RESOURCE COSTS, HEALTH OUTCOMES AND COST-EFFECTIVENESS IN STROKE CARE: EVIDENCE FROM THE OXFORD VASCULAR STUDY

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Hilary Term 2009

Thesis submitted for the degree of D.Phil.

ACKNOWLEDGEMENTS

The work presented in this thesis has benefited from the guidance of many people. I am extremely grateful for the support, encouragement and advice given by my two supervisors Prof. Alastair Gray and Prof. Peter Rothwell. Without their expertise this thesis would not have been possible.

I would like to thank my colleagues at the Health Economics Research Centre. Special thanks go to my two office colleagues who have stoically put up with me and my endless questions for the past three and a half years: Jose Leal and James Buchanan. My gratitude to Oliver Rivero-Arias for demystifying the complex world of STATA and Judit Simon for proof reading is also acknowledged. I would also like to thank the staff at the Oxford Vascular Study, whose work has made this thesis a reality. I am grateful to Sarah Welch and Linda Bull, for making time to introduce me to staff at the collaborating general practices, and to Louise Silver for her thorough insight of the study.

The financial support of the National Institute for Health Research, who funded my work for the past three years, is gratefully acknowledged. Further financial support for attendance at scientific meetings was received from HERC, the Department of Public Health and Wolfson College.

I would like to thank my whole family for their continued support, especially my parents and sister for their love and understanding. Finally, my most heart-felt thanks go to Dave for all he has done for me, and putting up with me over the last few months.

PUBLICATIONS AND PRESENTATIONS

Luengo-Fernandez R, Gray AM, Rothwell PM. Effect of urgent treatment for transient ischaemic attack and minor stroke on disability and hospital costs (EXPRESS study): a prospective population-based sequential comparison. *Lancet Neurol* 2009;**8**:235-43.

Luengo-Fernandez R, Gray AM, Rothwell PM. Costs of stroke using patient-level data: A critical review of the literature. *Stroke* 2009;**40**:e18-e23.

Luengo-Fernandez R, Gray AM, Rothwell PM. Population-based study of determinants of initial secondary care costs of acute stroke in the United Kingdom. *Stroke* 2006;**37**:2579-87.

Conference Presentations

National Institute for Health Research (NIHR). *Impact of urgent treatment for TIA and minor stroke on hospitalisation costs and disability: the EXPRESS study*. Annual NIHR Trainees Conference, 10-11 September 2008, Manchester. Poster presentation. Best poster prize.

World Stroke Congress (WSC). *Impact of urgent treatment for TIA and minor stroke on hospitalisation costs and disability: the EXPRESS study*. 5th WSC, 24-27 September 2008, Vienna. Oral presentation.

International Health Economics Association (iHEA). *Impact of disease on health-related quality of life: the case of cerebrovascular diseases*. iHEA 6th World Congress, 8-11 July 2007, Copenhagen. Oral presentation

Health Economist's Study Group (HESG*). A population-based study of determinants of initial secondary care costs of acute stroke in the UK*. HESG, 26-28 July 2006, York. Oral presentation

European Society of Cardiology and Spanish Society of Cardiology. *Cardiovascular disease in the 21st century society: socioeconomic perspectives and critical issues*. European Conference on the Future of Cardiology, 2-3 June 2006, Madrid. Oral presentation

ABSTRACT

Resource costs, health outcomes and cost-effectiveness in stroke care:

Evidence from the Oxford Vascular Study

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Introduction

Cerebrovascular events are a major cause of mortality, disability and healthcare resource use. Despite this, there is a lack of reliable information on their costs and outcomes, particularly related to transient ischaemic attacks (TIA) and minor stroke. Such information is vital to inform decisions about local and national service provision, and to provide reliable estimates for use in cost-effectiveness analyses.

Aims

This thesis estimates the costs and outcomes of stroke and TIA using data from a population-based study undertaken in a population of over 91,000 individuals in Oxfordshire (the Oxford Vascular Study – OXVASC). In addition, the thesis aims to estimate the short-term cost-effectiveness of two secondary stroke prevention programmes evaluated in a study nested within OXVASC.

Methods

Using multiple methods of case ascertainment, 1,282 patients were identified as having suffered a stroke or TIA, of which 1,199 (723 stroke and 476 TIA) patients consented to the study. Follow-up of patients took place at 1, 6, 12 and 24 months,

with data collected on patients' disability, medication usage, living arrangements, and quality of life. Healthcare resource use information was derived from hospital and primary care records, and priced using published unit costs.

Findings

Stroke patients had higher case-fatality rates than TIA patients (15% vs. 1%; $p<0.001$), with 5-year life expectancy being one year longer for TIA patients. For stroke and TIA survivors, the risk of disability remained higher, at around 30% at each of the four follow-ups, than at baseline (17%; $p<0.001$ for all follow-ups). After standardising for age and gender, average quality of life for stroke and TIA patients combined was significantly lower than English population norms ($p<0.001$ for all follow-ups). However, when quality of life was compared to population norms by event type, quality of life differences between TIA patients and English population norms no longer remained statistically significant. Important predictors of quality of life included event severity, baseline disability and recurrent vascular events.

Total costs were considerably higher 1-year after the initial stroke or TIA than for the year preceding it and, except for day cases, increases were observed for all resource-use categories. Five years after the index event, stroke patients incurred costs of £16,923 (95% CI: 15,149 to 18,858) per patient, significantly higher than those incurred by TIA patients, at £13,904 (95% CI: 11,488 to 16,657; $p=0.019$). In multivariate analyses, event severity was found to be a significant predictor of inpatient care resource use and costs, as were the presence of recurrent vascular events, especially stroke and coronary events.

For non-hospitalised patients, results showed that urgent outpatient specialist assessment and treatment reduced the 90-day risk of fatal or disabling stroke (0.4% vs. 5%, $p<0.001$) compared with less urgent assessment and treatment. In terms of resource usage, patients who were assessed and treated urgently had lower recurrent stroke hospitalisation (2% vs. 8%; $p=0.001$), and reduced overall number of days in hospital (average reduction of 4 days; $p=0.017$). These reductions in hospital resource usage generated savings of £643 per patient assessed and treated urgently in an outpatient clinic ($p=0.028$).

Conclusion

Despite the impact of stroke on death, disability and healthcare resource use, there is a lack of reliable information on costs and outcomes, especially for TIA and minor stroke. Through the use of a population-based study, the gold-standard study design when assessing the incidence and outcomes of TIA and stroke, this thesis provides healthcare decision makers and researchers with a wealth of data on the resource use patterns, costs and outcomes of TIA and stroke patients, and their main predictors.

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LIST OF ABBREVIATIONS

A&E	Accident and Emergency
AF	Atrial Fibrillation
AIDS	Acquired Immunodeficiency Syndrome
ANOVA	Analysis of Variance
AQoL	Assessment of Quality of Life
ASR	Age-Sex Register
AUD	Australian Dollar
BNF	British National Formulary
CINAHL	Current Index to Nursing and Allied Health Literature
CI	Confidence Interval
CT	Computed Tomography
CHD	Coronary Heart Disease
CVD	Cerebrovascular Disease
DALY	Disability Adjusted Life Year
ECG	Electrocardiogram
EQ-5D	Euroqol-5D
EQ-VAS	Euroqol Visual Analogue Scale
EU	European Union
EXPRESS	Early use of eXisting PREventive Strategies for Stroke study
GP	General Practitioner
HALex	Health and Activity Limitation Index
HCHS	Hospital and Community Health Services
HGH	Horton General Hospital
HSE	Health Survey for England

HIV	Human Immunodeficiency Virus
HUI	Health Utilities Index
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICER	Incremental Cost-Effectiveness Ratio
ICH	Intracerebral Haemorrhage
IMD	Index of Multiple Deprivation
IPW	Inverse Probability Weight
IQR	Interquartile Range
IS	Ischaemic Stroke
JRH	John Radcliffe Hospital
KMSA	Kaplan-Meier Sample Average
LoS	Length of Stay
MAUS	Multi-Attribute Utility Scale
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
mRS	modified Rankin Scale
NE	North East
NEMESIS	North-East Melbourne Stroke Incidence Study
NHIS	National Health Interview Survey
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NIHSS	National Institute of Health Stroke Scale
no.	Number

NOC	Nuffield Orthopaedic
NW	North West
OCE	Oxford Centre for Enablement
OCSP	Oxford Community Stroke Project
OECD	Organisation for Economic Co-operation and Development
OLS	Ordinary Least Squares
ORH	Oxford Radcliffe Hospitals
OXMIS	Oxford Myocardial Infarction Study
OXVASC	Oxford Vascular Study
PPP	Purchasing Power Parity
PVD	Peripheral Vascular Disease
RCT	Randomised Controlled Trial
RI	Radcliffe Infirmary
SAH	Subarachnoid Haemorrhage
S.D.	Standard Deviation
S.E.	Standard Error
SE	South East
SF-6D	Short-Form 6D
SF-12	Short-Form 12
SF-36	Short-Form 36
SG	Standard Gamble
SLSR	South London Stroke Register
SW	South West
TIA	Transient Ischaemic Attack
TTO	Time Trade Off

QALY	Quality Adjusted Life Year
UK	United Kingdom
US	Unknown Stroke
USA	United States of America
VAS	Visual Analogue Scale
VIF	Variance Inflation Factor
WHO	World Health Organisation

Currencies listed in Appendix 9

AUD	Australian Dollar
CAD	Canadian Dollar
CZK	Czech Koruna
DEM	German Mark
DKK	Danish Krona
EUR	Euro
GBP	British Pound Sterling
ITL	Italian Lira
JPY	Japanese Yen
NZD	New Zealand Dollar
SEK	Swedish Krona
USD	United States Dollar

CHAPTER 1

INTRODUCTION

1.1 INTRDODUCTION TO THE THESIS

The overall aim of this thesis is to provide improved estimates of costs and outcomes of stroke and transient ischaemic attacks (TIA) using data from a population-based incidence study in order to better inform decision making in the area of cerebrovascular disease treatment and prevention. By using individual patient data from a large population-based study, the thesis aims to:

1) estimate the level and predictors of health outcomes after stroke and TIA;
2) estimate the size and predictors of health care resource use and costs after stroke and TIA; and to
3) explore the cost-effectiveness of two different assessment programmes after minor stroke or TIA in order to prevent recurrent strokes.

Before developing these aims in more detail, a summary on the clinical aspects of stroke and TIA, including their epidemiology, effects on mortality and disability, and prevention and treatment options is given below.

1.2 CEREBROVASCULAR DISEASES

Cerebrovascular diseases designate all disorders in which one or more blood vessels of the brain are primarily impaired by a pathological process and as a result there is an area of brain transiently or permanently affected by ischaemia or bleeding.[1] There are numerous factors that can increase the risk of suffering a cerebrovascular disease. These risk factors can be associated with lifestyle factors

(e.g. smoking, physical inactivity, alcohol intake and obesity), presence of other co-morbidities (e.g. atrial fibrillation, heart disease, diabetes and hypertension), history of disease (i.e. previous stroke or TIA), and non-modifiable patient characteristics such as age and gender.[2-7]

The classification of cerebrovascular diseases is complex due to the heterogeneity of the disease. A list of all the conditions covered under cerebrovascular diseases is reported in **Appendix 1**, together with their coding under the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10).[8] In this thesis only the health outcomes, resource use and costs of patients suffering an acute cerebrovascular event, grouped into either stroke (ICD-10: I600 to I64X) or TIA (ICD-10: G450 to G459, H340 to H342, and H348) are investigated.

1.2.1 STROKE

The most common and generally used definition of stroke is that recommended by the World Health Organisation, which defines stroke as rapidly developing clinical symptoms and/or signs of focal, and at times global (applied to patients in deep coma and to those with subarachnoid haemorrhage), loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[9;10]

Stroke occurs when the blood supply to part of the brain is suddenly interrupted either by a clot or when blood vessels have become too narrow –generally known as ischaemic strokes-, or when a blood vessel in the brain bursts spilling blood into the spaces surrounding brain cells – generally known as haemorrhagic strokes.[11-13]

Disruption of the blood supply to the brain then causes brain cells to die as they no longer receive oxygen and nutrients carried in the blood. During the stroke, patients suffer a range of symptoms, which include sudden numbness or weakness, usually on one side of the body; sudden confusion or trouble speaking or understanding speech; sudden trouble seeing; sudden trouble with walking, dizziness, or loss of balance or coordination; and/or sudden severe headache with no known cause.[14-16]

Ischaemic stroke

The most frequent types of stroke are ischaemic strokes (also known as cerebral infarctions), which account for approximately 80 to 85% of all strokes in western populations.[17-19] An ischaemic stroke occurs when the blood supply to part of the brain is suddenly interrupted either by a clot or when blood vessels have become too narrow.[3;20-22]

Haemorrhagic stroke

A haemorrhagic stroke occurs when a blood vessel in the brain leaks or ruptures, resulting in bleeding into the brain, which can damage the parts of the brain affected by the bleeding.[23] Haemorrhagic strokes are much less common than ischaemic strokes, accounting for 15 to 20% of all strokes in western countries.[17-19] Haemorrhagic strokes can be divided into two main types: intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH).[13;17;24]

ICH is the most common type of haemorrhagic stroke accounting for 60 to 80% of all haemorrhagic strokes.[18] The main causes of ICH are a traumatic brain injury or abnormalities of the blood vessels, or when it is not caused by one of these

conditions, it is most commonly associated with high blood pressure.[2;7;25] The remaining haemorrhagic strokes are caused by SAH, which are characterized by the extravasation of blood into the space covering the brain that is filled with cerebrospinal fluid.[26] The leading cause of SAH is the rupture of an intracranial aneurysm, which accounts for approximately 80% of SAH cases.[27]

Although the risk of haemorrhagic stroke increases with age,[2;7] haemorrhagic strokes are relatively less common in older age groups than ischaemic strokes, especially SAH, which is most frequent in younger aged women.[13;28;29]

1.2.2 TRANSIENT ISCHAEMIC ATTACK

A transient ischaemic attack (TIA) is defined as an acute loss of focal cerebral or ocular function with symptoms lasting less than 24 hours.[30]

During a TIA, the blood supply to a part of the brain is briefly interrupted, generally for only a few minutes.[1] Symptoms tend to occur suddenly and are similar to those of stroke, albeit do not last as long, and leave little or no permanent damage to the brain.[31]

1.3 INCIDENCE, MORTALITY AND DISABILITY

Information about the incidence and outcome of cerebrovascular events is necessary to understand the likely impact of the disease, its risk factors and to assess the impact of prevention and treatment strategies.[32] However, cerebrovascular events are a heterogenous disorder with varying risk factor profiles, prognosis, and

presentation for medical attention that make collection of reliable incidence and outcome data challenging.

As a result, in order to obtain incidence and mortality data, studies should ideally have complete population-based ascertainment, and be based on multiple overlapping sources of information including hospital records, outpatient secondary care clinic notes, primary care clinic notes and death certificates.[10;18;32;33]

1.3.1 INCIDENCE OF STROKE AND TRANSIENT ISCHAEMIC ATTACKS

A recent review of the literature identified 15 population-based stroke incidence studies undertaken after 1990 and up to August 2002.[18] Results of this review showed that the incidence of first stroke ranged between 1.3 per 1000 in the populations of South London, UK and Erlangen, Germany and 3.4 per 1000 in Arcadia, Greece. In all populations, incidence rates varied markedly between age groups. For example, for those less than 45 years the incidence ranged from 0.1 to 0.3 per 1000 compared with 12.0 to 20.0 for those aged 75 to 84 years. After adjusting for age and gender, evidence from the South London population has also shown marked differences in stroke incidence between different ethnicities, with black people significantly more likely to suffer a stroke than white people (incidence rate ratio of 2.21; $p<0.0001$).[34]

Similarly, there have been a number of population-based studies assessing the incidence of TIA in different countries.[35-41] Results of these studies showed that the incidence of first-ever TIA ranged from 0.16 per 1000 in Novosibirsk, Russia to 0.80

in Segovia, Spain. As with stroke, there were marked increases in TIA incidence rates with increasing age.

1.3.2 MORTALITY AND DISABILITY

In both 1990 and 2001, cerebrovascular diseases were found to be the second cause of death in the world after ischaemic heart disease, accounting for 5.39 million (9.6%) of worldwide deaths in 2001.[42;43] In terms of disability, cerebrovascular diseases were also one of the principal causes of worldwide disease burden, accounting for 71.62 million Disability Adjusted Life Years (DALYS), and representing the second leading cause of disease burden in high-income countries.[43]

A synthesis of case-fatality rates from 13 out of the 15 population-based studies conducted after 1990 found that total case-fatality, defined as death within one-month of stroke onset, was 22.9%.[18] This proportion varied little between the 11 countries where these studies were undertaken. In terms of stroke type, ICH and SAH had the highest case fatality rates (ranging from 30% to 52% and 25% to 54%, respectively), with ischaemic strokes having the lowest case fatality rates (ranging from 11% to 20%).[44-50]

For stroke survivors, there is a high probability of disability, especially during the first months after stroke onset. The proportion of stroke cases resulting in significant impairment shortly after the event is estimated at around 60%.[17;51;52] Significant impairments faced by stroke patients include: hemiparesis (weakness in one side of the body), mobility problems, visual perception deficits, dysarthria (speech that is characteristically slurred, slow, and difficult to understand), depression, aphasia

(partial or total loss of the ability to communicate verbally or using written words), dysphagia (swallowing problems), and alteration of recent memory.

As with case fatality, disability after stroke varies substantially by stroke subtype as shown by results from a population-based study in Melbourne, Australia, which found that three months after stroke onset 75% of ICH cases resulted in substantial disability compared with 56% of ischaemic stroke cases.[53] Although stroke survivors improve over time, a great proportion of patients remain disabled. Studies have shown that between 40 to 50% of patients remain disabled at one and two-years after event, and therefore require assistance in their daily activities.[13;53-56]

Contrary to stroke, TIA, if not followed by a recurrent cerebrovascular event, is not associated with high case fatality or disability after the event.[57] However, TIAs act as a warning event of stroke, with approximately 15% of ischaemic strokes being preceded by a TIA, with the risk of stroke being highest shortly after TIA.[57;58]

1.4 TREATMENT

Due to its high-case fatality and disabling nature, stroke is considered to be a medical emergency, with guidelines recommending prompt medical attention and treatment.[12] As for TIA, due to the high risk of stroke after onset, TIA patients should also seek medical attention urgently.[57]

As discussed above, cerebrovascular events can occur either due to a clot or narrowing of blood vessels (ischaemic strokes), or when a blood vessel in the brain bursts (haemorrhagic strokes). Treatment will vary according to the type of event,

with diagnostic tests such as computed tomography (CT) or magnetic resonance imaging (MRI) performed to differentiate between the different events.[59]

1.4.1 TRANSIENT ISCHAEMIC ATTACK AND ISCHAEMIC STROKE

Effective treatments now exist in order to reduce the risk of further strokes after TIA or ischaemic stroke. Such treatments include antiplatelet agents (such as aspirin and clopidogrel), blood pressure lowering drugs, statins, anticoagulation for atrial fibrillation, and endarterectomy for cases with over 50% symptomatic carotid stenosis.[60-64] It has been predicted that use of such preventive treatments in appropriate patients would reduce long-term risk of recurrent stroke by 80% to 90%,[65] with their use being most effective shortly after stroke.[66;67]

1.4.2 HAEMORRHAGIC STROKE

In haemorrhagic strokes blood thinning agents, such as aspirin and other antiplatelets, must not be given to patients as the main objective of treatment is to remove blood that has accumulated in the brain and to relieve the resulting increased intracranial pressure.[23]

In patients with ICH, the least treatable of strokes,[68] the treatment options include surgical treatment to remove the blood, or drug treatment in order to limit the growth of the haematoma.[68;69] For patients suffering SAH due to a ruptured aneurysm, surgery is needed to repair the aneurysm either by a neurosurgical intervention to clip the aneurysm and prevent further bleeding, or by endovascular coiling in which a detachable platinum coil device is placed within the aneurysm to prevent further bleeding.[70;71] Medical treatment is also available for SAH patients to both reduce

the risk of repeat bleeding, and to treat vasospasm, whereby the blood vessels in the brain spasm, leading to a narrowing of the vessels, which might cause tissue death and ischaemia.[72]

1.5 APPLIED STUDY: THE OXFORD VASCULAR STUDY (OXVASC)

The Oxford Vascular Study (OXVASC), which began in April 2002 and is still ongoing, is a population-based study of all acute vascular events (TIA, stroke, acute coronary syndromes and peripheral vascular events) and elective surgical and endovascular interventions for subacute or chronic vascular disease. The OXVASC study population consists of over 91,000 individuals, irrespective of age, registered with 63 general practitioners across nine primary care practices in Oxfordshire. This thesis is based around the development of a costing and quality of life study of TIA and stroke patients recruited and followed-up during the first five years of OXVASC.

1.6 OBJECTIVES OF THE THESIS

1.6.1 OBJECTIVE 1: ESTIMATION OF HEALTH OUTCOMES AFTER A CEREBROVASCULAR EVENT

As reported above, cerebrovascular events exert a significant negative impact on a patient's life by affecting his/her ability to perform and carry out activities of daily living. It is therefore important that, when measuring the impact of stroke and TIA, a comprehensive assessment is undertaken in order to document the full impact of the disease. One proposed way of assessing the impact of illness is to use quality of life instruments, which facilitate the estimation of quality of life associated with different health states, and can be combined with survival information to generate Quality Adjusted Life Years (QALYs). In England, the National Institute for Health and

Clinical Excellence (NICE), the institution charged by the National Health Service (NHS) to assess the effectiveness and cost-effectiveness of health interventions, recognises QALYs as the most appropriate measure of health benefit.[73]

The first objective of this thesis is, therefore, to evaluate, using data from OXVASC, the quality of life of patients after a stroke or TIA, and to gain a better knowledge of its baseline predictors. In addition, other important health outcomes, which *a priori*, would also appear to be important determinants of quality of life will be evaluated, including the risk of recurrent vascular events, living arrangements after the event and patient disability. In order to generate QALYs, survival and life-years gained over the follow-up period after the cerebrovascular event will be evaluated.

1.6.2 OBJECTIVE 2: ESTIMATION OF HEALTHCARE RESOURCE USE AND COSTS AFTER A CEREBROVASCULAR EVENT

Costing studies are used to inform policy decisions on disease treatment, prevention and research. Lack of reliable information in costing studies might therefore hamper the effective planning of service provision or treatment for patients. Furthermore, with economic evaluations starting to quantify the additional benefit of extra research, given the evidence available, the need for unbiased evidence on the costs of disease is paramount.[74]

Using data from a population-based study (OXVASC), the healthcare costs per stroke and TIA patient will be estimated. This will provide the first estimates of both resource use and costs of TIA and stroke in the UK based on a completely unselected sample. Furthermore, as cerebrovascular events are a very

heterogenous disorder, the costs of different types and subtypes will be evaluated and compared, including the estimation of the size and predictors of longer-term health care costs.

1.6.3 OBJECTIVE 3: EXAMINING THE COST-EFFECTIVENESS OF ASSESSMENT METHODS FOR SECONDARY STROKE PREVENTION

As described earlier, stroke is a major cause of death and disability. With effective preventive treatments already in use, prevention strategies may have a big impact on healthcare systems such as the UK National Health Service (NHS). Although effective treatments now exist to prevent the risk of recurrent stroke shortly after minor stroke or TIA, the cost-effectiveness of interventions aimed at rapid assessment and treatment of patients are less well understood.

As part of OXVASC, the Early use of eXisting PREventive Strategies for Stroke (EXPRESS) study compared the impact on process of care and outcome of two changes to management of patients with TIA or minor stroke referred to a neurovascular clinic aimed at assessing and treating these patients urgently. Using the outcome and cost data collected under Objectives 1 and 2, the third objective of the thesis is to undertake a cost-effectiveness analysis of the EXPRESS study. The results derived will provide one of the first assessments of cost-effectiveness of interventions aimed at assessing and treating TIA and minor stroke patients urgently.

1.7 STRUCTURE FOR THE THESIS

The structure of the thesis is as follows:

Chapter 2 presents a review of the literature on the quality of life after a cerebrovascular event. The literature review includes a meta-analysis of published quality of life estimates after stroke or TIA. The chapter explores the samples used to derive quality of life estimates, and whether estimates are derived using two-step valuation (i.e. multi-attribute utility scales) or one-step valuation methods, and the impact of these different methods on the results.

Chapter 3 presents a critical review of the literature on the costs of cerebrovascular events based on recent observational studies. The literature review critically appraises the study designs and methods used in previous published studies by providing a number of criteria that every costing study evaluating the costs of cerebrovascular events should ideally fulfil.

Chapter 4 introduces the OXVASC study and describes its background, aims, design and main results. The chapter focuses on the study sample that will be used for the economic analyses by providing baseline characteristics on the study patients, including demographic characteristics (age and gender), event information (type and subtype of event, and severity), presence of previous co-morbidities and risk factors (such as smoking, previous vascular events, disability, diabetes and hypertension), and socio-economic characteristics (including living arrangements, marital status, education level, socio-economic class, and deprivation levels).

Chapter 5 outlines the measures used to quantify the outcomes of OXVASC patients after stroke or TIA. The chapter first presents the outcomes that are unidimensional in nature, such as disability and life expectancy after the event.

Outcomes expressed in terms of quality of life are then presented and combined together with survival data to form QALYs. Results of statistical analyses to evaluate the predictors of quality of life after the event and adjustment for missing data are also presented. The strengths and limitations of the analyses undertaken in this chapter are presented in the discussion section.

Chapter 6 outlines the development and results of the costing study based on OXVASC patients. The main elements of the costing study such as resource categories included, unit costs employed to value resource use, and statistical analyses used to evaluate the predictors of long-term healthcare costs and approaches of adjustment for censoring are outlined. In the discussion section the strengths and limitations of the analyses are also discussed.

Chapter 7 combines the cost and outcome data together under the economic analysis of the EXPRESS study, a study nested within OXVASC. The chapter first introduces the EXPRESS study and describes the study aims, design and main clinical effectiveness results. The main elements of the economic analysis alongside this cohort study and evaluation of costs and outcomes are outlined, with the strengths and limitations of the analysis being discussed.

Finally, **Chapter 8** summarises the conclusions of the thesis and its contributions to the better understanding of the nature and predictors of the costs and outcomes of cerebrovascular events. The chapter concludes with a discussion of future research suggested by this thesis.

CHAPTER 2

CEREBROVASCULAR EVENTS: A REVIEW OF QUALITY OF LIFE STUDIES

2.1 INTRODUCTION

As reported in **Chapter 1**, cerebrovascular events are a major source of morbidity, representing the second leading cause of burden in high-income countries and one of the leading causes of neurological impairment.[43;75] In particular, more than 50% of stroke survivors remain significantly disabled shortly after their event, with impairments frequently lasting over the long-run,[53;54] and with the severity of effects depending on clinical parameters such as event type and rapid treatment access.[56;66]

As a result, cerebrovascular events exert a significant negative effect on a patient's life by affecting speech, swallowing, ambulation, mood, and therefore the ability to perform and carry out activities of daily living.[17] It is therefore important that, when measuring the impact of stroke and transient ischaemic attack (TIA), a comprehensive assessment is undertaken in order to document the full impact of the event. One proposed way of assessing the impact of illness is to asses patients' health related quality of life, which has been defined as "how health impacts on an individual's ability to function and his or her perceived well-being in physical, mental and social domains of life".[76;77] There are numerous quality of life instruments, some of which facilitate the estimation of utility associated with particular health states, and so can be used to examine quality adjusted survival and the loss of quality adjusted life years (QALYs) as a result of the illness.[78;79]

In recent years, with the use of QALYs being advocated as the main measure of outcome to be used when performing economic evaluations of healthcare interventions,[73;80-82] there has been much research interest in measuring quality of life associated with disease and illness. This chapter will review studies reporting quality of life estimates for cerebrovascular events. The review will document the populations used to derive quality of life estimates, the methods used to derive these estimates, and whether differences in methods have an impact on the results.

2.2 QUALITY OF LIFE

Definitions of health outcome are varied, and include measures which are clinical in nature and unidimensional, e.g. life-years, number of recurrent events, or number of days with disability. Although these are relatively simple to measure, other important outcomes may be ignored when using such measures. For example, when additional life expectancy is gained due to treatment, the quality of such years may also be important to patients.[83] Furthermore, they do not facilitate comparisons across different disease areas.[73;80;81] This is of particular importance in the area of healthcare decision making when assessing which interventions generate best value for money and, therefore, should be prioritised. If different health outcomes are used to represent the effect of different interventions (e.g. additional number of breast cancers prevented for a new breast cancer screening programme, and additional strokes prevented for a secondary stroke prevention programme), then assessing which of these interventions to prioritise may be problematic. As a result, outcome measures, such as the QALY and the Disability Adjusted Life Year (DALY) were developed to take into account that an individual may be concerned with other aspects of life apart of its quantity.

DALYs were developed by the World Bank and World Health Organisation (WHO) in order to estimate the burden of disease and the benefits of healthcare across the world.[42;84] In a single measure, DALYs combine both the time lived with disability (i.e. years lost to disability) and the years lost due to premature mortality, with one DALY representing the loss of one year of full health. Years lost to disability are estimated by the average duration of the condition and a weight factor reflecting its severity, with weights ranging from 0 to 1, where 0 represents perfect health and 1 representing death. The years of lost life due to premature mortality correspond to the remaining life expectancy at the age in which the individual dies, with life expectancy set to that in Japan, the country with the highest life expectancy. DALYs also incorporate productivity weights, with more weight being given to years lived during years of potential working life than at younger and older ages.

DALYs have been frequently used by the WHO and World Bank in order to quantify the aggregate burden of disease, especially in developing countries, as an aid to prioritise healthcare expenditure.[85;86] Their use, however, in measuring patient-level outcomes, and as a result their use in cost-effectiveness analysis, has been less frequent, with QALYs being the preferred measure of outcome, especially in developed countries.[87]

In a similar way to DALYs, QALYs are a combination of both life expectancy and quality of life, with quality of life typically being measured on a scale from 0 to 1, where 0 represents death and 1 equates to full health (some health states might be deemed to be worse than death, in which case a negative value is used). Quality of

life valuations for different health states can be derived from a number of different populations, including: health care professionals, patients, those with experience of the disease e.g. caregivers, and from representative samples of the general public. However, there is no consensus on which population should provide quality of life estimates, with particular debate on whether the valuations of patients or the general public should be used.[80;88;89]

2.2.1 POPULATIONS USED TO VALUE HEALTH STATES

The main argument used to elicit valuations from patients is that they are the only ones who actually know what it is really like to be in those states and, therefore, are the only ones capable of expressing valid quality of life estimates.[89] In addition, when eliciting valuations from those experiencing a health state, there is no need to create descriptions of that state, which may be inaccurate and may generate misconceptions and/or biases in the general public.[89] Patients are likely to base their valuations solely on the effects of that condition on their well-being, whereas the general public may also be including their fears about a particular condition.

The main arguments against the use of patients to elicit valuations, are that patients, especially for lifetime conditions, accommodate and adapt to their particular health state,[90] and that the general public, as the taxpayer or insurance-payer, bears the monetary costs of health care decisions, and as such should also have a say in the valuation of outcomes.[91] Furthermore, there are also practical considerations that make valuations of particular health states by patients problematic. Patients suffering from conditions affecting the mind, for example, are likely to find valuing their own health state too cognitively difficult or might not understand what is required of them.

In other circumstances, for instance, when the patient is unconscious or is expected to die shortly, valuations from patients may prove impossible or unethical.

Although the debate is ongoing, it is increasingly becoming current practice to use valuations from the general public. For example, both in the USA and the UK, the most recent guidelines on the methods to be used when undertaking economic evaluations recommend that public valuations be used.[73;80;82] As a result, quality of life valuations by the general public are now commonly used in two-step valuation methods, in which patients identify the health state for their particular condition, and the public value its associated quality of life.[92;93] In one-step valuation methods, by contrast, either patients or members of the public are asked to value the quality of life of a particular condition. For patients, this will entail valuing their current health state, whereas for members of the public it will entail valuing a health state described to them.

2.2.2 ONE-STEP VALUATION METHODS

There are three different approaches to the elicitation of quality of life using one-step valuation methods:

1) Revealed preferences:

Quality of life can be assessed by examining the relationship between the health risks associated with individual patient choices and the benefits required in order to accept the risk. For example, patients experiencing health states with poor quality of life might *a-priori* be expected to be willing to accept greater health risks (e.g. by undergoing intensive surgery) in order to alleviate their condition. The strength of this

approach is that it is based on actual choices involving risk versus benefits, rather than hypothetical scenarios and preference statements.[81] However, the literature evaluating the role of revealed preferences in quality of life valuation is scarce as the observed trade-offs between health risk and benefit might be difficult to translate into the 0 to 1 scale needed to generate QALYs. Furthermore, evidence from studies evaluating the monetary value of health benefits by examining the trade-off between hazardous jobs and wages have found that values vary considerably and are very context specific.[81]

2) Psychophysical methods:

Individuals are asked to rate different health states either by placing them in a scale from worst to best (e.g. rating scale) or by asking them to compare different health states and then express how much more they prefer one to the other (e.g. magnitude estimation).

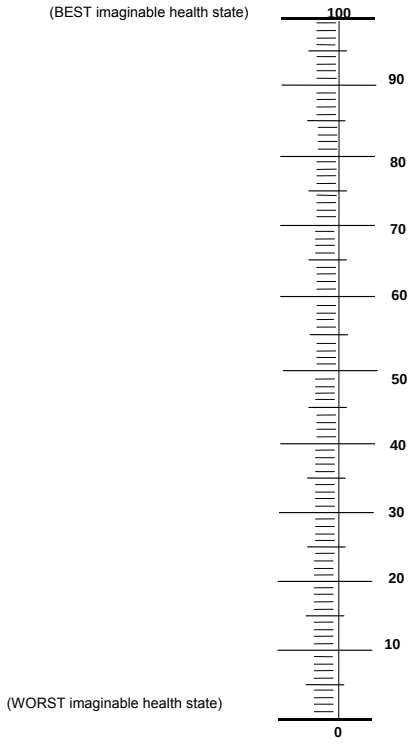

Figure 2.1 Visual Analogue Scale (VAS)

With the rating scale the individual is asked to locate particular health states on a straight line with dead/worst imaginable health state (typically valued as 0) at one end and full health/best imaginable health state (valued typically as100) at the other end of the line.[94;95] An example of a rating scale is the Euroqol Visual Analogue Scale (EQ-VAS), reported in **Figure 2.1**, which consists of a thermometer-like vertical line with endpoints labeled 0 “worst imaginable health state” and 100 “best imaginable health state”, demarcated in units of one and labeled in units of 10.[93]

In rating scales, individuals are either presented with a set of health states or are asked to report their own state and asked to rate them by placing them somewhere on the scale. This gives an indication of how health states are ranked, and of the intensity of an individual’s preferences.[81;95]

Although rating scales are fast to administer,[94] they have considerable disadvantages. Firstly, they are subject to end-of-scale bias, where individuals tend to avoid valuing health states at either end of the scale. Also, when valuing multiple health states, individuals tend to place health states evenly within the scale, regardless of health state desirability.[96;97] Secondly, it is questionable if it is a true interval scale, as it is unclear if changes in the lower end of the scale (e.g. from 10 to 20) are valued the same as changes in the upper end of the scale (e.g. from 80 to 90), making the results obtained from rating scales difficult to interpret.[81;94] Finally, rating scales are often seen as lacking any foundation in economic theory, in that there is no opportunity cost when valuing health states, i.e. there is no trade-off or choice involved when making judgments about health states.[94;98]

3) Choice-based methods:

Choice-based methods are based on the principle of trading-off one option against another, such as certainty against uncertainty in the standard gamble,[99] and life expectancy against quality of life in the time-trade-off approach.[100] From a health economics perspective, methods based on choice are preferred to choiceless methods such as the rating scale, which involve no trade-off and therefore may less accurately reveal true preferences.[94;96;101]

Standard gamble

The standard gamble (SG) is grounded in economic theory by being based directly on the axioms of utility theory presented by von Neumann and Morgenstern (1947),[99] which rest on the nature of individual preferences over uncertain prospects.

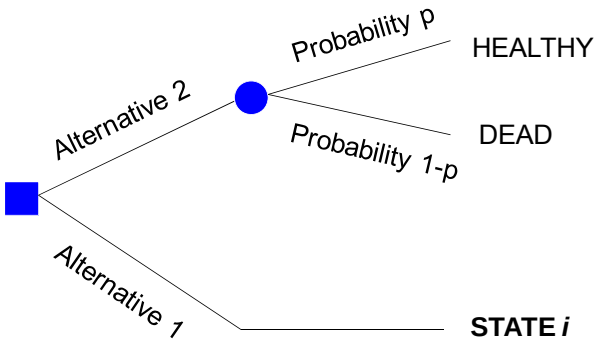

Figure 2.2 Standard gamble

In the SG, an individual is presented with two alternatives (**Figure 2.2**): Alternative 1, whereby the individual faces a certain outcome, i.e. remaining in health state *i* (i.e. the health state to be valued) for life; and Alternative 2, whereby the individual faces two possible outcomes, s/he is returned to perfect health immediately, with a

probability p, or s/he dies immediately, probability 1 – p. The probability p is then varied until the individual is indifferent between Alternative 1 or 2. This value of p is then the quality of life, or utility, associated with health state *i*: that is, the bigger the risk the individual is prepared to take to be returned to perfect health, the worse the health state *i* must be.

However, the SG is not easy to understand by members of the public. First, many individuals have great difficulty in understanding probabilities.[102] Additionally, although patients might be faced with life or death situations as part of treatment (e.g. invasive surgery with high mortality rates), participants from the general public may have difficulty understanding the concept of the SG, and will consider the hypothetical choice between the two alternatives as highly unrealistic since the choice between vast improvements in health and immediate death are not normally confronted.[94]

Time-trade-off (TTO)

In order to overcome the need to use probabilities to value health states in the SG approach, the time-trade-off (TTO) technique was developed.[100;102] In a TTO exercise (**Figure 2.3**), an individual is presented with two alternatives: Alternative 1, whereby the individual remains in state *i* for time *t* (i.e. individual's life expectancy in the state to be valued) followed by death; and Alternative 2, whereby the individual remains *x* time in a state of perfect health, where $x < t$, followed by death. Time *x* is then varied until the individual is indifferent between the two alternatives, at which point the quality of life for state *i* is given by x/t: that is, the shorter the time *x* the

patient is willing to live in a state of perfect health, the worse the health state *i* must be.

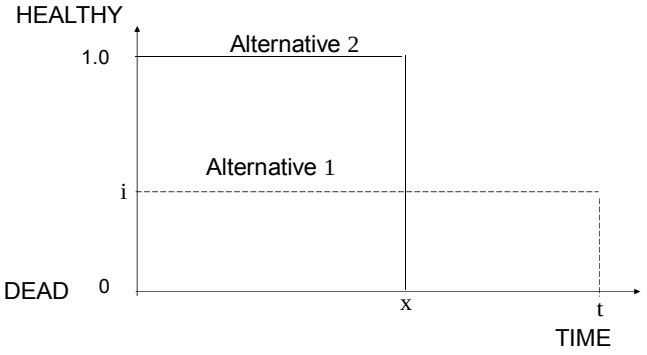

Figure 2.3 Time-trade-off

Like the SG, in the TTO individuals have to make a trade-off between different attributes, in this case between quantity and quality of life. However, although easier to understand than the SG, the hypothetical nature of the exercise still remains.[94] Furthermore, time preference might bias the results from the TTO, with some patients willing to sacrifice life expectancy in some distant future to reap the benefits of perfect health in the present.[103]

2.2.3 TWO-STEP METHODS: MULTI-ATTRIBUTE UTILITY SCALES

Estimating the quality of life associated with different conditions using the one-step methods described above can prove time consuming and complex. When using choice-based methods, individuals might have difficulty in understanding the hypothetical nature of the exercise. Furthermore, when using samples from the general public, simplistic scenarios that might not cover all the aspects of a condition have to be used in order for individuals to gain an insight of the disease and its

consequences. In order to bypass these problems numerous multi-attribute health status (MAUS) classifications with their corresponding valuations now exist.

One of the first MAUS classifications was the Rosser Index, which was designed initially to estimate the magnitude of change achieved in clinical trials.[104] It consisted of two dimensions, disability and distress, with eight levels of disability (none to unconscious) and four of distress (none to severe) giving a total of 32 possible health states, three of which were considered not to be applicable whilst unconscious. Quality of life weights for each health state were valued by a group of 70 individuals (consisting of nurses, patients, healthy individuals and doctors) using magnitude estimation.

Although the index is quick to complete, it has some important disadvantages. Firstly, the weighting exercise was undertaken on a small sample, and therefore is unlikely to reflect the views of the population as a whole.[105] Secondly, it was essentially developed for completion by hospital clinicians, therefore, clinicians' perceptions of a patient's health state could be different from those of the patient.[106] Thirdly, the Rosser Index only covered two possible health dimensions, disability and distress, ignoring other important health factors.[80] To mitigate some of these disadvantages, a revised version of the Rosser Index was released in the early 1990s.[107] Furthermore, since the development of the Rosser Index numerous MAUS classifications have been developed, which include the Health Utilities Index (HUI), the Short Form-36 (SF-36), the Assessment of Quality of Life (AQoL), the Health and Activity Limitation Index (HALex), and the Euroqol-5D (EQ-5D).

Health Utilities Index

There are currently two versions of the Health Utilities Index (HUI), the HUI2 and the HUI3.[92] The HUI2 consists of six domains (sensation, mobility, emotion, cognition, self-care and pain), including a seventh (fertility) when applicable, with each domain consisting of between 3 and 5 levels, giving rise to over 24,000 possible health states. Quality of life weights were derived from 293 Canadian parents, who valued 13 health states using the VAS and 4 using the SG.[108] For the remaining health states, quality of life was extrapolated using a multiplicative multi-attribute utility function, with values ranging from 0 (dead) to 1 (perfect health). Those states considered to be worse than dead, although identified, were still scored as 0.

The HUI3 was constructed based closely on the HUI2, the main changes being that the fertility domain was dropped and the sensation domain expanded into three attributes: vision, hearing and speech.[92] Furthermore, for certain domains, more levels were added, with each domain consisting of between 5 and 6 levels, giving rise to over 972,000 possible health states. Quality of life weights were derived from 504 members of the Canadian general public, who valued 24 health states using the VAS and 5 using the SG. Health states continued to be valued between 0 and 1, with both a multiplicative and multi-linear model being developed to estimate quality of life weights for all the health states.[109] The multiplicative model is the one recommended for use, with the multi-linear model being used to allow for various types of preference interactions among attributes.[81]

Both the HUI2 and HUI3 have been used extensively to measure quality of life, especially in North America.[92] Currently, it is recommended that the HUI3 be used

instead of the HUI2 as it has a more detailed descriptive system and population norms are available.[81] The HUI2 however, might provide better insights into the value of certain health states not covered in the HUI3, such as fertility. In addition, as health states in the HUI2 were valued using parent preferences, the HUI2 is the only preference based instrument specifically developed to be used in children.[110;111] Both the HUI2 and HUI3 are available in over 10 languages, although quality of life weights for the HUI2 have only been derived from populations in Canada and the UK, and only Canada for the HUI3.[92;111] In addition, a fee must be paid in order to obtain a license to access the full questionnaire and valuation functions.

Euroqol-5D

The Euroqol-5D (EQ-5D) consists of five attributes: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with each attribute then composed of three levels: 1) no problems; 2) some or moderate problems; and 3) unable to do, or extreme problems, giving rise to a total of 243 possible health states.[93;112]

A sample of health states has been valued using the TTO by a random sample of 3,337 members of the UK general public.[113;114] From this sample, a regression equation was derived to predict a quality of life estimate or "tariff" for all 243 health states, ranging from -0.59 to 1. Tariffs have also been derived using TTO in other countries, including: Denmark, Germany, Japan and Spain, with valuations for the Netherlands and US becoming available shortly.[93] In addition, a rating scale, i.e. the VAS depicted in **Figure 2.1**, is provided alongside the EQ-5D.

One of the main advantages of the EQ-5D is that it is cognitively simple, taking only a few minutes to complete, and self contained, which makes it ideal for use in postal surveys, in clinics and face-to-face and telephone interviews.[93] However, the EQ-5D has been criticised for being too narrow and insensitive to the outcomes of specific conditions.[98;115] Despite these disadvantages, the EQ-5D is considered to be the most appropriate choice in the UK to measure quality of life,[73] and is now available in over 20 language versions.[93]

Short Form-36 & Short Form-6D

The SF-36 consists of 8 domains: limitations in physical activities because of health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities because of physical health problems; bodily pain; general mental health (psychological distress and well-being); limitations in usual role activities because of emotional problems; vitality (energy and fatigue); and general health perceptions. Each of these 8 domains then consists of different items, ranging from 2 in the social functioning domain to 10 in the physical functioning one, with each item containing a different number of levels.[116]

The SF-36 permits scoring of each of the 8 domains, with each domain being scored from 0 to 100. The eight domain scores can be further summarized into two summary measures, the physical component summary and the mental component summary,[117] but it does not, produce a single quality of life estimate. For that reason a method was developed to derive a single quality of life estimate from the SF-36, known as the Short-Form 6D.[118] The SF-6D consists of 11 items from the SF-36, divided into 6 attributes (physical functioning, role limitations, social functioning, pain,

mental health and vitality) with 4 to 6 levels each, generating a total of 18,000 different health states. A total of 249 health states were then valued using the SG by a random sample of over 800 members of the UK general public. Using statistical techniques, a model was derived to estimate quality of life estimates for all the remaining health states, ranging from 0 (dead) to 1 (healthy). However, the worst state in the SF-6D has a quality of life estimate of 0.257. In addition, studies have been published which use a variety of methods to translate or map summary scores from the SF-36, or the SF-12 (a short form survey with 12 questions, all of which were selected from the SF-36), into the EQ-5D or the HUI in order to obtain quality of life estimates.[119-121]

With the SF-36 being the most widely used generic health outcome measure globally,[122] the SF-6D offers the possibility of evaluating quality in a way which enables QALY construction. Due to the large number of health states, the SF-6D has been shown to be more responsive to health changes than the EQ-5D.[123] However, the SF-6D takes longer to complete, and as a result increases the likelihood of non-completion. As with other instruments, the SF-6D has also been translated into other languages but valuations are only available for the UK. Although a license is required, this is available free of charge for all non-commercial applications including work funded by research councils, Government agencies and charities.

Assessment of Quality of Life (AQoL)

The AQoL consists of 15 questions equally divided into 5 dimensions: independent living, social relationships, physical senses, psychological well-being, and illness,

with each question having three possible levels.[124] In order to generate an overall quality of life score only the first four dimensions are used, giving rise to over 1 billion possible health states. A sample of health states was then valued using the TTO by a random sample of 169 patients in a large teaching hospital in Melbourne, Australia and 138 Melbourne residents selected at random from the telephone directory.[125] A multiplicative model was then derived to predict a quality of life estimate for all possible health states, ranging from -0.04 (worst possible health state, worse than death) to 1 (full quality of life).

The AQoL was created in order to overcome the perceived limitations of the EQ-5D, namely, its simplified and limited descriptive system responses and the omission of sensory perceptions.[126] However, the AQoL is one of the most complex MAUS instruments available, with health states valued using relatively small sample, which only valued a very small proportion of the billion of potential health states. Up until November 2007, over 50 studies using the AQoL to measure quality of life have been published,[127] with a great proportion of these studies being conducted in Australia, the only country for which country-specific valuations are available. Although registration is required for its use, the manual, instrument and valuation functions are all freely available.

The Health and Activity Limitation Index (HALex)

The Health and Activity Limitation Index (HALex) was derived from items in the US National Health Interview Survey (NHIS).[128] It consists of two attributes: perceived health and activity limitation, with 5 and 6 levels respectively, giving rise to 30 possible health states, ranging from “not limited in activity and in excellent perceived

health" to "needing help to perform self-care activities of daily living and being in poor perceived health". A further health state was then added to represent death.

At the time the HALex was developed, collection of preferences for each health state was not performed. Instead, using a variety of different steps, a model was used to assign scores for each of the 31 health states.[129] The first step was to assign a score for each of the six levels of activity limitation and the five levels of self-perceived health, using correspondence analysis. Secondly, a number of assumptions were made to value quality of life for certain health states. The healthiest state was assigned a score of 1.0 and the dead state a score of 0.0. In addition, it was assumed that the worst alive health state would have a quality of life of 0.10, and that a health state with "limited activities of daily living and excellent self-perceived health" was equally as bad as the health state with "no activity limitation and poor self-perceived health", which were both valued at 0.47. Finally, for the remaining 26 health states, quality of life was calculated using a multiplicative model.

The NHIS is a continuing, nationwide in-person survey of approximately 100,000 persons in the civilian non-institutionalized population.[130] The HALex, therefore, offers a method to assess the quality of life of many different conditions, diseases and health states experienced by NHIS respondents. However, the HALex is not based on any of the axioms of utility theory presented earlier, and is based on the assumptions of experts. As a result, its use has been restricted to retrospectively assessing the quality of life associated with certain conditions and diseases in NHIS respondents.[131]

2.3 REVIEW OF QUALITY OF LIFE STUDIES IN CEREBROVASCULAR EVENTS

With the increasing need to report outcomes of different interventions using an outcome measure that reflects both life expectancy and quality of life,[73;80] there has been research interest in estimating the quality of life of cerebrovascular event survivors. This research has been summarised in numerous reviews exploring the methods used to measure and estimate quality of life.[76;132-138]

Many of the previous literature reviews have explored the different measures given to individuals in order to assess quality of life after a stroke or TIA.[76;134;137;138] These have shown that there exists a vast array of outcome measures aimed at evaluating quality of life after a cerebrovascular event, with the review by Golomb et al. (2001)[76] identifying 33 different quality of life measures given to stroke patients. Results of these reviews have also shown that only a minority of studies have evaluated quality of life in cerebrovascular events using a single summary measure of quality of life, i.e. summarising quality of life from 0 to 1 (or 100), such as the ones introduced in **Section 2.2** of this chapter. Only a limited number of reviews have summarised the literature on studies reporting single summary measures of quality of life.[133;135;136]

The review undertaken by Tengs and colleagues was performed in order to assess the quality of life estimates for different stroke severities, i.e. minor, moderate and major.[135;136] As a result, studies which did not stratify their results by stroke severity were not included in the review. Another aim of the review was to perform a meta-analysis to estimate quality of life for different stroke severities, controlling for study design, elicitation technique, and participant sample.[136] Results of this analysis

showed that only stroke severity and the bounds of the scale used to elicit estimates were significant predictors of quality of life, while the elicitation method or sample used were not.

Post et al. (2001)[133] reviewed the literature for articles reporting empirical assessments of quality of life. Although the impact of stroke severity on quality of life was assessed, those studies not reporting severity of stroke were also included and treated as unspecified stroke. However, in this review, only studies evaluating quality of life through one-step valuation methods were included. Therefore, the eligibility criteria used in these reviews have the potential to omit numerous studies evaluating quality of life after stroke, and, furthermore, none of these reviews included studies evaluating the quality of life after a TIA.

The objective here is to present a review of the literature on the quality of life after a cerebrovascular event based on recent studies where individual patients were followed-up (e.g. observational studies and randomised controlled trials), which will complement the information presented in previous reviews. Another objective is to present a meta-analysis of published quality of life estimates, and identify the main predictors of published quality of life estimates.

2.3.1 METHODS

Inclusion criteria

For selection of relevant studies evaluating the quality of life after a cerebrovascular event the following criteria were used:

- Studies evaluating one or more cerebrovascular events;

- Studies in the English language;
- Studies published on or after January 1990, so as to make the results of the review applicable to present settings;
- Studies based in countries in the Organisation for Economic Co-operation and Development (OECD) or the European Union (EU), so as to generalise results of the review to a developed country setting;
- Quality of life estimates had to be derived from studies using patient-level data, which could include prospective and retrospective studies and randomised controlled trials (RCTs). Studies where estimates were derived from other studies or assumptions were excluded;
- Report the method of elicitation and the sample used;
- Report a single summary measure of quality of life, with those studies reporting multidimensional health status estimates only being excluded;
- Report quality of life estimates measured on a 0 to 1 or 0 to 100 scale. Studies using scales with negative lower bounds were also included;
- Report mean and/or median quality of life; and
- In order to exclude studies in which outliers could bias the results of the study, only those studies for which results were based on 20 patients or more were included in the review. In the case of trials and subgroups, only the results in those groups with 20 patients or more were included.

Search strategy

The electronic databases MEDLINE, EMBASE, Current Index to Nursing and Allied Health Literature (CINAHL) and the National Heath Service Economic Evaluation Database (NHS EED) were searched for studies published between 1 January 1990

and 31 January 2007. The electronic search strategy developed by Wardlaw et al. (2004)[59] was used for cerebrovascular event epidemiology (**Appendix 2**). To identify studies providing estimates of quality of life, this search strategy was combined with an adaptation of the electronic search strategy designed by the NHS EED.[139] The search strategy was broad so as to avoid missing any relevant studies. In addition, references in previous reviews, and in relevant studies identified in this review, were hand searched.

Data extraction

Titles and abstracts of all references were checked to identify articles of potential relevance. The full texts of all potential eligible studies and for those studies where relevance and/or eligibility was not clear from title and abstract were obtained.

Data were extracted using a proforma (**Appendix 3**), which included: country where study was based; patient population; sample used to elicit quality of life; method used to elicit estimates; results; and the limitations of the study

Quality criteria

As reported above, although recommendations have been made about the most suitable methods and respondents to elicit quality of life, there is still considerable debate about which are the most appropriate methods. Therefore, there is no gold standard against which relevant studies can be compared. As a result, no explicit quality criteria, were specified. However, as the eligibility criteria for this review were stringent, i.e. studies had to clearly report the methods and samples used to derive quality of life estimates a quality threshold was imposed in effect.

Statistical methods

A two-level random intercept model, weighted by sample size, was used to compare quality of life estimates between different groups (e.g. event severity). As a substantial proportion of studies reported more than one quality of life estimate, it was assumed that quality of life estimates (level-1) were nested within studies (level-2). Studies were considered as the random effect. All random effects models were estimated using the command `xtregre2` in STATA version 10.0.

A set of covariates was used to assess the importance of different characteristics on published quality of life estimates, including: event severity; population used to complete assessment; valuation method used; and for studies using patient or caregiver populations, the time elapsed between quality of life valuation and event onset. A final model, including all the above variables, was then developed to assess the independent predictors of quality of life.

For each model, the constant derived from the analysis gave the mean quality of life estimate for the reference case, with coefficients from the independent variables representing the estimated additive effects on the reference case.

2.3.2 RESULTS

Descriptive summary

In total, 61 articles meeting the inclusion criteria were identified and form the basis of this review. Of the included articles, 2 supplemented the results published in previous articles. Therefore, results from these articles were included as part of the

original article, giving a total of 59 separate studies. A list of all included studies is reported in **Appendix 4**.

Post et al. (2003)[133] identified a total of 23 published studies, with 20 being included in this review. Three studies were deemed not to fulfil the inclusion criteria: not conducted in an OECD/EU country;[140] sample size smaller than 20;[141] and the health states valued were not stroke/TIA specific.[142] Similarly, results of this review were compared to those from Tengs et al. (2003),[136] who included 20 studies in their review, with 9 being included in this review. Eleven studies were deemed not to fulfil the eligibility criteria: 5 studies obtained quality of life estimates from other published studies;[143-147] 3 obtained estimates using the authors' own assumptions ;[148-150] one was not conducted in an OECD/EU country;[140]in another one the health states valued were not stroke specific;[142] and a further study was published before 1990.[151]

Brief summaries of the methods used and results for each study are presented in **Appendix 5**. The 59 studies were predominantly published between 1997 and 2006, with only 6 studies being published between 1990 and 1996 (**Figure 2.4**). A large proportion of studies were based on populations from the USA (n=16, 27%), followed by the UK (n=15, 25%) and Canada (n=10, 17%). Only one study was based on populations from different countries, and was recorded as a multinational study.[152]

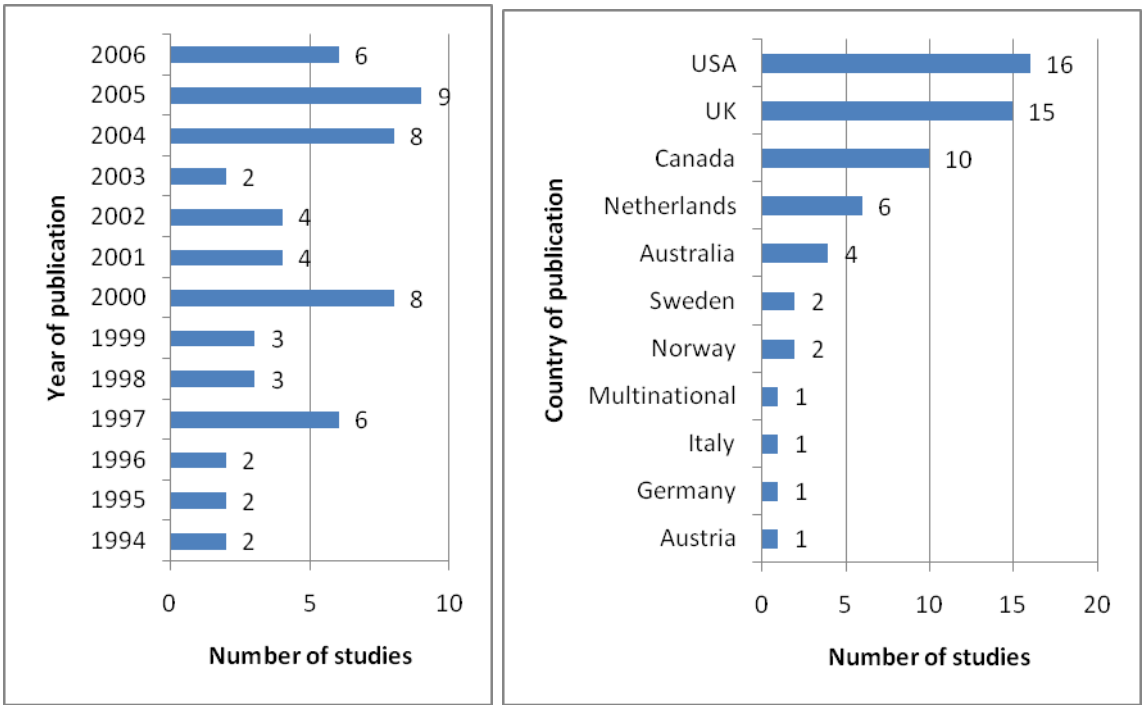

Figure 2.4 Year and country of publication

For each study, quality of life estimates were derived, whenever possible and applicable, by: study intervention; severity of event; study population; valuation method; and time elapsed between event and valuation. In total, from the 59 studies included in the review, 281 quality of life estimates were derived, representing an average of 4.8 estimates per study.

Cerebrovascular event investigated

Studies were classified by the type of cerebrovascular event investigated, as reported by the authors (**Figure 2.5**). 37 studies (63%) reported that quality of life for stroke was investigated. Other predominant cerebrovascular events investigated were ischaemic strokes only (IS, n=8, 14%) and both IS and intracerebral haemorrhages (ICH, n=4, 7%). Two (4%) studies reported that they had included all types of cerebrovascular diseases in their study populations.

