	.06	.08	.15	.77
Spatial memory accuracy - SPMSI	.08	.24	-.15	-.01	.73

Extraction Method: Principal Component Analysis.

Overall, the five factor solution produced here is in general agreement with the Wesnes et al. solution (Table 16). Both solutions come close to achieving simple structure with the majority of variables having primary loadings on one factor only, with minor loadings on other factors. The Executive Function factor that emerged here is absent from the Wesnes et al. solution because the tests were not administered. With the exception of the accuracy scores from the picture recognition and spatial working memory subtests that have smaller but primary loadings on Factor 2, the pattern of loadings on the remaining factors matches those of the Quality of Episodic Secondary Memory, Continuity of Attention and Quality of Working Memory from Wesnes et al.. However, the main difference between the solutions is the combining of Speed of Memory Index and Power of Attention from the Wesnes et al. solution into the single factor labelled Speed of Cognition here. Examination of the factor loadings from Wesnes et al. shows that although the choice reaction time subtest has a secondary loading on Speed of Memory Index, the magnitude of the primary loadings on Speed of Memory and Power of Attention suggests that the two factors are indeed distinct. As factor solutions are inherently changeable depending on the variables

entered into the analysis, it was possible that the inclusion of the executive function tests had prevented the Speed of Memory and Power of Attention factors emerging as separate factors here. To investigate this the factor analysis was repeated.

4.1.2 Solution 2: excluding tests of executive function

The PCA with Varimax rotation was repeated using the data from the hypertensive and normotensive groups combined, entering all cognitive variables except for the traditional neuropsychological tests of executive function. The correlation matrix remained the same as shown in Table 12, with the omission of the last four variables (TMTA, TMTB, VF_Animals, VF_FAS).

4.1.2.1 Statistical output

The eigenvalues and variance explained by the extracted components after performing PCA are shown in Table 17; four components had eigenvalues greater than unity explaining approximately 57% of the variance. The scree plot (Figure 21) showed that the slope began to flatten at the third component, accounting for approximately 51% of the variance. In order to compare with solution 1 the criterion of eigenvalues above 1 was used, resulting in four components selected for rotation. The unrotated component matrix is shown in Table 18. Varimax rotation with Kaiser normalization produced a rotated solution that converged after 6 iterations. The rotated four factor solution is shown in Table 19.

4.1.2.2 Simple structure

Similar to solution 1, the rotated component matrix shows that the factor solution is close to achieving simple structure with the majority of rows containing at least one loading close to zero. Each column contains at least as many loadings close to zero as there are factors, again with the exception of Factor 1. The majority of variables load primarily on one factor with low loadings on other factors.

Table 17: Eigenvalue and variance of components: solution 2

hypertensives and normotensives, excluding tests of executive function

Component	Initial Eigenvalues		
	Total	% of Variance	Cumulative %
1	5.809	32.274	32.274
2	2.055	11.417	43.692
3	1.266	7.031	50.723
4	1.057	5.874	56.597
5	.964	5.355	61.952
6	.910	5.057	67.009
7	.861	4.784	71.793
8	.824	4.580	76.372
9	.765	4.251	80.623
10	.669	3.715	84.339
11	.550	3.056	87.395
12	.487	2.703	90.097
13	.386	2.145	92.242
14	.355	1.971	94.213
15	.325	1.806	96.019
16	.260	1.443	97.462
17	.247	1.370	98.832
18	.210	1.168	100.000

Extraction Method: Principal Component Analysis.

Figure 21: Scree plot from PCA for solution 2

Hypertensives and normotensives, excluding tests of executive function

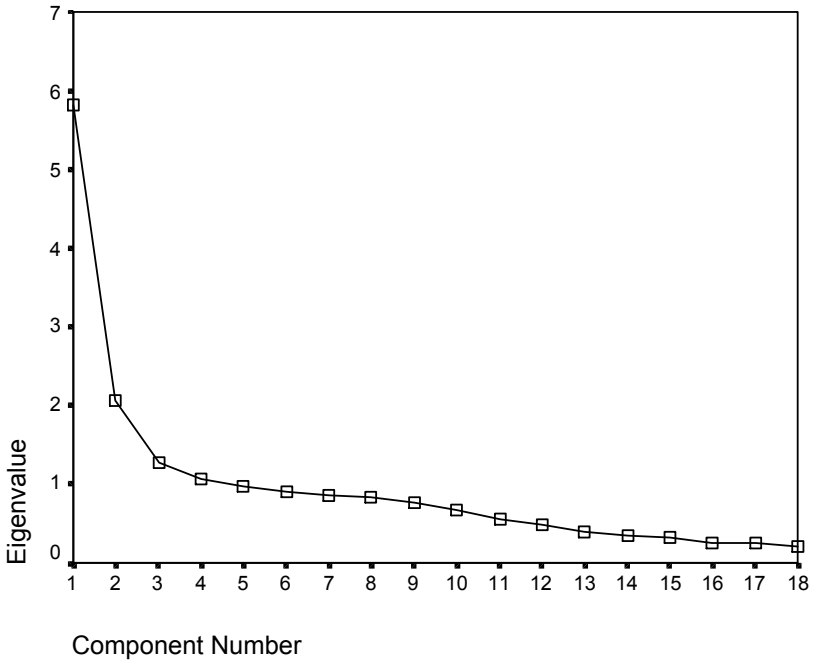


Table 18: Unrotated component matrix for solution 2. For variable definitions, see Appendix VIII

	Component			
	1	2	3	4
DPICRT	.81	.25	.02	.07
DRE2RT	.78	.10	-.26	.06
CRT2	.78	.32	.04	.07
DRE1RT	.78	.25	-.15	.05
MSRT	.74	.20	.26	-.26
VIGRT	.67	.25	-.02	-.02
SPMRT	.66	.23	.25	-.07
SRT	.64	.33	-.15	.00
DRECALL	-.54	.54	.12	.05
IRECALL	-.52	.50	.10	.09
DPICSI	-.39	.37	.00	-.01
SPMSI	-.37	.24	-.25	.06
DRE2SI	-.46	.51	.29	-.14
DRE1SI	-.45	.48	.37	.01
CRT2ACC	-.09	.47	-.29	-.15
VIGFA	.19	-.24	.58	.35
VIGACC	-.39	.11	-.44	-.32
MSSI	-.15	.23	-.29	.83

Extraction Method: Principal Component Analysis.

Table 19: Rotated component matrix solution 2

	Component			
	1	2	3	4
Choice reaction time - CRT2	.83	-.10	-.13	.02
Picture recognition RT - DPICRT	.82	-.18	-.14	.00
Immediate word recognition RT - DRE1RT	.79	-.24	.01	.06
Numeric working memory RT -MSRT	.73	-.08	-.19	-.39
Delayed word recognition RT - DRE2RT	.72	-.40	.06	.08
Simple reaction time - SRT	.72	-.11	.09	.04
Number vigilance RT - VIGRT	.70	-.13	-.04	-.04
Spatial memory RT - SPMRT	.68	-.03	-.24	-.19
Immediate word recognition acc - DRE1SI	-.13	.74	-.06	-.01
Delayed word recognition acc - DRE2SI	-.13	.74	.08	-.11
Delayed word recall accuracy - DRECALL	-.18	.72	.17	.14
Immediate word recall accuracy - IRECALL	-.18	.67	.15	.18
Delayed picture recognition acc - DPICSI	-.13	.47	.20	.09
Number vigilance false alarms - VIGFA	.03	-.03	-.74	.02
Number vigilance accuracy - VIGACC	-.27	.08	.62	-.05
Choice reaction time accuracy - CRT2ACC	.18	.28	.47	.07
Spatial memory accuracy - SPMSI	-.19	.25	.33	.23
Numeric working memory accuracy - MSSI	.00	.11	-.02	.91

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.

4.1.2.3 Interpretation

The exclusion of the tests of executive function resulted in a four factor solution compared to the five factors that emerged from solution 1. The remaining four factors match very well the factors from solution 1, the absence of the Executive Function factor being the obvious omission. Factor 1 of the repeated solution contains all of the variables that comprised the Speed of Cognition factor from solution 1; the exclusion of the tests of executive function did not lead to the discrimination of separate factors akin to those of Speed of Memory Index and Power of Attention from the Wesnes et al. study. As the Wesnes et al. solution produced five factors using almost identical variables, yet solution 2 produced only four, it was of interest to investigate how the variables would load if forced to fit to a five factor solution.

4.1.3 Solution 3: forced five factor solution

The PCA with Varimax rotation from solution 2 was repeated but replacing the eigenvalue criterion for component selection with a fixed number, thus forcing a five factor rotated solution.

4.1.3.1 Statistical output

The eigenvalues and scree plot were the same as those for solution 2. The unrotated component matrix is shown in Table 20. Varimax rotation with Kaiser normalization produced a rotated solution that converged after 6 iterations. The rotated five factor solution is shown in Table 21.

Table 20: Unrotated component matrix for forced five factor solution. For variable definitions, see Appendix VIII

	Component				
	1	2	3	4	5
DPICRT	.81	.25	.02	.07	.12
DRE2RT	.78	.10	-.26	.06	.15
CRT2	.78	.32	.04	.07	.00
DRE1RT	.78	.25	-.15	.05	.20
MSRT	.74	.20	.26	-.26	.15
VIGRT	.67	.25	-.02	-.02	.00
SPMRT	.66	.23	.25	-.07	-.13
SRT	.64	.33	-.15	.00	-.13
DRECALL	-.54	.54	.12	.05	.12
IRECALL	-.52	.50	.10	.09	.25
DPICSI	-.39	.37	.00	-.01	-.13
DRE2SI	-.46	.51	.29	-.14	-.05
DRE1SI	-.45	.48	.37	.01	-.05
VIGFA	.19	-.24	.58	.35	.14
VIGACC	-.39	.11	-.44	-.32	.20
MSSI	-.15	.23	-.29	.83	-.16
SPMSI	-.37	.24	-.25	.06	.62
CRT2ACC	-.09	.47	-.29	-.15	-.52

Extraction Method: Principal Component Analysis.

Table 21: Rotated component matrix for forced five factor solution

	Component				
	1	2	3	4	5
Picture recognition RT - DPICRT	.83	-.17	-.13	-.04	.00
Choice reaction time - CRT2	.83	-.10	-.06	-.14	.04
Immediate word recognition RT - DRE1RT	.81	-.24	-.02	.10	.04
Numeric working memory RT -MSRT	.75	-.07	-.17	-.11	-.38
Delayed word recognition RT - DRE2RT	.74	-.41	.03	.09	.06
Simple reaction time - SRT	.69	-.10	.18	-.15	.08
Number vigilance RT - VIGRT	.69	-.13	.01	-.10	-.03
Spatial memory RT - SPMRT	.66	-.01	-.11	-.33	-.13
Immediate word recognition acc - DRE1SI	-.14	.74	-.04	-.03	.01
Delayed word recognition acc - DRE2SI	-.14	.74	.10	.01	-.10
Delayed word recall accuracy - DRECALL	-.17	.71	.09	.25	.11
Immediate word recall accuracy - IRECALL	-.16	.66	.01	.36	.12
Delayed picture recognition acc - DPICSI	-.15	.47	.23	.02	.10
Number vigilance false alarms - VIGFA	.05	-.02	-.73	-.19	.03
Choice reaction time accuracy - CRT2ACC	.10	.28	.65	-.25	.16
Number vigilance accuracy - VIGACC	-.25	.07	.46	.46	-.13
Spatial memory accuracy - SPMSI	-.11	.22	.02	.76	.08
Numeric working memory accuracy - MSSI	-.02	.10	.01	.05	.93

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.

4.1.3.2 Simple structure

The rotated solution is not as close to achieving simple structure as the previous solutions as there is an increase in the magnitude of secondary loadings from a number of variables, such as immediate and delayed word recall accuracy. In particular, number vigilance accuracy loads equally across Factors 3 and 4 making it difficult to associate the variable with a factor. Compared to solutions 1 and 2, the factor matrix is more difficult to interpret.

4.1.3.3 Interpretation

The selection of five factors for rotation did not cause Factor 1 to diverge into two separate factors similar to those of Speed of Memory Index and Power of Attention from the Wesnes et al. solution. The additional factor emerged as Factor 4 and consisted of spatial memory accuracy with a lower loading of number vigilance accuracy, which was no longer as strongly associated with similar measures of attention. As the four factors from solution 2 matched very well with the factors from

Wesnes et al., albeit with the merging of Speed of Memory Index and Power of Attention, the additional factor from the forced five factor solution added very little. The loading of variables from the Speed of Memory Index and Power of Attention factors on Factor 1 in all three solutions, suggests that this is a robust factor in this sample. As the sample is a combination of normotensive and hypertensive individuals, the question arises as to whether Speed of Memory and Power of Attention would emerge as a single factor in both populations separately.

4.1.4 Solution 4: hypertensives only

The analysis of the hypertensive participants separately also presented the opportunity to test the robustness of the Executive Function factor within the sample. Therefore all cognitive variables were entered in the PCA analysis. The correlation matrix is shown in Table 22.

4.1.4.1 Statistical output

The eigenvalues and variance explained by the extracted components after performing PCA are shown in Table 23; six components had eigenvalues greater than unity explaining approximately 64% of the variance. Examination of the scree plot (Figure 22) showed that the slope began to flatten at the fifth component, accounting for approximately 59% of the variance. In order to be comparable to with solution 1, components were selected for rotation based on the eigenvalue criterion of greater than unity, therefore six components were selected for rotation, shown in Table 24. The rotated six factor solution is shown in Table 25.

Table 22: Correlation matrix of baseline cognitive data: hypertensives only. For variable definitions, see Appendix VIII

	DRE1SI	DRE1RT	SRT	VIGACC	VIGRT	VIGFA	CRT2ACC	CRT2	SPMSI	SPMRT	MSSI	MSRT	DRE2SI	DRE2RT	DPICSI	DPICRT	IRECALL	DRECALL	TMTA	TMTB	VF_Animals	VF_FAS
DRE1SI	1.00																					
DRE1RT	-.30	1.00																				
SRT	-.15	.50	1.00																			
VIGACC	.14	-.25	-.18	1.00																		
VIGRT	-.14	.48	.51	-.32	1.00																	
VIGFA	-.11	.13	.07	-.36	.09	1.00																
CRT2ACC	.12	-.05	.11	.20	.00	-.10	1.00															
CRT2	-.26	.54	.64	-.34	.62	.28	.02	1.00														
SPMSI	.28	-.11	-.11	.25	-.16	-.15	.00	-.25	1.00													
SPMRT	-.15	.39	.26	-.36	.38	.13	-.02	.44	-.28	1.00												
MSSI	.08	-.05	-.02	.06	.02	-.11	.11	-.01	.11	-.11	1.00											
MSRT	-.18	.50	.34	-.30	.44	.26	-.07	.54	-.19	.62	-.35	1.00										
DRE2SI	.61	-.31	-.24	.25	-.19	-.09	.21	-.22	.17	-.15	.08	-.21	1.00									
DRE2RT	-.39	.75	.48	-.17	.41	.13	-.04	.56	-.14	.37	-.02	.45	-.40	1.00								
DPICSI	.32	-.15	-.10	.09	-.17	-.09	.15	-.28	.21	-.19	.08	-.18	.27	-.24	1.00							
DPICRT	-.29	.61	.42	-.31	.44	.25	-.02	.62	-.16	.51	-.02	.65	-.30	.66	-.29	1.00						
IRECALL	.36	-.17	-.20	.21	-.21	-.19	.10	-.24	.25	-.13	.17	-.16	.40	-.28	.27	-.20	1.00					
DRECALL	.38	-.26	-.20	.22	-.19	-.20	.12	-.27	.25	-.21	.15	-.24	.43	-.33	.34	-.31	.72	1.00				
TMTA	-.23	.45	.27	-.20	.39	.09	-.13	.48	-.25	.31	-.07	.38	-.16	.44	-.28	.42	-.24	-.30	1.00			
TMTB	-.20	.44	.32	-.18	.35	.15	-.09	.52	-.24	.34	-.10	.35	-.17	.42	-.37	.39	-.31	-.35	.62	1.00		
VF_Animals	.22	-.36	-.35	.24	-.39	-.04	.02	-.46	.29	-.26	.09	-.30	.20	-.39	.32	-.32	.28	.29	-.36	-.41	1.00	
VF_FAS	.34	-.33	-.31	.13	-.35	.05	.05	-.37	.31	-.22	.09	-.23	.27	-.40	.29	-.25	.27	.32	-.35	-.35	.49	1.00

Table 23: Eigenvalue and variance of components for solution 4

Component	Initial Eigenvalues		
	Total	% of Variance	Cumulative %
1	7.046	32.029	32.029
2	2.073	9.421	41.450
3	1.529	6.948	48.398
4	1.288	5.855	54.253
5	1.119	5.085	59.338
6	1.058	4.811	64.149
7	.991	4.503	68.652
8	.904	4.110	72.762
9	.759	3.450	76.212
10	.744	3.380	79.591
11	.623	2.830	82.421
12	.532	2.419	84.840
13	.504	2.293	87.133
14	.460	2.093	89.225
15	.435	1.979	91.204
16	.386	1.753	92.957
17	.348	1.580	94.538
18	.307	1.397	95.934
19	.275	1.252	97.186
20	.229	1.040	98.226
21	.213	.968	99.194
22	.177	.806	100.000

Extraction Method: Principal Component Analysis.

Figure 22: Scree plot from PCA for solution 4

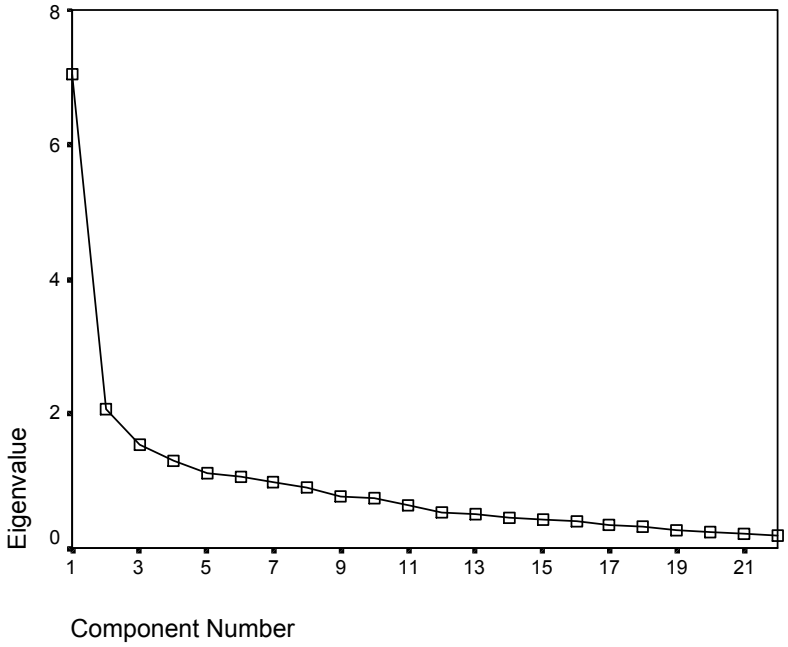

8
6
4
2
0
Eigenvalue
1
3
5
7
9
11
13
15
17
19
21
Component Number

Table 24: Unrotated component matrix for solution 4. For variable definitions, see Appendix VIII

	Component					
	1	2	3	4	5	6
CRT2	.79	.31	-.02	-.03	-.18	.07
DRE2RT	.75	.14	-.19	.32	.15	-.04
DPICRT	.75	.26	.14	.23	.10	-.01
DRE1RT	.73	.28	-.09	.29	.17	.00
MSRT	.67	.27	.39	-.03	.24	-.27
TMTB	.65	.02	-.11	-.34	.16	.21
VIGRT	.64	.32	-.08	-.04	-.18	.08
TMTA	.64	.06	-.11	-.28	.24	.26
VF_Animals	-.60	.02	.25	.33	.08	-.01
SRT	.59	.33	-.23	.15	-.24	-.14
SPMRT	.58	.25	.32	-.12	.08	-.12
DRECALL	-.56	.54	.00	-.02	.15	.12
VF_FAS	-.56	.15	.39	.24	-.01	.05
DRE2SI	-.50	.48	.06	-.49	-.03	.03
DRE1SI	-.49	.49	.14	-.34	-.04	.07
DPICSI	-.44	.35	.12	.22	-.18	-.20
IRECALL	-.49	.57	.01	.01	.25	.16
VIGFA	.28	-.07	.62	.08	-.31	.13
VIGACC	-.44	.03	-.51	-.01	.33	-.28
SPMSI	-.39	.25	-.08	.41	.31	.08
MSSI	-.16	.21	-.37	.26	-.39	.60
CRT2ACC	-.12	.34	-.30	-.07	-.45	-.53

Extraction Method: Principal Component Analysis.

Table 25: Rotated component matrix for solution 4

	Component					
	1	2	3	4	5	6
Immediate word recognition RT - DRE1RT	.81	-.13	-.20	-.02	-.02	-.09
Picture recognition RT - DPICRT	.78	-.11	-.17	.20	-.12	-.10
Delayed word recognition RT - DRE2RT	.77	-.16	-.35	-.08	.01	-.07
Choice reaction time - CRT2	.71	-.39	-.07	.28	.06	.12
Simple reaction time - SRT	.65	-.18	-.13	.04	.12	.34
Numeric working memory RT -MSRT	.65	-.12	-.01	.25	-.55	-.06
Number vigilance RT - VIGRT	.61	-.34	.00	.20	.11	.15
Spatial memory RT - SPMRT	.52	-.21	.05	.31	-.35	-.02
Trail-making test B (time) - TMTB	.38	-.66	-.04	.06	-.07	-.20
Verbal fluency for animals - VF_Animals	-.30	.64	.14	-.03	.01	-.12
Verbal fluency for letters - VF_FAS	-.25	.61	.29	.15	.02	-.10
Trail-making test A (time) - TMTA	.42	-.60	-.02	.03	-.04	-.28
Delayed picture recognition acc - DPICSI	-.06	.53	.29	.00	.05	.29
Spatial memory accuracy - SPMSI	.05	.52	.19	-.35	.15	-.21
Delayed word recognition acc - DRE2SI	-.26	-.02	.79	-.05	-.03	.17
Immediate word recognition acc - DRE1SI	-.21	.11	.74	.02	.01	.12
Immediate word recall accuracy - IRECALL	.01	.33	.68	-.24	.11	-.12
Delayed word recall accuracy - DRECALL	-.08	.34	.67	-.22	.14	-.03
Number vigilance accuracy - VIGACC	-.23	.11	.10	-.75	-.04	.11
Number vigilance false alarms - VIGFA	.11	.07	-.11	.74	-.08	-.07
Numeric working memory accuracy - MSSI	.04	.06	.12	.01	.88	.01
Choice reaction time accuracy - CRT2ACC	.06	.07	.13	-.16	.01	.81

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.

4.1.4.2 Simple structure

The criteria of simple structure are not as well met as in solution 1 as more variables have higher secondary loadings, making the factors less well-defined. Factor 6 has emerged based primarily on the loading from choice reaction time accuracy only, indicating that this is a weak factor.

4.1.4.3 Interpretation

Factor 1 again consists of the reaction time scores of the subtests from the CDR battery with no separation of the Power of Attention of Speed of Memory factors from the Wesnes et al. solution. The traditional tests of executive function load together as Factor 2, albeit with lower but primary loadings from delayed picture recognition

accuracy and spatial memory accuracy. With the exception of delayed picture recognition accuracy, Factor 3 consists of the same variables that constitute the Episodic Memory factor from solution 1 and that of Wesnes et al.. Factor 5 is defined by numeric working memory accuracy alone, as in solution 1. Factor 4 consists of two of the three variables that make up the Continuity of Attention factor from solution 1; the third variable, choice reaction time accuracy, here loads separately and forms the additional sixth factor in this solution. Given that choice reaction time accuracy loads with the other variables of Continuity of Attention in solution 1 and Wesnes et al.'s solution, and that the solution is less close to simple structure, the sixth factor is not very robust. Overall, the factor structure from solution 1 is demonstrated in the sample of hypertensives alone.

4.1.5 Solution 5: normotensives only

The analysis of the solution 4 was repeated using data from the normotensive participants only. The correlation matrix is shown in Table 26.

4.1.5.1 Statistical output

The eigenvalues and variance explained by the extracted components after performing PCA are shown in Table 27; six components had eigenvalues greater than unity explaining approximately 64% of the variance. It was difficult to determine the number of factors for rotation from examination of the scree plot (Figure 23) as there was little change in the angle of the slope between components 3 and 8. However, for comparability with solution 1, six components were selected for rotation (Table 28) based on the eigenvalues. The rotated six factor solution is shown in Table 29.

4.1.5.2 Simple structure

As in solution 4 using hypertensives only, the criteria of simple structure are not very well met as a higher number of variables have relatively large secondary loadings, making the factors less well-defined. A sixth factor has emerged again based primarily on the loading from a single variable, although different to that from solution 4.

4.1.5.3 Interpretation

As in all previous solutions, Factor 1 shows no separation into the Power of Attention of Speed of Memory factors from the Wesnes et al. solution. The second factor to emerge is very similar to the Episodic Memory factor rather than Executive Function, as in this solution the traditional tests of executive function load somewhat disparately; the verbal fluency variables load together, along with numeric working memory accuracy as Factor 3, but the Trail-Making Test variables have low loadings. Factor 4 has loadings from two of the attention test variables, whereas Factors 5 and 6 are weak factors defined by the single variables of spatial memory accuracy and number vigilance accuracy respectively. The solution is generally quite difficult to interpret due to the high number of secondary loadings, although the emergence of the reaction time subtests loading together as a single factor is a robust finding.

Table 26: Correlation matrix of baseline cognitive data: normotensives. For variable definitions, see Appendix VIII

	DRE1SI	DRE1RT	SRT	VIGACC	VIGRT	VIGFA	CRT2ACC	CRT2	SPMSI	SPMRT	MSSI	MSRT	DRE2SI	DRE2RT	DPICSI	DPICRT	IRECALL	DRECALL	TMTA	TMTB	VF_Animals	VF_FAS
DRE1SI	1.00																					
DRE1RT	-.22	1.00																				
SRT	-.10	.50	1.00																			
VIGACC	.05	-.10	-.14	1.00																		
VIGRT	-.23	.52	.60	-.10	1.00																	
VIGFA	.02	-.02	-.15	.06	-.06	1.00																
CRT2ACC	.10	.03	.15	-.04	-.04	-.23	1.00															
CRT2	-.12	.66	.70	-.07	.62	-.03	.01	1.00														
SPMSI	.07	-.16	-.14	.03	-.12	-.04	.19	-.14	1.00													
SPMRT	-.11	.54	.49	-.10	.43	.02	.02	.57	-.28	1.00												
MSSI	.15	.04	-.06	-.02	-.17	.07	.09	.00	.03	.05	1.00											
MSRT	-.23	.72	.50	-.05	.53	.01	.04	.68	-.19	.60	-.12	1.00										
DRE2SI	.41	-.13	-.07	.21	-.13	-.04	.17	-.08	.10	-.08	.03	-.07	1.00									
DRE2RT	-.30	.77	.43	-.12	.46	-.05	-.01	.56	-.21	.48	.02	.62	-.22	1.00								
DPICSI	.19	-.17	-.11	.11	-.19	-.16	.22	-.13	.09	-.12	.09	-.18	.22	-.20	1.00							
DPICRT	-.16	.77	.56	-.04	.53	-.01	.04	.70	-.20	.64	.05	.70	-.06	.69	-.16	1.00						
IRECALL	.31	-.35	-.23	.06	-.29	-.13	.13	-.26	.31	-.29	.10	-.33	.30	-.41	.31	-.31	1.00					
DRECALL	.40	-.26	-.19	.11	-.28	-.14	.23	-.19	.21	-.22	.11	-.30	.37	-.42	.24	-.26	.59	1.00				
TMTA	-.06	.39	.28	-.19	.37	.10	-.13	.39	-.20	.31	-.05	.39	-.09	.35	-.22	.36	-.27	-.26	1.00			
TMTB	-.12	.50	.40	-.12	.40	.07	-.13	.47	-.25	.41	-.05	.47	-.14	.44	-.21	.49	-.41	-.37	.63	1.00		
VF_Animals	.08	-.34	-.37	.04	-.41	-.07	.11	-.38	.13	-.25	.17	-.31	.10	-.31	.13	-.34	.35	.36	-.26	-.32	1.00	
VF_FAS	.08	-.24	-.28	.07	-.34	-.11	.13	-.27	.05	-.20	.18	-.32	.15	-.24	.27	-.26	.29	.34	-.34	-.31	.42	1.00

Table 27: Eigenvalue and variance of components for solution 5

Component	Initial Eigenvalues		
	Total	% of Variance	Cumulative %
1	6.944	31.566	31.566
2	2.272	10.325	41.891
3	1.411	6.412	48.303
4	1.310	5.955	54.258
5	1.138	5.172	59.430
6	1.019	4.633	64.063
7	.902	4.099	68.162
8	.813	3.697	71.859
9	.773	3.514	75.373
10	.718	3.263	78.635
11	.650	2.955	81.590
12	.598	2.716	84.306
13	.518	2.355	86.662
14	.504	2.291	88.952
15	.457	2.078	91.030
16	.387	1.759	92.789
17	.365	1.659	94.448
18	.321	1.460	95.909
19	.300	1.362	97.270
20	.230	1.044	98.314
21	.208	.944	99.258
22	.163	.742	100.000

Extraction Method: Principal Component Analysis.

Figure 23: Scree plot from PCA for solution 5

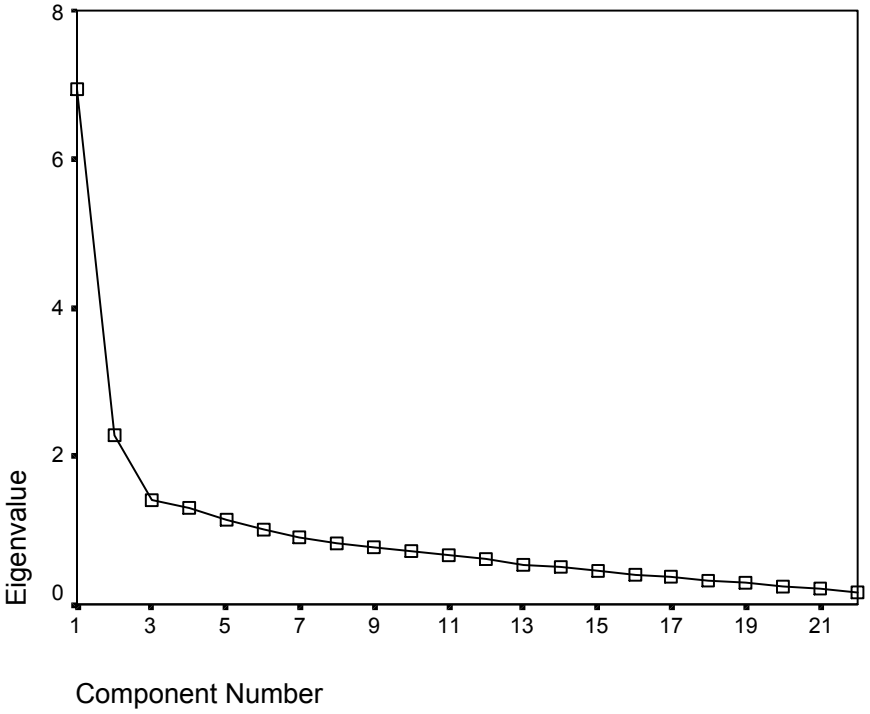


Table 28: Unrotated component matrix for solution 5. For variable definitions, see Appendix VIII

	Component					
	1	2	3	4	5	6
DRE1RT	.81	.24	-.09	.17	.06	.14
DPICRT	.81	.31	.00	.16	.12	.10
MSRT	.80	.21	-.01	.02	.14	.06
CRT2	.79	.34	.04	-.04	.02	.07
DRE2RT	.77	.07	-.21	.20	.09	.08
VIGRT	.72	.12	-.03	-.30	.02	.02
TMTB	.69	-.08	.26	.08	-.20	-.16
SPMRT	.68	.25	.03	.22	.04	-.09
SRT	.68	.34	-.07	-.23	-.09	-.06
TMTA	.57	-.10	.35	.02	-.38	-.11
IRECALL	-.57	.46	.06	-.09	-.13	.11
VF_Animals	-.53	.14	-.21	.38	-.10	-.01
VF_FAS	-.47	.26	-.28	.42	.10	-.21
DRECALL	-.53	.56	.14	-.02	-.10	.00
CRT2ACC	-.09	.55	-.32	-.13	-.12	.08
DRE2SI	-.26	.52	.48	-.10	.18	-.07
DPICSI	-.33	.42	-.07	.01	.17	-.27
DRE1SI	-.32	.39	.60	.00	-.22	-.09
VIGFA	.03	-.36	.48	.30	.09	.43
MSSI	-.10	.24	.02	.67	-.21	.30
VIGACC	-.17	.08	.24	.00	.81	.11
SPMSI	-.31	.19	-.15	-.35	-.12	.70

Extraction Method: Principal Component Analysis.

Table 29: Rotated component matrix for solution 5

	Component					
	1	2	3	4	5	6
Picture recognition RT - DPICRT	.89	-.08	.01	-.06	-.06	.03
Immediate word recognition RT - DRE1RT	.86	-.18	.03	-.06	-.01	-.04
Choice reaction time - CRT2	.84	.01	-.15	.00	.01	-.07
Numeric working memory RT -MSRT	.81	-.13	-.14	-.05	-.06	.03
Delayed word recognition RT - DRE2RT	.75	-.36	.04	-.04	-.09	-.03
Spatial memory RT - SPMRT	.73	-.03	.05	-.02	-.23	-.05
Simple reaction time - SRT	.71	.01	-.28	.19	.04	-.18
Number vigilance RT - VIGRT	.65	-.13	-.41	.03	.03	-.11
Trail-making test B (time) - TMTB	.54	-.03	-.19	-.26	-.34	-.33
Immediate word recognition acc - DRE1SI	-.14	.79	.07	-.08	-.03	-.11
Delayed word recognition acc - DRE2SI	.00	.73	-.02	.07	.01	.27
Delayed word recall accuracy - DRECALL	-.22	.61	.25	.29	.23	.05
Immediate word recall accuracy - IRECALL	-.30	.50	.20	.25	.35	.02
Numeric working memory accuracy - MSSI	.12	.13	.75	-.19	.10	-.10
Verbal fluency for letters - VF_FAS	-.26	.07	.57	.38	-.12	.19
Verbal fluency for animals - VF_Animals	-.37	.07	.56	.20	.05	.01
Number vigilance false alarms - VIGFA	-.04	.02	.12	-.78	.01	.12
Choice reaction time accuracy - CRT2ACC	.15	.16	.15	.49	.37	-.05
Delayed picture recognition acc - DPICSI	-.11	.31	.15	.45	-.06	.22
Spatial memory accuracy - SPMSI	-.16	.07	-.01	-.02	.87	.02
Number vigilance accuracy - VIGACC	-.03	.16	-.06	-.12	-.03	.85
Trail-making test A (time) - TMTA	.42	.08	-.21	-.32	-.26	-.47

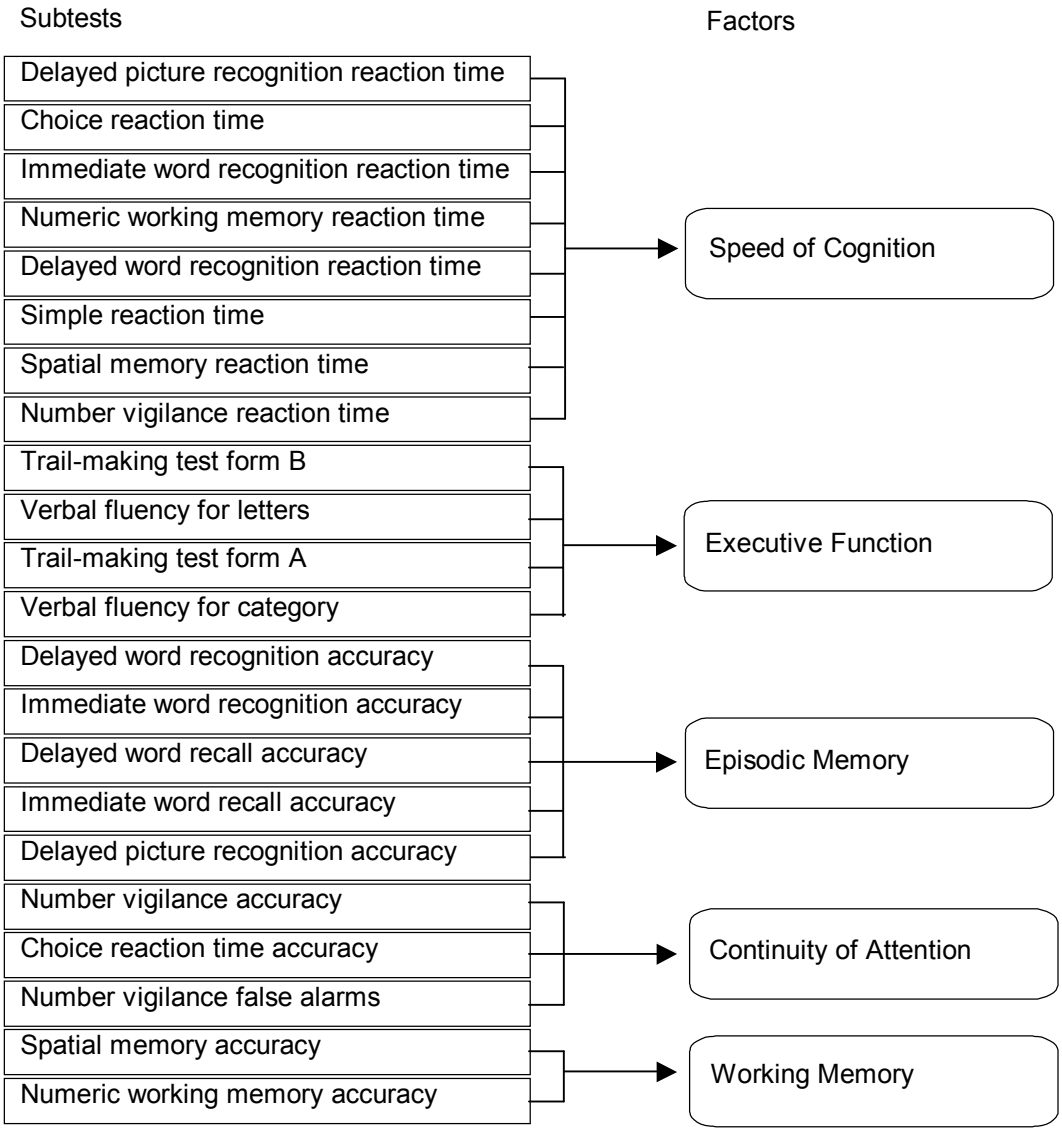
Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.

4.2 Factor analysis summary

Solution 1 included all cognitive variables in the analysis in order to help understand the intercorrelations between the subtests. The five factor solution was in good agreement with a previous factor analysis of the CDR battery [77], with two main exceptions: the emergence of an Executive Function factor consisting of traditional neuropsychological tests of executive function not administered in the Wesnes et al. study; and the variables constituting the Speed of Memory and Power of Attention factors in the Wesnes et al. solution loading as one factor labelled Speed of Cognition here. Further analyses excluding the executive function tests and on the normotensive and hypertensive populations separately, failed to cause the Speed of Cognition factor to diverge into two factors. Thus it appears that Speed of Cognition is a robust factor.

Therefore the five factor solution produced in solution 1 was used as the basis for subsequent analyses of the cognitive data. A diagrammatic representation of the relationship of subtests to factors is shown in Figure 24. Individual subtest scores were combined into composite factor scores for use in the analyses, as described in section 2.3.4.

Figure 24: The relationship of subtest variables to factors



CHAPTER 5: RESULTS – CANDESARTAN AND BP

This chapter presents the results of the Newcastle Cognitive Substudy in relation to the effects on blood pressure, cardiovascular outcomes and cognitive outcomes defined in the main SCOPE protocol. Comparison of the NCS results to the main SCOPE study is also presented.

5.1 Newcastle Cognitive Substudy

5.1.1 Study visit attendance

The majority of participants completed the cognitive assessment for the Newcastle Cognitive Substudy alongside their scheduled SCOPE study visit. However a small number of participants were unable or unwilling to perform the cognitive assessment on some occasions. In such cases, the follow-up data from the SCOPE study visit were still included in the analysis of BP-related and cardiovascular-related outcomes. The number of completed SCOPE study visits and cognitive assessments are shown in Table 30, as well as the number of cognitive assessments administered by the candidate. The majority of the assessments were performed in the research clinic, with only 9 visits that took place in the participants' homes. Because of the rolling recruitment period, not all participants were due for scheduled study visits beyond the minimum follow-up period of 36 months; the number of completed visits as a percentage of those due is shown for comparison. As expected, the percentage who attended each visit diminished over time due to the natural attrition associated with withdrawal of consent and death. At the closeout visit all participants, current and withdrawn, were invited to attend in order to minimise the loss to follow-up which accounted for the higher percentage attendance than the preceding three visits. Adjusting for the number of deceased participants at the SCOPE study close (n=36), the 193 completed closeout visits represented a 90% attendance rate.

Table 30: Number of completed SCOPE study visits

Visit	SCOPE visits attended	SCOPE visits attended/ visits due	Cognitive assessments attended	Cognitive assessments performed by candidate
months	n	%	n	n
Baseline	250	100	250	49
1	240	96	238	58
3	230	92	-	-
6	226	90	-	-
12	222	89	215	169
18	208	83	-	-
24	204	82	198	198
30	198	79	-	-
36	169	77	161	161
42	125	73	-	-
48	76	74	75	75
54	11	65	-	-
Closeout	193	77	182	182

5.1.2 Study drugs and antihypertensive medication

For the 250 participants in the cognitive substudy, the mean length of follow-up was 43.1 ±13.7 months (range 0-59 months) with no significant difference between the candesartan and placebo groups (44±13 vs. 42±14 months, t=1.11, p=.27). In the candesartan group, the mean dose of candesartan was 12±4 mg once daily; 76 (61%) participants continued treatment until study close; the average proportion of the

follow-up period spent on active treatment was 89%. Only 20% of participants in the placebo group were taking placebo with no additional BP-lowering therapy at the last study visit attended. Antihypertensive medications in the two groups at the study closeout visit are shown in Table 31.

Table 31: Antihypertensive therapy at study closeout visit.

Data shown are number of participants. Some participants were taking more than one additional BP-lowering drug. The total for thiazides includes participants receiving add-on 12.5 mg hydrochlorothiazide (HCTZ) as per study protocol. Participants receiving angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists at study close were not taking study medication.

	Candesartan	Placebo
	n=99	n=94
HCTZ (initiated before randomisation)	23	22
Thiazides (prescribed since randomisation)	22	40
Calcium-channel blockers	18	21
Beta-blockers	12	20
Angiotensin converting enzyme inhibitors	5	5
Angiotensin II receptor antagonists	1	2
Alpha-blockers	1	3
No additional antihypertensive therapy	39	20

5.1.3 Blood pressure

For those participants attending the closeout visit, BP fell from 165±8/88±7 mmHg at baseline to 141±16/74±9 mmHg at study close in the candesartan group (SBP, t=14.51, p<.001; DBP, t=13.98, p<.001), and from 166±8/89±7 to 149±20/77±10 mmHg in the placebo group (SBP, t=8.37, p<.001; DBP, t=11.88, p<.001). At the study closeout visit, the difference in BP was 8/3 mmHg lower in the candesartan group (SBP, t=3.07, p<.01; DBP, t=1.87, p=.06). The same results were found when analysed using the last observation carried forward.

The average BP across the study, calculated using data from all planned BP monitoring visits after baseline, was 146±11/78±6 mmHg in the candesartan group versus 153±10/81±7 mmHg in the placebo group (SBP, t=4.77, p<.001; DBP, t=4.16, p<.001). Comparison of the mean BP at each scheduled SCOPE study visit between the candesartan and placebo groups is shown in Figure 25. The initial reduction in BP from baseline to the 1 month and 3 month visits, achieved with the start of study treatment, was much greater in the candesartan group as expected. There is a smaller but clear reduction in BP in the placebo group which may be attributable to the placebo effect, as up until the 3 month visit participants received a maximum of 2 study tablets with no additional BP-lowering therapy beyond that being taken at randomisation. Alternatively, it is possible that non-pharmacological BP reductions could have occurred, perhaps due to modification of lifestyle factors prompted by participants' increased focus on BP by being involved in a hypertension trial. The BP difference between the groups remained at a similar magnitude until the 24 month visit, after which the size of the difference began to diminish due to the introduction of the lower BP target of <150/90 mmHg in accordance with BHS guidelines.

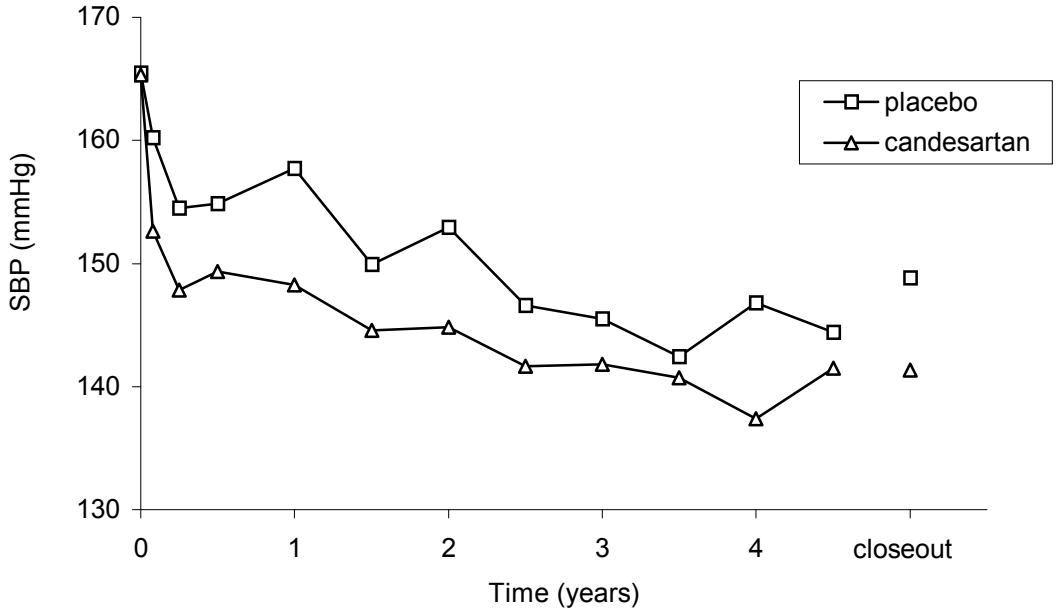
5.1.4 Cardiovascular outcomes

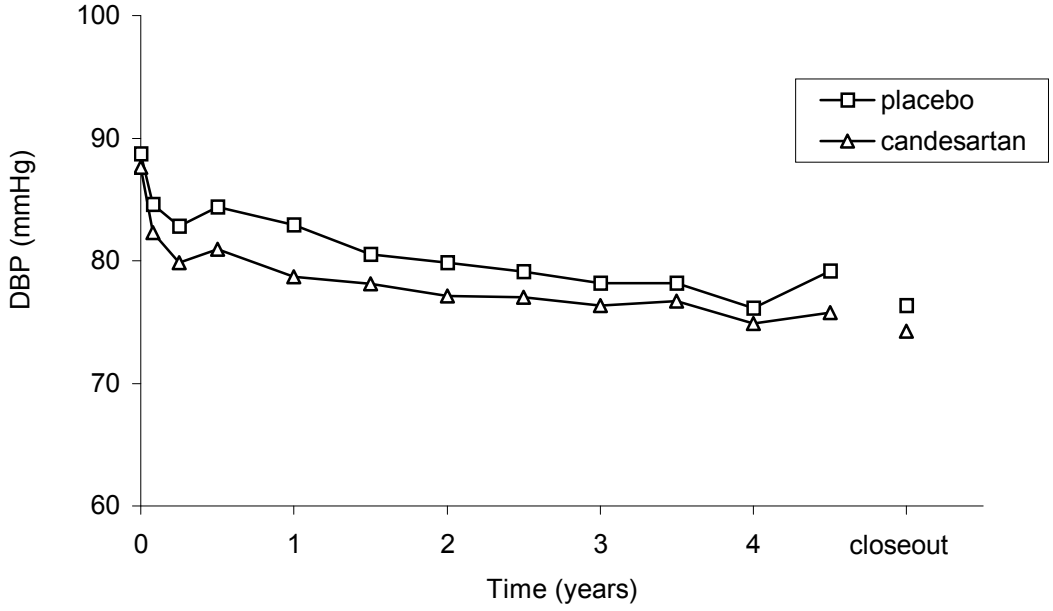
All reported cardiovascular events were evaluated and classified by an Independent Clinical Event Committee from the main SCOPE trial, blind to participants' study group allocation. Within the 250 participants in the Newcastle Cognitive Substudy, stroke occurred after randomisation in 15 participants (7 candesartan, 8 placebo) and myocardial infarction in 10 (3 candesartan, 7 placebo). Comparison of the clinical

event rate between groups was not planned or performed due to the lack of statistical power.

Figure 25: Blood pressure at each scheduled SCOPE study visit

Mean systolic (SBP) and diastolic (DBP) blood pressure at each scheduled SCOPE study visit: candesartan group versus placebo group in the Newcastle Cognitive Substudy





5.1.5 MMSE score and significant cognitive decline

Overall, cognitive function as measured by the MMSE was well maintained in both groups with a mean reduction of approximately a third of an MMSE point over the entire follow-up period. For those participants attending the closeout visit, the mean MMSE score fell from 28.7 ±1.3 at baseline to 28.3 ±2.3 at study close in the candesartan group ($t=1.78$, $p=.08$), and from 28.9 ±1.0 to 28.6 ±1.6 in the placebo group ($t=2.27$, $p<.05$). Between group comparisons showed no significant difference in mean MMSE score at the closeout visit ($t=-0.85$, $p=.28$), or in the change in MMSE score from baseline to study close between the candesartan and placebo groups (-0.38 ±2.1 vs. -0.33 ±1.4, $t=-0.21$, $p=.26$).

It was possible that an effect of treatment might have been obscured by the selective withdrawal of those participants with the greatest cognitive decline. In particular, participants diagnosed with dementia during the study were unable to continue with the SCOPE trial according to the main protocol, and those with significant cognitive decline were unable to provide informed consent for the extension of the follow-up period. Therefore the analyses were repeated using the last recorded MMSE score after baseline. Although the results showed the change in MMSE score to be slightly greater than the analyses based only on those participants attending the closeout visit, there were no significant differences between the candesartan and placebo groups in change scores (-0.55 ±2.3 vs. -0.49 ±1.9, $t=-0.23$, $p=.82$), or last recorded MMSE scores (28.2 ±2.3 vs. 28.3 ±2.3, $t=0.57$, $p=.57$).

Significant cognitive decline, defined as a reduction in MMSE score ≥ 4 points from baseline score on two consecutive occasions, was reported in 11 participants (7 candesartan, 4 placebo), three of whom were formally diagnosed as having dementia (1 candesartan, 2 placebo). As expected, the number of cases of dementia and significant cognitive decline were too low for meaningful statistical analysis.

5.2 The main SCOPE study

5.2.1 Summary results

The results of the main SCOPE study were reported by the SCOPE Executive Committee using an intention to treat analysis following the principles of last observation carried forward [85]. Including the participants in the Newcastle Cognitive Substudy, 4964 participants were randomised, with 4937 included in the analysis (2477 candesartan, 2460 placebo). The mean length of follow-up was 44.6 months. The mean dose of candesartan was 12 ±4 mg once daily and only 16% of the control group participants received placebo alone.

Mean BP was reduced from 166.0/90.3 mmHg to 145.2/79.9 mmHg in the candesartan group and from 166.5/90.4 mmHg to 148.5/81.6 mmHg in the placebo group ($p<.001$ for all). The mean difference in BP reduction of 3.2/1.6 mmHg in favour of the candesartan group ($p<.001$ for both) was considerably smaller than that predicted in the planning of the SCOPE study. The BP difference was, however, associated with a modest, statistically non-significant reduction in major cardiovascular events (risk reduction 10.9%, $p=.19$) and a marked reduction in non-fatal stroke (risk reduction 27.8%, $p=.04$).

Cognitive function was well maintained in both groups; MMSE score fell from 28.5 to 28.0 in the candesartan group and from 28.5 to 27.9 in the placebo group. There was no significant difference in the change in MMSE score (mean difference 0.15, $p=.20$), or the proportion of patients with significant cognitive decline (13.5 vs. 15.2 events per 1000 patient-years, $p>.20$) or dementia (6.8 vs. 6.3 events per 1000 patient-years, $p>.20$).

5.2.2 Comparison between NCS and SCOPE

Because the participants in the Newcastle Cognitive Substudy were randomised and treated according to the protocol of the main SCOPE study, the characteristics of the intervention such as the mean length of follow-up, mean dose of candesartan and the proportion receiving placebo without additional antihypertensive therapy were almost identical.

However, the difference in BP reduction between the candesartan and placebo groups was substantially larger in the Newcastle Cognitive Substudy than in the main SCOPE trial (approximately 8/3 vs. 3/2 mmHg). The Newcastle subsample was well-matched to the main SCOPE cohort at randomisation with very similar starting BP levels; BP reductions of a similar magnitude were observed in the placebo groups of both samples; therefore, the greater difference between the treatment groups is accounted for by the lower levels of BP achieved in the candesartan group in the Newcastle Cognitive Substudy compared to the main SCOPE study (approx. 141/74 vs. 145/80 mmHg). There was no *a priori* expectation that this would occur, therefore only post-hoc explanations can be offered as to why this was the case. One possibility is that the lower BP targets, instigated in accordance with British Hypertension Society guidelines midway through the study, were more vigorously enforced in the Newcastle centre than elsewhere. However, this would not necessarily produce a larger BP gap between groups as it would be expected to produce lower BP levels in the placebo group than those in the main study. Perhaps the likeliest explanation is better compliance with study medication at the Newcastle site, possibly due to having a dedicated study team in place.

In terms of cognition as measured by the MMSE score, the results of the Newcastle Cognitive Substudy and the main SCOPE study were very similar. Overall there was relatively little change in MMSE score, with a decline of less than 0.13 MMSE points per year. Similarly, the incidence of dementia in the SCOPE study of 6.5 cases per 1000 patient-years was in the lower range of what was expected. It was not surprising, therefore, that both sets of analyses found no significant effects of treatment on changes in MMSE score. The MMSE has a number of shortcomings as a serial measure of cognitive function. In particular, it provides a broad assessment of cognitive function initially designed as a screening tool, and not suited to detecting subtle cognitive changes over relatively short periods of time. Therefore, it is possible that any effects of candesartan on cognition may have been obscured by the lack of sensitivity of the measure. The extension of the cognitive assessment in the Newcastle Cognitive Substudy was designed to investigate this by using a battery of tests sensitive to subtle changes over time.

CHAPTER 6: RESULTS – EFFECT OF CANDESARTAN

This chapter presents the primary analysis of the effects of candesartan on reducing cognitive decline. Secondary analyses are presented for the efficacy subset, loss to follow-up, excluding participants suffering stroke and excluding participants taking beta-blockers. Acute effects are also shown.

6.1 Participants included in the primary analysis

As described in the Methods section 2.4.2, to calculate the primary outcome measure of the slope of decline for an individual, a minimum of two cognitive assessments 12 months apart were required. Due to the natural attrition associated with death and withdrawal of consent, follow-up cognitive data were unavailable for 22 participants. Participant flow is shown in Figure 26 according to the CONSORT guidelines. Of the 228 with calculable coefficients of decline, 159 (70%) participants completed the maximum number of assessments (4, 5 or 6 visits depending on time of recruitment); 14 (6%) had one missing data point; 23 (10%) had two missing data points; 22 (10%) missed three assessments; and 10 (4%) missed four assessments.

6.1.1 Baseline characteristics

In the sample of 228 participants with calculable coefficients of decline, there were no significant differences between the candesartan and placebo groups on baseline demographic characteristics (Table 32) with one exception: there was a 7% higher rate of previous MI in the candesartan group. Although it reached statistical significance, the difference appears to be a 'play of chance' from the whole sample of 250 randomised participants who had a high prevalence of MI (described in section 3.2.1), and was therefore a product of the randomisation procedure rather than a selective loss to follow-up of participants with previous MI in the placebo group. As in the whole recruited sample, there were no significant differences in baseline composite cognitive factor scores (Table 33).

Figure 26: CONSORT Flow Diagram

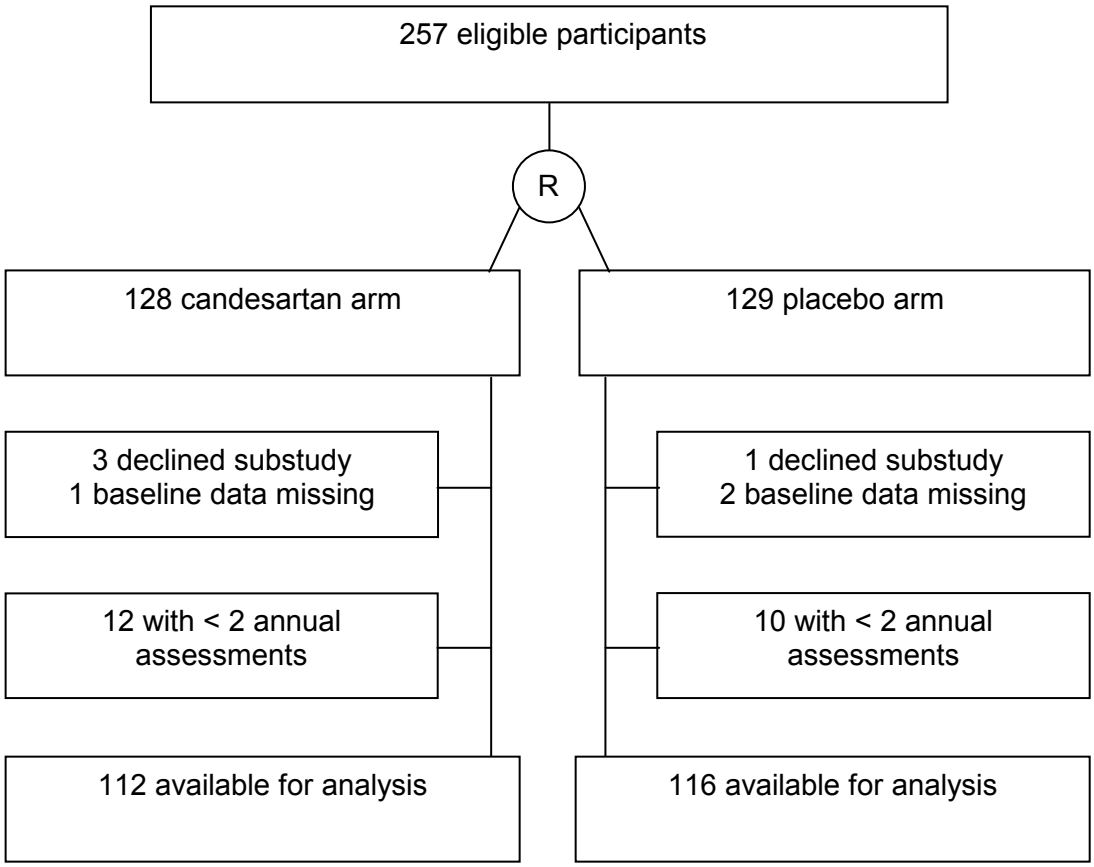


Table 32: Baseline demographics of Newcastle Substudy

Baseline demographic characteristics of hypertensive participants with calculable coefficients of decline in the Newcastle Cognitive Substudy randomised to candesartan versus placebo.