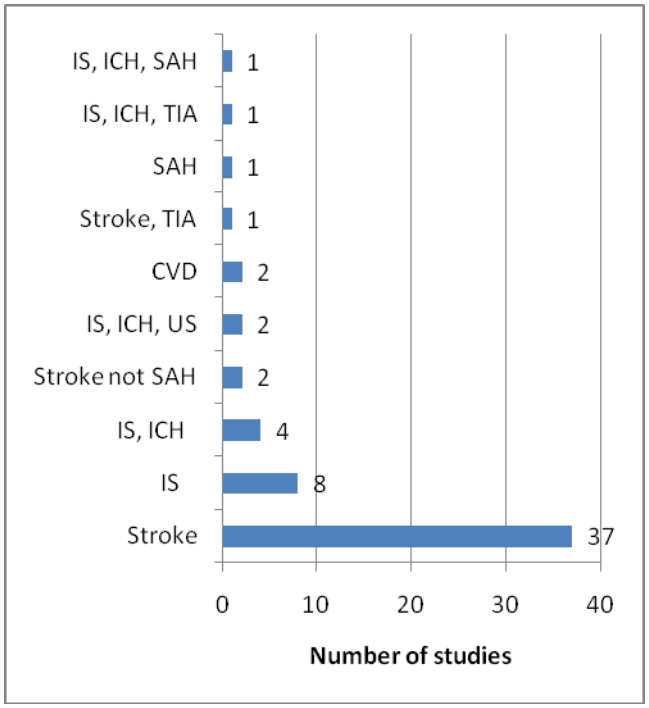

Figure 2.5 Event type assessed

IS: ischaemic stroke, ICH: intracerebral haemorrhage, SAH: subarachnoid haemorrhage, CVD: cerebrovascular disease, TIA: transient ischaemic attack, US: unknown stroke.

Event severity

Of 281 quality of life estimates, the majority (n=123, 44%) were for events with unspecified severity, i.e. estimates derived from studies not reporting event severity, or not stratifying results. For those reporting severity, 63 (22%) estimates were identified for severe events, with only 39 (14%) estimates being derived for moderate events (**Table 2.1**). Mean quality of life for minor cerebrovascular events was 0.79, significantly higher than for moderate events ($p<0.001$), which had a mean quality of life of 0.63 (i.e. 0.16 lower), and than those for severe events, which had a mean quality of life of 0.45 ($p<0.001$).

Table 2.1 Quality of life adjusted by event severity

Event severity	No.	QoL	Coefficient	95 % CI		p-value
Minor†	56	0.79	0.79	0.73	0.85	<0.001
Moderate	39	0.63	-0.16	-0.22	-0.10	<0.001
Severe	63	0.45	-0.34	-0.39	-0.28	<0.001
Unspecified	123	0.60	-0.19	-0.26	-0.12	<0.001

†Constant and reference case

Significant differences in quality of life were also found between moderate and severe cerebrovascular events (p=0.001), and severe events and those for which severity was not specified (p<0.001). There were no significant differences, however, between moderate and unspecified events (0.63 vs. 0.60, respectively; p=0.465), supporting the assumption that those studies not specifying the severity of the events being valued included a mixture of event severities in their samples.

Valuation method

In total, 164 quality of life estimates were valued using one-step methods and 117 using two-step methods.

When only the effect of valuation method on quality of life was taken into account in the regression model (**Table 2.2**), quality of life estimates were significantly higher when they were derived using one-step valuation methods rather than two-step methods (0.58 vs. 0.53, p=0.027). After adjusting for event severity the valuation method used was still found to have a significant influence on the quality of life reported (p=0.019 – **Table 2.2**).

Table 2.2 Quality of life adjusted by event severity and valuation method

	Unadjusted				Severity-adjusted			
	QoL	**Coeff**	**95% CI**	**p<|z|**	**QoL**	**Coeff**	**95% CI**	**p<|z|**
Constant †	0.58	0.58	0.54,0.62	<0.001	0.81	0.81	0.75,0.87	<0.001
Valuation								
Two-step: MAUS	0.53	-0.05	-0.10,-0.01	0.027	0.76	-0.05	-0.09,-0.01	0.019
Event severity								
Moderate					0.65	-0.16	-0.22,-0.10	<0.001
Severe					0.48	-0.33	-0.39,-0.28	<0.001
Unspecified					0.62	-0.19	-0.25,-0.12	<0.001

†Reference case: Unadjusted - One-step elicitation method; Severity-adjusted: one-step elicitation method and minor event.

One-step valuation methods

Of the 41 studies using one-step methods to derive quality of life, a total of 109 quality of life estimates were derived using the rating scale, 31 using TTO, and 24 using SG.

Table 2.3 Quality of life adjusted by event severity and valuation method

	Unadjusted				Severity-adjusted			
	QoL	**Coeff**	**95% CI**	**p<|z|**	**QoL**	**Coeff**	**95% CI**	**p<|z|**
Constant †	0.56	0.56	0.51,0.62	<0.001	0.67	0.67	0.60,0.73	<0.001
Valuation								
TTO	0.57	0.01	-0.06,0.08	0.803	0.77	0.10	0.05,0.14	<0.001
SG	0.66	0.10	-0.03,0.23	0.138	0.84	0.17	0.09,0.25	<0.001
Event severity								
Moderate					0.52	-0.15	-0.20,-0.10	<0.001
Severe					0.32	-0.35	-0.40,-0.30	<0.001
Unspecified					0.61	-0.06	-0.14,0.01	0.109

†Reference case: Unadjusted - One-step elicitation method using rating scales; Severity-adjusted: one-step elicitation method using rating scales and minor event.

When only the effect of the valuation method on quality of life was taken into account (**Table 2.3**), there were no significant differences in quality of life between rating scales and TTO (0.56 vs. 0.57, respectively; p=0.803), and rating scales and SG (0.56 vs. 0.66, respectively; p=0.138). Differences in quality of life estimates

between SG and TTO were also found not to be statistically significant (p=0.178 – results not shown in **Table 2.3**). However, as shown in **Table 2.3**, the direct valuation method used was found to be a significant predictor of quality of life after adjusting for event severity. For example, the quality of life for a minor event valued using a rating scale was 0.67 compared to 0.77 for a minor event valued using the TTO (p<0.001) and 0.84 when valued using the SG (p<0.001).

Two-step valuation methods

Of the 26 studies deriving quality of life estimates using two-step methods, 47 estimates were derived using the EQ-5D, 23 using the HUI3, 22 using the SF-36 (derived estimates using 10 published algorithms), 17 using the HUI2, 7 using the AQoL and 1 using the HALex. Due to the small number of estimates derived from the latter two scales, the two scales were combined together into a single variable in the analysis.

When only the effect of the method used on quality of life was taken into account (**Table 2.4**), there were no significant differences in quality of life between the EQ-5D and the SF-36 (0.56 vs. 0.65, respectively; p=0.294) and the EQ-5D and the HUI3 (0.56 vs. 0.51, respectively; p=0.272). However, significant differences were found between the EQ-5D and the HUI2 (0.56 vs. 0.69, respectively; p=0.017), and the EQ-5D and AQoL/HALex scales (0.56 vs. 0.45, respectively; p<0.001).

After adjusting for event severity (**Table 2.4**), significant differences in quality of life between the EQ-5D and HUI3 were identified (p=0.008), whereas those between the

HUI2 and EQ-5D disappeared (p=0.964). Significant differences remained between the EQ-5D and the HALex/AQoL scales.

Table 2.4 Quality of life adjusted by event severity and valuation method

	Unadjusted				Severity-adjusted			
	QoL	**Coeff**	**95% CI**	**p<|z|**	**QoL**	**Coeff**	**95% CI**	**p<|z|**
Constant†	0.56	0.56	0.51,0.61	<0.001	0.87	0.87	0.77,0.98	<0.001
Valuation								
HUI-2	0.69	0.13	0.02,0.24	0.017	0.87	0.002	-0.11,0.12	0.964
HUI-3	0.51	-0.05	-0.14,0.04	0.272	0.76	-0.11	-0.20,-0.03	0.008
HALex/AQoL	0.45	-0.11	-0.21,-0.02	0.024	0.68	-0.19	-0.30,-0.07	0.002
SF-36 mappings	0.65	0.09	-0.07,0.24	0.294	0.80	-0.07	-0.10,0.23	0.432
Event severity								
Moderate					0.67	-0.20	-0.33,-0.08	0.001
Severe					0.52	-0.35	-0.45,-0.25	<0.001
Unspecified					0.63	-0.24	-0.35,-0.13	<0.001

†Reference case: Unadjusted - Two-step elicitation method using EQ-5D; Severity-adjusted: two-step elicitation method using EQ-5D and minor event.

Population

As described above, quality of life valuations by the general public are now commonly used in two-step valuation methods, in which patients generally identify the health state for their particular condition, and the public value its associated quality of life. As a result, to determine the impact of different populations on quality of life valuations, only those estimates derived using one-step valuation methods were used in this analysis.

In total, 118 quality estimates derived from stroke/TIA patients were obtained, 23 from at-risk patients, 6 from patient caregivers, 6 from a mixture of different populations, and 11 from healthy individuals or experts. Due to the small number of estimates derived from the latter two populations, in the regression models the two populations were combined into a single variable.

Table 2.5 Quality of life adjusted by event severity and population

	Unadjusted				Severity-adjusted			
	QoL	**Coeff**	**95% CI**	**p<|z|**	**QoL**	**Coeff**	**95% CI**	**p<|z|**
Constant†	0.63	0.63	0.60,0.66	<0.001	0.75	0.75	0.71,0.80	<0.001
Population								
At risk patients	0.35	-0.28	-0.40,-0.16	<0.001	0.45	-0.30	-0.41,-0.18	<0.001
Caregivers	0.58	-0.05	-0.12,0.02	0.128	0.71	-0.04	-0.09,0.01	0.106
Experts/healthy	0.25	-0.38	-0.65,-0.11	0.005	0.38	-0.37	-0.59,-0.15	0.001
Mixture	0.51	-0.12	-0.26,0.02	0.094	0.63	-0.12	-0.25,0.02	0.072
Event severity								
Moderate					0.64	-0.11	-0.16,-0.07	<0.001
Severe					0.51	-0.24	-0.29,-0.20	<0.001
Unspecified					0.62	-0.13	-0.18,-0.08	<0.001

†Reference case: Unadjusted - estimates derived from cerebrovascular event patients; Severity-adjusted: minor event, estimates derived from cerebrovascular event patients

Not controlling for event severity (**Table 2.5**), there were significant differences in quality of life between cerebrovascular event patients and those at risk of suffering a cerbrovascular event (0.63 vs. 0.35, respectively; p<0.001) and experts/healthy individuals (0.63 vs. 0.25, respectively; p=0.005). There were no significant differences, however, between the quality of life estimates obtained from cerebrovascular event patients and those from caregivers (p=0.128).

As shown in **Table 2.5**, after adjusting for severity, significant differences in quality of life estimates remained between cerebrovascular event patients and at-risk patients. The quality of life for a minor event derived from cerebrovascular event patients was significantly higher than that for minor events derived from at risk-patients (0.75 vs. 0.45, respectively; p<0.001), and that derived from studies using either experts or healthy individuals (0.75 vs. 0.38, respectively; p=0.001).

Follow-up period

The effect of time elapsed between onset of cerebrovascular event and follow-up on quality of life was assessed. Excluded from this analysis were those estimates derived from studies where quality of life was derived using hypothetical scenarios (n=12; 20%) and those were follow-up duration was not reported (n=8; 14%). A total of 231 estimates were derived, of which 33 (14%) were derived less than one month after the cerebrovascular event; 82 (35%) between one and 3 months after the event; 60 (26%) between 6 months and less than one year after the event; 31 (13%) at one year; and 25 (11%) more than one year after the event.

Table 2.6 Quality of life adjusted by event severity and duration of follow-up

	Unadjusted				Severity-adjusted			
	QoL	**Coeff**	**95% CI**	**p<|z|**	**QoL**	**Coeff**	**95% CI**	**p<|z|**
Constant†	0.63	0.63	0.57,0.68	<0.001	0.84	0.84	0.78,0.91	<0.001
Follow-up								
< 1 month	0.46	-0.17	-0.24,0.09	<0.001	0.69	-0.15	-0.21,-0.09	<0.001
3 to <12 months	0.61	-0.02	-0.08,0.03	0.393	0.85	0.01	-0.04,0.05	0.801
1 year	0.65	0.02	-0.06,0.09	0.667	0.86	0.02	-0.05,0.08	0.616
> 1 year	0.57	-0.06	-0.17,0.06	0.332	0.67	-0.17	-0.27,-0.06	0.002
Event severity								
Moderate					0.70	-0.14	-0.20,-0.09	<0.001
Severe					0.52	-0.32	-0.37,-0.26	<0.001
Unspecified					0.64	-0.20	-0.27,-0.13	<0.001

†Reference case: Unadjusted – estimates derived between one and 3 months; Severity-adjusted - minor event, estimates derived between one and 3 months

When only the effect of time between event onset and follow-up on quality of life was taken into account (**Table 2.6**), quality of life was significantly lower at follow-ups of less than one-month than between one and 3 months follow-up (0.46 vs. 0.63, respectively; p<0.001). However, there were no significant differences in quality of life estimates when these were derived between one and 3 months after the event and those obtained between over 3 months and less than one year after the event

(p=0.393), at one year (p=0.667), and when quality of life was obtained more than one year after the event (p=0.332).

After adjusting for event severity (**Table 2.6**), statistically significant differences remained between quality of life estimates obtained less than one month after event and those obtained between one and three months after event (p<0.001). Furthermore, results of the regression model showed that for follow-up periods of more than one year quality of life was significantly lower than that obtained at one to 3 months after the event. For example, for a minor event, quality of life at one to 3 months was 0.84 (i.e. the reference case) compared with 0.67 more than one year after event onset (p=0.002).

Multivariate analyses

Four different models were developed in order to assess the independent predictors of quality of life, with each varying depending on the explanatory variables used:

Model 1: severity, one- or two-step valuation method, and follow-up period;

Model 2: severity, valuation method, and follow-up period;

Model 3: severity, one-step valuation method, and population used; and

Model 4: severity, one-step valuation method, population used and follow-up period;

The population variable was not included in models 1 and 2 as in two-step methods patients generally identify the health state for their particular condition, and the public value its associated quality of life. As a result, it was not possible to categorise the population used for studies deriving estimates using two-step methods.

Table 2.7 Predictors of quality of life estimates derived from published studies

	Model 1		Model 2		Model 3		Model 4	
	QoL	**Coeff**	**QoL**	**Coeff**	**QoL**	**Coeff**	**QoL**	**Coeff**
Constant†	***0.87***	***0.87***	***0.83***	***0.83***	***0.78***	***0.78***	***0.75***	***0.75***
Event severity								
Moderate	***0.73***	***-0.14***	***0.69***	***-0.14***	***0.64***	***-0.14***	***0.65***	***-0.10***
Severe	***0.58***	***-0.29***	***0.55***	***-0.28***	***0.48***	***-0.30***	***0.51***	***-0.24***
Unspecified	***0.67***	***-0.20***	***0.65***	***-0.18***	***0.62***	***-0.16***	***0.62***	***-0.13***
Valuation method a)								
Two-step: MAUS	***0.79***	***-0.08***						
Valuation method b)								
TTO			***0.92***	***0.09***	***0.91***	***0.13***	***0.87***	***0.12***
SG					***0.99***	***0.21***		
HUI-2			0.79	-0.04				
HUI-3			***0.60***	***-0.23***				
EQ-5D			***0.79***	***-0.04***				
HALex/AQoL			***0.69***	***-0.14***				
SF-36 mappings			0.86	0.03				
Population								
At risk patients					***0.45***	***-0.33***		
Care givers					0.82	0.04	***0.79***	***0.04***
Experts/healthy					***0.52***	***-0.26***		
Mixture					***0.57***	***-0.21***		
Follow-up duration								
< 1 month	***0.73***	***-0.14***	***0.69***	***-0.14***			***0.66***	***-0.09***
3 to <12 months	0.88	0.03	0.85	0.02			***0.79***	***0.04***
1 year	0.88	0.01	0.84	0.01			***0.79***	***0.04***
> 1 year	***0.73***	***-0.14***	*0.73*	*-0.10*			0.68	-0.07
Between study variance	0.089		0.073		0.07		0.049	
Within study variance	0.088		0.076		0.06		0.066	
Intra class correlation	0.495		0.474		0.450		0.644	
R^2	0.392		0.513		0.737		0.467	

Italics and bold: significant at p<0.05; *Italics*: significant at p<0.10

†Reference case:
Model 1: Minor event, one-step valuation, derived at 1 to 3 months;
Model 2: Minor event, rating scale elicitation, derived at 1 to 3 months;
Model 3: Minor event, rating scale elicitation, derived from cerebrovascular patients at 1 to 3 months;
Model 4: Minor event, rating scale elicitation, derived from cerebrovascular patients.

Results from the four models reported in **Table 2.7**, showed similar and consistent results between them. In terms of event severity, the four models, as with the univariate analysis reported earlier, showed that minor events were associated with significantly higher quality of life than moderate, severe and unspecified events (p<0.001 in each case).

As before, after controlling for other covariates, one-step valuation methods yielded higher quality of life estimates than those derived from two-step valuation methods, with quality of life being 0.08 lower when measured with two-step valuation methods (**Table 2.7**, models 1 and 2). Results showed that, after controlling for other covariates, the HUI3, the EQ-5D and the HALex/AQoL were associated with significantly lower quality of life estimates than those obtained using rating scales.

Results of the four models also showed that cerebrovascular event patients rated quality of life higher than other population groups, although for caregivers the difference was smaller and did not reach statistical significance in model 4. After controlling for other covariates, statistically significant differences remained between quality of life estimates obtained less than one month after event and those obtained between one and three months after event ($p<0.001$).

2.4 DISCUSSION

This chapter has contributed to the overall thesis by providing a brief overview on different ways to assess quality of life. This chapter has also presented a review and meta-analysis of published studies on the quality of life after a cerebrovascular event.

The review identified a total of 59 studies, of which 32 (54%) did not report and/or stratify quality of life estimates by event severity. Results from the meta-analysis showed that event severity was consistently a significant predictor of quality of life in all model specifications, with both moderate and severe events having markedly lower quality of life than minor events after controlling for other explanatory variables.

Although intuitive, this result highlights the importance of stratifying quality of life estimates by event severity.

Also highlighted in the meta-analysis were significant differences in quality of life when estimates were obtained using two-step valuation methods instead of one-step techniques. This difference has not been observed in previous meta-analyses of quality of life, which have either only included estimates based on one-step valuation methods or have included estimates obtained from two-step methods in the one-step valuation technique used to value such scales (e.g. EQ-5D estimates would be included under TTO).[135;153-156]

At first, this finding could appear to be counter intuitive. Over 60% of estimates derived using direct elicitation techniques were obtained using rating scales, which have been shown, in this and previous analyses, to produce significantly lower quality of life estimates than either the TTO or SG,[136;154;155] which are more commonly used to elicit quality of life in two-step valuation measures. As a result, one would expect estimates derived from two-step valuation methods to be higher than those obtained using one-step valuation methods. However, two-step valuation methods, such as the EQ-5D or HUI, use non-patient populations to value health states, and these populations have been shown earlier to report significantly lower quality of life than patients. As a result, this reduction in quality of life due to the population used could outweigh the increase in quality of life obtained when using rating scales.

The differences in quality of life among different populations identified in this analysis, are in contrast to those obtained by Tengs et al. (2003),[136] who found no significant differences between patients and community members (p=0.973) or experts (p=0.106). The analysis undertaken by Tengs et al. (2003)[136] was based on 20 studies including only 53 quality of life estimates, as opposed to the 281 estimates included in this analysis. Results from this analysis are also in line with those observed in meta-analyses of the quality of life in Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) and prostate cancer.[154;155]

This meta-analysis also measured the impact of time between event onset and quality of life elicitation, the impact of which has not been examined in previous meta-analyses of quality of life. The *a-priori* hypothesis was that the longer patients had to recover from the cerebrovascular event the higher the quality of life would be. Results of the analysis showed that quality of life was significantly lower shortly after the event than at follow-ups of between one and three months. However, at follow-ups of more than one year, quality of life was found to decrease again. This could be partly explained by patients growing older and suffering from other or related comorbidities, or from other unobserved features of the study design or samples used.

Several limitations to this review and meta-analysis of the literature should be noted. Although, the review was very broad, studies were only sifted and assessed by a single reviewer, and results from some eligible studies conducted in EU or OECD countries were excluded as these were not published in English. Secondly, there may be other variables not included in the regression models that could predict

quality of life, such as age and gender, presence of co-morbidities, other disease characteristics, side effects, and/or the effects of treatment or rehabilitation. However, as not all studies reported such characteristics, only those variables widely reported were included in the analysis. Thirdly, for certain variables (i.e. population and valuation method) some sub-groups had to be grouped together, in order to reduce the number of covariates in the regression model in a bid to reduce collinearity.

2.5 CONCLUSION

A review and meta-analysis of published quality of life estimates has been presented in this chapter. A considerable number of studies have reported quality of life for stroke, but only a limited number have investigated quality of life in other cerebrovascular events such as TIA. The review and meta-analysis highlighted the marked and significant differences in quality of life depending on event severity. After controlling for other possible covariates, quality of life for a minor event was found to be 0.84, compared with 0.69 for moderate events and 0.54 for severe events. However, despite these marked differences, results from the review showed that a significant proportion of studies did not report the severity of events being evaluated and/or did not stratify results by event severity. Results from the meta-analysis also showed that direct elicitation techniques yielded significantly higher quality of life estimates than those derived from multi-attribute utility scales. This finding will be further assessed in this thesis (**Chapter 5**) when quality of life derived from the EQ-5D will be compared to that derived using a rating scale in patients included in the Oxford Vascular study (OXVASC), details of which are presented in **Chapter 4**.

CHAPTER 3

CEREBROVASCULAR EVENTS: A REVIEW OF COSTING STUDIES

3.1 INTRODUCTION

As discussed in **Chapter 1**, cerebrovascular events are a major source of mortality and morbidity,[43] and one of the principal causes of hospital and care-home resource utilisation.[75] It is therefore, not surprising that the high incidence and serious consequences of cerebrovascular events make it a major cause of health service use and healthcare expenditure, creating much research interest in the costs of stroke and transient ischaemic attacks (TIA).

In this chapter a review of the literature based on studies based on individual patient data will be employed to assess the published costs of cerebrovascular events and to critically appraise the study designs and methods used. Specifically, this chapter will set out a number of criteria that every costing study evaluating the costs of stroke and TIA should ideally fulfil.

3.2 COSTING STUDIES

A costing study consists of the identification, measurement and valuation of all resources related to an illness, under which all resources consumed by patients are measured and ascribed using a monetary value.[157]

3.2.1 ROLE OF COSTING STUDIES

Studies estimating the costs of a particular disease either use an incident based approach or a prevalence approach, with use of a particular design being determined by the objective of the study.

The incidence approach takes into account the costs incurred over a period of time, starting at disease onset and finishing at end of follow-up or death of the patient.[158] The incidence approach is generally used to estimate the cost of a particular disease or event per person, for example, cost per stroke patient. Results of these studies are then used to estimate the cost-effectiveness of specific interventions to prevent or treat illness.[80;81]

The prevalence approach, by contrast, estimates the cost of a disease within a given time period, normally one year, whereby all costs within the most recent year for which data are available are measured, regardless of disease onset.[158;159] This type of study is generally used to estimate the costs for all patients with a particular disease or event within a given region or country, which are then used to inform choices concerning clinical and research priorities by providing a measure of the economic burden of a particular health problem.[157;160]

In addition, by providing evidence on the costs of different diseases, and the role they play in determining cost-effectiveness of interventions, costing studies also have a major role in informing decisions about service provision and resource allocation. For example, the healthcare system may allocate more resources to prevent and/or treat a disease with a high medical and economic burden for which

cost-effective interventions exist for its prevention and/or treatment. However, how informative a costing study is to policy makers or analysts assessing cost-effectiveness will depend on the number of resource use categories that are evaluated.

3.2.2 RESOURCE USE CATEGORIES

There are three main types of resource use categories:[80;81;161] 1) those related to the direct medical costs of preventing, screening, diagnosing and treating a disease (referred here as direct medical costs); 2) those related to the direct non-medical costs of the disease, i.e. those costs related to the disease that are not the responsibility of the healthcare system (referred here as direct non-medical costs; and 3) productivity losses associated with the disease.

The resource use categories included under the direct medical costs heading are:[81;162;163]

- Screening and diagnostic tests, which will include all the tests used to screen and/or diagnose a disease;
- Inpatient care, which include: accident and emergency (A&E) visits, acute inpatient stay, rehabilitation stay, and interventions and investigations;
- Outpatient care, including: visits to the specialist and hospital clinics once discharged from hospital;
- Day care, whereby treatment, respite or palliative care is offered in a healthcare setting without the need of the patient being hospitalised;
- Community healthcare; which will include: visits to the general practitioner (GP) and nurse both at home and surgery, use of healthcare transport including

hospital cars and ambulances, and home visits by rehabilitation staff such as physiotherapy and occupational therapy; and

- Medications, i.e. all the drugs and medications consumed by the patient in order to prevent or treat a disease.

Under the direct non-medical costs heading, the following resource use categories would be included:[81;162;163]

- Social care, which are services provided by social services, including: provision of home help and/or home adaptations required due to the disease, social worker visits, nursing and residential care, and provision of meals on wheels;
- Social benefits, these are benefits provided by the State or national insurance schemes, and include: 1) transfer payments, e.g. payments to patients who are unable to work due to their disease; and 2) payment for service, e.g. payments to families for taking care of a disabled relative;[164]
- Travel costs, these include the costs borne by patients and/or their carers while travelling to and from centre of care; and
- Out-of-pocket expenses, which include payments made by the patient or their caregivers due to the disease. Such expenses would include home or vehicle adaptations not covered by social services, extra home or domestic helpers, or over the counter medications.

Finally, under the lost productivity heading, the following resources would be included:[80;81;162;163]

- Productivity losses due to illness, which are the costs associated with work absenteeism due to illness and/or the costs associated with lower productivity while at work;
- Productivity losses due to death, which are the costs associated with early mortality, i.e. the number of working years lost due to the disease; and
- Productivity losses due to care-giving. These informal care costs are the time (work and/or leisure) that friends and relatives forgo in order to provide unpaid care for patients.

3.3 REVIEW OF COSTING STUDIES IN CEREBROVASCULAR EVENTS

The high cost of cerebrovascular events to the world's healthcare systems, and to society in general (including productivity losses and informal care costs) has created much research interest in the costs of stroke and TIA. As a result numerous studies have been published estimating the cost of stroke and/or TIA, and these have been summarised in numerous literature reviews.[158;165-171]

Previous literature reviews have tended to focus on specific types of costing studies. A proportion have focused on costing studies used as part of an economic evaluation,[166-168;170] in which only studies evaluating the costs and effects of two or more stroke/TIA interventions were included. Others have included both incidence- and prevalence-based studies, in which the costing methods were reported in full, i.e. the main objective was to estimate the costs of stroke and/or TIA,[158;165;169;171] including studies in which resource use was derived either from primary research (i.e. using patient level data) or secondary research (i.e. using previously published studies), making comparisons between studies difficult. In any case such eligibility

criteria have the potential to omit numerous observational studies evaluating the costs of stroke and TIA.

The objective here is to present a review of the literature on the costs of cerebrovascular events based on recent studies where individual patients were followed-up, which will complement the information presented in previous reviews. This study will only focus on incidence-based studies as they are an area of intensive research and provide the inputs to economic evaluations of different interventions.[158] Furthermore, prevalence-based studies generally use data from many different sources, and are not based solely on primary research. Another objective is to present a critical review of study design and methods used in the included studies by assessment against four pre-defined quality criteria.

3.3.1 METHODS

Inclusion criteria

For selection of relevant studies evaluating the costs of stroke and/or TIA the following criteria were used:

- Studies evaluating one or more cerebrovascular events;
- Studies in the English language;
- Studies published on or after January 1990, so as to make the results of the review applicable to present settings;
- Studies based in countries in the Organisation for Economic Co-operation and Development (OECD) or the European Union (EU), in order to generalise results of the review to a developed country setting

- When determining total costs, resource use had to be derived from studies using patient-level data, which could include prospective and retrospective studies and randomised controlled trials (RCTs). Studies where resource use was derived from other studies, modelling or expert opinion, were excluded.
- When determining total costs, prices or unit costs could be derived from any source, including published studies, administrative data, national account data, assumptions or authors' own study.
- Studies reporting mean and/or median costs. Those studies not reporting mean costs, but reporting total costs and the number of patients in the study sample were also included as a mean cost could be calculated.
- In order to exclude studies in which outliers could bias the results of the study, only those studies for which results were based on 20 patients or more were included in the review. In the case of trials, only the results in those groups with 20 patients or more were included.

Search strategy

The electronic databases MEDLINE, EMBASE, Current Index to Nursing and Allied Health Literature (CINAHL), and the National Health Service Economic Evaluation Database (NHS EED) were searched for studies published between 1 January 1990 and 31 January 2007. An electronic search strategy developed by Wardlaw et al. (2004)[59] was used for cerebrovascular event epidemiology (**Appendix 2**), which was combined with an adaptation of the electronic search strategy designed by the NHS EED (**Appendix 6**)[139] to identify published cost-effectiveness studies. The search strategy was broad so as to avoid missing any relevant studies. In addition,

references in previous reviews on the costs of stroke and/or TIA, and in relevant studies identified in this review, were hand search for potential references.

Data extraction

Titles and abstracts of all references were checked to identify articles of potential relevance. The full texts of all potential eligible studies and for those studies where relevance and/or eligibility was not clear from title and abstract were obtained.

From the included studies data were extracted using a proforma specially derived for this thesis (**Appendix 7**). Data extracted for each study included: country where study was based; patient population and sample; study design used to derive resource use; sources for unit costs/prices; costs included; time horizon, use of discounting and year of costing; results; and the limitations of the study.

Quality criteria

Included studies were then quality assessed using four pre-defined quality criteria in order to ascertain if the results of the studies were valid and meaningful.

1. Use of appropriate costing methodologies:

Guidelines have been drawn up in order to improve the quality of economic evaluations by agreeing acceptable methods.[80;139;172] As a costing study is an integral part of an economic evaluation, these guidelines can also be used to determine the quality of partial economic evaluations.

In order to determine the criteria that costing studies should fulfil, a shortened version of the checklist used by the British Medical Journal to assess the quality of economic evaluations was used.[172] This shortened checklist was modified from that used to evaluate costing studies in clinical guidelines,[163] and covered the following issues: a) study design: whether the objectives of the study are clearly reported and the economic perspective (i.e. who bears the costs) was reported and justified; b) data collection: whether the resource use and unit cost data collection were reported and the methods used appropriate; and c) analysis and interpretation of results: how results were analysed and interpreted by the authors. For each of the 15 questions in the checklist (**Appendix 8**), one point was awarded for every "Yes" in the checklist and no points for each question answered "No". For three questions in the checklist, a third category "NA" was included as the question might not be relevant to a number of studies.

2) Use a study sample which is representative of the overall population:

It is important that studies evaluating the costs of cerebrovascular events are based on an unselected sample including all relevant patients. The general view is that population-based studies with full case ascertainment are the most accurate sources of information on disease incidence, mortality and outcome.[32;46] For example, previous studies have often only included hospitalised patients, who are easier to identify, omitting minor stroke or TIA patients who are managed in the community.[173] Therefore, by focusing on an unselected study sample, inclusion bias will be minimised.

3) Take into account pre-morbid resource use:

Cerebrovascular events are associated with old age and often occur in patients with other co-morbidities.[174] Such patients are, therefore, likely to consume substantial healthcare resources even if they had not suffered a cerebrovascular event. As a result, in order to avoid overestimating costs, a costing study should only include those costs that could be attributable to these conditions. However, as cerebrovascular events may aggravate non-related conditions,[175] studies should also compare resource use before and after the initial event in order to assess if there are any differences in all-cause resource use.

4) Assess the costs incurred by different groups of patients:

Costs of cerebrovascular events vary substantially between individuals and are likely to depend on the pathologic subtype and severity of the event, the particular etiology, and other characteristics such as age, sex, and comorbidity.[176;177] As a result, reporting the average cost of stroke/TIA, without taking into account its severity or subtype, may be meaningless when assessing the cost-effectiveness of stroke interventions. Therefore, studies should ideally report the costs of cerebrovascular events according to patient characteristics, event subtype and etiology.

3.3.2 RESULTS

Descriptive summary

In total, 130 articles meeting the inclusion criteria were identified and form the basis of this review. An additional article meeting the inclusion criteria was not included in the review as it was work related to the latter part of this thesis.[173] Of the included articles, 10 supplemented the results published in previous articles. Therefore,

results from these articles were included as part of the original article, with a total of 120 studies, therefore, being included. A list of all the studies included is provided in **Appendix 9**. In addition, brief summaries of the methods used and results for each study are presented in **Appendix 10.1** and **Appendix 10.2**, respectively. For convenience, the review results sections of this chapter refer to studies by their consecutive number (in squared brackets) within these tables.

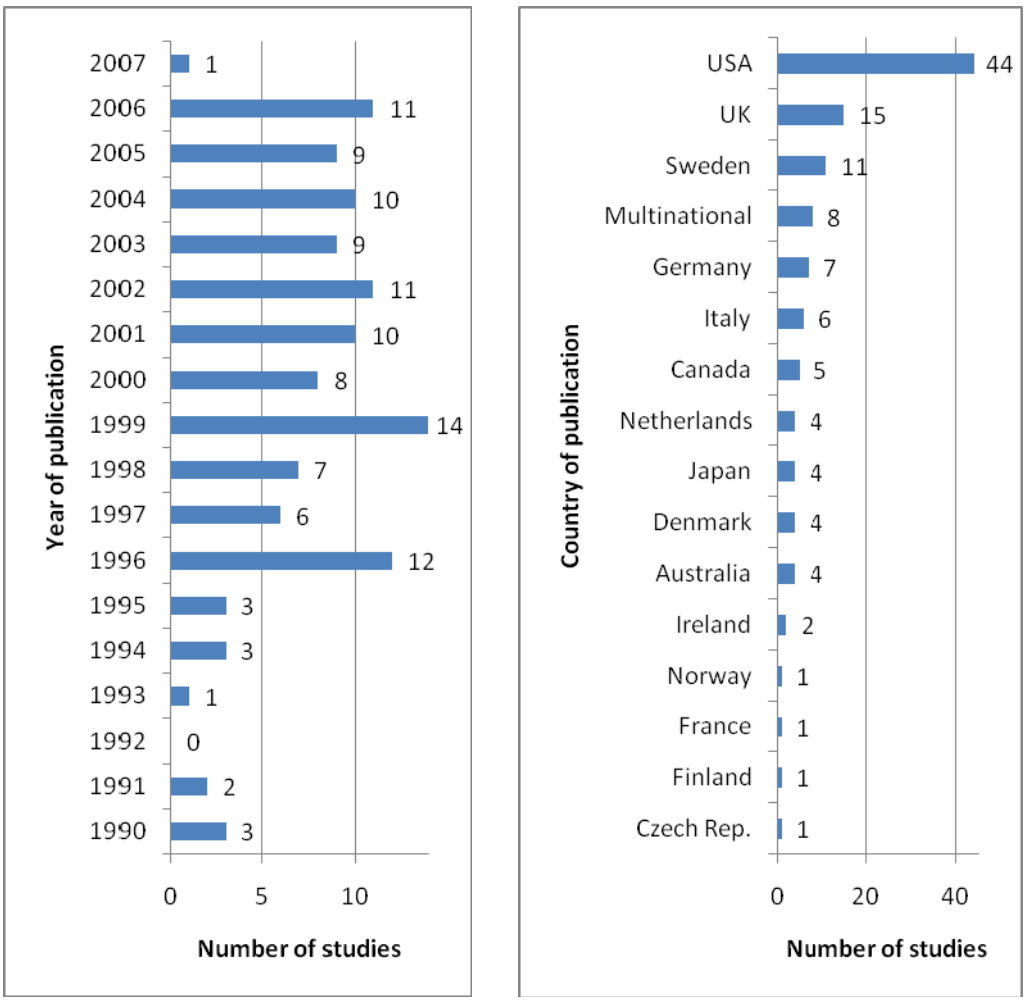

Figure 3.1 Country and year of publication

Studies were predominantly published between 1996 and 2006, with only 12 studies being published between 1990 and 1995 (**Figure 3.1**). A large proportion of included

studies were based exclusively on populations from the USA (n=44, 37%), followed by the UK (n=15, 13%) and Sweden (n=11, 9%). 8 studies were based on populations from different countries, and were recorded as multinational studies.

Study population

Included articles were classified by the type of cerebrovascular event investigated in the study by examining details of the study population as reported by the authors (**Figure 3.2**).

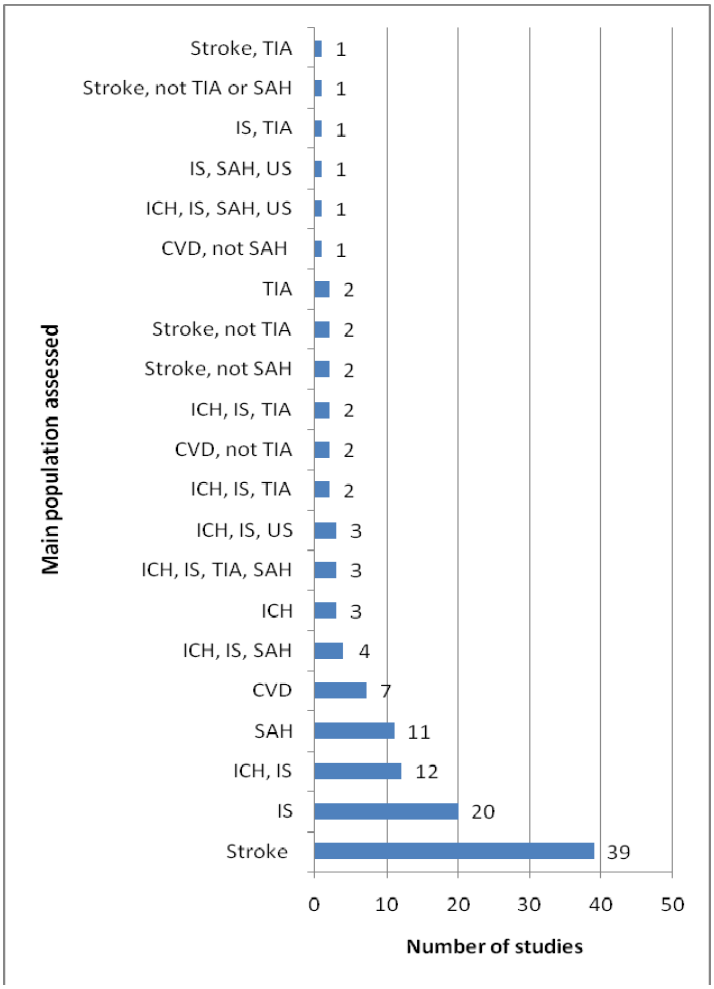

Figure 3.2 Main population assessed

IS: ischaemic stroke, ICH: intracerebral haemorrhage, SAH: subarachnoid haemorrhage, CVD: cerebrovascular disease/disorders, TIA: transient ischaemic attack, US: unknown stroke.

39 studies (33%) reported that a stroke population was used. Other predominant study populations included were ischaemic strokes only (IS, n=20, 17%) and both IS and intracerebral haemorrhages (ICH, n=12, 10%). The authors of 7 (6%) studies reported that all types of cerebrovascular disease were included in their study populations [6][12][23][24][43][59][61], with only 4 of these studies adequately reporting the ICD-9 or -10 codes used to define cerebrovascular diseases [23][43][59][61].

Source of data

Depending on how the study participants were identified and included into the study, relevant studies were categorised into one of three study designs:

1) Randomised controlled trials (RCTs), whereby patients were assigned to one of two or more groups and offered different interventions, with chance alone dictating the group the patient was assigned to.[178;179]
2) Retrospective observational studies, whereby outcomes and resource use data in patients where cerebrovascular events had already occurred were recorded by reviewing historical data or records.[179]
3) Prospective observational studies, whereby patients are followed-up to assess possible outcomes, such as death and resource use.[179] Prospective studies were also assessed to see if they were a population-based cohort study, with case ascertainment from multiple overlapping sources of information.[18]

A total of 25 (21%) studies were classified as RCTs, 46 (38%) as retrospective studies, and 49 (41%) as prospective studies, of which 5 were classified as population-based studies [15][41][56][59][107]. Of the population based studies, one

was based on the North-East Melbourne Stroke Incidence Study (NEMESIS) [15], which was conducted in Australia, two were based on samples derived from the Erlangen Stroke Project [56][107], which was conducted in Germany and two were based on samples derived from the Rochester Stroke Register [41][59], which was conducted in the USA.

Cost categories

Studies were reviewed to identify the number of resource use categories included. **Table 3.1** shows the number of studies including each of the 13 cost categories that could have been included, using the definitions of costs reported above. 115 (96%) studies included one or more direct medical costs, with the majority (n=111, 93%) including hospital inpatient care costs. Other direct medical costs included by a sizeable proportion of studies were outpatient and community health care, whereas day care costs were only included by 23 (19%) studies.

Table 3.1 Cost categories included

Cost category	No. of studies (%)
Direct medical costs	
Diagnostic tests	48 (40)
Inpatient care	111 (93)
Outpatient care	55 (46)
Day care	23 (19)
Community healthcare	55 (46)
Medication	41 (34)
Direct non-medical costs	
Social care	48 (40)
Social benefits	0
Travel costs	10 (8)
Out-of-pocket	4 (3)
Productivity costs	
Productivity loss (illness)	6 (5)
Productivity loss (death)	0
Informal care-giving	8 (7)

Direct non-medical costs were included by 49 (41%) studies. In this category, social care was the type of cost most often included (n=48, 40%), with most studies including nursing or residential home care. Only a small proportion of studies included travel and out-of-pocket costs, and none included social payments or transfers. Productivity losses were only included by 11 (9%) studies, of which 8 included informal care-giving costs and 6 included productivity losses due to illness. No study included productivity losses due to premature death.

Quality of methodology, reporting and analysis

In general, the included studies were of adequate quality. After reviewing studies using the quality checklist (**Appendix 8**), the average score for the 120 included studies was 9.45 (S.D. 1.78, median 9), which was scored in most cases out of 12 or 13, as three questions in the checklist did not apply to many studies (i.e. reporting indirect costs separately, results of currency conversions and use of discount rate).

In terms of study design, virtually all studies stated a research question (99%) and all reported sufficient details about the economic perspective adopted in the analysis. However, only 45 (38%) studies reported quantities of resources separately from their unit costs and 48 (40%) did not report any currency details and/or the years to which the costs applied. Studies did, however, generally report appropriate details of the participants from whom valuations were obtained (98%), and 88 (73%) studies appropriately reported the methods used in the estimation of resource use and costs.

Studies generally reported the time horizon over which patients could incur costs (n=115, 96%), but of the 8 studies for which the time horizon was more than one

year, only 2 appropriately discounted future costs [56] [72]. In terms of statistical analyses, 86 (72%) studies provided results of statistical tests either by providing standard deviations and 95% confidence intervals, or by reporting results of comparisons between patient groups (e.g. t-tests) or multivariate analyses. Finally, all studies answered the study question, with virtually all (n=118, 98%) deriving their conclusions from the data reported. However, a significant proportion of these studies (n=32, 27%) did not report the limitations of their analyses.

Pre-morbid resource use

An analysis of pre-morbid resource use was not applicable in 47 (39%) studies, as costs were only estimated for the hospitalisation period immediately after the index event; therefore all costs could be directly attributed to the cerebrovascular event. In the remaining 73 studies, 16 (22%) assessed the costs that could be directly attributed by: 1) comparing the costs of cerebrovascular patients to those with no cerebrovascular history (n=6); 2) only including the direct costs of the events under investigation (n=3); or 3) comparing previous resource use to resource use after the cerebrovascular event (n=7). In the other 57 studies it was inferred, therefore, that all-cause resource use was included in the analyses.

Subgroup analyses

In total 52 (43%) studies presented their cost results for different patient groups and/or performed a multivariate analysis to assess predictors of costs. For the 50 studies that reported costs by patient subgroups, **Table 3.2** shows the different groups used to report cost results. The most common grouping was by event

severity, which was undertaken by 20 (39%) studies. Other common groups used to report cost results were event type (n=16, 31%), and age (n=15, 29%).

Table 3.2 Sub-groups used to report cost results

Sub-group	No. of studies (%)
Age	15 (29%)
Gender	9 (18%)
Survival during study period	7 (14%)
Severity of event	20 (39%)
Presence/history of co-morbidities	6 (12%)
Event type	16 (31%)
Living arrangements	11 (22%)
Functional ability	3 (6%)
History of stroke/TIA	5 (10%)
Ethnicity	2 (4%)

Costs of stroke

The average and/or median cost of a cerebrovascular event is reported in **Appendix 10.2** for each study. These costs are, however, difficult to compare with one another as different studies have included different populations, which vary in severity and therefore cost. Studies have also been undertaken in numerous countries and over different time periods. Furthermore, the inclusion of different healthcare cost categories by different studies will make any comparisons difficult.

The majority of studies included stroke, ischaemic stroke, or a combination of ischaemic and intracerebral haemorrhage populations (**Figure 3.2**). Cost estimates from the studies using these populations were compared. Excluded from this analysis were those studies that evaluated costs of: overall cerebrovascular events without providing costs for each event type; TIA only; and intracerebral or

subarachnoid haemorrhage only. As the number of studies estimating the costs of these events were small, separate analyses for these were not undertaken.

To reduce potential sources of heterogeneity across studies, a number of studies were excluded from the review of stroke costs: only included subarachnoid haemorrhage (n=11); did not include hospitalisation costs (n=10); considered overall costs of all cerebrovascular events (n=10); only reported median costs (n=5); only included costs of recurrent hospitalisations (n=5); only included intracerebral haemorrhages (n=4); only included TIA (n=2); and only included intensive or mental health care costs (n=2). Overall, the cost estimates published in 71 (59%) studies were compared, out of which 165 estimates of stroke costs were derived. Cost estimates were converted to 2006 prices, using the healthcare component of the consumer price index for direct costs, and wage inflation indices for indirect costs.[180-184] All costs were converted into US dollars. However, as comparisons using currency exchange rates do not reflect real price differences between countries,[157] costs were further adjusted using the purchasing power parity (PPP) method.[181]

On average, the mean cost of a stroke was $19,018 (median: $14,571), ranging from $468 to $146,149 (the results from two studies reporting costs over $100,000 are not shown in **Figure 3.3**). A total of 55 (33%) cost estimates only included hospitalisation costs, with only 2 of these including subsequent hospitalisation costs. For those studies including more cost categories, 65% of overall costs were due to initial hospitalisation.

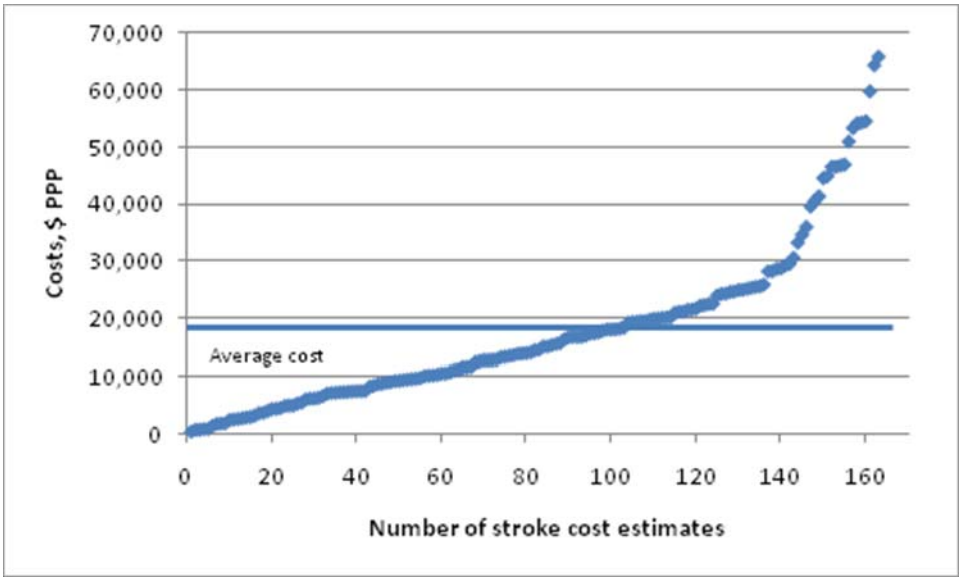

Figure 3.3 Cost of stroke in 71 published studies

Table 3.3 shows that there was a clear association between follow-up duration and costs, with mean costs varying from $10,216 when follow-up was between 3 and less than 6 months to $28,525 one-year after event. Studies with longer time horizons, i.e. time in which patients can incur costs, on average, also reported significantly higher costs (p<0.0001). Only two studies evaluated costs over a period of more than one year.

Table 3.3 Cost of stroke in 71 studies by follow-up period

Follow-up duration	No.	Mean ($)	Median ($)	Range ($)
Hospital discharge	53	17,250	10,202	468-65,725
3 to <6 months	40	10,216	8,312	763-25,611
6 to <12 months	22	16,973	17,195	7,473-25,341
12 months	48	28,525	19,635	7,342-146,149
More than 12 months	2	36,213	36,213	25,509-46,516

Other potential reasons for the variation in costs were examined. Results showed that costs were significantly higher if charges were used to value resource use rather than unit costs ($27,835 vs. $16,102, p<0.0001). Factors which did not influence

costs were the type of stroke included (i.e. overall stroke or ischaemic), study design used (i.e. prospective, retrospective or RCT) and the number of cost categories included, although the inclusion of productivity costs did generate significantly higher costs ($24,341 vs. $18,600, p=0.016).

The main reason for differences in costs estimates was the country in which the study was undertaken (p<0.0001). Even after taking into account the impact of price differentials average costs varied ten fold from $2,822 in Eastern Europe to $22,377 in the UK and $28,253 in the USA (**Table 3.4**). Large differences in costs were also found within a same country. For the USA, for which 53 estimates of stroke costs were identified, costs ranged from $7,309 to $146,149.

Table 3.4 Cost of stroke in 71 studies by geographic location

Geographic region	No.	Mean ($)	Median ($)	Range ($)
Eastern Europe	13	2,822	1,865	468-11,523
Western Europe	40	9,438	7,437	1,448-25,909
Sweden	14	24,548	24,984	7,413-54,157
UK	27	22,377	15,720	5,026-107,860
Japan	6	12,883	8,901	8,266-22,566
USA	53	28,253	21,006	7,309-146,149
Other (New Zealand, Australia, Canada)	12	16,762	14,229	7,473-44,874

3.4 DISCUSSION

This chapter reviews the results of studies estimating the costs of cerebrovascular events using an incident-based approach, in which the costs incurred from event onset to end of follow-up or death, are estimated for each patient. The results of this chapter support the findings of existing reviews.[158;165-171]

Despite efforts to make studies as comparable as possible, results from this chapter showed that the published costs of stroke varied considerably, with average costs ranging from $468 to $146,149. The review identified a ten fold difference between stroke costs in Eastern Europe and those in the UK or the USA. Such big differences between countries were also found in studies who evaluated the costs of stroke in different countries using the same methodology and patient inclusion criteria.[176;185-190] For example, the study by Grieve et al. (2001)[188] found wide differences in the average costs of stroke between 10 European countries after adjusting for casemix and event severity, ranging from $763 in Latvia to $9,662 in Denmark (costs adjusted to 2006 prices). Such differences in average costs were explained by differences in average hospital length of stay, which ranged from 8.3 days in Spain to over 30 days in Finland and London, unit costs, and level of care provided once patient was discharged from hospital.

However, large differences in costs were also found within a same country. For the USA the difference between the highest and lowest published estimate varied twenty-fold. Results from this review found that length of follow-up, use of charges to price resource use, inclusion of productivity costs and study nationality all significantly increased costs. In addition, as shown in **Appendix 10.1** the different study methodologies and patient samples (e.g. different casemix and event severity) used could have explained the wide differences in average costs observed.

Such variations in the published costs of stroke will have an impact on the results of economic evaluations assessing the cost-effectiveness of stroke interventions. For example, when assessing the cost-effectiveness of new interventions to prevent

stroke, the higher the costs of stroke the more likely the intervention is to be cost-effective. This could potentially result in the selective quotation of costs in secondary health economic analyses, with authors including those costs that are more likely to produce the desired results. Furthermore, such variations in results, which might be perceived as a lack of reliable evidence, might hamper the effective provision of services and treatment.[191] In order to ascertain the validity of costing studies of cerebrovascular events and to make results more comparable across studies, this review set out a number of criteria that studies should ideally fulfil.

Results from this chapter showed that the costing methodologies of the included studies were of adequate quality, partly explained by the fact that since the mid-1990s journals such as the British Medical Journal and the Journal of the American Medical Association have incorporated guidelines that health economic studies must fulfil. Although studies generally reported the time horizon (n=115, 96%), this was generally short. Only 8 studies estimated the costs for a cerebrovascular event over a period of more than one year, with two of these appropriately discounting future costs. The rationale for discounting is that, in economic terms, benefits and costs accruing over the long term should be given less weight than those occurring in the near future as individuals generally prefer to receive benefits sooner and incur costs in the future.[83] Furthermore, of the 71 studies reporting mean stroke costs, only 2 studies used long-term follow-up periods, none of which discounted costs incurred after the first year. These short time horizons might explain why, for those studies including multiple cost categories, 65% of overall stroke costs were due to initial hospitalisation costs alone.

The second criterion assessed was the use of a study sample which was representative of the overall population, with the use of a population-based study being set as the gold-standard. Only 5 (4%) studies were found to be population-based, with the rest of studies including only hospitalised patients, which are easier to identify, or patients included in a clinical trial, which could have strict eligibility criteria. In countries with relatively low hospitalisation rates after stroke, such as the UK, the use of population-based studies to determine accurate and reliable cost data after a cerebrovascular event will be particularly important. For example, in the UK only 62% of strokes are hospitalised,[173] compared with 85% in Australia.[46]

Studies were assessed to identify if costs were directly attributable or associated to the cerebrovascular event. Only a minority of studies fulfilled this criterion by 1) comparing the costs of cerebrovascular patients to those with no cerebrovascular history; 2) only including the direct costs of the events under investigation; or 3) comparing previous resource use to that after the event. It could be argued that studies only including the costs that were directly attributable to the event, might not include all the costs associated with the disease. For example, female stroke patients are more likely to fracture their hip than those without stroke.[192] In the majority of studies no explicit explanation was given as to the nature of costs included (i.e. all-cause or event-related), with the implicit understanding that all-cause resource use was included. This makes the impact of disease on costs difficult to determine, as a proportion of these costs could be incurred by the presence of other co-morbidities.[175;177] Finally, studies were assessed as to whether cost data were reported by patient subgroups. As results from population based studies have shown, costs of cerebrovascular events can vary widely in terms of clinical and

demographic characteristics.[193;194] However, only a minority of studies presented results by different patient groups or undertook multivariate analyses.

Several limitations to this literature review should be noted. Results from some eligible studies were excluded as these were not published in English. This might have biased the results of the review, as studies in non-English speaking countries generally reported lower costs than those based in the UK or the USA. Although efforts were made to make the published costs of stroke more comparable and to evaluate the causes for the variation in published costs, other important characteristics, such as stroke severity or service configuration, where not taken into account as these were not reported in many of the studies. As a result, the influence of these potential confounders might make the results of the univariate analyses performed in this chapter imprecise.

3.5 CONCLUSION

In this chapter the costs of cerebrovascular events, as reported by studies including patient-level data, were reviewed. Data on the costs of stroke and TIA were provided by a substantial number of studies. However, the review showed large variations in the populations and samples studied, methods, and costs included that limit comparability between studies. The review highlighted the lack of cost data derived from population-based studies, which as discussed in this chapter are the most accurate sources of information on disease incidence, mortality and outcome, and therefore costs.

In the following chapters of this thesis the costs incurred after a cerebrovascular event will be estimated using data from the Oxford Vascular (OXVASC), a population-based study undertaken in Oxfordshire, UK, details of which are presented in the next chapter.

CHAPTER 4

THE OXFORD VASCULAR STUDY (OXVASC)

4.1 INTRODUCTION

Over the previous chapters it has been discussed that population-based studies with full case ascertainment are the most accurate sources of information on disease incidence, mortality, outcome and costs. As seen in both **Chapters 2** and **3**, no population-based study in the UK has assessed the quality of life or costs associated with stroke and/or transient ischaemic attack (TIA). As a result, there is no study within a UK setting reporting estimates of costs and outcomes of stroke and TIA patients with an unselected patient sample.

The main objectives of this thesis are to estimate accurately the costs and quality of life associated with stroke and TIA using data from an unselected study sample, and to explore the variables that influence or predict them. In order to do this, the resource use and outcome data of patients identified in the Oxford Vascular Study (OXVASC) will be used. This chapter presents an overview of OXVASC, the rationale and background of this study, and details on the OXVASC study sample that will be included in the analysis of costs and outcomes. A summary is also given at the end of the chapter of the main published clinical findings based on OXVASC.

4.2 THE OXFORD VASCULAR STUDY (OXVASC)

4.2.1 BACKGROUND

The main reason for basing OXVASC in Oxfordshire was that previous population-based incidence studies of TIA and acute stroke had been undertaken from 1981 to

1986 through the Oxford Community Stroke Project (OCSP),[195;196] as well as acute myocardial infarction in the mid 1990s through the Oxford Myocardial Infarction Study (OXMIS).[197] As a result, by using the same case definition and methods of ascertainment as in these two studies, the time trends in incidence, case fatality, disability rates, and risks of recurrences could be evaluated.

OXVASC is funded from a variety of sources, including the UK Medical Research Council, the Dunhill Medical Trust, the Stroke Association, the BUPA foundation, the UK National Institute for Health Research, and the Thames Valley Primary Care Partnership.

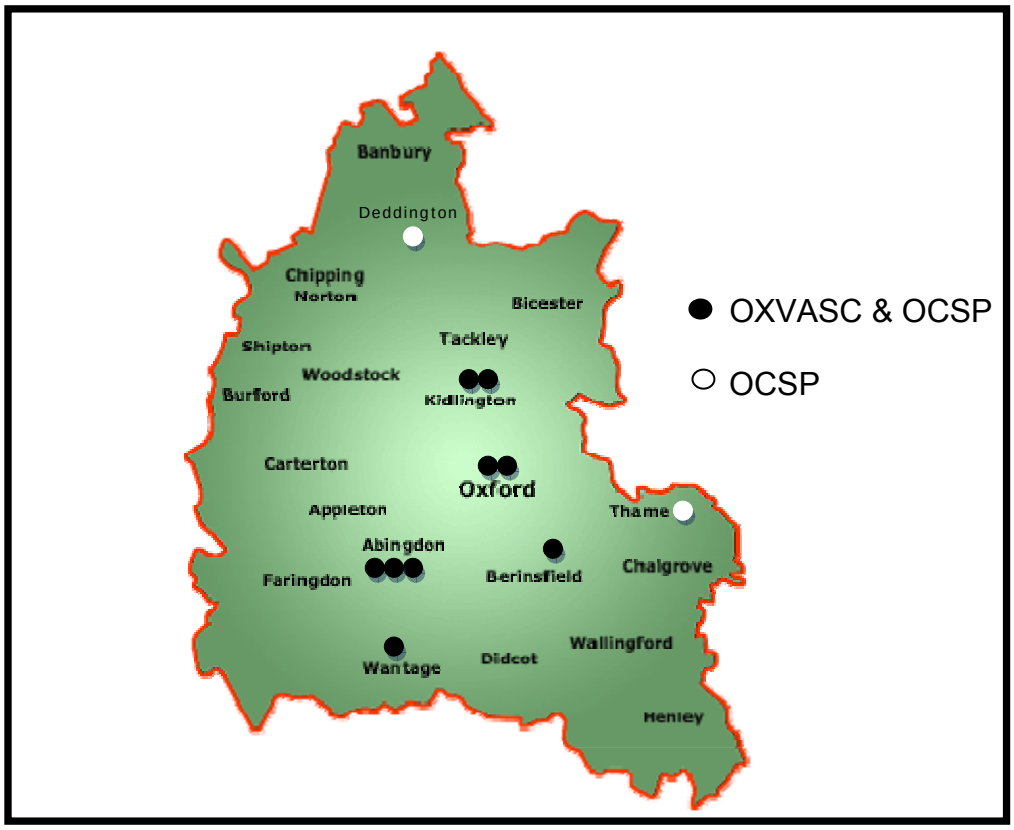

Figure 4.1 OCSP and OXVASC collaborating general practices

OXVASC includes 9 general practices that were involved in both OCSP and OXMIS. Details of these general practices are provided in **Appendix 11**. The collaborating practices were chosen if they: a) had an accurate computerised age-sex register (ASR); b) were willing to refer any patient with a suspected acute cerebrovascular event and; c) were computerised allowing searches for cerebrovascular diagnostic codes. For practical reasons OXVASC was limited to using general practices that referred to the Oxford Radcliffe NHS Trust Hospitals (ORH NHS Trust) including the John Radcliffe, the Radcliffe Infirmary and the Churchill Hospital. As a result two practices (Thame and Deddington) that were involved in OCSP were excluded (**Figure 4.1**).

4.2.2 STUDY POPULATION

The population comprised 91,161 patients (using the average population between 2002 and 2007) who were fully registered with 63 general practitioners (GPs) based in 9 general practices across Oxfordshire.

All patients in whom an acute vascular event (i.e. acute coronary, cerebrovascular, and peripheral vascular event) was suspected were considered for inclusion in OXVASC, with registration of patients beginning on 1st April 2002 and continuing to date. This thesis will, however, only include those patients who were ascertained as having a TIA and/or stroke. Patients who had a vascular event whilst temporarily away from Oxfordshire were included, but visitors who were not normally resident and registered with a GP were excluded.

Stroke and TIA were defined in OXVASC using the standard definitions reported in **Chapter 1**. In fatal cases without clinical assessment the diagnosis of stroke was made only if there was clear autopsy evidence of recent acute infarction, or intracerebral or subarachnoid haemorrhage as the primary cause of death. In the event of any non-autopsied suspected stroke death, all available records were reviewed and the registered GP was approached to try to confirm or exclude the diagnosis.

For TIA and minor stroke not requiring hospital admission, collaborating GPs notified the OXVASC of any patient whom they thought may have had an episode of acute neurological dysfunction caused by cerebrovascular disease. In addition, patients were ascertained using a combination of prospective daily searches for acute events (hot pursuit) and retrospective searches of hospital-care and primary-care administrative and diagnostic coding data (cold pursuit). Hot pursuit was based on the following:

1. Daily searches of emergency department admission and symptom or diagnosis registers;
2. Daily administrative listing of all admissions for all patients registered in the 9 general practices included in the study;
3. Daily visits to the acute medical admissions unit, coronary care unit, cardiology ward, acute stroke unit, and vascular surgery ward, as well as neurology and cardiothoracic surgery wards;
4. Daily identification via bereavement officers of patients who were dead on hospital arrival or who died soon after;

5. Review of outpatient clinics for patients with TIA and stroke not needing immediate admission; and
6. Daily assessment of all patients undergoing diagnostic angiography, angioplasty, or stenting in any territory to identify previous acute events.

Cold pursuit procedures were:

1. Monthly searches of general practice diagnostic codes relating to NHS or private care;
2. Monthly practice-specific listings of all patients admitted to all acute and community NHS hospitals;
3. Monthly listings of all referrals for brain or cerebrovascular imaging;
4. Monthly visits to the coroner's office;
5. Review of all death certificates in the study's general practices; and
6. Practice-specific listings of all ICD-10 death codes registered centrally.

The direct methods to determine the completeness of these different ascertainment strategies for stroke were investigated during the first year of OXVASC using two direct assessment methods.[198] In order to identify those patients that had not been notified to the study but who had presented to medical attention, anonymised primary care electronic patient records were accessed. Secondly, in order to estimate the number of individuals who had had a stroke but who had not presented to medical attention, a subset of the population considered to be at high risk for stroke (i.e. patients with an acute coronary or peripheral vascular event) were interviewed and followed-up. Using the hot and cold pursuit methods of ascertainment, as well as the two direct assessment methods, a total of 128 incident

strokes were identified. In comparison, using the hot and cold pursuit methods only, a total of 126 (98%) incident strokes were identified, suggesting that the ascertainment methods used in OXVASC are near complete.[199]

4.2.3 INITIAL MEDICAL ASSESSMENT

All suspected TIA and stroke patients were assessed by a study clinician as soon as possible after index event either in a hospital ward, in a daily dedicated clinic, or at home. Informed formal written patient consent was sought, and if this was not possible assent from a relative was obtained. At assessment, detailed data were collected, which included information on:

History and timing of presentation

When a suspected case was identified the source of such identification was recorded together with the date on which the case was identified, with all subsequent methods of case finding also being recorded. Records were also taken of any pre-existing disability, the speed of onset, any specific triggers or other associated symptoms.

Past medical history

Previous acute vascular events were recorded to assess whether the presenting event was first-in-a-lifetime or recurrent. Any history of previous TIA or stroke, including dates, duration and vascular territory of TIAs and strokes were judged from patient history and medical record.

Vascular risk factors

Vascular risk factors were recorded as present if known to patient or recorded in GP or hospital notes. Risk factor data collected were:

- Hypertension: Recorded if the patient or the medical record gave a history of persistent hypertension for which the patient had been treated either with lifestyle or pharmaceutical management;
- Diabetes: History of diabetes was recorded including age at diagnosis, type of diabetes and treatment used;
- Hyperlipidaemia: Regarded as present if the patient or the medical records showed any evidence that the patient had been given lifestyle advice or drug management for lipid lowering. Pre-morbid blood pressures and cholesterol measurements were also collected;
- Smoking: Cigarette, pipe and cigar smoking were recorded. For current smokers, the number of cigarettes (ounces, if “roll-ups”) smoked in a day together with the number of years smoked was recorded. For ex-smokers, the calendar year when the patient gave up smoking and the number of years smoked was recorded; and
- Other risk factors: Including atrial fibrillation (whether paroxsymal, persistent or permanent), clinical diagnosis of heart failure, and familial history of vascular events.

Medication usage

The names of all medications the patient was taking on a regular basis up to the time the event began were recorded. Medication use was derived either from patient self-report or GP notes.

Independence prior to the index event

Independence was measured by the modified Rankin scale (mRS).[200] The scale, measures independence rather than being task oriented and gives a good impression of self-care (**Appendix 12**). It ranges from 0 (no symptoms at all) to 5 (severe disability), with 6 representing death.

Neurological assessment

Patients with TIA and stroke were given a thorough neurological examination using the National Institute of Health Stroke Scale (NIHSS).[201] The NIHSS is a 15-item scale covering level of consciousness, pupillary response, gaze, visual loss, facial palsy, motor-arm, motor-leg, plantar reflex, limb ataxia, sensory loss, neglect, dysarthria, and language. It is observer rated, with items having 3- or 4-point response scales, scored 0 to 3 (with 0 being normal).

The scale is scored from 0 up to a maximum of 42, with 0 being no neurological deficit. For the purposes of this thesis, cerebrovascular event severity is coded as minor for NIHSS scores lower than 3, moderate for NIHSS scores between 3 and 10, severe for NIHSS scores between 11 and 20, and very severe for NIHSS scores above 20.

Social history

Information was gathered on place of residence, if the patient lived accompanied, and if so by whom, most recent occupation, socioeconomic class, ethnic origin, age when left full time education, and deprivation. Socio-economic class was coded using the Standard Occupational Classification Scheme, based on most recent occupation.[202] If retired, the patients' last job was recorded. In the case of a child or

a spouse who did not work the occupation of the parent or partner was taken. Deprivation was measured by post-code of residence using the index of multiple deprivation (IMD),[203] which contains information on access to services and housing, education, employment, health, housing and income.

4.2.4 CEREBROVASCULAR EVENT DIAGNOSIS

TIA and stroke cases were classified by two study physicians. Details of all potential strokes were also reviewed regularly by two consultant neurologists and a consultant neuroradiologist. To ensure accurate classification, all stroke cases had a full clinical assessment, electrocardiogram (ECG), and carotid Doppler, with echocardiography being carried out if clinically appropriate. To differentiate between ischaemic and haemorrhagic strokes, patients underwent brain imaging using either computed tomography (CT) and/or magnetic resonance imaging (MRI), results of which were reported and coded by a consultant neuroradiologist. For fatal cases, post-mortem reports were obtained and reviewed.

4.2.5 FOLLOW-UP OF CEREBROVASCULAR EVENT PATIENTS

The objective of follow-up was to assess clinical, functional and psychological outcomes, identify reasons for failure to utilise effective strategies for secondary prevention, and screen for recurrent vascular events. Follow-up of TIA and stroke patients, which was carried out by a study research nurse, took place at 1, 6 and 12 months, and then at 2 and 5 years after their index event. However, as the maximum follow-up of patients for this thesis was 5 years post index event the vast majority of patients had not reached this follow-up. Therefore, information from the 5-year follow-up was not considered.

Patients were invited to attend a follow-up hospital clinic at the Radcliffe Infirmary, Oxford, for their follow-up at 1, 6 and 12 months, and at 2 years. For patients who were still hospitalised during their follow-up, or who were unable to attend the clinic appointment due to health or mobility problems, a research nurse visited them either at hospital or at home. In some instances, when either a home, hospital or clinic visit was not possible, the patient was offered follow-up via the telephone.

At follow-up, patients were screened for recurrent vascular events, with any patient considered to have had a recurrent event being reassessed by a study physician. In addition, detailed data were collected, which included information on:

- Location and type of follow-up, which included information on where the follow-up took place;
- Independence, which was measured using the mRS;
- Medication usage, with the names of all medications the patient was currently taking on a regular basis being recorded;
- Living arrangements, i.e. place of residence at time of follow-up;
- Qualify of life, which was measured using the Euroqol-5D (EQ-5D) and Euroqol-visual analogue scale (EQ-VAS). The Euroqol was used to measure quality of life as it is considered to be the most appropriate choice in England when measuring quality of life.[73] In addition, during the first year of OXVASC (i.e. patients recruited between 1 April 2002 and 31 March 2003), patients were asked to recall their quality of life before their index event using the EQ-5D. Unfortunately, until February 2004 (i.e. 18 months after the beginning of OXVASC) information on quality of life was not assessed at the 6 month follow-up; and

- Changes in risk factors, such as smoking status and blood pressure readings.

4.3 STUDY SAMPLE

As reported earlier, OXVASC started recruiting patients on 1 April 2002 and is ongoing. For the purposes of this thesis, all cerebrovascular event patients recruited between 1 April 2002 and 31 March 2007 (the first 5 complete years of OXVASC) were included in all the analyses. Patients were followed-up until 30 April 2007, with a minimum follow-up of 1 month and maximum follow-up of 5 years and 1 month.

Of a population of 91,161 individuals, 1,282 patients were ascertained as having suffered a cerebrovascular event. Of these, 83 (7%) patients, or their relatives in their behalf, refused consent to the study, and were not included in any of the analyses, with the remaining 1,199 patients forming part of the final study sample.

Table 4.1 Baseline characteristics for patients refusing/not refusing consent

	Refused study (n=83)	Consent (n=1199)	p>z
Mean age (S.D.)	79 (1.2)	74 (0.4)	<0.001
Event type, n (%)			0.001
TIA	18 (4)	476 (96)	
Stroke	65 (8)	723 (92)	
Gender, (n%)			0.025
Male	29 (5)	571 (95)	
Female	54 (8)	628 (92)	
GP surgery, n (%)			0.012
Beaumont St.	9 (11)	73 (89)	
Berinsfield	8 (9)	85 (91)	
East Oxford	12 (15)	66 (85)	
Exeter St.	2 (3)	58 (97)	
Kidlington & Yarnton	3 (4)	79 (96)	
Malthouse	18 (5)	359 (95)	
Marcham	6 (4)	146 (96)	
Stert St.	9 (6)	136 (94)	
Wantage	16 (8)	197 (92)	

As shown in **Table 4.1**, patients who refused consent into the study were significantly more likely to be females (p=0.025), older (p<0.001), and have suffered a stroke (p=0.001). There were also significant differences in consent rates between the 9 study practices (p=0.012), with consent rates varying between 85% and 97%.

4.3.1 EVENT CHARACTERISTICS

Of the 1,199 included patients, a total of 723 (60%) suffered a stroke as the index event during the study period, with the remaining 476 (40%) suffering a TIA. The most common types of strokes were ischaemic strokes, with a total of 590 patients (82% of strokes) suffering one, followed by intracerebral haemorrhages (ICH - 7%) and subarachnoid haemorrhages (SAH – 5%). For 45 (6% of strokes) patients their stroke was undetermined (**Table 4.2**).

Table 4.2 Event characteristics

	All events (n=1199)	TIA (n=476)	Stroke (n=723)
Stroke type, n (%)			
Ischaemic stroke	590 (49)	N/A	590 (82)
ICH	51 (4)	N/A	51 (7)
SAH	37 (3)	N/A	37 (5)
Unknown stroke	45 (4)	N/A	45 (6)
Probability of event			
Definite	951 (79)	328 (69)	623 (86)
Probable	88 (7)	54 (11)	34 (5)
Possible – pragmatically treated	127 (11)	91 (19)	36 (5)
Not coded	33 (3)	3 (1)	30 (4)
NIHSS score, mean (S.D.)	3.0 (5.8)	0.1 (0.7)	5.0 (6.9)
<3, n (%)	781 (65)	466 (98)	315 (44)
3 to 10	260 (22)	9 (2)	251 (35)
11 to 20	75 (6)	0	75 (10)
>20	31 (3)	0	31 (4)
Missing	52 (4)	1 (0.2)	51 (7)

Cerebrovascular events were either classified as definite, probable or pragmatically treated. Definite events were those with a very clear clinical history, where the clinician had no doubt whatsoever. Probable events were those very likely to be cerebrovascular, but where the diagnosis of stroke or TIA was purely clinical, and therefore might occasionally be wrong. Possible - pragmatically treated events were those treated as stroke or TIA on the basis that there was no other obvious diagnosis.

A total of 951 (79%) events were classified as definite, with more strokes being classed in this group than TIAs (86% vs. 69%). Of those events that were pragmatically treated (n=127, 11%) due to the possibility of having suffered a cerebrovascular event, more TIAs were classed in this way than strokes (19% vs. 5%, respectively). 33 (3%) events were not coded (1% of TIAs and 4% of strokes).

Initial severity of event was measured by the neurological impairment as determined by the NIHSS during first clinical assessment. NIHSS scores were determined for 1,147 (96%) patients (**Table 4.2**). Initial severity was significantly higher for strokes than for TIA (mean NIHSS 5.0 vs. 0.1, respectively, $p<0.001$), with no TIA patient having an NIHSS score above 10, as opposed to stroke patients, with 106 (15%) having scores above 10, of which 31 (4%) had scores above 20.

4.3.2 PATIENT DEMOGRAPHICS

The mean age of the study sample was 74 years, with the majority of patients being aged 75 years or over (**Table 4.3**). Overall, there were slightly more women than

men (52% vs. 48%, respectively) in the study sample. However, approximately the same number of males and females suffered a stroke as their index event.

Table 4.3 Patient demographics

	All events (n=1199)	TIA (n=476)	Stroke (n=723)
Mean age (S.D.)	74 (13)	73 (13)	75 (13)
<65, n (%)	264 (22)	115 (24)	149 (21)
65 to 74	283 (24)	125 (26)	158 (22)
≥ 75	652 (54)	236 (50)	416 (58)
Gender, n (%)			
Male	571 (48)	206 (43)	365 (50)
Female	628 (52)	270 (57)	358 (50)
GP practices, n (%)			
Beaumont St.	73 (6)	35 (7)	38 (5)
Berinsfield	85 (7)	36 (8)	49 (7)
East Oxford	66 (6)	24 (5)	42 (6)
Exeter St.	58 (5)	24 (5)	34 (5)
Kidlington & Yarnton	79 (7)	29 (6)	50 (7)
Malthouse	359 (30)	135 (28)	224 (31)
Marcham	146 (12)	63 (13)	83 (11)
Stert St.	136 (11)	50 (11)	86 (12)
Wantage	197 (17)	80 (17)	117 (16)

The practices with the largest number of patients registered with them, such as the Malthouse (Abingdon) and the practice in Wantage, provided most patients to the study (30% and 17%, respectively), whilst the smallest practices, such as the two in Kidlington, provided between 5% and 7% of the study population each (**Table 4.3**).

Figure 4.2 shows how the 1,199 index cerebrovascular events occurring between April 2002 and March 2007 were distributed amongst the first 5 years of OXVASC. The highest number of index cerebrovascular events occurred during the first year of OXVASC (n=271, 23%), whilst the lowest was during the fifth year of OXVASC, with a total of 212 (18%) events.

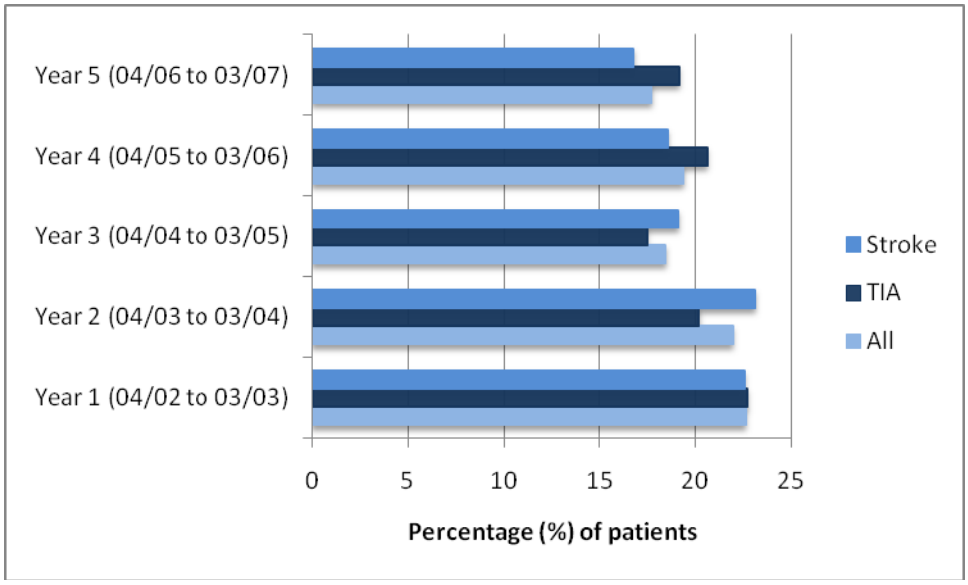

Figure 4.2 Distribution of events during the first 5 years of OXVASC

4.3.3 PREVIOUS HISTORY OF DISEASE AND DISABILITY

Stroke patients generally had higher morbidity rates than TIA patients (**Table 4.4**), with more stroke patients having histories of myocardial infarction (MI - p=0.076), stroke (p<0.001), peripheral vascular disease (PVD – p=0.025), hypertension (p=0.003), and atrial fibrillation (p=0.038) than TIA patients.

Table 4.4 History of disease and disability

History, n (%)	All events (n=1199)	TIA (n=476)	Stroke (n=723)
MI†	149 (12)	50 (10)	99 (14)
TIA†	169 (14)	90 (19)	79 (11)
Stroke†	187 (16)	54 (11)	133 (18)
PVD†	102 (9)	30 (6)	72 (10)
Angina†	191 (16)	73 (15)	118 (16)
Hypertension†	687 (57)	249 (52)	438 (61)
Atrial fibrillation†	212 (18)	71 (15)	141 (20)
Diabetes†	140 (12)	65 (13)	75 (10)
Disability (mRS>2)‡	191 (16)	66 (14)	125 (17)
Smoking status*			
Never	537 (45)	217 (45)	320 (44)
Ex-smoker	498 (42)	195 (41)	303 (42)
Current smoker	153 (13)	62 (13)	91 (13)

†Missing: All 7; TIA 1; Stroke 6, ‡Missing: All 88; TIA 17; Stroke 71, *Missing: All 11; TIA 2; Stroke 9

Furthermore, stroke patients were more likely to be disabled (as determined by mRS of 3 or more) than TIA patients (17% vs. 14%, respectively, p=0.037). TIA patients, on the other hand were more likely to have had a previous TIA than stroke patients (p<0.001). However, there were no significant differences between TIA and stroke patients in terms of history of angina, diabetes, or smoking status.

4.3.4 SOCIO-ECONOMIC CHARACTERISTICS

The great majority of patients (79%) lived in their own homes before their index event, with patients generally living with someone else (**Table 4.5**). Approximately half of all patients (48%) were married, with a sizeable proportion of the study sample being widowed (30%). The ethnicity of the study sample was not tabulated as the vast majority of patients were white (97%), with the other main ethnic groups being Black Caribbean, Pakistani and Indian (1%, 0.7% and 0.6%, respectively).

Due to the advanced age of the sample (mean age 74 years, **Table 4.3**), the majority of patients were retired (67%) and only 145 (12%) patients were still in full-time employment at the time of their event (**Table 4.5**). In terms of socioeconomic status, the majority of patients were classified in the middle groups (i.e. II, 3M and 3N) with approximately 60% of patients being in these three socioeconomic groups. Patients were also assigned into one of five quintiles representing the distribution of areas in England and Wales in terms of deprivation. The greatest proportion of patients lived in the least deprived areas of England and Wales, with 45% of patients living in areas in the fifth quintile, and a further 28% in the fourth quintile. By contrast, only 16 (1%) patients lived in the most deprived of areas (**Table 4.5**). Except for deprivation,

for which there was no missing data, for all other socioeconomic characteristics approximately 10% of all the data were missing (7% for TIA patients and 12% to 13% for stroke patients).

Table 4.5 Social history

Social history†	All events (n=1199)	TIA (n=476)	Stroke (n=723)
Place of residence			
Own home	948 (79)	397 (83)	551 (76)
Friends/relatives	28 (2)	7 (1)	21 (3)
Warden housing	53 (4)	17 (4)	36 (5)
Care home	32 (3)	12 (3)	20 (3)
Other (convent…)	10 (1)	4 (1)	6 (1)
Missing	128 (11)	39 (8)	89 (12)
Live alone‡	355 (30)	129 (27)	226 (31)
Marital status			
Married	575 (48)	243 (51)	332 (46)
Widowed	363 (30)	134 (28)	229 (32)
Single	57 (5)	25 (5)	32 (4)
Separated	59 (5)	31 (7)	28 (4)
Partnered	24 (2)	12 (3)	12 (2)
Missing	121 (10)	31 (7)	90 (12)
Employment status			
Full time	145 (12)	58 (12)	87 (12)
Part time	70 (6)	37 (8)	33 (5)
Caring for home	19 (2)	8 (2)	11 (2)
Unemployed	16 (1)	4 (1)	12 (2)
Unable to work	24 (2)	9 (2)	15 (2)
Retired	804 (67)	328 (69)	476 (66)
Student	3 (0.3)	2 (0.4)	1 (0.1)
Missing	118 (10)	30 (7)	88 (12)
Socio-economic class			
Professional (I)	93 (8)	43 (9)	50 (7)
Managerial (II)	235 (20)	116 (24)	119 (16)
Skilled non-manual (3N)	254 (21)	88 (18)	166 (23)
Skilled manual (3M)	204 (17)	90 (19)	114 (16)
Partly skilled (IV)	123 (10)	50 (11)	73 (10)
Non-skilled (V)	139 (12)	54 (11)	85 (12)
Armed forces	8 (1)	5 (1)	3 (0.4)
Missing	143 (12)	30 (6)	113 (16)
Age left education, mean (SD)*	16 (4)	17 (4)	16 (4)
Deprivation, IMD score (SD)	9.6 (6.5)	9.3 (6.1)	9.8 (6.7)
Quintile 1 (most deprived)	16 (1)	4 (1)	12 (2)
Quintile 2	63 (5)	22 (5)	41 (6)
Quintile 3	242 (20)	91 (19)	151 (21)
Quintile 4	337 (28)	143 (30)	194 (27)
Quintile 5 (least deprived)	541 (45)	216 (46)	325 (45)

†Reported as n (%), unless otherwise stated
‡Missing: All 117; TIA 34; Stroke 83
*Missing: All 135; TIA 29; Stroke 106

4.4 PUBLISHED RESULTS FROM OXVASC

Results based on OXVASC have been published widely.[174;204-207] These have covered the incidence of different acute vascular events, changes in stroke incidence rates over time, and the risk of early stroke recurrence, with a summary of the key clinical findings being given below.

4.4.1 INCIDENCE AND CASE-FATALITY OF VASCULAR EVENTS

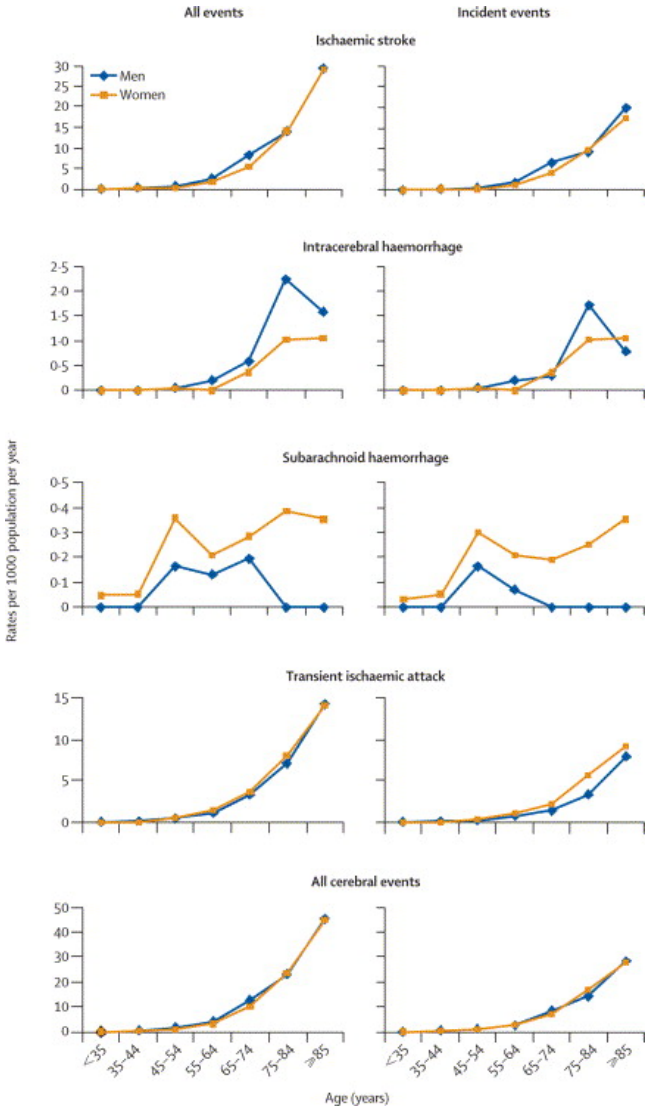

Figure 4.3 Age-specific rates of all events and incident events

Figure derived from Rothwell et al. (2005)[174]

Based on patients recruited between April 2002 and March 2005 the burden of all acute cardiovascular events was measured by prospectively studying event rates, incidence and 30-day case fatality rates of all acute symptomatic arterial vascular events.[174] The authors identified 2,024 acute vascular events occurring in 1,657 individuals, of which, 918 (45%) were cerebrovascular (618 stroke, 300 TIA), 856 (42%) were coronary vascular, 188 (9%) were peripheral vascular, and 62 were unclassifiable deaths. For all vascular events, except SAH, both event and incidence rates rose steeply with age (**Figure 4.3** shows rates for cerebrovascular events).

In terms of 30-day case fatality, no differences between event types were observed, after adjusting for age and gender. Case-fatality, however, rose steeply for all events after the age of 65 ($p<0.001$, see **Figure 4.4**, which did not include TIA case-fatality as it was very low).

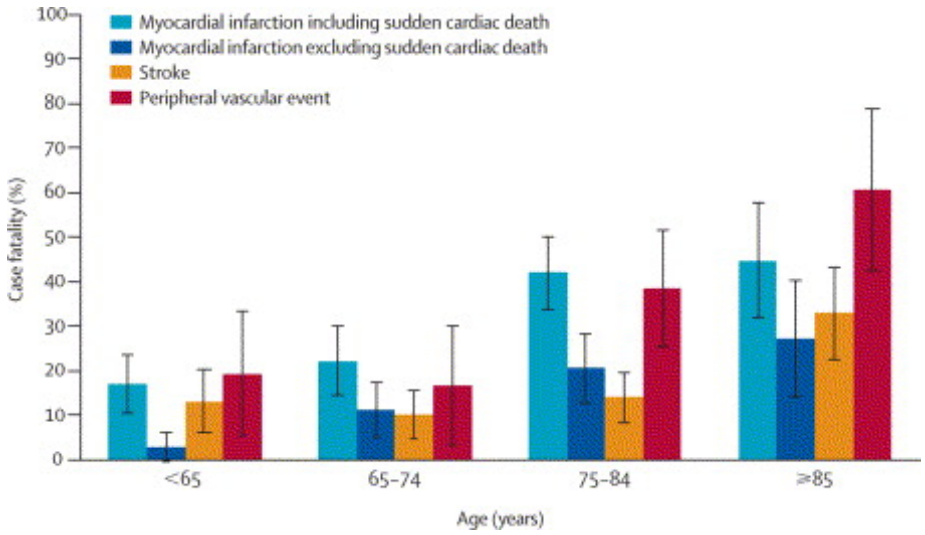

Figure 4.4 30-day case-fatality rates

Derived from Rothwell et al. (2005). Error bars indicate 95% CIs.

The study conclusions indicated the fact that the steep rise in event rates with age for all event types had implications for prevention strategy. Rothwell et al. (2005)[174] also highlighted that their results had shown that acute cerebrovascular events were at least as frequent as acute coronary events.

4.4.2 CHANGES IN STROKE INCIDENCE

To ascertain changes in incidence of TIA and stroke between 1981-84 and 2002-04, TIA and stroke incidence rates from OCSP (1981-84) and OXVASC (2002-04) were compared using the comparable case-definition and diagnosis.[207] The authors compared the 429 incident strokes and 87 incident TIAs occurring during OCSP with the 262 incident strokes and 93 incident TIAs occurring during the first two years of OXVASC. Results from this study showed, that despite more complete case-ascertainment in OXVASC than in OCSP and a 33% increase in those aged 75 or older in OXVASC, age- and gender-adjusted incidence of first-ever stroke fell by 29% ($p<0.001$ – **Figure 4.5**), with major reductions in incidence also found for non-minor strokes.

The authors also observed that reductions in the incidence of first-ever strokes were accompanied by significant reductions in premorbid risk factors including smoking, mean total cholesterol, and mean systolic and diastolic blood pressures, with major increases in premorbid treatment with antiplatelet, lipid lowering, and blood pressure lowering drugs (all $p<0.001$).

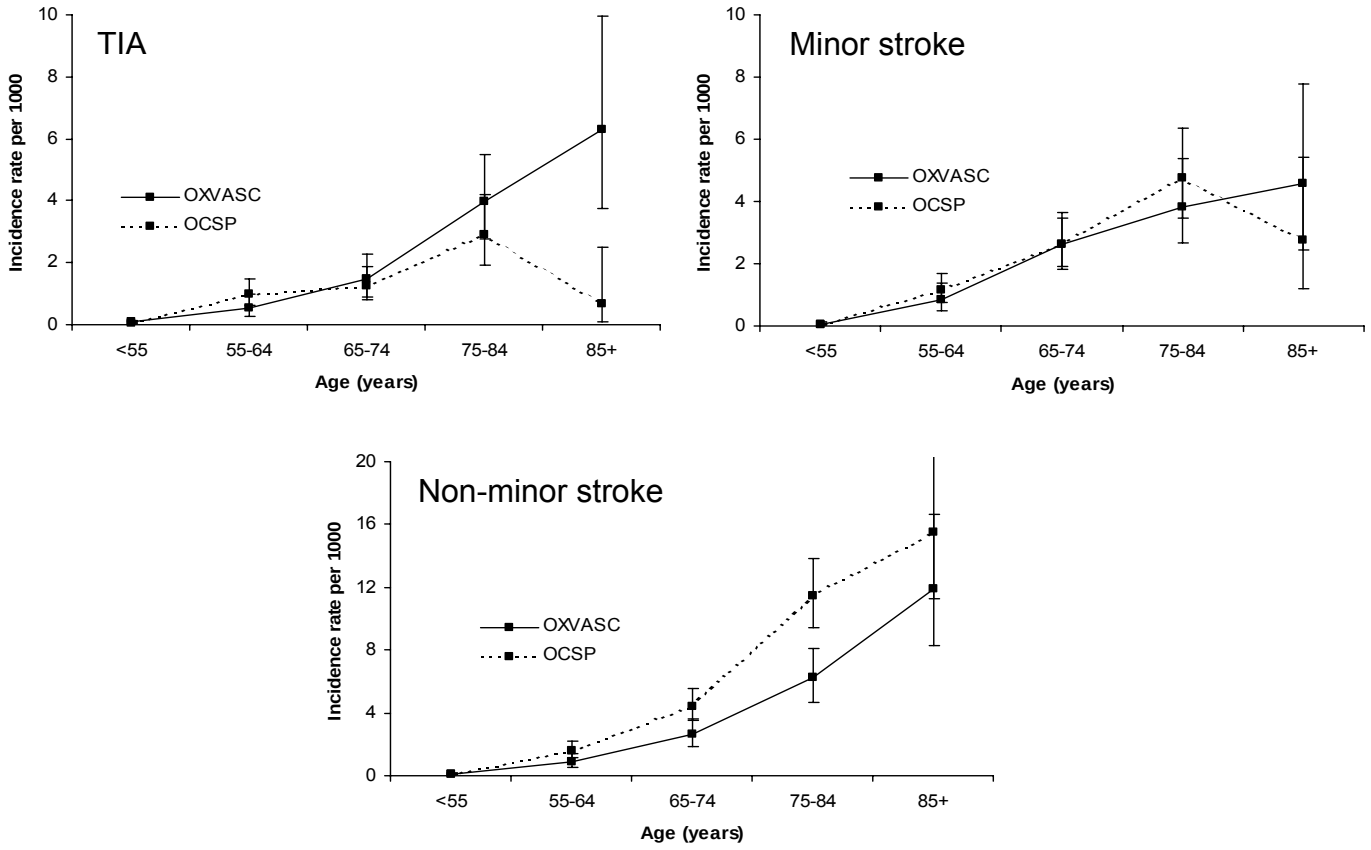

Figure 4.5 Age-specific incidence of TIA, minor stroke and non-minor stroke

Derived from Rothwell et al. (2004).[207] Error bars indicate 95% CIs.

4.5 DISCUSSION

The Oxford Vascular study (OXVASC) is the first ever study of the incidence, risk factors and outcome of all acute vascular events in the same population comprising over 91,000 individuals registered in 9 general practices throughout Oxfordshire. With multiple and overlapping methods of case ascertainment, ascertainment of cerebrovascular events in the OXVASC population has been shown to be virtually complete. This provides both a large study sample and a non-biased representative sample of TIA and strokes in the population. With 1,282 first-ever in the study period TIAs or stroke (i.e. 1 April 2002 to 31 March 2007), a total of 83 patients refused to participate in OXVASC. Although patients refusing consent were different from those

agreeing to participate in the study (they were significantly more likely to be females, older, suffered a stroke, as well as registered in different GP practices) the refusal rate was very low (6.5%), and as such does not make the final sample of 1,199 patients unrepresentative of the study population.

In addition to the rigorous ascertainment, TIA and stroke patients were rigorously assessed, in most cases, shortly after their index event. This assessment not only covered clinical and risk factor data but also of socio-economic factors. This wealth of baseline characteristics will prove very useful later in this thesis when evaluating the predictors of patient outcomes (**Chapter 5**) and healthcare costs (**Chapter 6**). However, for many of the socioeconomic characteristics, as well as disability before the event, over 10% of the data were missing, with a higher proportion of the data missing for stroke than TIA cases (12% vs. 7%). Reasons for missing data included: inability to undertake a full clinical assessment, especially if patient was aphasic; unwillingness to answer certain questions, e.g. education or current/past employment; ascertainment with considerable delay, making a thorough clinical assessment unpractical (this was the case mainly for patients ascertained by retrospective reviews of the general practices' records); and, finally, for patients whose stroke or TIA was defined as possible, a proportion of them did not receive a thorough clinical assessment. Such missing data will generate issues when analysing the outcome, resource use and cost data over the following chapters, issues which will be covered in **Chapters 5** and **6** of the thesis.

Stroke and TIA patients were also assessed in detail at follow-up. These assessments, which were undertaken regularly during the first year after the index

event, not only screened patients for possible recurrent vascular events but provided detailed data on outcome, including quality of life, disability and functional ability, living arrangements, and medication usage. Such data will form an integral part of **Chapter 5** of this thesis, which will examine the outcomes and quality of life data of patients suffering a TIA or stroke. Furthermore, the medication usage information will allow an examination of changes in medication consumption before and after the index event (**Chapter 6**).

The main limitation of OXVASC, however, is that the population may not be representative of the UK population as whole. As shown earlier, 45% of the study sample lived in areas ranked in the least deprived quintile in England and Wales, with only 6% of the sample living in the two most deprived quintiles. As a result, the OXVASC sample was less socially deprived than in the UK as a whole, and could be considered "too middle class" to make the results generalisable to the rest of the country. However, OXVASC, together with the South London Stroke Register (SLSR),[208] is one of the few studies in the UK assessing the incidence and outcome of stroke and TIA using a population-based study, making its results more generalisable than those from other UK studies, which generally include more severe strokes that require hospitalisation.

4.6 CONCLUSION

This chapter has provided a summary of the background, methods and objectives of OXVASC. The significant strengths of OXVASC have been highlighted, especially its rigorous ascertainment and assessment of cases, as well as the follow-up patients receive, and the low number of patients refusing consent into the study. The chapter

has also summarised the key characteristics of the study sample from which resource use, cost, outcome, and quality of life information will be derived. In particular the event characteristics, risk factors, previous disease history, and socio-economic characteristics of the included patients have all been reported, which has also highlighted the extent of missing data in some of these baseline characteristics. Health outcomes after the index cerebrovascular event for the patients summarised in this chapter are presented in **Chapter 5**, whilst resource use and costs incurred are presented in **Chapter 6**.

CHAPTER 5

HEALTH OUTCOMES AFTER A CEREBROVASCULAR EVENT: EVIDENCE FROM OXVASC

5.1 INTRODUCTION

As previously discussed, population-based studies with full case ascertainment are the gold-standard study design when studying disease incidence and outcomes. In **Chapter 4**, details of the Oxford Vascular study (OXVASC), a large prospective population-based study evaluating the incidence of cerebrovascular events, were presented. As part of the study, OXVASC undertook detailed follow-up of patients, providing an excellent source of data to evaluate health outcomes such as disability and health-related quality of life after a stroke or transient ischaemic attack (TIA).

In **Chapter 2** a meta-analysis of published quality of life estimates after stroke or TIA was presented. The analysis showed that after controlling for methodological differences across studies, event severity was a strong predictor of quality of life. However, the impact of other potentially important determinants, such as comorbidities, age, gender, and socioeconomic characteristics was not assessed, as many studies did not report estimates for these subgroups. Results of this meta-analysis also showed that one-step elicitation techniques yielded significantly higher quality of life values than those derived from two-step multi-attribute utility scales.

Using the OXVASC sample presented in **Chapter 4**, the objective of this chapter is to evaluate the quality of life of patients after a stroke or TIA, and to gain a better knowledge of its baseline predictors. This chapter also evaluates whether the

significant differences observed between quality of life estimates derived from one- and two-step evaluation methods in different studies are observed in the context of a single large study.

In addition, other important health outcomes, which *a-priori*, would also appear to be important determinants of quality of life are evaluated, including the risk of recurrent vascular events, living arrangements after event, and patient disability. In order to generate Quality Adjusted Life-Years (QALYs), the preferred health outcome measure in the UK,[73;82] life expectancy is also evaluated.

5.2 METHODS

5.2.1 OUTCOME MEASURES

The primary outcomes used for this analysis were: 30-day case fatality; life years gained over a 5-year period; 5-year risk of recurrent vascular events, including stroke, TIA, coronary heart disease (CHD) and peripheral vascular disease (PVD); living arrangements after index event; patient disability as measured using the modified Rankin Scale (mRS); and quality of life as measured using the Euroqol-5D (EQ-5D) and the Euroqol Visual Analogue Scale (EQ-VAS). Quality of life and survival data were then combined in order to estimate the QALYs gained over a 2-year period.

5.2.2 CLINICAL FOLLOW-UP

Outcome information was derived from the clinical follow-ups, details of which are reported in **Chapter 4**. Briefly, patients were followed-up at 1, 6, 12 and 24 months after their index event by a study research nurse. Patients were screened for

recurrent vascular events, asked about their current living arrangements, assessed using the mRS, and given both the EQ-5D and the EQ-VAS.

In addition, recurrent vascular events were identified using the hot and cold pursuit methods reported in **Chapter 4**. Patient deaths were identified from a number of sources including: GP notification, hospital records and bereavement officers, review of death certificates, and routine searches of the Oxford Radcliffe Hospital's Patient Administration System.

5.2.3 STATISTICAL ANALYSIS

Survival

Case-fatality, defined as mortality within 30 days after event, was reported as a proportion, with exact 95% confidence intervals (CI) computed. Statistical differences were evaluated using standard chi-square tests. Predictors of case-fatality were determined by logistic multivariate analysis. Potential baseline predictors examined included event characteristics, age and gender, and past history of disease and disability, all of which are reported in detail in **Chapter 4**.

In the analyses for this thesis patients were only followed-up until 30 April 2007. Therefore, past this date, there was no information as to whether the patient was alive or dead, and as a result they were treated as censored. For each follow-up year the numbers of patients alive, censored or dead were computed. This information enabled estimation of the survivor function using the Kaplan-Meier estimate of the survival curve.[209] Using the results of the survivor function, the life years gained over

the 5-year period after index event were estimated with 95% CIs calculated non-parametrically from 1000 bootrstrap estimates.[210]

Life-years accrued from one year after the index event were discounted using an annual rate of 3.5%.[211] As reported in **Chapter 3**, the economic rationale for discounting is that individuals generally prefer to receive benefits sooner rather than later, and as such benefits accruing over the long term should be given less weight than those occurring in the near future.[83] In this case, life-years gained were considered a benefit, and those gained after one year were discounted to take into account this positive time preference rate.

Recurrent event risk

Information on recurrent vascular events was available from event onset until death or end of follow-up. Recurrent event risk was calculated using the cumulative hazard function, estimated by summing the recurrent event risks at each time interval in which an event occurred, and adjusting them for both death and censoring.[209] As patients could have more than one recurrent vascular event of the same type (e.g. suffer two recurrent strokes), only the first recurrent event of the same type was considered when estimating the cumulative hazard function. In addition, the incidence of recurrent vascular events in stroke and TIA patients was compared using a Poisson regression model.

Living arrangements

Information on patients' living arrangements post-event was collected at each clinical follow-up by asking patients if they lived in: their own home; friends' or relatives'

home; nursing home; residential home; hospital; intermediate care (e.g. community hospital); or in sheltered accommodation. Those patients not living in their own home or with friends/relatives were considered to be institutionalised. Both living location and institutionalisation were reported as proportions, with differences being evaluated using standard chi-square tests.

Disability

Information on independence was collected at each clinical follow-up using the mRS, with disability being defined as scores of between 3 and 5. Disability was reported as a proportion and exact 95% CIs computed. Statistical differences were evaluated using standard chi-square tests.

To determine the baseline predictors of disability at each follow-up period logistic multivariate analyses were performed. Potential baseline predictors examined included: event characteristics, age and gender, past history of disease and disability, and socio-economic characteristics (**Chapter 4**). Both age and National Institute of Health Stroke Scale (NIHSS) score, used to measure initial stroke severity, were included into the multivariate analyses as categorical variables, due to observed non-linear effects on outcomes.[173] Also included in the multivariate analyses were the presence of any recurrent vascular events between event onset and follow-up point.

Quality of life

Quality of life was measured using the EQ-5D and EQ-VAS. However, during the first 18 months of OXVASC, quality of life was not assessed at the 6-month follow-up

visit, resulting in a large proportion of patients having no quality of life data at this time point.

Responses to the EQ-5D were converted into quality of life estimates using UK population tariffs.[113;114] Results from the EQ-VAS were divided by 100 in order to compare results between it and the EQ-5D. Quality of life estimates are reported as means with standard deviation (S.D.). Differences between the two instruments were compared using a paired Student's t-test. Although data were not normally distributed, the large sample size available ensured that the central limit theorem applied, and therefore the use of parametric tests was considered technically valid.[209] Differences in quality of life were evaluated using a two-tailed Student's t-test. For subgroups with more than two categories, differences were compared using analysis of variance (ANOVA). A multivariate regression analysis was also performed to assess the relationship between quality of life and potential baseline clinical and socio-economic predictors.

As detailed in **Chapter 2**, the values of the EQ-5D and EQ-VAS are bounded between -0.59 and 1, and between 0 and 100, respectively. Patient responses giving rise to quality of life values at the low end of the bounds are not very common. However, responses giving rise to quality of life values at the upper end are more frequent, with approximately 50% of representative samples of the UK and US populations reporting no problems in each of the EQ-5D domains.[212;213] Failure to account for this upper ceiling using ordinary linear least-squares (OLS) regression analyses will, therefore, result in biased and inconsistent estimates.[214;215]

In order to overcome these limitations, a tobit model was used in all multivariate analyses of quality of life with upper censoring at 1 and 100 for the EQ-5D and EQ-VAS, respectively. To avoid the problems of heteroscedastic and non-normally distributed error terms prevalent in tobit models,[212;213;216] which produce inconsistent estimates of the regression coefficients' standard errors,[214;215] a tobit model with robust standard errors, obtained using 1000 bootstrap replications, was used.

Impact of stroke and TIA on quality of life

The impact of the cerebrovascular event on quality of life was measured by: 1) comparing quality of life before the index cerebrovascular event to that of the four follow-ups post-event; and 2) comparing quality of life for stroke and TIA patients to population norms. Quality of life before the event was obtained by asking patients to recall their health state before the index event using the EQ-5D, which was given to patients as part of their one-month follow-up. However, retrospective quality of life was only assessed during the first year of OXVASC (April 2002 to March 2003).

Population norms were available from the 1996 Health Survey for England (HSE),[217] which derived EQ-5D responses from a representative sample of the English population. In order to make comparisons, quality of life estimates from OXVASC patients were standardised using the same age and gender structure as the HSE sample. However, due to the small numbers of young stroke and TIA patients, patients under the age of 35 were excluded from both the HSE and OXVASC samples. Using tobit regression analyses, differences in quality of life between the two samples were assessed controlling for age and gender.

Quality Adjusted Life-Years (QALYs)

QALYs gained over a two-year period were estimated by combining average estimates of survival and EQ-5D quality of life derived from the overall-patient sample. This aggregate approach was used as calculating QALYs for each individual patient has been found to be problematic and could lead to biased results in situations with censored survival times.[218]

Survival was estimated using the Kaplan-Meier survival function two years post-event, as this was the last point for which quality of life information was available. A quality-adjusted survival curve was generated by plotting, against time, the product of the mean quality of life of patients living at time *t* and the probability of surviving to time *t*, with *t* being set to one month, in order to create 24 month periods. The area under this quality-adjusted survival curve then gave the mean quality-adjusted survival for the population.[218]

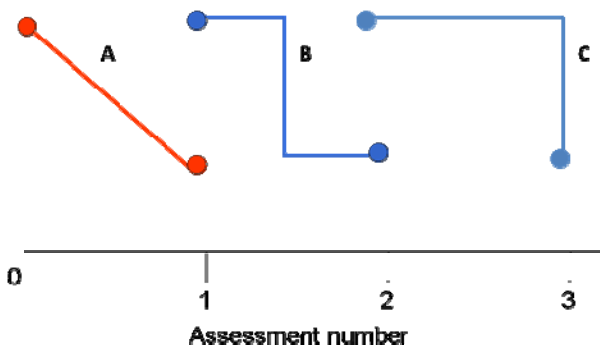

Figure 5.1 Handling quality of life changes between follow-ups

Derived from Billingham et al. (1999)[218]

As quality of life was only evaluated at four time points rather than at regular one-month intervals, quality of life was assumed to change linearly between the four

follow-up periods (**A** in **Figure 5.1**) rather than changing at the midpoint between follow-ups (**B**), or being maintained from one follow-up to another (**C**). It was also assumed that quality of life between the event onset and one month was the same as that reported in the one-month follow-up.

Results were reported as QALYs with 95% CIs calculated non-parametrically from 1000 bootstrap estimates. As with life-years gained, benefits accrued after the first year were discounted at an annual rate of 3.5%.

Statistical significance and diagnostic checks

All statistical analyses were undertaken using STATA version 10. Statistical significance was set at $p<0.050$. The goodness-of-fit of each regression model was assessed using McFadden's Adjusted R^2. In all multivariate analyses model specification was tested using Preigbon's link test.[219] Multicollinearity was measured from the tolerance value and its inverse, the variance inflation factor (VIF).[220] The tolerance value is the amount of variability of a single covariate not explained by other covariates, whereas VIF indicates the extent of effects of other covariates on the variance of a selected covariate. As a result, very small tolerance values (<0.1) or high VIF values (>10) indicate high collinearity.[220]

Missing data

Missing information might lead to bias in analyses as respondents may vary from non-respondents, and to a loss of statistical power as missing data reduce the available sample size.[221] In OXVASC, approximately 18% of the total dataset was missing due to reasons not explained by censoring or death. Previous reviews of

methods to deal with missing data have recommended the use of multiple imputation techniques to deal with missing data.[221-223] These techniques, which replace missing values with a set of *m* plausible values using a wide range of different regression models,[224;225] were used to impute for missing data cases. Using linear, logistic, ordered logistic and multinomial logistic regression, 5 replacement values (*m*=5) were generated for each missing case, generating 5 imputed datasets. Missing follow-up values in censored patients were not imputed as there was no information as to whether the patient was still alive.

Due to the longitudinal nature of the study, missing data were not imputed using a single equation. As a considerable proportion of follow-up information was missing due to death or censoring, using a single equation to impute for missing follow-up cases would have generated data for these cases, which could lead to incorrect imputation results in other cases. Data were therefore imputed using four sequential equations, with one equation imputing data for baseline and one-month follow-up information, and the remaining three imputing data for each of the three subsequent follow-ups. Once the data were imputed, the multivariate analyses presented before were repeated by combining information from the 5 imputed datasets using the STATA `micombine` command.[226]

In order to account for missing information in quality of life data, QALYs were also calculated using the results from the 5 imputed datasets. For each dataset, survival information was combined with the average quality of life. To obtain an overall summary estimate for the 5 datasets, QALYs gained were averaged across datasets. As there is no agreed method on how to report overall 95% CIs from

different multiple imputed datasets, a conservative approach was adopted, with 95% CIs being calculated from the lowest and highest 95% CI in the 5 datasets.

5.3 RESULTS

A total of 1282 patients suffered a cerebrovascular event (788 strokes and 494 TIA) between April 2002 and March 2007 (**Chapter 4**). The analyses in this chapter are based on a total patient sample of 1,199 consenting patients (723 strokes and 476 TIA). However, 8 TIA patients were followed-up as stroke patients as their TIA was only identified when they sought medical attention for a subsequent stroke. As a result, stroke was used as the index event for these patients, with a total of 731 patients being followed-up for stroke and 468 for TIA.

5.3.1 THIRTY-DAY CASE-FATALITY AND SURVIVAL

A total of 114 (10%; 95% CI: 8% to 11%) patients died within 30 days of their index event. As shown in **Table 5.1**, 30-day case-fatality was significantly higher in stroke patients (15%; 95% CI: 12% to 17%) than in TIA patients (1%; 95% CI: 0% to 2%; p<0.001). By stroke subtype, case-fatality also varied significantly between patient groups with intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH) having the highest case-fatality rates, 40% (95% CI: 27% to 54%) and 41% (95% CI: 24% to 57%), respectively, compared to 8% (95% CI: 6% to 10%) for ischaemic stroke patients (p<0.001). For the 45 cases of unknown stroke, 30-day case-fatality was 53% (95% CI: 38% to 68%).

Table 5.1 Predictors of 30-day case-fatality

Variable	No.	% case-fatal (95% CI)	Univariate analysis (p>|z|)	Multivariate analysis (p>|z|)
Age (years)			<0.001	
<65	264	6 (3 to 8)		0.037
65 to 74	283	4 (2 to 7)		0.006
≥75	652	13 (11 to 16)		Reference case
Gender			0.799	
Male	571	9 (7 to 12)		Reference case
Female	628	10 (7 to 12)		0.043
Previous disability				
No	920	5 (3 to 6)	<0.001	Reference case
Yes	191	13 (8 to 17)		0.046
History of stroke			0.364	
No	1004	9 (7 to 11)		Reference case
Yes	188	11 (6 to 16)		0.345
History of AF			0.009	
No	980	8 (7 to 10)		Reference case
Yes	212	14 (9 to 19)		0.009
History of hypertension			0.090	
No	505	8 (5 to 10)		Reference case
Yes	687	11 (8 to 13)		0.383
History of angina			0.273	
No	1001	9 (7 to 11)		Reference case
Yes	191	12 (7 to 16)		0.732
History of MI			0.036	
No	1043	9 (7 to 10)		Reference case
Yes	149	14 (8 to 20)		0.122
History of diabetes			0.331	
No	1052	10 (8 to 12)		Reference case
Yes	140	7 (3 to 11)		0.944
History of PVD			0.008	
No	1090	9 (7 to 10)		Reference case
Yes	102	17 (9 to 24)		0.579
Smoking status			0.586	
Never smoked	537	10 (8 to 13)		Reference case
Ex-smoker	498	9 (6 to 11)		0.605
Current smoker	153	8 (4 to 12)		0.256
Event subtype			<0.001	
Stroke	731	15 (12 to 17)		
Ischaemic	597	8 (6 to 10)		Reference case
ICH	52	40 (27 to 54)		0.001
SAH	37	41 (24 to 57)		0.410
Unknown	45	53 (38 to 68)		0.001
TIA	468	1 (0 to 2)		0.368
Event severity (NIHSS)			<0.001	
<3	781	1 (1 to 2)		Reference case
3 to 10	260	15 (11 to 19)		0.110
11 to 20	75	24 (14 to 34)		<0.001
>20	31	74 (58 to 91)		<0.001
30-day recurrent stroke			0.915	
No	1097	10 (8 to 11)		Reference case
Yes	102	10 (4 to 16)		<0.001
30-day recurrent TIA			0.003	N/A
No	1136	10 (8 to 12)		
Yes	63	0		
30-day recurrent CHD			0.008	
No	1183	9 (8 to 11)		Reference case
Yes	16	31 (6 to 57)		0.591
30-day recurrent PVD			<0.001	N/A
No	1197	9 (8 to 11)		
Yes	2	100		
			No. Prob> χ^2 Adj. R^2	1084 <0.001 0.359

Results of the multivariate analysis showed that event subtype and severity remained strong predictors of increased case-fatality (**Table 5.1**). Compared to ischaemic stroke, ICH (p=0.001)and unknown stroke (p=0.001) were predictive of increased case-fatality rates. Results also showed that females were at higher risk of dying within 30 days of their index event than males (p=0.043), with age also being a predictive factor of increased case-fatality (p<0.050). After controlling for other factors, those suffering a recurrent stroke within 30 days of their index event were significantly more likely to die (p<0.001), which contrasted with the non-significant results observed in the univariate analysis.

Table 5.2 Proportion of patients alive, censored or dead by follow-up period

Follow-up	Alive, no. (%)			Censored, no. (%)			Dead, no. (%)		
	All	Stroke	TIA	All	Stroke	TIA	All	Stroke	TIA
6months	999 (83)	553 (76)	446 (95)	19 (2)	11 (2)	8 (2)	181 (15)	167 (23)	14 (3)
1 year	870 (73)	476 (65)	394 (84)	110 (9)	60 (8)	50 (11)	219 (18)	195 (27)	24 (5)
2 years	582 (49)	329 (45)	253 (54)	359 (30)	189 (26)	170 (36)	258 (22)	213 (29)	45 (10)
3 years	374 (31)	208 (28)	166 (35)	528 (44)	285 (39)	243 (52)	297 (25)	238 (33)	59 (13)
4 years	172 (14)	90 (12)	82 (18)	706 (59)	390 (53)	316 (68)	321 (27)	251 (34)	70 (15)
5 years	14 (1)	6 (1)	8 (2)	856 (71)	468 (64)	388 (83)	329 (27)	257 (35)	72 (15)

The proportion of patients alive, dead or censored at each follow-up is shown in **Table 5.2**. Of the 1,199 patients suffering a TIA or stroke, 14 (1%) patients were known to be alive after 5 years, with the majority of patients (n=856, 71%) being censored, and over a quarter (27%) dead. Mean follow-up for all patients was 761 (S.D. 555) days, with follow-up for TIA patients being considerably longer, 867 (S.D. 522) days, than for stroke patients, 693 (S.D. 566) days (p<0.001).

Using the information in **Table 5.2** survival was estimated using Kaplan-Meier survival curves. **Figure 5.2** shows how survival during the first months after the index event fell steeply, and then more gradually as time proceeded. Due to the high levels

of censoring three years post-event uncertainty around the survival function increased, as shown by the widening 95% CIs.

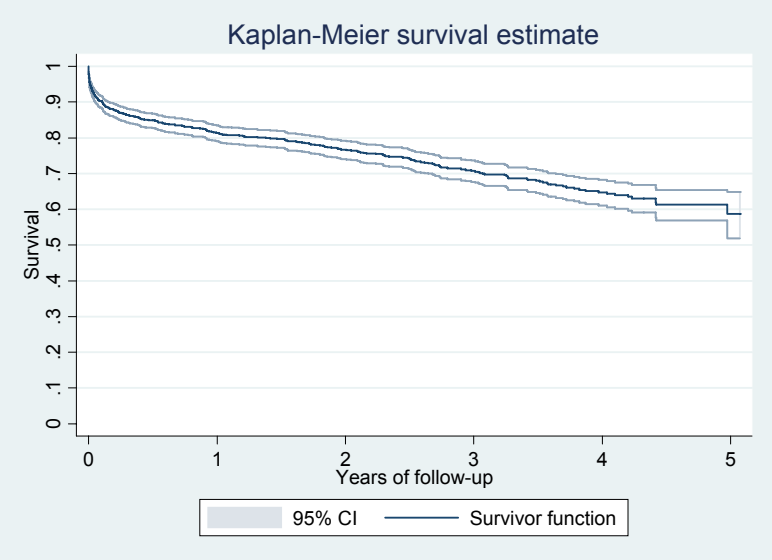

Figure 5.2 Kaplan-Meier survival curve for all 1,199 OXVASC patients

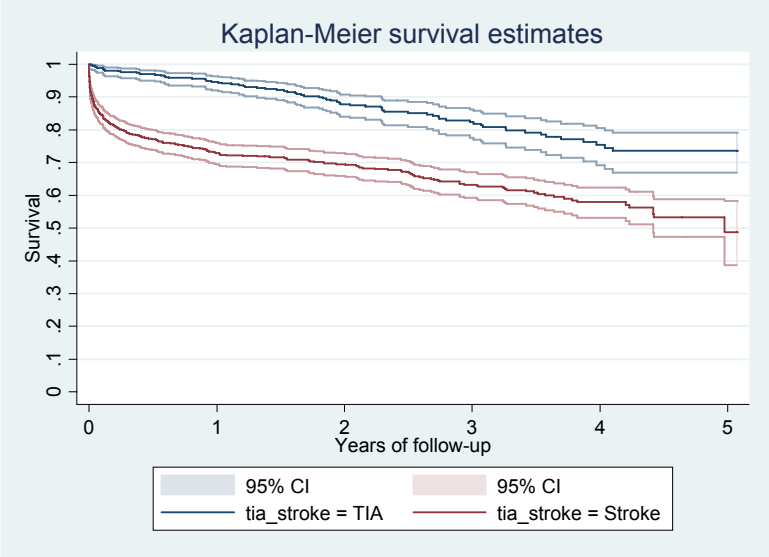

Figure 5.3 Kaplan-Meier survival curves for stroke and TIA patients

Survival between TIA and stroke patients was also compared (**Figure 5.3**). Although survival rates for stroke patients fell steeply in the first months after the event, those

for TIA patients fell gradually throughout the 5 years. There was also a clear difference in survival rates between TIA and stroke patients. However, due to the uncertainty caused by censoring of patients, this difference became less significant as the follow-up period increased.