Data shown are mean and (SD), or percentages.

	Candesartan	Placebo	t / χ^2	p
	n=112	n=116		
Age, years	76 (4)	76 (5)	.32	.75
Females	54%	53%	.00	.99
Education, years	10 (2)	10 (2)	.18	.61
NART errors	18 (8)	18 (9)	.57	.82
MMSE score	29 (1)	29 (1)	.61	.54
SBP mmHg	165 (8)	166 (8)	.56	.43
DBP mmHg	88 (7)	89 (7)	.63	.20
Smokers	14%	17%	.37	.54
HCTZ at enrolment	28%	28%	.00	.99
Previous MI	10%	3%	5.2	.02
Previous stroke	5%	3%	1.2	.28
Atrial fibrillation	3%	5%	.94	.33

NART = New Adult Reading Test; MMSE = Mini-Mental State Examination; SBP = systolic blood pressure; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; MI = myocardial infarction.

Table 33: Baseline cognitive performance: candesartan vs placebo groups

Comparison of baseline performance on the composite cognitive factors between the candesartan and placebo groups, for hypertensive participants with calculable coefficients of decline. A higher score indicates better performance except for Speed of Cognition, where a lower score indicates better performance

Data shown are mean and (SD)

Factor	Candesartan		Placebo		t	p
	n=112		n=116			
Speed of Cognition	6398	(1090)	6570	(1257)	-1.1	.27
Continuity of Attention	92.2	(2.6)	92.5	(3.0)	-.83	.41
Episodic Memory	217	(50)	231	(54)	-1.6	.11
Working Memory	1.57	(0.33)	1.61	(0.35)	-.45	.34
Executive Function	1.18	(3.01)	1.37	(3.33)	-.45	.65

6.1.2 Effects on BP and cardiovascular outcomes

In order to determine whether the effects of candesartan on BP and cardiovascular outcomes observed in the whole Newcastle Cognitive Substudy sample (section 5.1.3) were similar in the 228 participants with calculable slopes of decline, the analyses were repeated using this subsample.

The mean length of follow-up was 45.8 ±9.3 months (range 14-59 months) with no significant difference between the candesartan and placebo groups (46.5±8.9 vs. 45.1±9.8 months, t=1.19, p=.24). In the candesartan group, the mean dose of candesartan was 12±4 mg once daily; 76 participants continued treatment until study close representing 68% of the sample; the average proportion of the follow-up period spent on active treatment was 88%. Only 19% of participants in the placebo group were taking placebo with no additional BP-lowering therapy at the last study visit attended.

As all of the participants that attended the closeout visit also had calculable coefficients of decline, the results of the effects of candesartan on BP and MMSE scores at study close were the same as the analyses based on the whole recruited sample. The incidence of major cardiovascular events was also similar, with 12 sustaining stroke (4 candesartan, 8 placebo) and 8 myocardial infarction (3 candesartan, 5 placebo) within the 228 participants with follow-up cognitive data.

Thus, at the closeout visit, BP fell from 165±8/88±7 mmHg at baseline to 141±16/74±9 mmHg at study close in the candesartan group (SBP, t=14.51, p<.001; DBP, t=13.98, p<.001), and from 166±8/89±7 to 149±20/77±10 mmHg in the placebo group (SBP, t=8.37, p<.001; DBP, t=11.88, p<.001). At the study closeout visit, the difference in BP was 8/3 mmHg lower in the candesartan group (SBP, t=3.07, p<.01; DBP, t=1.87, p=.06).

6.2 Primary analysis: effect of candesartan on cognitive decline

The primary analysis compared the rate of cognitive decline between the candesartan and placebo groups on an intent-to-treat basis. The univariate general linear model procedure was used to compare decline on each cognitive factor between the two groups, controlling for age, estimated pre-morbid IQ and baseline cognitive function as covariates. As the tests of equivalence of the randomised groups found no baseline differences on the pre-specified demographic variables, no additional covariates were added to the model.

Table 34 shows the results of the general linear model assessing the effect of treatment on the rate of cognitive decline for each composite factor. The candesartan group showed significantly less decline in Attention and Episodic Memory than the placebo group, with a similar trend for Speed of Cognition. Cohen's D effect sizes were in the small to medium range using the generally-accepted conventions (0.2 = small effect; 0.5 = medium effect; 0.8 = large effect). There were no differences in the rate of decline in Working Memory or Executive Function. The average annual rates of decline expressed as a percentage of baseline composite score are also shown in the table, and illustrate more clearly the magnitude and direction of the differences.

Figures 27-31 display graphically the average annual percentage change, extrapolated for the mean length of follow-up. The gradient of the lines in relation to each other shows the different trajectories of cognitive function between the groups. For the Speed of Cognition factor (Figure 27), the result does not reach statistical significance due to the larger variance in the placebo group, although a trend in favour of the candesartan group is visible. For Attention (Figure 28) there is a small but clear divergence of the two groups, representing an annual decline of 0.5% in the placebo group compared to almost no change in the candesartan group. For Episodic Memory (Figure 29), the trajectories are clearly different with the placebo group declining and the candesartan group showing improvements of a similar magnitude, although the graph itself appears somewhat distorted because of the different, but non-significant starting points. On the Working Memory factor (Figure 30), the candesartan and placebo groups are almost identical, with both groups improving slightly over time, perhaps reflecting a practice effect on the tasks involved. The Executive Function factor (Figure 31) shows the greatest annual percentage decline of the five factors, with both groups having similar trajectories, suggesting no effect of treatment but that this factor is the most susceptible to the effects of age.

Table 34: Primary analysis of change in cognition: candesartan vs placebo groups

Primary analysis: comparison of change in cognition between the candesartan and placebo groups, as measured by coefficients of decline on five composite factor scores, in all participants with calculable coefficients. Adjusted for age, New Adult Reading Test errors and baseline performance. Negative values indicate decline in performance over time.

Data shown are mean and (SD).

	Coefficients of Decline				Effect Size	Annual Percentage Change from Baseline	
	Candesartan	Placebo				Candesartan	Placebo
Cognitive factor	n=112	n=116	F	p	Cohen's D	%	%
Speed of Cognition	-2.3 (25.2)	-17.4 (89.2)	2.1	.15	.26	-0.4	-3.2
Attention	0.004 (0.088)	-0.036 (0.184)	4.2	.04	.28	0.1	-0.5
Episodic Memory	0.14 (1.38)	-0.22 (1.21)	4.3	.04	.28	0.8	-1.1
Working Memory	0.0014 (0.0119)	0.0010 (0.0118)	0.02	.90	.03	1.1	0.7
Executive Function	-0.0031 (0.0616)	-0.0023 (0.0739)	0.004	.95	-.01	-3.2	-2.0

Figure 27: Trajectories of the coefficients of decline: Speed of Cognition

Diagrammatic comparison of the trajectories of the coefficients of decline, for the candesartan and placebo groups, on the Speed of Cognition factor. As a higher score indicates poorer performance on this factor, the scale has been reversed.

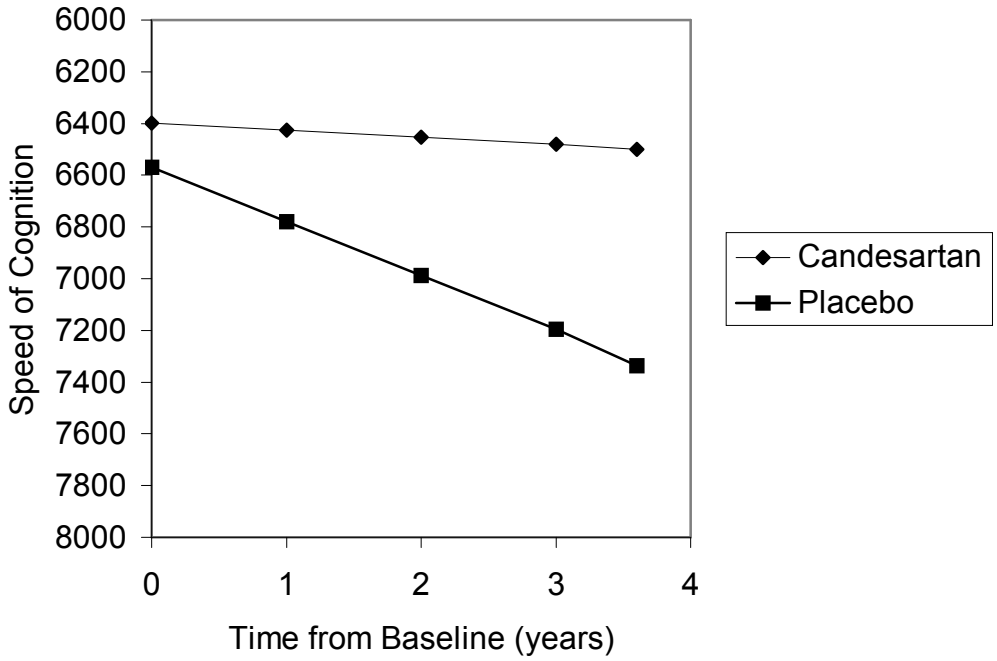


Figure 28: Trajectories of the coefficients of decline: Attention

Diagrammatic comparison of the trajectories of the coefficients of decline, for the candesartan and placebo groups, on the Attention factor.

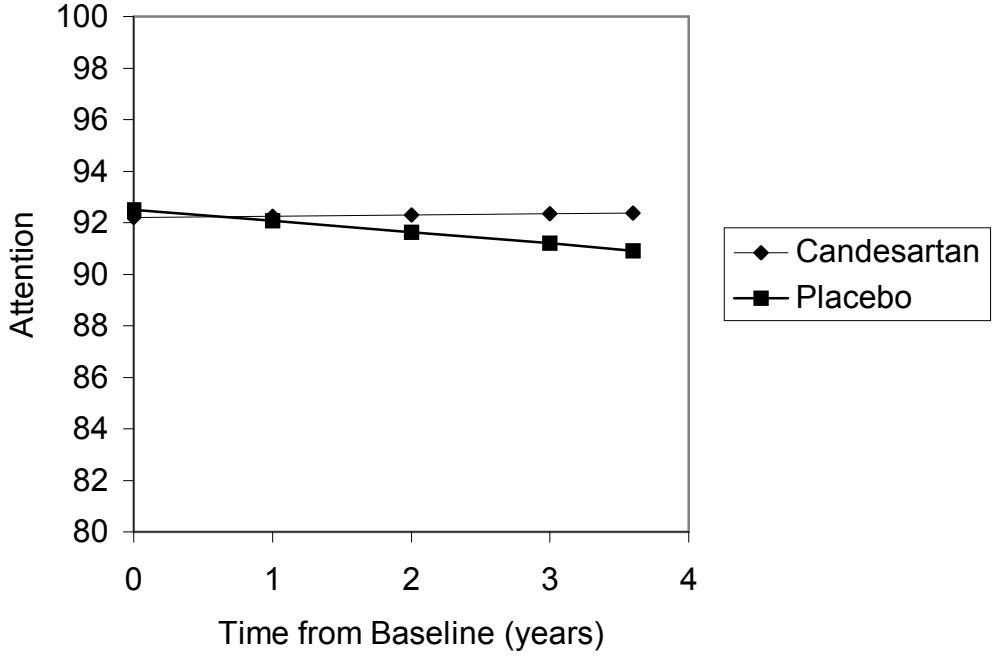


Figure 29: Trajectories of the coefficients of decline: Episodic Memory

Diagrammatic comparison of the trajectories of the coefficients of decline, for the candesartan and placebo groups, on the Episodic Memory factor

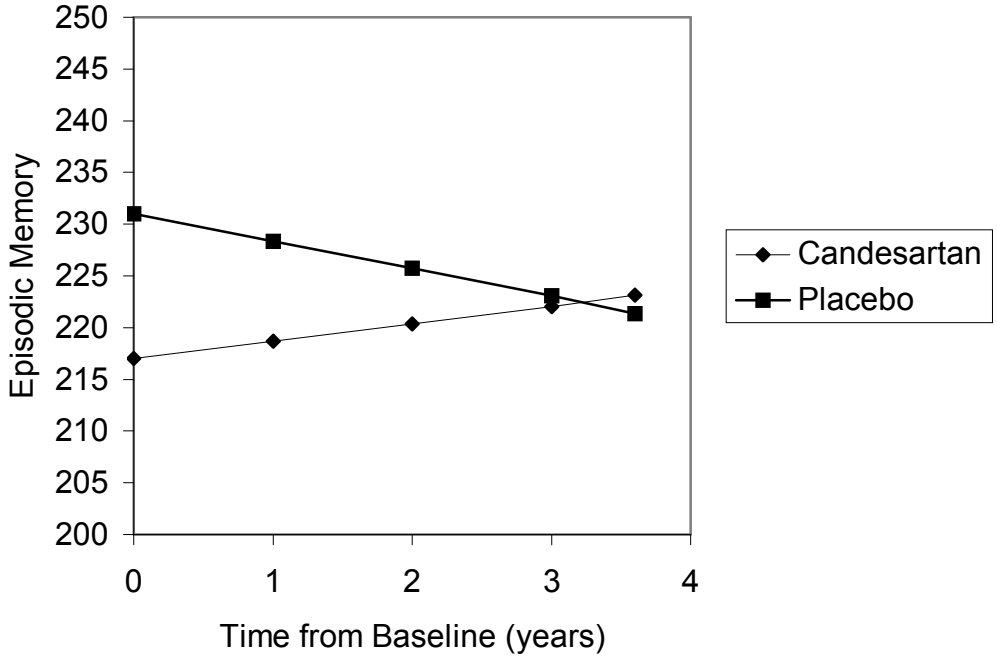


Figure 30: Trajectories of the coefficients of decline: Working Memory

Diagrammatic comparison of the trajectories of the coefficients of decline, for the candesartan and placebo groups, on the Working Memory factor.

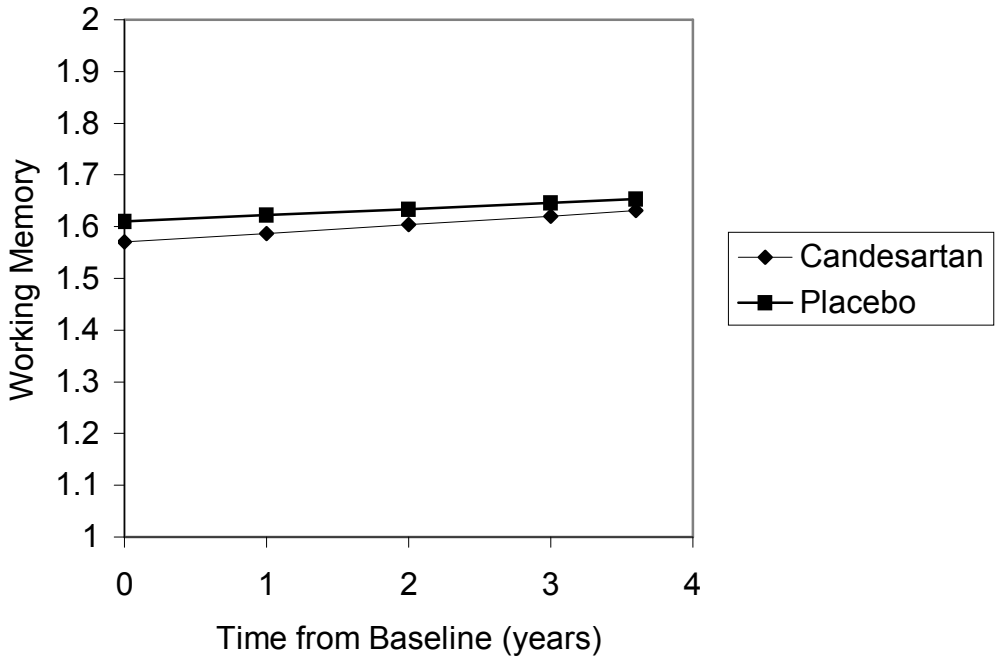
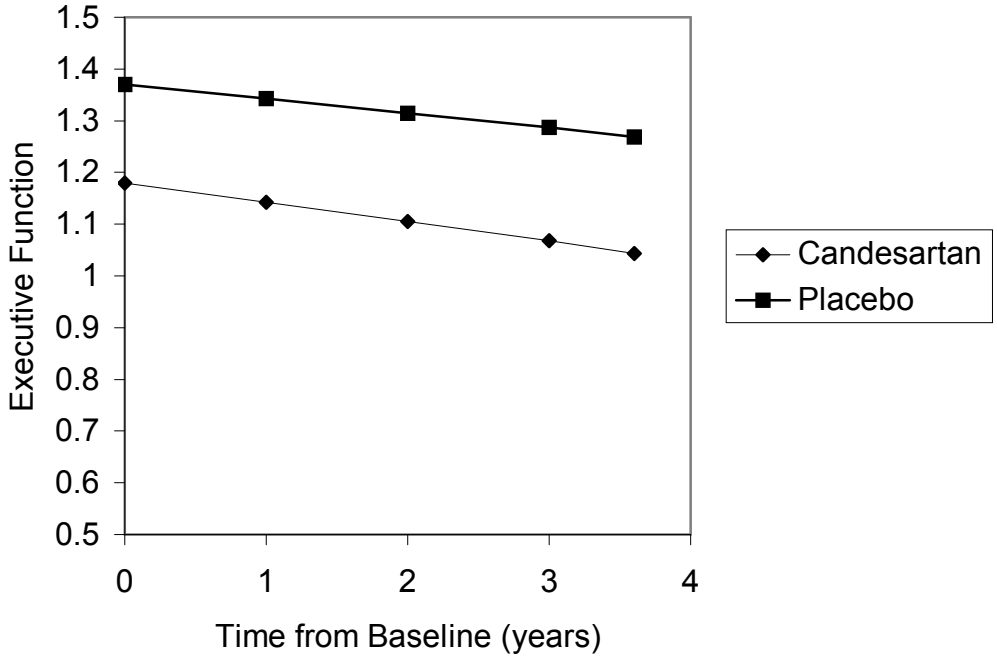


Figure 31: Trajectories of the coefficients of decline: Executive Function

Diagrammatic comparison of the trajectories of the coefficients of decline, for the candesartan and placebo groups, on the Executive Function factor.



6.3 Secondary analyses: efficacy analysis

6.3.1 Baseline characteristics

In contrast to the intent-to-treat analysis where data from all participants were entered into the analysis regardless of compliance, in the efficacy analysis only those participants who remained on allocated treatment throughout the study formed the evaluable subset. The baseline demographic characteristics of the candesartan and placebo groups in the efficacy analysis are shown in Table 35. There were no significant differences between the groups, and as a subset, they closely matched the whole group of participants with calculable coefficients of decline from which they were selected. Similarly, there were no differences between the groups on baseline composite cognitive factor scores (Table 36).

6.3.2 Effects on BP and cardiovascular outcomes

The mean length of follow-up was 48.7 ±6.1 months (range 37-59 months) with no significant difference between the candesartan and placebo groups (49±6 vs. 49±6 months, t=.09, p=.93). In the candesartan group, the mean dose of candesartan was 14±3 mg once daily. Only 17% of participants in the placebo group were taking placebo with no additional BP-lowering therapy throughout the study..

At the closeout visit, BP fell from 165±8/88±6 mmHg at baseline to 140±15/73±9 mmHg at study close in the candesartan group (SBP, t=14.61, p<.001; DBP, t=13.84, p<.001), and from 165±8/89±7 to 146±15/75±8 mmHg in the placebo group (SBP, t=10.90, p<.001; DBP, t=12.39, p<.001). At the study closeout visit, the difference in BP was 6/2 mmHg in favour of the candesartan group (SBP, t=2.42, p=.02; DBP, t=1.33, p=.19).

At study close there were no significant differences in MMSE scores between the candesartan and placebo groups (28.5±2.1 vs. 28.6±1.5, t=.32, p=.75) with only minor changes from the baseline scores (28.7±1.2 vs. 28.8±1.1).

The incidence of stroke was in proportion to the whole group analysis, with 9 participants sustaining stroke (2 candesartan, 7 placebo). However, none of the participants in the efficacy subset sustained myocardial infarction. This most probably reflected the medical decisions made after the clinical event had occurred, with medical practitioners recommending the withdrawal of study medication in the treatment of myocardial infarction, making those participants ineligible for the efficacy analysis.

Table 35: Baseline demographics: efficacy analysis

Baseline demographic characteristics of candesartan versus placebo participants in the efficacy analysis of the Newcastle Cognitive Substudy.

Data shown are mean and (SD), or percentages.

	Candesartan	Placebo	t / χ^2	p
	n=77	n=75		
Age, years	75 (4)	76 (4)	-1.2	.22
Females	57%	53%	.22	.64
Education, years	10 (2)	10 (2)	-.05	.96
NART errors	19 (9)	18 (9)	.70	.49
MMSE score	29 (1)	29 (1)	-.89	.38
SBP mmHg	165 (8)	165 (8)	-.18	.86
DBP mmHg	88 (6)	89 (7)	-.68	.50
Smokers	14%	14%	.02	.89
HCTZ at enrolment	21%	20%	.00	.93
Previous MI	8%	1%	3.6	.06
Previous stroke	6%	1%	2.7	.10
Atrial fibrillation	0%	3%	2.1	.15

NART = New Adult Reading Test; MMSE = Mini-Mental State Examination; SBP = systolic blood pressure; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; MI = myocardial infarction.

Table 36: Baseline cognitive performance: efficacy analysis

Comparison of baseline performance on the composite cognitive factors between the candesartan and placebo groups, for participants in the efficacy analysis of the Newcastle Cognitive Substudy. A higher score indicates better performance except for Speed of Cognition, where a lower score indicates better performance

Data shown are mean and (SD)

Factor	Candesartan		Placebo		t	p
	n=77		n=75			
Speed of Cognition	6226	(1046)	6423	(1161)	-1.1	.27
Continuity of Attention	92.2	(2.6)	92.8	(2.5)	-.1.5	.15
Episodic Memory	222	(52)	237	(55)	-1.5	.14
Working Memory	1.59	(0.33)	1.61	(0.38)	-.32	.75
Executive Function	1.33	(2.87)	1.73	(3.16)	-.81	.42

6.3.3 Effect on cognitive decline

The univariate general linear model procedure was used to compare decline on each cognitive factor between the two groups, controlling for age, estimated pre-morbid IQ and baseline cognitive function as covariates. As there were no baseline differences on the demographic variables, no additional covariates were added to the model.

Table 37 shows the results of the general linear model assessing the effect of treatment on the rate of cognitive decline for each composite factor. In contrast to the primary analysis, the efficacy analysis found no significant differences between the groups on any of the cognitive factors. However, for the Attention and Episodic Memory factors, the candesartan group showed small improvements over time compared to small declines in the placebo group, similar in magnitude to those observed in the primary analysis but failing to reach statistical significance. There was no trend observed on the Speed of Cognition factor due to the placebo group not showing the decline on this factor that was evident in the primary analysis, and with a much lower standard deviation. In general, the annual percentage change from baseline was smaller than observed in the primary analysis, due in some part to differences in the baseline scores

between the datasets; participants included in the efficacy analysis performed better at baseline on the cognitive factors than the whole group from which they were selected.

Table 37: Efficacy analysis on change in cognition: candesartan vs placebo groups

Efficacy analysis: comparison of change in cognition between the candesartan and placebo groups, as measured by coefficients of decline on five composite factor scores, in participants who remained on treatment throughout the study. Adjusted for age, New Adult Reading Test errors and baseline performance. Negative values indicate decline in performance over time.

Data shown are mean and (SD).

	Coefficients of Decline				Annual Percentage Change from Baseline	
	Candesartan	Placebo			Candesartan	Placebo
Cognitive factor	n=77	n=75	F	P	%	%
Speed of Cognition	-0.03 (18.8)	0.18 (15.0)	0.0	.93	-0.01	0.03
Attention	0.012 (0.058)	-0.033 (0.051)	1.0	0.30	0.2	-0.4
Episodic Memory	0.12 (0.93)	-0.09 (0.92)	1.7	0.19	0.6	-0.5
Working Memory	0.0010 (0.0068)	0.0015 (0.0070)	0.6	0.43	0.8	1.1
Executive Function	0.0091 (0.0372)	-0.0003 (0.0475)	1.3	0.26	8.2	-0.2

6.3.4 Efficacy analysis versus intent-to-treat

An efficacy analysis is often performed to demonstrate the pharmacological efficacy of a compound, and as it includes only those participants who are compliant throughout, the observed effect is usually greater than that of an intent-to-treat analysis. Here though, the effect of candesartan on cognitive decline appears to be weaker as the differences between the groups are smaller and statistically non-significant. However, the main characteristic that distinguishes the efficacy analysis, and the reason that intent-to-treat analyses are often preferred, is that the evaluable subset is selected post-hoc based on observations after baseline. Therefore the properties of randomisation do not apply and the possibility of systematic bias cannot be ruled out.

By virtue of the fact they were selected by their compliance, participants included in the efficacy analysis had a higher average dose of candesartan and greater average length of follow-up. The reduction in BP from baseline was greater than that observed in the intent-to-treat analysis, particularly in the placebo group, which resulted in a smaller BP difference between the candesartan and placebo groups at study close (6/2 mmHg, efficacy analysis vs. 8/3 mmHg, intent-to-treat). The smaller BP difference, combined with fewer participants in each group available for analysis, may account for the absence of significant differences due to a lack of statistical power.

However, the efficacy subset does also appear to be qualitatively different from the intent-to-treat sample as a whole. In particular, none of the participants who experienced myocardial infarction during the trial were included in the efficacy subset. Also, comparison of Table 33 and Table 39 suggests that participants in the efficacy subset had better cognitive performance at baseline. With the reduced variance on all factors indicated by the smaller standard deviations, this suggests that the efficacy subset consisted of the healthier and more cognitively able participants who were less likely to exhibit cognitive decline.

6.3.5 Efficacy subset versus the remainder of participants

This was borne out by an unplanned post-hoc comparison between the participants included in the efficacy analysis and the remaining participants with calculable

coefficients of decline from the Newcastle Cognitive Substudy (i.e. participants included in the intent-to-treat analysis but not eligible for the efficacy analysis). The baseline demographic characteristics of the two groups (Table 38) show that the efficacy subset were younger and less likely to have a history of atrial fibrillation. In terms of baseline cognitive performance, participants included in the efficacy subset performed significantly better on the Speed of Cognition factor and Episodic Memory, with a trend towards better performance in Executive Function (Table 39).

By definition, the participants that were not included in the efficacy subset were less compliant and therefore had a lower mean dose of candesartan compared to the efficacy subset (12±4 vs. 14±3 mg once daily, $t=2.4$, $p=.02$). Similarly, for those participants attending the closeout visit (n=37), BP at study close was significantly higher than that of the efficacy subset (SBP 155±25 vs. 143±15 mmHg, $t=-3.9$, $p<.01$; DBP 79±12 vs. 74±9 mmHg, $t=-3.0$, $p<.01$).

Table 40 shows the results of the univariate general linear model comparing the average slopes of decline for the two groups on each factor, controlling for age, estimated pre-morbid IQ and baseline cognitive function as covariates. Participants in the efficacy subset exhibited significantly less decline in Attention and Speed of Cognition, with almost no annual percentage change from baseline, and a notable learning effect in Executive Function. Perhaps more interestingly, the standard deviations of the decline coefficients on all factors were much smaller in the efficacy subset, suggesting that this subset was more homogenous as a group in terms of cognitive function, as well individually more stable over time. Again, it must be noted though that the selection of the efficacy subset was not at random and the analyses were post-hoc. It is therefore not possible to determine cause and effect: whether compliance throughout the study led to less decline in cognitive function, or whether those participants who exhibited less decline in cognitive function were more likely to be compliant and thus be selected for the efficacy analysis.

Table 38: Baseline demographics: 'Efficacy' vs 'Remainder'

Baseline demographic characteristics of participants included in the efficacy analysis (Efficacy) versus participants included in the intent-to-treat analysis but not eligible for the efficacy analysis (Remainder).

Data shown are mean and (SD), or percentages.

	Efficacy	Remainder	t / χ^2	p
	n=152	n=76		
Age, years	75 (4)	77 (5)	-2.2	.03
Females	55%	50%	.56	.45
Education, years	10 (2)	10 (2)	.14	.89
NART errors	18 (9)	18 (8)	.44	.66
MMSE score	29 (1)	29 (1)	.35	.73
SBP mmHg	165 (8)	165 (9)	-.11	.91
DBP mmHg	88 (6)	88 (8)	-.07	.94
Smokers	14%	20%	1.4	.24
HCTZ at enrolment	27%	29%	.10	.75
Previous MI	5%	9%	1.9	.17
Previous stroke	4%	4%	0.0	1.0
Atrial fibrillation	1%	9%	8.3	.004

NART = New Adult Reading Test; MMSE = Mini-Mental State Examination; SBP = systolic blood pressure; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; NSAIDs = non-steroidal anti-inflammatory drugs; MI = myocardial infarction.

Table 39: Baseline cognitive performance: ‘Efficacy’ vs ‘Remainder’

Comparison of baseline performance on the composite cognitive factors between participants included in the efficacy analysis (Efficacy) versus participants included in the intent-to-treat analysis but not eligible for the efficacy analysis (Remainder). A higher score indicates better performance except for Speed of Cognition, where a lower score indicates better performance.

Data shown are mean and (SD)

Factor	Efficacy		Remainder		t	p
	n=152		n=76			
Speed of Cognition	6323	(1105)	6809	(1259)	-3.0	.003
Continuity of Attention	92.5	(2.5)	92.1	(3.2)	.88	.38
Episodic Memory	229	(54)	213	(48)	1.9	.05
Working Memory	1.60	(0.35)	1.57	(0.32)	.60	.55
Executive Function	1.53	(3.01)	0.76	(3.45)	1.7	.09

Table 40: Change in cognition: ‘Efficacy’ vs ‘Remainder’

Comparison of change in cognition between participants included in the efficacy analysis (Efficacy) versus participants included in the intent-to-treat analysis but not eligible for the efficacy analysis (Remainder), as measured by coefficients of decline on five composite factor scores. Adjusted for age, New Adult Reading Test errors and baseline performance. Negative values indicate decline in performance over time.