Overall, the life-years gained over a 5-year period were 3.67 (95% CI: 3.57 to 3.77) years, with that for stroke patients being 3.31 (95% CI: 3.17 to 3.44) years compared to 4.24 (95% CI: 4.11 to 4.36) years of life after TIA. Compared to TIA patients, stroke patients lost 0.93 (95% CI of difference: 0.71 to 1.14) years over a 5-year period. After discounting, the life-years gained over a 5-year period were 3.49 (95% CI: 3.40 to 3.58) years, with that for stroke patients being 3.15 (95% CI: 3.02 to 3.27) years compared to 4.03 (95% CI: 3.91 to 4.15) years for TIA patients.

5.3.2 RECURRENT VASCULAR EVENT RISK

The 5-year risk of a recurrent event was 21% for stroke, 17% for TIA, 10% for CHD and approximately 1% for PVD (**Figure 5.4**).

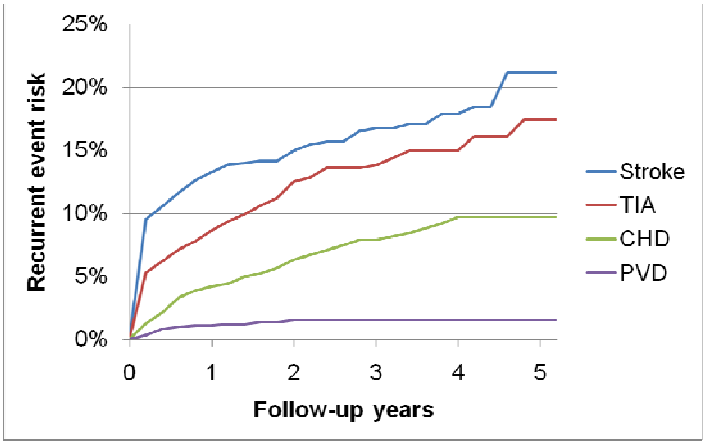

Figure 5.4 Risk of recurrent vascular event for all 1,199 OXVASC patients

Figures 5.5 and **5.6** show the risk of recurrent vascular events in stroke and TIA patients, respectively. The risk of a recurrent stroke and CHD event were similar for stroke and TIA patients (20% and 10%, respectively), TIA patients were more likely to have a recurrent TIA than stroke patients by the end of the 5-year follow-up (14% vs. 24%; p<0.001). In both stroke and TIA patients the risk of recurrent PVD events remained constant throughout the 5 years, with a trend, verging on significance, for stroke patients to have a higher risk of suffering a recurrent PVD (p=0.050).

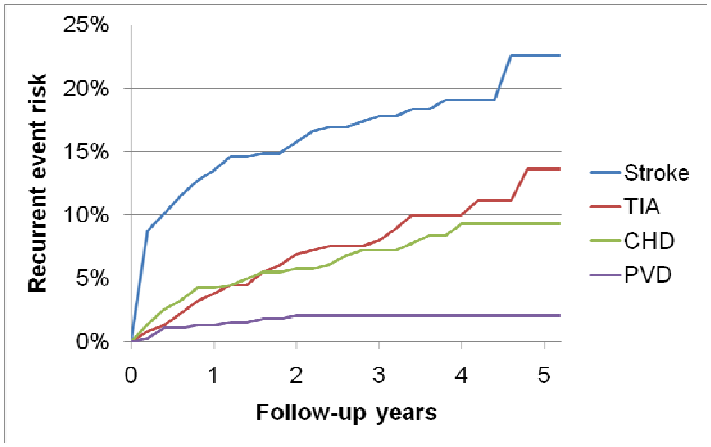

Figure 5.5 Risk of recurrent vascular event for stroke patients

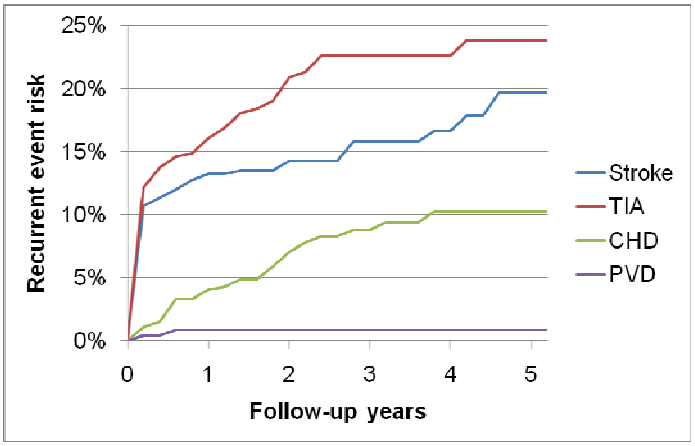

Figure 5.6 Risk of recurrent vascular events for TIA patients

5.3.3 LIVING ARRANGEMENTS

Data on living arrangements were available for approximately 80% of patients in each of the four follow-ups, with more data being available for stroke than TIA patients (**Table 5.3**).

At one-month follow-up, 647 (74%) patients were living at their own home, with a considerable minority living either in hospital (14%) or in intermediate care settings (6%). In total, one month after the stroke or TIA, one quarter of patients (n=215) were living in institutionalised settings, with institutionalisation rates being significantly higher in stroke than TIA patients (35% vs. 9%; p<0.001).

At six-month follow-up, the proportion of patients living at their own homes was higher than that at one month (84% vs. 74%; p<0.001), with a lower proportion of patients being hospitalised (**Table 5.3**). However, the proportion of patients living in either residential, nursing care homes or sheltered accommodation was significantly higher (p<0.001) at six months than at one month. As before, a higher proportion of stroke patients were institutionalised than TIA patients (18% vs. 10%; p=0.001).

Living arrangements at both the one- and two-year follow-ups were very similar. For each follow-up, 86% of patients lived at home, with only 2% of patients living either in hospital or in intermediate care centres (**Table 5.3**). The proportion of patients living in institutionalised settings was 12% and 13% at one and two years, with the majority of them living in either nursing or sheltered accommodation. In contrast with the

Table 5.3 Living arrangements after index cerebrovascular event

	1 month, n (%)			6 months, n (%)			1 year, n (%)			2 years, n (%)		
	All n=1085	TIA n=463	Stroke n=622	All n=999	TIA n=446	Stroke n=553	All n=870	TIA n=394	Stroke n=476	All n=582	TIA n=253	Stroke n=329
Own home	647 (74)	317 (89)	330 (63)	672 (84)	308 (89)	364 (81)	610 (86)	276 (88)	334 (84)	385 (86)	162 (89)	223 (86)
Relative's home	17 (2)	4 (1)	13 (2)	14 (2)	6 (2)	8 (2)	18 (3)	7 (2)	11 (3)	7 (2)	3 (2)	4 (2)
Nursing home	11 (1)	8 (2)	3 (1)	29 (4)	10 (3)	19 (4)	30 (4)	6 (2)	24 (6)	20 (4)	4 (2)	16 (6)
Residential home	11 (1)	3 (1)	8 (2)	16 (2)	3 (1)	13 (3)	14 (2)	7 (2)	7 (2)	7 (2)	4 (2)	3 (1)
Hospital	125 (14)	9 (3)	116 (22)	17 (2)	8 (2)	9 (2)	8 (1)	5 (2)	3 (1)	5 (1)	1 (1)	4 (2)
Intermediate care	51 (6)	8 (2)	43 (8)	17 (2)	2 (1)	15 (3)	8 (1)	4 (1)	4 (1)	4 (1)	2 (1)	2 (1)
Sheltered accommodation	17 (2)	5 (1)	12 (2)	35 (4)	11 (3)	24 (5)	22 (3)	8 (3)	14 (4)	20 (4)	7 (4)	13 (5)
Total instiutionalised	215 (24)	33 (9)	182 (35)	113 (14)	34 (10)	80 (18)	82 (12)	30 (10)	52 (13)	56 (13)	18 (10)	38 (14)
Data cases	879 (81)	354 (76)	525 (84)	800 (80)	348 (78)	452 (82)	710 (82)	313 (79)	397 (83)	448 (77)	183 (72)	265 (81)
Missing cases	206 (19)	109 (24)	97 (16)	199 (20)	98 (22)	101 (18)	160 (18)	81 (21)	79 (17)	134 (23)	70 (28)	64 (19)
Multiple imputation results												
Institutionalised												
Yes	256 (24)	44 (9)	213 (34)	149 (15)	44 (10)	105 (19)	104 (12)	38 (10)	65 (14)	90 (15)	34 (13)	57 (17)
No	829 (76)	419 (91)	409 (66)	850 (85)	402 (90)	448 (81)	766 (88)	356 (90)	411 (86)	492 (85)	219 (87)	272 (83)

statistical differences identified between TIA and stroke patients in previous follow-ups, none were observed at one and two years (p=0.146 and p=0.157, respectively).

5.3.4 PATIENT DISABILITY

The proportion of patients at each mRS score is reported, by follow-up, in **Table 5.4**. Although there were only 7% of missing cases for baseline mRS, follow-up data were missing for between 18% and 24% of patients depending on follow-up. At baseline only 17% (n=191) of patients were disabled. By contrast, after the index event, disability levels were significantly higher at each follow-up point than at baseline (p<0.001), with approximately 30% of patients being disabled across all follow-ups (**Table 5.4**). There were no significant differences, however, in disability levels between different follow-ups after the event.

By event type, disability levels for TIA patients did not differ significantly between baseline and for each of the four follow-ups after the event (**Table 5.4**). However, for stroke patients disability levels rose considerably from 19% (n=125) before the event to 43% (n=213) one month after (p<0.001), with approximately 36% of patients being disabled at the 6-, 12- and 24-month follow-ups, also a significant difference compared to baseline levels (p<0.001).

Table 5.4 Rankin score after index cerebrovascular event

mRS	Before event, n (%)			1-month, n (%)			6-months, n (%)			1-year, n (%)			2-years, n (%)		
	All n=1199	TIA n=468	Stroke n=731	All n=1085	TIA n=463	Stroke n=622	All n=999	TIA n=446	Stroke n=553	All n=870	TIA n=394	Stroke n=476	All n=582	TIA n=253	Stroke n=329
0	400 (36)	173 (38)	227 (34)	145 (17)	99 (28)	46 (9)	151 (18)	95 (27)	56 (12)	102 (15)	72 (23)	30 (8)	61 (14)	40 (22)	21 (8)
1	373 (34)	163 (36)	210 (32)	280 (33)	155 (43)	125 (25)	282 (34)	139 (39)	143 (30)	241 (34)	125 (41)	116 (29)	145 (33)	66 (36)	79 (30)
2	147 (13)	49 (11)	98 (15)	164 (19)	52 (15)	112 (23)	150 (18)	54 (15)	96 (20)	160 (23)	56 (18)	104 (26)	113 (25)	44 (24)	69 (26)
3	149 (13)	53 (12)	96 (15)	128 (15)	31 (9)	97 (20)	159 (19)	49 (14)	110 (23)	138 (20)	34 (11)	104 (26)	88 (20)	24 (13)	64 (24)
4	40 (4)	12 (3)	28 (4)	92 (11)	15 (4)	77 (16)	56 (7)	14 (4)	42 (9)	46 (7)	17 (6)	29 (7)	27 (6)	7 (4)	20 (8)
5	2 (0.2)	1 (0.2)	1 (0.2)	44 (5)	5 (1)	39 (8)	26 (3)	4 (1)	22 (5)	14 (2)	3 (1)	11 (3)	10 (2)	0	10 (4)
>2	191 (17)	66 (15)	125 (19)	264 (31)	51 (14)	213 (43)	241 (29)	67 (19)	174 (37)	198 (28)	54 (18)	140 (36)	125 (28)	31 (17)	94 (36)
Data cases	1111 (93)	451 (96)	660 (90)	853 (79)	357 (77)	496 (80)	824 (82)	355 (80)	469 (85)	701 (81)	307 (78)	394 (83)	444 (76)	181 (72)	263 (80)
Missing cases	88 (7)	17 (4)	71 (10)	232 (21)	106 (23)	126 (20)	175 (18)	91 (20)	84 (15)	169 (19)	87 (22)	82 (17)	138 (24)	72 (28)	66 (20)
Multiple imputation results															
0	425 (35)	180 (39)	245 (33)	181 (17)	124 (27)	57 (9)	186 (19)	119 (27)	67 (12)	129 (15)	91 (23)	38 (8)	82 (14)	57 (23)	25 (7)
1	395 (33)	167 (36)	228 (31)	349 (32)	195 (42)	154 (25)	349 (35)	179 (40)	170 (31)	300 (35)	161 (41)	139 (29)	186 (32)	94 (37)	92 (28)
2	161 (13)	51 (11)	110 (15)	205 (19)	73 (16)	131 (21)	179 (18)	69 (15)	111 (20)	198 (23)	75 (19)	122 (26)	137 (24)	56 (22)	81 (25)
3	170 (14)	55 (12)	115 (16)	171 (16)	46 (10)	125 (20)	190 (19)	59 (13)	131 (24)	168 (19)	44 (11)	124 (26)	117 (20)	34 (14)	83 (25)
4	45 (4)	12 (3)	32 (4)	118 (11)	18 (4)	99 (16)	65 (7)	15 (3)	50 (9)	58 (7)	19 (5)	39 (8)	43 (7)	10 (4)	33 (10)
5	2 (0.2)	1 (0.2)	1 (0.2)	61 (6)	6 (1)	55 (9)	30 (3)	5 (1)	25 (5)	18 (2)	4 (1)	14 (3)	17 (3)	2 (1)	15 (5)
>2	217 (18)	68 (15)	148 (20)	350 (32)	70 (15)	279 (45)	285 (29)	79 (18)	206 (37)	244 (28)	67 (17)	177 (37)	177 (30)	46 (18)	131 (40)

Predictors of patient disability after index TIA or stroke

Univariate predictors of patient disability in each of the four follow-ups are reported in **Appendix 13**. The section in this chapter will focus on the results of the multivariate logistic regressions undertaken in order to identify the baseline predictors of disability at 1, 6, 12 and 24 months after the index event.

Table 5.5 shows the results of the logistic regression analyses for patients with complete baseline and mRS data. Results showed that event severity, as measured using the NIHSS, was one of the strongest predictors of increased disability levels at each follow-up. After controlling for other covariates, patients suffering more severe events (NIHSS≥3) were significantly more likely to be disabled than those with less severe events (NIHSS<3) in each of the four follow-ups ($p<0.001$). Another strong predictor of increased post-event disability was disability before the event, with disabled patients at baseline being more likely to be disabled after the event than those who were not ($p<0.001$ for all follow-ups).

Patients' age at time of event was also found to be a predictor of disability after index TIA or stroke. Patients aged between 65 to 74 years were significantly less likely to be disabled than those aged 75 years or more, at 1, 6 and 12 months after the index event (**Table 5.5**). At 24 months, despite age 65 to 74 years having a similar impact on post-event disability as at 6 and 12 months (as determined by the regression coefficients) differences did not reach statistical significance ($p=0.086$).

Table 5.5 Predictors of disability (mRS>2): complete-case analysis

Variable	1 month		6 months		1 year		2 years	
	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z
Age (years)								
<65	-0.55	0.224	-4.22	0.331	-0.43	0.348	-0.62	0.275
65 to 74	-0.92	0.004	-0.67	0.028	-0.71	0.035	-0.73	0.086
≥75	Reference case		Reference case		Reference case		Reference case	
Gender								
Female	Reference case		Reference case		Reference case		Reference case	
Male	-0.09	0.742	-0.39	0.153	-0.41	0.187	-0.12	0.756
Previously disabled	3.18	<0.001	3.01	<0.001	3.58	<0.001	4.23	<0.001
History of stroke	0.61	0.038	0.22	0.476	0.15	0.675	-0.65	0.207
History of TIA	-0.87	0.021	-0.31	0.343	-0.33	0.372	0.21	0.626
History of AF	0.53	0.074	0.38	0.204	0.21	0.532	0.31	0.459
History of hypertension	-0.09	0.710	0.10	0.682	-0.04	0.882	-0.22	0.530
History of angina	-0.19	0.641	0.19	0.591	-0.13	0.765	-0.49	0.394
History of MI	-0.22	0.609	-0.25	0.523	-0.01	0.988	-1.65	0.016
History of diabetes	-0.05	0.898	0.25	0.505	0.69	0.097	0.53	0.306
History of PVD	0.50	0.246	0.33	0.428	0.65	0.178	-0.35	0.561
Smoking status								
Never	Reference case		Reference case		Reference case		Reference case	
Previous	-0.18	0.495	0.02	0.936	-0.14	0.648	0.64	0.103
Current	-0.45	0.292	0.14	0.741	0.64	0.128	0.02	0.971
Event type								
TIA	Reference case		Reference case		Reference case		Reference case	
Stroke	0.96	0.002	0.45	0.116	1.01	0.002	0.77	0.069
Event severity (NIHSS)								
<3	Reference case		Reference case		Reference case		Reference case	
3 to 10	1.89	<0.001	1.61	<0.001	1.30	<0.001	2.05	<0.001
>10	5.15	<0.001	5.41	<0.001	4.56	<0.001	5.50	<0.001
Probability of event								
Definite	Reference case		Reference case		Reference case		Reference case	
Probable†	-1.64	0.027	-1.36	0.036	-1.11	0.188	-0.83	0.401
Possible	0.22	0.660	0.44	0.347	0.16	0.767	N/A	N/A
Not coded	-1.23	0.179	-1.26	0.159	-0.49	0.587	N/A	N/A
Recurrent stroke	1.84	<0.001	1.19	<0.001	1.13	<0.001	0.64	0.111
Recurrent TIA	0.04	0.922	0.18	0.687	0.21	0.384	0.70	0.134
Recurrent CHD	1.61	0.186	1.87	0.010	1.98	0.001	2.48	<0.001
Recurrent PVD	N/A	N/A	0.96	0.497	N/A	N/A	1.72	0.119
Residence before event								
Own home	Reference case		Reference case		Reference case		Reference case	
With relative	-0.28	0.687	-0.69	0.327	-1.07	0.209	-3.15	0.080
Warden housing	-0.44	0.403	-0.98	0.068	-0.70	0.298	-1.22	0.144
Care home	-0.63	0.551	1.03	0.313	0.99	0.407	0.82	0.614
Other	-0.78	0.567	-1.17	0.458	-1.11	0.717	N/A	N/A
Lived alone	0.06	0.881	-0.54	0.146	-0.80	0.056	-0.10	0.052
Marital status								
Married	Reference case		Reference case		Reference case		Reference case	
Widow	0.54	0.182	1.03	0.007	1.14	0.008	1.70	0.003
Single	1.19	0.031	1.43	0.007	1.50	0.010	2.59	<0.001
Separated	-0.10	0.886	0.13	0.845	0.60	0.415	0.78	0.361
Partnered	-0.39	0.712	-1.64	0.213	-0.56	0.587	0.70	0.414

Table 5.5 (cont.). Predictors of disability (mRS>2): complete-case analysis

Variable	1 month		6 months		1 year		2 years	
	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z
Age left education	-0.09	0.069	0.01	0.844	-0.03	0.552	0.001	0.847
Socio-economic class								
I	0.63	0.298	-0.44	0.456	0.77	0.230	-0.24	0.766
II	0.27	0.449	-0.05	0.883	0.71	0.067	0.54	0.264
III-N	0.16	0.675	-0.16	0.642	0.04	0.915	-0.11	0.825
III-M	Reference case		Reference case		Reference case		Reference case	
IV	0.25	0.555	-0.06	0.897	0.13	0.788	0.41	0.505
V	0.09	0.822	-0.03	0.936	0.42	0.345	-0.03	0.955
Employment status								
Full-time	-0.22	0.653	-1.11	0.043	-0.92	0.096	-0.98	0.128
Part-time	0.13	0.790	-0.35	0.490	-1.22	0.071	-1.37	0.116
Home carer	0.50	0.520	-0.72	0.335	-0.23	0.777	-1.22	0.470
Unemployed	1.31	0.244	1.44	0.184	1.00	0.404	1.50	0.250
Cannot work	-0.10	0.937	0.72	0.393	0.44	0.635	-0.48	0.699
Retired	Reference case		Reference case		Reference case		Reference case	
Deprivation (IMD score)	0.02	0.217	0.01	0.655	-0.01	0.625	-0.02	0.411
Constant	-1.69	0.077	-2.20	0.014	-2.02	0.038	-2.89	0.022
	No.	821	No.	799	No.	682	No.	431
	$p>\chi^2$	<0.001	$p>\chi^2$	<0.001	$p>\chi^2$	<0.001	$p>\chi^2$	<0.001
	Adj. R^2	0.399	Adj. R^2	0.334	Adj. R^2	0.329	Adj. R^2	0.277

†For the 2-year follow-up, patients with possible or un-coded events were all found to be non-disabled. Therefore, in order for these variables to be included in the regression, they were aggregated with probable events.

In all four follow-ups disability levels were found to be higher in patients suffering a stroke rather than TIA. However, after controlling for other factors, these differences were only found to be significant at the 1- and 12-month follow-ups (p=0.002 for both), with a trend emerging for increased disability in stroke patients at two years (p=0.069). In addition, those patients whose cerebrovascular event was coded as probable were significantly less likely to be disabled one and 6 months after their event than those whose event was coded as definite (**Table 5.5**).

Suffering a subsequent stroke or coronary event after the index event significantly increased disability levels post-event. Patients suffering a recurrent stroke between the index event and follow-up were more likely to be disabled at 1, 6 and 12 months

(p<0.001 in all cases). Subsequent coronary events had a similar impact on disability levels as recurrent strokes, with recurrent CHD events being a predictor of increased disability 6, 12 and 24 months post index TIA or stroke (**Table 5.5**).

Presence of certain comorbidities at time of event also had an impact on disability levels post-event. For example, patients with a history of stroke were significantly more likely to be disabled one month after the event than those without (p=0.038). By contrast, disability levels at one month were significantly lower in those patients with a history of TIA (p=0.021), and those at 2 years were significantly lower for those with a history of myocardial infarction (MI – p=0.016).

In terms of socio-economic characteristics only marital status was found to be an independent predictor of disability in all four follow-ups. After controlling for other covariates, patients who were single at time of event had higher disability levels than married patients (**Table 5.5**). Similarly, disability levels in widowed patients were also significantly higher 6, 12 and 24 months post-event. There was some evidence that patients in full-time employment at the time of event were less likely to be disabled than retired patients, after controlling for other baseline factors. However, these differences were only found to be significant at 6 months (p=0.043), with a trend being observed one year post-index event (p=0.096).

The logistic regressions presented above were repeated to include multiple-imputed information for missing cases (**Table 5.6**). Both event severity and previous disability remained strong predictors of increased disability at each follow-up point. However, after imputing data for missing cases, the results now showed that disability levels

Table 5.6 Predictors of disability (mRS>2): multiple imputation

Variable	1 month		6 months		1 year		2 years	
	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z
Age (years)								
<65	-0.77	0.103	-0.71	0.081	-0.62	0.168	-0.61	0.256
65 to 74	-0.98	0.001	-0.76	0.009	-0.57	0.065‡	-0.71	0.092
≥75	Reference case		Reference case		Reference case		Reference case	
Gender								
Female	Reference case		Reference case		Reference case		Reference case	
Male	-0.06	0.835	-0.20	0.430	-0.33	0.211	0.01	0.967
Previously disabled	2.81	<0.001	2.84	<0.001	3.32	<0.001	3.81	<0.001
History of stroke	0.43	0.117‡	0.07	0.809	0.14	0.682	-0.61	0.202
History of TIA	-0.57	0.153‡	-0.18	0.538	-0.24	0.533	0.04	0.926
History of AF	0.45	0.103	0.49	0.123	0.39	0.249	0.48	0.204
History of hypertension	-0.10	0.678	0.04	0.854	-0.08	0.745	-0.07	0.837
History of angina	-0.17	0.657	0.05	0.885	0.12	0.753	-0.52	0.322
History of MI	-0.14	0.684	-0.17	0.622	-0.22	0.586	-0.93	0.092‡
History of diabetes	0.08	0.820	0.40	0.227	0.66	0.069	0.55	0.237
History of PVD	0.63	0.154	0.32	0.437	0.75	0.096	-0.05	0.935
Smoking status								
Never	Reference case		Reference case		Reference case		Reference case	
Previous	-0.16	0.550	-0.08	0.755	-0.22	0.463	0.31	0.353
Current	-0.41	0.321	-0.09	0.805	0.46	0.251	0.35	0.459
Event type								
TIA	Reference case		Reference case		Reference case		Reference case	
Stroke	1.02	0.001	0.54	0.042*	1.02	0.007	0.81	0.033*
Event severity (NIHSS)								
<3	Reference case		Reference case		Reference case		Reference case	
3 to 10	1.69	<0.001	1.37	<0.001	1.17	<0.001	1.73	<0.001
>10	5.18	<0.001	5.02	<0.001	4.51	<0.001	4.80	<0.001
Probability of event								
Definite	Reference case		Reference case		Reference case		Reference case	
Probable†	-1.27	0.045	-0.85	0.168‡	-0.67	0.403	-0.63	0.278
Possible	-0.03	0.945	-0.10	0.800	-0.30	0.527	N/A	N/A
Not coded	-0.92	0.334	-0.79	0.338	-0.50	0.537	N/A	N/A
Recurrent stroke	1.72	0.009	1.20	<0.001	1.11	<0.001	1.00	0.005*
Recurrent TIA	0.07	0.838	-0.11	0.800	0.21	0.391	0.22	0.627
Recurrent CHD	2.04	0.058	1.91	0.004	1.85	0.001	1.94	0.001
Recurrent PVD	N/A	N/A	0.57	0.666	N/A	N/A	1.72	0.078
Residence before event								
Own home	Reference case		Reference case		Reference case		Reference case	
With relative	0.09	0.899	-0.57	0.428	-0.67	0.375	-1.67	0.130
Warden housing	0.08	0.887	-0.67	0.178	-0.58	0.382	-0.80	0.233
Care home	0.01	0.994	1.33	0.177	1.38	0.236	0.69	0.584
Other	-0.25	0.832	0.06	0.962	-0.55	0.736	N/A	N/A
Lived alone	0.23	0.505	-0.34	0.284	-0.49	0.192	-0.63	0.165
Marital status								
Married	Reference case		Reference case		Reference case		Reference case	
Widow	0.18	0.642	0.64	0.055‡	0.72	0.048	1.14	0.022
Single	0.84	0.171‡	1.20	0.012	1.34	0.015	2.12	0.003
Separated	-0.31	0.616	-0.21	0.729	0.35	0.588	0.81	0.249
Partnered	-0.48	0.648	-1.63	0.150	-0.80	0.391	0.30	0.735

Table 5.6 (cont.). Predictors of disability (mRS>2): multiple imputation

Variable	1 month		6 months		1 year		2 years	
	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z
Age left education	-0.08	0.096	-0.01	0.903	-0.04	0.375	-0.03	0.584
Socio-economic class								
I	0.52	0.346	-0.63	0.243	0.25	0.630	-0.21	0.770
II	0.16	0.610	-0.18	0.579	0.57	0.130	0.46	0.285
III-N	0.05	0.882	-0.24	0.456	0.01	0.970	0.17	0.695
III-M	Reference case		Reference case		Reference case		Reference case	
IV	0.12	0.759	-0.09	0.809	0.02	0.963	0.41	0.420
V	0.03	0.938	0.09	0.820	0.66	0.106	0.64	0.245
Employment status								
Full-time	0.14	0.752	-0.53	0.278‡	-0.67	0.178	-1.21	0.041*
Part-time	0.17	0.754	-0.38	0.417	-1.21	0.053	-1.19	0.099
Home carer	0.60	0.391	-0.58	0.480	-0.25	0.769	-1.17	0.459
Unemployed	1.52	0.111	0.94	0.328	-0.02	0.984	0.56	0.622
Cannot work	0.93	0.342	0.55	0.523	0.46	0.622	-0.87	0.533
Retired	Reference case		Reference case		Reference case		Reference case	
Deprivation (IMD score)	0.01	0.523	-0.01	0.931	-0.01	0.573	-0.01	0.546
Constant	-1.46	0.096	-1.83	0.025	-1.73	0.053‡	-2.30	0.032
	No. 1085 $p>\chi^2$ <0.001 Adj. R^2 0.383		No. 999 $p>\chi^2$ <0.001 Adj. R^2 0.325		No. 870 $p>\chi^2$ <0.001 Adj. R^2 0.334		No. 582 $p>\chi^2$ <0.001 Adj. R^2 0.312	

†At two years, patients with possible or un-coded events were all found not to be disabled. As a result, they were aggregated with probable events.
‡Difference in significance: variables found to be significant (p<0.050) in the complete-case analysis.
*Difference in significance: variables not found to be significant (p≥0.050) in the complete-case analysis.

were significantly higher in stroke than TIA patients in all follow-ups, not just at one and 12 months, as in the complete-case analysis. In addition, those patients suffering recurrent strokes after the index event were significantly more likely to be disabled at each follow-up point than those who did not (**Table 5.6**).

Other minor differences between the results of the complete-case and multiple imputation analyses were also observed. Differences in disability levels between age groups were no longer found to be statistically significant at one year (p=0.065). The predictive value of marital status on post-event disability was diminished after imputing for missing cases, with no differences being observed between single and married patients at one month (p=0.171) and between single and widowed patients

at 6 months (p=0.055). Full-time employment was also no longer found to be a significant predictor of disability at six months (p=0.278), but in contrast with the complete-case analysis, differences between patients in full-time employment and retired patients became significant at two years (p=0.041 - **Table 5.6**).

5.3.5 QUALITY OF LIFE

Table 5.7 shows the proportion of patients at each level of each EQ-5D domain. In the 1-month follow-up, a high proportion of patients (73%, n=561) reported no problems in self-care. However, 50% (n=390) of patients reported having at least some mobility problems and some or extreme problems in performing their usual activities (48%, n=366). The majority of patients reported having no pain or discomfort (62%, n=472), and similarly the majority (66%, n=504) reported no anxiety or depression.

Only responses to the mobility (p=0.028) and usual activities (p=0.008) domains varied significantly between the 1- and 6-month follow-ups, with a higher proportion of patients reporting no problems in the 6-month follow-up. A significantly lower proportion of patients reported no problems in mobility at one year than in the 6-month follow-up (p=0.008 - **Table 5.7**).

At the 2-year follow-up, the proportion of patients reporting no problems in each of the domains fell when compared to both the 6- and 12-month follow-ups. However, significant differences across EQ-5D domains at two years and the 6- and 12-month follow-ups were only identified for mobility (p=0.048 in both comparisons). In addition, there were significantly more patients reporting having some or extreme

Table 5.7 EQ-5D responses by follow-up period

Domain	EQ-5D attribute, n (%)														
	All patients					TIA					Stroke				
	Mobility	Self-care	Activities	Pain	Anxiety	Mobility	Self-care	Activities	Pain	Anxiety	Mobility	Self-care	Activities	Pain	Anxiety
1-month															
No	380 (49)	561 (73)	404 (52)	472 (62)	504 (66)	195 (58)	284 (85)	242 (72)	211 (63)	234 (70)	185 (43)	277 (64)	162 (37)	261 (61)	270 (63)
Some	350 (45)	173 (22)	258 (34)	261 (34)	229 (30)	137 (41)	47 (14)	81 (81)	111 (33)	91 (27)	213 (49)	126 (29)	177 (41)	261 (34)	138 (32)
Extreme	40 (5)	35 (5)	108 (14)	32 (4)	32 (4)	3 (1)	3 (1)	12 (4)	12 (4)	9 (3)	37 (9)	32 (7)	96 (22)	32 (4)	23 (5)
Total	770	769	770	765	765	335	334	335	334	334	435	435	435	431	431
6-months															
No	306 (53)	445 (77)	337 (58)	344 (59)	408 (70)	144 (56)	216 (84)	174 (68)	150 (58)	177 (69)	162 (50)	229 (71)	163 (50)	194 (60)	231 (71)
Some	262 (45)	116 (20)	192 (33)	206 (35)	154 (27)	111 (43)	36 (14)	67 (26)	92 (36)	70 (27)	151 (46)	80 (25)	125 (39)	114 (35)	84 (26)
Extreme	14 (2)	20 (3)	51 (9)	31 (5)	19 (3)	2 (1)	5 (2)	16 (6)	15 (6)	10 (4)	12 (4)	15 (5)	35 (11)	16 (5)	9 (3)
Total	582	581	580	581	581	257	257	257	257	257	325	324	323	324	324
1-year															
No	314 (47)	492 (74)	361 (54)	388 (58)	476 (71)	163 (55)	245 (83)	194 (65)	186 (63)	220 (75)	151 (41)	247 (67)	167 (45)	202 (54)	256 (69)
Some	348 (52)	159 (24)	253 (38)	252 (38)	175 (26)	134 (45)	48 (16)	84 (28)	100 (34)	69 (23)	214 (58)	111 (30)	169 (46)	152 (41)	106 (29)
Extreme	6 (1)	17 (3)	54 (8)	27 (4)	15 (1)	0	4 (1)	19 (6)	31 (3)	6 (2)	6 (2)	13 (4)	35 (9)	17 (5)	9 (2)
Total	668	668	668	667	666	297	297	297	296	295	371	371	371	371	371
2-years															
No	191 (45)	312 (73)	224 (52)	240 (56)	290 (68)	91 (51)	144 (81)	109 (61)	106 (59)	122 (68)	100 (40)	168 (68)	115 (46)	134 (54)	168 (68)
Some	224 (52)	97 (23)	161 (38)	169 (40)	126 (30)	86 (48)	30 (17)	56 (31)	67 (37)	53 (30)	138 (56)	67 (27)	105 (42)	102 (41)	73 (29)
Extreme	12 (3)	18 (4)	42 (10)	18 (4)	11 (3)	2 (1)	5 (3)	14 (8)	6 (3)	4 (2)	10 (4)	13 (5)	28 (11)	12 (5)	7 (3)
Total	427	427	427	427	427	179	179	179	179	179	248	248	248	248	248

mobility problems two years after the index event than at the 1-month follow-up (55% vs. 50% respectively; p=0.022).

EQ-5D responses were converted into quality of life estimates using UK population tariffs (**Table 5.8**). One month after TIA or stroke, the average quality of life was 0.70 (S.D. 0.31), and although improvement was found at 6 months, 0.72 (S.D. 0.29), this difference was not statistically significant (p=0.152). Stroke patients did, however, report higher quality of life at six than at one month (p=0.045). One year after stroke or TIA, the average quality of life was 0.73 (S.D. 0.27), representing a higher quality of life than at one month (p=0.045). However, two years after the index event, quality of life was similar to that reported at one month (0.70 for both follow-ups; p=0.878).

Table 5.8 EQ-5D quality of life by follow-up period

Follow-up	Complete cases, mean (S.D.)			Multiple imputation, mean (S.D.)		
	All	TIA	Stroke	All	TIA	Stroke
1-month	0.70 (0.31)	0.78 (0.24)	0.64 (0.34)	0.66 (0.34)	0.77 (0.26)	0.58 (0.38)
Total no.	762	333	429	1085	463	622
6-months	0.72 (0.29)	0.75 (0.28)	0.70 (0.30)	0.70 (0.29)	0.73 (0.28)	0.67 (0.31)
Total no.	580	257	323	999	446	553
1-year	0.73 (0.27)	0.78 (0.25)	0.69 (0.27)	0.71 (0.29)	0.77 (0.26)	0.66 (0.31)
Total no.	666	295	371	870	394	476
2-year	0.70 (0.28)	0.75 (0.27)	0.67 (0.29)	0.67 (0.30)	0.74 (0.27)	0.62 (0.32)
Total no.	427	179	248	582	253	329

At follow-up, EQ-5D responses were missing for 29%, 42%, 23% and 27% at the 1-, 6-, 12- and 24-month follow-ups, respectively. Due to the considerable amount of missing data, multiple-imputation of missing cases was undertaken (**Table 5.8**). After imputing for missing cases, average quality of life was lower in all four follow-ups than that for complete cases.

Quality of life estimates derived using the EQ-VAS are reported in **Table 5.9**. One month after the index event average quality of life was 72 (S.D. 20). Quality of life significantly improved at six months, with patients reporting an average of 75 (p=0.040), and also at one and two years after the index event (p=0.010 and p=0.001, respectively).

Table 5.9 EQ-VAS quality of life by follow-up period

Follow-up	Complete cases, mean (S.D.)			Multiple imputation, mean (S.D.)		
	All	TIA	Stroke	All	TIA	Stroke
1-month	72 (20)	76 (17)	70 (21)	71 (21)	75 (18)	68 (23)
Total no.	728	319	409	1085	463	622
6-months	75 (19)	74 (19)	75 (19)	75 (19)	74 (19)	76 (19)
Total no.	566	253	313	999	446	553
1-year	76 (18)	76 (17)	74 (19)	75 (19)	75 (18)	74 (19)
Total no.	640	285	355	870	394	476
2-year	75 (18)	76 (18)	75 (18)	75 (18)	75 (18)	74 (18)
Total no.	418	173	245	582	253	329

Results of the EQ-VAS were divided by 100 to allow for comparisons with the EQ-5D. Overall, for all follow-ups, quality of life estimates derived using the EQ-5D were lower than those obtained using the EQ-VAS, with statistically significant differences identified at the 6-month (p=0.031) and 2-year follow-ups (p=0.012), and emerging trends observed at one month (p=0.050). The difference in results between the EQ-5D and EQ-VAS was even more marked for stroke patients, with the EQ-5D consistently showing significantly lower quality of life estimates than the EQ-VAS.

Although mean EQ-5D scores were significantly lower than mean EQ-VAS scores, the distribution of quality of life estimates derived from the two instruments had similarities across the four follow-ups (**Figures 5.7** to **5.10**). There was a

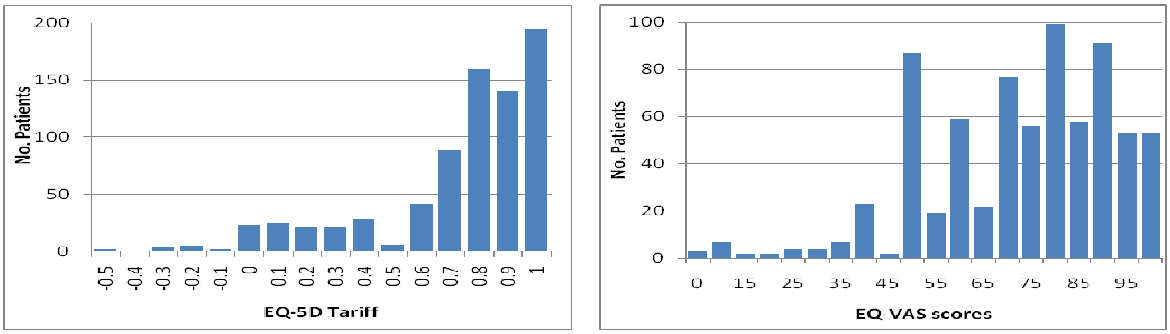

Figure 5.7 One-month quality of life

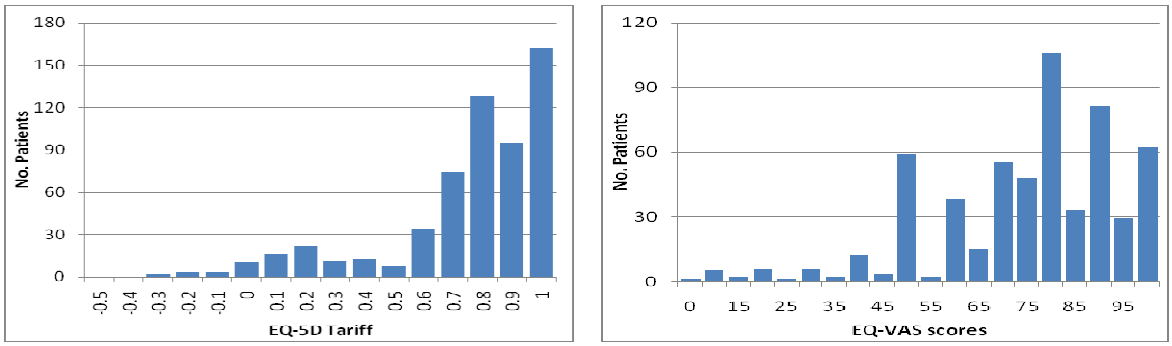

Figure 5.8 Six-month quality of life

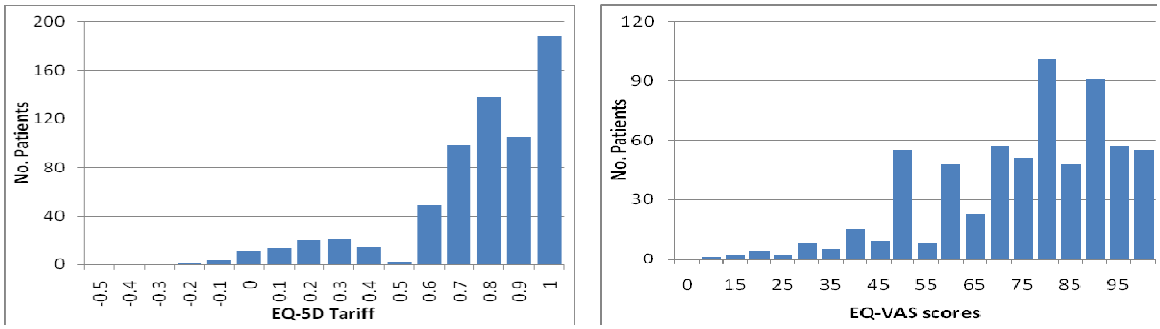

Figure 5.9 One-year quality of life

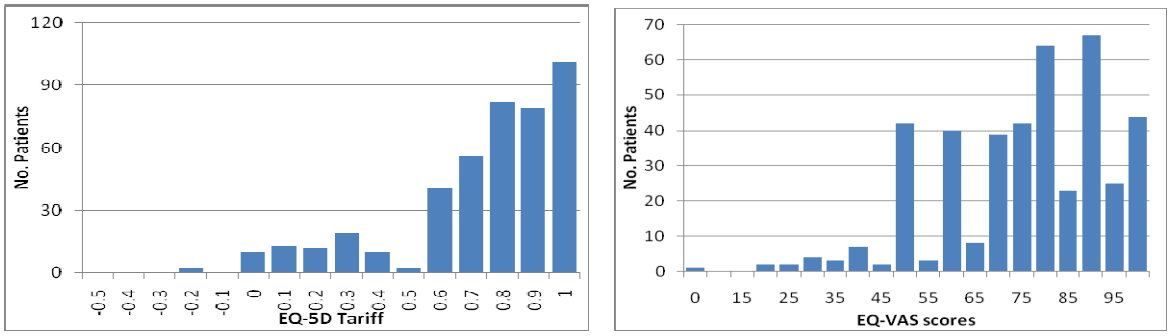

Figure 5.10 Two-year quality of life

considerable number of patients reporting quality of life estimates at the upper-levels of each scale (i.e. 1.0 for the EQ-5D and 100 for the EQ-VAS). The figures also show the relatively low numbers of patients reporting very low quality of life after their cerebrovascular event.

Predictors of EQ-5D quality of life after index TIA or stroke

Univariate predictors of patients' quality of life in each of the four follow-ups after the event are reported in **Appendix 14**. The present section in this chapter will focus on the results of the tobit regressions undertaken in order to identify the baseline predictors of EQ-5D quality of life at 1, 6, 12 and 24 months after stroke or TIA. As a result, predictors of EQ-VAS quality of life, both for the complete-case and multiple-imputation analyses, are reported in **Appendix 15**.

Table 5.10 shows the results of the tobit regression analyses for those patients with complete information. Results showed that event severity was one of the strongest predictors of decreased quality of life. Except for the one-year follow-up, patients with NIHSS scores between 3 and 10 had lower quality of life than those with scores below 3. For those patients with NIHSS scores above 10, quality of life was significantly lower than for those patients with scores below 3 ($p<0.001$ for all follow-ups). Another strong predictor of quality of life was disability before the event, with disabled patients at baseline reporting significantly lower quality of life than those who were not ($p\leq0.001$ for all follow-ups).

Gender was also found to be a predictor of quality of life after index TIA or stroke, with male patients reporting significantly higher quality of life than females, after

Table 5.10 Predictors of EQ-5D quality of life: complete-case analysis

Variable	1 month		6 months		1 year		2 years	
	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z
Age (years)								
<65	-0.33	0.599	0.01	0.959	0.02	0.700	0.08	0.167
65 to 74	0.05	0.144	0.05	0.195	0.06	0.043	0.07	0.081
≥75	Reference case		Reference case		Reference case		Reference case	
Gender								
Female	Reference case		Reference case		Reference case		Reference case	
Male	0.10	0.002	0.03	0.456	0.07	0.022	0.09	0.024
Previously disabled	-0.21	<0.001	-0.24	<0.001	-0.25	<0.001	-0.21	0.001
History of stroke	-0.03	0.404	0.04	0.377	-0.02	0.542	0.07	0.162
History of TIA	0.01	0.808	-0.01	0.804	0.02	0.649	-0.09	0.025
History of AF	-0.08	0.026	-0.04	0.384	-0.02	0.611	-0.01	0.910
History of hypertension	-0.05	0.093	-0.02	0.536	-0.05	0.081	0.01	0.963
History of angina	0.03	0.459	0.02	0.570	-0.03	0.478	-0.07	0.184
History of MI	0.05	0.306	0.02	0.740	0.01	0.754	0.12	0.042
History of diabetes	-0.05	0.293	-0.11	0.048	-0.12	0.011	-0.11	0.045
History of PVD	-0.14	0.010	-0.11	0.070	-0.03	0.500	-0.01	0.945
Smoking status								
Never	Reference case		Reference case		Reference case		Reference case	
Previous	-0.02	0.631	-0.02	0.592	-0.03	0.420	-0.07	0.091
Current	-0.03	0.499	-0.06	0.304	-0.05	0.240	-0.08	0.143
Event type								
TIA	Reference case		Reference case		Reference case		Reference case	
Stroke	-0.09	0.004	-0.05	0.150	-0.08	0.008	-0.07	0.064
Event severity (NIHSS)								
<3	Reference case		Reference case		Reference case		Reference case	
3 to 10	-0.15	<0.001	-0.10	0.018	-0.05	0.125	-0.17	<0.001
>10	-0.62	<0.001	-0.40	<0.001	-0.31	<0.001	-0.36	<0.001
Probability of event								
Definite	Reference case		Reference case		Reference case		Reference case	
Probable	0.04	0.346	-0.03	0.577	0.01	0.901	0.06	0.826
Possible	0.02	0.704	-0.06	0.362	0.11	0.048	0.05	0.484
Not coded	0.17	0.051	-0.05	0.634	-0.07	0.448	-0.68	0.008
Recurrent stroke	-0.15	0.001	-0.17	0.001	-0.11	0.002	-0.06	0.133
Recurrent TIA	-0.07	0.201	-0.05	0.075	-0.02	0.484	0.01	0.642
Recurrent CHD	-0.10	0.549	0.02	0.925	-0.08	0.272	-0.15	0.004
Recurrent PVD	N/A	N/A	0.67	0.705	-0.19	0.157	-0.23	0.004
Residence before event								
Own home	Reference case		Reference case		Reference case		Reference case	
With relative	0.06	0.444	0.09	0.381	-0.13	0.137	0.11	0.717
Warden housing	-0.04	0.578	-0.06	0.490	-0.11	0.092	-0.01	0.939
Care home	0.08	0.472	-0.07	0.749	0.08	0.616	-0.08	0.492
Other	-0.11	0.512	-0.27	0.268	-0.14	0.195	N/A	N/A
Lived alone	-0.03	0.578	-0.01	0.882	-0.01	0.979	0.06	0.340
Marital status								
Married	Reference case		Reference case		Reference case		Reference case	
Widow	-0.02	0.753	-0.03	0.617	-0.04	0.438	-0.10	0.113
Single	-0.01	0.965	0.05	0.508	-0.11	0.119	-0.19	0.018
Separated	0.08	0.305	-0.07	0.432	0.03	0.762	-0.04	0.682
Partnered	0.03	0.811	0.07	0.644	0.03	0.730	-0.01	0.957

Table 5.10 (cont.). Predictors of EQ-5D quality of life: complete-case analysis

Variable	1 month		6 months		1 year		2 years	
	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z
Age left education	0.01	0.153	0.01	0.524	0.01	0.621	0.01	0.450
Socio-economic class								
I	-0.02	0.787	-0.02	0.784	0.01	0.816	-0.10	0.257
II	0.02	0.610	0.02	0.700	-0.02	0.577	-0.02	0.684
III-N	0.04	0.370	0.01	0.897	-0.04	0.398	-0.04	0.375
III-M	Reference case		Reference case		Reference case		Reference case	
IV	-0.04	0.423	-0.07	0.167	-0.11	0.029	-0.18	0.003
V	0.01	0.968	0.08	0.226	0.03	0.600	-0.04	0.439
Employment status								
Full-time	0.09	0.087	0.17	0.003	0.10	0.081	0.16	0.010
Part-time	0.09	0.077	0.10	0.150	0.05	0.329	0.10	0.192
Home carer	-0.03	0.743	-0.03	0.716	-0.01	0.969	-0.14	0.298
Unemployed	-0.23	0.142	-0.33	0.184	0.04	0.887	-0.01	0.915
Cannot work	-0.04	0.612	-0.18	0.191	0.04	0.716	-0.09	0.444
Retired	Reference case		Reference case		Reference case		Reference case	
Deprivation (IMD score)	-0.01	0.342	-0.01	0.360	-0.01	0.962	0.01	0.687
Constant	0.70	<0.001	0.85	<0.001	0.82	<0.001	0.71	<0.001
	No.	748	No.	571	No.	655	No.	415
	$p>\chi^2$	<0.001	$p>\chi^2$	<0.001	$p>\chi^2$	<0.001	$p>\chi^2$	<0.001
	Adj. R^2	0.236	Adj. R^2	0.091	Adj. R^2	0.174	Adj. R^2	0.223

controlling for other covariates, at 1, 12 and 24 months after the index event. Patients' age by contrast was only found to be a predictor of quality of life at one year post-event, with patients aged 65 to 74 reporting significantly higher quality of life than those aged over 75 years (**Table 5.10**).

In all four follow-ups quality of life was found to be lower in stroke than TIA patients. However, after controlling for other factors, these differences were only found to be significant at one and 12 months (p=0.004 and p=0.008, respectively), with a trend emerging for decreased quality of life in stroke patients at the 2-year follow-up (p=0.064). In addition, those patients suffering recurrent strokes between the index event and 1-, 6- and 12-month follow-up reported significantly lower quality of life than those who did not. Patients suffering one or more recurrent CHD events

between index event and the 24-month follow-up reported significantly lower quality of life two years post-event (**Table 5.10**).

Presence of certain comorbidities at time of event also had an impact on quality of life. After controlling for other covariates, patients with diabetes had significantly lower quality of life 6, 12 and 24 months post-event than those without the disease (**Table 5.10**). At one month, history of atrial fibrillation and PVD were found to be predictors of decreased quality of life (p=0.026 and p=0.010, respectively). At two years, history of TIA was found to be a predictor of reduced quality of life (p=0.025), whereas MI history was found to be a predictor of improved quality of life (p=0.042).

No single socio-economic characteristic was found to be an independent predictor of quality of life in all four follow-ups. Despite patients in full-time employment reporting higher quality of life, after controlling for other covariates, significant differences between them and retired patients were only identified at 6 and 24 months post event (p=0.003 and p=0.010, respectively). Trends for improved quality of life did, however, emerge at 1 and 12 months post event (p=0.087 and p=0.081, respectively). Socio-economic class was found to be a predictor at one and two years post-event, with partly skilled patients (class IV) reporting significantly lower quality of life than skilled manual patients (class III-M). In addition, at the 2-year follow-up, single patients had significantly lower quality of life than married patients (**Table 5.10**).

The regression analyses presented above were repeated to take into account the impact of missing data on the results (**Table 5.11**). For the 1- and 12-month follow-

Table 5.11 Predictors of EQ-5D quality of life: multiple imputation

Variable	1 month		6 months		1 year		2 years	
	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z
Age (years)								
<65	-0.01	0.790	0.01	0.936	0.06	0.193	0.10	0.113
65 to 74	0.05	0.119	0.03	0.345	0.05	0.095†	0.07	0.078
≥75	Reference case		Reference case		Reference case		Reference case	
Gender								
Female	Reference case		Reference case		Reference case		Reference case	
Male	0.09	<0.001	0.02	0.545	0.07	0.015	0.05	0.126†
Previously disabled	-0.24	<0.001	-0.20	<0.001	-0.27	<0.001	-0.25	<0.001
History of stroke	-0.02	0.585	0.06	0.087	-0.02	0.460	0.08	0.110
History of TIA	-0.02	0.664	-0.02	0.573	-0.01	0.915	-0.09	0.014
History of AF	-0.08	0.011	-0.08	0.017‡	-0.03	0.328	-0.01	0.754
History of hypertension	-0.03	0.272	-0.02	0.440	-0.03	0.262	-0.01	0.749
History of angina	0.02	0.630	0.05	0.195	-0.03	0.479	-0.03	0.570
History of MI	0.06	0.233	0.03	0.487	0.02	0.660	0.06	0.286†
History of diabetes	-0.05	0.230	-0.11	0.006	-0.12	0.006	-0.10	0.054†
History of PVD	-0.17	0.001	-0.15	0.001‡	-0.02	0.651	-0.01	0.943
Smoking status								
Never	Reference case		Reference case		Reference case		Reference case	
Previous	-0.01	0.943	-0.01	0.668	-0.02	0.522	-0.06	0.082
Current	-0.02	0.555	-0.05	0.207	-0.06	0.152	-0.14	0.008‡
Event type								
TIA	Reference case		Reference case		Reference case		Reference case	
Stroke	-0.08	0.004	-0.03	0.352	-0.09	0.001	-0.08	0.003‡
Event severity (NIHSS)								
<3	Reference case		Reference case		Reference case		Reference case	
3 to 10	-0.17	<0.001	-0.10	0.011	-0.03	0.308	-0.14	0.001
>10	-0.69	<0.001	-0.46	<0.001	-0.43	<0.001	-0.39	<0.001
Probability of event								
Definite	Reference case		Reference case		Reference case		Reference case	
Probable	0.05	0.236	-0.02	0.744	-0.02	0.777	0.04	0.706
Possible	0.03	0.463	-0.06	0.211	0.09	0.046	0.06	0.292
Not coded	0.01	0.271	-0.10	0.267	-0.02	0.823	-0.31	0.117†
Recurrent stroke	-0.15	<0.001	-0.15	<0.001	-0.14	<0.001	-0.09	0.012‡
Recurrent TIA	-0.05	0.311	-0.07	0.006‡	-0.02	0.466	0.02	0.551
Recurrent CHD	-0.12	0.306	0.01	0.848	-0.07	0.223	-0.08	0.180†
Recurrent PVD	N/A	N/A	0.20	0.530	-0.026	0.053	-0.28	0.001
Residence before event								
Own home	Reference case		Reference case		Reference case		Reference case	
With relative	0.06	0.551	0.10	0.259	-0.14	0.082	0.07	0.705
Warden housing	-0.05	0.522	-0.06	0.279	-0.08	0.134	-0.02	0.774
Care home	0.12	0.262	-0.18	0.069	0.03	0.779	-0.07	0.508
Other	-0.10	0.499	-0.32	0.015‡	-0.21	0.158	N/A	N/A
Lived alone	-0.02	0.652	-0.01	0.912	-0.02	0.598	0.02	0.668
Marital status								
Married	Reference case		Reference case		Reference case		Reference case	
Widow	0.01	0.998	-0.02	0.600	-0.05	0.334	-0.09	0.099
Single	0.01	0.867	-0.04	0.539	-0.09	0.226	-0.16	0.015
Separated	0.10	0.141	-0.03	0.652	0.04	0.566	-0.02	0.773
Partnered	-0.04	0.721	-0.01	0.998	-0.03	0.721	-0.07	0.444

Table 5.11 (cont.). Predictors of EQ-5D quality of life: multiple imputation

Variable	1 month		6 months		1 year		2 years	
	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z
Age left education	0.01	0.117	0.01	0.049‡	0.01	0.286	0.01	0.439
Socio-economic class								
I	-0.02	0.770	-0.01	0.775	0.03	0.624	-0.10	0.135
II	0.01	0.718	0.03	0.457	-0.03	0.422	-0.04	0.337
III-N	0.02	0.560	-0.01	0.951	-0.03	0.447	-0.09	0.045‡
III-M	Reference case		Reference case		Reference case		Reference case	
IV	-0.03	0.467	-0.03	0.407	-0.09	0.049	-0.18	0.001
V	-0.01	0.910	0.03	0.531	0.03	0.501	-0.08	0.118
Employment status								
Full-time	0.08	0.168	0.13	0.002	0.06	0.167	0.13	0.019
Part-time	0.07	0.111	0.09	0.077	0.02	0.707	0.09	0.211
Home carer	-0.01	0.942	-0.03	0.664	0.02	0.789	-0.21	0.244
Unemployed	-0.16	.319	-0.15	0.274	-0.16	0.337	0.01	0.985
Cannot work	-0.07	0.594	-0.13	0.222	0.09	0.403	-0.10	0.364
Retired	Reference case		Reference case		Reference case		Reference case	
Deprivation (IMD score)	-0.01	0.481	-0.01	0.973	-0.01	0.794	0.01	0.807
Constant	0.68	<0.001	0.75	<0.001	0.79	<0.001	0.82	<0.001
	No. 1085 $p>\chi^2$ <0.001 Adj. R^2 0.319		No. 999 $p>\chi^2$ <0.001 Adj. R^2 0.183		No. 870 $p>\chi^2$ <0.001 Adj. R^2 0.252		No. 582 $p>\chi^2$ <0.001 Adj. R^2 0.287	

†Difference in significance: variables found to be significant (p<0.050) in the complete-case analysis.
‡Difference in significance: variables not found to be significant (p≥0.050) in the complete-case analysis.

ups, including the imputed values for missing cases into the regression models did not change any of the results of the complete-case analyses. The only exception was for age, whereby at 12 months being aged 65 to 74 years was no longer a predictor of increased quality of life.

For the 6-month follow-up, a number of variables not found to be significant predictors in the complete case-analyses, were now significant independent predictors of quality of life. History of atrial fibrillation (p=0.017) and PVD (p=0.001), recurrent TIAs (p=0.006) and living in a convent, college, or similar accommodation (p=0.015), were all found to be significantly associated with lower quality of life. By

contrast, age at which patients left education was positively associated with increased quality of life (p=0.049).

Differences between the results of the complete-case and multiple-imputation analyses at the 2-year follow-up were the most marked. When missing cases were imputed, gender (p=0.126), history of MI and diabetes (p=0.286 and p=0.054, respectively), probability of event (p=0.117 for un-coded events), and recurrent CHD events (p=0.180), were no longer found to be independent predictors of quality of life. However, suffering a stroke as the index event (p=0.003) and suffering a recurrent stroke between index event and 2-year follow-up (p=0.012), were now found to be independent predictors of reduced quality of life (**Table 5.11**). In addition, skilled non-manual workers (class III-N) were also found to report significantly lower quality of life than skilled manual workers (p=0.045).