Data shown are mean and (SD).

	Coefficients of Decline				Annual Percentage Change from Baseline	
	Efficacy	Remainder			Efficacy	Remainder
Cognitive factor	n=152	n=76	F	P	%	%
Speed of Cognition	0.1 (17.0)	-30.1 (110.1)	3.3	0.001	0.0	-5.3
Attention	0.004 (0.05)	-0.057 (0.24)	3.1	0.003	0.1	-0.7
Episodic Memory	0.02 (0.93)	-0.17 (1.90)	1.0	0.34	0.1	-1.0
Working Memory	0.0013 (0.0069)	0.0011 (0.0181)	0.1	0.91	1.0	0.8
Executive Function	0.0045 (0.0427)	-0.0039 (0.1048)	0.8	0.40	3.5	-6.2

6.3.6 Efficacy analysis: summary

The efficacy analysis did not reproduce the significant effects of candesartan on cognitive decline that were observed in the primary analysis. This was perhaps due to the lower number of cases, and the smaller BP difference between the candesartan and placebo groups at study close, reducing the statistical power of the analysis. However, as a selective subset of the participants in the intent-to-treat analysis, the efficacy analysis participants were not representative as they appeared more cognitively able at baseline and remained healthier during the study than the group as a whole. Direct statistical comparison of the participants included in the efficacy analysis versus the remainder of participants from the intent-to-treat analysis, showed that the efficacy group were younger and performed significantly better at baseline on two of the cognitive factors. The efficacy subset showed significantly less decline in Attention and Speed of Cognition, and as a group showed less variation in the coefficients of decline than those participants not included in the efficacy subset. Although the results did not show a more pronounced effect of candesartan as may have been expected, they demonstrate the value of the intent-to-treat method as the primary analysis. The collection and inclusion of all follow-up data from as many randomised participants as possible in the primary analysis provided a different picture to that of the efficacy analysis; one that would have been distorted by the selective characteristics of the sample if the efficacy analysis was solely relied upon.

6.4 Secondary analyses: loss to follow-up

Attrition within any study is inevitable but an important factor as it can affect the generalisability of the results and the statistical power of the analyses. To maximise the number of participants available for the primary analysis, all participants, including those withdrawn during the study, were invited to attend the closeout visit. Of the 250 participants recruited to the Newcastle Cognitive Substudy, cognitive follow-up data were unavailable for 22 cases giving a sample size of 228 for the primary analysis: 4 were still participating in the study but died before the first annual assessment; 10 withdrew before the first annual assessment and were deceased at closeout; 8 withdrew consent and declined the invitation to attend at closeout.

Excluding the deceased participants, the withdrawal of consent from only 8 participants represented a follow-up success rate of 96%.

The baseline characteristics of participants included in the primary analysis and those with less than two cognitive assessments are compared in Table 41. Participants without follow-up data were older, more likely to be smokers, and more likely to have a history of myocardial infarction; there were no significant differences on other baseline demographic variables. Although there were no significant differences on the composite cognitive factors at baseline, the withdrawn participants performed slightly worse on each of the factors (Table 42), perhaps reflecting their older age and poorer health.

It was particularly important to demonstrate that there were no systematic differences between those who completed the study and those who did not. As the cases of loss to follow-up were roughly evenly distributed between the randomised groups (12 candesartan, 10 placebo, $\chi^2 = .24$, p=.63), selective attrition due to treatment allocation was not evident. Thus, although the participants lost to follow-up were not completely representative of those included in the primary analysis, the lack of association with treatment allocation indicated that the properties of randomisation between the candesartan and placebo groups remained intact.

Table 41: Baseline demographics: primary analysis vs 'lost to follow-up'

Data shown are mean and (SD), or percentages.

	Primary analysis	Loss to follow-up	t / χ^2	p
	n=228	n=22		
Age, years	76 (4)	78 (6)	-2.3	.02
Females	54%	50%	.09	.75
Education, years	10 (2)	9 (1)	1.4	.15
MMSE score	29 (1)	29 (2)	.20	.84
NART errors	18 (9)	18 (8)	.44	.66
SBP mmHg	165 (8)	165 (11)	.02	.98
DBP mmHg	88 (7)	87 (10)	.91	.36
Smokers	16%	41%	8.4	.004
HCTZ at enrolment	27%	23%	.24	.62
Previous MI	6%	23%	7.9	.005
Previous stroke	4%	0%	.90	.34
Atrial fibrillation	4%	9%	1.3	.26

NART = New Adult Reading Test; MMSE = Mini-Mental State Examination; SBP = systolic blood pressure; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; NSAIDs = non-steroidal anti-inflammatory drugs; MI = myocardial infarction.

Table 42: Baseline cognitive performance: primary analysis vs 'lost to follow-up'

Comparison of baseline performance on the composite cognitive factors between participants included in the primary analysis versus participants lost to follow-up. A higher score indicates better performance except for Speed of Cognition, where a lower score indicates better performance.

Data shown are mean and (SD)

Factor	Primary analysis		Loss to follow-up		t	p
	n=228		n=22			
Speed of Cognition	6485	(1178)	6790	(2351)	-1.0	.30
Continuity of Attention	92.0	(2.8)	91.6	(2.8)	1.2	.25
Episodic Memory	224	(53)	219	(50)	.35	.72
Working Memory	1.59	(0.34)	1.49	(0.40)	1.2	.23
Executive Function	1.27	(3.17)	0.84	(2.69)	.60	.55

6.5 Secondary analyses: excluding participants suffering stroke

It is well known that stroke has a detrimental effect on cognitive function. To investigate the possibility that the differences between the candesartan and placebo groups observed in the primary analysis were influenced by the incidence of stroke, the analyses were repeated excluding participants that suffered fatal/non-fatal stroke (4 candesartan, 8 placebo) during the study. The baseline characteristics of the participants included in the primary analysis and suffering stroke during the trial (Stroke) and participants not suffering from stroke (Non-stroke) are shown in Table 43. Participants suffering stroke were more likely to be male, older in age, more likely to smoke and have a history of myocardial infarction, although as the number of participants in the stroke group was low, none of the differences at baseline reached statistical significance. The stroke group also had higher baseline BP and poorer MMSE scores. The baseline composite factor scores of the participants with and without stroke are shown in Table 44. The stroke group had poorer performance on all

cognitive factors, with significant differences in Episodic Memory and Executive Function.

The primary analysis was repeated excluding the 12 participants suffering stroke during the trial. The results in Table 45 show that the significant effects of candesartan on Attention and Episodic Memory persisted when participants with stroke were excluded, indicating that the results of the primary analysis were not due to the influence of stroke-related cognitive dysfunction during the study. Overall the exclusion of participants with stroke made little difference to the average slopes of decline or annual percentage change from baseline, with the exception of Executive Function.

In the primary analysis the average annual change in Executive Function from baseline was -3.2% and -2.0% for the candesartan and placebo groups respectively. Excluding participants with stroke from the analysis indicated a slight annual improvement of 0.2% in the candesartan group and a smaller decline of -1.1% in the placebo group, though the differences between groups remained non-significant. The data showed that participants who went on to suffer stroke during the study had performed significantly worse on Executive Function at baseline, and as the percentage is calculated as a change from baseline values, the results of the analyses to some extent simply reflect this. However, the average slopes of decline also differ between the analyses suggesting that there is perhaps an association between stroke and Executive Function. The nature of such a relationship is not easily discernible from the data. The measurement of Executive Function took place before the stroke occurred and therefore may be a risk factor or predictive of future stroke. However, poor Executive Function at baseline may reflect subclinical cerebrovascular disease such as leukarosis and the presence of white matter changes. Or it is possible that both poor Executive Function and future stroke may be under the influence of a third factor.

Table 43: Baseline demographics: 'Stroke' vs 'Non-stroke'

Data shown are mean and (SD), or percentages.

	Non-stroke	Stroke	t / χ^2	p
	n=216	n=12		
Age, years	76 (4)	77 (5)	.79	.43
Females	54%	42%	.71	.40
Education, years	10 (2)	10 (2)	.58	.56
NART errors	18 (9)	21 (8)	1.2	.23
MMSE score	29 (1)	28 (2)	-1.7	.09
SBP mmHg	165 (8)	170 (9)	1.9	.06
DBP mmHg	88 (7)	92 (6)	1.8	.06
Smokers	15%	33%	2.9	.09
HCTZ at enrolment	28%	25%	.04	.83
Previous MI	6%	17%	2.4	.12
Previous stroke	4%	8%	.64	.42
Atrial fibrillation	4%	0%	.52	.47

NART = New Adult Reading Test; MMSE = Mini-Mental State Examination; SBP = systolic blood pressure; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; NSAIDs = non-steroidal anti-inflammatory drugs; MI = myocardial infarction.

Table 44: Baseline cognitive performance: ‘Stroke’ vs ‘Non-stroke’

Comparison of baseline performance on the composite cognitive factors between participants suffering a fatal or non-fatal stroke during the study (Stroke) versus the remaining participants who did not (Non-stroke). A higher score indicates better performance except for Speed of Cognition, where a lower score indicates better performance.

Data shown are mean and (SD)

Factor	Non-stroke		Stroke		t	p
	n=216		n=12			
Speed of Cognition	6457	(1161)	7003	(1420)	1.6	.12
Continuity of Attention	92.4	(2.8)	91.1	(2.6)	-1.6	.12
Episodic Memory	227	(52)	174	(45)	-2.8	.005
Working Memory	1.59	(0.34)	1.56	(0.38)	-.34	.73
Executive Function	1.41	(3.01)	-1.15	(4.92)	-2.8	.006

Table 45: Secondary analysis: change in cognition excluding stroke

Secondary analysis: comparison of change in cognition between the candesartan and placebo groups, as measured by coefficients of decline on five composite factor scores, excluding participants suffering fatal/non-fatal stroke during the study. Adjusted for age, New Adult Reading Test errors and baseline performance. Negative values indicate decline in performance over time.

Data shown are mean and (SD).

	Coefficients of Decline				Annual Percentage Change from Baseline	
	Candesartan	Placebo			Candesartan	Placebo
Cognitive factor	n=108	n=108	F	P	%	%
Speed of Cognition	-1.8 (25.2)	-16.5 (92.0)	2.0	0.16	-0.3	-3.0
Attention	0.005 (0.086)	-0.035 (0.189)	3.9	0.05	0.1	-0.5
Episodic Memory	0.20 (1.32)	-0.18 (1.21)	5.5	0.02	0.0	-1.1
Working Memory	0.0017 (0.0117)	0.0012 (0.0121)	.03	0.85	1.3	0.9
Executive Function	0.0002 (0.0591)	-0.0015 (0.0757)	.11	0.75	0.2	-1.1

6.6 Secondary analyses: excluding participants taking beta-blockers

There has been concern in the literature that the use of beta-blockers in the treatment of hypertension may lead to impairment of cognitive function. At the closeout visit, the number of participants in the placebo group taking beta-blockers as additional antihypertensive therapy was almost double that of the candesartan group (20 vs. 12) (Table 31). In order to investigate whether the results of the primary analysis were independent of beta-blocker use, the primary analysis was repeated excluding all participants that had taken beta-blockers at any time after randomisation. In line with the proportions at closeout, the number taking beta-blockers at any time was higher in the placebo group (n=30) than the candesartan group (n=18), giving a sample size of 180 for the repeated analysis.

The baseline demographic characteristics of the participants who took beta-blockers and those who did not take beta-blockers at any time during the study are compared in Table 46. The rate of hydrochlorothiazide use at enrolment was significantly higher in participants who went on to be prescribed beta-blockers during the study than those who did not. As thiazides are recommended as the first line of antihypertensive therapy in UK general practice, the higher rate is not surprising for those participants requiring additional medication. Also, as participants receiving antihypertensive therapy at study entry were standardised to hydrochlorothiazide, the beta-blocker group could include participants receiving hydrochlorothiazide at enrolment but subsequently changed to beta-blockers during the study, rather than receiving it as a second additional antihypertensive medication. Baseline performance on the composite factor scores is compared in Table 47 and shows no significant differences between the two groups, although there is a trend towards better performance on Speed of Cognition for the beta-blocker group. The exclusion of participants taking beta-blockers made no significant difference to the primary analysis (Table 48).

Table 46: Baseline demographics: 'Beta-blockers' vs 'Beta-blocker free'

Data shown are mean and (SD), or percentages.

	Beta-blocker free	Beta-blockers	t / χ^2	p
	n=180	n=48		
Age, years	76 (5)	75 (4)	-.66	.51
Females	52%	60%	1.2	.28
Education, years	10 (2)	10 (2)	-1.8	.08
NART errors	18 (9)	17 (9)	-.62	.54
MMSE score	29 (1)	29 (1)	1.3	.19
SBP mmHg	165 (8)	167 (7)	1.2	.22
DBP mmHg	88 (7)	88 (7)	-.70	.48
Smokers	17%	13%	.51	.48
HCTZ at enrolment	24%	42%	6.0	.01
Previous MI	6%	8%	.51	.48
Previous stroke	4%	2%	.56	.46
Atrial fibrillation	4%	4%	.01	.93

NART = New Adult Reading Test; MMSE = Mini-Mental State Examination; SBP = systolic blood pressure; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; NSAIDs = non-steroidal anti-inflammatory drugs; MI = myocardial infarction.

Table 47: Baseline cognitive performance: ‘Beta-blockers’ vs ‘Beta-blocker free’

Comparison of baseline performance on the composite cognitive factors between participants who took beta-blocker medication at any time during the study (Beta-blockers) versus the remaining participants who did not (Beta-blocker free). A higher score indicates better performance except for Speed of Cognition, where a lower score indicates better performance.

Data shown are mean and (SD)

Factor	Beta-blocker free		Beta-blockers		t	p
	n=180		n=48			
Speed of Cognition	6554	(1215)	6229	(1002)	-1.7	.09
Continuity of Attention	92.2	(2.9)	92.8	(2.3)	1.3	.21
Episodic Memory	223	(54)	228	(47)	.45	.65
Working Memory	1.58	(0.34)	1.61	(0.35)	.41	.68
Executive Function	1.11	(3.32)	1.87	(2.53)	1.5	.14

Table 48: Secondary analysis: change in cognition excluding participants taking beta-blockers

Secondary analysis: comparison of change in cognition between the candesartan and placebo groups, as measured by coefficients of decline on five composite factor scores, excluding participants taking beta-blockers at any time during the study. Adjusted for age, New Adult Reading Test errors and baseline performance. Negative values indicate decline in performance over time.

Data shown are mean and (SD).

	Coefficients of Decline				Annual Percentage Change from Baseline	
	Candesartan	Placebo			Candesartan	Placebo
Cognitive factor	n=94	n=86	F	P	%	%
Speed of Cognition	-0.4 (21.4)	-23.1 (102.9)	3.1	0.08	0.0	-4.1
Attention	0.001 (0.086)	-0.045 (0.211)	5.2	0.02	0.0	-0.6
Episodic Memory	0.27 (1.41)	-0.32 (1.30)	8.0	0.005	1.5	-1.7
Working Memory	0.0016 (0.0122)	0.0012 (0.0132)	.07	0.79	1.2	0.9
Executive Function	-0.0004 (0.0613)	-0.0055 (0.0818)	.28	0.60	-0.4	-6.3

6.7 Acute drug effects

To compare acute changes between the treatment groups, the difference from baseline scores was calculated for each composite from the CDR battery. The traditional tests of Executive Function were not administered as 1 month due to concerns over learning effects in the measures as parallel forms were not available. The results (Table 49) show no significant differences between the groups in change scores between baseline and 1 month, indicating no acute effect of candesartan treatment at one month.

Table 49: Assessment of acute drug effects

Comparison of change scores from baseline to 1 month on the composite cognitive factors between candesartan and placebo groups. A higher score indicates improved performance except for Speed of Cognition, where a lower score indicates improved performance.

Data shown are mean and (SD)

Factor	Candesartan		Placebo		t	p
	n=109		n=113			
Speed of Cognition	-158	(737)	-176	(648)	0.19	.85
Continuity of Attention	0.6	(2.7)	0.3	(2.7)	0.58	.56
Episodic Memory	1.1	(40)	-5.0	(41)	0.94	.35
Working Memory	0.06	(0.4)	0.07	(0.4)	-0.17	.87

CHAPTER 7: RESULTS – COMPARISON WITH NORMOTENSIVE COHORT

This chapter presents the data from the normotensive participants to assess their suitability as a normative comparison group. The primary analysis of the effect of candesartan on cognitive decline is repeated with the normotensive data included to put the treatment effects into context. The relationship of BP as a continuous variable is then explored.

7.1 Normotensive control group: follow-up visits

7.1.1 Study visit attendance

Unlike the hypertensive participants for whom entry into the Newcastle Cognitive Substudy was an optional addition to the main SCOPE study and the cognitive assessments were conducted alongside their scheduled study visits, the normotensives were recruited solely for entry into the substudy. Therefore at follow-up visits where cognition assessments were due (i.e. annual visits after baseline), there were no instances where BP-related and cardiovascular-related outcomes were assessed in the absence of cognitive data. All of the normotensive assessments were performed in the research clinic, versus 9 visits in the hypertensive cohort that took place in the participants' homes.

The number of completed normotensive study visits are shown in Table 50, including the 6-monthly visits where BP, MMSE and concomitant medications only were assessed. The number of cognitive assessments administered by the candidate is also shown. Because of the rolling recruitment period, not all participants were due for scheduled study visits beyond the minimum follow-up period of 36 months. As expected, the percentage who attended each visit diminished over time due to the natural attrition associated with withdrawal of consent, and death. At the closeout visit all participants, current and withdrawn, were invited to attend in order to minimise the loss to follow-up.

7.1.2 Study visit attendance: comparison with hypertensive cohort

The proportion of cognitive assessments performed, calculated as a percentage of those due, is also shown for the hypertensive cohort in Table 50 (note: the values represent cognitive assessments performed, and therefore differ from those in Table 30, where the data shown are SCOPE study visits attended). Differential attrition rates between groups can be a concern, particularly when using a non-randomised control group for normative comparison. However, the percentage of cognitive assessments successfully conducted was almost identical between the normotensive and hypertensive cohorts at each timepoint, supporting the suitability of the normotensives as a normative control group in the Newcastle Cognitive Substudy.

The proportion of completed closeout cognitive assessments as a percentage of the sample recruited was similar between the two groups (normotensives 70% vs hypertensives 73%) as shown in Table 50. Adjusting for the number of deceased participants at the close of the normotensive study (n=13), the 179 closeout assessments represents a 74% completion rate of those possible. For approximately the same number of assessments conducted, due to the greater number of deaths in the hypertensive cohort (n=36), the completion rate as a proportion of visits possible was higher in the hypertensive cohort at 85%. Although it was not permitted to elicit reasons for attendance/ refusal to attend the closeout visit, it is possible that the prospect of receiving a full medical check-up, routine laboratory blood tests and ECG within the SCOPE study was perceived as advantageous and made it more likely for withdrawn hypertensive participants to consent to return for the closeout visit than the normotensives, where such procedures were not performed after baseline.

Table 50: Number of completed normotensive cohort study visits

Visit	Normotensive visits attended	Cognitive assessments performed by candidate	Normotensive cognitive assessments performed/ due	Hypertensive cognitive assessments performed/ due
months	n	n	%	%
Baseline	256	256	100	100
1	248	248	97	95
6	233	-	-	-
12	223	223	87	86
18	216	-	-	-
24	203	203	79	79
30	193	-	-	-
36	175	166	68	64
42	113	-	-	-
48	35	33	77	74
54	12	-	-	-
Closeout	179	0	70	73

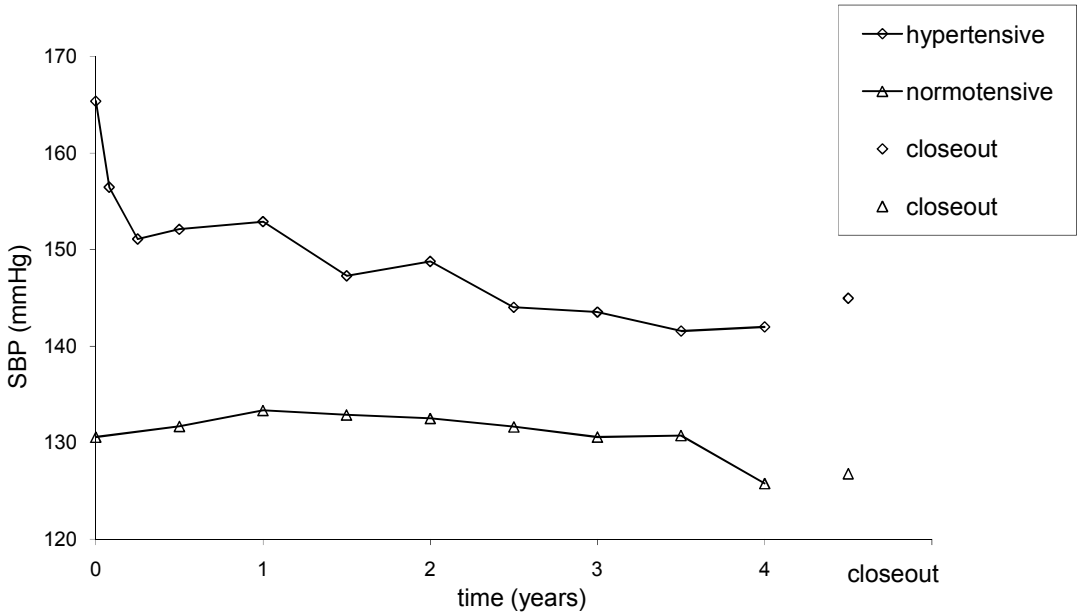
7.2 Normotensive control group: blood pressure

7.2.1 Blood pressure measurements

For the normotensive participants attending the closeout visit, BP changed from 131±11/73±7 mmHg at baseline to 127±14/72±6 mmHg at study close (SBP, t=3.18, p=.002; DBP, t=1.45, p=.148). Similar results were found when analysed using the last observation carried forward (129±14/73±7 mmHg). The average BP across the study, calculated using data from all planned BP monitoring visits after baseline, was 131±10/74±6 (SBP, t=-1.14, p=.254; DBP, t=-.98, p=.328). The mean BP levels at each scheduled study visit compared to the combined hypertensive group are shown in Figure 32; Figure 33 shows the normotensive, candesartan and placebo groups separately

Figure 32: BP at each scheduled SCOPE study visit: normotensive group

Mean systolic (SBP) and diastolic (DBP) blood pressure at each scheduled SCOPE study visit: normotensive group versus hypertensive group in the Newcastle Cognitive Substudy



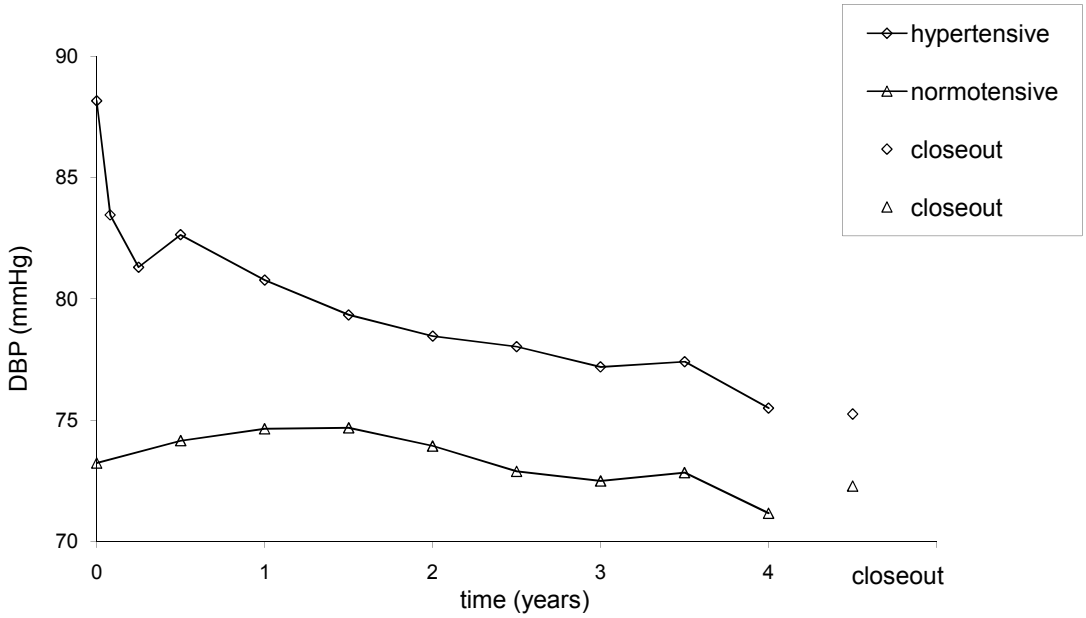
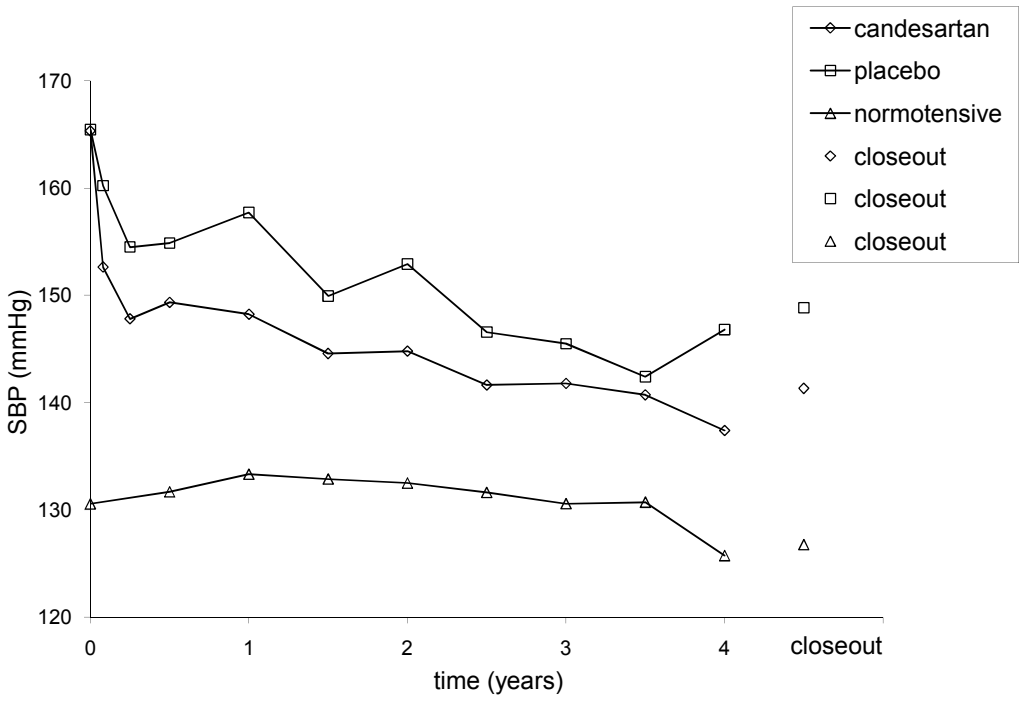
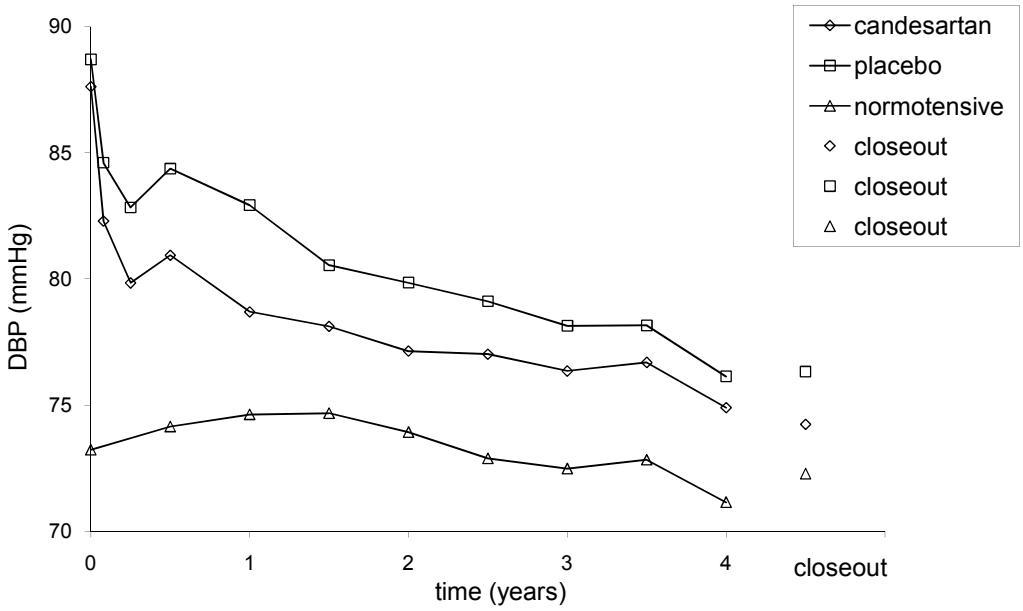


Figure 33: BP at each scheduled visit: three group comparison

Mean systolic (SBP) and diastolic (DBP) blood pressure at each scheduled SCOPE study visit: normotensive group versus candesartan and placebo groups in the Newcastle Cognitive Substudy





7.2.2 Antihypertensive medication use

The normotensive participants were free from antihypertensive medication at the time of enrolment. However as a non-intervention, observational control group, no restrictions could be placed on the prescription of concomitant medications by the participants' general practitioners, including antihypertensive therapy during the study. Indeed, if BP was raised and confirmed by a repeat BP check after a minimum of 14 days, a letter was sent to the participant's general practitioner informing them of the BP readings and suggesting monitoring in accordance with routine care (described in Methods 2.2.3).Twenty-seven participants received one or more antihypertensive medications during the follow-up period; the number prescribed each type of antihypertensive medication is shown in Table 51.

Table 51: Antihypertensive therapy: normotensive control group

Data shown are number of participants per medication class. Some participants were taking more than one BP-lowering drug.

	Normotensives
	n=256
Thiazides	8
Calcium-channel blockers	7
Beta-blockers	11
Angiotensin converting enzyme inhibitors	8
Angiotensin II receptor antagonists	2
Alpha-blockers	0
No antihypertensive therapy	229

7.2.3 Treated vs. untreated normotensives

Comparison of the baseline characteristics of normotensive participants prescribed antihypertensive medication versus those that remained untreated during the study showed that treated normotensives had higher significantly higher baseline SBP and a trend towards higher DBP, as shown in Table 52.

Table 52: Baseline characteristics of treated vs untreated normotensives
Data shown are means (SD) or percentages.

	Treated normotensives	Untreated normotensives	p
	n=27	n=229	
Age, years	76 (4)	76 (4)	.72
Females	52%	43%	.39
MMSE score	29 (2)	29 (1)	.66
SBP mmHg	134 (9)	130 (11)	.03
DBP mmHg	75 (6)	73 (7)	.07
Smokers	22%	15%	.54
Previous MI	7%	3%	.32
Previous stroke	4%	0%	.07
Atrial fibrillation	4%	2%	.49

MMSE = Mini-Mental State Examination; SBP = systolic blood pressure; DBP = diastolic blood pressure; MI = myocardial infarction.

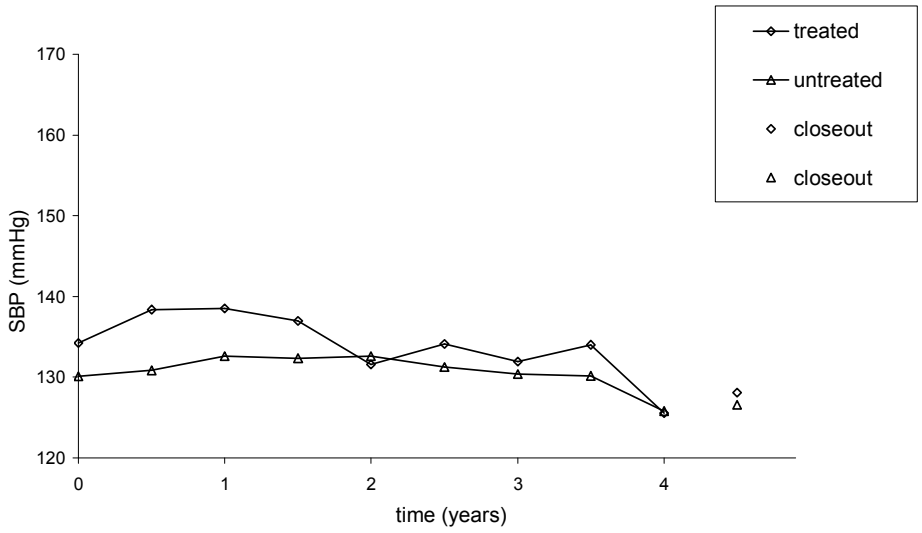
For the normotensive participants attending the closeout visit, in those who remained untreated during the study BP fell slightly from 129±11/73±7 mmHg at baseline to 127±14/73±6 mmHg at the closeout visit (SBP, t=2.62, p=.010; DBP, t=.63, p=.528); for the normotensives prescribed antihypertensives, BP was reduced from 134±7/75±7 to 128±12/71±5 mmHg (SBP, t=2.13, p=.046; DBP, t=2.58, p=.018). The mean of

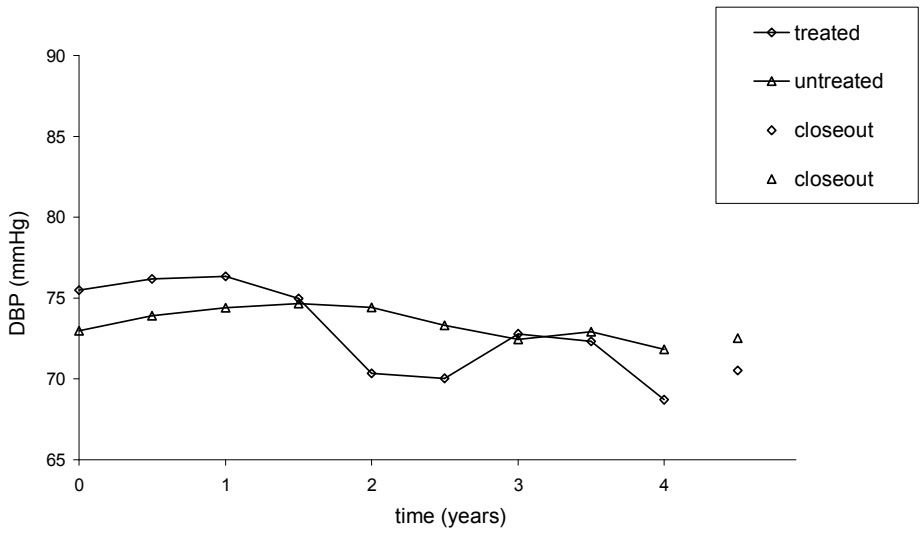
individual changes in BP from baseline to closeout was greater in the treated normotensive group compared to untreated normotensives (SBP 6±13 vs 3±14 mmHg, t=1.00, p=.317; DBP 4±8 vs 0±8, t=2.18, p=.031) reflecting the action of the antihypertensive therapy.

The average BP across the study, calculated using data from all planned BP-monitoring visits after baseline, was 131±10/74±6 mmHg in the untreated group versus 133±9/73±5 mmHg in the treated group (SBP, t=1.07, p=.286; DBP, t=.74, p=.463). Comparison of the mean BP at each scheduled SCOPE study visit between the untreated normotensives versus normotensives receiving antihypertensive medication during the follow-up period is shown in Figure 34. The figures show that mean BP was more variable between visits in the treated group than the untreated normotensives, the rises in BP likely precipitating the need for antihypertensive medication. Although the figures appear to indicate that BP fell sharply between the 42 month and 48 month visits, due to the rolling recruitment period the mean BP at the 48 month visit was calculated on only 35 participants, and only 7 of those in the group receiving antihypertensive medication. Therefore the 48 month BP values could reflect a sampling bias more than a true reduction in BP in the groups at this timepoint.

Figure 34: BP at each scheduled visit: treated vs untreated normotensives

Mean systolic (SBP) and diastolic (DBP) blood pressure at each scheduled SCOPE study visit: normotensive group participants treated with antihypertensive vs untreated





7.3 Normotensive control group: length of follow-up

7.3.1 Length of follow-up

For the 256 normotensive controls in the cognitive substudy, the mean length of follow-up was 38±17 months (range 0-60 months) compared to 43±14 months (range 0-59 months) for the 250 hypertensive participants (t=3.82, p<.001). For the normotensives and hypertensives with calculable slopes of decline, the difference in length of follow-up was smaller (43±11, range 12-60 months vs 46±9, range 12-59 months) but remained statistically significant (t=2.99, p=.003). However, the follow-up length in the hypertensive group corresponded to the scheduled SCOPE study visits, and hypertensive participants were encouraged to attend even after withdrawing from the Newcastle Cognitive Substudy to reduce loss to follow-up in the main SCOPE study. Of more relevance to the cognitive outcomes is length of follow-up to the last cognitive assessment performed, as these data inform the calculation of the slopes of decline. Although numerically a slightly longer follow-up period in the hypertensive group remained (45±13, range 12-60 months), it was not statistically significant (t=1.53, p=.126) and represented a difference of only 47 patient years between the normotensives (801 patient years) and the hypertensives (848 patient years).

7.4 Suitability of normotensive control group

As a non-randomised observational group, the suitability of the normotensive controls for use as a normative comparison group was very important. As described in the Methods section 2.2.5, the normotensives were recruited to the Newcastle Cognitive Substudy using the same inclusion/exclusion criteria applied to the hypertensive participants entering the main SCOPE trial, with the single exception of the entry BP levels and antihypertensive medication use. As far as possible the same study procedures were applied to the normotensives during follow-up, although no restrictions could be placed on the use of antihypertensive medications prescribed during the study, and there was no requirement or provision for the routine medical checks at the closeout visit. In terms of the number of scheduled follow-up visits

attended, number of cognitive assessments contributing to the slopes of decline, and the length of follow-up, the normotensives were very comparable to the hypertensive cohort. Although a small proportion of normotensives required antihypertensive medication to control their BP during the study, as the purpose of the control group was to provide a naturalistic, observational comparison to put the changes in the hypertensive groups into context, the treated normotensives were included in the comparison group. This was the a priori intention because it represented the more conservative analysis approach, as to exclude them could possibly bias the sample towards those participants less likely to show cognitive decline, because of the known association between hypertension and poorer cognition.

7.5 Participants included in the normotensive comparison

7.5.1 Calculable coefficients of cognitive decline

As described in the Methods section 2.4.2, to calculate the outcome measure of the slope of decline for an individual, a minimum of two cognitive assessments 12 months apart were required. Due to the natural attrition associated with death and withdrawal of consent, follow-up cognitive data were unavailable for 32 normotensive participants. Of the 224 with calculable coefficients of decline, 159 (71%) participants completed the maximum number of assessments (4, 5 or 6 visits depending on time of recruitment); 31 (14%) had one missing data point; 20 (9%) had two missing data points; 12 (5%) missed three assessments; and 2 (1%) missed four assessments. The number of calculable coefficients of decline was comparable to that of the hypertensive group (224 normotensives versus 228 hypertensives) as shown in Figure 35. The proportion of missing data was almost identical, with the maximum number of assessments informing the slopes of decline for approximately 70% of participants in both groups (hypertensive cohort described in section 6.1). For the normotensives, a smaller proportion of participants had three or four missing assessments. However, rather than reflecting better participation for the normotensives per se, this was more likely the product of a higher proportion of withdrawn hypertensives returning to attend the closeout visit.

7.6.2 Baseline characteristics

Comparison of the normotensive and hypertensive participants with calculable coefficients of decline showed that there were no significant differences in baseline demographics (), other than those already identified between the overall recruited cohorts (detailed in 3.3.1): within groups there was an approximate 1:1 ratio of males to females, although comparison between groups showed that the proportion of males was slightly higher in the normotensive group; the prevalence of previous stroke was higher in the hypertensive group as expected, given the established relationship between hypertension and cardiovascular disease; and by definition normotensive participants had lower SBP and DBP.

Figure 35: Participant flow in the Newcastle Cognitive Substudy

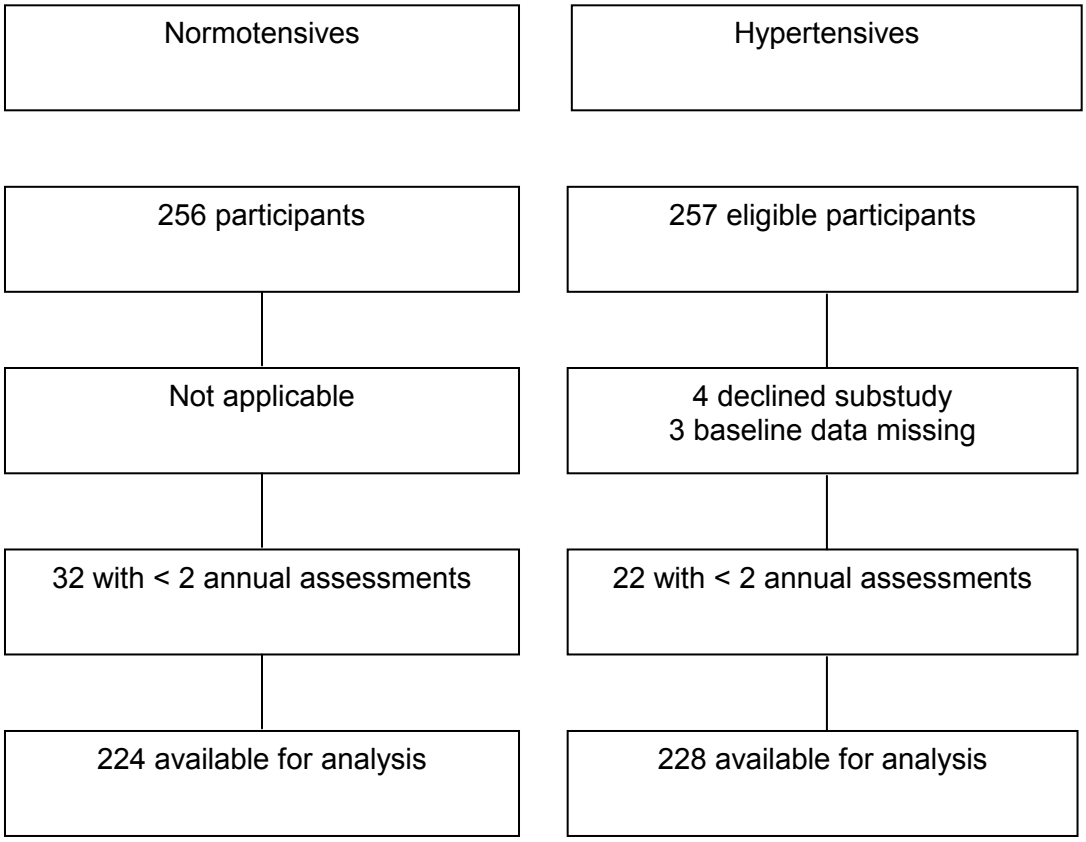


Table 53: Baseline demographics: normotensive vs hypertensives

Baseline demographic characteristics of normotensive participants versus hypertensive participants with calculable coefficients of decline in the Newcastle Cognitive Substudy.

Data shown are mean and (SD), or percentages.

	Normotensives	Hypertensives	t / χ^2	p
	n=224	n=228		
Age, years	76 (4)	76 (4)	-.35	.73
Females	42%	54%	6.04	.01
Education, years	10 (2)	10 (2)	.49	.62
NART errors	18 (9)	18 (9)	.32	.75
MMSE score	29 (1)	29 (1)	-.62	.54
SBP mmHg	131 (11)	165 (8)	38.43	<.001
DBP mmHg	74 (7)	88 (7)	22.52	<.001
Smokers	17%	13%	1.19	.28
HCTZ at enrolment	n/a	28%	-	-
Previous MI	4%	6%	1.61	.20
Previous stroke	1%	4%	4.44	.04
Atrial fibrillation	2%	4%	1.11	.29

NART = New Adult Reading Test; MMSE = Mini-Mental State Examination; SBP = systolic blood pressure; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; MI = myocardial infarction.

7.6.3 Baseline cognitive function

Comparison of the composite scores at baseline between the normotensive and hypertensive participants with calculable slopes of decline is shown in Table 54. Similar to the comparison of the overall recruited cohorts on the subtests of the CDR battery and tests of executive function detailed in section 3.4, the hypertensive participants performed significantly worse than the normotensives on the majority of the composite domains, with the exception of Continuity of Attention. Baseline differences in cognition were expected, and supported the *a priori* inclusion of baseline performance as a covariate in the general linear models (described in section 2.5.2).

Table 54: Baseline cognitive performance: normotensives vs hypertensives

Comparison of baseline performance on the composite cognitive factors between the normotensive and hypertensive groups, in participants with calculable coefficients of decline. A higher score indicates better performance except for Speed of Cognition, where a lower score indicates better performance

Data shown are mean and (SD)

Factor	Normotensives		Hypertensives		t	p
	n=224		n=228			
Speed of Cognition	6040	(1140)	6485	(1178)	4.08	<.001
Continuity of Attention	92.5	(2.2)	92.3	(2.8)	-.57	.57
Episodic Memory	241	(42)	224	(53)	-3.49	.001
Working Memory	1.71	(0.26)	1.59	(0.34)	-4.37	<.001
Executive Function	2.56	(2.83)	1.27	(3.18)	-4.50	<.001

7.6 Three-group comparison of cognitive decline

7.6.1 Repeat of primary analysis

The primary analysis of the Newcastle Cognitive Substudy compared the rate of cognitive decline between the hypertensive participants randomised to candesartan or placebo on an intent-to-treat basis. To put the rates of decline and magnitude of differences between the treatment groups into context, the primary analysis was repeated with the inclusion of the follow-up data from the normotensive controls. The univariate general linear model procedure was used to compare decline on each cognitive factor between the three groups, controlling for age, estimated pre-morbid IQ and baseline cognitive function as covariates.

Table 55 shows the results of the general linear models comparing the candesartan and placebo groups to the normotensive controls on the rate of cognitive decline for each composite factor. Where the F statistic was significant, post-hoc pairwise comparison to the normotensive group using the Least Squared Difference was also examined.

The placebo group showed significantly greater decline on Attention than the normotensive group, with no difference found between the candesartan group and the normotensive controls. For the Episodic Memory composite, where significant benefits were seen with candesartan compared to placebo in the primary analysis, although the overall model did not reach significance, the summary statistics show that the placebo group experienced a level of decline approximately twice that of the normotensive group, in contrast to a similar magnitude of improvement with candesartan compared to normotensive controls. Similarly for the Speed of Cognition composite, although not supported statistically, the placebo group showed the greatest declines, with the candesartan group exhibiting less decline than the normotensives. As in the primary analysis there was relatively little to distinguish between the groups on Executive Function, or Working Memory, although the normotensive group showed small declines in comparison to improvements of a similar size seen in both hypertensive groups.

Table 55: Three group comparison: normotensives vs candesartan vs placebo groups

Three group comparison of cognitive decline: comparison of change in cognition between the normotensive group versus the candesartan and placebo groups, as measured by coefficients of decline on five composite factor scores, in all participants with calculable coefficients. Adjusted for age, New Adult Reading Test errors and baseline performance. Negative values indicate decline in performance over time.

Data shown are mean and (SD).

	Coefficients of Decline					Pairwise Comparisons	
	Normotensives	Candesartan	Placebo			vs. Candesartan	vs. Placebo
Cognitive factor	n=224	n=112	n=116	F	p	p	p
Speed of Cognition	-6.6 (20.4)	-2.3 (25.2)	-17.4 (89.2)	2.3	.10	.21	.23
Attention	0.006 (0.096)	0.004 (0.088)	-0.036 (0.184)	4.7	.01	.80	.003
Episodic Memory	-.09 (1.11)	0.14 (1.38)	-0.22 (1.21)	2.6	.08	.10	.35
Working Memory	-0.0010 (0.0117)	0.0014 (0.0119)	0.0010 (0.0118)	.05	.96	.77	.97
Executive Function	-0.0020 (0.0510)	-0.0031 (0.0616)	-0.0023 (0.0739)	.09	.92	.73	.74

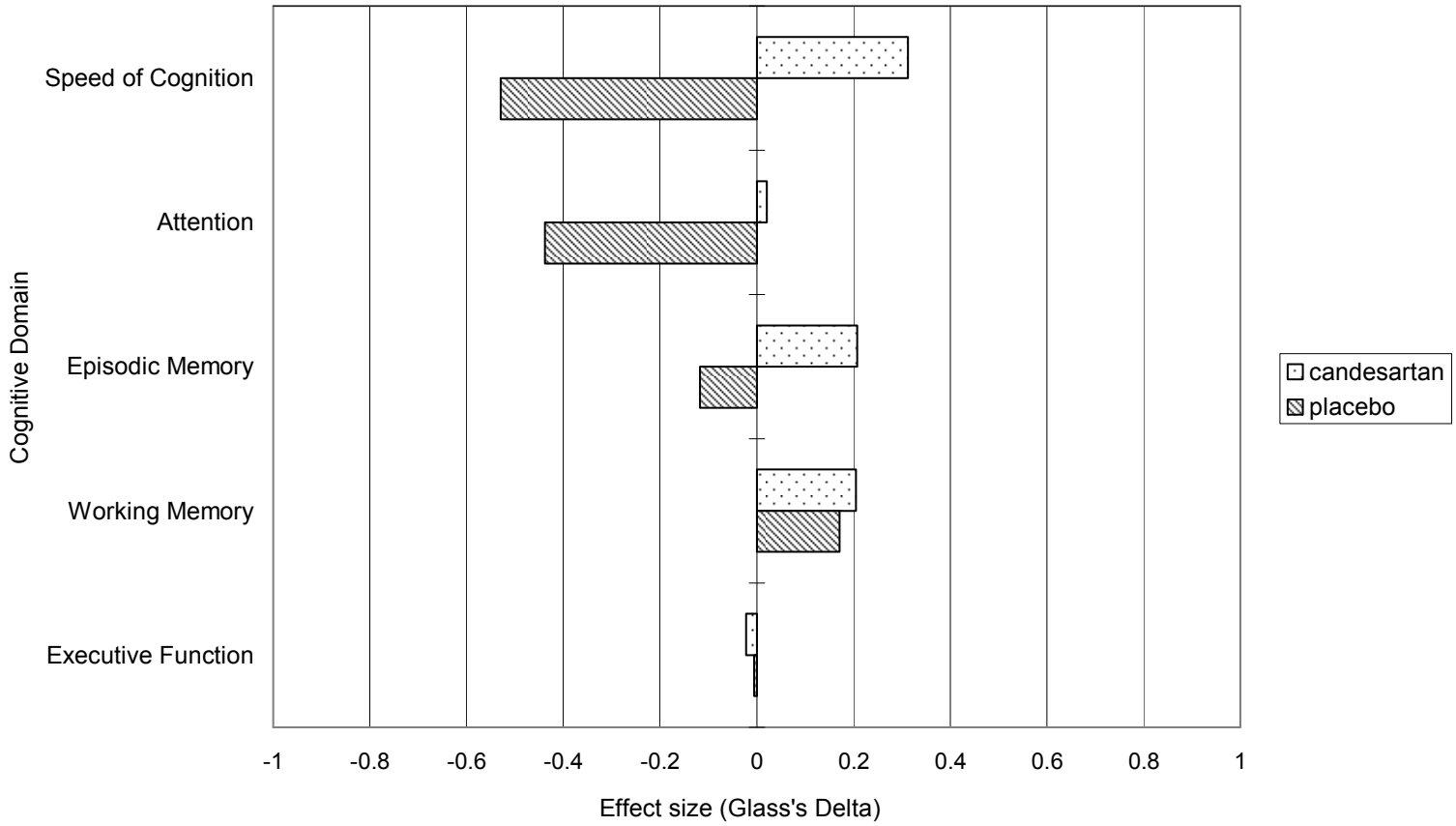
7.7.2 Effect sizes

The effect size calculations using Glass's Delta compared the change over time in the candesartan and placebo groups relative to the changes observed in the normotensive group. Figure 36 shows the magnitude of effects on each cognitive domain, where the zero line indicates the normotensive group for comparison: positive values represent better performance over time relative to the normotensives (either larger improvements or smaller declines); negative values represent worse performance over time relative to the normotensives (either larger declines or smaller improvements). Glass's Delta can be conceptualised as the number of standard deviations separating each treatment group from the normative reference group and interpreted using the generally-accepted conventions (0.2 = small effect; 0.5 = medium effect; 0.8 = large effect).

The largest differences appeared for Speed of Cognition where the placebo group showed a medium-sized decline compared to the change experienced by the normotensives, in contrast to less decline than the normotensives shown by the candesartan group. Similarly for Episodic Memory, the placebo group showed a small-to-medium size decline in comparison to the small decline in the normotensive group, whereas the candesartan group showed improvement over time. For Attention, the placebo group showed a small-to-medium decline, whereas change over time in the candesartan group matched that of the normotensives, showing minor improvements in both groups. For Working Memory, both hypertensive groups showed small improvements over time contrasted with similar-sized declines in the normotensives to produce a small effect size indicating improvement. However, the relative improvements could potentially be an artefact of the significantly different starting points of the hypertensive groups compared to the normotensives (Table 54), as no significant effects were found in the General Linear Models where baseline performance was controlled for as a covariate. For Executive Function there was little difference between any of the groups with effect sizes close to zero.

Figure 36: Effect sizes for candesartan and placebo groups compared to normotensive controls

Effect sizes for each cognitive domain, calculated using Glass's Delta for the candesartan and placebo groups in comparison to the normotensive control group. For each domain, negative values indicate worse performance over time (larger declines or smaller improvements) in comparison to the normotensives; positive values indicate better performance (smaller declines or larger improvements) relative to the normotensives.



7.7 Exploratory analyses: blood pressure as a continuous variable

7.7.1 Rationale

At the inception of the Newcastle Cognitive Substudy, the BP eligibility criteria created a minimum SBP gap of 10 mmHg between the normotensive and hypertensive groups at recruitment, expected to be maintained due to the treatment target of <160/90 mmHg. Approximately 6 months after the end of the recruitment period in the SCOPE study, new British Hypertension Society guidelines recommended a lower treatment target BP of <150/90 mmHg applicable to patients in the study population, which was implemented at participants' next scheduled study visit. As this was the upper BP bound for the ongoing normotensive recruitment, and the level above which recommendations were made to normotensive participants' general practitioners for additional BP-monitoring/treatment during the study, the 10 mmHg SBP gap between groups was no longer maintained. Therefore, although there were differences in the group means, there was overlap between groups in the distribution of average SBP and DBP over the course of the study, as shown in Figure 37. Although participants were defined according to BP at the time of recruitment, changes in BP during the study resulted in crossover of the boundaries, i.e. some 'normotensive' participants became hypertensive during the study; likewise some 'hypertensive' participants were well-controlled on BP-lowering therapy and achieved normotensive BP levels. The distribution of SBP and DBP at the closeout visit is shown in Figure 39. Examination of the frequency distribution of the average BP over the study follow-up period (Figure 38) showed that SBP and DBP were both approximately normally distributed. As such, BP in the study could be considered a continuous variable regardless of the original group allocation.

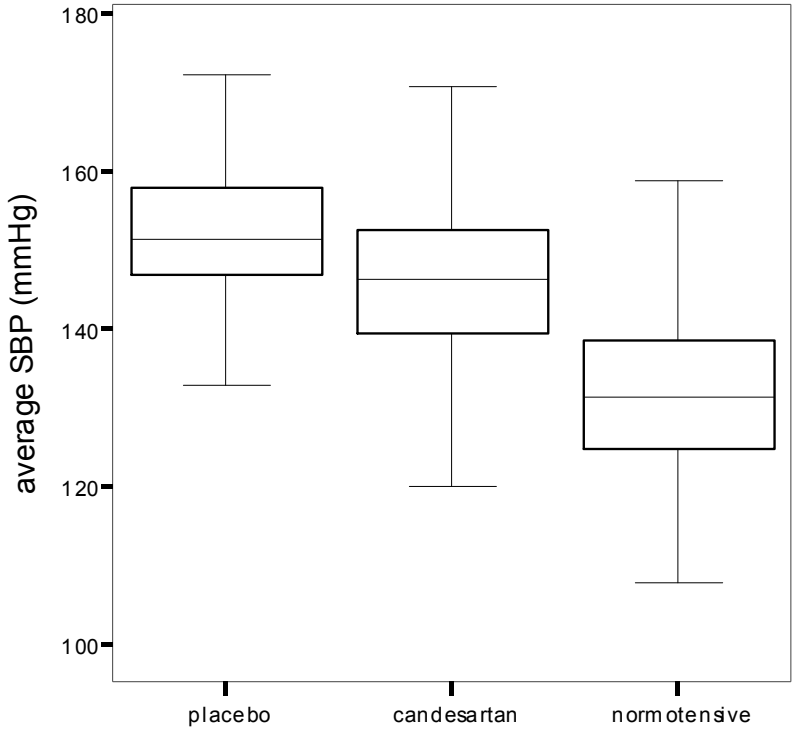
7.7.2 Analysis

Average BP over the course of the study was chosen as the variable of interest as this best reflected the overall 'burden' of BP, and coincided with the time period over which cognitive decline was measured.

The association between average BP over the course of the study and rate of cognitive decline was assessed using partial correlations, performed on the combined data from hypertensive and normotensive participants with calculable slopes of decline, controlling for factors known to affect cognitive function (age, estimated pre-morbid IQ and baseline cognitive function).

Figure 37: Boxplot SBP and DBP for three groups

Data shown are minimum, first quartile, median, third quartile, and maximum (excl. outliers, n=7).