5.3.6 CEREBROVASCULAR EVENT IMPACT ON QUALITY OF LIFE

Average quality of life for patients aged over 34 years in the HSE sample was 0.83 (S.D. 0.24). After standardising for age and gender, average quality of life for stroke and TIA patients combined was 0.74 at one month, 0.76 at 6 months, 0.80 at one year, and 0.75 at two years post-event, significantly lower than that for the HSE sample ($p<0.001$ for all follow-ups). However, when quality of life was compared to population norms by event type, quality of life differences between TIA patients and the HSE sample no longer remained statistically significant.

Information on quality of life before the index event was collected for 165 patients recruited in the first year of OXVASC. When asked to recall their quality of life before

the event, patients reported an average quality of life of 0.79 (S.D 0.24), which was significantly higher than the average reported at one (0.70; p<0.001), 6 (0.72; p=0.004), 12 (0.73; p=0.006), and 24 (0.70; p<0.001) months after their event.

There was some evidence, however, that patients suffering more severe events tended to report higher quality of life than those suffering milder events. Patients suffering a stroke recalled a higher quality of life before the event than patients suffering a TIA (0.81 vs. 0.77; p=0.217). Patients with NIHSS scores under 3 reported a quality of life of 0.78 (S.D. 0.25), compared to 0.80 (S.D. 0.25) for patients with NIHSS scores between 3 and 10, and 0.93 (S.D. 0.13) for those with scores above 10. However, due to small patient numbers, these differences did not reach statistical significance (p=0.229).

5.3.7 QALYs

After stroke or TIA, the QALYs gained over a two-year period were 1.19 (95%: 1.16 to 1.23) years (**Table 5.12**). There was a significant difference between the number of QALYs gained by stroke and TIA patients, with TIA patients gaining 0.42 (95% CI of the difference: 0.34 to 0.49) QALYs more than stroke patients. Significant differences were also observed depending on event severity. The QALYs gained by patients with a minor event (NIHSS<3) was 1.37 (95% CI: 1.33 to 1.41) QALYs compared with 0.92 (95% CI: 0.85 to 0.98) QALYs for those suffering a moderate event (NIHSS 3 to 10), and 0.40 (95% CI: 0.30 to 0.50) QALYs for those suffering a severe event (NIHSS>10).

Table 5.12 Quality adjusted life expectancy

	Complete cases, days (95% CI)		Multiple imputation, days (95% CI)	
	Undiscounted	**Discounted**	**Undiscounted**	**Discounted**
All patients	1.19 (1.16 to 1.23)	1.18 (1.15 to 1.22)	1.15 (1.11 to 1.19)	1.14 (1.10 to 1.18)
Stroke type				
TIA	1.45 (1.41 to 1.50)	1.44 (1.39 to 1.48)	1.42 (1.38 to 1.47)	1.41 (1.36 to 1.46)
Stroke	1.03 (0.99 to 1.08)	1.02 (0.98 to 1.07)	0.97 (0.92 to 1.02)	0.96 (0.92 to 1.02)
Event severity				
Minor	1.37 (1.33 to 1.41)	1.36 (1.32 to 1.39)	1.37 (1.33 to 1.41)	1.36 (1.32 to 1.40)
Moderate	0.92 (0.85 to 0.98)	0.91 (0.84 to 0.97)	0.87 (0.78 to 0.96)	0.87 (0.78 to 0.95)
Severe	0.40 (0.30 to 0.50)	0.39 (0.30 to 0.49)	0.24 (0.15 to 0.33)	0.24 (0.15 to 0.33)
Differences				
TIA vs. stroke	0.42 (0.34 to 0.49)	0.41 (0.34 to 0.48)	0.45 (0.37 to 0.53)	0.44 (0.37 to 0.53)
Minor vs. moderate	0.45 (0.36 to 0.54)	0.45 (0.36 to 0.53)	0.49 (0.40 to 0.60)	0.49 (0.41 to 0.60)
Minor vs. severe	0.97 (0.85 to 1.09)	0.96 (0.84 to 1.08)	1.13 (1.03 to 1.22)	1.12 (1.02 to 1.21)
Moderate vs. severe	0.52 (0.38 to 0.65)	0.51 (0.38 to 0.65)	0.63 (0.51 to 0.76)	0.63 (0.50 to 0.70)

When missing EQ-5D data were imputed, results showed that QALYs gained were lower than in the complete-case analysis, especially for more severe events (**Table 5.12**). For example, whereas in the complete-case analysis QALYs gained were 0.40 (95% CI: 0.30 to 0.50) for severe events, multiple imputation results showed these to be as low as 0.24 (95% CI: 0.15 to 0.33).

5.4 DISCUSSION

This chapter began by assessing one-month case-fatality and survival. Results showed that stroke patients had significantly higher case-fatality rates than TIA patients (15% vs. 1%), with 5-year life expectancy being approximately one year longer for TIA patients. Fatality rates also differed significantly between stroke types, with ischaemic strokes having the lowest case-fatality (8%) and ICH and SAH having the highest (40% and 41%, respectively). High case-fatality rates for SAH and ICH have also been documented in previous population-based studies carried out across different geographic areas.[44-50]

Patients surviving their index event had a substantial risk of suffering a recurrent stroke (20%) or CHD event (10%) five years after their index event. In line with other studies,[66;67] the risk of recurrent stroke was found to be at its highest shortly after the initial event, implying that for secondary stroke prevention to work effectively, patients should be assessed and treated urgently after a stroke or TIA. Following on from these results, **Chapter 7** will investigate, using outcome and cost data from OXVASC patients, the impact of an intervention aimed at reducing the delay to rapid assessment and treatment of TIA and minor stroke on patient disability and costs.

Survivors also faced a high risk of becoming disabled, with results showing that disability levels post-index event remained significantly higher than baseline levels. Independent drivers of post-event disability included age, event severity, recurrent CHD and stroke, and marital status. In addition, results showed that stroke patients faced a significantly higher risk of disability than TIA patients. As identified in other population-based studies,[53-56] results showed that although stroke patients improved over time, disability levels remained high two years after stroke onset.

Stroke and TIA not only had a negative impact on life expectancy and disability, but also on patients' quality of life. Evidence from a subset of patients showed that post-event quality of life was significantly worse than before the event. In addition, when compared to English population norms, quality of life for stroke patients was significantly lower after controlling for age and gender. In addition, severe events were associated with significantly lower quality of life than milder events, with other important predictors including disability before event, co-morbidities such as diabetes, atrial fibrillation or history of PVD, recurrent vascular events and gender.

The results from the meta-analysis presented in **Chapter 2** were also observed when using OXVASC data. After controlling for baseline characteristics, severity of event was found to be a significant predictor of reduced quality of life. In addition, the results also confirmed that the EQ-VAS was associated with higher quality of life than when derived using the EQ-5D. In this chapter, statistically significant differences in quality of life derived from the two instruments were identified at the 6-month and 2-year follow-ups, with emerging trends appearing at one month.

Despite the advantages of OXVASC in determining outcomes after stroke or TIA, the limitations of the analyses should also be noted. Firstly, 18% of the dataset was missing due to factors not explained by death or censoring, with much of it being due to missing information on outcome data. Reasons for missing data on living arrangements, disability and quality of life information included: refusal by patients to be followed-up face to face; patients being too disabled/ill to complete a thorough face to face follow-up interview, especially for severe stroke patients; and for patients whose events were coded as possible due to clinical uncertainty in the diagnosis, a proportion of them were not followed-up. Due to the advanced age of the study sample, there was no evidence of a significant number of patients being lost to follow-up due to relocation to areas outside of Oxfordshire. Patients who were not followed-up face to face, were, however, still followed-up for recurrent vascular events or death using the methods of hot and cold pursuit described in **Chapter 4**.

After imputing for missing cases, results showed that average quality of life was lower than in the complete-case analysis. In particular, differences were greatest for

the most severe events (NIHSS>10). These differences could be explained by the fact that severe event cases had a relatively higher proportion of missing data than other severity groups. In addition, the number of patients in this event severity category was considerably lower than for other severity groups, therefore, increasing the uncertainty in the imputed quality of life for these patients.

There was also some evidence suggesting that patients suffering a severe event and reporting no quality of life information were in poorer health than those with follow-up data. For example, for severe events, mean NIHSS was significantly higher for those with missing quality of life information than for those with complete data (15.7 vs. 13.7; p=0.007), with a trend emerging for patients with missing data to be disabled at baseline compared to those with complete data (33% vs. 13%; p=0.072).

Secondly, in order to quantify the impact of stroke or TIA on quality of life, quality of life data before the event are needed. However, its prospective measurement was difficult as patients were not identified until after event onset. As a result, retrospective measurements relying on patients' recollections of their health status are often used.[227-229] In OXVASC, for those patients recruited in the first year only, quality of life before the event was assessed by asking patients to retrospectively complete the EQ-5D.

There was some evidence that patients suffering more severe events reported higher retrospective quality of life than those suffering minor events. One explanation could be that patients suffering more severe events enjoyed higher quality of life than those suffering less severe events. However, another more

plausible explanation, also observed in studies assessing quality of life before prostate cancer[228] and injury,[227] is that patients, after suffering an intervening traumatic event, re-evaluate their prior health state in light of their current experience and exaggerate quality of life levels before the event.

Thirdly, by the end of the 5-year follow-up period approximately 70% of patients were censored, which increased the uncertainty around the survival estimate. Furthermore, quality-adjusted life expectancy was not estimated for the whole 5-year period, as quality of life data was only available 2 years post-event. Although OXVASC patients are being interviewed at 5 years, at the end of data collection for this analysis (30 April 2007) less than 10 patients had been followed-up, and, as a result, this information was not used.

Fourthly, the multivariate regression analyses performed in this chapter to assess the independent predictors of case fatality, disability and quality of life included a large number of covariates. In each regression analysis, significance was set at $p<0.050$, i.e. there was a 5% chance of a false positive result when there was no real difference (Type I error).[214] Therefore, some of the significant results observed in these analyses might have occurred just by chance. Although a number of tests (Bonferroni, Newman-Keuls, Duncan and Scheffe) have been proposed, no simple or totally satisfactory solution has been devised as these tests tend to be conservative and err on the side of non-significance.[230]

Finally, despite 1,199 patients being included in the study, the impact of high-case fatality, censoring and attrition reduced the available study sample. As a result, for

certain characteristics, for example stroke subtype, where there were relatively low numbers of surviving ICH and SAH patients, and socio-economic class, with low numbers of patients at both ends of the scale, the sample size was too small to detect any statistically significant results.

5.5 CONCLUSION

This chapter has quantified the health outcomes experienced by patients after stroke or TIA. The results presented here have shown that cerebrovascular events, especially stroke, pose a significant negative impact on patients' life-expectancy and quality of life, mainly through increased disability levels. Although stroke survivors showed some improvement over time, patients never attained the independence and quality of life levels they enjoyed before the event. In addition, event severity, history of disability and recurrent strokes had an independent negative impact on quality of life and disability. The impact of recurrent strokes on patient health outcomes and costs will be further examined in **Chapter 7**. This chapter will assess the costs and outcomes of an intervention undertaken as part of OXVASC, aimed at reducing the risk of recurrent stroke by reducing the delays to clinical assessment and treatment that TIA and minor stroke patients face in order to reduce the risk of recurrent stroke.

CHAPTER 6

HEALTHCARE RESOURCE USE AND COSTS AFTER A CEREBROVASCULAR EVENT: EVIDENCE FROM OXVASC

6.1 INTRODUCTION

A review of the literature on the costs of stroke and transient ischaemic attack (TIA) was presented in **Chapter 3**. Results from the review showed that costs of cerebrovascular events, when derived from patient-level data, varied considerably, mainly due to differences in the country of origin, populations studied, methods, and cost categories included in each study. Even in studies conducted in the same country, important cost variations were identified, with estimates from the USA, for example, varying twenty-fold. Such variations in the published costs of stroke could have a considerable impact on the results of economic evaluations assessing the cost-effectiveness of stroke interventions.

In a bid to ascertain the validity of stroke and TIA costing studies and to make results more comparable across them, the review set out a number of criteria that studies should ideally fulfil: 1) use of appropriate costing methodologies; 2) use of population-based cohorts; 3) take into account pre-morbid resource use and costs; and 4) assess costs for different patient sub-groups, or be explicit about the patient characteristics on which the findings are based. Except for the use of appropriate costing methodologies, only a small proportion of studies complied with the other three criteria. Most importantly, only 5 of the 120 studies included were based on data derived from population-based studies.

Using the OXVASC sample presented in **Chapter 4**, the objective of this chapter is to evaluate, using a population-based study, the healthcare resource use and costs incurred by patients after a stroke or TIA, and to gain a better knowledge of the main univariate and multivariate predictors of costs 5 years after the index event. This chapter also evaluates, by comparing resource use and costs one year before and after, the extent to which healthcare resource use consumption and costs increased after the index event.

6.2 METHODS

6.2.1 ECONOMIC PERSPECTIVE

The perspective adopted in this analysis was that of the National Health Service (NHS). The direct healthcare costs included were: primary care (including home and surgery visits involving a nurse; and home, surgery and telephone consultations involving a general practitioner - GP); outpatient care (including outpatient diagnostic tests); accident and emergency (A&E); emergency transport; and hospitalisations, day cases and hospital length of stay (LoS – which included all inpatient diagnostic tests and procedures).

The costs of medications over the five year follow-up were not included in the analysis. Although medication usage was assessed at follow-up, this only covered the first two years after TIA or stroke and no information as to the quantity and duration of each medication was provided. However, information on the number of medications taken and their type is reported in a separate analysis.

6.2.2 RESOURCE USE

Resource use data for each patient was obtained from the date of the index TIA or stroke until 30 April 2007. Therefore, minimum follow-up was one month and maximum was 61 months. In addition, for each resource use category, the resources consumed within the 12 months prior to the index event were also obtained.

Primary care

The primary care resource use data included in the analysis were: home and surgery consultations with a nurse; and home, surgery and telephone consultations with a GP. Resource use was obtained by reviewing the computerised primary care records of consenting patients with a TIA or stroke in each of the 9 general practices detailed in **Chapter 4**. Due to the amount of information to be collected, the data collection was recorded in a special proforma (**Appendix 16**). In this proforma, the number of consultations, for each year of follow-up, was tallied and then totalled in each of the different categories of primary care resource use.

Outpatient care

The number of outpatient visits was derived from the computerised hospital records of the Oxford Radcliffe Hospitals (ORH) NHS Trust, which included any outpatient visits to the John Radcliffe Hospital (JRH), the Radcliffe Infirmary (RI), Churchill and Banbury's Horton General Hospital (HGH). The computerised records contained detailed information on the date of the visit, speciality, clinician responsible, and whether it was a new or continuing visit. The visits also included outpatient visits for any diagnostic investigations such as computerised tomography (CT) or magnetic resonance imaging (MRI). Under the ORH records, however, certain diagnostics,

including CT and MRI, were coded under the speciality for which the patient was referred, so for example CT and MRI were coded as vascular outpatient care visits.

Emergency care

The number of visits to the A&E departments of the JRH, RI Eye Hospital and the HGH was derived from the ORH Trust's computerised records. For each visit, the date and hospital in which the patient received care was recorded.

Additionally, for patients visiting the JRH's A&E department, records included details on the patients' method of transport to A&E and the person/institution responsible for their referral. However, this additional information was only available for visits to A&E after 2002. Therefore, for the great majority of patients recruited in the first year of OXVASC (i.e. April 2002 to March 2003), there was no information on the method of transport and referral for the 12 months before the index event. As a result, the only pre-event information not collected was the method of transport or referral to A&E.

Inpatient care

Data on day cases, hospitalisations, and LoS were derived from the computerised records of the ORH NHS Trust, which contained information on all day cases and hospitalisations for the JRH, RI, Churchill Hospital, Banbury's HGH, and 9 community hospitals throughout Oxfordshire (Abingdon, Bicester, Chipping Norton, Didcot, Henley-on-Thames, Oxford, Wallingford, Wantage and Witney).

For each spell in hospital, information was recorded on the date of admission and discharge, transfers between different wards and the dates of these transfers, and

the medical speciality of each ward. Day cases were defined as those in which the patient was discharged in the same day as that in which he/she was admitted. Hospitalisations were defined as those spells in hospital in which the patient was admitted for at least one night. LoS for each hospitalisation spell was calculated as the number of days between hospital admission and hospital discharge. LoS in each medical ward was also calculated.

In addition, a proportion of patients received prolonged intensive inpatient rehabilitation in the Oxford Centre for Enablement (OCE), which is part of the Nuffield Orthopaedic (NOC) NHS Trust. For these hospitalisation spells, one of the OXVASC research nurses obtained all the admission and discharge information pertaining to consenting OXVASC patients.

Medications

Medication usage was derived from patients at the 1, 6, 12 and 24 month follow-ups after index event (more detailed information on the OXVASC follow-up visits can be found in **Chapter 4**). For pre-morbid (i.e. before the event) medications, patients were asked at the initial OXVASC clinical assessment to recall the medications they were taking at the time of the event. For each medication, the main active ingredient, as reported in the British National Formulary (BNF),[231] was recorded as well as the BNF chapter for which that medication was licensed.

Vascular and non-vascular resource use

For resource use after the index event, an attempt was made to establish if the resources consumed by the patient were due to vascular causes (i.e. TIA, stroke,

coronary heart disease, or peripheral vascular disease) or non-vascular causes (i.e. everything else). For primary care and outpatient visits, this was found not to be possible as the exact reasons for the visit were generally not made clear, or because the patient was assessed for multiple conditions. However, for emergency and inpatient care resource use, the cause was possible to determine using the methods of hot pursuit detailed in **Chapter 4**, matching vascular event dates recorded as part of OXVASC with admission dates, or linking resource use information with hospital discharge coding. In the few instances where the cause of admission was not clear, the OXVASC senior neurologist (Prof. Peter Rothwell) determined the cause of hospitalisation by reviewing the patients' medical notes.

6.2.3 COSTS

All NHS resource use was priced using unit costs, with all costs being valued in 2006/07 UK pounds sterling (£). When unit costs were obtained from sources detailing costs before 2006/07, costs were updated using the Hospital and Community Health Services (HCHS) pay and price inflation index.[232]

Unit costs

Unit costs of primary care resource use were obtained from the compendium on Unit Costs of Health and Social Care.[232] Primary care nurse visits were valued at £24 for a home visit, and £9 for a surgery visit. GP visits were valued at £55 for a home visit, £34 for a surgery visit, and £21 for a telephone consultation.

Outpatient (including any outpatient investigations performed) and A&E visits were priced using unit costs derived from the schedule of reference costs for NHS

trusts.[233] An A&E visit was priced at £89.46. For outpatient visits, the NHS reference costs schedule provides unit costs for outpatient visits according to speciality, clinician responsible (e.g. whether medical doctor or nurse), and whether the visit represented a new episode of care or an ongoing one. As the resource use data collected included this information, outpatient visits were priced accordingly. For each speciality, an average cost per visit is reported in **Appendix 17**.

The unit cost of emergency ambulance transportation was derived from the compendium on Unit Costs of Health and Social Care and valued at £337 per journey.[232] The unit cost of air ambulance transportation was derived from a published study.[234] After updating costs to 2006/07 prices,[232] the unit cost of an air ambulance journey was priced at £892.

For each hospital ward, the unit costs per day case/day in hospital were mainly derived from the schedule of NHS reference costs,[233;235] and the 2003/04 NHS trust financial returns.[236] The only exception was for the cost per day in a stroke unit, which was derived from published studies.[173;237] For each speciality ward, the unit cost per day in hospital and day case is reported in **Appendix 18** and **Appendix 19**, respectively, together with the source from which it was derived. The unit costs employed to price inpatient resource use also included the costs of treatments, investigations and interventions typically performed in each speciality ward.

Total costs

For each resource use category, the numbers of resources consumed were multiplied by their unit cost. These were then summed over all resource categories to obtain a total cost for each patient.

As with health outcomes, in economic terms, costs accruing over the long term should be given less weight than those occurring in the near future due to individuals' time preferences (i.e. individuals are willing to receive benefits sooner and incur costs later).[81;83] Therefore, given this positive time preference, total care costs were discounted to present values using an annual rate of 3.5%.[211]

6.2.4 STATISTICAL ANALYSIS

All statistical analyses were undertaken using STATA version 10. For all univariate and multivariate analyses, statistical significance was set at $p<0.050$.

Univariate analysis

The average number of medications being consumed at each follow-up point was reported alongside their 95% confidence intervals (CI), which were derived assuming a normal distribution of the mean. The number of patients taking each particular medication was reported as a proportion, with 95% CIs being computed. Statistical differences were evaluated using standard chi-square tests for proportions and Student's t-test for mean number of medications.[209]

As medication information was derived at follow-up, in the same way as quality of life, living arrangements and disability (**Chapter 5**), there was a considerable amount of missing data. In order to assess the impact of missing data on the results, missing

data on the number of medications being consumed at each follow-up point was imputed using the same techniques as those reported in **Chapter 5**.

The number of primary, outpatient and emergency care visits, as well as the number of day cases and hospitalisations were treated as count data, and reported as rates (i.e. number of visits/hospitalisations per patient follow-up year) together with their 95% CIs, which were derived assuming a Poisson distribution.[209] Total costs, and the number of days in hospital were treated as continuous variables. The total number of days in hospital was calculated by summing the LoS in each hospitalisation spell. As the number of days in hospital was dependent on whether the patient was hospitalised or not, mean estimates were reported for those patients that were hospitalised.

However, as shown in **Chapter 5**, for a great proportion of patients the follow-up period was less than 5 years and as a result these patients had censored resource use and cost data. For count data, the shorter follow-up for censored patients was taken into account in the denominator used to calculate the rate (i.e. years of follow-up). However, for continuous data, such as days in hospital and costs, it is well accepted that ignoring the issue of censoring will result in biased mean estimates.[238] Therefore, costs and days in hospital were adjusted for censoring using the method developed by Lin et al. (1997).[239]

Using this method, the study period was partitioned into smaller one month time periods (61 months after index event). For each period, the mean costs and days in hospital for all patients alive at the beginning of the period were estimated. These

mean estimates were then weighted by the Kaplan Meier Sample Average (KMSA) estimator, i.e. the probability of survival in a given time period, conditional on having survived the previous period.[239] The weighted estimates were then summed over all periods to obtain an estimate of the mean censored costs and mean censored days in hospital. Bootstrap estimation, which was performed 1000 times, was used to derive 95% CIs around the mean-censored adjusted cost and resource use estimates.[210]

All resource estimates and costs are presented for all patients, and separately for stroke and TIA patients. However, results from the review presented in **Chapter 3** showed that inpatient care accounted for the highest proportion of total costs after a cerebrovascular event. As a result, a more in-depth univariate analysis was undertaken to explore if statistically significant differences in day-cases, hospitalisations and days in hospital, conditional on admission, were observed across clinical, demographic and socio-economic characteristics. For count variables, significant differences between sub-groups were tested using a Poisson distribution.[209]

Due to censoring, costs and days in hospital, conditional on admission, were evaluated using a cross-sectional time series dataset,[240] in which the costs and days in hospital observed in each of the 61 month follow-up periods were estimated, and clustered at the level of the patient. For patients who died during their follow-up, days in hospital and costs were set to 0 for all periods after death. Statistical differences between sub-groups were then evaluated using analysis of variance (ANOVA).[209] To allow for censoring, all ANOVA analyses were adjusted using inverse probability

weighted (IPW) estimators,[240-242] in order to place a higher weight on those observations that were more likely to be censored, given the patient's characteristics.

To obtain IPW estimators, a series of logistic regressions were estimated for response (i.e. outcome=1, the patient was not censored and resource use and cost data were obtained) and non-response (i.e. outcome=0, the patient was censored and no resource use and cost data could be obtained), conditional on the patients' individual characteristics, for each of the 61 follow-up periods. Results from these regressions provided the probability of not being censored at the beginning of each follow-up period, given the individual characteristics of each patient. The inverse of this probability was then calculated to obtain the IPW estimator. These IPW estimators were then included in the ANOVA analysis performed for each patient characteristic. In STATA the command used to weight each observation by the IPW was `pweight`.

Resource use and costs one year before and after index cerebrovascular event

For each category, resource use and costs 12 months before the index TIA or stroke were compared with the resource use patterns and costs 12 months after the event. For count variables, resource use rates before and after the event were reported together with their S.E. Rate differences between the two time-periods were reported alongside 95% confidence intervals (CI), with statistical differences evaluated assuming a Poisson distribution.[209]

For patients recruited in the fifth year of OXVASC (i.e. April 2006 onwards), the follow-up period was less than one year, and as a result these patients had censored

resource use and cost data. To adjust for censoring, the method developed by Lin et al. (1997)[239] reported above was employed. For this analysis, however, the follow-up period after the event was broken into 12 one-month periods. Mean costs and days in hospital were reported alongside S.E., with mean differences between the two time-periods being reported alongside 95% CIs. S.E.s and 95% CIs were derived in both cases from 1000 bootstrap estimates.[210]

Multivariate analysis

The predictors of total costs over the 5-year follow-up period were examined in multivariate regression analyses. In addition, as inpatient care was shown to account for the biggest proportion of costs after a cerebrovascuar event (**Chapter 3**), it was deemed important to evaluate which patient characteristics independently predicted inpatient care resource use.

Due to censoring, costs and days in hospital, conditional on admission, were evaluated using a cross-sectional time series dataset.[240] In the multivariate analyses, however, the dataset was dynamic in that the models included the lags of the resource use/cost estimates as covariates, i.e. the costs or resource use consumption observed in the previous time period.[240] For these analyses, the study period was partitioned into smaller one year time periods (5 years after index event), and the costs and resource use consumption observed at each year of follow-up were estimated. As patients could have a maximum of 5 observations (i.e. costs and resource use for each year of follow-up), in all the regressions performed observations were clustered at the level of the patient.

For both costs and inpatient care resource use after the index TIA or stroke, the predictors examined included event characteristics, age and gender, past history of disease and disability, socio-economic characteristics, presence of any recurrent vascular events during each follow-up year, and costs or resource use incurred during the previous year. In the multivariate regression analysis of inpatient care resource use, a two-part model was used. For day cases and hospitalisations, a logistic regression was performed assessing the baseline predictors of hospital admission in each year of follow-up. Conditional on being hospitalised in a given year, the number of days in hospital was logarithmically transformed to normalise the distribution and regressed over the same covariates as those used for hospitalisation using ordinary least squares (OLS). For costs, the data were also logarithmically transformed and then regressed over baseline covariates, recurrent events, and previous costs. Due to the high-case fatality rates and mortality, especially after stroke, the costs incurred during the 5-year follow-up period could, amongst other things, depend on patients' survival time. As a result, for total costs, two separate regression analyses were undertaken one for patients who died during follow-up and another one for patients who survived.

Except for the analysis of costs in patients who died, to allow for patient non-response (i.e. missing data due to censoring) all observations in the regression analyses were weighted using the IPW,[240-242] using the methods reported in the univariate analysis section. Goodness-of-fit of each regression model was assessed using McFadden's Adjusted R^2. Model specification was tested using Preigbon's link test.[219] Multicollinearity was measured from the tolerance value and its inverse, the variance inflation factor (VIF).[220]

6.3 RESULTS

A total of 1282 patients suffered a cerebrovascular event (788 strokes and 494 TIA) between April 2002 and March 2007 (**Chapter 4**). The analyses in this chapter are based on a total patient sample of 1,199 consenting patients (723 strokes and 476 TIA). As reported in **Chapter 5**, average follow-up was 761 (S.D. 555) days, which translated into 2,480 patient years of follow-up (1,134 for TIA patients and 1,346 for stroke patients). By the end of the 5-year follow-up period, a total of 856 (71%) patients were categorised as being censored.

6.3.1 RESOURCE USE AND COSTS ONE YEAR BEFORE AND AFTER INDEX CEREBROVASCULAR EVENT

Resource use

For all resource use categories, except day cases, resource use 12 months after the index cerebrovascular event was significantly higher than for the 12 months preceding the event (**Table 6.1**).

For 17 (1%) patients, the medical primary care records were not identified, and as a result primary care resource use was estimated for 1,182 (473 TIA and 709 stroke) patients. For these patients, there was a considerable increase in the number of visits to the GP (including home, surgery and telephone visits – **Table 6.1**). The number of GP visits increased from 6,983 12 months before the event to 9,865 12 months after the index event, translating into 6.00 and 10.84 visits per patient year before and after the event, respectively, a significant increase of 4.83 (95% CI: 4.69 to 4.99) GP visits per patient year. During the 12 months before and after the index

event there were 4,655 and 5,311 nurse visits, respectively. This translated into 4.01 and 5.84 nurse visits per patient year for the 12 months before and after the event, respectively, representing an increase of 1.83 (95% CI: 1.76 to 1.90; p<0.001) visits per patient year. Significant increases in both GP and nurse visits 12 months after index event were also identified for TIA and stroke patients (**Table 6.1**).

Table 6.1 Resource use one year before and after index cerebrovascular event

	Before (S.E.)	After (S.E.)	Difference (95% CI) (After – Before)	p>|z|
Mean number of visits per patient per follow-up year†				
Primary care: GP				
All patients	6.00 (0.01)	10.84 (0.01)	4.83 (4.69 to 4.99)	<0.001
TIA	6.47 (0.01)	10.73 (0.01)	4.26 (4.06 to 4.56)	<0.001
Stroke	5.71 (0.01)	10.95 (0.01)	5.23 (5.02 to 5.45)	<0.001
Primary care: nurse				
All patients	4.01 (0.01)	5.84 (0.01)	1.83 (1.76 to 1.90)	<0.001
TIA	4.13 (0.01)	6.16 (0.01)	2.03 (1.92 to 2.16)	<0.001
Stroke	3.93 (0.01)	5.57 (0.01)	1.63 (1.55 to 1.72)	<0.001
A&E visits				
All patients	0.26 (0.01)	0.74 (0.03)	0.48 (0.41 to 0.54)	<0.001
TIA	0.26 (0.02)	0.54 (0.04)	0.28 (0.20 to 0.36)	<0.001
Stroke	0.27 (0.04)	0.90 (0.02)	0.64 (0.55 to 0.73)	<0.001
Outpatient visits				
All patients	1.74 (0.04)	5.28 (0.07)	3.54 (3.37 to 3.71)	<0.001
TIA	1.59 (0.06)	5.37 (0.11)	3.78 (3.53 to 4.03)	<0.001
Stroke	1.85 (0.05)	5.22 (0.10)	3.37 (3.15 to 3.59)	<0.001
Day cases				
All patients	0.34 (0.02)	0.32 (0.02)	0.02 (-0.03 to 0.07)	0.412
TIA	0.16 (0.02)	0.33 (0.03)	0.17 (0.11 to 0.24)	<0.001
Stroke	0.42 (0.02)	0.34 (0.03)	-0.08 (-0.15 to -0.01)	0.029
Hospitalisations				
All patients	0.31 (0.02)	0.99 (0.03)	0.68 (0.61 to 0.76)	<0.001
TIA	0.24 (0.02)	0.64 (0.04)	0.40 (0.31 to 0.49)	<0.001
Stroke	0.35 (0.02)	1.28 (0.05)	0.93 (0.82 to 1.03)	<0.001
Mean days in hospital, conditional on admission†				
All patients	20 (2)	43 (2)	23 (17 to 28)	<0.001
TIA	15 (3)	35 (5)	20 (16 to 29)	<0.001
Stroke	23 (3)	45 (3)	22 (16 to 29)	<0.001

†For all resource use categories, excepting primary care, estimates were derived from the 1,199 (476 TIA and 723 stroke) patients included in OXVASC. For primary care, due to missing primary care records in 17 patients, estimates were derived from 1,182 (473 TIA and 709 stroke) patients.

The number of A&E visits rose from 316 during the 12 months before the index stroke or TIA to 701 during the 12 months after the event. For each patient year, this translated into 0.26 and 0.74 visits for the year before and after the event, respectively, an increase of 0.48 (95% CI: 0.41 to 0.54; p<0.001) visits per patient year (**Table 6.1**). For stroke patients, visits rose by 0.64 (95% CI of the difference: 0.55 to 0.73; p<0.001) per patient year. For TIA patients, although the increase in attendances was smaller than that for stroke patients, a significant increase of 0.28 (95% CI: 0.20 to 0.36; p<0.001) visits per patient year was observed.

During the 12 months before and after the index event there were 2090 and 5007 outpatient visits, respectively. This translated into 1.74 and 5.28 visits per patient year for the 12 months before and after the event, respectively, representing an increase of 3.54 (95% CI: 3.37 to 3.71; p<0.001) visits per patient year (**Table 6.1**). For TIA patients, visits per patient year increased by 3.78 (95% CI: 3.53 to 4.03; p<0.001), with a similar significant increase observed for stroke patients (3.37 visits per patient year; 95% CI: 3.15 to 3.59; p<0.001).

The overall number of day cases did not vary significantly for the 12 months before and after the index event (**Table 6.1**). However, when these were stratified by event type, significant differences were found for both stroke and TIA patients, although these were in opposite directions. For TIA patients, the number of day cases significantly increased 12 months after the index event by 0.17 (95% CI: 0.11 to 0.24; p<0.001) per patient year, whereas for stroke patients, the number of day cases significantly decreased by 0.08 (95% CI: -0.15 to -0.01) per patient year.

The actual number of hospitalisations increased by 572 in the 12 months after the index event (939 after the event vs. 367 before the event), a significant increase of 0.68 (95% CI: 0.61 to 0.76; p<0.001) hospitalisations per patient year. Conditional on being hospitalised, the number of days in hospital was also significantly higher 12 months after the event (increase of 23 days; 95% CI: 17 to 28). Significant increases in both hospitalisations and days in hospital, conditional on admission, were also observed for TIA and stroke patients (**Table 6.1**).

Costs

Costs one year before and after the index TIA or stroke were estimated for those patients with data on all the resource use categories assessed. As a result, the 17 patients for whom primary care resource use was not assessed due to missing primary care records were not included in the analysis. Therefore, the cost estimates presented in **Table 6.2** are based on 1,182 (473 TIA and 709 stroke) patients.

Due to the significant increases in consumption in nearly all of the resource use categories investigated, total average costs were significantly higher 12 months after the index TIA or stroke than for the 12 months preceding the event (**Table 6.2**). Total average costs increased from £1,652 12 months before the event to £7,709 12 months after the index stroke or TIA, a significant increase of £6,057 (95% CI of the difference: 5,266 to 6,855) per patient. The increased costs in hospitalisations, £5,564 (95% CI: 4,797 to 6,349) per patient, explained for much of the increase in total costs. For stroke patients, average total costs 12 months after the event increased considerably more than for TIA patients, with costs increasing by £7,514

(95% CI: 6,447 to 8,560) for stroke patients compared to a smaller increase of £3,893 (95% CI: 2,797 to 5,104) for TIA patients (**Table 6.2**).

Table 6.2 Costs one year before and after index cerebrovascular event

	Before (S.E.)	After (S.E)	Difference (95% CI) (After – Before)
Mean costs, £†			
Primary care			
All patients	245 (7)	365 (9)	120 (105 to 137)
TIA	252 (12)	404 (13)	152 (130 to 174)
Stroke	240 (9)	339 (12)	99 (79 to 121)
A&E			
All patients	23 (2)	53 (2)	30 (26 to 34)
TIA	23 (2)	45 (3)	22 (17 29)
Stroke	24 (2)	59 (3)	35 (30 to 41)
Outpatient care			
All patients	164 (9)	520 (15)	356 (332 to 381)
TIA	147 (11)	606 (20)	459 (428 to 489)
Stroke	175 (13)	464 (22)	289 (251 to 326)
Inpatient day cases			
All patients	143 (56)	128 (12)	-15 (-126 to 57)
TIA	72 (16)	149 (21)	77 (33 to 119)
Stroke	191 (87)	113 (13)	-78 (-255 to 30)
Inpatient hospital care			
All patients	1077 (139)	6641 (467)	5564 (4797 to 6349)
TIA	712 (148)	3894 (672)	3182 (2113 to 4396)
Stroke	1321 (196)	8487 (620)	7166 (6133 to 8206)
TOTAL COSTS			
All patients	1652 (156)	7709 (468)	6057 (5266 to 6855)
TIA	1205 (160)	5098 (678)	3893 (2797 to 5104)
Stroke	1951 (220)	9465 (624)	7514 (6447 to 8560)

† Mean costs are reported alongside standard errors (S.E.). Mean cost differences are reported alongside 95% CIs.

6.3.2 TWO-YEAR MEDICATION CONSUMPTION

The average number of medications consumed by patients is reported in **Table 6.3**. Although there were only 3% of missing cases for pre-morbid medication usage, follow-up data were missing for between 19% and 28% of patients depending on follow-up (after taking into account the number of patients who were either censored or dead at each follow-up point).

Before the index event, the average number of medications consumed was 3.69 (S.D. 2.75), with 150 (13%) patients reporting no medication usage. By contrast, after the index TIA or stroke, the average number of medications consumed were significantly higher at each follow-up point than before the event ($p<0.001$ for all follow-ups), with more than 5 medications being taken, on average, across the four follow-up periods (**Table 6.3**). There were no significant differences, however, in medication usage between the different follow-ups after event. Results of the multiple imputation analysis showed comparable results.

Table 6.3 Medications consumed after index cerebrovascular event[a]

	Complete cases, mean (S.D.)			Multiple imputation, mean (S.D.)		
	All patients	**TIA**	**Stroke**	**All patients**	**TIA**	**Stroke**
Baseline	3.69 (2.75)	3.67 (2.76)	3.70 (2.75)	3.68 (2.76)	3.68 (2.79)	3.69 (2.74)
No. patients	1159	449	710	1199	476	723
1 month	5.33 (2.61)	5.20 (2.29)	5.42 (2.82)	5.36 (2.68)	5.19 (2.47)	5.49 (2.83)
No. patients	853	359	494	1085	463	622
6 months	5.55 (2.72)	5.54 (2.49)	5.57 (2.88)	5.50 (2.75)	5.42 (2.56)	5.57 (2.91)
No. patients	780	338	442	999	446	553
1 year	5.57 (2.70)	5.38 (2.45)	5.72 (2.88)	5.53 (2.71)	5.40 (2.51)	5.64 (2.88)
No. patients	704	306	398	870	394	476
2 years	5.92 (3.01)	5.79 (2.89)	6.02 (3.10)	5.92 (3.08)	5.72 (2.98)	6.08 (3.21)
No. patients	420	179	241	582	253	329

By event type, the average number of medications significantly increased between the four follow-ups after the event and baseline ($p<0.001$ for all follow-ups both for stroke and TIA). Comparisons between TIA and stroke patients showed that there were no significant differences in the number of medications being consumed either at baseline or at follow-up (**Table 6.3**).

[a] As with other outcome data collected at follow-up, 8 TIA patients were followed-up as stroke patients because their TIA was only identified when they sought medical attention for a subsequent stroke. As a result, for the analysis of medications, a total of 731 patients were followed-up for stroke and 468 for TIA.

Details of the 30 most consumed medications at each follow-up point, including the BNF chapter for which they were licensed, are given in **Appendix 20**. The top four medications consumed at each follow-up, including before the event, were aspirin, bendroflumethiazide, atenolol and simvastatin, all of which were coded under BNF chapter 2 (i.e. cardiovascular system). However, the proportion of patients consuming these medications increased significantly between baseline and each of the four follow-ups after the index event. For example, the proportion of patients taking aspirin increased significantly from 43% (n=499) at baseline to above 70% at each follow-up after the event ($p<0.001$ for all follow-ups). Likewise for simvastatin, the proportion of patients taking this medication significantly increased from 18% (n=207) to over 60% at each proceeding follow-up ($p<0.001$ for all follow-ups)

6.3.3 FIVE-YEAR RESOURCE USE

Primary care

The computerised GP records for 17 patients were not obtained. Therefore, primary care resource patterns were derived for 1,182 (473 TIA and 709 stroke) patients.

Table 6.4 Primary care resource use after index cerebrovascular event

	All patients (n=1,182)	TIA (n=473)	Stroke (n=709)
Mean number of visits per patient per follow-up year (95% CI)			
Nurse visits			
Total	6.06 (5.96 to 6.16)	6.50 (6.35 to 6.65)	5.67 (5.54 to 5.81)
Home	1.29 (1.24 to 1.34)	1.23 (1.17 to 1.30)	1.34 (1.28 to 1.41)
Surgery	4.77 (4.68 to 4.86)	5.27 (5.13 to 5.41)	4.33 (4.22 to 4.45)
GP visits			
Total	9.02 (8.90 to 9.15)	9.23 (9.05 to 9.41)	8.85 (8.48 to 9.01)
Home	1.16 (1.12 to 1.21)	0.98 (0.92 to 1.04)	1.33 (1.27 to 1.40)
Surgery	5.70 (5.60 to 5.80)	6.03 (5.59 to 6.18)	5.40 (5.25 to 5.54)
Telephone	2.16 (2.10 to 2.22)	2.22 (2.13 to 2.31)	2.11 (2.03 to 2.19)

After index TIA or stroke, there were a total of 13,978 nurse visits, of which 2,975 (21%) were home visits and 11,003 (79%) were surgery visits, and 20,821 GP visits, 2,687 (13%) of which were home visits, 13,145 (63%) were surgery visits and 4,989 (24%) were telephone consultations. In terms of average number of visits per patient year, the most common type of consultation was surgery visits to the GP, with 5.70 (95% CI: 5.60 to 5.80) visits per patient year, followed by surgery visits to the community nurse (4.77 visits per patient year; 95% CI: 4.68 to 4.86 – **Table 6.4**). When home, surgery and telephone consultations were added together, stroke patients had significantly fewer visits to the GP per year than TIA patients (average difference -0.38 visits per patient year; 95% CI difference: -0.63 to -0.14, p=0.022). However, stroke patients had significantly more GP home visits than TIA patients (1.33 vs. 0.98; 95% CI difference: 0.26 to 0.44, p<0.001).

Emergency care

After the index TIA or stroke there were 1,179 visits to an A&E department, with 675 (56%) patients attending A&E at least once during the follow-up period, representing 0.48 (95% CI: 0.45 to 0.50) visits per patient year (**Table 6.5**).

Table 6.5 A&E resource use after index cerebrovascular event

	All patients (n=1199)	TIA (n=476)	Stroke (n=723)
Mean number of visits per patient per follow-up year (95% CI)			
A&E visits			
Total	0.48 (0.45 to 0.50)	0.39 (0.35 to 0.42)	0.55 (0.51 to 0.59)
Vascular	0.22 (0.21 to 0.24)	0.15 (0.13 to 0.17)	0.29 (0.26 to 0.32)
Non-Vascular	0.25 (0.23 to 0.27)	0.24 (0.21 to 0.27)	0.26 (0.23 to 0.29)

There were a total of 1,047 (87%) visits to the A&E department of the JRH, with the great majority (83%) of patients arriving to A&E by emergency ambulance (**Table**

6.6). For a sizeable proportion of visits, the method of transport was unknown, although it was clear from the medical records that patients transported by ambulance were not coded in this category. For over 75% (n=796) of A&E visits, patients were referred directly by the emergency services after contact by the patient, or his/her relatives, through 999 telephone services (**Table 6.7**).

Table 6.6 Method of transport for those patients visiting A&E at the JRH

	No. (n=1047)	%
Ambulance	870	83.09
Private transport	15	1.43
Public transport	1	0.10
Air ambulance	1	0.10
Other/Unknown†	159	15.19

†No patient transported by ambulance was coded as Other/Unknown.

Table 6.7 Method of referral for those patients visiting A&E at the JRH

Method of referral	No. (n=1047)	%
Emergency services	796	76.03
Self/relative/friend	129	12.32
GP	85	8.12
Healthcare provider	13	1.24
Work place	6	0.57
NHS Direct	1	0.10
Other/Unknown	17	1.62

Outpatient care

After the index cerebrovascular event there were 8,807 outpatient visits. Over 25% (n=2,308) of outpatient visits were made to the neurology department, 12% (n=1,041) were to vascular medicine (speciality under which CT and MRI were included) and a further 12% (n=1020) were to the ophthalmology department. A full list of the speciality to which the outpatient visits were made is given in **Appendix 17**.

In terms of number of visits per patient year, on average, patients had 3.55 (95% CI: 3.48 to 3.63) outpatient visits per patient year, with a similar number of outpatient

visits per patient year for both stroke and TIA patients (3.53, 95% CI: 3.43 to 3.63; and 3.57, 95% CI: 3.47 to 3.69, respectively).

Inpatient care

After the index cerebrovascular event there was a total of 1,461 hospitalisations, 770 (53%) of which were due to vascular causes, and 834 day cases, of which 121 (15%) were due to vascular causes. A considerable minority of patients (38%, n=451), were not hospitalised during the entire follow-up after TIA or stroke, a proportion which was significantly higher for TIA than stroke patients (50% vs. 29%; p<0.001).

Table 6.8 Inpatient resource use after index cerebrovascular event

	All patients (n=1199)	TIA (n=476)	Stroke (n=723)
Mean number of admissions per patient per follow-up year (95% CI)			
Day cases			
Total	0.34 (0.31 to 0.36)	0.33 (0.30 to 0.37)	0.34 (0.31 to 0.37)
Vascular	0.05 (0.04 to 0.06)	0.03 (0.02 to 0.05)	0.06 (0.05 to 0.08)
Non-Vascular	0.29 (0.27 to 0.31)	0.30 (0.27 to 0.33)	0.28 (0.25 to 0.31)
Hospitalisations			
Total	0.59 (0.56 to 0.62)	0.45 (0.42 to 0.50)	0.70 (0.66 to 0.75)
Vascular	0.31 (0.29 to 0.33)	0.18 (0.15 to 0.20)	0.42 (0.39 to 0.46)
Non-Vascular	0.28 (0.26 to 0.30)	0.28 (0.25 to 0.31)	0.28 (0.25 to 0.31)
Mean days in hospital, conditional on hospital admission (95% CI), due to:			
All causes	60 (55 to 66)	55 (43 to 68)	62 (56 to 69)
Vascular causes only	46 (41 to 52)	44 (33 to 55)	47 (42 to 52)
Non-vascular causes only	44 (37 to 50)	41 (30 to 52)	46 (36 to 54)

When calculated in rates, there were 0.59 (95% CI: 0.56 to 0.62) hospitalisations per patient year and 0.34 (95% CI: 0.31 to 0.36) day cases per patient year (**Table 6.8**). For stroke patients, vascular hospitalisations accounted for a higher proportion of total hospitalisations than for TIA patients (60% vs. 40%, p=0.029). However, for both TIA and stroke patients, only a small proportion of day cases were due to

vascular causes (**Table 6.8**). A break-down of days in hospital, and number of day cases, by clinical speciality is shown in **Appendix 18** and **19**, respectively.

When only hospitalisations for vascular causes were considered (i.e. non-vascular resource use was excluded from the analysis), conditional on at least one hospitalisation, the average days in hospital was 46 (95% CI: 41 to 52) per patient (**Table 6.8**). When the same analysis was undertaken, this time for non-vascular hospitalisations, mean days in hospital, conditional on admission was 44 (95% CI: 37 to 50) days, similar to that for vascular causes. Overall, irrespective of cause, mean days in hospital after the 5 year follow-up period after index stroke or TIA conditional on at least one hospital admission was 60 (95% CI: 55 to 66) days[b].

By event type, stroke patients were significantly more likely to be hospitalised than TIA patients (0.70 vs. 0.45 hospitalisations per patient year, respectively; p<0.001), with a trend for stroke patients to have increased number of days in hospital than TIA patients, conditional on at least one hospitalisation (62 vs. 55 days; p=0.077 – **Table 6.8**).

Differences in hospitalisation rates were also identified in terms of stroke subtype (p=0.014; data not shown in the table). Unknown and intracerebral haemorrhagic strokes had the highest hospitalisation rates (1.60 and 1.24 hospitalisations per patient year, respectively) followed by ischaemic strokes and SAH (0.98 and 0.96 hospitalisations per patient year). Conditional on at least one hospital admission,

[b]As shown in Table 6.8, the sum of the number of days in hospital conditional on vascular and non-vascular causes did not equal the overall number of days in hospital (i.e. conditional on any hospitalisation). This was because a considerable proportion of patients did not have hospitalisations for both causes.

however, both ischaemic stroke and SAH patients had the highest number of days in hospital (65 days in both cases), with ICH patients spending 45 days in hospital over the 5-year follow-up and unknown strokes, due to very high case fatality (**Chapter 5**), spending 24 days in hospital over the 5-year follow-up period ($p<0.001$).

As results from the published literature have shown that inpatient care costs represent the highest proportion of total care costs (**Chapter 3**), a univariate and multivariate analysis identifying the predictors of inpatient care resource was performed. Results of the univariate analyses are presented in **Appendix 21**, with those from the multivariate regression analyses being reported in **Table 6.9**.

Results of the regressions showed that after the index cerebrovascular event, there were no significant differences, after controlling for other covariates, between stroke and TIA in terms of the probability of having at least one hospital admission during the 5 years after the index event, or, conditional on being hospitalised, in the number of days in hospital (**Table 6.9**). However, severity of event, as measured using the National Institute of Health Stroke Scale (NIHSS), was a strong predictor of both increased hospitalisation and days in hospital, with patients with scores between 3 to 10 and 11 to 20, more likely to be hospitalised than those with scores under 3. For patients with NIHSS scores above 20, relatively low numbers and high-case fatality rates resulted in no significant differences in resource use being observed when compared to those with scores under 3. Although age did not significantly predict the likelihood of hospitalisation after the index event, patients aged 75 years or more, once hospitalised, were significantly more likely to have longer hospitalisation spells than those under 65 years ($p=0.015$) or those age 65 to 74 years ($p=0.040$).

Table 6.9 Multivariate predictors of inpatient resource use

Variable	Days cases		Hospitalisations		Hospital days†	
	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z
Lagged resource use	0.69	<0.001	0.41	<0.001	0.01	0.010
Age (years)						
<65	0.09	0.713	-0.17	0.279	-0.50	0.015
65 to 74	0.20	0.207	0.08	0.585	-0.38	0.04
≥75	Reference case		Reference case		Reference case	
Gender						
Female	Reference case		Reference case		Reference case	
Male	0.11	0.413	0.06	0.581	-0.12	0.329
Previously disabled	-0.37	0.061	-0.08	0.542	0.37	0.003
History of stroke	-0.09	0.547	0.03	0.841	-0.02	0.871
History of TIA	0.23	0.127	-0.05	0.721	-0.07	0.590
History of AF	0.04	0.806	0.17	0.171	0.37	0.002
History of hypertension	-0.07	0.587	-0.01	0.879	-0.06	0.586
History of angina	0.19	0.322	0.33	0.025	-0.28	0.068
History of MI	0.19	0.309	-0.04	0.805	-0.18	0.280
History of diabetes	-0.13	0.543	0.13	0.395	0.23	0.111
History of PVD	0.13	0.488	0.31	0.067	0.12	0.507
Smoking status						
Never	Reference case		Reference case		Reference case	
Previous	0.21	0.128	-0.05	0.605	0.02	0.853
Current	0.08	0.667	0.08	0.659	-0.12	0.538
Event type						
TIA	Reference case		Reference case		Reference case	
Stroke	0.02	0.881	0.01	0.997	0.15	0.264
Event severity (NIHSS)						
<3	Reference case		Reference case		Reference case	
3 to 10	0.31	0.049	0.48	<0.001	0.37	0.008
11 to 20	-0.60	0.043	0.55	<0.001	1.20	<0.001
> 20	-1.05	0.018	0.17	0.531	0.54	0.187
Probability of event						
Definite	Reference case		Reference case		Reference case	
Probable	0.54	0.062	-0.12	0.640	-0.64	0.001
Possible	-0.01	0.972	-0.20	0.408	-0.26	0.400
Not coded	-0.24	0.633	-0.37	0.276	-0.24	0.419
Recurrent stroke	0.36	0.060	1.99	<0.001	0.62	<0.001
Recurrent TIA	0.54	<0.001	0.43	<0.001	-0.04	0.750
Recurrent CHD	0.67	0.001	3.46	<0.001	0.30	0.005
Recurrent PVD	-0.12	0.872	3.30	0.007	0.59	0.130
Residence before event						
Own home	Reference case		Reference case		Reference case	
With relative	0.55	0.234	-0.33	0.177	-0.46	0.044
Warden housing	0.36	0.196	0.46	0.035	-0.11	0.588
Care home	-0.60	0.252	-0.62	0.008	-1.34	<0.001
Other	-0.43	0.545	-0.43	0.347	-0.42	0.424
Lived alone	-0.12	0.553	-0.08	0.580	-0.13	0.432
Marital status						
Married	Reference case		Reference case		Reference case	
Widow	-0.39	0.062	0.22	0.199	0.38	0.045
Single	0.12	0.711	0.46	0.056	0.64	0.008
Separated	0.06	0.800	0.22	0.321	0.33	0.193
Partnered	0.34	0.225	0.02	0.962	0.19	0.565

Table 6.9 (cont.). Multivariate predictors of inpatient resource use

Variable	Days cases		Hospitalisations		Hospital days†	
	Coeff.	**P>z**	**Coeff.**	**P>z**	**Coeff.**	**P>z**
Age left education	-0.01	0.669	-0.03	0.055	-0.02	0.202
Socio-economic class						
I	0.35	0.258	0.24	0.355	0.24	0.317
II	0.04	0.808	-0.07	0.604	0.18	0.290
III-N	0.06	0.764	-0.20	0.196	-0.09	0.583
III-M	Reference case		Reference case		Reference case	
IV	-0.03	0.878	-0.22	0.180	0.16	0.382
V	-0.04	0.847	-0.07	0.646	0.15	0.317
Employment status						
Full-time	-0.49	0.094	-0.11	0.604	-0.27	0.307
Part-time	-0.16	0.513	-0.69	0.005	0.12	0.569
Home carer	0.75	0.170	-0.31	0.283	1.01	0.002
Unemployed	-0.12	0.817	-0.27	0.490	0.24	0.644
Cannot work	-0.22	0.604	-0.60	0.097	-0.20	0.666
Retired	Reference case		Reference case		Reference case	
Deprivation (IMD score)	0.02	0.041	0.01	0.866	-0.02	0.031
Constant	-2.71	<0.001	-1.41	<0.001	2.68	<0.001
	No.[c]	3431	No.[b]	3431	No.[b]	882
	Clusters	1006	Clusters	1006	Clusters	631
	$p>\chi^2$	<0.001	$p>\chi^2$	<0.001	p>F	<0.001
	Adj. R^2	0.018	Adj. R^2	0.107	Adj. R^2	0.202

†Hospital days conditional on admission and logarithmically transformed to normalise the distribution

Vascular disease recurrence, be it stroke, TIA, coronary heart disease (CHD) or peripheral vascular disease (PVD) was also a strong predictor of increased likelihood of hospitalisation (p<0.010 for all cases – **Table 6.9**). However, conditional on being hospitalised, only patients suffering a recurrent stroke (p<0.001) or recurrent CHD (p=0.005), had a significantly higher number of days in hospital.

Except for history of angina (p=0.025), history of other cerebrovascular event risk factors were not found to be independent predictors of hospital admission. However, patients who were disabled at time of event (p=0.003) or had a history of atrial fibrillation (AF - p=0.002) were significantly more likely to have longer spells in

[c] In the regression analyses, No. reflects the number of years of patient follow-up with clusters reflecting the number of patients for which resource use data and baseline characteristics were available.

hospital than those without history of disability or atrial fibrillation. In terms of previous resource utilisation, patients with higher resource usage in the previous year (i.e. more likely to be hospitalised and higher number of days in hospital) were significantly more likely to be hospitalised ($p<0.001$) and significantly more likely to have longer spells in hospital ($p=0.010$) than those with lower resource usage.

In terms of socio-economic characteristics, both place of residence and employment status before the index stroke or TIA were found to be independent predictors of hospitalisation, and conditional on admission, days in hospital after the event (**Table 6.9**). Patients who were living in warden housing at the time of their index event, were significantly more likely to be subsequently hospitalised than patients living in their own homes ($p=0.035$), whilst those who were living in institutionalised care homes were significantly less likely to be admitted to hospital after the index TIA or stroke ($p=0.008$), and if hospitalised, have lower days in hospital ($p<0.001$). In addition, for those patients living with relatives at the time of the event, days in hospital were significantly shorter than for those living in their own home ($p=0.044$).

In terms of employment status, patients who were in paid employment at the time of the event were less likely to be subsequently admitted into hospital than retired patients, although this difference was only found to be significant for those employed part-time ($p=0.005$). For hospitalised patients, those who were either widowed ($p=0.045$) or single ($p=0.008$) had significantly higher number of days in hospital than married patients, after controlling for other covariates, whereas those living in areas of higher deprivation (i.e. higher index for multiple deprivation (IMD) scores), spent

significantly less time in hospital, once admitted, than those living in relatively less deprived areas (p=0.031).

6.3.4 FIVE-YEAR COSTS

Primary care

Five years after the index TIA or stroke, the average cost of primary care nursing visits was £291 (95% CI: 256 to 328) per patient, and that of GP care was £1,076 (95% CI: 1,017 to 1,136 – **Table 6.10**). The biggest component of GP primary care costs was surgery visits, with a cost of £670 (95% CI: 632 to 709) per patient, followed by home visits (£236; 95% CI: 204 to 269).

Table 6.10 Primary care costs after index cerebrovascular event

	All patients (n=1182)	TIA (n=473)	Stroke (n=709)
	Mean costs, £ (95% CI)		
Nurse costs			
Total	291 (256 to 328)	344 (291 to 403)	254 (211 to 305)
Home	131 (98 to 167)	143 (91 to 199)	124 (83 to 175)
Surgery	160 (148 to 174)	201 (180 to 225)	130 (116 to 145)
GP costs			
Total	1076 (1017 to 1136)	1238 (1142 to 1341)	963 (881 to 1043)
Home	236 (204 to 269)	224 (181 to 270)	247 (202 to 293)
Surgery	670 (632 to 709)	813 (754 to 870)	568 (517 to 622)
Telephone	170 (152 to 190)	201 (172 to 230)	148 (126 to 172)

TIA patients incurred nursing costs of £344 (95% CI: 291 to 403) and GP costs of £1,238 (95% CI: 1,142 to 1,341) per patient over the 5 years after their index event (**Table 6.10**). Stroke patients incurred nursing costs of £254 (95% CI: 211 to 305) and GP costs of £963 (95% CI: 881 to 1,043) per patient.

Emergency care

After including the costs of A&E visits and ambulance transport, the average cost of emergency care was £487 (95% CI: 441 to 538) over the 5 years after the index TIA

or stroke (**Table 6.11**), with over 70% of emergency costs being due to ambulance costs (£358; 95% CI: 321 to 398). TIA patients incurred average costs of £452 (95% CI: 371 to 539), whereas those for stroke patients were slightly higher at £509 (95% CI: 451 to 571) per patient.

Table 6.11 Emergency care costs after index cerebrovascular event

	All patients (n=1199)	TIA (n=476)	Stroke (n=723)
Mean costs, £ (95% CI)			
Ambulance			
Total	358 (321 to 398)	323 (259 to 391)	380 (336 to 428)
Vascular	153 (138 to 169)	116 (90 to 143)	176 (161 to 194)
Non-Vascular	206 (175 to 238)	207 (157 to 259)	204 (166 to 241)
A&E			
Total	129 (119 to 141)	129 (109 to 150)	129 (115 to 143)
Vascular	48 (44 to 52)	39 (32 to 47)	53 (49 to 58)
Non-Vascular	82 (72 to 92)	90 (75 to 106)	76 (64 to 87)
Total costs			
Total	487 (441 to 538)	452 (371 to 539)	509 (451 to 571)
Vascular	201 (181 to 223)	155 (123 to 192)	229 (208 to 250)
Non-Vascular	288 (249 to 329)	293 (231 to 364)	280 (232 to 331)

Outpatient care

The average cost of outpatient care visits and diagnostic investigations over the 5-year follow-up period was £1,156 (95% CI: 1085 to 1221). Although the number of visits per patient year were similar for stroke and TIA patients (3.53 vs. 3.57), as the follow-up for TIA patients was longer due to lower mortality, average outpatient care costs were higher for TIA patients, £1,343 (95% CI: 1,239 to 1,451), than for stroke patients, £1,031 (95% CI: 941 to 1,126).

Inpatient care

The average cost of inpatient care was £12,279 (95% CI: 10,895 to 13,697) over the 5 years after the index TIA or stroke (**Table 6.12**), with over 95% of inpatient care costs being due to hospitalisations (£11,819; 95% CI: 10,461 to 13,248). Stroke

patients incurred average inpatient care costs of £13,402 (95% CI: 11,900 to 15,035) per patient over the 5 years following their event, with over 65% of overall inpatient care costs being due to vascular causes (£8,828; 95% CI: 7,653 to 10,104). For TIA patients, just under half of all inpatient care costs (£10,428; 95% CI: 8,028 to 13,101) were due to vascular causes (£4,748; 95% CI: 3,207 to 6,446).

Table 6.12 Inpatient secondary care costs after index cerebrovascular event

	All patients (n=1199)	TIA (n=476)	Stroke (n=723)
	Mean costs, £ (95% CI)		
Day cases			
Total	460 (380 to 558)	540 (375 to 743)	402 (337 to 470)
Vascular	44 (36 to 53)	37 (24 to 53)	48 (37 to 58)
Non-Vascular	416 (337 to 515)	502 (337 to 705)	354 (291 to 424)
Hospitalisation			
Total	11819 (10461 to 13248)	9888 (7521 to 12629)	13000 (11510 to 14639)
Vascular	7182 (6175 to 8200)	4711 (3176 to 6410)	8781 (7609 to 10059)
Non-Vascular	4637 (3777 to 5514)	5177 (3756 to 6809)	4219 (3352 to 5276)
Overall costs			
Total	12279 (10895 to 13697)	10428 (8028 to 13101)	13402 (11900 to 15035)
Vascular	7226 (6213 to 8250)	4748 (3207 to 6446)	8828 (7653 to 10104)
Non-Vascular	5053 (4164 to 5965)	5680 (4252 to 7386)	4573 (3663 to 5650)

Total costs

The total cost per patient five years after index stroke or TIA, and the proportion of costs incurred in each resource use category, is reported in **Table 6.13**. Except for primary care, for other resource use categories the costs reported are slightly different from those reported in the sections above, as the costs reported in Table **6.13** exclude the 17 patients for whom primary care records were not identified. Overall, the total cost 5 years after index TIA or stroke was £15,783 (95% CI: 14,323 to 17,482) per patient, with inpatient care representing the highest proportion of total costs (78%), followed by primary care costs (9% - **Table 6.13**).

Five years after index event, stroke patients incurred costs of £16,923 (95% CI: 15,149 to 18,858) per patient, significantly higher than those incurred by TIA patients, at £13,904 (95% CI: 11,488 to 16,657; p=0.019). In addition, for stroke patients a significantly higher proportion of total costs were due to vascular inpatient care costs than for TIA patients (53% vs. 34%; p<0.001). **Table 6.13** also reports discounted average care costs. After discounting costs incurred after the first year of index TIA or stroke, the average cost was £15,279 (95% CI: 13,901 to 16,862), with that for TIA and stroke patients being £13,335 and £16,481, respectively.

Table 6.13 Total care costs after index cerebrovascular event

Care costs	All patients		TIA		Stroke	
	Mean £ (95% CI)	%	Mean £ (95% CI)	%	Mean £ (95% CI)	%
Primary	1367 (1294 to 1451)	9	1582 (1463 to 1714)	11	1218 (1115 to 1325)	7
Emergency	489 (443 to 540)	3	446 (367 to 537)	3	514 (462 to 567)	3
Vascular	182 (164 to 201)	1	154 (122 to 191)	1	231 (213 to 248)	1
Non-vascular	307 (278 to 339)	2	292 (229 to 363)	2	283 (238 to 329)	2
Outpatient	1174 (1102 to 1251)	7	1339 (1244 to 1451)	10	1060 (964 to 1161)	6
Inpatient	12352 (11013 to 13904)	78	10250 (7948 to 12800)	74	13670 (12048 to 15454)	81
Vascular	7270 (6481 to 8182)	46	4667 (3175 to 6298)	34	9005 (7748 to 10386)	53
Non-vascular	5083 (4532 to 5722)	32	5583 (4210 to 7216)	40	4664 (3709 to 5807)	28
TOTAL COSTS						
Un-discounted	15783 (14323 to 17482)		13904 (11488 to 16657)		16923 (15149 to 18858)	
Discounted	15279 (13901 to 16862)		13335 (11082 to 15939)		16481 (14754 to 18331)	

The average costs incurred by patients during the five-year follow-up are reported in **Figure 6.1**. In addition, for each resource use category, the costs incurred over the follow-up period are graphed in **Appendix 22**. As shown in **Figure 6.1** the time period in which the highest costs were incurred was the first few months after the index event. During this time, costs for stroke patients were considerably higher than those incurred by TIA patients. As time progressed, however, costs fell rapidly and remained relatively stable, both for stroke and TIA patients, after the first year of follow-up post index event. At the end of the 4-year follow-up, however, there was an increase in average total costs. This increase was observed due to the fact that with

a high proportion of censored patients during this time period any hospitalisation had a considerable impact on average costs.

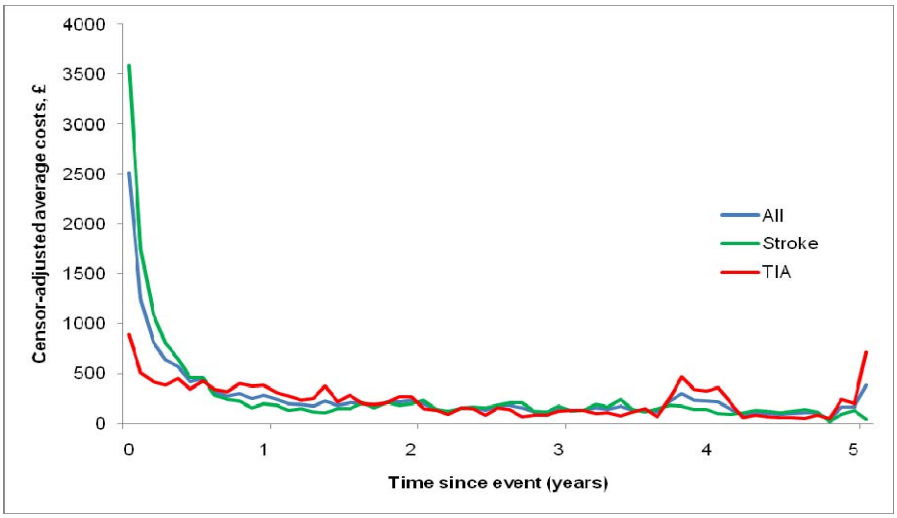

Figure 6.1 Average total costs of care over time

By stroke subtype (data not shown in any table), although considerable differences were observed in mean total costs, due to small numbers no significant differences were observed across patient groups (p=0.052). Five years after index event, SAH patients incurred the highest costs at £28,984 (95% CI: 12,030 to 52,739) per patient, ICH patients incurred average costs of £16,737 (95% CI: 11,498 to 22,902) followed by ischaemic stroke patients, with an average cost of £16,620 (95% CI: 15,151 to 18,382). High case-fatality in patients with unknown strokes caused these patients to have the lowest costs, with patients incurring average costs of £6,455 (95% CI: 4,009 to 9,603). A univariate analysis comparing total 5-year costs in other patient subgroups is reported in **Appendix 23**.

Due to the considerable number of patients who died during follow-up, to better understand the predictors of total costs during the 5-year follow-up, the multivariate

analyses were stratified for surviving and non-surviving patients. In both analyses, recurrent vascular events during follow-up, place of residence and marital status at time of event, and level of costs incurred over the previous year were all independent predictors of 5-year total costs. Results of these regression analyses are reported in **Table 6.14**.

For both surviving and non-surviving patients, suffering a recurrent stroke, TIA or CHD event was a significant predictor of increased total costs over the 5-year follow-up period (**Table 6.14**), after controlling for other covariates. Place of residence at time of event was also found to be a multivariate predictor of total costs, with those living in a nursing/residential care home at time of event incurring significantly less costs after the cerebrovascular event than those living in their own homes ($p=0.004$ in both analyses). For both analyses, the level of costs incurred during the previous year was a predictor of total costs. In surviving patients, increased costs over the previous year were a significant predictor of increased subsequent costs ($p<0.001$). However, for non-surviving patients, increased costs during the previous year were a significant predictor of decreased subsequent costs ($p<0.001$), as patients with higher resource usage over the previous year were more likely to die sooner than those with lower resource usage.

Other patient characteristics were also found to predict total costs in surviving patients. History of angina and PVD events before the index TIA or stroke significantly increased costs over the 5-year follow-up ($p=0.011$ and $p<0.001$,

Table 6.14 Multivariate predictors of total care costs

Variable	Surviving patients†		Patients who died†	
	Coeff.	P>z	Coeff.	P>z
Lagged costs	0.01	<0.001	-0.01	<0.001
Age (years)				
<65	-0.22	0.286	-0.90	0.127
65 to 74	-0.02	0.877	0.20	0.555
≥75	Reference case		Reference case	
Gender				
Female	Reference case		Reference case	
Male	-0.24	0.088	0.52	0.090
Previously disabled	-0.22	0.533	-0.35	0.171
History of stroke	-0.13	0.494	0.41	0.194
History of TIA	0.06	0.651	-0.16	0.551
History of AF	0.25	0.098	0.27	0.327
History of hypertension	0.06	0.636	-0.02	0.922
History of angina	0.55	0.011	0.17	0.538
History of MI	-0.23	0.255	-0.23	0.493
History of diabetes	-0.01	0.974	0.48	0.186
History of PVD	0.88	<0.001	-0.58	0.179
Smoking status				
Never	Reference case		Reference case	
Previous	-0.07	0.623	0.20	0.439
Current	0.16	0.442	-0.34	0.462
Event type				
TIA	Reference case		Reference case	
Stroke	-0.24	0.119	0.18	0.567
Event severity (NIHSS)				
<3	Reference case		Reference case	
3 to 10	0.43	0.038	0.39	0.227
11 to 20	0.41	0.307	0.70	0.073
> 20	1.97	<0.001	-0.32	0.511
Probability of event				
Definite	Reference case		Reference case	
Probable	-0.27	0.442	-0.83	0.238
Possible	-0.07	0.744	0.03	0.962
Not coded	-0.35	0.355	0.02	0.986
Recurrent stroke	1.79	<0.001	2.54	<0.001
Recurrent TIA	0.59	<0.001	1.29	0.003
Recurrent CHD	1.14	<0.001	3.00	<0.001
Recurrent PVD	2.03	<0.001	2.02	0.154
Residence before event				
Own home	Reference case		Reference case	
With relative	-0.95	0.086	-0.63	0.123
Warden housing	0.50	0.251	-0.35	0.460
Care home	-0.99	0.004	-1.40	0.004
Other	0.29	0.697	-0.98	0.134
Lived alone	-0.38	0.083	-0.60	0.053
Marital status				
Married	Reference case		Reference case	
Widow	0.16	0.449	0.06	0.865
Single	0.90	0.013	0.45	0.280
Separated	0.13	0.595	0.96	0.053
Partnered	0.34	0.286	-0.31	0.457

Table 6.14 (cont.). Multivariate predictors of total care costs

Variable	Surviving patients†		Patients who died†	
	Coeff	P>z	Coeff.	P>z
Age left education	-0.03	0.194	-0.09	0.083
Socio-economic class				
I	0.44	0.114	0.55	0.343
II	0.02	0.917	0.31	0.387
III-N	-0.09	0.679	-0.14	0.685
III-M	Reference case		Reference case	
IV	-0.04	0.869	0.12	0.777
V	0.22	0.437	0.40	0.307
Employment status				
Full-time	-0.46	0.039	0.62	0.382
Part-time	-0.08	0.632	-0.52	0.694
Home carer	0.09	0.808	0.66	0.218
Unemployed	-0.88	0.103	0.35	0.744
Cannot work	-0.59	0.337	0.41	0.525
Retired	Reference case		Reference case	
Deprivation (IMD score)	-0.01	0.274	0.01	0.823
Constant	6.95	<0.001	5.56	<0.001
	No.[d]	2189	No.	628
	Clusters	777	Clusters	219
	p>F	<0.001	p>F	<0.001
	Adj. R^2	0.140	Adj. R^2	0.122

†For both multivariate analyses, costs were logarithmically transformed to normalise the distribution.

respectively - **Table 6.14**). Event severity was also found to be a significant predictor of total costs in surviving patients, with those with NIHSS scores of between 3 and 10 (p=0.038), and those with scores above 20 (p<0.001) incurring significantly higher costs than those with scores below 3. Patients who were single at time of event were significantly more likely to incur higher costs than those who were married (p=0.013). In addition, after controlling for other covariates, patients in full-time employment at the time of the event incurred significantly lower costs than retired patients (p=0.039).

[d] In the regression analyses, No. reflects the number of years of patient follow-up with clusters reflecting the number of patients for which cost data and baseline characteristics were available.

6.4 DISCUSSION

This chapter assesses the NHS healthcare resource use and associated costs incurred by patients over the 5 years after their index stroke or TIA, using data from a large population based cohort study. The results presented here showed the costs of stroke and TIA to be considerable. Results showed that 5 years after the index cerebrovascular event, the average cost per patient was £15,783 (95% CI: 14,323 to 17,482), most of which was driven by inpatient care costs. Costs for TIA patients were £13,904 (95% CI: 11,488 to 16,657), lower than the £16,923 (95% CI: 15,149 to 18,858) incurred by stroke patients.

In the review of studies evaluating the costs of stroke (**Chapter 3**), results showed that the average published cost of stroke in the UK, after adjusting for purchasing power parity, was $22,377 (range: 5,026 to 107,860) in 2006 prices, which translates into an average cost of approximately £17,000. Although this figure is not considerably different from the average cost of stroke identified in this chapter (£16,923), the length of follow-up must be taken into account when comparing cost estimates. Of the 14 studies evaluating the costs of stroke in the UK none used a follow-up period of over 12 months, compared to the 5 year follow-up used in the current analyses.

As a result, when only the one-year costs of stroke in OXVASC patients are considered (£9,465), these are considerably lower than those generally reported in the UK literature. One reason for this difference could be that a number of published studies included cost categories not included in this thesis, such as social care and informal care costs. However, more importantly, all the published studies reporting

costs of stroke for the UK only included patients hospitalised shortly after their stroke. The analyses presented in this chapter, however, included a high proportion of minor strokes, which do not normally present to hospital after the event,[173] and consequently have lower healthcare costs.

The analyses presented in this chapter, also compared the one-year costs before and after the index cerebrovascular event. As shown in **Chapter 4**, when presenting the patient sample on which the analyses were based, TIA and stroke occur mainly in relatively old patients (mean age of OXVASC patients was 74 years). In addition, these patients tend to suffer from previous co-morbidities, with over half of all patients having a medical history of hypertension and over 15% being disabled before the event (**Chapter 4**). As a result, it is likely that stroke and TIA patients would utilise substantial health care resources irrespective of cerebrovascular event onset. Therefore, in order to estimate the impact of stroke and TIA on subsequent resource use consumption and costs, resource use and costs incurred were compared for the 12 months before and after the index cerebrovascular event.

In line with other patient-level costing studies evaluating the costs before and after stroke,[243-248] results showed that total costs per patient were significantly and considerably higher after the cerebrovascular event, and except for day cases, these increases were observed for all resource-use categories. However, despite the large increases in costs 12 months after the cerebrovascular event (£6,057 on average), the costs incurred by patients over the one year preceding the event were considerable (£1,652 per patient).

In particular, patients who went on to develop a stroke incurred significantly higher costs during the 12 months before the event than TIA patients, a fact that could be explained by the higher number of co-morbidities and risk factors in stroke patients (**Chapter 4**). The predictive power of previous resource use and costs was also observed in the dynamic multivariate analyses performed. After controlling for other covariates, lagged resource use and costs (i.e. resource use and costs incurred over the previous year) were also found to predict subsequent higher healthcare consumption and costs.

For inpatient care, which accounted for over 78% of total costs 5 years after the index event, the cause of resource usage was assessed and categorised as vascular (i.e. stroke, TIA, CHD or PVD) or non-vascular (i.e. everything else). Over the 5 years after the index cerebrovascular event, inpatient care costs due to non-vascular causes (£5,083 per patient) were shown to remain relatively stable. For each year after the event, non-vascular inpatient care costs were approximately £1,017 per patient, a similar cost to the inpatient care costs incurred during the year preceding the event (£1,077 per patient). Therefore, for inpatient care, there was no suggestion that cerebrovascular events increased non-vascular related inpatient care resource use during the 5-year follow-up.

Results of the analyses also showed that, after the first year following index cerebrovasular event, most of the inpatient and emergency care costs were due to non-vascular causes. Low levels of resource usage due to vascular causes after the first months post-stroke have also been documented in the literature. Caro et al. (2006)[175] evaluated causes of hospitalisation in 18,695 ischaemic stroke patients

over an average follow-up period of 4.5 years, and found that after being discharged from hospital post-index event only 22% of subsequent hospitalisations were due to cardiovascular causes.

As in other population-based studies evaluating the costs of cerebrovascular events,[44;193;245] total care costs were found to vary considerably depending on patients' characteristics. Although total care costs after stroke and TIA did not vary significantly after controlling for other covariates, event severity was found to be a significant predictor of inpatient care resource use and total costs in surviving patients. Recurrent vascular events, especially stroke and CHD events, also significantly increased hospitalisations, subsequent days in hospital, and overall care costs. Following on from these results, the next chapter (**Chapter 7**) will investigate, using the cost and outcome data from OXVASC patients presented in this chapter and **Chapter 5**, respectively, the impact of an intervention aimed at reducing the delay to rapid assessment and treatment of TIA and minor stroke on patient health outcomes and hospitalisation costs.

The main advantage of using OXVASC when determining healthcare resource use consumption after stroke or TIA was that patients included in the analyses were derived from an unselected patient sample, representative of the study population. Therefore, minor strokes and TIA, which do not normally present to hospital after the event,[173] and are therefore more difficult to ascertain and identify, were included in the study. As a result, selection bias, in which only more severe strokes are included as they are easier to identify, was minimised, making the results presented here of use to decision makers and other health economists when assessing service

provision or evaluating the cost-effectiveness of different healthcare interventions for stroke or TIA. In addition, the detailed clinical assessments and follow-ups undertaken by OXVASC shortly after the event and at regular time points after the event provided valuable information on patient characteristics used in both the multivariate and univariate analyses.

However, despite the advantages of OXVASC in determining resource use after stroke or TIA, the limitations of the analyses presented here should also be noted. Firstly, as reported in the discussion section of **Chapter 5**, by the end of 5-year follow-up over 70% of patients were censored. This considerable amount of censoring resulted in resource use and cost estimates over the last year of follow-up being based on a small proportion of patients, therefore increasing the uncertainty around mean estimates, and decreasing the generalisability of these long-term results. However, as shown in the figures depicting how average costs varied over time, after the first year after the index event, costs remained, in general, relatively stable over the remaining follow-up time.

Secondly, although there was no missing data on healthcare resource usage (except for data on primary care resource use for 17 patients whose computerised records were not located), missing data on baseline patient characteristics reduced the overall sample size in the multivariate analyses. However, the amount of missing data was considerably less than for health outcomes, with less than 17% (n=203) of patients having missing information on one or more covariates. As a result, multiple-imputation analyses,[225;226] such as those undertaken in the multivariate analyses presented in the previous chapter, were not deemed necessary for this analysis.

Thirdly, although there was information on medication usage, this was obtained by patients' recalling the medication they were taking before the event, and at 1, 6, 12 and 24 months after the event. As a result, it was not possible to determine, precisely, the amounts of each medication consumed and the duration of usage. Ideally information on medication usage could have been obtained from the detailed records held by patients' GPs. However, as this would have taken a vast amount of time for me to collect it was decided that follow-up information would be used instead.

Fourthly, as in the multivariate analyses presented in **Chapter 5**, the multivariate analyses performed in this chapter to assess the independent predictors of hospital resource use and costs included a large number of covariates. In each regression analysis, significance was set at $p<0.050$, i.e. there was a 5% chance of a false positive result when there was no real difference (Type I error).[214] Therefore, some of the significant results observed in these analyses might have occurred just by chance.

Fifthly, although 40% of studies included in the literature review presented in **Chapter 3** included the costs of social care, namely residential or nursing home care, these costs were not included in this study. In OXVASC, information on nursing and residential care was only obtained through patient self-report and only for the first two years after the index TIA or stroke (details of living arrangements at each of the four OXVASC follow-ups are reported in **Chapter 5**).

Results from other population based studies assessing costs after stroke have found these costs to be considerable. Results from the North East Melbourne Stroke Incidence Study (NEMESIS), found that one year after stroke, costs of nursing care amounted to AUD 2,173 per patient, with acute hospitalisation and inpatient rehabilitation accounting for AUD 6,651 and AUD 5,122, respectively.[193] Evidence from the Erlangen Stroke Registry found that nursing home care costs averaged €1,687 in the first year after stroke, and €1,157 in each of the four subsequent years, representing 9% and 21% of total care costs, respectively.[44;194]

In addition, other relevant costs of providing care to stroke and TIA patients, such as outpatient rehabilitation, including physiotherapy, and occupational therapy, were not included in the analyses. However, anecdotal evidence from the first year of OXVASC, where such data were obtained through patient self-report, showed very small usage. Resource use in other NHS hospitals in Oxfordshire, including the Warneford (a psychiatric hospital) and the NOC, with the exception of inpatient intensive rehabilitation care provided at OCE, were not included in the analyses. However, there was no evidence after reviewing patients' primary care records, of many OXVASC patients utilising health care resources from non-ORH Trust hospitals.

From a broader societal perspective, the analyses presented in this chapter did not evaluate other important costs associated with the opportunity cost of unpaid care provided by friends and families and productivity losses associated with premature death or mobility. As shown in **Chapter 5**, over 35% of stroke patients remained disabled two years after their initial event and therefore required help in their

activities of daily living. In addition, with approximately 19% of all strokes identified in OXVASC occurring in patients who were still in paid employment, there was potential for the productivity losses due to stroke to be considerable.

Finally, despite 1,199 patients being included in the study, the impact of high-case fatality and censoring reduced the available study sample. As a result, for certain characteristics, for example stroke subtype, where there were relatively low numbers of surviving ICH and SAH patients, and socio-economic class, with low numbers of patients at both ends of the scale, the sample size was too small to detect any statistically significant results.

6.5 CONCLUSION

This chapter has quantified the NHS resource use and associated costs incurred by patients after stroke or TIA. The results presented here have shown that 12 months after the index cerebrovascular event resource use consumption in virtually all NHS resource use categories significantly increased when compared to the 12 months preceding the event. Over the 5 years following the cerebrovascular event, the costs incurred by patients were considerable, at £15,783 per patient (discounted costs: £15,279). In addition, after controlling for other observed patient characteristics, recurrent stroke and CHD, significantly increased hospitalisations, subsequent days in hospital, and overall care costs. The impact of recurrent strokes on patient health outcomes and costs will be further examined in the next chapter. **Chapter 7** will assess the costs and outcomes of an intervention undertaken as part of OXVASC, aimed at reducing the risk of recurrent stroke by reducing the delays to clinical assessment and treatment that TIA and minor stroke patients face.

CHAPTER 7

COST-EFFECTIVENESS OF SECONDARY STROKE PREVENTION: EVIDENCE FROM THE EXPRESS STUDY

7.1 INTRODUCTION

Over the previous two chapters evidence from the Oxford Vascular study (OXVASC) has shown that suffering a recurrent stroke after index stroke or transient ischaemic attack (TIA) significantly increased healthcare resource use and costs, and had a significant negative impact on patient survival, independence levels and quality of life. As a result, interventions that reduce the risk of recurrent stroke might generate substantial savings to the healthcare service and improve patient health outcomes.

Cost-effective treatments now exist to prevent recurrent strokes in the long-term after a TIA or minor stroke,[60;61;63;64;249] with use of appropriate interventions predicted to reduce the long-term risk of recurrent stroke by as much as 80-90%.[65] However, with a risk of recurrent stroke of about 8% seven days after TIA or minor stroke,[250-252] there is a short window of opportunity for prevention. In the UK, which has relatively low hospitalisation rates for TIA and minor stroke,[173] this would entail faster access to outpatient specialist care, as approximately half of all these patients currently wait more than 14 days to be assessed and treated.[12] Until recently, however, there were no reliable estimates of the effectiveness, let alone cost-effectiveness, of interventions aimed at reducing the delay to rapid assessment and treatment for such patients.

The Early use of eXisting PREventive Strategies for Stroke (EXPRESS) study was the first large study aimed at determining the effect of more rapid treatment after TIA and minor stroke in patients who are not admitted directly to hospital.[253] EXPRESS was a rigorous observational study of the phased introduction of urgent assessment and treatment, nested within OXVASC. Using data from EXPRESS, the objective of this chapter is to perform an economic evaluation to assess whether faster access to outpatient specialist care and treatment reduces healthcare resource use and costs and improves patient health outcomes.

7.2 ECONOMIC EVALUATION

An economic evaluation is the comparative analysis of alternative course of actions (i.e. healthcare interventions) in terms of both inputs (i.e. healthcare resources and their costs) and consequences (i.e. health outcomes).[81] With rapidly rising healthcare expenditures and limited healthcare resources, the use of economic evaluation is becoming increasingly popular amongst different healthcare systems, including the UK National Health Service (NHS), as a means of prioritising healthcare spending to interventions that are most likely to improve the health of the population given the resources available.[254-256]

7.2.1 TYPES OF ECONOMIC EVALUATION

There are different types of frameworks for combining costs and benefits within an economic evaluation framework. Whilst the approach to measuring costs is the same in all frameworks, they differ in the way health outcomes are measured and valued.

Cost-effectiveness analysis

In cost-effectiveness analysis, benefits are measured in "natural units", which are clinical in nature and unidimensional, e.g. life-years, number of recurrent events, or number of days with disability. Although these are relatively simple to measure, other important outcomes may be ignored when using such measures. For example, when additional life expectancy is gained due to treatment, the quality of such years may also be important to patients.[83] Another limitation of this type of analysis, is that it does not facilitate comparisons across different disease areas when different outcomes have been used.[73;80;81]

Cost-utility analysis

In economic evaluation, cost-utility analysis has become synonymous with the quality-adjusted life year (QALY) framework,[257] outlined in **Chapter 2**. The main difference between cost-effectiveness and cost-utility analysis is that the latter incorporates utilities in its outcome measure and outcomes are, generally, represented in terms of QALYs. Cost-utility analysis can, therefore, be seen as an improvement on cost-effectiveness analysis as it attempts to combine more than one outcome measure (e.g. both quality and quantity of life in the case of QALYs). In addition, comparisons across different disease areas can be made as all outcomes are measured using the same metric.

Cost-benefit analysis

In cost-benefit analysis both costs and benefits are measured in monetary terms. The advantage of this framework is that the decision over whether or not to adopt an intervention will be based on whether benefits (i.e. health outcomes valued in

monetary terms) outweigh the costs. However, there are inherent difficulties in measuring health outcomes in monetary terms, not least the ethical objections to measuring life in monetary terms.[257]

Cost-consequences analysis

In a cost-consequences analysis, instead of combining the costs and effects, all the costs and outcomes are reported separately. This framework has been advocated for its simplicity and ease of interpretation, and because it allows decision makers to impute their own values to the different costs and consequences.[258] However, a disadvantage of this approach is the difficulty of comparing outcomes between different interventions in order to prioritise them.

7.2.2 DECISION RULES IN ECONOMIC EVALUATION

In both cost-effectiveness and cost-utility analyses at least two interventions are compared, with one representing the new intervention and the other one the comparator (i.e. current practice). Results of these analyses are then often presented on the cost-effectiveness plane with the comparator in the centre and the incremental effects and costs on the horizontal and vertical axes, respectively. This break-up of the plane then generates four distinct quadrants (**Figure 7.1**). In the South-East (SE) quadrant the new intervention is both more effective and less costly, and it is therefore said to be dominant over the comparator. In the North-West (NW) quadrant the new intervention is more costly and less effective, and is therefore dominated by the comparator.

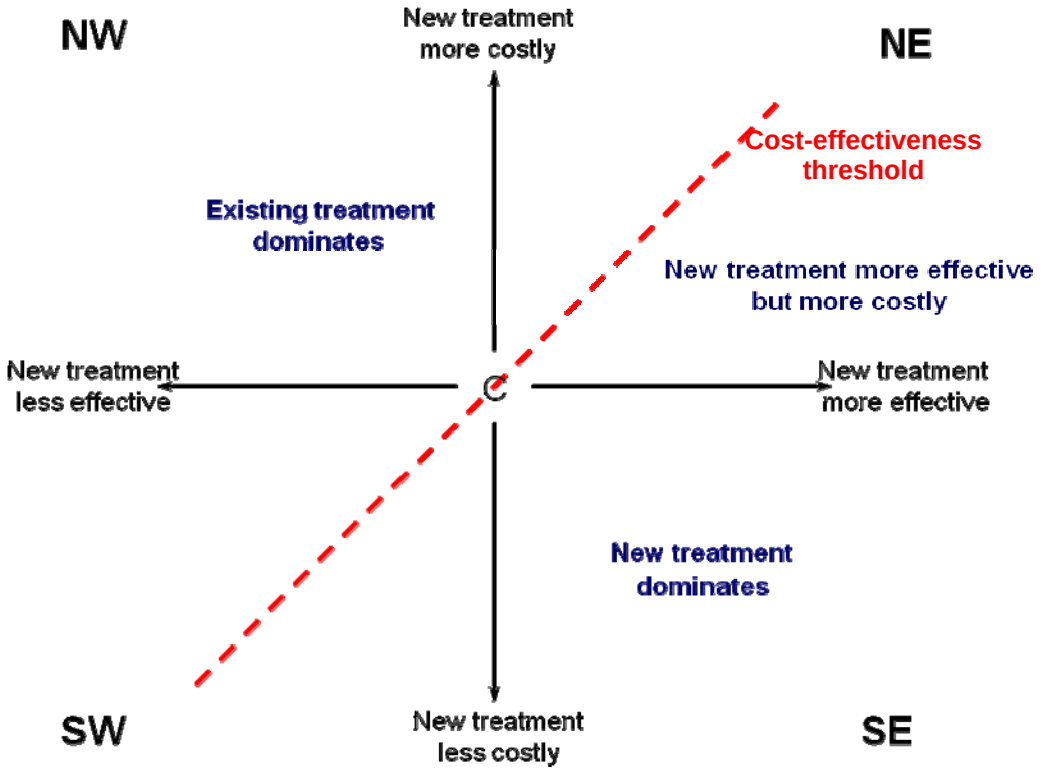

Figure 7.1 Cost-effectiveness plane

In the North-East (NE) quadrant on the cost-effectiveness plane the new intervention is more effective, but also costs more than the comparator. In the South-West (SW), by contrast, the new intervention is less effective but is less costly. As a result, in both the NE and SW quadrants a trade-off between effects and costs has to be made. By dividing the difference in costs between the two interventions (i.e. difference between intervention and comparator costs) by the difference in effects between the two interventions (i.e. difference between intervention and comparator outcomes) the results can be expressed as a summary incremental cost-effectiveness ratio (ICER).

If the ICER, i.e. the additional cost for each additional benefit gained, is below what the decision maker is willing to pay for each additional benefit/outcome then the new

intervention is cost-effective. However, if the ICER is above the maximum willingness to pay of the decision maker then the new intervention is not cost-effective. In **Figure 7.1**, the maximum willingness to pay for each additional unit of benefit, also known as cost-effectiveness threshold, is depicted by the dotted line. Any new intervention falling below this threshold is deemed to be cost-effective.

In the UK, the National Institute for Health and Clinical Excellence (NICE) [82] has published guidance suggesting that any intervention with an ICER below £20,000 per QALY gained should be adopted. For those with ICERs between £20,000 and £30,000 per QALY, NICE reported that other reasons for adopting the intervention, such as ethical considerations or equity issues, should be explicitly reported. Finally, NICE suggested that those interventions with ICERs above the £30,000 should not be adopted.

7.3 ECONOMIC EVALUATION OF SECONDARY STROKE PREVENTION

Using data from the EXPRESS study, a rigorous observational study of the phased introduction of early assessment and treatment, nested within OXVASC (**Chapter 4**), this chapter evaluates, using a cost-consequence analysis, the costs and outcomes of two interventions aimed at reducing the risk of recurrent stroke.

7.3.1 THE EXPRESS STUDY

The EXPRESS study intervention was the reduction in delay to assessment and initiation of treatment via the OXVASC neurovascular clinic on 01/10/2004.[253] In the previous 30 months (phase-1: 01/04/2002 to 30/09/2004), general practitioners (GP) referred any patient suspected of having suffered a TIA or non-disabling stroke. The

OXVASC team then contacted the patient to arrange a clinic appointment as quickly as possible. After clinic assessment, the GP was faxed a report including any treatment recommendations. In October 2004 (phase-2), the mode of access to the outpatient clinic was changed and treatment was initiated in the clinic. GPs were requested to send all patients directly to the study clinic immediately after they presented for medical attention, with no need to prearrange referral, and treatment was initiated immediately in clinic. In both phases, the initial clinical assessment and follow-up protocols were the same as those reported in **Chapter 4**.

7.3.2 OUTCOME MEASURES

The primary outcome in the EXPRESS study was the 90-day risk of recurrent stroke.[253] Outcome measures included in this analysis were hospital admission, length of stay (LoS), total hospital costs during the 90 days after the event, and patient disability, as measured using the modified Rankin Scale (mRS), or death at 6 months. The 90-day follow-up period for resource use was used in order to reflect the duration of follow-up in the effectiveness study,[253] whilst the 6-month follow-up period for disability was used as mRS data were not collected at 90 days because recovery from stroke often continues beyond 90 days. In addition, a longer time horizon for the analysis would have resulted in a large proportion of patients in phase-2 being censored.

As part of OXVASC, quality of life was assessed using the Euroqol-5D (EQ-5D), results of which are presented in **Chapter 5**. However, during the first 18 months of OXVASC, the EQ-5D was not given as part of the 6-month follow-up. EQ-5D data

were missing for over 57% (n=168) of patients in phase-1, and, as a result, quality of life was not included as an outcome measure.

The methods on how hospital resource use data were derived are reported in detail in **Chapter 6**. Briefly, resource use data were derived from central administrative sources and patient records, which provided information on the dates of hospital admission and discharge, as well as information on patient transfers between specialty wards. For any patient hospitalised before the 90-day follow-up but with LoS extending beyond that time period, LoS was estimated until hospital discharge. All-cause (i.e. TIA, stroke, other vascular, and non-vascular disease) hospitalisation and LoS were examined. For vascular hospitalisations a more in-depth analysis was performed by examining overall days in hospital, LoS conditional on admission, and costs, stratified by those due to recurrent stroke and those due to other vascular causes. Cause of hospitalisation was examined by hot pursuit, or by matching event dates to hospitalisation, linking hospital information with discharge coding, and by review of hospital notes by the OXVASC senior neurologist. Unit costs were obtained from national reference costs and attached to each day spent in each specialty ward.[233;236] Costs were standardised to 2006-2007 prices by use of the NHS hospital and community health services inflation index.

Patient disability was assessed at 6 months and defined as mRS score between 3 and 5. As patients could have been disabled before their index event, new disability, combined with death at 6 months, was also assessed. New disability was defined as the progression between no disability before event (i.e. pre-event mRS<3) to

disability 6 months after index event (i.e. 6-month mRS>2). More details on how disability was assessed are reported in **Chapter 5**.

7.3.3 STATISTICAL ANALYSES

Categorical outcomes, including hospitalisations and disability, were reported as proportions and exact 95% confidence intervals (CI) computed. Statistical differences for categorical variables were evaluated using standard chi-square tests. Resource use and hospitalisation costs were reported as means. To account for the skewed nature of resource use and cost data, 95% CI were calculated non-parametrically from 10,000 bootstrap estimates.[210]

To asses the main predictors of hospital vascular admission, days in hospital, and total costs, a two-part model was used. A logistic regression model was used to assess the predictors of hospital admission. Conditional on admission, a general gamma linear model assuming a log identity was used to determine baseline predictors of days in hospital and costs at 90-day follow-up.[259] Logistic multivariate analyses were performed to determine prognostic indicators of new patient disability or death, and overall disability or death, at 6 months. For the multivariate analysis of new disability or death, those patients already disabled before their index event were excluded from the analysis, as the main objective was to observe progression from either no baseline disability to disability or death 6 months after event, or baseline disability to death 6 months after event.

Potential baseline predictors included in the regression models were gender; age; previous history of myocardial infarction (MI), angina, peripheral vascular disease

(PVD), hypertension, previous stroke, or diabetes; smoking status; age left education; event type (TIA or stroke); stroke severity (as measured using the National Institute of Health Stroke Scale - NIHSS score); and disability prior to event (mRS 3 to 5). Both age and NIHSS score were included in the analyses as categorical variables, due to observed non-linear effects on outcomes, resource use and costs.[173] Further regression models were undertaken by including both age and NIHSS score as continuous variables, and by including the quadratic terms of age and NIHSS score. Results showed that models were best specified when both age and NIHSS score were included as categorical variables. Statistical significance was set at $p<0.05$. Diagnostic tests to check for model specification were performed using Preigbon's link test.

7.3.4 RESULTS

Table 7.1 Number of patients seeking medical attention

Medical attention	Phase-1 (n=634)	Phase-2 (n=644)	Total (n=1278)
Whole population	634	644	1278
Hospital-based care	285	322	607
Discharged from A&E	33	54	87
Inpatient care	252	268	520
Outpatient care	323	297	620
Referred to EXPRESS clinic	310	281	591
Referred to other clinics	13	16	29
Not referred to secondary care	26	25	51

Table derived from Rothwell et al. (2007)[253]

Of the 1,282 patients ascertained as having suffered a cerebrovascular event (**Chapter 4**), 55 patients either died in the community before medical assessment or suffered a subarachnoid haemorrhage (SAH), and were not included in the

EXPRESS study. Of the remaining patients, 634 patients sought medical attention after a first stroke or TIA in phase-1 and 644 after a first event in phase-2 (i.e. 1278 first presentations, with 51 patients seeking medical attention after an event in both phases – **Table 7.1**). A total of 607 presentations (285 in phase-1 and 322 in phase-2) were direct to emergency services or were already in hospital at the time of stroke. Of the 620 referrals with TIA or stroke to outpatient services, 591 (95.3%) were referred direct to the study clinic (310 in phase-1 and 281 in phase-2), and form the sample for this study.

Table 7.2 Baseline characteristics for patients referred to the EXPRESS clinics

	Phase-1 (n=310)	**Phase-2 (n=281)**	**p>|z|**
Baseline:			
Age (years)			0.930
<80	207 (67)	189 (67)	
≥80	103 (33)	92 (33)	
Males	141 (46)	132 (47)	0.717
Previous MI	36 (12)	37 (13)†	0.637
Previous PVD	18 (6)	20 (7)†	0.502
Previous angina	57 (18)	42 (15)†	0.280
Hypertension	167 (54)	164 (59)†	0.230
Previous stroke	55 (18)	41 (15)†	0.318
Diabetes	36 (12)	37 (13)†	0.544
Smoking status:			0.644
Never	143 (46)	118 (42)†	
Ex-smoker	125 (40)	120 (43)	
Current	42 (14)	41 (15)	
Baseline mRS, median (IQR)	1 (0-2)	1 (0-1.5)†	0.129
Prior antiplatelet	139 (45)	109 (39)‡	0.137
Prior statin	63 (20)	89 (32)‡	0.002
Age left education (years), mean (S.D.)	16 (3)	17 (3)	0.390
Acute event:			0.107
TIA	156 (50)	160 (57)	
Stroke	154 (50)	121 (43)	
NIHSS score, median (IQR)	0 (0-1)	0 (0-1)†	0.266

Modified from Rothwell et al. (2007)[253]

†Missing: 1 case
‡Missing: 2 cases
All data expressed as n (%), except where specified. IQR – Interquartile range

Baseline characteristics were similar in the two phases of the study, except for an increase in the proportion of patients using statins at presentation in phase 2 compared with in phase 1 (p=0.002; **Table 7.2**). Furthermore, as shown in **Table 7.1**, there were no significant differences between the phases in the numbers of patients not referred to secondary care, or in the proportion of patients who were referred or who self-referred to acute hospital services versus those referred to outpatient services.

90-day recurrent stroke risk

Details of the effectiveness of the phase-2 clinic in reducing the 90-day risk of recurrent stroke after TIA or minor stroke have been reported elsewhere.[253] A brief summary of the main results is reported here. EXPRESS showed that the phase-2 clinic significantly reduced the number of 90-day recurrent strokes (n=6, 2%) compared to the phase-1 clinic (n=32, 10%; p<0.001). These reductions in the 90-day recurrent stroke risk were due to:

1) Shorter delays in seeking medical attention in primary care to assessment in clinic (3 days in phase-1 vs. less than 1 day in phase 2; p<0.001), resulting in fewer recurrent strokes after presentation to primary care but before assessment in the phase-2 clinic (3 recurrent strokes) than there were in phase-1 (11 recurrent strokes; p=0.048); and
2) Faster access to antiplatelet treatment and blood-pressure lowering drugs in phase-2 than phase-1, with the median time from seeking medical attention to first prescription of one of the treatments recommended by the study clinic in phase-1 being 20 days, compared with a delay of 1 day in phase-2 (p<0.0001).

Patient disability

Results of the analyses undertaken as part of this chapter, and not presented in the original EXPRESS publication, showed that the phase-2 clinic significantly reduced the number of recurrent fatal strokes compared to phase-1 (1 vs. 8; p=0.027), the number of disabling strokes (0 vs. 8; p=0.007), and overall, the number of fatal or disabling strokes (1 vs. 16; p<0.001).

Table 7.3 Health outcomes at 6 months

6-month outcomes, n (%)	Phase 1 (n=310)	Phase 2 (n=281)†	P>|z|
mRS score			0.001
0	69 (23)	59 (22)	
1	106 (36)	125 (46)	
2	50 (17)	53 (20)	
3	52 (18)	32 (12)	
4	16 (5)	1 (0.4)	
5	3 (1)	1 (0.4)	
Death	14 (4)	9 (3)	0.410
Change in disability‡			
Regression	8 (3)	8 (3)	0.831
Progression	33 (11)	16 (6)	0.031
Disability progression/death	47 (15)	25 (9)	0.022

†Disability at 6-months missing in 1 case, disability before event missing in 1 case
‡Disability regression defined as disability before event and no disability at 6 months. Disability progression defined as no disability before event and disability at 6 months.

Table 7.3 reports the 6-month outcomes for all patients in the EXPRESS study. Six months after their index event 14 (4%) patients in phase-1 and 9 (3%) in phase-2 died (p=0.410). mRS scores at 6 months were significantly higher for patients in phase-1 than for patients in phase-2 (p=0.001). There were no differences in the proportion of patients changing from disability at baseline to no disability at 6 months, with 8 patients in each phase improving this way (p=0.831). However, a higher proportion of patients progressed from no disability at baseline to disability at

6-months in phase-1 (n=33, 11%) than in phase-2 (n=16, 6%; p=0.031). Therefore, in phase-1, a total of 47 (15%) patients had either died or become disabled since their initial event compared to 25 (9%) in phase-2 (p=0.022).

Table 7.4 Predictors of disability and death at six months

	New disability/death		Overall disability/death	
	Coeff.	**p>|z|**	**Coeff.**	**p>|z|**
Phase-2	-0.60	0.034	-0.55	0.040
Age (years)				
<65	-1.03	0.019	-0.70	0.077
65 to 74	-0.52	0.114	-0.42	0.205
≥75	Reference case		Reference case	
Gender				
Female	Reference case		Reference case	
Male	-0.47	0.109	-0.17	0.546
History of hypertension	-0.14	0.621	-0.49	0.083
History of diabetes	-0.26	0.599	0.03	0.938
History of stroke	0.66	0.058	0.54	0.107
History of MI	0.04	0.929	-0.27	0.555
History angina	-0.24	0.569	-0.11	0.793
History of PVD	0.71	0.162	0.89	0.067
Previously disabled	N/A	N/A	3.32	<0.001
Smoking status				
Never	Reference case		Reference case	
Previous	0.02	0.940	0.01	0.990
Current	-0.35	0.492	-0.24	0.614
Age left education	-0.07	0.156	-0.07	0.133
Event type				
TIA	Reference case		Reference case	
Stroke	0.30	0.297	-0.09	0.740
Event severity (NIHSS)				
≤3	Reference case		Reference case	
>3	1.26	0.004	1.39	0.002
Constant	-0.89	0.434	-0.22	0.841
	No.	516	No.	588
	$p>\chi^2$	<0.001	$p>\chi^2$	<0.001
	Adj. R^2	0.038	Adj. R^2	0.283

Regression analyses were undertaken to determine the baseline predictors of death or new disability, and of death or overall disability (**Table 7.4**). Event severity assessed by NIHSS (NIHSS score>3; p=0.004) was an independent predictor of death or new disability at 6-months, whereas assessment during phase-2 (p=0.034)

or being aged under 65 years (p=0.019) were significantly associated with reduced new disability or death. Similarly, assessment in phase-2 was associated with reduced death or overall disability at 6-months (p=0.040). Event severity (p=0.002) and previous disability (p<0.001) were independent predictors of increased overall disability or death (**Table 7.4**).

Hospital-based care resource use

57 (18%) patients referred to the study clinic in phase-1 were admitted to hospital during the 90-day follow-up period, compared to 50 (18%) during phase-2 (p=0.852 - **Table 7.5**). No significant differences in reasons for hospitalisation were found, except for recurrent strokes, with 25 (8%) patients being hospitalised for recurrent stroke in phase-1 compared to 5 (2%) in phase-2 (p=0.001). There was a substantially lower number of bed-days in phase-2 than in phase-1, with a total of 672 bed-days in phase-2 compared to 1,957 in phase-1 (**Table 7.5**). This translated into an average reduction of 4 (95% CI: -8 to -1) hospital bed-days per patient referred to the clinic in phase-2 compared to phase-1 (p=0.017).

Table 7.5 All-cause hospital admission and bed-days

	Phase-1 (n=310)	**Phase-2 (n=281)**	**p>|z|**
All hospitalisations, n (%)	57 (18)	50 (18)	0.852
Non-vascular	9 (3)	12 (4)	0.370
Vascular	48 (16)	38 (14)	0.500
Carotid surgery	9 (3)	10 (4)	0.651
Complications	11 (4)	18 (6)	0.108
Recurrent stroke	25 (8)	5 (2)	0.001
Angiography	0	2 (1)	0.226
Coronary heart disease	3 (1)	1 (0.4)	0.626
PVD	0	2 (1)	0.226
Total number of bed days	1957	672	
Mean days (S.D)	6 (24)	2 (11)	0.017

The total number of days in hospital due to any vascular disease was significantly lower in phase-2 than in phase-1 (427 vs. 1,365 days, respectively; average reduction of 3 days, 95% CI: -6 to -1; p=0.016). **Table 7.6** shows that the reduction in days in hospital during phase-2 was driven by reductions in hospitalisation days due to recurrent stroke, with days in hospital due to other vascular causes not varying significantly between phases. Conditional on hospital admission, LoS for patients admitted in phase-1 was 29 (S.D. 52) days, compared to 11 (S.D. 11) days for those admitted in phase-2, a reduction of 17 (95% CI: -36 to -4; p=0.020) days per patient. There was some evidence, furthermore, that patients who had suffered a recurrent stroke in phase-2 had shorter LoS than those in phase-1 after their recurrent stroke, with mean LoS of 15 (S.D. 29) days in phase-2 compared to 32 days (S.D. 60) in phase-1, a non-significant average reduction of 17 (95% CI: -46 to 20; p=0.366) days.

Table 7.6 Resource use for admissions relating to vascular disease

	Phase-1 (n=310)	Phase-2 (n=281)	Difference (2-1)	p>|z|
Total hospital days	1365	427	-938	0.016†
Recurrent stroke	1147	90	-1057	0.005†
Other vascular	218	337	119	0.314†
Total costs, £	336,183	123,817		
Mean‡	1084 (5038)	441 (2331)	-643 (-1342 to -103)	0.028
Recurrent stroke	888 (4945)	77 (1027)	-811 (-1496 to -342)	0.003
Other vascular	197 (1131)	364 (2105)	167 (-63 to 495)	0.196

†To obtain p-values, the total number of days in hospital was averaged across the number of patients.
‡Mean costs reported alongside S.D. Mean cost differences reported alongside 95% CI.

Table 7.6 shows the average hospital costs due to vascular causes incurred in each phase. In phase-1, the average hospitalisation costs were £1,084 (S.D. 5,038) compared to £441 in phase-2 (S.D. 2,231), a reduction of £643 (95% CI: -1,342 to

-103; p=0.028) per patient. As with LoS, the reduction in hospital costs during phase-2 was generated by significant reductions in hospitalisation costs due to recurrent stroke (p=0.003). For patients suffering a recurrent stroke, the mean hospital cost incurred after the recurrent stroke was £7,081 per patient (£7,623 in phase-1 vs. £4,188 in phase-2; p=0.420). Hospitalisation costs due to other vascular causes did not differ significantly between the two phases (p=0.196).

Table 7.7 Predictors of resource use and hospital costs

	Hospital admission		LoS conditional on admission		Total costs	
	Coeff.	**p>|z|**	**Coeff.**	**p>|z|**	**Coeff.**	**p>|z|**
Phase-2	0.00	0.989	-0.84	0.010	-0.66	0.025
Age (years)						
<65	0.44	0.226	-0.56	0.181	-0.54	0.155
65 to 74	0.19	0.611	0.41	0.419	0.18	0.694
≥75	Reference case		Reference case		Reference case	
Gender						
Female	Reference case		Reference case		Reference case	
Male	0.12	0.653	-0.32	0.366	-0.31	0.328
History of hypertension	-0.21	0.418	0.43	0.225	0.36	0.248
History of diabetes	-0.12	0.765	-0.10	0.856	-0.98	0.846
History of stroke	-0.63	0.099	0.67	0.219	0.55	0.256
History of MI	-0.16	0.721	-0.87	0.126	-0.71	0.170
History angina	0.53	0.168	-0.12	0.841	-0.32	0.542
History of PVD	1.19	0.005	0.25	0.591	0.14	0.724
Previously disabled	0.64	0.066	0.85	0.035	0.76	0.033
Smoking status						
Never	Reference case		Reference case		Reference case	
Previous	-0.57	0.056	0.32	0.423	0.29	0.412
Current	0.53	0.153	-0.51	0.231	-0.64	0.101
Age left education	-0.09	0.088	-0.03	0.631	-0.04	0.436
Event type						
TIA	Reference case		Reference case		Reference case	
Stroke	0.14	0.611	0.21	0.557	0.00	0.999
Event severity (NIHSS)						
≤3	Reference case		Reference case		Reference case	
>3	1.78	<0.001	0.29	0.499	0.24	0.521
Constant	-1.02	0.343	3.49	0.011	9.71	<0.001
	No. 589 $p>\chi^2$ <0.001 Adj.R^2 0.035		No. 86		No. 86	

Most patients (85%) referred to the EXPRESS clinics were not hospitalised, and therefore did not incur any hospitalisation costs. A two-part regression model was undertaken to determine the baseline predictors of hospital admission for vascular reasons (i.e. if patients incurred hospitalisation costs), hospital LoS and hospitalisation costs conditional on admission (**Table 7.7**). History of PVD and severity of stroke (NIHSS score>3) were independent predictors of overall hospital admission. Conditional on hospital admission, the phase-2 clinic was an independent predictor of reduced LoS and hospitalisation costs, whereas patients who were disabled prior to their event were significantly more likely to have increased LoS and hospitalisation costs (**Table 7.7**).

As the study clinics in phase-1 and phase-2 were conducted over different time periods, external factors could explain the observed differences in LoS between phases. Hospital admissions for the 607 (285 in phase-1 and 322 in phase-2) patients who attended emergency services or were in hospital at the time of event were also evaluated. Results showed there were no statistically significant differences in LoS between the two phases in these patients (mean LoS: 31 days in both phases; p=0.891), suggesting that unmeasured temporal trends did not affect overall hospital stay during the two time periods.

7.4 DISCUSSION

In the UK, the majority of patients with TIA or minor stroke are managed in outpatient clinics after GP referral. This results in approximately half of all patients waiting for over 14 days to be assessed and treated,[12] time in which recurrent stroke risk is at its highest. The EXPRESS study showed that urgent assessment of TIA and minor

stroke, in combination with early initiation of preventive treatment, not only reduced the risk of early recurrent stroke by about 80%,[253] but that 90-day hospital resource use, hospitalisation costs, and disability at 6 months were also reduced.

There was also some evidence to suggest that urgent assessment and treatment might be reducing the severity of recurrent strokes, with 16 recurrent strokes in phase-1 being either fatal or disabling compared to 1 in phase-2. Results also showed that patients with recurrent stroke had shorter LoS and costs after hospitalisation for recurrent stroke, lower case fatality and lower new disability rates in phase-2 than in phase-1. However, due to the small number of recurrences during phase-2, the analysis was not powered to detect these differences reliably.

Results from this chapter identified that urgent assessment and treatment of TIA and minor stroke reduced overall days in hospital and generated savings of £643 per patient referred to the clinic. Additionally, the reductions in disability rates at six months might lead to diminished longer-term health-service usage in the community. The phase-2 clinic costs, not included in these results, are likely to be a small proportion of savings.

Recently published guidelines by NICE on stroke and TIA management, quoted unpublished evidence showing that outpatient clinics offering urgent care and treatment to TIA and minor stroke patients generated additional costs when compared to a weekly clinic of £94 per patient (£410 vs. £316, respectively).[260] Therefore, if the additional cost of setting up an EXPRESS phase-2 clinic was similar to that reported by NICE, these additional costs would not negate the considerable

savings in hospital LoS and costs (£643 per patient) associated with urgent assessment and treatment of TIA and minor stroke patients, and the potential savings in community care costs due to reduced disability rates.

This is the first rigorous study investigating the impact of urgent assessment and treatment of TIA and stroke not requiring urgent hospitalisation on resource use and costs. Although the study was not a randomised comparison, the control group was prospectively accrued and included all patients presenting for medical attention in the whole study population. Randomisation of individuals was not feasible, as patients would not consent to possible allocation to delayed specialist assessment and treatment. Furthermore, in contrast to populations recruited in most randomised controlled trials, one-third of study patients were aged 80 years or over.[261]

However, there were some limitations to this study. Firstly, external biases to the study, such as changes in health policy or management between the two phases, could have, in theory, explained the reductions in hospital stay and costs. However, it was shown that for non-recurrent stroke hospital admissions, LoS and costs did not differ between phases, and for patients assessed either by the emergency services or in hospital, resource use patterns were the same during the two phases.

Secondly, only hospitalisation costs and disability over a relatively short time-period (i.e. 90-day and 6-month after event, respectively) were considered. As a result the long-term consequences of urgent assessment and treatment are unknown. The 90-day follow-up period for resource use was used in order to reflect the duration of follow-up in the effectiveness study,[253] whilst the 6-month follow-up period for

disability was used as mRS data were not collected at 90 days because recovery from stroke often continues beyond 90 days. Results in the literature, and from earlier on in this thesis, have also shown that the majority of hospitalisation costs occur in the months shortly after stroke, with the costs of further hospitalisations being relatively small.[193;262-264]

Thirdly, during the first 18 months of OXVASC the EQ-5D was not included as part of the follow-up questionnaires. As a result, quality of life information was missing for over 57% of phase-1 patients, and therefore was not assessed in this analysis. This meant that a cost-utility analysis, the preferred economic evaluation framework by NICE,[73] was not undertaken.

Fourthly, the study did not quantify the costs to the health service of setting up outpatient clinics for the urgent assessment and treatment of TIA and minor stroke. As a result the analysis was qualified as a cost-consequences analysis. The phase-2 clinic was set-up as part of the OXVASC research study, and it was not clear what part of these costs might be incurred if such clinics were set up as part of routine practice to reduce waiting times and lists for TIA and minor stroke patients. OXVASC did not incur any additional costs during phase-2 in terms of additional clinical staff or administrative support. The only observable additional cost during phase-2 would be extra medication costs, as medication was started earlier than during phase-1. Undoubtedly, the introduction of outpatient clinics, similar to that in phase-2, would involve additional costs to the health service. As reported above, preliminary evidence from NICE showed that the additional cost of an urgent clinic, similar to that

of phase-2, would incur additional costs of approximately £94 per patient, when compared to a weekly minor stroke/TIA clinic.[260]

Finally, the results presented here are likely to be conservative, as currently in average UK practice, many TIA and minor stroke patients wait more than 14 days to be assessed, investigated and treated,[12] compared to the 3-day delay between first event and specialist assessment in phase-1 of EXPRESS.[253]

7.5 CONCLUSION

In conclusion, results from this chapter showed that, irrespective of patient characteristics, early assessment and initiation of treatment in TIA or minor stroke patients not only reduced the risk of early recurrent stroke by 80%, but also reduced length of stay, acute hospitalisation costs, and disability rates. Further follow-up is required to determine the long-term outcome, costs, and therefore long-term cost-effectiveness of early assessment and treatment, but these short-term results suggest that service provision for TIA and minor stroke similar to that in phase-2 of the EXPRESS study is likely to be cost-effective.

CHAPTER 8

CONCLUSION

8.1 INTRODUCTION

The overall aim of this thesis was to provide improved estimates of the costs and outcomes of stroke and transient ischaemic attack (TIA) using data from a population-based incidence cohort study in order to better inform decision making in the area of stroke treatment and prevention. The Oxford Vascular Study (OXVASC), the population-based cohort study underpinning the analyses presented in this thesis, has provided a unique dataset to evaluate the outcomes, resource use and costs experienced by patients after a stroke or TIA.

Due to its population-based nature, OXVASC included all cerebrovascular events presenting for medical attention, including TIA and minor stroke, which are generally not hospitalised after the event, and are therefore more difficult to identify and recruit in either trials or cohort studies. As a result, this makes the results from OXVASC more complete and reliable than those derived from many other studies.[32;173] In addition, the detailed clinical assessments undertaken by OXVASC clinicians shortly after the event provided a detailed history of the patients' demographic, event, and socio-economic characteristics, which were then used in multivariate analyses to determine the main predictors of health outcomes, resource use and costs.

As detailed in **Chapter 1** the thesis was structured around addressing three main objectives:

1) estimate the level and predictors of health outcomes after stroke and TIA;
2) estimate the size and predictors of health care resource use and costs after stroke and TIA; and to
3) explore the cost-effectiveness of two different assessment programmes after minor stroke or TIA in order to prevent recurrent strokes.

In order to fulfil these objectives the thesis was structured in the following way: **Chapters 2** and **3** presented a critical review of the literature on quality of life and costs, respectively, after TIA or stroke. **Chapter 4** introduced the Oxford Vascular Study (OXVASC), the population-based study from which the patient sample used to obtain outcome, resource use and cost data after stroke and TIA was derived. **Chapter 5** reported the outcomes experienced by OXVASC patients in terms of case-fatality, 5-year survival and risk of recurrent vascular events, living arrangements after TIA or stroke, disability and quality of life. In **Chapter 6** the healthcare resource use patterns and costs incurred by patients over the 5 years proceeding their index cerebrovascular event were described. Finally, **Chapter 7**, combined the costs and outcome data together in order to estimate the cost-effectiveness of two secondary stroke prevention interventions assessed as part of the Early use of eXisting PREventive Strategies for Stroke (EXPRESS) study, a before and after study nested within OXVASC.