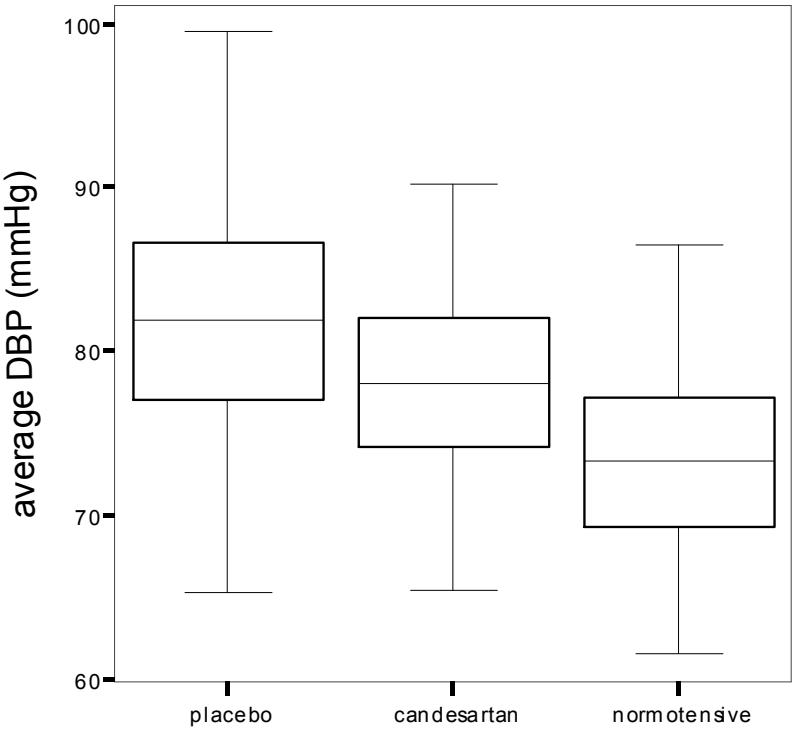
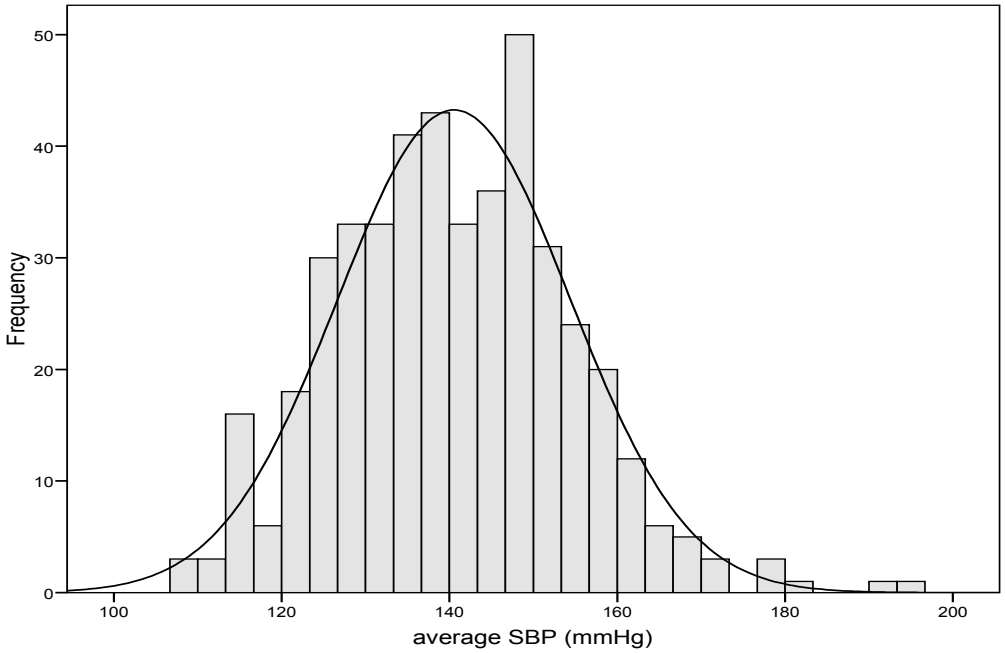


Figure 38: Histogram of average SBP and DBP



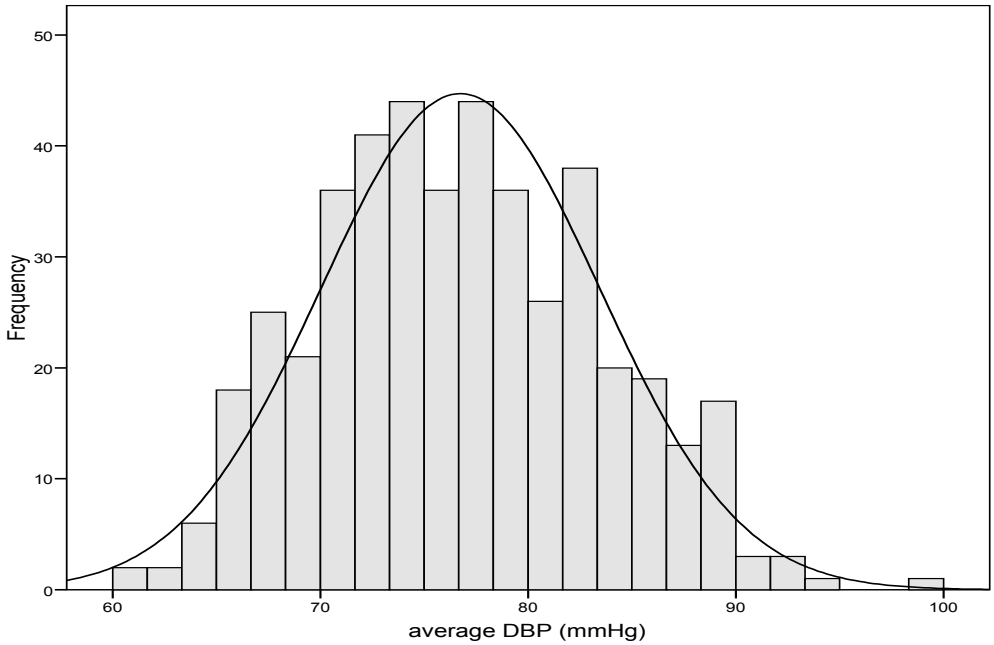
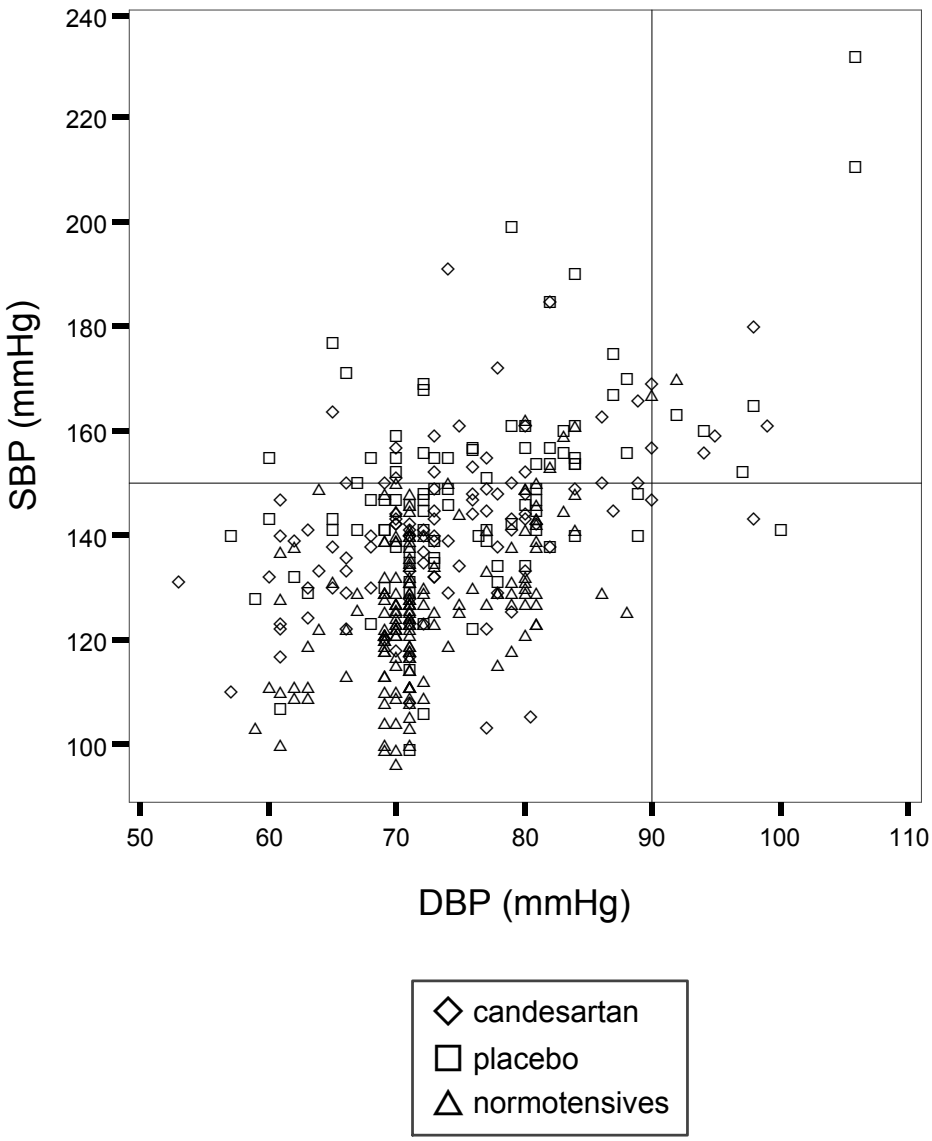


Figure 39: Distribution of SBP and DBP at the closeout visit

Distribution of systolic (SBP) and diastolic blood pressure (DBP) at the closeout visit, by group. Reference lines indicate the normotension criteria of 150/90 mmHg.



7.7.3 Relationship of average BP and cognitive decline

The partial correlation coefficients were very low and not statistically significant, except for a correlation of -.10 between DBP and Attention, and a trend towards significance for the correlation of -.09 between Attention and SBP (Table 56). The correlations were negative, indicating an association between higher BP across the study and greater decline in Attention (a negative slope indicating impairment). However the magnitude of the correlations were small, accounting for approximately 1% of the variance only.

The results suggest that BP 'burden' as measured by average BP over the study period is not a major contributing factor to cognitive decline, over and above the variance accounted for by age, IQ and baseline cognition.

Table 56: Partial correlations of BP and cognitive decline

Partial correlation analyses performed on the coefficients of decline for the hypertensive and normotensives combined, controlling for age, New Adult Reading Test errors and baseline cognitive function. Negative correlations indicate higher BP associated with greater cognitive decline/ lower BP associated with lesser cognitive decline.

Values are Pearson correlation coefficients, with two-tailed significance tested at the 0.05 level.

Cognitive domain	SBP		DBP	
	r	p	r	p
Speed of Cognition	-.07	.14	-.03	.60
Attention	-.09	.07	-.10	.03
Episodic Memory	-.07	.20	-.03	.58
Working Memory	.03	.59	.03	.56
Executive Function	-.03	.52	-.07	.18

CHAPTER 8: DISCUSSION

8.1 Executive summary

The primary analysis from the Newcastle Cognitive Substudy of the SCOPE trial suggests that there is potential for angiotensin-receptor-blocker (ARB)-based antihypertensive treatment to reduce the cognitive decline associated with hypertension in older adults. With an average systolic BP difference of 8 mmHg between the candesartan-treated and placebo-treated groups, significant reductions were found in the rate of decline over 3-5 years for the cognitive domains of Attention and Episodic Memory. There was also a trend for benefit to Speed of Cognition, although the result failed to reach statistical significance because of the large standard deviation in the placebo group. There were no differences in the rates of change between groups on Working Memory or Executive Function. Although differences were seen on the Attention composite, and aspects of attention are necessarily involved to some extent in performing working memory and executive function tasks, the emergence of Attention from the principal components analysis as a distinct factor supports the notion that the scores were free to vary independently. Comparison with normative data from the well-matched normotensive control group showed the decline on Speed of Cognition to be similar for the candesartan group, who showed improvements in Attention and Episodic Memory relative to the normotensives. Based on the accepted interpretation of effect sizes, the magnitude of effects were in the small-to-medium range. However, as hypertension is a chronic condition, with prolonged treatment even small effects could be clinically important. The results provide support for further studies with larger numbers of participants and longer duration to determine the efficacy of ARBs or other BP-lowering treatments in preventing the cognitive sequelae of hypertension.

The Newcastle Cognitive Substudy also demonstrated differential effects on the various domains of cognitive function that were not detected in the main SCOPE trial using a brief global measure (MMSE), supporting the comprehensive measurement of cognition in future trials. In particular, the use of computerised testing methods

showed that such assessment is feasible with older adults, bringing the benefits of standardisation of test stimuli, reduction of administrator bias, millisecond precision timing, and electronic data capture. Using factor analysis, the number of outcome variables was reduced in a meaningful way to maintain statistical power. The calculation of coefficients of decline using individual regression plots maximised the quality of the data by taking into account the repeated nature of assessments, and was able to handle missing datapoints and the variable length of follow-up. This approach provides a sensitive methodology for detecting cognitive change over time.

8.2 Main findings

8.2.1 Baseline results

Previous studies have generally shown hypertension to be associated with adverse effects on cognition, and analysis of the baseline data from the Newcastle Cognitive Substudy (NCS) comparing the normotensive and hypertensive cohorts confirmed this. Although very well-matched on baseline demographic characteristics, as expected the hypertensive group had a higher prevalence of previous cardiovascular and cerebrovascular disease, prior BP-lowering medication use, as well as a higher rate of psychotropic medication, which could possibly have accounted for the differences in cognitive function. The previously-published work of Dr Frances Harrington [84] excluded participants with these factors to compare the hypertensive and normotensive participants from the NCS that differed only in BP levels. A very similar pattern of subtle deficits was found with hypertensives performing less well than normotensives on the majority of subtests reported. Although psychotropic medications such as benzodiazepines are known to impair cognition, psychopharmacological therapy use was not controlled for in the primary analysis because patients were stable on the medications at study entry (the eligibility criteria excluded patients with treatment instigated within 6 months of enrolment), and psychotropic therapy was included in the randomisation stratification. The identification of impairments associated with hypertension was important as it supported the notion that hypertensives carry a deficit that can be targeted for reversal

or prevention with treatment. More importantly, as the NCS participants were community-dwelling individuals recruited from GP surgeries, it provided support that the NCS sample was representative of normotensives and hypertensives in the general population in this regard.

Similarly, the NCS hypertensives were well-matched to the participants in the main SCOPE trial with regard to the means and distributions of factors known to affect cognitive function such as age, SBP, DBP, and baseline MMSE scores. There were minor differences in the ratio of males to females, proportion of smokers, history of MI and percentage receiving antihypertensive therapy. As a single centre in an international multicentre trial, any site- or country-specific effects would ideally be tested, but as the raw data from the main SCOPE trial were not available, more detailed analyses were not possible. Albeit with this caveat, it was reassuring that the NCS sample was generally representative of the main SCOPE cohort and that the results could be extrapolated with some confidence.

8.2.2 Comparison to the main SCOPE trial

The intention-to-treat LOCF analysis of the 4964 patients in the main SCOPE study reported a modest, statistically non-significant reduction in major cardiovascular events with candesartan-based treatment (risk reduction 11%, p=.19), and a reduction in the secondary outcomes of non-fatal stroke (risk reduction 28%, p=.04) and all stroke (risk reduction 24%, p=.056) [85]. The mean difference in BP reduction was approximately 3/2 mmHg in favour of the candesartan group, considerably smaller than predicted in the planning of the trial. The results were somewhat disappointing in relation to the effects of cognitive decline and prevention of dementia, with mean MMSE scores falling approximately 0.5 of a point in both groups and the proportion of patients with significant cognitive decline or developing dementia being no different. In the NCS, the BP difference at the closeout visit was larger than that of the main SCOPE study at 8/3 mmHg. However, similar to the main trial, the change in MMSE scores from baseline was small at approximately a third of an MMSE point, and was no different between the treatment groups (incidence of dementia was too low to be meaningfully analysed). In contrast, using the Cognitive Drug Research (CDR) computerised assessment system and traditional measures of executive

function, significant beneficial effects of candesartan-based treatment were found in reducing decline on a number of cognitive domains, even with a much smaller sample size than the main SCOPE trial. Specifically, benefits to Attention and Episodic Memory were seen with candesartan-based treatment compared to placebo, and a reduction in decline on Speed of Cognition, although this failed to reach statistical significance. Effect sizes were in the small-to-moderate range.

Although compared to the main SCOPE study the NCS achieved a larger BP difference between treatment groups, which may have contributed to the effects seen with candesartan, the comparable results between the studies on the MMSE suggest that BP difference per se is not sufficient to account for the group differences. Rather, the sensitivity of the assessment methods used for detecting change is more likely. The MMSE was originally developed as a screening measure and is widely used for this purpose worldwide by physicians and in clinical trials. However, it has a number of shortcomings as a serial measure of cognitive function. In particular, it has no recognised parallel forms, meaning that repeated testing over relatively short periods of time can result in learning effects of the test stimuli, thus obscuring any real declines. The baseline characteristics of the SCOPE study [83] showed that the participants were well-functioning at study entry, with a mean MMSE score of 28.5, and approximately a third scoring the maximum of 30, making ceiling effects a real possibility. Indeed, subsequent unplanned post-hoc analyses were performed and the authors concluded that both learning and ceiling effects did occur in the main SCOPE trial [86]. Another drawback of the MMSE is that it is a global assessment of cognitive function, providing a brief snapshot based on a summed score only. Although within the MMSE there are individual items regarding different functions, it does not allow for detecting change in specific aspects of cognition, and as a paper-and-pencil measure it does not adequately tap into relevant domains such as attention. Therefore, even when overall change is detected, it is not always clear which specific areas of cognition are affected.

These measurement issues were identified and addressed, and formed the rationale behind the NCS. The use of computerised testing provided a sensitive assessment of a range of cognitive functions with a validated tool, as the CDR system has been used in a large number of clinical trials across all phases of the drug development process [68].

Importantly, parallel forms were used to prevent learning of task stimuli across visits and a training assessment was performed prior to the baseline assessment to familiarise participants with the use of the system and reduce procedural learning effects. For the assessment of executive function however, traditional paper-and-pencil measures were employed as the CDR system does not have any tasks that cover this domain, and as with the MMSE, these traditional tests also suffer from a lack of parallel forms.

The factor analyses employed in the NCS provided a method for reducing the number of potential analysis variables, by combining the individual subtests into meaningful composite scores based on empirical data. Factor analyses have been performed previously with data from the CDR system in healthy middle-aged volunteers [77] and patients with Dementia with Lewy Bodies [69] producing very similar factors, and the approach has been recommended [74] and used in studies of hypertension and cognition [26]. By using PCA with varimax rotation, the fewest factors explaining the maximum amount of variance were extracted. The factor solution chosen produced five factors labelled: Speed of Cognition, Attention, Episodic Memory, Working Memory and Executive Function. By definition, within each factor the subtest variables were highly correlated; between factors the variables were as uncorrelated as possible. Based on the factor solution, the individual subtest variables were combined into composite scores representing these five relatively independent domains of cognition. By combining the variables in this way, the risk of Type I error was reduced and changes in cognition were more easily characterised. Compared to the MMSE, the test battery in the NCS provided a comprehensive and sensitive assessment of cognitive function that was able to detect changes in specific domains of cognition, whilst maintaining statistical power.

A further issue that may have contributed to the lack of effects seen on the cognitive outcomes in the main SCOPE trial was the use of statistical analyses that failed to fully take account of the repeated measures design of the study. The analysis of change in MMSE scores was based on the intention-to-treat LOCF principle, comparing the baseline and last observation scores between the treatment groups. For the assessment of significant cognitive decline, a reduction in MMSE score of 4 points or more at two consecutive visits had to occur. Because of the rolling recruitment

period, the length of follow-up for an individual could vary between 36 and 60 months. On the assumption that a longer follow-up period gives more opportunity for decline to occur, it is possible that effects in the patients with longer follow-up could have been obscured by a lack of change in patients with shorter follow-up. In addition, the data from the repeated MMSE assessments were only used to inform the 'significant cognitive decline' criterion, and not used in the analysis of MMSE scores overall, meaning that the full quality of the data collected was not utilised. In contrast, the NCS used data from all annual visits to calculate individual slopes of decline on the five composite scores for each participant, taking account of the high inter-visit correlations seen with repeated cognitive assessments of the same individual. By using the number of months from baseline in the regressions, variations in the timing of the assessments, missed assessments, and differential length of follow-up between participants were easily dealt with in the analysis. Therefore, the combination of the measure used and the statistical approach may both have contributed to the lack of effects seen in the main SCOPE trial. It is a matter for speculation whether the use of more sensitive cognitive measures, or a greater difference in BP between the treatment groups, as observed in the NCS, would have produced differences in cognitive decline in the main SCOPE study.

8.3 Results in context

The results from the NCS add to the equivocal evidence from previous randomised, controlled trials of antihypertensive medication that have cognitive or dementia-related endpoints. In the SHEP study no differences were found over a five year follow-up period between a diuretic and/or beta-blocker treatment group and placebo on a range of cognitive tests [41], although it has been suggested the loss to follow-up of cognitively-impaired participants may have obscured the true effect of treatment [42]. Similarly, no differences in cognition were found between older adults randomised to a diuretic, beta-blocker or placebo treatment over 54 months in the MRC treatment trial of hypertension [44]. This finding is particularly interesting as the study used the same statistical methodology for analysing the repeated assessment data, albeit using a different battery of cognitive tests. However, the MRC study and the NCS studies are not directly comparable because of major differences in the design and treatment regimes.

The main evidence in support of the benefits of antihypertensive treatment on cognitive outcomes comes from the Syst-Eur trial. Participants randomised to active treatment with the calcium-channel blocker nitrendipine for isolated systolic hypertension showed a 50% reduction in the incidence of dementia over the two-year follow-up period compared to placebo, although on average there was little change in MMSE scores between the groups [46]. The dementia findings were reinforced when follow-up was extended for a further 2 years as an open-label study [47]. However, the robustness of the findings has since been questioned as the actual number of dementia endpoints was low (n=32) and the confidence intervals of relative risk were wide, ranging from no effect to a 76% reduction [48].

Comparability between studies is a major problem highlighted in a recent Cochrane review of BP-lowering for the prevention of cognitive impairment and dementia in patients with hypertension but no history of cerebrovascular disease [87]. The systematic review only selected double-blind randomised controlled trials, and as the MRC treatment study was single-blind it was not included. Comparing the SHEP, Syst-Eur and SCOPE studies was reported as problematic as large numbers of patients left the double-blind treatment, particularly in SCOPE where the changes in BP treatment target guidelines resulted in a high proportion of participants receiving additional open-label antihypertensive therapy. The meta-analysis performed on the incidence of dementia data from the 3 studies found no significant difference between treatment and placebo, and although there was an 11% relative risk reduction of dementia with BP-lowering, the effect was not significant. Change in MMSE was not reported in the SHEP study, and the combined results from Syst-Eur and SCOPE did not indicate a significant benefit of treatment. The authors concluded that there was no convincing evidence that BP-lowering prevents cognitive decline or dementia.

Post-hoc analyses of the SCOPE trial data have further investigated the effects on dementia and cognitive decline. To permit direct comparison with the SHEP and Syst-Eur studies, a pre-defined subgroup analysis of patients with isolated systolic hypertension (ISH) was performed [88]. From the 4964 patients randomised, 1518 met the criteria for ISH (SBP>160 mmHg and DBP<90 mmHg); 754 randomised to candesartan and 764 to the placebo group. BP was significantly reduced in both groups with a between-group difference of 2/1 mmHg. The relative risk of all stroke

(fatal and non-fatal) was reduced by 42% with candesartan-based treatment. As in the total SCOPE cohort, baseline MMSE was high at 28.6 in both groups and reduced by approximately 0.5 of a point, with no significant difference in change scores between the groups. There was no significant difference in the incidence of dementia (the incidence of significant cognitive decline was not reported).

Post-hoc analysis of SCOPE patients not receiving additional antihypertensive therapy after randomisation (n=2098) was also performed [89], more closely reflecting the original design of the study as a placebo-controlled trial (although 12.5mg HCTZ was permitted as per protocol) [59]. Blood pressure fell by 21.8/11.0 mmHg in the candesartan group (n=1253) and by 17.2/8.4 mmHg in the placebo group (n=845), and benefits were seen with candesartan in the relative risk of major cardiovascular events, cardiovascular mortality and total mortality. Despite a greater BP difference of 4.7/2.6 mmHg than in the total SCOPE cohort, there were no differences between the candesartan and placebo groups on change in MMSE scores, as both groups fell approximately .5 of a point from the baseline of 28.5. Similarly, no differences were observed between groups in the proportion of patients with significant cognitive decline or developing dementia.

A further post-hoc analysis looked at the influence of baseline cognitive function on the SCOPE outcomes, and compared the effects of candesartan in patients with lower cognitive function (LCF defined as MMSE 24 to 28; n=2070) and higher cognitive function (HCF defined as MMSE 29 to 30; n=2867) separately [86]. In the LCF group, change in MMSE score was significant smaller with candesartan-based treatment (-0.04) compared to placebo (-0.53), but there was no difference between treatments in the HCF group (-0.80 vs. -0.73). The proportion of patients with significant cognitive decline did not differ between the candesartan or placebo groups in either the LCF or HCF analyses. However, the incidence was higher in LCF than in HCF participants (6.6% vs. 3.6%, $p<.001$), as was the incidence of dementia (4.4% vs. 1.0%, $p<.001$). The additional post-hoc analyses were performed as the authors accepted that the MMSE had limitations and suffered from practice and ceiling effects in the SCOPE trial. This supports the call for the use of more sensitive cognitive tests, such as those used in the NCS, to be included in trials where cognitive outcomes are of interest.

Against the backdrop of previous intervention studies with cognitive outcomes, the NCS adds to the evidence base showing beneficial effects of antihypertensive treatment. At the very least the evidence overall demonstrates that antihypertensive therapy is not detrimental to cognition. However, none of the studies to date have been designed with the prevention of cognitive decline as the primary outcome. Although the NCS was a substudy of the main SCOPE trial, it demonstrates that comprehensive cognitive testing can be employed in such trials with the correct analysis approach and methodology. Placebo controlled trials are no longer justified on ethical grounds because of the known benefits of antihypertensive treatment on reducing cardiovascular events, therefore any future trial with cognition as a primary outcome would be a head-to-head comparison. Due to the high proportion of participants receiving additional therapy, the NCS was to a large extent a comparison of two antihypertensive regimens rather than a true placebo-controlled trial, yet because of the methodology employed was still able to detect differences between them.

8.4 Possible mechanisms of action

8.4.1 Blood pressure reduction

The effects of the candesartan-based treatment in the NCS were observed with an average BP difference of 8/3 mmHg between the groups across the study, which was greater than that observed in the main SCOPE trial. There are a number of potential mechanisms by which BP could influence cognitive decline, including the rate of cerebral atrophy, white matter lesion progression, or the occurrence of silent brain infarction. In a subset of the NCS participants, serial MRI scans were performed two years apart and volumetric changes in white matter hyperintensities and atrophy were measured. Hypertension was associated with increased rates of whole brain atrophy and white matter changes, and there was a trend for candesartan treatment to reduce the risk [90].

The analysis of BP as a continuous variable did not find BP ‘burden’, as measured by the average BP over the study period, to be a major contributing factor to cognitive decline over and above the variance accounted for by age, IQ and baseline cognition. The correlation analyses could reflect a true absence of an association over the full

range of BP, or perhaps suggest a threshold effect. The implication would be that there is a cut-off beyond which further BP-lowering confers no additional benefit to cognition. A prospective study of intensive BP-lowering regimens would be required to fully test this hypothesis.

8.4.2 Drug class effect

Although there was a difference in BP maintained between the treatment groups, BP in the placebo group was significantly reduced in the study due to the unavoidably high use of additional therapy to meet the treatment target guidelines. As the effect size analysis showed that placebo participants experienced cognitive decline despite the significant reduction in BP, this suggests beneficial effects in the candesartan group could be due to non BP-related pharmacological properties of AT_1 receptor antagonism. Diminished regional cerebral blood flow responses during some memory tasks have been found in hypertensives using positron emission tomography [91]. As a vasodilator capable of crossing the blood-brain barrier, it is possible that candesartan could affect cognition via improved cerebral perfusion. Pre-treatment with candesartan was found to be protective against ischemia by normalising the cerebral blood flow response in spontaneously hypertensive rats [92].

Similarly, there is evidence from behavioural and neurochemical studies that angiotensin II can induce inhibition of cholinergic-mediated brain function [93]; the action of candesartan would be expected to reduce this inhibition and therefore improve aspects of cognition such as attention. Two previous studies have also found the suggestion of beneficial effects of similar ARBs to candesartan. Hypertensive patients aged 75-89 years were randomised to losartan or atenolol, and despite equivalent reductions in BP, improvements were seen on an episodic memory task in the losartan group compared to no change with atenolol over 6 months [94]. Similar benefits specific to episodic memory were seen in an open-label study of valsartan or enalapril over 16 weeks by the same group [95].

Whether the effects seen in the NCS result from the BP differences between the treatment groups or reflect a drug class effect is a matter for speculation as the study

was not designed to test these hypotheses. To do so would require a head-to-head comparison of different classes of compounds, with well controlled BP targets.

8.5 Strengths of study

The NCS was a randomised controlled trial based on the main SCOPE study, and as a result benefited from the study infrastructure in terms of administration, study drug blinding and data monitoring. The well-designed substudy was supported by a dedicated multi-disciplinary team to aid the smooth running of the study and ensure the quality of the data. The substudy was particularly strong for having an additional normotensive group for normative comparison to put the magnitude of cognitive changes into context.

Attrition and loss to follow-up are major concerns in longitudinal studies as they can introduce bias if there are systematic differences between treatment groups. Efforts were made on a practical level to maintain participation including the provision of dedicated parking spaces for study visits, reimbursement of travel expenses or pre-booked taxis, a dedicated direct dial telephone line to study staff, regular newsletters and an annual social/educational event for participants. This helped reduce attrition, and the high proportion of participants attending the closeout visit provided valuable long-term data that may otherwise have been lost to follow-up.

The use of computerised testing was found to be a highly effective approach in the NCS. In addition to being the most appropriate method of assessing attention because of the sensitive timing mechanism, computerised testing standardised the presentation of test stimuli to reduce administrator bias. The availability of validated parallel forms enabled repeated testing without learning effects, and permitted training sessions to be performed to familiarise participants with study procedures and reduce practice effects. The test battery used covered a range of cognitive functions enabling the differential effects on cognition to be investigated. The factor analytic methods reduced the number of outcome variables in a meaningful way to maintain statistical power, and the calculation of slopes of decline using individual regression plots adequately dealt with missing data and variations in length of follow-up.

8.6 Limitations

The main limitation of the NCS is that it was a single-centre study and without access to the main trial database it is difficult to fully assess how generalisable the findings are to the full study population. However, with the exception of the greater BP difference between groups at the end of trial which was most likely due to better compliance at the Newcastle centre, all of the comparison statistics conducted suggest the NCS cohort was representative of the main trial.

As it was a substudy, the NCS was not powered to the same extent as the main trial, and was not designed to determine efficacy of candesartan as a treatment to prevent cognitive decline. Despite this, significant benefits were seen using the comprehensive test battery in much smaller sample size compared to the MMSE in the main SCOPE trial. The sensitivity of the computerised battery was primarily responsible for this. Regarding the assessment of executive function, as the CDR system does not measure this specifically, traditional neuropsychological tests were used. These pencil-and-paper tests have inherent limitations, most notably the lack of parallel forms, and in future studies alternative tests with better psychometric properties might usefully be considered (e.g. the Color Trails Test is analogous to the standard Trail-Making Test but has validated parallel forms).