Over the following sections of this last chapter, the main findings and challenges surrounding the three objectives of this thesis are highlighted. The chapter concludes by highlighting the main implications for future research in the area of health economics surrounding cerebrovascular events.

8.2 HEALTH OUTCOMES AFTER A CEREBROVASCULAR EVENT

8.2.1 MAIN FINDINGS

In England, the National Institute for Health and Clinical Excellence (NICE), the institution charged by the National Health Service (NHS) to assess the effectiveness and cost-effectiveness of health interventions, recognises Quality-Adjusted Life-Years (QALYS), as the most appropriate measure of health benefit.[73] In order to generate QALYs, reliable and up-to-date information is required on both duration and quality of life.

In order to identify previous published work evaluating quality of life after stroke or TIA, **Chapter 2** presented a literature review on quality of life after a cerebrovascular event, based on recent studies where individual patients were followed-up. In addition, to evaluate the main predictors of published quality of life estimates, a meta-analysis of all identified studies was undertaken. The review identified a total of 59 separate studies published between January 1990 and end January 2007, most of which only evaluated quality of life after stroke, with only 3 (5%) evaluating quality of life after a TIA.

Results from the meta-analysis showed that event severity was consistently a significant predictor of quality of life in all model specifications, with both moderate and severe events having markedly lower quality of life than minor events after controlling for other explanatory variables. Although intuitive, this result highlights the importance of stratifying quality of life estimates by event severity, with 32 (54%) studies not reporting and/or stratifying quality of life estimates by event severity. The

review also highlighted significant differences in published quality of life estimates when studies used different methods and populations to elicit quality of life. However, the impact of other potentially important determinants of quality of life, such as comorbidities, age, gender, and socioeconomic characteristics were not assessed, as many studies did not report estimates for these subgroups.

Using data from a large population-based cohort study of all acute vascular events within a population of over 90,000 individuals in Oxfordshire, the Oxford Vascular Study (details of which were reported in **Chapter 4**), quality of life after stroke or TIA, and its baseline predictors, were then evaluated. In addition, other important health outcomes, which *a-priori* could also appear to be important determinants of quality of life were evaluated, including the risk of recurrent vascular events, living arrangements after event, and patient disability.

Results from **Chapter 5** showed that case-fatality, i.e. death within 30 days after index event, was significantly higher for stroke than TIA patients (15% vs. 1%, respectively). Case-fatality rates also differed significantly between stroke types, with ischaemic strokes having the lowest case-fatality (8%) and intracerebral haemorrhages (ICH) and subarachnoid haemorrhages (SAH) having the highest (40% and 41%, respectively). Stroke survivors faced a high risk of becoming disabled, with results showing that disability levels post-index event remained significantly higher than before the event. Although patients' health improved over time, results showed that disability levels remained significantly higher two years after stroke than before event onset. For TIA patients, however, no significant

increase in disability levels after index event was identified when compared to baseline levels.

Stroke not only had a negative impact on life expectancy and disability, but also on patients' quality of life. When compared to English population norms, quality of life for stroke patients was significantly lower after controlling for age and gender. In addition, in line with the results obtained in **Chapter 2**, severe events were associated with significantly lower quality of life than milder events. Other important predictors of quality of life, after controlling for other patient characteristics, included disability before event, co-morbidities such as diabetes, atrial fibrillation or history of peripheral vascular disease (PVD), recurrent vascular events and gender.

8.2.2 CHALLENGES IN EVALUATING PATIENT HEALTH OUTCOMES

Despite the considerable benefits of using OXVASC to evaluate health outcomes after stroke or TIA, there were a number of challenges in doing so. Perhaps, the greatest challenge was dealing with the amount of missing data in certain outcome measures. Except for vascular event recurrence and death, which were obtained using the methods of hot and cold pursuit detailed in **Chapter 4**, living arrangements, disability and quality of life information were derived from patient self-report at follow-up.

After accounting for censoring and death, outcome data were missing for approximately 20% of patients at each of the four follow-up points. Furthermore, for 42% of patients there was missing quality of life data at the 6-month follow-up due to the EQ-5D not being administered during the first 18 months of OXVASC. Reasons

for missing data included: patients refusing follow-up; patients being too severely disabled/ill to complete a follow-up assessment; patients being missed or not attending their scheduled follow-up visits; and a proportion of patients whose events were coded as possible due to uncertainty in the clinical diagnosis, were not followed up face to face. Due to the advanced age of the patient sample, there was little evidence, however, of patients relocating to other areas, and therefore being lost to follow-up. In addition, due to missing information on baseline characteristics such as socio-economic status, place of residence, marital status and employment status before the event, albeit to a much lesser extent than for outcome information, the number of cases available for multivariate analyses was further diminished.

As missing information might lead to bias in analyses as respondents may vary from non-respondents, and to a loss of statistical power as missing data reduce the available sample size,[221] the impact of missing data on the results of the multivariate analyses was investigated using multiple imputation techniques.[225] Both for disability and quality of life, results of the analyses with complete-case information and those in which missing cases were imputed were compared, with no considerable differences between the results of the two methods being observed.

8.3 COSTS AFTER A CEREBROVASCULAR EVENT

8.3.1 MAIN FINDINGS

The high incidence and serious consequences of cerebrovascular events make it a major cause of health service use and healthcare expenditure, creating much research interest in the costs of stroke and TIA. In **Chapter 3** a review of the literature based on studies based on individual patient data was presented. This

review both assessed and critically appraised the study designs and methods used in each included study. The review identified a total of 120 separate studies published between January 1990 and end January 2007, evaluating the costs of cerebrovascular events, with only a small minority of studies including TIA in their study samples. The review showed that costs of stroke varied considerably, mainly due to differences in the country of origin, populations studied, methods, and cost categories included in each study. Even in studies conducted in the same country, important cost variations were identified, with estimates from the USA, for example, varying twenty-fold.

As was argued in **Chapter 3**, such variations in the published costs of stroke will have an impact on the results of economic evaluations assessing the cost-effectiveness of stroke interventions. For example, when assessing the cost-effectiveness of new interventions to prevent stroke, the higher the costs of stroke the more likely the intervention is to be cost-effective. This could potentially result in the selective quotation of costs in secondary health economic analyses, with authors including those costs that are more likely to produce the desired results. In order to ascertain the validity of costing studies of cerebrovascular events and to make results more comparable across studies, the review set out a number of criteria that studies should ideally fulfil. These included:1) use of appropriate costing methodologies; 2) use of population-based studies; 3) taking into account pre-morbid resource use and costs; and 4) assessment of costs for different patient sub-groups.

With the exception of the use of appropriate costing methodologies, only a small proportion of studies complied with the other three criteria. Most importantly, only

5[193;194;245;265;266] of the 120 studies included were based on data derived from population-based cohorts. The use of population-based cohort studies was deemed important as studies evaluating the costs of stroke and TIA are based on an unselected sample including all relevant patients. The general view is that population-based cohort studies with full case ascertainment are the most accurate sources of information on disease incidence, mortality and outcome.[18;32]

Using the OXVASC sample presented in **Chapter 4**, **Chapter 6** evaluated the healthcare resource use and costs incurred by patients over the 5 years post-index stroke or TIA, and their main univariate and multivariate predictors. As TIA and stroke occur mainly in relatively old patients suffering other co-morbidities, it is likely that stroke and TIA patients would utilise substantial health care resources irrespective of cerebrovascular event onset. Therefore, in order to estimate the impact of stroke and TIA on subsequent resource use consumption and costs, resource use and costs incurred were compared for the 12 months before and after the index cerebrovascular event.

Results of the cost analyses showed that total costs per patient were significantly and considerably higher after the cerebrovascular event, and except for day cases, these increases were observed for all resource-use categories. However, despite the large increases in costs 12 months after the cerebrovascular event (£6,057 on average), the costs incurred by patients over the one year preceding the event were considerable (£1,652 per patient).

Overall, for the 5 years after the index cerebrovascular event, results showed the average cost per patient to be £15,783 (95% CI: 14,323 to 17,482), most of which was driven by inpatient care costs (78%). Stroke patients incurred average costs of £16,923 (95% CI: 15,149 to 18,858) significantly more than for TIA patients, who incurred average costs of £13,904 (95% CI: 11,488 to 16,657; p=0.019). However, after controlling for other event and patient characteristics, including event severity, in the multivariate analyses, these differences were no longer found to be significant. In the multivariate analysis, event severity was found to be a significant predictor of inpatient care resource use and total costs in surviving patients. Recurrent vascular events, especially stroke and coronary heart disease (CHD) events, also significantly increased hospitalisations, subsequent days in hospital, and overall care costs.

8.3.2 CHALLENGES IN EVALUATING RESOURCE USE AND COSTS

As with health outcomes, OXVASC offered a large non-biased dataset of patients from which healthcare resource use and costs could be derived. In addition, the detailed clinical and socio-economic information collected shortly after the index event, provided a wealth of information that was useful in determining the predictors of resource use and costs in multivariate analyses. However, there were a number of challenges in obtaining and evaluating the data.

By far the biggest challenge was the amount of healthcare resource use information to be collected. Except for inpatient care resource use at the Oxford Centre for Enablement (OCE), I derived the remaining inpatient, outpatient, emergency and primary care resource use from patients' medical records. This involved reviewing the hospital and primary care medical records of 1,199 patients, each with a mean

follow-up of over two years in addition to the 12 months before the event. Inpatient, outpatient and emergency care resource use were derived from the Oxford Patient Administration System (PAS), an Oxford Radcliffe Hospitals (ORH) NHS trust centrally held database containing the medical records of all patients. Primary care resource use was derived by visiting each of the 9 general practices included in OXVASC.

Due to the time spent on data collection for these key resource use categories, resource usage for other care services was not derived due to lack of time. These included 1) medications, which could have been derived from patients' primary care records; 2) community rehabilitation visits, which could have been derived from inspecting referral letters by the patient's general practitioner (GPs); 3) other outpatient and inpatient care resource use provided by non-ORH hospitals, including the Nuffield Orthopaedic Centre (NOC) and the Warneford Hospital; and 4) care provided by social services, including respite care, meals on wheels, and nursing and residential home care.

Another challenge faced when estimating costs over the 5-year period after the index stroke or TIA was the censoring of patients, with over 70% of patients being censored by the end of the 5-year follow-up period. As ignoring the issue of censoring results in a miss-estimation of mean costs,[238] costs, as well as days in hospital, were adjusted for censoring using standard methods.[239] In addition, the multivariate analyses undertaken to determine the predictors of both costs and inpatient care resource use were also weighted by the probability of being censored, given each patient's baseline characteristics, in order to adjust for censoring.[241] Such

weighting was undertaken as some patients, given their characteristics, were more likely to be censored than others. For example, due to higher case-fatality rates for severe strokes, these patients were significantly less likely to be censored than those with mild TIAs, who were more likely to survive the observed follow-up period and therefore to be censored.

8.4 COST-EFFECTIVENESS OF SECONDARY STROKE PREVENTION

8.4.1 MAIN FINDINGS

Results from both **Chapter 5** and **6** showed that recurrent vascular events, in particular recurrent stroke, significantly increased case-fatality, disability, health care resource usage and total costs, as well as reducing patient's quality of life. With an observed 20% cumulative risk of developing a recurrent stroke in the 5 years after initial TIA or stroke (**Chapter 5**), there is a sizeable opportunity to design cost-effective interventions that reduce the risk of recurrent stroke.

As was argued earlier, cost-effective treatments are now available to prevent recurrent stroke in the long-term after a TIA or minor stroke. However, as shown in **Chapter 5**, there is a high risk of recurrent stroke very shortly after initial TIA or stroke, and therefore for preventive treatment to be effective there is only a short window of opportunity. In the UK, for these treatments to work effectively this would entail faster access to outpatient specialist care, as approximately half of all TIA and minor stroke patients currently wait more than 14 days to be assessed and treated.[12] Using data from The Early use of eXisting PREventive Strategies for Stroke (EXPRESS) study, a rigorous observational study of the phased introduction of early assessment and treatment, nested within OXVASC, **Chapter 7** evaluated the costs

and outcomes of two interventions (phase-1: delayed access to specialist assessment and treatment; and phase-2: urgent access to specialist assessment and treatment) aimed at reducing the risk of recurrent stroke.

EXPRESS showed that the phase-2 clinic significantly reduced the number of 90-day recurrent strokes (n=6, 2%) compared to the phase-1 clinic (n=32, 10%; p<0.001).[253] Results from **Chapter 7**, showed that not only did the phase-2 clinic reduce recurrent stroke risk but in particular reduced the 90-day risk of fatal or disabling stroke (1/281 vs. 16/310, p<0.001). In terms of resource usage, although the phase-2 clinic did not reduce all-cause hospitalisation rates, those for recurrent stroke were significantly lower in phase-2 (5 vs. 25; p=0.001), which reduced the overall number of hospital bed-days compared to phase-1 (672 vs. 1,957 days, an average reduction of 4 days in hospital; p=0.017). When only vascular hospitalisations were considered (i.e. those due to stroke, TIA, peripheral vascular disease and coronary heart disease) days in hospital were also lower in phase-2 (427 vs. 1,365 days; p=0.016), generating savings of £643 per patient referred to the phase-2 clinic (p=0.028).

Although further follow-up is required to determine the long-term outcome, costs, and therefore long-term cost-effectiveness of early assessment and treatment, these short-term results suggest that service provision for TIA and minor stroke similar to that in phase-2 of the EXPRESS study is likely to be cost-effective. In addition, they reinforce the steps that have already been taken in the UK in changing routine practice in the care of TIA and minor stroke patients. Recently published NICE guidelines on stroke prevention and treatment,[260] in light of the first results from EXPRESS,[253] now recommend that any patient suspected of having suffered a TIA

or minor stroke should be immediately treated with aspirin and seen by a specialist clinician as soon as possible.

8.4.2 CHALLENGES IN EVALUATING THE COST-EFFECTIVENESS OF SECONDARY STROKE PREVENTION

As EXPRESS was nested within OXVASC, outcome, resource use and cost data collected for **Chapters 5** and **6** were used for the economic analysis of EXPRESS. As a result, except for a few patients recruited in the latter stages of phase-2 of EXPRESS (where the inpatient care resource use did not cover the whole of the 90 day follow-up period), the analysis of the EXPRESS study did not involve any further collection of data. However, despite much of the data required for the economic evaluation of the EXPRESS study being available and ready to analyse, a number of challenges were encountered.

EXPRESS was not a randomised controlled trial, but rather an observational study conducted over two different time periods. Therefore, temporal changes in referral patterns, patient characteristics, resource use patterns, or other potential sources of bias could have affected the results. However, every effort was taken both in the design of EXPRESS and in the analysis of results to minimise the possibility of such biases. The control group in EXPRESS (i.e. phase-1) was prospectively accrued and included all patients presenting to medical attention in the whole study population, thereby, minimising any potential for selection bias. Therefore EXPRESS should not be confused with studies using “historical controls”, in which a control group is assembled retrospectively, with consequent potential for both incomplete ascertainment of cases and selection bias.

There was also no evidence of confounding (i.e. that some other factor had changed between phase-1 and phase-2 in addition to the study intervention). First, the change in recurrence rate in phase-2 occurred immediately in October 2004 when the new clinic was introduced rather than slowly over the five years of the study. Second, there was no evidence of any substantial change in the characteristics of patients presenting with TIA or stroke between the two periods, other than a small increase in the proportion on pre-morbid statin treatment – due mainly to re-presentation of patients treated in phase-1. To control for potential differences in patients' baseline characteristics, multivariate analyses were undertaken to identify if the phase-2 clinic was significantly associated with outcome. Results of these analyses confirmed that the phase-2 clinic was found to be significantly associated with reduced days in hospital, hospitalisation costs and progression to disability or death.

Although the treatment effect was very large (an 80% relative reduction in 90-day risk of stroke), this size of effect was consistent with previous studies modelling the likely impact of multiple combined treatment modalities in secondary prevention after TIA or stroke,[65] and was plausible given the very substantial difference in delay to prescription of treatment between the two phases of EXPRESS. The study therefore essentially compared intensive treatment with minimal treatment during the first few high risk days and weeks after TIA and minor ischaemic stroke. Furthermore, in contrast to populations recruited in most randomised controlled trials,[261] OXVASC, in which EXPRESS was nested, included many older patients (one-third were aged 80 years or over).

Another problem with non-randomised non-blinded studies is that process of care outcomes, such as hospital admission, are potentially more prone to bias since such decisions might be influenced by knowledge of prior treatment. It is possible that, for example, physicians in phase-2 worked harder not to admit patients with minor stroke symptoms. However, there was no evidence for this bias as overall hospitalisation rates were similar in both phases. Only hospitalisations for recurrent stroke were found to be significantly lower in phase-2 than in phase-1, which were driven by significantly fewer recurrent strokes in phase-2. Out of the 6 recurrent strokes in phase-2, 5 (83%) patients were hospitalised, compared to 25 out of the 32 recurrent strokes in phase-1 (78%). In fact, admissions for reasons other than recurrent stroke were non-significantly higher in phase-2. In addition, no evidence of external biases in resource use patterns, such as changes in health policy or management between the two phases, which might have explained the reductions in hospital stay and associated costs, were identified. Results of EXPRESS showed that for non-recurrent stroke hospital admissions, days in hospital and costs did not differ between phases, and for patients presenting directly to hospital inpatient services rather than the EXPRESS study clinic, resource use patterns were the same during the two phases.

Although a cost-utility analysis would have been the preferred method of economic evaluation when comparing the two secondary stroke prevention interventions,[73;267] this type of evaluation was not possible, and a cost-consequences analysis was performed instead. First, during the first 18 months of OXVASC the EQ-5D was not included as part of the follow-up questionnaires. As a result, quality of life information

was missing for over 57% of phase-1 patients, and was, therefore, not assessed. As a result, it was not possible to generate QALYs.

Secondly, the study did not quantify the costs to the health service of setting up outpatient clinics for the urgent assessment and treatment of TIA and minor stroke. The phase-2 clinic was set-up as part of the OXVASC research study, and it was not clear what part of these costs might be incurred if such clinics were set up as part of routine practice. Undoubtedly, the introduction of outpatient clinics, similar to that in phase-2, would involve additional costs to the health service.

Finally, due to insufficient follow-up of patients in a great proportion of phase-2 patients, the time horizon over which costs and outcomes were assessed was relatively short (i.e. 90 days for resource use and costs and 6 months for disability and death). It was decided, therefore, to describe the evaluation as a cost-consequences analysis, rather than a cost-effectiveness analysis.

8.5 GENERALISABILITY OF THE RESULTS

At the end of each chapter in this thesis, the limitations of the analyses undertaken have been reported in detail. However, one of the limitations of the research conducted in this thesis, and not covered in any of the previous chapters, is the generalisability of the results presented to other settings.

It has been argued throughout the thesis that population-based cohort studies such as OXVASC, on which all outcome and cost analyses presented are based, are the most accurate sources of information on stroke and TIA incidence, health outcomes,

resource use and costs, as they are based on an unselected sample including all relevant patients. It is hoped, therefore, that the results on outcomes, costs and resource use presented in **Chapters 5** and **6**, will be useful in order to inform decisions about service provision and resource allocation, and to estimate the cost-effectiveness of specific interventions to prevent or treat illness. Reliable estimates of the costs of disease are also valuable to other researchers, particularly as an input to decision-analytic models, which are becoming ever more popular to assess the cost-effectiveness of healthcare interventions. These allow synthesis of available evidence, including cost and quality of life data, allow extrapolation of trial results, and are useful to determine cost-effectiveness when randomised controlled trials (RCT) are either too costly or inappropriate.[268]

However, despite these considerable advantages, there are some issues that might affect the generalisability of the results presented in this thesis. First, OXVASC not only identified cases with stroke or TIA, but actively followed them up after the event. Shortly after TIA or stroke, patients were assessed in detail by an OXVASC clinician, which recommended the most appropriate treatment and care pathway for the patient. In addition, patients were seen at regular follow-up visits by trained research nurses, which amongst other things, screened patients for presence of recurrent events, compliance with medication, and control of hypertension.

In addition, for non-hospitalised patients, after September 2004 (i.e. phase-2 of EXPRESS), any patient suspect of TIA or stroke was urgently referred to the OXVASC outpatient clinic, where treatment was commenced without delay. Even non-hospitalised patients recruited before September 2004, received better

standards of care than in current UK practice, where patients routinely wait more than 14 days to be assessed, investigated and treated,[12] compared to the 3-day delay between first event and specialist assessment in phase-1 of EXPRESS.

It is likely, therefore, that the outcomes and costs presented in **Chapters 5** and **6** are more favourable than for other UK stroke and TIA patients. Due to the aggressive treatment non-hospitalised patients received, the estimates of vascular event recurrence risk after TIA or stroke will be an underestimate of those faced by patients in UK current practice. In addition, as vascular event recurrence was found to be an independent predictor of decreased patient health and increased resource use and costs, the likely reduced risk of recurrent events in OXVASC patients, probably resulted in them incurring lower costs and experiencing better health outcomes than those receiving current UK-levels of care.

Another factor limiting the results presented in this thesis is that the OXVASC population might not be representative of the UK population as whole. As shown in **Chapter 4**, 45% of the study sample lived in areas ranked in the least deprived quintile in England and Wales, with only 6% of the sample living in the two most deprived quintiles. As a result, the OXVASC sample was less socially deprived than in the UK as a whole, and could be considered “too middle class” to make the results generalisable to the rest of the country. However, OXVASC is one of the few studies in the UK assessing the incidence and outcome of stroke and TIA using a population-based study, making its results more generalisable than those from other UK studies, which generally include more severe strokes requiring hospitalisation.

Another population-based study conducted in the UK, the South London Stroke Register (SLSR),[208] has evaluated the incidence of stroke in an inner-city urban area, with a more deprived and ethnically diverse population (63% white, 28% black and 9% from other ethnicities) than OXVASC, where the sample was 97% white. Results from the SLSR have shown that incidence rates for stroke, after adjusting for age and gender were significantly higher in black than white people (incidence rate ratio of 2.21; $p<0.0001$).[34] Results in the same population have also showed survival differences across ethnicities, with black stroke patients, in general, significantly more likely to survive their stroke than white patients.[269] As a result, it would be extremely interesting to compare the resource use patterns, costs and quality of life outcomes from the OXVASC and SLSR populations.

8.6 SUGGESTIONS FOR FUTURE RESEARCH

This thesis has evaluated the long-term levels and predictors of health outcomes, resource use and costs in stroke and TIA patients, in addition to evaluating the short-term cost-effectiveness of interventions aimed at reducing the risk of recurrent stroke. Throughout the research undertaken, a number of further themes have emerged that would have enhanced the quality of the research, and are highlighted here as areas of further research.

First, in light of the ongoing nature of OXVASC, currently in its seventh year, any new analyses on the costs and outcomes after TIA or stroke would include additional patients, making the results more generalisable and increasing the sample size required to detect statistically significant results between patient sub-groups in univariate and multivariate analyses. In particular, due to low incidence and high-

case fatality of certain stroke subtypes such as ICH and SAH, a larger sample size will make it possible to establish with more precision the nature of any differences in outcome and cost.

Secondly, and in addition to the first point, the ongoing nature of OXVASC will allow a longer follow-up period for analysis providing valuable information on the long-term outcomes after stroke or TIA and on long-term patient recovery. In addition, a longer follow-up of patients would reduce the proportion of patients being censored in the analyses of costs, reducing the uncertainty around the mean estimates and increasing the precision and generalisability of the results. Such data, therefore, could then be used to evaluate the long-term cost-effectiveness of the EXPRESS outpatient clinics.

Finally, as part of OXVASC the incidence of other vascular events, in addition to stroke and TIA, was evaluated, with CHD and PVD patients also being recruited and followed-up in a similar fashion to cerebrovascular patients. As a result, further research could evaluate the quality of life, disability, resource use patterns and costs of CHD and PVD patients. Such data would then allow for formal comparisons of outcome and cost between them and stroke.

8.7 CONCLUDING REMARKS

Stroke is a major cause of death, disability and use of health-care resources. Despite this, there is a lack of reliable information on costs and outcomes, particularly in TIA and minor stroke. Such information is vital not only to inform decisions about service provision both locally and nationally, but also to provide reliable estimates for use in

cost-effectiveness analysis of prevention and treatment strategies. Through the use of a population-based study on TIA and stroke in Oxfordshire, this thesis provides healthcare decision makers and researchers with a wealth of data on the resource use patterns, costs and outcomes of TIA and stroke patients, and their main predictors. Hopefully the evidence and results presented in this thesis will add new insights to the understanding of the burdens placed by cerebrovascular events on the health system at large and to individual patients.

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APPENDIX 1:

CEREBROVASCULAR DISEASE CLASSIFICATION

ICD-10	Cerebrovascular disease
G450-G459	Transient cerebral ischaemic attack
G460-G468	Vascular brain syndromes in cerebrovascular disease
H340-H342	Retinal artery ischaemia
H348	Retinal vascular occlusions
I600-I609	Subarachnoid haemorrhage
I610-I619	Intracerebral haemorrhage
I620-I629	Other intracranial haemorrhages
I630-I639	Cerebral infarction
I64X	Non-specified stroke
I650-I670	Cerebral artery occlusion and dissection of cerebral arteries
I671-I698	Other and chronic cerebrovascular diseases

APPENDIX 2:

EPIDEMIOLOGY & QUALITY OF LIFE SEARCH STRATEGIES

Glossary of OVID terms:

/ Medline subject heading (MESH)

.tw Identifies the word specified in the title or abstract

$ Identifies any word beginning with the text preceding it

or The article only has to be found in one of the search terms

and The article must be found in all the search terms

not Retrieves articles that contain the first search term and exclude the second

adjn Retrieves articles that contain search terms within a specified number (n) of words of each other in any order

.pt Identifies the publication type

.so Includes a display of all the basic information needed to locate a study

.sh MESH used by indexers to describe the content of an article

Table Medline search strategy: cerebrovascular event epidemiology

Medline terms	
1. exp cerebrovascular disorders/	16. thrombo$.tw.
2. stroke$.tw.	17. (intracranial or (venous adj5 sinus$) or (sagittal adj5 venous) or (saggittal adj5 vein)).tw.
3. cerebrovascular$.tw.	18. 16 and 17
4. (cerebral or cerebellar or brainstem or vertebrobasilar).tw.	19. transient isch?emic attack$.tw.
5. (infarct$ or isch?emi$ or thrombo$ or emboli$).tw.	20. reversible isch?emic neurologic$ deficit.tw.
6. 4 and 5	21. venous malformation$.tw.
7. carotid$.tw.	22. arteriovenous malformation$.tw.
8. (cerebral or intracerebral or intracranial or parenchymal).tw.	23. 21 or 22
9. (brain or intraventricular or brainstem or cerebellar).tw.	24. 11 and 23
10. (infratentorial or supratentorial or subarachnoid).tw.	25. exp aphasia/
11. 8 or 9 or 10	26. hemianopsia/
12. (haemorrhage or hemorrhage or haematoma or hematoma).tw.	27. hemiplegia/
13. (bleeding or aneurysm).tw.	28. (aphasi$ or dysphasi$ or hemianop$).tw.
14. 12 or 13	29. (hemiplegi$ or hemipar$).tw.
15. 11 and 14	30. 25 or 26 or 27 or 28 or 29
16. thrombo$.tw.	31. or/1-3,6-7,15,18-20,24,30
17. (intracranial or (venous adj5 sinus$) or (sagittal adj5 venous) or (saggittal adj5 vein)).tw.	32. leukomalacia, periventricular/
	33. cerebral anoxia/
	34. exp dementia, vascular/
	35. exp vascular headache/
	36. migrain$.tw.
	37. 32 or 33 or 34 or 35 or 36
	38. 31 not 37

Table Embase search strategy: cerebrovascular event epidemiology

Embase terms	
1. exp cerebrovascular disease/ 2. stroke$.tw. 3. cerebrovascular$.tw. 4. (cerebral or cerebellar or brainstem or vertebrobasilar).tw. 5. (infarct$ or isch?emi$ or thrombo$ or emboli$).tw. 6. 4 and 5 7. carotid$.tw. 8. (cerebral or intraventricular or brainstem or cerebellar).tw. 9. (infratentorial or supratentorial or subarachnoid).tw. 10. (brain or intraventricular or brainstem or cerebellar).tw. 11. 8 or 9 or 10 12. (haemorrhage or hemorrhage or haematoma or hematoma).tw. 13. (bleeding or aneurysm).tw. 14. 12 or 13 15. 11 and 14 16. thrombo$.tw.	13. (bleeding or aneurysm).tw. 14. 12 or 13 15. 11 and 14 16. thrombo$.tw. 17. (intracranial or (venous adj5 sinus$) or (sagittal adj5 venous) or sagittal vein).tw. 18. 16 and 17 19. transient isch?emic attack$.tw. 20. reversible isch?emic neurologic$ deficit$.tw. 21. venous malformation$.tw. 22. arteriovenous malformation$.tw. 23. 21 or 22 24. 11 and 23 25. exp aphasia/ 26. dysphasia/ 27. hemianopia/ 28. hemiplegia/ 29. hemiparesis/ 30. (aphasi$ or dysphasi$ or hemianop$).tw. 31. (hemipleg$ or hemipar$).tw. 32. exp carotid artery surgery/ 33. or/1-3,6-7,15,18-20,24-32

Table CINAHL search strategy: cerebrovascular event epidemiology

CINAHL search terms	
1. exp cerebrovascular disorders/ 2. stroke$.tw. 3. cerebrovascular$.tw. 4. (cerebral or cerebellar or brainstem or vertebrobascular).tw. 5. (infarct$ or isch?emi$ or thrombo$ or emboli$).tw. 6. 4 and 5 7. carotid$.tw. 8. (cerebral or intraventricular or brainstem or cerebellar).tw. 9. (infratentorial or supratentorial or subarachnoid).tw. 10. (brain or intraventricular or brainstem or cerebellar).tw. 11. 8 or 9 or 10 12. (haemorrhage or hemorrhage or haematoma or hematoma).tw.	13. (bleeding or aneurysm).tw. 14. 12 or 13 15. 11 and 14 16. thrombo$.tw. 17. (intracranial or (venous adj5 sinus$) or (sagittal adj5 venous) or sagittal vein).tw. 18. 16 and 17 19. transient isch?emic attack$.tw. 20. reversible isch?emic neurologic$ deficit$.tw. 21. venous malformation$.tw. 22. arteriovenous malformation$.tw. 23. 21 or 22 24. 11 and 23 25. exp aphasia/ 26. (aphasi$ or dysphasi$ or hemianop$).tw. 27. (hemipleg$ or hemipar$).tw. 28. exp carotid stenosis/ 29. or/1-3,6-7,15,18-20,24-28

Table Medline search strategy: quality of life

Medline terms	
1. exp quality of life/ 2. qol.tw. 3. qaly$.tw. 4. qald$.tw. 5. qale$.tw. 6. qtime$.tw. 7. hye.tw. 8. hyes.tw.	9. (utility or utilities).tw. 10. “life quality”.tw. 11. (sf-36 or sf36).tw. 12. euroqol.tw. 13. (Eq-5d or eq5d).tw. 14. “health utilities index”.tw. 15. or/1-14

Table Embase search strategy: quality of life

Embase terms	
1. exp “Quality of Life”/ 2. qol.tw. 3. qaly$.tw. 4. qald$.tw. 5. qale$.tw. 6. qtime$.tw. 7. hye.tw. 8. hyes.tw.	9. (utility or utilities).tw. 10. “life quality”.tw. 11. (sf-36 or sf36).tw. 12. euroqol.tw. 13. (Eq-5d or eq5d).tw. 14. “health utilities index”.tw. 15. or/1-14

Table CINAHL search strategy: quality of life

CINAHL terms	
1. exp “Quality of Life”/ 2. qol.tw. 3. qaly$.tw. 4. qald$.tw. 5. qale$.tw. 6. qtime$.tw. 7. hye.tw. 8. hyes.tw.	9. (utility or utilities).tw. 10. “life quality”.tw. 11. (sf-36 or sf36).tw. 12. euroqol.tw. 13. (Eq-5d or eq5d).tw. 14. “health utilities index”.tw. 15. or/1-14

APPENDIX 3:

QUALITY OF LIFE STUDY PROFORMA

INCLUDE: ☐ YES ☐ NO

1) Authors and publication date:

2) Title:

3) Country:

4) Objective: ……
……
……

5) Setting:……
……
……

6) Patient population: ……
……
……

7) Patient sample: ……
……
……

8a) QoL estimates derived from:

☐ Patients
☐ General population
☐ Experts
☐ Care givers

8b) Using:

☐ Generic measures
……. Go to Question 9

☐ Direct elicitation
……. Go to Question 10

9a) Generic measures:

☐ Rosser Index
☐ EQ-5D
☐ 15D
☐ SF-12
☐ Health Utilities Index (HUI)
☐ Quality of Well Being (QWB)
☐ SF-36

9b) Converted into utilities?

☐ Yes
☐ No

Using:

……

10) Direct elicitation:

☐ Standard Gamble
☐ Time trade-off
☐ VAS
☐ Person trade-off

11) Utility values combined with survival to form QALYs?

☐ Yes
☐ No

12) Result(s):

……
……
……
……

13) Comments, limitations of the study:

……
……
……
……

14) Conclusions:

……
……
……
……

APPENDIX 4:

INCLUDED QUALITY OF LIFE STUDIES

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APPENDIX 5: METHODS & RESULTS OF INCLUDED QUALITY OF LIFE STUDIES

Study ID	Country	Event type	Population	Valuation	Subgroup analysis	Time since event	Sample	Mean quality of life
Baker 2004 [1]	UK	Stroke	General population	SG	Event severity	N/A	28	Mild stroke: 0.55 Severe stroke: 0.14
Bosworth 2000 [2]	USA	IS and ICH	Stroke patients	TTO	Depression	Between 1 and 12 months	327	0.76
Cup 2003 [3]	Netherlands	Stroke	Stroke patients	EQ-5D	None	Between 2 and 6 months	26	0.34
Dennis 2006 [4]	Australia, Belgium, Brazil, Canada, Czech Rep., Denmark, Hong Kong, India, Italy, New Z'nd, Poland, Portugal, Ireland, Turkey, UK	Moderate stroke, excluding SAH	Stroke patients	EQ-5D	None	6 months	3492	0.59
Donnelly 2005 [5]	UK	Stroke	Stroke patients	VAS	Study interventions (hospital rehab-HR vs. community rehab-CR)	1 month and 6 months	HR / CR One month: 54 / 59 Six months: 46 / 51	HR / CR One month: 59 / 61 Six months: 68 / 66
Dorman 2000 [6]	UK	Stroke	Stroke patients	EQ-5D and VAS	Two different cohorts, event severity	Between 43 and 104 weeks	Stroke register / trial Mild: 41 / 123 Moderate: 52 / 137 Severe: 54 / 564	Stroke register / trial EQ-5D Mild: 0.88 / 0.88 Moderate: 0.74 / 0.71 Severe: 0.38 / 0.31 VAS Mild: 77 / 77 Moderate: 65 / 67 Severe: 58 / 48
Dorman 1997 [7]	UK	Stroke	Stroke patients & caregivers	VAS	Study population	3 months	Stroke patients: 122 Caregivers: 122	Stroke patients: 64 Caregivers: 62
Dorman 1997 [8]	UK	Stroke	Stroke patients	VAS	Event severity	Between 43 and 104 weeks	Mild: 51 Moderate: 51 Severe: 51	Mild: 73 Moderate: 62 Severe: 62
Duncan 1997 [9]	USA	Mild stroke and TIA	Stroke and TIA patients	TTO and VAS	Study population	595 days on average	Mild stroke / TIA: 304 / 184	Mild stroke / TIA VAS: 66 / 72 TTO: 0.76 / 0.83

Study ID	Country	Event type	Population	Valuation	Subgroup analysis	Time since event	Sample	Mean quality of life
Duncan 2000 [10]	USA	Stroke	Stroke patients	TTO	Modified Rankin score (mRS)	12 months	mRS 0 / 1 : 77 / 77 mRS 2 / 3: 77 / 76 mRS 4 / 5: 76 / 76	mRS 0 / 1 : 0.93 / 0.88 mRS 2 / 3: 0.73 / 0.69 mRS 4 / 5: 0.54 / 0.34
Evans 2002 [11]	UK	Severe IS	Stroke patients	VAS	Study interventions (stroke unit vs. stroke team), small- and large- vessel disease (SVD and LVD)	3 and 12 months	SVD / LVD Stroke unit 3 months: 49 / 80 12 months: 49 / 80 Stroke Team 3 months: 54 / 84 12 months: 54 / 84	SVD / LVD Stroke unit 3 months: 70 / 75 12 months: 80 / 80 Stroke Team 3 months: 60 / 60 12 months: 75 / 75
Franceschini 2003 [12]	Italy	Stroke	Stroke patients & caregivers	VAS	Study population	12 months	Stroke patients: 528 Caregivers: 528	Stroke patients: 57 Caregivers: 54
Fruhwald 2001 [13]	Austria	IS	Stroke patients	VAS	None	Between 3 and 12 days	50	77
Gage 1995 [14]	USA	Stroke	Patients at risk of stroke	TTO	Event severity and recurrent stroke	N/A	57	Mild stroke: 0.75 Moderate stroke: 0.39 Recurrent stroke: 0.12
Gage 1996 [15]	USA	Stroke	Patients at risk of stroke	TTO and SG	Event severity	N/A	70	TTO / SG Mild: 0.76 / - Moderate: 0.39 / 0.26 Severe: 0.11 / -
Glasziou 1994 [16]	Australia	Stroke	Stroke patients	TTO	None	Unknown	714	0.79
Glick 1999 [17]	USA	SAH	SAH patients	HUI2 and VAS	Event severity and place of residence	3 months	Good recovery: 465 Moderate disability : 82	Recovery / disability VAS: 80 / 68 HUI2 utility: 0.90 / 0.76 HUI2 value: 0.64 / 0.33
Gold 1998 [18]	USA	CVD	CVD patients	HALEX	None	Unknown	866	0.47
Goldstein 2002 [19]	USA	IS	Stroke patients & caregivers	HUI2 and HUI3	Event severity and study population	Approximately 100 days	Stroke patient / caregiver Mild: 35 / 32 Moderate: 20 / 36 Severe: 21 / 38	Stroke patient / caregiver HUI2 Mild: 0.76 / 0.73 Moderate: 0.54 / 0.42 Severe: 0.41 / 0.38 HUI3 Mild: 0.56 / 0.58 Moderate: 0.15 / 0.03 Severe: 0.16 / 0.01
Gore 1995 [20]	USA	Stroke	Stroke patients	TTO	Event severity	30 days	Minor: 60 Moderate: 32	Minor: 0.89 Moderate: 0.81

Study ID	Country	Event type	Population	Valuation	Subgroup analysis	Time since event	Sample	Mean quality of life
Grootendorst 2000 [21]	Canada	Stroke	Stroke patients	HUI3	None	Unknown	173	0.54
Haacke 2006 [22]	Germany	IS, ICH and TIA	Stroke and TIA patients	EQ-5D, HUI2, HUI3, VAS	Event type, event severity, gender, age, anxiety, depression, cognitive ability	4 years	Stroke ant TIA: 77 Independent: 47 Severe disability: 30	VAS / EQ-5D Stroke ant TIA: 56 / 0.73 Independent: 68 / 0.86 Severe disability: 46/0.44 HUI2 / HUI3 Stroke ant TIA: 0.67/0.47 Independent: 0.77/0.65 Severe disability:0.44/0.60
Hafsteinsdottir 2005 [23]	Netherlands	Severe stroke	Stroke patients	VAS	Study interventions (neurodevelopmental vs. no treatment)	6 and 12 months	Treatment / no treatment 6 months: 206 / 198 12 months: 93 / 95	Treatment / no treatment 6 months: 49 / 50 12 months: 50 / 50
Hallan 1999 [24]	Norway	Stroke	General population, stroke patients and patients at risk of stroke	SG, TTO, VAS	Event severity, study population, marital status and age	N/A	General population: 46 Stroke patients: 46 Patients at risk: 46	Mild / severe SG General pop.: 0.91 / 0.56 Stroke patients:0.95/0.91 Patients at risk:0.95/0.66 Total sample SG: 0.91 / - TTO: 0.88 / 0.51 VAS: 0.71 / 0.31
Indredavik 1998 [25]	Norway	Stroke	Stroke patients	VAS	None	5 years	25	0.78
Kalra 2004 [26]	UK	Stroke	Stroke patients	VAS	Study interventions (caregiver training vs. no training)	3 and 12 months	Training / no training 3 months: 139 / 129 12 months: 134 / 127	Training / no training 3 months: 60 / 50 12 months: 65 / 60
Kalra 2005 [27]	UK	Stroke	Stroke patients	VAS	Barthel Index (BI) and study interventions (stroke team-ST, stroke unit-SU, domiciliary care-DC)	12 weeks and 12 months	SU / DC / ST BI 0-4: 33 / 27 / 22 BI 5-9: 45 / 25 / 35 BI 10-14: 31 / 37 /44 BI >14: 29 / 34 / -	12 weeks / 12 months SU BI 0-4: 60 / 75 BI 5-9: 75 / 80 BI 10-14: 75 / 83 BI >14: 75 / 85 DC BI 0-4: 55 / 60 BI 5-9: 70 / 75 BI 10-14: 77 / 85 BI >14: 75 / 85 ST BI 0-4: 50 / 50 BI 5-9: 65 / 75 BI 10-14: 67 / 75

Study ID	Country	Event type	Population	Valuation	Subgroup analysis	Time since event	Sample	Mean quality of life
Kwa 1996 [28]	Netherlands	IS	Stroke patients	VAS	Barthel Index (BI), age, gender, educational level, infarct volume, living arrangements, aphasia and cognitive function	28 months on average	BI > 94: 59 BI < 95: 39	BI > 94: 64 BI < 95: 50
Lai 2001 [29]	USA	Stroke, excluding SAH	Stroke patients	TTO	Event severity	3 months	Minor: 57 Moderate: 84	Minor: 0.90 Moderate: 0.80
Lenert 1997 [30]	USA	Stroke	General population and experts	SG, VAS	Study population	N/A	Experts: 30 General population: 30	SG / VAS General pop.: 0.66 / - Experts: 0.50 / - All sample: 0.60 / 25
Maddigan 2005 [31]	Canada	Stroke	Stroke patients	HUI3	Presence of co-morbidities	Unknown	218	0.74
Man-Son-Hing 2000 [32]	Canada	Stroke	Patients at risk of stroke	VAS	Event severity	N/A	42	Minor: 70 Severe: 16
Mathias 1997 [33]	USA	IS	Stroke patients and caregivers	HUI2	Study population	Less than 3 months	Stroke patients: 33 Caregivers: 33	Stroke patients: 0.64 Caregivers: 0.64
Mayo 2002 [34]	Canada	IS and ICH	Stroke patients	VAS	None	6 months	434	68
Mittmann 1999 [35]	Canada	Stroke	Stroke patients	HUI3	Gender and age	Unknown	176	0.68
Mittmann 2001 [36]	Canada	Stroke	Stroke patients	HUI3	None	Unknown	73	0.87
Morgan 2006 [37]	UK	CVD	CVD patients	EQ-5D	Presence of co-morbidities	Unknown	341	0.42
Murphy 2001 [38]	UK	Stroke	General population, patients at risk of stroke and experts	SG	Event severity and study population	N/A	At risk patients: 22 Experts & gen. pop.: 20	At risk patients/ experts & gen. pop. Mild: 0.78 / 0.88 Moderate: 0.30 / 0.68 Severe: 0.00 / 0.014
Olsson 2006 [39]	Sweden	IS, ICH and SAH	Stroke and SAH patients	EQ-5D and VAS	None	6 to 8 weeks and 6 months	6 to 8 weeks: 52 6 months: 52	EQ-5D / VAS 6 to 8 weeks: 0.32 / 56 6 months: 0.21 / 48
Park 2005 [40]	UK	IS and ICH	Stroke patients	EQ-5D and VAS	Study interventions (real acupuncture vs. sham acupuncture)	2 weeks	Real: 56 Sham: 60	EQ-5D / VAS Real: 0.64 / 60 Sham: 0.64 / 50
Paul 2005 [41]	Australia	IS and ICH	Stroke patients	AQoL	None	5 years	356	0.50

Study ID	Country	Event type	Population	Valuation	Subgroup analysis	Time since event	Sample	Mean quality of life
Pickard 2004 [42]	USA	IS	Stroke patients and caregivers	EQ-5D, HUI3 and VAS	Study population	Shortly after stroke, 1 month, 3 months and 6 months	Patients / caregivers: Baseline: 124 / 124 1 month: 104 / 104 3 months: 100 / 100 6 months: 95 / 95	EQ-5D / VAS / HUI3 Patients Baseline: 0.31 / 61 / 0.21 1 month: 0.55 / 64 / 0.42 3 months: 0.61 / 69 /0.45 6 months: 0.62 / 70 /0.44 Caregivers Baseline: 0.24 / 51 /0.21 1 month: 0.51 / 64 / 0.36 3 months: 0.56 / 66 /0.42 6 months: 0.59 / 69 /0.44
Pickard 2005 [43]	Canada	IS	Stroke patients	SF-36, converted into utilities using algorithms	Algorithm used	3 weeks and 6 months	3 weeks: 124 6 months: 99	3 weeks / 6 months Algorithm 1: 0.61 / 0.70 Algorithm 2: 0.55 / 0.67 Algorithm 3: 0.48 / 0.62 Algorithm 4: 0.48 / 0.62 Algorithm 5: 0.47 / 0.62 Algorithm 6: 0.55 / 0.62 Algorithm 7: 0.49 / 0.63 Algorithm 8: 0.51 / 0.59 Algorithm 9: 0.66 / 0.75 Algorithm 10: 0.60 / 0.66
Pickard 2005 [44]	Canada	IS	Stroke patients	EQ-5D, HUI2, HUI3, SF-6D and VAS	Improvement	3 weeks and 6 months	3 weeks: 124 6 months: 98	EQ-5D / VAS 3 weeks: 0.31 / 61 6 months: 0.62 / 70 HUI2 / HUI3 / SF-6D 3 weeks: 0.51 /0.19/0.55 6 months: 0.64/0.44/0.68
Ryan 2006 [45]	UK	Stroke	Stroke patients	EQ-5D and VAS	Study interventions (intensive rehabilitation vs. less intensive)	2 weeks and 3 months	Intensive / less intensive 2 weeks: 44 / 45 3 months: 35 / 32	EQ-5D / VAS 2 weeks Intensive: 0.56 / 60 Less intensive: 0.52 / 70 3 months Intensive: 0.71 / 70 Less intensive: 0.54 / 70
Salbach 2006 [46]	Canada	Stroke	Stroke patients	VAS	None	6 months	89	65
Samsa 1998 [47]	USA	Severe stroke	Patients at risk of stroke	TTO	Presence of aphasia	N/A	1183	0.23

Study ID	Country	Event type	Population	Valuation	Subgroup analysis	Time since event	Sample	Mean quality of life
Samsa 2004 [48]	USA	Stroke	Stroke patients	TTO and VAS	Barthel Index (BI)	1 month, 6 months and 12 months	1 / 6 / 12 months BI 0-60: 37 / <20 / <20 BI 65-90: 119 / 91 / 55 BI 95-100: 173 / 176 /113	TTO / VAS 1 month BI 0-60: 0.58 / 53 BI 65-90: 0.72 / 55 BI 95-100: 0.79 / 63 6 months BI 65-90: 0.74 / 60 BI 95-100: 0.80 / 68 12 months BI 65-90: 0.69 / 61 BI 95-100: 0.80 / 71
Shin 1997 [49]	Canada	Stroke	Patients at risk of stroke	SG	Event severity	N/A	31	Minor: 0.81 Severe: 0.45
Solomon 1994 [50]	USA	Stroke	Patients at risk of stroke	VAS	Event severity, and presence of language, cognitive and motor deficits	N/A	117	Minor: 51 Moderate: 40 Severe: 8
Sturm 2002 [51]	Australia	IS, ICH and unknown stroke	Stroke patients	AQoL	Event type	3 months	51	0.40
Sturm 2004 [52]	Australia	IS, ICH and unknown stroke	Stroke patients	AQoL	Event severity, event type, discharge location, gender, age, socioeconomic class and presence of co-morbidities	2 years	NIHSS score 0-5: 190 6-10: 75 11-15: 44 >15: 102	NIHSS score 0-5: 0.45 6-10: 0.20 11-15: 0.06 >15: 0.01
Sulch 2000 [53]	UK	Stroke	Stroke patients	VAS	Study interventions (integrated care pathway-ICP vs. standard care-SC)	4,12 and 26 weeks	ICP / SC 4 weeks: 67 / 67 12 weeks: 64 / 64 26 weeks: 62 / 62	ICP / SC 4 weeks: 41 / 44 12 weeks: 59 / 65 26 weeks: 63 / 72
Thomson 2000 [54]	UK	Stroke	Patients at risk of stroke	SG	Event severity	N/A	54	Minor: 0.64 Severe: 0.19
van den Berg 2006 [55]	Netherlands	Stroke	Stroke patients	EQ-5D	None	Unknown	218	0.47
van der Gaag 2005 [56]	UK	Stroke	Stroke patients	EQ-5D	None	Baseline and 6 months	Baseline: 38 6 months: 28	Baseline: 0.58 6 months: 0.72
van Exel 2004 [57]	Netherlands	Stroke	Stroke patients	EQ-5D	Barthel Index (BI)	2 and 6 months	31 for each BI sub-group and follow-up	2 months / 6 months BI 0-4: -0.14 / -0.11 BI 5-9: 0.06 / 0.09 BI 10-14: 0.41 / 0.33 BI 15-19: 0.61 / 0.56 BI 20: 0.76 / 0.81

Study ID	Country	Event type	Population	Valuation	Subgroup analysis	Time since event	Sample	Mean quality of life
van Exel 2005 [58]	Netherlands	Stroke	Stroke patients	EQ-5D	Hospital providing care (hospital 1, 2 and 3 provided specialised stroke care vs. hospital 4, which provided conventional care)	6 months	Hospital 1: 151 Hospital 2: 111 Hospital 3: 149 Hospital 4: 187	Hospital 1: 0.66 Hospital 2: 0.47 Hospital 3: 0.48 Hospital 4: 0.53
Ytterberg 2000 [59]	Sweden	Stroke	Stroke patients	VAS	Study interventions (hospital vs. GP follow-up) and age	3 months	Hospital follow-up: 46 GP follow-up: 49	Hospital follow-up: 60 GP follow-up: 61

APPENDIX 6:

COST SEARCH STRATEGIES

Table Medline search strategy: costs

Medline terms	
1. economics/ 2. exp "costs and cost analysis"/ 3. value of life/ 4. exp economics, hospital/ 5. exp economics, medical/ 6. economics, nursing/ 7. economics, pharmaceutical/ 8. exp models, economic/	9. exp "fees and charges"/ 10. exp budgets/ 11. ec.fs. 12. (cost or costs or costed or costly or costing$).tw. 13. (economic$ or pharmacoeconomic$ or price$ or pricing).tw. 14. or/1-13

Table Embase search strategy: costs

Embase terms	
1. socioeconomics/ 2. exp health care cost/ 3. exp health economics/ 4. exp cost/ 5. exp fee/	6. exp budget/ 7. (cost or costs or costed or costly or costing$).tw. 8. (economic$ or pharmacoeconomic$ or price$ or pricing).tw. 9. or/1-8

Table CINAHL search strategy: costs

CINAHL terms	
1. exp economics/ 2. exp "financial management"/ 3. exp "financial support"/ 4. exp "financing organized"/ 5. exp "business"/ 6. or/2-5 7. 1 not 6 8. health resource allocation.sh. 9. health resource utilization.sh. 10. 8 or 9 11. 7 or 10 12. (cost or costs or costed or costly or costing$).tw.	13. (economic$ or pharmacoeconomic$ or price$ or pricing$).tw. 14. 12 or 13 or 11 15. editorial.pt. 16. letter.pt. 17. news.pt. 18. or/15-17 19. 14 not 18 20. "animal studies"/ 21. 19 not 20 22. cochrane library.so. 23. 21 not 22

APPENDIX 7:

COSTING STUDY PROFORMA

TYPE: ☐ PATIENT ☐ AGGREGATE **INCLUDE: ☐ YES ☐ NO**

1) Authors and publication date:

2) Title:

3) Country:

4) Objective:……
……
……

5)Setting:……..
……
……

6) Patient population:……
……
……

7) Patient sample:……..
……
……

8) Resource use derived from:

☐ RCT
☐ Literature review
☐ Expert opinion
☐ Questionnaire
☐ Retrospective observational study
☐ Prospective observational study
☐ Modelling

9) Unit cost data derived from:

☐ National references
☐ Charges
☐ Previous studies
☐ Own costs

10) Perspective of analysis:

☐ Societal
☐ Health care system
☐ Health care provider
☐ Patient and family
☐ Third party payer
☐ Other……..