8.7 Future work

The NCS provides a sound methodology for the design of the cognitive aspects of future studies. Indeed, an international, multicenter, cognitive substudy of the PRoFESS study (Prevention Regimen For Effectively avoiding Second Strokes) has recently been completed using the same measures and statistical approach for determining cognitive decline. With 565 participants, the study provides a sizeable sample for repeating the factor analyses on the same measures. This would serve as a useful validation of the cognitive domains and the use of the composite scores as analysis outcomes.

To determine the efficacy of antihypertensive treatments for the primary prevention of cognitive decline and dementia, larger clinical trials of adequate duration using sensitive measures need to be designed around cognitive endpoints. However, long-

term placebo-controlled studies in hypertension are now deemed unethical because of the known cardiovascular benefits of treatment. As the BP treatment guidelines have lowered target BP over time, and physicians maintain better BP control in their patients, achieving large BP reductions in studies will become more difficult. If a threshold effect exists, even intensive BP-lowering may not demonstrate effects on cognition. Therefore future studies might usefully target populations that are at higher risk for cognitive decline, such as post-stroke patients, or putative prodromal dementia states such as Mild Cognitive Impairment or Age-Associated Memory Impairment. Thus it remains to be seen whether antihypertensive treatment will become the first line of defence in preventing dementia and cognitive decline, but given the known cardiovascular benefits of treatment, it continues to be an avenue of investigation worth pursuing.

APPENDICES

Appendix I: Characteristics of cross-sectional studies

Characteristics of cross-sectional studies investigating the relationship between blood pressure and cognitive function

Authors	Study design/ analysis	N	Age (years)	BP criteria (mmHg)	Exclusion criteria	Inclusion criteria	Neuropsychological/ cognitive tests	Conclusions
[10]	group comparison HT vs. NT	20:20	mean 49:51	HT DBP >105	history of neurological disorder, diabetes or alcoholism	newly diagnosed, untreated, males only	WAIS (digit span, arithmetic, vocabulary, block design, object assembly, digit symbol substitution), vigilance / SRT, Purdue pegboard, WCST, WMS (logical memory), Rey-Osterreith Figure, DeRenzi Rods Test, Tonal Memory test, Token Test, BDAT	hypertensives sig. slower on SRT, reduced digit span
[11]	ordinal logistic regression controlling for age, sex, education, anti-hypertensive medication, alcohol & smoking	2032	55-89	none; for analysis definite HT SBP ≥160 and/or DBP ≥95	history of stroke	subjects from Framingham Heart Study	WAIS (digit span, similarities), WMS (logical memory immediate and delayed, visual reproduction, paired-associate learning, word fluency)	No sig. association between BP and cognition
[13]	linear logistic regression controlling for age, sex, education, medication, history of stroke,	3627	≥65	none; for analysis HT SBP ≥140 and/or DBP ≥90	none	non-institutionalised	story retelling test for immediate & delayed memory, WAIS (digit span), Pfeiffer Mental Status Questionnaire	small but sig. association between increased DBP and lower digit span; no consistent pattern across tests

Authors	Study design/ analysis	N	Age (years)	BP criteria (mmHg)	Exclusion criteria	Inclusion criteria	Neuropsychological/ cognitive tests	Conclusions
	depression, alcohol, smoking, self-assessed health							
[14]	hierarchical regression analysis controlling for age, sex, education; tested SBP, DBP, anti-hypertensive medication and vascular risk factors	943	stratified for age; 24-81	none; for analysis HT SBP ≥140 and/or DBP ≥90	overt cerebrovascular disease (incl. stroke), Parkinson's, dementia, epilepsy, psychotropic medication	MMSE ≥24	word learning task, concept shifting task, Stroop Colour Word Test, letter/ digit substitution test, word fluency	no linear relationship between BP and cognition; when age, sex & education adjusted for, HT did worse on letter/ digit substitution than matched controls
[15]	correlation; multivariate analyses controlling for age & IQ: subjects divided into 3 groups	598	>70; mean 76	none; low ≤135/75 med 136-181/ 76-95 high >181/95	prescription medication, any reported health problems	healthy subjects from Healthy Old People in Edinburgh (HOPE) study	MMSE, NART	MMSE correlated negatively with SBP, but not DBP; after adjusting for age & IQ, sig. association of high SBP & high DBP with low MMSE
[16]	logistic regression analysis	1106	65-95; mean 74	none; mean 145/82	cerebrovascular disease, psychotropic medication		MMSE	DBP predicted impairment (MMSE <24) in over 75s, but not in 65-74 year olds

Authors	Study design/ analysis	N	Age (years)	BP criteria (mmHg)	Exclusion criteria	Inclusion criteria	Neuropsychological/ cognitive tests	Conclusions
[18]	correlation; stepwise linear regression; multiple logistic regression controlling for age, sex & education	2225	60-100; mean 70	isolated systolic HT: SBP 160-219 and DBP <95	dementia		MMSE	SBP contributed weakly to MMSE compared to age & education; for women SBP correlated negatively with MMSE
[19]	group comparison HT vs. NT	17:27	>60; mean 77:75	HT SBP >165 and/or DBP >95 or taking anti-hypertensive medication	stroke/ TIA Parkinson's, dementia, epilepsy, psychiatric disorders, chronic disease, alcohol abuse	anti-hypertensive medication replaced with placebo 2 weeks prior	WAIS (digit span), word list generation, finger tapping, SRT, CRT, visual search/ cancellation, Buschke-Fuld selective verbal reminding, 3 words – 3 shapes test, Weigl sorting test	HT impaired on attention tasks (tapping and incidental memory) but not memory or judgement tasks
[20]	HT vs. NT matched pairs; ANOVA tested effects of age, hypertension and medication	90 pairs	40-79 in 10-year bands	HT SBP ≥180 or DBP ≥100 or taking anti-hypertensive medication; NT DBP ≤90 and 12m of no anti-hypertensive medication or raised BP	history of stroke		letter cancellation, WAIS (digit span, digit-symbol substitution), Rey Auditory Verbal Learning test	trend for HT to perform worse; sig. worse on Verbal Learning (recall and retention)

BDAT = Boston Diagnostic Aphasia Test; BMI = Body Mass Index; CRT = Choice Reaction Time; HT = hypertensive; MMSE = Mini-Mental State Examination; NT = normotensive; SRT = Simple Reaction Time; TIA = transient ischemic attack; WAIS = Wechsler Adult Intelligence Scale; WCST = Wisconsin Card Sort Test; WMS = Wechsler Memory Scale.

Appendix II: Characteristics of retrospective longitudinal studies

Characteristics of retrospective longitudinal studies investigating the relationship between blood pressure and cognitive function

Authors	Study design/ analysis	Sample	Exclusion criteria	Inclusion criteria	Neuropsychological / cognitive tests	Conclusions
[12]	longitudinal BP readings (chronicity and average SBP & DBP) and cognitive function. ordinal logistic regression/ linear regression stratified by anti-hypertensive use in last 2 yrs; adjusted for age, sex, alcohol, education, occupation, smoking.	n = 1993; ♂ 1175; age: 55-89; BP criteria: none, for analysis HT SBP ≥160 and/or DBP ≥95; follow-up yrs: 26	previous stroke, unknown anti-hypertensive medication status, missing neuropsychological data	sample from Framingham Heart Study [11]	education-adjusted composite of: WAIS (digit span, similarities), WMS (logical memory immediate and delayed, visual reproduction, paired-associate learning, word fluency)	no association between cognitive performance and BP for subjects on anti-hypertensives. Chronicity and average SBP & DBP levels were inversely related to cognitive performance in untreated subjects. For previously treated subjects, sig. relation between cognitive impairment and probability of being off medication at testing
[24]	compared average BP when untreated and cognitive test performance at follow-up; multivariate linear regression controlling for age, education, gender, occupation, alcohol, smoking.	n = 1702; age: 55-89; BP criteria: none; follow-up yrs: cognitive testing 12-14 yrs after final BP measurements	previous stroke	sample from Framingham Heart Study [11]	WAIS (digit span, similarities), WMS (logical memory immediate and delayed, visual reproduction, paired-associate learning, word fluency)	BP levels and chronicity were inversely related to composite score and measures of attention and memory (logical memory, visual reproductions, digit span backwards), for full sample, subsample untreated at BP measurements, and subsample untreated throughout study
[96]	reanalysed data from [24] using multiple linear	n = 1695;	excl. 7 subjects with unknown anti-	same as [24]	same as [24]	interaction effects of age × BP level and age × chronicity were

Authors	Study design/ analysis	Sample	Exclusion criteria	Inclusion criteria	Neuropsychological / cognitive tests	Conclusions
	regression to assess interaction effects of age and BP	age analysed as continuous variable and groups (55-64; 65-74; 75-88)	hypertensive medication status			trivial or non-significant. Independent associations between BP and cognition remained
[25]	reanalysed data from [24] using multiple binary logistic regression to calculate odds ratios for poor cognitive performance for increases in DBP, SBP and age	n = 1695; criteria same as [24]	excl. 7 subjects with unknown anti-hypertensive medication status	same as [24]	Performance in the lower 50th and 25th percentiles on tests from [24]	BP and chronicity were inversely associated with performance on visual and verbal memory tests. Age was inversely associated with performance on all tests. Odds for poor performance were higher for age than BP variables
[27]	multiple logistic regression controlling for age and education	n = 3735 males; age: mean 78 at follow-up; BP criteria: none, for analysis SBP low <110, normal 110-139, borderline 140-159, high >160 follow-up yrs: mean 25	none	community and institutionalised subjects from the Honolulu Heart Program	CASI scores grouped for analysis as good 92-100, intermediate 82-91, poor <82.	risk for intermediate and poor cognitive function increased with level of midlife SBP category. Every 10 mmHg SBP increase was associated with increased risk of intermediate (7%) and poor (9%) cognitive function. Adjustment for CVA, CHD and subclinical atherosclerosis reduced strength of relationship to 5%. No association with midlife DBP.

Authors	Study design/ analysis	Sample	Exclusion criteria	Inclusion criteria	Neuropsychological / cognitive tests	Conclusions
[28]	multivariate models adjusting for age, education, occupation, stroke diagnosis, medications affecting BP	n = 999 males; age: 69-75, mean 72.4; BP criteria: none; for analysis: DBP <71, 75-80, 85-90, 95-100, ≥105 follow-up yrs: 20	none	population-based cohort from Uppsala, Sweden	composite score derived from transformed MMSE & Trail-Making Test A & B; outcome analysed as continuous and dichotomised at lowest quintile	high baseline DBP (but not SBP) predicted impaired cognitive function at follow-up, even after excluding previous stroke. Cross-sectional data at 70yrs showed high 24h ABPM, non-dipping, insulin resistance and diabetes associated with low cognitive function. Strongest in untreated subjects.
[29]	Compared trackers (SBP high in midlife & follow-up) with normal (consistently low/ medium, or increasing over follow-up) and decreasers (decreasing from high/ medium to medium/ low) GLM adjusting for age, education, depression, stroke, anti-hypertensive medication	n = 717 males; age: mean 75 at follow-up; BP criteria: none, for analysis SBP low <120, medium 120-139, high ≥140; follow-up yrs: 30	analysis of cognitive data excluded 7 subjects with MMSE <23	Western Collaborative Group Study subjects: healthy, white males, free from heart disease at baseline	verbal memory, psychomotor speed and verbal fluency factors from PCA of measures (Iowa screening battery, MMSE, DSS, color Trail-Making Test, Color-Word Interference Test, CVLT)	High SBP trackers performed worse than normals on verbal memory SBP decreasers performed worse on psychomotor speed than normals. No differences in verbal fluency.
[30]	multivariate regression models using age, gender, education, class, length of follow-up,	n = 387; ♂235; age: 70-88, mean	prescription medication or any reported health problems at	healthy subjects from Healthy Old People in Edinburgh	NART, fluid intelligence (RPM), memory score (derived from	demographic variables, pre-morbid IQ and BP accounted for 39% of variance in RPM at follow-up, but only 12% of

Authors	Study design/ analysis	Sample	Exclusion criteria	Inclusion criteria	Neuropsychological / cognitive tests	Conclusions
	NART, SBP & DBP, for subjects who remained healthy throughout and whole sample	75 at baseline; BP criteria: none; for analysis DBP low <80; medium 80-90; high >90 follow-up yrs: 4	baseline	(HOPE) study [15]	immediate and delayed logical memory subtests of WMS-revised)	memory variance. BP was related prospectively to fluid intelligence but not memory
[31]	BP measurements taken at 3 visits over first 15 yrs; cognitive data measured twice in following 10 yrs. Chi-square test and ANOVAS to examine association of midlife SBP category with demographic, avge BP, CVD, CHD, PAD, and cognitive change	n = 392 males; age: mean 72.5 at follow-up; BP criteria: none, for analysis SBP low <120, normal 120-139, high ≥140, mixed: no pattern across visits; follow-up yrs: 25	none	subgroup of National Heart, Lung, and Blood Institute (NHBLI) Twin Study	MMSE, DSS, BVRT, verbal fluency	Mean 10-yr decline on DSS observed for all midlife SBP groups with high SBP group declining most, low SBP least. Low SBP group showed no decline on MMSE; other 3 groups did, with mixed group showing greatest decline. Verbal fluency tended to increase over time with no differences between groups. No differences on BVRT.

ABPM = ambulatory blood pressure monitoring; BVRT = Benton Visual Retention Test; CASI = Cognitive Abilities Screening Instrument incorporating Hasegawa Dementia Scale, Mini-Mental State Examination and the Modified Mini-Mental State Examination; CHD = coronary heart disease; CVA = cerebrovascular accident; CVD = cerebrovascular disease; CVLT = California Verbal Learning Test; DSS = digit-symbol substitution subtest of the Wechsler Adult Intelligence Scale; GLM = general linear model; PAD = peripheral arterial disease; PCA = principal components analysis

Appendix III: Characteristics of prospective longitudinal studies

Characteristics of prospective longitudinal studies investigating the relationship between blood pressure and cognitive function

Authors	Study design/ analysis	Sample	Exclusion criteria	Inclusion criteria	Neuropsychological / cognitive tests	Conclusions
[32]	multiple logistic regression controlling for age, gender, education, anti-hypertensive medication, cardiac dysrhythmia, heart failure, stroke, CHD, BP	n = 924; age: 75+; BP criteria: none follow-up yrs: mean 3.4	dementia/ mild cognitive impairment	Kingsholmen Project population sample	MMSE	minor decline (0.4 points per annum). 23.4% declined more than 10%. Age, lower education and stroke predicted decline for women. Education and stroke, not age in men. In women, SBP reduction correlated with decline
[33]	multiple regression controlling for age, gender, area of residence, NART & RPM, self-report depression, antidepressant meds, SBP, DBP, anti-hypertensive meds, cholesterol, BMI, smoking, ischaemia	n = 2567; age: 65-74 BP criteria: SBP 160-209 mmHg follow-up yrs: 4.5	serious cardiovascular, cerebrovascular or intercurrent illness; anti-hypertensive medication at baseline. Subjects were randomised to beta-blocker, thiazide diuretic or placebo	subjects enrolled in the Medical Research Council trial of the treatment of moderate hypertension	PALT co-efficient (slope of the regression line for each subject by regressing PALT scores on time)	decline on PALT associated with age, male gender, rural residence, depression and low intelligence (NART & RPM). No sig. associations for cardiovascular variables (incl. SBP or DBP, mean SBP over follow-up, trial therapy). No association between untreated (placebo) group and PALT decline
[34]	general factorial MANOVA, adjusting for baseline cognitive function, APOE, alcohol, education, diet, lifetime smoking, social class,	n = 387; mean age: 70.2; mean SBP: 184	as [33]	as [33]	log transformed MMSE controlling for baseline cognitive function (PALT, TMT A &	poor cognition at Time 2 associated with greater history of dementia, older age, abstinence from alcohol before 60, less decline in SBP over trial period. Decline in SBP became

Authors	Study design/ analysis	Sample	Exclusion criteria	Inclusion criteria	Neuropsychological / cognitive tests	Conclusions
	'history of dementia' loading	mmHg follow-up yrs: mean 9-12			RPM)	non-significant when 41 dementia cases excluded
[35]	multiple logistic regression adjusting for age, gender, education, income, alcohol, depressive symptoms, APOE, baseline cognitive function	n = 1373; age: 59-71, mean 65 at baseline; BP criteria: none; for analysis HT SBP≥160 and/or DBP≥95 or taking anti-hypertensives; follow-up yrs: 4	stroke during follow-up	subjects from the Epidemiology of Vascular Ageing (EVA) study	decline on MMSE ≥ 4	risk of decline over 4 years was increased with high BP. Chronicity was also associated with increased risk of decline. Untreated hypertensives at greater risk than treated hypertensives
[36]	stepwise regression analysis: age, education, social class, health status, medication use, SBP, DBP, NART-IQ, MMSE	n = 387; age: 70-88, mean 75 at baseline; BP criteria: none; follow-up yrs: 4	as [30]	healthy subjects from Healthy Old People in Edinburgh (HOPE) study; as [30]	change in MMSE scores	baseline variables predicted approx. a quarter of the variance in change scores. Age and high SBP increase risk of cognitive decline; higher NART-IQ scores are protective. Effect of SBP on decline was less for subjects who remained both disease and medication-free
[37]	multivariate regression models controlling for age, gender, education	n = 2068; age: 65-81 at	institutionalised	subjects from the Hypertension Detection and	9-item Pfeiffer Mental Status Questionnaire, 6-	no strong linear association between BP and cognition. No effect of BP on memory, or

Authors	Study design/ analysis	Sample	Exclusion criteria	Inclusion criteria	Neuropsychological / cognitive tests	Conclusions
	and time of evaluation	baseline; BP criteria: none; for analysis SBP low <130, med 130-139, high ≥160; follow-up yrs: 6 & BP from 9 yrs pre-baseline		Follow-up Program (HDFP)	item East Boston Memory Test	change over time on either test. For Mental Status Qu., SBP≥160 9yrs prior to baseline was associated with increased errors at follow-up. U-shaped association found between baseline SBP & DBP and errors with low and high BP groups performing worse
[38]	multivariate analyses controlling for age, gender, education, race, study site, CNS-relevant medication	n = 10,963; age: 47-70 at baseline; BP criteria: none; for analysis HT SBP≥140 or DBP≥90 or taking anti-hypertensives at baseline; follow-up yrs: 3.6-8.8, mean 6	history of stroke or transient ischemic attack	population sample from the Artherosclerosis Risk in Communities (ARIC) study	Delayed Word Recall test, digit-symbol substitution (WAIS-revised), Word Fluency (F, A & S)	presence of hypertension at baseline was associated with greater decline on the digit-symbol substitution test. Presence of diabetes was associated with greater decline in scores on the digit-symbol substitution test and word fluency

APOE = apolipoprotein-E allelic status; BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; DBP = diastolic blood pressure; HT = hypertensive; MMSE = Mini-Mental State Examination; NART = New Adult Reading Test; PALT = Paired Associate Learning Test; RPM = Raven's Progressive Matrices; SBP = systolic blood pressure; SD = standard deviation; TMT A = Trail-Making Test form A; WAIS = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale.

Appendix IV: Characteristics of intervention studies

Characteristics of prospective studies investigating the effect of antihypertensive medication on cognitive function

Authors	Study design / antihypertensive medication	Sample / target BP levels	Exclusion criteria	Inclusion criteria	Neuropsychological / cognitive tests	Conclusions
[43]	single-blind, randomised, placebo-controlled thiazide diuretic vs. β-blocking agent additional therapy: adalat	n = 2401; age: 65-74, mean 70.3; BP criteria: SBP 160-209 and DBP ≤113 target: SBP <150 (160-179 at entry) or SBP <160 (180-209 at entry); follow-up: 1 & 9m	major physical illness	Medical Research Council trial; untreated hypertensives from primary care	NART, RPM, PALT, TMT A, self-rating depression questionnaire	No significant differences at 1 or 9 months on any neuropsychological tests. BP was significantly reduced at 9 month in treatment groups compared to placebo
[44]	same as [43]	n = 2584; entry criteria same as [43]; follow-up: 4.5 years	same as [43]	same as [43]	PALT, TMT A; coefficient of change calculated as the slope of the regression line of test score on time	No significant differences between groups on cognitive outcomes, for intention-to-treat and protocol analysis. Also no differences in group remaining on allocated medication only
[50]	phase I: single-blind, randomised, placebo-controlled HCTZ/ triamterene vs. atenolol	n = 25; age: 61-79, mean 70.6;	neurological/ psychiatric disorder, cardiovascular	MMSE ≥26	Automated Psychomotor Test (APT) battery: DSS, CAT, CRT,	Target BP achieved in 18/20 subjects in treatment group. Improvement on DSS, CAT,

Authors	Study design / antihypertensive medication	Sample / target BP levels	Exclusion criteria	Inclusion criteria	Neuropsychological / cognitive tests	Conclusions
	vs. nifedipine vs. captopril; 2-week placebo run-in	BP criteria: placebo phase SBP ≥165 and DBP 95-125; target: SBP <165 and DBP <95; follow-up: 1 & 4 weeks (baseline at end of placebo run-in phase)	disease, hypertensive end organ damage, drugs affecting CNS, moderate alcohol intake		Critical Flicker Fusion Threshold, Cognitive Flexibility Test, PWAT, Inspection Time Threshold	PWAT and Inspection Time Threshold at 1 week. Further improvement at 4 weeks on CAT only. No change in placebo group or 2 non-responders to treatment. Age, education, social status or handedness not related to improvement
[50]	phase II: double-blind, randomised, cross-over study of nifedipine vs. captopril; 2-week placebo run-in, 2 week treatment, 2 week placebo washout, 2 week treatment	n = 13; age: mean 67.9; BP criteria: as above follow-up: 6 weeks (baseline at end of placebo run-in phase)	as above	as above	abbreviated Automated Psychomotor Test (APT) battery: DSS, CAT, CRT, PWAT	Target BP achieved with nifedipine and captopril. Improvement seen on DSS, CAT, CRT and PWAT. No differences in BP control or APT improvement between the two antihypertensives. Phase I & II suggest improvement due to BP control rather than direct CNS effect of drugs
[41]	phase III: multicentre, double-blind, randomised, placebo-controlled, stepped-care treatment of thiazide and/or atenolol vs placebo	n = 4736; age: 60-94, mean 72 BP criteria SBP 160-220 & DBP<90 follow-up: annual for	not reported	Isolated systolic hypertension	DSS, Addition test, Finding A's, Boston Naming, Letter sets test, delayed recognition span	Little change in cognition in either group over 5 years. Concluded the absence of detrimental effects

Authors	Study design / antihypertensive medication	Sample / target BP levels	Exclusion criteria	Inclusion criteria	Neuropsychological / cognitive tests	Conclusions
		mean 5 years				
[45]	double-blind, randomised trial of captopril vs. bendrofluazide; 2-week placebo run-in phase	n = 81; age: 70-85, mean 76.1; BP criteria: median SBP 160-220 & DBP 100-120 or SBP 180-220 & DBP ≥85; follow-up: 0, 4, 12 & 24 weeks	symptomatic hypotension, heart failure, MI or heart condition in last 6 months, diabetes, or haematological, renal or hepatic dysfunction	newly-diagnosed hypertensive, community-residents with mild cognitive impairment (MMSE 20-28)	NART, Logical Memory (immediate & delayed), PALT, RPM, ASRT, TMT A	No differences between treatment groups on cognitive tests at any time points (repeated measures ANOVA). Subjects with greatest DBP reduction at 24 weeks had improved ASRT & PALT scores compared to subjects with lowest DBP drop. No effects for SBP
[46]	double-blind, RCT of nitrendipine plus possible enalapril/HCTZ	n = 2418; age: 60+, mean 70 BP criteria: SBP 160-219 & DBP <95 follow-up: 24m	no dementia	Isolated systolic hypertension	MMSE, dementia diagnosis	50% reduction in incidence of dementia with active treatment. No change in MMSE in either group. Open-label follow-up supported dementia finding
[51]	double-blind, randomised trial of losartan vs. HCTZ; 2-week untreated run-in phase	n = 69; age: 30-73, divided into <60 & ≥60 for analysis; BP criteria: DBP 90-114 in run-in phase;	recent MI, stroke, renal or liver failure, congestive heart failure	uncomplicated essential hypertension, homogenous for BMI, min 5 years education	MMSE, Sandoz Clinical Assessment Geriatric (SCAG)	Both treatments significantly lowered BP; losartan more effective than HCTZ. The losartan group showed significant improvement in MMSE and SCAG scores; HCTZ changes were non-

Authors	Study design / antihypertensive medication	Sample / target BP levels	Exclusion criteria	Inclusion criteria	Neuropsychological / cognitive tests	Conclusions
		follow-up: 26m				significant
[49]	open-label, randomised trial of cilazipril vs. atenolol in hypertensives previously atenolol-treated. Atenolol withdrawn in treatment group at week 0; treatment started at week 2	n = 26; age: 65-84, mean 72.3; BP criteria: DBP >90 after atenolol withdrawal; follow-up: 2, 6, 10 & 18 weeks	CVA in last 2 years, recent MI, diabetes, drug or alcohol abuse history, psychotropic medication	atenolol-treated for min 1 year identified from GP records	CDR battery consisting of: SRT, digit vigilance, CRT, memory scanning, delayed word recognition, picture recognition	Trend for improvement on all subtests at 2 weeks for atenolol withdrawal vs. atenolol group; significant for CRT. Pattern of further improvement at 6, 10 and 18 weeks. Differences between groups due to improvement in treatment group and decline in atenolol group

ASRT = Anomalous Sentences Repetition Task; BMI = body mass index; CAT = Continuous Attention Test; CDR = Cognitive Drug Research computerised assessment battery; CNS = central nervous system; CRT = Choice Reaction Time; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DSS = digit-symbol substitution subtest of the Wechsler Adult Intelligence Scale; HCTZ = hydrochlorothiazide; MI = myocardial infarction; MMSE = Mini-Mental State Examination; NART = New Adult Reading Test; PALT = Paired Associate Learning Test; PWAT = Paired Word Association Test; RPM = Raven's Progressive Matrices; SBP = systolic blood pressure; SRT = simple reaction time; TMT A = Trail-Making Test form A

Appendix V: Trail-Making Test administration instructions

SCOPE substudy: Instructions for administering the Trail-Making Test

Every time the Trail-Making Test is administered, the participant should fill in the sample before completing the actual test. The participant will require a black ballpoint pen.

TRAIL-MAKING TEST FORM A: SAMPLE

Show the participant the sheet 'TRAIL-MAKING TEST FORM A: SAMPLE' and read aloud the following instructions:

Here are some numbers. Beginning at number 1, I'd like you to draw a line from 1 to 2, 2 to 3, 3 to 4, and so on until you reach the end. Draw the line as fast as you can.

If the participant completes the sample successfully, go on to the next CRF page and administer 'TRAIL-MAKING TEST FORM A'.

If the participant does not successfully complete the sample, explain where they went wrong by following the guidelines below: 'How to correct errors during completion of Form A sample sheet'.

TRAIL-MAKING TEST FORM A

Show the participant the sheet 'TRAIL-MAKING TEST FORM A' and read aloud the following instructions:

On this page are numbers from 1 to 25. Do the test the same way, beginning at number 1. and drawing a line from 1 to 2, 2 to 3, and so on, in order until you reach the end. Remember to work as fast as you can.

Start timing as soon as the participant begins.

Errors should be called to the participant's attention immediately in a minimally intrusive way by saying "*No*". If a mistake is made, the participant has to proceed from the last circle that was completed successfully. Do not stop timing if errors are made.

Stop timing as soon as the participant has completed the task. Record the time taken in the space provided at the bottom of the sheet.

HOW TO CORRECT ERRORS DURING COMPLETION OF FORM A SAMPLE SHEET

The following explanations of mistakes are acceptable:

1. *You started with the wrong circle. This is where you start.* (point to circle 1)
2. *You missed this circle* (point to the circle omitted). *You should go from 1 to 2, 2 to 3, and so on, until you reach the circle marked 'END'* (point to circles as you speak).
3. *Please keep the pen on the paper, and continue right on to the next circle*
4. If the participant cannot complete the sample, take their hand and guide the pen through the trail. Allow the participant to re-try the sample sheet.

SCOPE substudy: Instructions for administering the Trail-Making Test

Every time the Trail-Making Test is administered, the participant should fill in the sample before completing the actual test. The participant will require a black ballpoint pen.

TRAIL-MAKING TEST FORM B: SAMPLE

Show the participant the sheet 'TRAIL-MAKING TEST FORM B: SAMPLE' and read aloud the following instructions:

On this page are some numbers and letters. Beginning at number 1, draw a line from 1 to A, A to 2, 2 to B, B to 3, and so on until you reach the end. Remember, first you have a number, then a letter, then a number, and so on. Draw the lines as fast as you can.

If the participant completes the sample successfully, go on to the next CRF page and administer 'TRAIL-MAKING TEST FORM B'.

If the participant does not successfully complete the sample, explain where they went wrong by following the guidelines below: 'How to correct errors during completion of Form B sample sheet'.

TRAIL-MAKING TEST FORM B

Show the participant the sheet 'TRAIL-MAKING TEST FORM B' and read the following instructions:

On this page are both numbers and letters. Do this the same way as before, beginning at number 1, and drawing a line from 1 to A, A to 2, 2 to B, and so on, in order, until you have reached the end point. Remember, first you have a number and then a letter, then a number and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can.

Start timing as soon as the participant begins.

Errors should be called to the participant's attention immediately in a minimally intrusive way by saying "*No*". If a mistake is made, the participant has to proceed from the last circle that was completed successfully. Do not stop timing if errors are made.

Stop timing as soon as the participant has completed the task. Record the time taken in the space provided at the bottom of the sheet.

HOW TO CORRECT ERRORS DURING COMPLETION OF FORM B SAMPLE SHEET

The following explanations of mistakes are acceptable:

1. *You started with the wrong circle. This is where you start.* (point to circle 1)
2. *You missed this circle* (point to the circle omitted). *You should go from 1 to A, A to 2, 2 to B, B to 3, and so on, until you reach the circle marked 'END'* (point to circles as you speak).
3. *Please keep the pen on the paper, and continue right on to the next circle*
4. If the participant cannot complete the sample, take their hand and guide the pen through the trail. Allow the participant to re-try the sample sheet.

Appendix VI: Verbal Fluency test administration instructions

SCOPE substudy: Instructions for administering the Verbal Fluency Test

In this task the participant is given 60 seconds to say aloud as many words as possible that they can think of, beginning with a designated letter, or belonging to a designated category. The test administrator is required to write the words in the CRF as they are spoken.

1. Words beginning with the letter F

Read aloud the following instructions:

I will say a letter of the alphabet, and then I want you to say for me as many words that begin with that letter, as quickly as you can. For instance, if I say B you might give me the words bad, battle, and bed. I do not want you to use words which are names of people or places, such as Bob or Boston. Also, do not use the same word again with a different ending such as eat and eating. Any questions?

Check that the participant understands the instructions. When they are ready to begin read aloud the instruction:

Begin when I say the letter. The first letter is F.

Start the stopwatch. Write all the words in the CRF as the participant generates them. You will need to work quickly. Stop the task after 60 seconds. At the end of the task, check you have written legible answers. If an answer could be one of two words that have different meanings but sound the same when spoken (e.g. find and fined), ask the participant to clarify what the word means, or to spell it.

2. Words beginning with the letter A

Read aloud the following instructions:

I would like you to do the same again but with a different letter of the alphabet. Begin when I say the letter. This time the letter is A.

Start the stopwatch. Write all the words in the CRF as the participant generates them. Stop the task after 60 seconds. At the end of the task, check you have written legible answers.

3. Words beginning with the letter S

Read aloud the following instructions:

Again, I would like you to do the same but with a different letter. This time the letter is A.

Start the stopwatch. Write all the words in the CRF as the participant generates them. Stop the task after 60 seconds. At the end of the task, check you have written legible answers.

4. Animals

Read aloud the following instructions:

This next task is slightly different. I would like you to tell me the names of as many animals as you can. It does not matter what letter of the alphabet they begin with. So, when I say begin, please give me as many animals you can think of. Begin now.

Start the stopwatch. Write all the words in the CRF as the participant generates them. Stop the task after 60 seconds. At the end of the task, check you have written legible answers.

Appendix VII: CDR task instructions

Protocol Number: SCOPE substudy
Study code: NEWSCOPE/SCOPESUB
English Patient Task Instructions

Task Instructions for the CDR Cognitive Assessment System

Please do not let the patient consume drinks containing caffeine (tea, coffee, Coca-Cola) or smoke for one hour prior to commencing or whilst performing the CDR tests.

Please ensure that you are using the correct paperwork and disk for the patient you are about to test.

For all tasks, please ensure that the patient responds as quickly as possible.

Each task is initiated by the administrator pressing the 'Enter' key once he/she is sure the patient understands what to do. Prior to each task, (excepting the word and picture presentations), the administrator should always make sure that the patient's fingers are positioned on the response buttons so that the speed of the response can be precisely measured.

Practice Choice Reaction Time:

Administrator: Please read the following instructions to the patient:

> *Either the word 'YES' or the word 'NO' will appear on the screen. Every time you see the word 'YES' you should press the 'YES' button as quickly as you can. Every time you see the word 'NO' you should press the 'NO' button as quickly as you can.*

Administrator: Once you are sure the patient understands the task, press the 'Enter' key to initiate the task.

Word Presentation and Immediate Word Recall:

Administrator: Please read the following instructions to the patient.

> *Twelve words will appear in the middle of the screen, one at a time. Try to remember as many as you can. Immediately after the last word has been shown, some instructions will appear on the screen informing you that you have one minute to tell me as many of the words as you can remember. You may tell me the words that you remember in any order. Near the end of the test session, in about 20 minutes time, you will again be asked to tell me as many of the words as you can remember, but without seeing them again. So it is important to get the words fixed firmly in your mind.*

Administrator: Once you are sure the patient understands the task, press the 'Enter' key to initiate the task.

Immediate Word Recognition:

Administrator: Please read the following instructions to the patient:

> *You will again see a list of words one at a time on the screen. For each word, if you think it is one of those you have just seen, you should press the 'YES' button as quickly as you can, but if you do not remember seeing the word just now, you should press the 'NO' button as quickly as you can.*

Administrator: Once you are sure the patient understands the task, press the 'Enter' key to initiate the task.

Picture Presentation:

Administrator: Please read the following instructions to the patient:

> *A series of pictures will appear on the screen, one at a time. Please look at each picture carefully as it appears and try to remember as many as you can.*

Administrator: Once you are sure the patient understands the task, press the 'Enter' key to initiate the task.

Simple Reaction Time:

Administrator: Please read the following instructions to the patient:

> *Every time you see the word 'YES' on the screen, you should press the 'YES' button as quickly as you can.*

Administrator: Once you are sure the patient understands the task, press the 'Enter' key to initiate the task.

Number Vigilance:

Administrator: Please read the following instructions to the patient:

> *A number will appear on the right-hand side of the screen and remain there.*

Administrator: Please press the 'Enter' key to initiate this digit.

> *Then a series of numbers will appear, one at a time, in the middle of the screen. Every time the number in the middle is the same as the number on the right, press the 'YES' button as quickly as you can.*

Administrator: Once you are sure the patient understands the task, press the 'Enter' key to initiate the task.

Under no circumstances should this task be paused. Please restart if the task is interrupted.

Choice Reaction Time:

Administrator: Please read the following instructions to the patient.

> *Either the word 'YES' or the word 'NO' will appear on the screen. Every time you see the word 'YES' you should press the 'YES' button as quickly as you can. Every time you see the word 'NO' you should press the 'NO' button as quickly as you can.*

Administrator: Once you are sure the patient understands the task, press the 'Enter' key to initiate the task.

Spatial Working Memory:

Please read the following task instructions to the patient:

> *A picture of a house with 9 windows will appear on the screen. 4 of the windows will be lit and 5 will be dark. Please try to remember the positions of the lit windows.*

Press the 'Enter' key for the house to be shown on the screen. The house will remain on the screen for 15 seconds. The screen will then go blank. The researcher should now show the laminated diagram of the house to the patient with the following instructions:

> Point to the windows that were lit.

Once you are sure that the patient has remembered the positions of the lit windows, continue with the task instruction.

> *Now for each house which appears on the screen, you should press the 'YES' button if the window was lit in the original house and you should press the 'NO' button if the window was dark in the original house.*

Once you are sure the patient understands the task, press the 'Enter' key to initiate the task.

Numeric Working Memory:

Administrator: Please read the following instructions to the patient:

> *Please try to remember the 3 numbers that will now come on the screen one at a time. Say each number aloud to help you remember it.*

Administrator: Please press the 'Enter' key for the numbers to be shown on the screen. Following their presentation, please ask the patient to repeat the 3 numbers to ensure that he/she has remembered them.

Administrator: Please continue by reading the following instructions.

> *Now for each number which appears on the screen, you should press the 'YES' button as quickly as you can, if it is one of the numbers you are remembering, and you should press the 'NO' button as quickly as you can, if it is any other number.*

Administrator: Once you are sure the patient understands the task and remembers the 3 numbers, press the 'Enter' key to initiate the next stage of the task.

Delayed Word Recall:

Administrator: Read the following instructions to the patient.

> *Now we are going back to the list of words you saw at the beginning of this testing session. You have one minute to tell me as many of the words that you can still remember. You can tell me the same words that you remembered in the immediate word recall task, as well as any others you think were on the list.*

Administrator: Once you are sure that the patient understands the instructions, press the 'Enter' key to initiate the test

Delayed Word Recognition:

Administrator: Please read the following instructions to the patient.

> *You will again see a list of words one at a time on the screen. For each word, if you think it is one of those you tried to remember earlier, you should press the 'YES' button as quickly as you can, but if you do not remember seeing the word earlier, you should press the 'NO' button as quickly as you can.*

Administrator: Once you are sure the patient understands the task, press the 'Enter' key to initiate the task.

Picture Recognition:

Administrator: Please read the following instructions to the patient.

> *Now you are going to see some pictures one at a time on the screen. For each picture, if you think it is one of those you saw earlier and tried to remember, you should press the 'YES' button as quickly as you can, but if you do not think you saw it earlier, you should press the 'NO' button as quickly as you can.*

Administrator: Once you are sure the patient understands the task, press the 'Enter' key to initiate the task.

Appendix VIII: Data characteristics of the CDR variables

* indicates variables entered into the factor analyses. Format denotes the [maximum number of characters].[number of decimal places]

Task Data element	Abbreviation	Format	Example	Unit	Derivation	Range
Practice Choice Reaction Time						
Practice Choice Reaction Time Accuracy	CRT1ACC	6.2	XXX.XX	%	Percentage of stimuli responded to correctly	0 to 100
Practice Choice Reaction Time Mean	CRT1	8.2	XXXXX.XX	msec	Mean speed of individual correct responses	150 to 30000
Immediate Word Recall						
* Immediate Word Recall Words Correctly Recalled	IRECALL	2.0	XX	#	Number of words correctly recalled	0 to 12
Immediate Word Recognition						
Immediate Word Recognition Original Stimuli Accuracy	DRE1OACC	6.2	XXX.XX	%	Percentage of original stimuli correctly identified	0 to 100
Immediate Word Recognition New Stimuli Accuracy	DRE1NACC	6.2	XXX.XX	%	Percentage of novel stimuli correctly identified	0 to 100

Task Data element	Abbreviation	Format	Example	Unit	Derivation	Range
* Immediate Word Recognition Sensitivity Index	DRE1SI	6.3	-X.XXX	#	Sensitivity Index	-1 to 1
* Immediate Word Recognition Speed Mean	DRE1RT	8.2	XXXXX.XX	msec	Mean speed of individual correct responses to all stimuli	250 to 30000
Simple Reaction Time						
* Simple Reaction Time Mean	SRT	8.2	XXXXX.XX	msec	Mean speed of individual correct responses	100 to 30000
Number Vigilance (now known as Digit Vigilance)						
* Number Vigilance Targets Detected	VIGACC	6.2	XXX.XX	%	Percentage of targets responded to within time window	0 to 100
* Number Vigilance Speed	VIGRT	7.2	XXXX.XX	msec	Mean speed of individual responses to targets within time window	100 to 1500
* Number Vigilance False Alarms	VIGFA	3.0	XXX	#	Number of responses falling outside of specified time window	0 to 999
Choice Reaction Time						
* Choice Reaction Time Accuracy	CRT2ACC	6.2	XXX.XX	%	Percentage of stimuli responded to correctly	0 to 100

Task Data element	Abbreviation	Format	Example	Unit	Derivation	Range
* Choice Reaction Time Mean	CRT2	8.2	XXXXX.XX	msec	Mean speed of individual correct responses	150 to 30000
Spatial Working Memory						
Spatial Working Memory Original Stimuli Accuracy	SPMOACC	6.2	XXX.XX	%	Percentage of original stimuli correctly identified	0 to 100
Spatial Working Memory New Stimuli Accuracy	SPMNACC	6.2	XXX.XX	%	Percentage of novel stimuli correctly identified	0 to 100
* Spatial Working Memory Sensitivity Index	SPMSI	6.3	-X.XXX	#	Sensitivity Index	-1 to 1
* Spatial Working Memory Speed Mean	SPMRT	8.2	XXXXX.XX	msec	Mean speed of individual correct responses to all stimuli	150 to 30000
Numeric Working Memory (previously known as Memory Scanning)						
Numeric Working Memory Original Stimuli Accuracy	MSOACC	6.2	XXX.XX	%	Percentage of original stimuli correctly identified	0 to 100
Numeric Working Memory New Stimuli Accuracy	MSNACC	6.2	XXX.XX	%	Percentage of novel stimuli correctly identified	0 to 100
* Numeric Working Memory Sensitivity Index	MSSI	6.3	-X.XXX	#	Sensitivity Index	-1 to 1

Task Data element	Abbreviation	Format	Example	Unit	Derivation	Range
* Numeric Working Memory Speed Mean	MSRT	8.2	XXXXX.XX	msec	Mean speed of individual correct responses to all stimuli	150 to 30000
Delayed Word Recall						
* Delayed Word Recall Words Correctly Recalled	DRECALL	2.0	XX	#	Number of words correctly recalled	0 to 12
Delayed Word Recognition						
Delayed Word Recognition Original Stimuli Accuracy	DRE2OACC	6.2	XXX.XX	%	Percentage of original stimuli correctly identified	0 to 100
Delayed Word Recognition New Stimuli Accuracy	DRE2NACC	6.2	XXX.XX	%	Percentage of novel stimuli correctly identified	0 to 100
* Delayed Word Recognition Sensitivity Index	DRE2SI	6.3	-X.XXX	#	Sensitivity Index	-1 to 1
* Delayed Word Recognition Speed Mean	DRE2RT	8.2	XXXXX.XX	msec	Mean speed of individual correct responses to all stimuli.	250 to 30000
Picture Recognition						
Picture Recognition Original Stimuli Accuracy	DPICOACC	6.2	XXX.XX	%	Percentage of original stimuli correctly identified	0 to 100

Task Data element	Abbreviation	Format	Example	Unit	Derivation	Range
Picture Recognition New Stimuli Accuracy	DPICNACC	6.2	XXX.XX	%	Percentage of novel stimuli correctly identified	0 to 100
* Picture Recognition Sensitivity Index	DPICSI	6.3	-X.XXX	#	Sensitivity Index	-1 to 1
* Picture Recognition Speed Mean	DPICRT	8.2	XXXXX.XX	msec	Mean speed of individual correct responses to all stimuli	250 to 30000
Trail-Making Test						
* Trail-Making Test Form A	TMTA	3.0	XXX	secs	Time taken to complete	0 to 300
* Trail-Making Test Form B	TMTB	3.0	XXX	secs	Time taken to complete	0 to 300
Verbal Fluency						
* Letters F, A and S	VF_FAS	3.0	XXX	#	Number of correct words	0 to 200
* Animals	VF_Animals	3.0	XXX	#	Number of correct words	0 to 200

REFERENCES

1. Population by age: United Kingdom. 2007. (Accessed June, 2008, at http://www.statistics.gov.uk/cci/nugget.asp?ID=949.)

2. Editors of The American Heritage Dictionaries. The American Heritage Medical Dictionary: Houghton Mifflin Company; 2007.

3. Spreen O, Strauss E. A compendium of neuropsychological tests: Administration, norms, and commentary. 2nd ed. New York: Oxford University Press; 1997.

4. Starr JM, Inch S, Cross S, Deary IJ. Seven-year follow-up of blood pressure in the Healthy Old People in Edinburgh (HOPE) cohort. J Hum Hypertens 2000;14:773-8.

5. Stott DJ, Bowman A. Blood pressure and aging. J Hum Hypertens 2000;14:771-.

6. High blood pressure. 2004. (Accessed June, 2008, at http://www.netdoctor.co.uk/diseases/facts/hypertension.htm.)

7. Sever P, Beevers G, Bulpitt C, et al. Management guidelines in essential hypertension: Report of the second working party of the British Hypertension Society. BMJ 1993;306:983-7.

8. SHEP Co-operative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. JAMA 1991;265:3255-64.

9. Medical Research Council Working Party. MRC trial of treatment of hypertension in older adults: principal results. BMJ 1992;304:405-12.

10. Boller F, Vrtunski PB, Mack JL, Kim Y. Neuropsychological correlates of hypertension. Archives of Neurology 1977;34:701-5.

11. Farmer ME, White LR, Abbott RD, et al. Blood pressure and cognitive performance. Am J Epidemiol 1987;126(6):1103-14.

12. Farmer ME, Kittner SJ, Abbott RD, Wolz MM, Wolf PA, White LR. Longitudinally measured blood pressure, antihypertensive medication use and cognitive performance: The Framingham study. Journal of Clinical Epidemiology 1990;43:475-80.

13. Scherr PA, Hebert LE, Smith LA, Evans DA. Relation of blood pressure to cognitive function in the elderly. Am J Epidemiol 1991;134(11):1303-15.
14. van Boxtel MP, Gaillard C, Houx PJ, Buntinx F, de Leeuw PW, Jolles J. Can the blood pressure predict cognitive task performance in a healthy population sample? J Hypertens 1997;15(10):1069-76.
15. Starr JM, Whalley LJ, Inch S, Shering PA. Blood pressure and cognitive function in healthy old people. J Am Geriatr Soc 1993;41(7):753-6.
16. Cacciatore F, Abete P, Ferrara N, et al. The role of blood pressure in cognitive impairment in an elderly population. Osservatorio Geriatrico Campano Group. J Hypertens 1997;15(2):135-42.
17. Jorm AF, Henderson AS, Kay DWK. Educational level differences on the Mini-Mental State: the role of test bias. Psychological Medicine 1988;18:727-31.
18. Seux ML, Thijs L, Forette F, et al. Correlates of cognitive status of old patients with isolated systolic hypertension: the Syst-Eur Vascular Dementia Project. J Hypertens 1998;16(7):963-9.
19. Palombo V, Scurti R, Muscari A, et al. Blood pressure and intellectual function in elderly subjects. Age and Ageing 1997;26(2):91-8.
20. Battersby C, Hartley K, Fletcher AE, et al. Cognitive function in hypertension: a community based study. J Hum Hypertens 1993;7:117-23.
21. Ramsay LE, Williams B, Johnston GD, et al. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. J Hum Hypertens 1999;13(9):569-92.
22. Beevers G, Lip GYH, O'Brien E. ABC of hypertension: blood pressure measurement. BMJ 2001;322:981-5.
23. Skoog I, Lernfelt B, Landahl S, et al. 15-year longitudinal study of blood pressure and dementia. Lancet 1996;347:1141-5.
24. Elias MF, Wolf PA, D'Agostino RB, Cobb J, White LR. Untreated blood pressure level is inversely related to cognitive functioning: The Framingham Study. Am J Epidemiol 1993;138:353-64.
25. Elias PK, D'Agostino RB, Elias MF, Wolf PA. Blood pressure, hypertension, and age as risk factors for poor cognitive performance. Exp Aging Res 1995;21(4):393-417.

26. Elias MF, Elias PK, D'Agostino RB, Silbershatz H, Wolf PA. Role of age, education, and gender on cognitive performance in the Framingham Heart Study: Community-based norms. Experimental Aging Research 1997;23:201-35.
27. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. JAMA 1995;274(23):1846-51.
28. Kilander L, Nyman H, Boberg M, Hansson L, Lithell H. Hypertension is related to cognitive impairment: A 20-year follow-up of 999 men. Hypertension 1998;31(3):780-6.
29. Swan GE, Carmelli D, Larue A. Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults. Stroke 1998;29(11):2334-40.
30. Deary IJ, Starr JM, MacLennan WJ. Fluid intelligence, memory and blood pressure in cognitive aging. Personality & Individual Differences 1998;25(4):605-19.
31. Swan GE, DeCarli C, Miller BL, et al. Association of midlife blood pressure to late-life cognitive decline and brain morphology. Neurology 1998;51(4):986-93.
32. Zhu L, Viitanen M, Guo Z, Winblad B, Fratiglioni L. Blood pressure reduction, cardiovascular diseases, and cognitive decline in the mini-mental state examination in a community population of normal very old people: a three-year follow-up. J Clin Epidemiol 1998;51(5):385-91.
33. Prince M, Lewis G, Bird A, Blizard R, Mann A. A longitudinal study of factors predicting change in cognitive test scores over time, in an older hypertensive population. Psychol Med 1996;26(3):555-68.
34. Cervilla J, Prince M, Joels S, Lovestone S, Mann A. Long-term predictors of cognitive outcome in a cohort of older people with hypertension. British Journal of Psychiatry 2000;177:66-71.
35. Tzourio C, Dufouil C, Ducimetiere P, Alperovitch A. Cognitive decline in individuals with high blood pressure: A longitudinal study in the elderly. Neurology 1999;53(9):1948-52.
36. Starr JM, Deary IJ, Inch S, Cross S, MacLennan WJ. Blood pressure and cognitive decline in healthy old people. J Hum Hypertens 1997;11(12):777-81.
37. Glynn RJ, Beckett LA, Hebert LE, Morris MC, Scherr PA, Evans DA. Current and remote blood pressure and cognitive decline. JAMA 1999;281(5):438-45.

38. Knopman D, Boland LL, Mosley T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56:42-8.
39. Mohr E, Walker D, Randolph C, Sampson M, Mendis T. Utility of clinical trial batteries in the measurement of Alzheimer's and Huntington's dementia. Int Psychogeriatr 1996;8(3):397-411.
40. Keefover RW. Aging and cognition. Neurologic Clinics of North America 1998;16(3):635-48.
41. Applegate WB, Pressel S, Wittes J, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables. Results from the systolic hypertension in the elderly program. Arch Intern Med 1994;154:2154-60.
42. Di Bari M, Pahor M, Franse LV, et al. Dementia and disability outcomes in large hypertension trials: lessons learned from the Systolic Hypertension in the Elderly Program (SHEP) trial. Am J Epidemiol 2001;153(1):72-8.
43. Bird AS, Blizard RA, Mann AH. Treating hypertension in the older person: an evaluation of the association of blood pressure level and its reduction with cognitive performance. J Hypertens 1990;8(2):147-52.
44. Prince MJ, Bird AS, Blizard RA, Mann AH. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's treatment trial of hypertension in older adults. BMJ 1996;312:801-5.
45. Starr JM, Whalley LJ, Deary IJ. The effects of antihypertensive treatment on cognitive function: results from the HOPE study. J Am Geriatr Soc 1996;44(4):411-5.
46. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998;352(9137):1347-51.
47. Forette F, Seux ML, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) Study. Arch Intern Med 2002;162:2046-52.
48. Feigin V, Ratnasabapathy Y, Anderson C. Does blood pressure lowering treatment prevents dementia or cognitive decline in patients with cardiovascular and cerebrovascular disease? Journal of the Neurological Sciences 2005;229-230:151- 5.

49. Hearing SD, Wesnes KA, Bowman CE. Beta blockers and cognitive function in elderly hypertensive patients: withdrawal and consequences of ACE inhibitor substitution. International Journal of Geriatric Psychopharmacology 1999;2:13-7.
50. Kalra L, Jackson S, Swift C. Effect of antihypertensive treatment on psychomotor performance in the elderly. J Hum Hypertens 1993;7:285-90.
51. Tedesco MA, Ratti G, Mennella S, et al. Comparison of losartan and hydrochlorothiazide on cognitive function and quality of life in hypertensive patients. Am J Hypertens 1999;12(11):1130-4.
52. Hansson L, Zanchetti A, Carruthers SG, et al for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755-62.
53. Elmfeldt D, George M, Hubner R, Olofsson B. Candesartan cilexetil, a new generation angiotensin II antagonist, provides a dose dependent antihypertensive effect. J Hum Hypertens 1997;11(Suppl. 2):S49-53.
54. McInnes GT, O'Kane KP, Jonker J, Roth J. the efficacy and tolerability of candesartan cilexetil in an elderly hypertensive population. J Hum Hypertens 1997;11(Suppl. 2):S75-80.
55. Barnes JM, Barnes NM, Costall B, Horovitz ZP, Naylor RJ. Angiotensin II inhibits the release of [3H]acetylcholine from rat entorhinal cortex in vitro. Brain Research 1989;492:136-43.
56. Barnes NM, Champaneria S, Costall B, Kelly ME, Murphy DA, Naylor RJ. Cognitive enhancing actions of DUP 753 detected in a mouse habituation paradigm. Neuroreport 1990;1:239-42.
57. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-15.
58. Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester P-O. Mortality and morbidity in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). Lancet 1991;338:1281-5.
59. Hansson L, Lithell H, Skoog I, et al. Study on COgnition and Prognosis in the Elderly (SCOPE). Blood Press 1999;8(3):177-83.

60. Guidelines Sub-Committee. Guidelines for the management of mild hypertension: memorandum from a World Health Organization/ International Society of Hypertension meeting. J Hypertens 1993;11:905-18.
61. Morris J. The Clinical Dementia Rating (CDR): Current version and scoring rules. Neurology 1993;43:2412.
62. Jorm AF, Jacomb PA. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): Socio-demographic correlates, reliability, validity and some norms. Psychological Medicine 1989;19(4):1015-22.
63. Simpson P, Surmon D, Wesnes K, Wilcock G. The Cognitive Drug Research computerized assessment system for demented patients: a validation study. Int J Geriatr Psychiatry 1991;6:95-102.
64. Reitan R. Validity of the trailmaking test as an indicator of organic brain damage. Perceptual Motor Skills 1958;8:271-6.
65. Nelson HE, O'Connell A. Dementia: The estimation of premorbid intelligence levels using the New Adult Reading Test. Cortex 1978;14:234-44.
66. Broadbent DE, Cooper PF, Fitzgerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. British Journal of Clinical Psychology 1982;21:1-16.
67. Yesavage J, Brink T, Rose T, et al. Development and Validation of a Geriatric Depression Screening Scale: A Preliminary Report. Journal of Psychiatric Research 1982;17:37-49.
68. Cognitive Drug Research Ltd. Scientific Publications. May 2007 ed. Goring-on-Thames: CDR Ltd.; 2007.
69. Wesnes KA, McKeith IG, Ferrara R, et al. Effects of rivastigmine on cognitive function in dementia with Lewy bodies: A randomised placebo-controlled international study using the Cognitive Drug Research computerised assessment system. Dementia and Geriatric Cognitive Disorders 2002;13(3):183-92.
70. Day S, Fayers P, Harvey D. Double data entry: What value, what price? Controlled Clinical Trials 1998;19:15-24.
71. Perneger PV. What's wrong with Bonferroni adjustments. BMJ 1998;316:1236-8.
72. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. BMJ 1995;310:170.

73. Feise RJ. Do multiple outcome measures require p-value adjustment? BMC Medical Research Methodology 2002;2:8.
74. Elias MF, Elias PK. Hypertension affects neurobehavioral functioning: So what's new? Psychosomatic Medicine 1993;55:51-4.
75. Blumenthal JA, Madden DJ, Pierce TW, Siegel WC, Appelbaum M. Hypertension affects neurobehavioral functioning. Psychosomatic Medicine 1993;55:44-50.
76. Waldstein SR, Jennings JR, Ryan CM, et al. Hypertension and neuropsychological performance in men: Interactive effect of age. Health Psychol 1996;15(2):102-9.
77. Wesnes KA, Ward T, McGinty A, Petrini O. The memory enhancing effects of a Ginko biloba/ Panax ginseng combination in healthy middle-aged volunteers. Psychopharmacology 2000;152:353-61.
78. Cattel RB. The scientific use of factor analysis. New York: Plenum; 1978.
79. Thurstone LL. Multiple factor analysis: A development and expansion of vectors of the mind. Chicago: University of Chicago Press; 1947.
80. Child D. The essentials of factor analysis. 3rd ed. London: Continuum International Publishing Group; 2006.
81. Kline P. An easy guide to factor analysis. Cornwall: TJ Press (Padstow) Ltd; 1994.
82. Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ 1990;300:230-5.
83. Hansson L, Lithell H, Skoog I, et al. Study on COgnition and Prognosis in the Elderly (SCOPE): Baseline Characteristics. Blood Press 2000;9(2-3):146-51.
84. Harrington F, Saxby BK, McKeith IG, Wesnes K, Ford GA. Cognitive performance in hypertensive and normotensive older subjects. Hypertension 2000;36:1079-82.
85. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens 2003;21:875-86.
86. Skoog I, Lithell H, Hansson L, et al. Effect of baseline cognitive function and antihypertensive treatment on cognitive and cardiovascular outcomes: Study on COgnition and Prognosis in the Elderly (SCOPE). Am J Hypertens 2005;18:1052-9.

87. McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. Cochrane Database of Systematic Reviews 2006;Issue 2. Art. No.: CD004034. DOI: 10.1002/14651858.CD004034.pub2.
88. Papademetriou V, Farsang C, Elmfeldt D, et al. Stroke prevention with the angiotension II type-1 receptor blocker candesartan in elderly patients with isolated systolic hypertension: the Study on Cognition and Prognosis in the Elderly (SCOPE). Journal of the American College of Cardiology 2004;44:1175-80.
89. Lithell H, Hansson L, Skoog I, et al. The Study of COgnition and Prognosis in the Elderly (SCOPE): outcomes in patients not receiving add-on therapy after randomization. J Hypertens 2004;22:1605-12.
90. Firbank MJ, Wiseman RM, Burton EJ, Saxby BK, O' Brien JT, Ford GA. Brain atrophy and white matter hyperintensity change in older adults and relationship to blood pressure. Journal of Neurology 2007;254:713-21.
91. Jennings JR, Muldoon MF, Ryan CM, et al. Cerebral blood flow in hypertensive patients: An initial report of reduced and compensatory blood flow responses during performance of two cognitive tasks. Hypertension 1998;31:1216-22.
92. Nishimura Y, Ito T, Saavedra JM. Angiotensin II AT1 blockade normalizes cerebrovascular autoregulation and reduces cerebral ischemia in spontaneously hypertensive rats. Stroke 2000;31:2478-86.
93. Barnes JM, Barnes NM, Costall B, et al. ACE inhibition and cognition. In: MacGregor GA, Sever PS, eds. Current advances in ACE inhibition. London: Churchill Livingstone; 1989:159-71.
94. Fogari R, Mugellini A, Zoppi A, et al. Influence of losartan and atenolol on memory function in very elderly hypertensive patients. J Hum Hypertens 2003;17:781-5.
95. Fogari R, Mugellini A, Zoppi A, et al. Effects of valsartan compared with enalapril on blood pressure and cognitive function in elderly patients with essential hypertension. European Journal of Clinical Pharmacology 2004;59:863-8.
96. Elias MF, D'Agostino RB, Elias PK, Wolf PA. Neuropsychological test performance, cognitive functioning, blood pressure, and age: the Framingham Heart Study. Exp Aging Res 1995;21(4):369-91.