11) Time frame of analysis……

12) Costs included:

Direct medical

☐ direct treatment……

☐ inpatient……

☐ outpatient……

☐ day care……

☐ community health care……

☐ medication……

Direct non-medical

☐ social care……

☐ social benefits……

☐ travel costs……

☐ caregiver out-of pocket……

Lost productivity

☐ income foregone (illness)……

☐ income foregone (death)……

☐ income foregone (caregiving)……

Others:……

13) Currency:…… **14) Year of costing:……**

15) Was discounting used? ☐ Yes **……%** ☐ No ☐ N/A

16) Result(s):

……

……

17) Comments, limitations of the study:

……

……

18) Conclusions:

……

……

APPENDIX 8:

QUALITY CHECKLIST FOR COSTING STUDIES

		Yes	No	N/A
Study design				
1.	The research question is stated	☐	☐	
2.	The economic perspective of the study is clearly stated and justified	☐	☐	
Data collection				
1.	Details of the subjects from whom valuations were obtained are given	☐	☐	
2.	Indirect costs (if included) are reported separately	☐	☐	☐
3.	Quantities of resources are reported separately from their unit costs	☐	☐	
4.	Methods for the estimation of quantities and unit costs are described	☐	☐	
5.	Currency and price data are recorded	☐	☐	
6.	Details of currency of price adjustments for inflation or currency conversion are given	☐	☐	☐
Analysis and interpretation of results				
1.	Time horizon of costs is stated	☐	☐	
2.	The discount rate is stated	☐	☐	☐
3.	Details of statistical tests and confidence intervals are given for stochastic data	☐	☐	
4.	Appropriate sensitivity analysis is performed	☐	☐	
5.	The answer to the study question is given	☐	☐	
6.	Conclusions follow from the data reported	☐	☐	
7.	Conclusions are accompanied by the appropriate caveats	☐	☐	

APPENDIX 9:

COST STUDIES INCLUDED IN THE REVIEW

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APPENDIX 10.1: METHODS USED BY COSTING STUDIES

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Alberts 1996 [1]	USA	Cerebrovascular disorders, not TIA	Prospective cohort	Patients discharged from neurology and other services of the Department of Medicine	USD Not reported	Charges	Diagnostic tests, inpatient care	No subgroup analysis
Anderson 2000 [2]	Australia	Stroke, not SAH	RCT	Medically stable patients suitable for early hospital discharge	AUD 1997/98	Costs	Inpatient care, outpatient care, day care, community health care, social care, travel costs, out-of-pocket, income foregone (caregiving)	No subgroup analysis
Andersson 2002 [3]	Sweden	Stroke	Prospective cohort	Patients needing continuous rehabilitation after discharge from acute care ward	SEK 2000	Costs	Inpatient care, community health care, social care	Regression analysis: gender, age, housing, incident / recurrent, diabetes, atrial fibrillation, angina, hypertension, dependency
Beech 1999 [4]	UK	IS, SAH, unknown stroke	RCT	Patients who were medically stable and able to transfer independently or with the aid of a caregiver	GBP 1997	Costs	Diagnostic tests, inpatient care, outpatient care, day care, community health care, social care	No subgroup analysis
Bowen 1994 [5]	USA	Cerebrovascular disease, not SAH	Retrospective cohort	Patients admitted to hospital	USD Not reported	Charges	Diagnostic tests, inpatient care	Regression analysis: age
Brandle 2003 [6]	USA	Cerebrovascular disease	Retrospective cohort	Diabetic patients who survived first year after stroke	USD 2000	Charges	Inpatient care, outpatient care, medication	No subgroup analysis
Caro 2000/01 [7]	Austria, Belgium, Canada, Denmark, Finland, France, Germany, Netherlands Norway, Sweden, UK, USA	IS	RCT	Patients presenting with substantial neurological deficits within 6 hours after event onset	USD 1996	Costs	Inpatient care, outpatient care, community health care, social care	Subgroup analysis: age, comorbidity, stroke subtype, functional level, severity Regression analysis: age, gender, comorbidity, stroke subtype, functional level, severity

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Caro 2006 [8]	Canada	IS	Retrospective cohort	Adults diagnosed with an ischaemic stroke between 1990 and 1995	CAD 2002	Costs	Inpatient care	No subgroup analysis
Chan 1997 [9]	USA	Stroke	Retrospective cohort	Patients discharged from rehabilitation hospitals from 1987 to 1994	USD 1994	Charges	Inpatient care	No subgroup analysis
Claesson 2000/05 [10]	Sweden	Stroke	RCT	Patients aged 70 or more years with an acute admission to hospital due to stroke	SEK 1996	Costs	Diagnostic tests, inpatient care, outpatient care, community health care, social care, travel costs, income foregone (caregiving)	Subgroup analysis: stroke severity, survival over study period, cognitive impairment
Clarke 2003 [11]	UK	ICH, IS, SAH, unknown stroke	RCT	Patients with newly diagnosed type 2 diabetes between 1977 and 1997	GBP 1997/1999	Costs	Inpatient care, outpatient care, community health care	Subgroup analysis: survival
Cristina 1991 [12]	Italy	Cerebrovascular disease	Prospective cohort	Patients admitted to hospital in 1986	ITL 1986	Charges	Diagnostic tests	Subgroup analysis: type of event Regression analysis: co-morbidities, hypertension, marital status, type of event, age, gender, history of cerebrovascular disease
Dennis 2006 [13]	Australia, Belgium, Brazil, Canada, Czech Rep., Denmark, Hong Kong, India, Italy, New Z'nd, Poland, Portugal, Ireland, Turkey, UK	Stroke, not SAH, not TIA	RCT	Patients admitted to hospital within 7 days of stroke onset, with clinicians uncertain about best feeding policy	GBP 2002/03	Costs	Inpatient care	No subgroup analysis

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Deutsch 2006 [14]	USA	Stroke	Retrospective cohort	Medicare beneficiaries with a recent stroke completing treatment in 1996 or 1997	USD 1997	Charges	Inpatient care	No subgroup analysis
Dewey 2001/03/04 [15]	Australia	ICH, IS, unknown stroke	Prospective cohort	Patients suffering first-ever in-a-lifetime stroke in Melbourne, Australia	AUD 1997	Costs	Inpatient care, outpatient care, day care, community health care, medication, social care, out-of pocket, income foregone (illness), income foregone (caregiving)	Subgroup analysis: event subtype, incident or recurrent
Di Matteo 2004 [16]	New Zealand	Stroke, TIA	Retrospective cohort	Patients discharged or dead with a diagnosis of stroke	NZD Not reported	Charges	Inpatient care	No subgroup analysis
Diringer 1999 [17]	USA	IS	Prospective cohort	Patients admitted to the neurology service and seen by the stroke management and rehabilitation team	USD Not reported	Costs* *Using cost to charge ratios	Diagnostic tests, inpatient care, medication	Subgroup analysis: stroke severity Regression analysis: stroke severity, heparin use, atrial fibrillation, gender, concurrent disease
Dobrez 2004 [18]	USA	Stroke	Retrospective cohort	Stroke patients on their first admission to a rehabilitation hospital between 1994 and 1998	USD 2002	Costs* *Using cost to charge ratios	Inpatient care	Regression analysis: age, gender, motor function, cognitive function,
Dodel 2004 [19]	Germany	ICH, IS, TIA	Prospective cohort	All patients admitted with a diagnosis of stroke or TIA during January to June 2000	EUR 2002	Costs	Diagnostic tests, inpatient care, outpatient care, community health care, medication	Subgroup analysis: event type, stroke severity
Donnelly 2004 [20]	UK	Stroke	RCT	Patients having experienced a stroke during the 4 weeks preceding hospital admission	GBP Not reported	Costs	Inpatient care, outpatient care, day care, community health care	No subgroup analysis
Elliott 1996 [21]	USA	SAH	Retrospective cohort	Patients admitted to hospital between September 1983 and August 1993	USD 1995	Charges	Diagnostic tests, inpatient care	Subgroup analysis: Hunt & Hess grade on admission
Evers 2002 [22]	Netherlands	Stroke	Retrospective cohort	Patients discharged from hospital between 1996 and 1998	EUR Not reported	Costs	Diagnostic tests, inpatient care	Regression analysis: Stroke severity, presence of co-morbidities, gender

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Evers 2002 [23]	Netherlands	Cerebrovascular disease	Retrospective cohort	Patients hospitalised between 1987 to 1995 with a primary diagnosis of stroke	EUR 1995	Costs	Inpatient care*, outpatient care, day care, community health care *Note: only included mental healthcare costs	Regression analysis: age, event type
Fahlman 2006 [24]	USA	Cerebrovascular disease	Retrospective cohort	Medicare beneficiaries with a full year of prescription data	USD 2000	Costs	Medication	No subgroup analysis
Fjaertoft 2005[25]	Norway	Stroke	RCT	Patients admitted to a stroke unit	EUR Not reported	Costs	Inpatient care, day care, community health care, social care	Subgroup analysis: stroke severity
Freburger 1999 [26]	USA	Stroke	Retrospective cohort	Patients admitted to hospital	USD 1996	Charges	Inpatient care	Regression analysis: age, gender, race, stroke severity
Fukuhara 1996 [27]	USA, Japan	ICH, IS	Retrospective cohort	Patients discharged from hospital between January 1989 and December 1990	USD 1989-1990	Charges	Diagnostic tests, inpatient care, medication	Subgroup analysis: stroke subtype
Gaetani 1998 [28]	Italy	SAH	Retrospective cohort	Patients undergoing surgery for SAH	ITL Not reported	Charges	Inpatient care	Regression analysis: vasospasm, re-bleeding, hydrocephalus, aneurysm location, multiple aneurysms, time of surgery, age
Gerzeli 2005 [29]	Italy	ICH, IS	Prospective cohort	Patients admitted to hospital with first ever stroke and CT confirmed event	EUR Not reported	Costs	Diagnostic tests, inpatient care, outpatient care, community health care, medication, social care, travel costs, caregiver out-of pocket, income foregone (illness), income foregone (caregiving)	Regression analysis: sex, age, previous disability, FIM at admission
Gladman 1994 [30]	UK	Stroke	RCT	Patients discharged from hospital to their own home	GBP 1989-1990	Costs	Inpatient care*, day care, community health care *Note: Only included readmissions	No subgroup analysis
Glick 1998 [31]	9 European countries, Australia, New Z'nd	SAH	RCT	Patients with confirmed SAH	USD PPP 1993	Costs	Diagnostic tests, inpatient care, medication	Subgroup analysis: gender Regression analysis: severity, gender, age

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Goeree 2005 [32]	Canada	ICH, IS, TIA	Prospective cohort	Patients admitted to hospital emergency rooms	CAD 2004	Costs	Diagnostic tests, inpatient care, outpatient care, community health care, medication, social care, caregiver out-of pocket, income foregone (illness), income foregone (caregiving)	Subgroup analysis: event type, age, discharge destination, marital status, chronic heart failure, diabetes
Gosman-Hedstrom 2002 [33]	Sweden	Stroke	RCT	Patients admitted to the emergency room between February 1993 and May 1994 and who were living in their own house before event	SEK 1996	Costs	Social care	Subgroup analysis: Survival
Gosman-Hedstrom 2002 [34]	Sweden	Stroke	RCT	Patients admitted to the emergency room between February 1993 and May 1994 and who were living in their own house before event	SEK 1996	Costs	Social care	No subgroup analysis
Grieve 2000 [35]	Denmark, UK	ICH, IS	Prospective cohort	Patients admitted to hospital with first ever stroke	USD PPP 1995	Costs	Diagnostic tests, inpatient care, outpatient care, day care, community health care, social care	No subgroup analysis
Grieve 2001 [36]	Denmark, Finland, France, Italy, Latvia, Lithuania, Portugal, Spain, UK	ICH, IS	Prospective cohort	Patients admitted to hospital with first ever stroke	USD PPP 1998	Costs	Diagnostic tests, inpatient care, outpatient care, community health care, social care	No subgroup analysis
Grieve 2001 [37]	Austria, Denmark, France, Germany, Hungary, Latvia, Lithuania, Poland, Portugal, Spain, UK	ICH, IS	Prospective cohort	Patients admitted to hospital with first ever stroke	USD PPP 1995	Costs	Diagnostic tests, inpatient care	Subgroup analysis: Survival

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Grieve 2005 [38]	Denmark, Finland, France, Italy, Latvia, Lithuania, Portugal, Spain, UK	ICH, IS	Prospective cohort	Patients admitted to hospital with first ever stroke and who survived the first three months after event	USD PPP 1998	Costs	Diagnostic tests, inpatient care, outpatient care, community health care, social care	No subgroup analysis
Gubitz 1999 [39]	Canada	TIA	Prospective cohort	All acute cases admitted to the Acute Stroke Service between January 1994 to December 1996	CAD Not reported	Costs	Diagnostic tests, inpatient care	No subgroup analysis
Harlacher 2000/01 [40]	Germany	ICH, IS, unknown stroke	Prospective cohort	Patients aged 65 years or more admitted for acute or rehabilitative treatment	EUR Not reported	Costs	Diagnostic tests, inpatient care	Subgroup analysis: stroke severity
Hass 2001 [41]	USA	Stroke	Prospective cohort	Patients with confirmed nursing home usage	USD Not reported	Charges	Social care	No subgroup analysis
Hass 1995 [42]	Sweden	Stroke, not TIA	Prospective cohort	Patients admitted to hospital between December 1987 and August 1988	SEK 1998	Costs	Inpatient care, outpatient care, social care, travel costs	Subgroup analysis: initial function ability Regression analysis: initial functional ability, marital status, functional ability at 12 months, diabetes mellitus, age
Havlovicova 2001 [43]	Czech Rep.	Cerebrovascular disease	Retrospective cohort	Patients admitted to hospital between January 1997 and December 1997	CZK 1997	Costs	Diagnostic tests, inpatient care, medications	No subgroup analysis
Henderson 2001 [44]	UK	ICH, IS, unknown stroke	Prospective cohort	Patients discharged from hospital during the fiscal years 1994/95 and 1995/96	GBP 1996/97	Costs	Inpatient care, outpatient care, community health care, medication, travel costs	No subgroup analysis
Hesse 1996 [45]	Germany	Stroke	Retrospective cohort	Hemiparetic patients referred to hospital and treated in the rehabilitation clinic	DEM Not reported	Costs	Social care	No subgroup analysis
Hickenbotto 2002 [46]	USA	Stroke	Prospective cohort	Elderly population reporting physician diagnosed stroke	USD 1999	Costs	Income foregone (caregiving)	No subgroup analysis
Holloway 1996 [47]	USA	ICH, IS, TIA, SAH	Retrospective cohort	Patients admitted to one of 5 academic hospitals	USD 1992	Costs* *Using cost to charge ratios	Inpatient care	Subgroup analysis: age, discharge destination, event type, survival

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Holmqvist 1996 [48]	Sweden	Stroke	Prospective cohort	Hospitalised stroke patients	SEK Not reported	Costs	Inpatient care, outpatient care, day care, community health care	No subgroup analysis
Jorgensen 1997 [49]	Denmark	Stroke	Prospective cohort	Stroke patients admitted to hospital between September 1991 and September 1993	DKK Not reported	Costs	Inpatient care	No subgroup analysis
Kalafut 2000 [50]	USA	IS, TIA	RCT	Patients with a clinical diagnosis of TIA or IS	USD Not reported	Costs	Inpatient care, community health care, medication	No subgroup analysis
Kalra 2004 & Patel 2004 [51]	UK	Stroke	RCT	Patients admitted to a stroke rehabilitation unit, which were independent before event	GBP 2001/02	Costs	Inpatient care, outpatient care, day care, community health care, social care, income foregone (caregiving)	No subgroup analysis
Karinen 1999 [52]	Finland	SAH	RCT	Patients aged 16-70 years with a ruptured aneurysm	USD 1996	Costs	Inpatient care, medication	No subgroup analysis
Kavanagh 1999 [53]	UK	Stroke	Retrospective cohort	Adults in communal establishments and households for who stroke was reported as a condition underlying their disability	GBP 1994/95	Costs	Inpatient care, outpatient care, day care, community health care, social care	Subgroup analysis: stroke severity
Keith 1995 [54]	USA	Stroke	Retrospective cohort	Patients admitted to hospital with right or left hemiplegia	USD Not reported	Charges	Inpatient care	No subgroup analysis
Kelley 1990 [55]	USA	Stroke	Prospective cohort	Patients with admitted to hospital with acute stroke	USD Not reported	Costs	Diagnostic tests, inpatient care, medication	No subgroup analysis
Kolominsky-Rabas 2006 [56]	Germany	Ischaemic stroke	Prospective cohort	Community residents with suspected first ever ischaemic stroke	EUR 2004	Costs	Inpatient care, outpatient care, community health care, medication, social care	Subgroup analysis: gender
Kramer 1997 [57]	USA	ICH, IS, TIA, SAH	RCT	Medicare patients having an acute hospital stay within 30 days of event	USD Not reported	Charges	Inpatient care, outpatient care, community health care, medication, social care	No subgroup analysis
Lee 2007 [58]	USA	ICH, IS, SAH	Retrospective cohort	Medicare patients suffering from first ever stroke	USD 2001	Charges	Inpatient care, out-patient care, day care, community health care, medication, social care	Subgroup analysis: event type, discharge disposition

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Leibson 1996 [59]	USA	Cerebrovascular disease	Prospective cohort	Patients who suffered an event between January 1987 and December 1989	USD 1989	Charges	Inpatient care, outpatient care	Type of event, gender, age, residence
Mamoli 1999 [60]	Italy	IS	Prospective cohort	Patients admitted to a semi-intensive treatment room and ward during 1996	ITL 1996	Costs	Diagnostic tests, inpatient care, medication	Subgroup analysis: event subtype. Regression analysis: age, rankin score, discharge destination, event subtype
McGowan 2003 [61]	Ireland	Cerebrovascular disease	Retrospective cohort	Patients admitted to a single teaching hospital between January 1999 and January 2000	EUR 1999	Costs	Diagnostic tests, inpatient care, medication	No subgroup analysis
McNamee 1998 [62]	UK	Stroke	RCT	Patients admitted within 72 hours of event with no co-morbidity likely to affect rehabilitation	GBP 1995/96	Costs	Inpatient care, outpatient care, day care, community health care, social care	Subgroup analysis: stroke severity
McNaughton 2002 [63]	New Zealand	Stroke	Prospective cohort	Patients admitted to hospital during 1997	NZD Not reported	Costs	Inpatient care, community healthcare, social care	Subgroup analysis: ethnicity
Mitchell 1996 [64]	USA	IS	Retrospective cohort	Medicare patients admitted to hospital between January and September 1991	USD Not reported	Costs* *Using cost to charge ratios	Diagnostic tests, inpatient care, social care	Subgroup analysis: physician speciality
Moloney 2006 [65]	Ireland	ICH, IS, TIA	Retrospective cohort	Patients admitted acutely to hospital via the emergency department between January 2002 and October 2004	EUR Not reported	Costs	Inpatient care	Regression analysis: age, gender, other comorbidities, disability
Monane 1996 [66]	USA	IS	Retrospective cohort	Patients aged 65 years or more who were admitted to hospital between 1982 and 1995	USD Not reported	Charges	Inpatient care	Subgroup analysis: third party payer
Moodie 2006 [67]	Australia	ICH, IS	Prospective cohort	Patients presenting to hospital 3 days after event onset	AUD 1998	Costs	Diagnostic tests, inpatient care, outpatient care, community healthcare, medication, social care	Subgroup analysis: previous stroke history

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Morgan 2000 [68]	Australia	SAH	Prospective cohort	Patients admitted within 72 hours of their event and who underwent surgical clipping	AUD Not reported	Costs	Diagnostic tests, inpatient care, medication	No subgroup analysis
Newell 1998 [69]	USA	IS	Retrospective cohort	Hospitalised patients	USD Not reported	Charges	Diagnostic tests, inpatient care, medication	Subgroup analysis: physician speciality
Olsson 2006 [70]	Sweden	ICH, IS, SAH	Prospective cohort	Patients referred as outpatients to a university day hospital rehabilitation centre	EUR Not reported	Costs	Outpatient care, day care	No subgroup analysis
Osberg 1990 [71]	USA	Stroke	Retrospective cohort	Patients over 18 years old with rehabilitation stay in hospital over 7 days, and who were discharged into the community	USD Not reported	Charges	Inpatient care, outpatient care	Subgroup analysis: third party payer Regression analysis: severity, payer
Patel 2004 / Kalra 2005 [72]	UK	Stroke	RCT	Patient presenting for medical care at least 72hours after event, who were later admitted to hospital	GBP 1997/98	Costs	Inpatient care, outpatient care, day care, community health care, medication, social care, income foregone (caregiving)	No subgroup analysis
Persson 1990 [73]	Sweden	Stroke, not SAH	Prospective cohort	Patients treated for first stroke in a neurological ward	SEK Not reported	Costs	Diagnostic tests, inpatient care, outpatient care, day care, community health care, medication, social care	Subgroup analysis: age, gender
Porsdal 1998 [74]	Denmark	TIA	Prospective cohort	Patients admitted to hospital between November 1994 and November 1995	DKK 1995	Costs	Diagnostic tests, inpatient care, outpatient care, day care, community health care, medication, social care	Regression analysis: gender, age
Porsdal 1999 [75]	Denmark	IS	Prospective cohort	Patients admitted to hospital between November 1994 and November 1995	DKK 1995	Costs	Diagnostic tests, inpatient care, outpatient care, day care, community health care, medication, social care, travel costs	Subgroup analysis: severity, death during inpatient care Regression analysis: Barthel Index, death during inpatient care
Porsdal 1999 [76]	Denmark	ICH	Prospective cohort	Patients admitted to hospital between November 1994 and November 1995	DKK 1995	Costs	Diagnostic tests, inpatient care, outpatient care, day care, community health care, medication, social care, travel costs	Subgroup analysis: death during study period

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Puskas 2000 [77]	USA	Stroke	Prospective cohort	Patients undergoing primary coronary operation between 1988 and 1996	USD Not reported	Costs	Inpatient care	No subgroup analysis
Quaglini 2004 [78]	Italy	IS	Prospective cohort	Patients admitted to hospital between February1998 and April 1999	EUR Not reported	Costs	Diagnostic tests, inpatient care, outpatient care	Regression analysis: NIHHS at admission, Barthel Index
Reed 2001 [79]	USA	ICH, IS, TIA, SAH	Retrospective cohort	Patients aged 18 or more who were hospitalised in 1998	USD Not reported	Costs* *Using cost to charge ratios	Inpatient care	Subgroup analysis: event type, age, rurality, discharge disposition Regression analysis: rurality, age, severity, discharge disposition
Reynolds 1998 [80]	USA	IS	Retrospective cohort	Patients admitted to hospital and referred for a formal swallowing evaluation	USD Not reported	Charges	Inpatient care	Subgroup analysis: presence of pneumonia
Ricci 1998 [81]	USA	IS	Retrospective cohort	Medicare patients with at least one medical claim suffering a first ever event	USD Not reported	Charges	Inpatient care, outpatient care, community healthcare, social care	No subgroup analysis
Roderick 2001 [82]	UK	Stroke	RCT	Patients admitted to hospital between October 1995 and June 1997	GBP 1996/97	Costs	Inpatient care*, outpatient care, day care, community health care, social care *Note: did not include acute inpatient care, only readmissions	No subgroup analysis
Rodgers 2003 [83]	UK	Stroke	RCT	Stroke patients admitted within previous 10 days and with upper limb impairment	GBP 2000/01	Costs	Inpatient care, outpatient care, community healthcare	No subgroup analysis
Roos 2002 [84]	Netherlands	SAH	Prospective cohort	Patients admitted to hospital during February 1996 and February 1997	EUR 2001	Costs	Diagnostic tests, inpatient care, outpatient care, community healthcare, social care, travel costs	No subgroup analysis
Rossi 2006 [85]	Italy	ICH, IS	Prospective cohort	Patients admitted to an intensive care unit (ICU) between 1999 and 2000	EUR 2000	Costs	Diagnostic tests, inpatient care*, medication *Note: only includes costs while at ICU	Subgroup analysis: event type

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Rossnagel 2005 [86]	Germany	ICH, IS, TIA	Prospective cohort	Patients assessed by a neurologist at the emergency department at least 7 days before event	EUR Not reported	Costs	Inpatient care, outpatient care, community healthcare, medication, social care, travel costs, income foregone (illness)	Subgroup analysis: age, event type, gender, NIHSS
Roth 2002 [87]	USA	ICH, IS	Prospective cohort	Patients admitted for initial comprehensive acute inpatient stroke rehabilitation	USD Not reported	Charges	Inpatient care	Subgroup analysis: medical intubation
Russell 2006 [88]	USA	ICH	Retrospective cohort	Health plan patients aged 18 years or more hospitalised during July 1999 and June 2002	USD Not reported	Charges	Diagnostic tests, inpatient care, outpatient care, community healthcare, medications, social care	Subgroup analysis: survival until hospital discharge
Russell 2006 [89]	USA	ICH	Retrospective cohort	Patients discharged from hospital who were aged 18 years or more	USD Not reported	Costs* *Using cost to charge ratios	Inpatient care	Subgroup analysis: age, gender, race, location, severity Regression analysis: age, gender, race, location, severity
Samsa 1999 [90]	USA	IS	Retrospective cohort	Medicare patients aged 65 years or older admitted to hospital during 1991	USD 1991	Costs* *Using cost to charge ratios	Inpatient care, outpatient care, community healthcare, medications, social care	Subgroup analysis: incident/recurrent, age, gender Regression analysis: gender, ethnicity, age, other co-morbidities
Samsa 2002 [91]	USA	IS	RCT	Patients aged 18 years or more having moderate to severe deficits	USD 1996	Costs	Inpatient care, outpatient care, community healthcare, medications, social care	No subgroup analysis
Schlenker 1997 [92]	USA	Stroke	Retrospective cohort	Medicare patients aged 65 years or more hospitalised within the last 30 days after event	USD 1993	Costs	Inpatient care*, social care *Note: did not include acute inpatient care, only readmissions	Regression analysis: Barthel Index, pre-stroke walking distance, medical status, MMSE score, age, caregiver
Sloan 1999 [93]	USA	ICH, IS	Retrospective cohort	Medicare patients who lived in the community or nursing homes reporting a functional limitation	USD 1994	Charges	Inpatient care, outpatient care, community healthcare, social care	No subgroup analysis

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Sloss 2004 [94]	USA	IS	Retrospective cohort	Patients with established artherosclerotic conditions admitted to hospital	USD Not reported	Charges	Diagnostic tests, inpatient care, outpatient care, community healthcare, medications	Subgroup analysis: third party payer
Smurawska 1994 [95]	Canada	Stroke	Retrospective cohort	Patients admitted for first-ever stroke during January 1991 and December 1992	CAD Not reported	Costs	Diagnostic tests, inpatient care, medications	Subgroup analysis: gender, severity
Spieler 2002/ 03/04 [96]	France	IS	Prospective cohort	Patients with infarct proven by scan	EUR 1997	Charges	Inpatient care, outpatient care, community healthcare, medications, social care	Subgroup analysis: Rankin, incident/ recurrent
Stachniak 1996 [97]	USA	SAH	Retrospective cohort	Patients undergoing craniotomy and surgical clipping	USD Not reported	Costs	Inpatient care	Subgroup analysis: age
Suarez 2004 [98]	USA	SAH	Retrospective cohort	Adult patients undergoing endovascular or surgical clipping treatment	USD Not reported	Costs	Inpatient care	No subgroup analysis
Taylor 1997 [99]	USA	SAH	Retrospective cohort	Adult patients admitted to hospital	USD Not reported	Charges	Inpatient care	Subgroup analysis: geographical location
Taylor 1999 [100]	USA	ICH, IS, SAH	Retrospective cohort	Hospitalised patients reporting 1 more limitations in activities of daily living	USD 1994	Charges	Inpatient care, outpatient care, community healthcare, social care	Subgroup analysis: type of hospital
Teng 2003 [101]	Canada	Stroke	RCT	Patients with persistent motor deficits who had caregivers willing and able to provide live-in care	CAD 1997/98	Costs	Inpatient care, outpatient care, community healthcare, social care	No subgroup analysis
Thorngren 1991 [102]	Sweden	Stroke, not TIA	Prospective cohort	Patients admitted to hospital during February 1986 to February 1987	SEK 1986	Costs	Inpatient care, day care, community health care, social care	Subgroup analysis: severity, age
Tu 2003 [103]	Japan	IS	Retrospective cohort	Patients discharged from hospital between July 1995 and June 1999	JPY Not reported	Charges	Diagnostic tests, inpatient care, medications	Subgroup analysis: age, gender, severity, hypertension, diabetes, ischaemic heart disease, cancer, discharge disposition Regression analysis: same variables as used in subgroup analysis

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Tung 1999 [104]	USA	Stroke	RCT	Patients who had suffered a myocardial infarction	USD 1993	Costs	Inpatient care, outpatient care, social care	Subgroup analysis: event type, severity
Van Exel 2005 [105]	Netherlands	Stroke	Prospective cohort	Hospitalised patients between September 1999 and May 2000	EUR Not reported	Costs	Diagnostic tests, inpatient care, outpatient care, community healthcare, medications, social care	Subgroup analysis: geographical location
Von Koch 2001/01 [106]	Sweden	Stroke	RCT	Patients admitted to hospital between September 1993 and April 1996	SEK Not reported	Costs	Diagnostic tests, inpatient care, outpatient care, day care, community health care, social care	No subgroup analysis
Ward 2005 [107]	Germany	IS	Prospective cohort	Patients with first ever in a lifetime stroke admitted to hospital between 1994 and 1998	EUR 2000	Costs	Inpatient care, outpatient care, community healthcare, social care	Subgroup analysis: discharge destination, Barthel Index
Weimar 2003 [108]	Germany	ICH	Prospective cohort	Patients admitted to hospital between 1998 and October 1999	EUR Not reported	Costs	Diagnostic tests, inpatient care, outpatient care, community healthcare, income foregone (illness)	Subgroup analysis: gender, age, Barthel Index, Rankin score
Wentworth 1996 [109]	USA	Cerebrovascular disorders, not TIA	Retrospective cohort	Medicare patients admitted to hospital between December 1990 and December 1994	USD Not reported	Charges	Inpatient care	No subgroup analysis
Wilby 2003 [110]	UK	SAH	Prospective cohort	Patients presenting to hospital between 1994 and 2001 in poor clinical grade	GBP 2001	Costs	Diagnostic tests, inpatient care	No subgroup analysis
Williams 2002 [111]	USA	IS	Retrospective cohort	Patients admitted to hospital between July 1993 and June 1998	USD Not reported	Charges	Inpatient care	Subgroup analysis: hyperglycaemia
Wolfe 1995 [112]	UK	Stroke	Prospective cohort	Patients under the age of 75 years experiencing their first stroke between August 1989 and July 1991	GBP 1991/92	Costs	Diagnostic tests, inpatient care, outpatient care, community healthcare,	Subgroup analysis: geographical location
Wolfe 1997 [113]	UK	Stroke	Prospective cohort	Patients recruited between November 1991 and May 1993	GBP Not reported	Costs	Diagnostic tests, community healthcare	No subgroup analysis
Yagura 2005 [114]	Japan	Stroke	Prospective cohort	Patients admitted to hospital and not requiring physical assistance prior to event	USD Not reported	Costs	Inpatient care	Subgroup analysis: FIM score

Study ID	Country	Event type	Type of study	Patient population	Currency/ price year	Costs/ charges	Costs included	Subgroup & regression
Yoneda 2003 [115]	Japan	IS	Prospective cohort	Patients admitted to hospital	JPY 2001	Costs	Diagnostic tests, inpatient care, medications	Subgroup analysis: stroke subtype
Yoneda 2005 [116]	Japan	ICH, IS	Prospective cohort	Patients admitted to hospital between October 2000 and December 2001 within 72 hours of event	USD PPP 2001	Costs	Diagnostic tests, inpatient care, medications	Subgroup analysis: event type, stroke subtype, incident/ recurrent, age
Young 1993 [117]	UK	Stroke	RCT	Patients discharged from hospital between January 1988 and September 1988 with a diagnosis of first-ever stroke	GBP 1988/89	Costs	Day care, community health care, social care	No subgroup analysis
Yu 2004 [118]	USA	ICH, IS, SAH	Retrospective cohort	Patients suffering a stroke between October 1999 and September 2000	USD 2000	Charges	Inpatient care, outpatient care, medications	No subgroup analysis
Yundt 1996 [119]	UK	SAH	Retrospective cohort	Patients admitted with non-traumatic SAH between June 1993 and December 1994	USD Not reported	Costs* *Using cost to charge ratios	Diagnostic tests, inpatient care, medications	Subgroup analysis: SAH type, vasospasm, Hunt & Hesse grade (severity)
Zethraeus 1999 [120]	Sweden	Stroke	Retrospective cohort	Patients admitted for stroke for the first time between January 1993 and March 1995	SEK 1994	Costs	Inpatient care, outpatient care, community healthcare, medications, income foregone (illness)	No subgroup analysis

APPENDIX 10.2: RESULTS OF COSTING STUDIES

Study ID	Checklist score	Time horizon	Discounting	Sample size	Mean cost	Median cost
Alberts 1996 [1]	8/12	Hospital discharge	N/A	Baseline period: Neurology: 262 Dept. Medicine: 41 Post-education period: Neurology: 141 Dept. Medicine: 17	Baseline period: Neurology: USD 13,149 Dept. Medicine: USD 15,727 Post-education period: Neurology: USD 14,564 Dept. Medicine: USD 22,684	Baseline period: Neurology: USD 10,234 Dept. Medicine: USD 12,980 Post-education period: Neurology: USD 10,641 Dept. Medicine: USD 19,030
Anderson 2000 [2]	13/13	6 months	N/A	Early discharge: 42 Conventional hospital: 44	Early discharge: AUD 8,040 Conventional hospital: AUD 10,054	Not reported
Andersson 2002 [3]	10/12	12 months	N/A	Hospital group: 68 Home group: 53	Hospital group: SEK 194,700 Home group: SEK 190,500	Not reported
Beech 1999 [4]	11/12	12 months	N/A	Community therapy: 167 Conventional care: 164	Community therapy: GBP 6,800 Conventional care: GBP 7,432	Not reported
Bowen 1994 [5]	8/12	Hospital discharge	N/A	Before protocol: 221 Not treated by protocol: 71 Treated by protocol: 54	Before protocol: USD 8,831 Not treated by protocol: USD 7,717 Treated by protocol: USD 6,764	Before protocol: USD 7,072 Not treated by protocol: USD 7,044 Treated by protocol: USD 4,756
Brandle 2003 [6]	8/12	12 months	N/A	88	Not reported	USD 26,600
Caro 2000/01 [7]	10/13	12 weeks	N/A	1,341	France: USD 11,703* Germany: USD 9,840* Sweden: USD 14,492* UK: USD 13,668* *Note: total cost when applying local costs from each country to all patients	Not reported
Caro 2006 [8]	8/12	12 months	N/A	18,695	CAD 1,284	Not reported
Chan 1997 [9]	10/13	Hospital discharge	N/A	190,921 hospital discharges, of which 40% were due to stroke	Before base year: USD 34,896 Base year: USD 43,054 After base year: USD 39,111	Not reported
Claesson 2000/05 [10]	11/13	12 months	N/A	Stroke unit: 166 General ward: 83	Stroke unit: SEK 170,674 General ward: SEK 191,473	Not reported
Clarke 2003 [11]	10/12	12 months	N/A	271	Fatal stroke: GBP 3,383 Non-fatal stroke: GBP 2,376	Not reported
Cristina 1991 [12]	9/12	Hospital discharge	N/A	240	Haemorrhagic: LIT 4,645,681 Ischaemic: LIT 3,984,016 TIA: LIT 4,347,000 Others: LIT 4,309,250	Not reported
Dennis 2006 [13]	8/12	12 months	N/A	Supplements: 2001 No supplements: 2012 Avoid tube: 427 Early tube: 428 Nasogastric tube (NG): 158 PEG: 162	Supplements: GBP 7,406 No supplements: GBP 7,482 Avoid tube: GBP 9,819 Early tube: GBP 10,072 NG: GBP 12,001 PEG: GBP 12,645	Not reported

Study ID	Checklist score	Time horizon	Discounting	Sample size	Mean cost	Median cost
Deutsch 2006 [14]	9/12	Hospital discharge	N/A	Inpatient rehabilitation facility (IRF) 54,914 Skilled nursing facility (SNF): 3,810	Not reported	IRF: USD 12,230 SNF: USD 6,215
Dewey 2001/03/04 [15]	12/13	12 months	N/A	275	AUD 18,956	Not reported
Di Matteo 2004 [16]	6/12	Hospital discharge	N/A	Before stroke unit: 100 Stroke unit: 100	Before stroke unit: NZD 3,560 Stroke unit: NZD 4,464	Not reported
Diringer 1999 [17]	9/12	Hospital discharge	N/A	191	Not reported	USD 4,408
Dobrez 2004 [18]	9/12	Hospital discharge	N/A	793	USD 31,884	USD 28,670
Dodel 2004 [19]	10/12	Hospital discharge	N/A	340	EUR 3,500	EUR 3,030
Donnelly 2004 [20]	8/12	12 months	N/A	Hospital rehabilitation: 20	First six months: GBP 13,337 Second six months: GBP 11,734	Not reported
Elliott 1996 [21]	10/13	Hospital discharge	N/A	437	Hunt & Hess I: USD 65,949 Hunt & Hess II: USD 83,232 Hunt & Hess III: USD 99,369 Hunt & Hess IV: USD 108,690 Hunt & Hess V: USD 96,194	Hunt & Hess I: USD 26,058 Hunt & Hess II: USD 60,749 Hunt & Hess III: USD 75,595 Hunt & Hess IV: USD 97,679 Hunt & Hess V: USD 75,168
Evers 2002 [22]	9/12	Hospital discharge	N/A	731	EUR 4,021	Not reported
Evers 2002 [23]	10/13	5 years before & after event	Not undertaken	2,020, of which 377 had mental health care contacts	Stroke patients: EUR 24,768 Non stroke patients: EUR 18,439	Not reported
Fahlman 2006 [24]	12/13	12 months	N/A	447	Paid by patient: USD 554 Paid by insurer: USD 415	Not reported
Fjaertoft 2005 [25]	11/13	12 months	N/A	Extended stroke unit services (ESUS): 160 Ordinary stroke unit services (OSUS): 160	ESUS: EUR 18,937 OSUS: EUR 21,824	Not reported
Freburger 1999 [26]	9/12	Hospital discharge	N/A	6,342	USD 9,145	Not reported
Fukuhara 1996 [27]	9/13	Hospital discharge	N/A	Japan: 464 USA hospital 1: 548 USA hospital 2: 539	Japan: USD 7,641 USA hospital 1: USD 15,458 USA hospital 2: 14,297	Japan: USD 5,831 USA hospital 1: USD 10,811 USA hospital 2:10,258
Gaetani 1998 [28]	7/12	Hospital discharge	N/A	Early surgery: 56 Delayed surgery: 60	Early surgery: ITL 18,589.30 Delayed surgery: 17,831.82	Not reported
Gerzeli 2005 [29]	11/13	6 months	N/A	449	EUR 11,607	Not reported
Gladman 1994 [30]	9/12	6 months	N/A	Home rehabilitation: 162 Hospital rehabilitation: 165	Home rehabilitation: GBP 408.20 Hospital rehabilitation: GBP 320.30	Not reported

Study ID	Checklist score	Time horizon	Discounting	Sample size	Mean cost	Median cost
Glick 1998 [31]	12/13	Hospital discharge	N/A	Vehicle: 255 Tirilizad 6mg/kg: 257 Tirilizad 2mg/kg: 250 Tirilizad 0.6mg/kg: 257	Vehicle: USD PPP 19,835 Tirilizad 6mg/kg: USD PPP 22,498 Tirilizad 2mg/kg: USD PPP 19,957 Tirilizad 0.6mg/kg: USD PPP 19,060	Not reported
Goeree 2005 [32]	12/13	12 months	N/A	TIA: 135 Ischaemic stroke: 188 Haemorrhagic stroke: 42	TIA: CAD 17,769 Ischaemic stroke: CAD 53,576 Haemorrhagic stroke: CAD 56,573	Not reported
Gosman-Hed-strom 2002 [33]	10/13	12 months	N/A	Stroke unit group: 160 General ward group: 76	Stroke unit group: SEK 1,053 General ward group: SEK 2,068	Not reported
Gosman-Hedstrom 2002 [34]	11/13	12 months	N/A	Stroke unit group: 116 General ward group: 57	Stroke unit group: Months 0-3: SEK 2,344 Months 4-12: SEK 1,983 General ward group: Months 0-3: SEK 3,775 Months 4-12: SEK 1,939	Not reported
Grieve 2000 [35]	13/13	12 months	N/A	London: 328 Copenhagen: 297	London: USD PPP 8,825 Copenhagen: USD PPP 12,448	Not reported
Grieve 2001 [36]	13/13	3 months	N/A	Riga (Latvia): 252 Kaunas A (Lithuania): 80 Kaunas B (Lithuania): 237 Menorca (Spain): 49 Warsaw (Poland): 149 Kuopio (Finland): 43 Almada (Portugal): 108 Florence (Italy): 136 Dijon (France): 132 Turku B (Finland): 71 London (UK): 108 Turku A (Finland): 95 Copenhagen: 297	Riga: USD PPP 466 Kaunas A: USD PPP 1,517 Kaunas B : USD PPP 2,241 Menorca: USD PPP 2,262 Warsaw: USD PPP 2,876 Kuopio: USD PPP 3,749 Almada: USD PPP 4,387 Florence: USD PPP 5,223 Dijon: USD PPP 5,333 Turku B: USD PPP 5,820 London: USD PPP 7,344 Turku A: USD PPP 7,808 Copenhagen: USD PPP 8,512	Not reported
Grieve 2001 [37]	11/13	Hospital discharge	N/A	Portugal: 110 Spain: 52 UK: 106 Austria: 89 France: 138 Germany A: 94 Germany B: 141 Denmark: 318 Hungary: 418 Poland: 128 Lithuania A: 84 Lithuania B: 237 Latvia: 317	Portugal: USD PPP 2,056 Spain: USD PPP 1,161 UK: USD PPP 3,317 Austria: USD PPP 5,164 France: USD PPP 1,522 Germany A: USD PPP 4,072 Germany B: USD PPP 2,606 Denmark: USD PPP 2,097 Hungary: USD PPP 979 Poland: USD PPP 1,253 Lithuania A: USD PPP 597 Lithuania B: USD PPP 499 Latvia: USD PPP 220	Not reported

Study ID	Checklist score	Time horizon	Discounting	Sample size	Mean cost	Median cost
Grieve 2005 [38]	11/13	3 months	N/A	Spain: 32 Portugal: 73 Latvia: 145 Italy: 109 Finland 1: 37 France: 105 Lithuania 1: 62 Poland: 92 Lithuania 2: 186 Denmark: 246 UK: 73 Finland 2: 81 Finland 3: 57	Spain: USD PPP 2,805 Portugal: USD PPP 5,405 Latvia: USD PPP 550 Italy: USD PPP 4,155 Finland 1: USD PPP 6,170 France: USD PPP 6,203 Lithuania 1: USD PPP 1,439 Poland: USD PPP 1,659 Lithuania 2: USD PPP 4,072 Denmark: USD PPP 9,311 UK: USD PPP 6,515 Finland 2: USD PPP 9,599 Finland 3: USD PPP 9,036	Not reported
Gubitz 1999 [39]	7/13	Not reported	Unclear if required	110	CAD 9,425	Not reported
Harlacher 2000/01 [40]	8/12	Hospital discharge	N/A	53	EUR 4,951	Not reported
Hass 2001 [41]	10/13	5 to 6 years	Not undertaken	Minor stroke: 36 Major stroke: 58	Minor stroke: USD 49,935.60* Major stroke: USD 43,401.60* *Note: Estimated by multiplying reported length of stay and unit cost	Not reported
Hass 1995 [42]	9/12	12 months	N/A	189	SEK 204,489	Not reported
Havlovicova 2001 [43]	8/13	Hospital discharge	N/A	224	CZK 50,054	Not reported
Henderson 2001 [44]	10/12	Would appear 12 months	N/A	41	Estimated using 4 different unit costs: Variable costs: GBP 4,065 Fixed & variable costs: GBP 6,877 Other studies: GBP 6,504 Tariffs: GBP: 5,432	Not reported
Hesse 1996 [45]	9/13	12 months	N/A	194	DEM 1,317	Not reported
Hickenbottom 2002 [46]	11/12	12 months	N/A	No other problem: 281 Stroke with problem: 375	Stroke no health problem: USD 3,700 Stroke with problem: USD 7,900	Not reported
Holloway 1996 [47]	10/12	Hospital discharge	N/A	SAH: 218 ICH: 258 IS: 908 TIA: 303	SAH: USD 39,994 ICH: USD 21,535 IS: USD 9,882 TIA: USD 4,653	SAH: USD 32,911 ICH: USD 12,881 IS: USD 6,824 TIA: USD 3,794
Holmqvist 1996 [48]	9/12	12 months	N/A	63	SEK 86,758	Not reported
Jorgensen 1997 [49]	7/12	Hospital discharge	N/A	1,197	DKK 72,950	Not reported
Kalafut 2000 [50]	6/12	Not reported	N/A	Unfractioned heparin: 24 Low-molecular-weight heparin (LMWH): 24	Unfractioned heparin: USD 2,231 LMWH: USD 2,130	Not reported

Study ID	Checklist score	Time horizon	Discounting	Sample size	Mean cost	Median cost
Kalra 2004 & Patel 2004 [51]	13/13	12 months	N/A	Informal care giving training: 151 No informal care giving training: 149	Informal care giving training: GBP 11,429 No informal care giving training: GBP 15,520	Not reported
Karinen 1999 [52]	9/13	Hospital discharge	N/A	Nimodipine treatment: 62 Placebo: 65	Nimodipine treatment: USD 9,981 Placebo: USD 9,208	Not reported
Kavanagh 1999 [53]	10/12	12 months	N/A	Patients living at: Home: 518 Private and voluntary establishments: 197 Local authority establishments: 137 NHS establishments: 233	Home: GBP 3,787* Private and voluntary establishments: GBP 18,224* Local authority establishments: GPB 22,287* NHS establishments: GBP 44,136* *Note: authors reported mean weekly costs. Costs reported here have been converted to annual costs	Not reported
Keith 1995 [54]	7/12	Hospital discharge	N/A	Acute rehabilitation: 331 Sub-acute rehabilitation: 97	Acute rehabilitation: USD 29,201 Sub-acute rehabilitation: USD 12,148	Not reported
Kelley 1990 [55]	7/12	Hospital discharge	N/A	25	USD 21,908.50* *Note: Estimated by multiplying reported mean length of stay and mean unit cost per day	Not reported
Kolominsky-Rabas 2006 [56]	12/13	12 months and 5 years	3% per annum	821	One-year time horizon: EUR 15,140 Five-year time horizon: EUR 29,837	Not reported
Kramer 1997 [57]	9/12	6 months	N/A	Rehabilitation facility: 250 Sub-acute nursing: 85 Traditional nursing facility: 62	Rehabilitation facility: USD 23,133 Sub-acute nursing facility: USD 15,552 Traditional nursing facility: USD 11,699	Not reported
Lee 2007 [58]	10/13	Hospital discharge and 4 years	Not undertaken	SAH: 342 ICH: 1,957 IS: 9,131	Initial hospitalisation: SAH: USD 18,162 ICH: USD 10,552 IS: USD 6,190 4-year time horizon: SAH: USD 48,327 ICH: 38,023 IS: USD 39,396	Not reported
Leibson 1996 [59]	11/12	12 months before and after event	N/A	289	Not reported	12 months before stroke: USD 1,000 12 months after stroke: USD 12,000
Mamoli 1999 [60]	9/12	Hospital discharge	N/A	245	ITL 5,087,000	ITL 4,624,000
McGowan 2003 [61]	8/13	Hospital discharge	N/A	30	EUR 6,722	Not reported

Study ID	Checklist score	Time horizon	Discounting	Sample size	Mean cost	Median cost
McNamee 1998 [62]	12/12	6 months	N/A	Early supported discharge (ESD): 46 Conventional hospital care (CHC): 46	ESD: GBP 7,155 CHC: GBP 7,480	Not reported
McNaughton 2002 [63]	11/12	12 months	N/A	Europeans: 148 Non-Europeans: 33	Europeans: NZD 18,340 Non-Europeans: NZD 23,350	Not reported
Mitchell 1996 [64]	9/12	3 months	N/A	Neurologist: 4,363 Internist: 11,043 Family practitioner (FP): 7,182 Combination of internist and FP: 9,769 Other specialist: 4,672	Neurologist: USD 15,919 Internist: USD 13.065 FP: USD 11,838 Combination of internist and FP: USD 16,777 Other specialist: 13,216	Not reported
Moloney 2006 [65]	7/12	Not reported	Would appear not to be relevant	715	Not reported	EUR 3,995
Monane 1996 [66]	7/12	Hospital discharge	N/A	745	Not reported	USD 8,470
Moodie 2006 [67]	11/12	28 weeks	N/A	Stroke care unit (SCU): 102 Mobile service (MS): 209 Conventional care (CC): 84	SCU: AUD 15,382 MS: AUD 15,903 CC: AUD 12,251	Not reported
Morgan 2000 [68]	6/12	Hospital discharge	N/A	40	AUD 24,379	Not reported
Newell 1998 [69]	9/13	Hospital discharge	N/A	Before efficiency programme: Internal medicine: 200 Neurologist: 156 After efficiency programme: Internal medicine: 201 Neurologist: 198	Before efficiency programme: Internal medicine: USD 7,402 Neurologist: USD 6,739 After efficiency programme: Internal medicine: USD 7,004 Neurologist: USD 6,246	Not reported
Olsson 2006 [70]	8/13	6 to 8 weeks	N/A	52	EUR 11,730	Not reported
Osberg 1990 [71]	8/12	12 months	N/A	Low cost users: 49 High cost users: 24	Low cost users: USD 23,338* High cost users: USD 62,887* *Note: Estimated by adding mean costs for each resource use category	Not reported

Study ID	Checklist score	Time horizon	Discounting	Sample size	Mean cost	Median cost
Patel 2004 / Kalra 2005 [72]	13/13	12 months	N/A	Stroke unit: 148 Stroke team: 147 Domiciliary care: 140	Informal care priced at minimum wage: Stroke unit: GBP 16,574 Stroke team: GBP 12,512 Domiciliary care: 10,296 Informal care priced at home help wage Stroke unit: GBP 26,738 Stroke team: GBP 18,498 Domiciliary care: GBP 17,226	Not reported
Persson 1990 [73]	8/13	24 months	Not undertaken	Males: 60 Females: 65	Costs during first year after onset: Males: SEK 86,634 Females: SEK 105,736 Costs during second year after onset: Males: SEK 41,528 Females: SEK 107,357	Not reported
Porsdal 1998 [74]	10/13	12 months	N/A	73	DKK 18,800	DKK 11,500
Porsdal 1999 [75]	11/13	12 months	N/A	385	DKK 142,900	DKK 69,800
Porsdal 1999 [76]	11/13	12 months	N/A	85	DKK 123,200	DKK 35,500
Puskas 2000 [77]	7/12	Hospital discharge	N/A	Stroke: 201 No stroke: 9,265	Stroke: USD 33,477 No stroke: USD 17,505	Not reported
Quaglini 2004 [78]	9/12	Hospital discharge	N/A	351	EUR 3,218	Not reported
Reed 2001 [79]	8/12	Hospital discharge	N/A	SAH: 1,124 ICH: 3,139 IS: 18,740 TIA: 7,861	SAH: USD 23,777 ICH: USD 10,241 IS: USD 5,837 TIA: USD 3,350	SAH: USD 16,493 ICH: USD 5,510 IS: USD 4,213 TIA: USD 2,623
Reynolds 1998 [80]	7/12	Hospital discharge	N/A	Pneumonia: 81 No pneumonia: 21	Not reported	Pneumonia: USD 27,764 No pneumonia: USD 9,753
Ricci 1998 [81]	9/13	12 months before and after stroke	N/A	3,784	Before stroke: USD 6,972 After stroke: USD 12,024	Not reported
Roderick 2001 [82]	12/12	6 months	N/A	Domiciliary care: 54 Day hospital: 58	Domiciliary care: GBP 3,070 Day hospital: GBP 2,428	Domiciliary care: GBP 2,208 Day hospital: GBP 1,568
Rodgers 2003 [83]	8/12	6 months	N/A	Stroke unit care and upper limb rehabilitation: 61 Stroke unit care: 62	Not reported	Stroke unit care and upper limb rehabilitation: GBP 5,575 Stroke unit care: GBP 5,435
Roos 2002 [84]	10/13	12 months	N/A	110	EUR 24,435	Not reported
Rossi 2006 [85]	10/12	Discharge from ICU	N/A	Ischemic stroke: 19 Non-traumatic intracranial haemorrhage: 98	Ischemic stroke: EUR 904 Non-traumatic intracranial haemorrhage: EUR 2,658	Not reported

Study ID	Checklist score	Time horizon	Discounting	Sample size	Mean cost	Median cost
Rossnagel 2005 [86]	13/14	12 months	N/A	558	EUR 11,466	Not reported
Roth 2002 [87]	8/12	Hospital discharge	N/A	1,553	USD 37,671* *Note: Estimated by multiplying reported mean length of stay and mean unit cost per day	Not reported
Russell 2006 [88]	10/12	12 months	N/A	Hospital survivor: 304 Non-survivors: 189	Survived hospitalisation: USD 44,395 Non-survivors: USD 16,466	Not reported
Russell 2006 [89]	8/12	Hospital discharge	N/A	13,239	USD 15,256	Not reported
Samsa 1999 [90]	10/13	24 months	Not undertaken	Incident stroke: 44,386 Recurrent stroke: 4,947	Incident stroke: Initial hospitalisation: USD 7,091 Month 1 to 3: USD 10,104* Month 4 to 12: USD 12,249* Month 13 to 24: USD 14,016* Recurrent stroke: Initial hospitalisation: USD 6,939 Month 1 to 3: USD 9,945* Month 4 to 12: USD 15,300* Month 13 to 24: USD 18,960* *Note: costs were reported as dollars per patient month, converted here to per patient	Not reported
Samsa 2002 [91]	12/12	3 months	N/A	Ancrod treatment: 244 Placebo: 251	Ancrod treatment: USD 17,424 Placebo: USD 17,618	Not reported
Schlenker 1997 [92]	11/13	Hospital discharge	N/A	Rehabilitation facility: 290 Skilled nursing facility: 193	Rehabilitation facility: USD 2,184 Skilled nursing facility: USD 1,424	Not reported
Sloan 1999 [93]	10/13	6 months	N/A	Admitted in 1984: 100 Admitted in 1989: 75 Admitted in 1993/94: 70	Admitted in 1984: USD 11,000 Admitted in 1989: USD 12,800 Admitted in 1993/94: USD 16,600	Not reported
Sloss 2004 [94]	9/12	6 months	N/A	Commercial insurance: 108 Medicare: 133	All costs: Commercial: USD 13,406 Medicare: USD 18,625 Attributable costs: Commercial: USD 10,267 Medicare: USD 16,280	Not reported
Smurawska 1994 [95]	6/12	Hospital discharge	N/A	285	CAD 27,500	Not reported
Spieler 2002/ 03/04 [96]	10/12	18 months	N/A	435	EUR 19,513	Not reported
Stachniak 1996 [97]	7/12	Hospital discharge	N/A	Aged <65 years: 172 Aged $\geq$ 65 years: 47	Not reported	Aged <65 years: USD 33,861 Aged $\geq$ 65 years: USD 22,849

Study ID	Checklist score	Time horizon	Discounting	Sample size	Mean cost	Median cost
Suarez 2004 [98]	9/13	Hospital discharge	N/A	Albumin therapy: 63 No albumin therapy: 37	Albumin therapy: USD 62.000 No albumin therapy: USD 81,000	Not reported
Taylor 1997	7/12	Hospital discharge	N/A	Surgically treated: New York: 747 California: 324 Medically treated: New York: 3,866 California: 2,856	Surgically treated: New York: USD 46,690 California: USD 33,870 Medically treated: New York: USD 17,591 California: USD 12,395	Not reported
Taylor 1999 [100]	11/13	6 months	N/A	For profit hospital: 77 Government hospital: 129 Non-profit hospital: 347 Minor teaching hospital:124 Major teaching hospital:116	For profit hospital: USD 11,840 Government hospital: USD 9,097 Non-profit hospital: USD 12,681 Minor teaching hospital: USD 14,216 Major teaching hospital: US 13,874	Not reported
Teng 2003 [101]	12/12	4 months	N/A	Early supported discharge (ESD): 58 Usual care: 56	Early supported discharge (ESD): CAD 7,784 Usual care: CAD 11,065	Not reported
Thorngren 1991 [102]	9/12	12 months	N/A	Major stroke: 196 Minor stroke: 62	Major stroke: SEK 129,000 Minor stroke: SEK 36,000	Not reported
Tu 2003 [103]	9/13	Hospital discharge	N/A	316	JPY 1,097,498	JPY 968,925
Tung 1999 [104]	10/12	12 months	N/A	Stroke: 321 No-stroke: 2,566	Stroke: USD 40,192 No-stroke: USD 25,098	Not reported
Van Exel 2005 [105]	10/12	6 months	N/A	598	EUR 16,000	Not reported
Von Koch 2001/01 [106]	8/12	12 months	N/A	Home rehabilitation: 39 Hospital rehabilitation: 38	Home rehabilitation: SEK 71,959 Hospital rehabilitation: SEK 91,453	Not reported
Ward 2005 [107]	8/12	3 months	N/A	491	EUR 15,540	Not reported
Weimar 2003 [108]	12/13	Hospital discharge and 12 months	N/A	578, of which 266 survived hospitalisation period	Acute hospitalisation costs: EUR 5,301 Costs after hospitalisation: EUR 10,135* *Note: Estimated by adding mean costs for each resource use category	Not reported
Wentworth 1996 [109]	5/13	Hospital discharge	N/A	Not reported	Hospitalised patients during 1990 to 1991: USD 14,076 Hospitalised patients during 1994: USD 10,740	Not reported
Wilby 2003 [110]	10/12	6 months	N/A	166	GBP 12,048	Not reported
Williams 2002 [111]	9/12	Hospital discharge	N/A	Blood glucose < 130 mg/dL: 385 Blood glucose $\geq$ 130 mg/dL: 258	Not reported	Blood glucose < 130 mg/dL: USD 5,262 Blood glucose $\geq$ 130 mg/dL: USD 6,611

Study ID	Checklist score	Time horizon	Discounting	Sample size	Mean cost	Median cost
Wolfe 1995 [112]	8/12	12 months	N/A	Inner city area: 220 Rural area: 236	Inner city area: GBP 3,555 Rural area: GBP 2,466	Not reported
Wolfe 1997 [113]	8/12	6 months	N/A	Before guideline implementation: 175 During guideline implementation: 149 After guideline implementation: 144	Before guideline implementation: GBP 417 During guideline implementation: GBP 440 After guideline implementation: GBP 458	Not reported
Yagura 2005 [114]	7/13	Hospital discharge	N/A	Stroke rehabilitation unit (SRU): 91 General rehabilitation ward (GRW): 87	SRU: USD 24,229.60 GRW: USD 21,705.60 *Note: Estimated by multiplying reported mean length of stay and mean unit cost per day	Not reported
Yoneda 2003 [115]	12/13	Hospital discharge	N/A	179	JPY 1,033,120	Not reported
Yoneda 2005 [116]	10/13	Hospital discharge	N/A	Ischaemic stroke (IS): 913 Intracerebral haemorrhage (ICH): 200	IS: USD PPP 8,662 ICH: USD PPP 10,260	IS: USD PPP 7,051 ICH: USD PPP 8,301
Young 1993 [117]	10/12	2 months	N/A	Home physiotherapy: 52 Day hospital: 43	Not reported	Home physiotherapy: GBP 385 Day hospital: GBP 620
Yu 2004 [118]	9/12	12 months	N/A	73,071	USD 14,679	Not reported
Yundt 1996 [119]	9/12	Hospital discharge	N/A	112	USD 24,951	Not reported
Zethraeus 1999 [120]	11/13	12 months before and after event	N/A	25	Healthcare costs: Before event: SEK 5,800 Healthcare SEK 95,874 Productivity loss (before event – after event): SEK 71,731	Not reported

APPENDIX 11:

COLLABORATING GENERAL PRACTICES

GP practice	Address	Senior partner	Average population (2002 to 2007)
Church Street Practice Wantage	The Health Centre Mably Way, Grove Wantage OX12 9BN	Dr. P. Brian	12,191
Berinsfield Health Centre Berinsfield	Fane Drive, Berinsfield OX10 7NE	Dr. M. Agass	5,183
The Abingdon Surgery Abingdon	65 Stert Street, Abingdon OX14 3LB	Dr. N. Crossley	9,950
The Malthouse Surgery Abingdon	The Charter, Abingdon OX14 3JY	Dr. F. Debney	20,375
Family Health Centre Abingdon	Marcham Road, Abingdon OX14 1BT	Dr. P. Robertson	12,671
19 Beaumont Street Oxford	19 Beaumont Street, Oxford OX1 2NA	Dr. P. Maclennan	12,399
Bartlemas Surgery Oxford	East Oxford Health Centre, Manzil Way, Oxford OX4 1XD	Dr. T. Nicholson-Lailey	7,985
Kidlington Medical Practice Kidlington	Exeter Close, Kidlington OX5 1AP	Dr. K. Pandher	5,793
Exeter Surgery Kidlington	Exeter Close, Oxford Road, Kidlington, OX5 1AP	Dr. S. Street	4,614

APPENDIX 12:

MODIFIED RANKIN SCORE

Modified Rankin Score

Do you have any symptoms?	Yes/No
Are you able to look after yourself and carry out normal activities?	Yes/No
Does anyone else help pay the bills, do the shopping, cleaning etc?	Yes/No
Do you need someone to help you walk?	Yes/No
Do you need help to wash yourself?	Yes/No
Do you need to be lifted in and out of bed?	Yes/No

0 = no symptoms at all
1 = no significant disability despite symptoms: able to carry out all usual duties and activities
2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3 = moderate disability: requiring some help, but able to walk without assistance
4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance
5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6 = death

Rankin Score ☐

APPENDIX 13:

UNIVARIATE PREDICTORS OF PATIENT DISABILITY

Patient disability one month after the cerebrovascular event

At one month follow-up, 264 (31%, 95% CI: 28 to 34) patients were disabled. By event type, 213 (43%) stroke patients were disabled compared to 51 (14%) TIA patients ($p<0.001$). No significant differences were found between different stroke subtypes ($p=0.116$). Patients with NIHSS scores lower than 3 had significantly ($p<0.001$) lower disability rates (17%) than those with scores of between 3 and 10 (59%) and than those with scores above 10 (96%).

Other significant predictors of increased disability were being previously disabled (81% vs. 22%; $p<0.001$), history of atrial fibrillation (43% vs. 28%; $p<0.001$), history of stroke (48% vs. 28%; $p<0.001$), having suffered a definite event (34% vs. 8%, 20% and 19% for probable, possible and uncoded events, respectively; $p<0.001$), and suffering a recurrent stroke within 30-days of the index event (52% vs. 29%; $p<0.001$). By contrast previous history of TIA and suffering a recurrent TIA within 30-days of the index event significantly reduced the probability of one-month disability ($p=0.020$ and $p=0.016$, respectively).

In terms of socio-economic characteristics there were significant differences in terms of patients' living arrangements, marital and employment status before the event, and education levels. Patients who were married at the time of their event were less likely to be disabled than widowed and single patients (22% vs. 46% and 46%, respectively, $p<0.001$). Approximately 42% of patients living alone were disabled compared to 26% for those living with someone else ($p<0.001$). Patients in paid

employment were significantly less likely to be disabled than unemployed, retired, or patients who were unable to work (15% vs. 22%, 27%, 35%, respectively; p<0.001).

Patient disability six months after the cerebrovascular event

At six-month follow-up, 241 (29%, 95% CI: 26 to 32) patients were disabled. By event type, 174 (37%) stroke patients were disabled compared to 67 (19%) TIA patients (p<0.001). As at one month, no significant differences were found between different stroke subtypes (p=0.090). Patients with NIHSS scores lower than 3 had significantly (p<0.001) lower disability levels (19%) than those with scores of between 3 and 10 (49%) and than those with scores above 10 (95%).

The clinical variables which were univariate predictors of increased disability at one-month, mainly remained independent predictors of disability 6 months post-event, including previous history of stroke (p<0.001), atrial fibrillation (p=0.049) and disability (p<0.001). Results showed that patients suffering a recurrent stroke (46% vs. 27%; p<0.001) or CHD (60% vs. 29%; p=0.008) within six months of the index event were significantly more likely to be disabled. As with one-month disability there were significant differences in six-month disability levels depending on patients' living arrangements before the event (<0.001), marital status (p<0.001), education levels (p=0.025) and employment status (<0.001).

Patient disability one year after the cerebrovascular event

At 1-year follow-up, 198 (28%, 95% CI: 25 to 32) were disabled. By event type, 144 (37%) stroke patients were disabled compared to 54 (18%) TIA patients (p<0.001). No significant differences were found between different stroke subtypes (p=0.583). Patients with NIHSS scores lower than 3 had significantly (p<0.001) lower disability

rates (19%, n=99) than those with scores of between 3 and 10 (47%, n=67), and than those with scores above 10 (91%, n=29).

Significant differences were found amongst patients in terms of previous disability ($p<0.001$) and history of stroke ($p=0.002$). Patients who suffered a recurrent stroke between index event and 12-month follow-up were also more likely to be disabled (47% vs. 25%; $p<0.001$) as were those patients suffering a recurrent CHD event (60% vs. 27%; $p=0.003$). In a similar fashion as in the 1- and 6-month follow-ups, living arrangements before event ($p<0.001$), marital status ($p<0.001$), education levels ($p=0.020$), and employment status ($p<0.001$) were all univariate predictors of 1-year disability.

Patient disability two years after the cerebrovascular event

At 2-year follow-up, a total of 125 (28%, 95% CI: 24 to 32) patients were disabled. By event type, 94 (36%) stroke patients were disabled compared to 31 (17%) TIA patients ($p<0.001$), with no significant differences being identified for stroke subtypes ($p=0.446$). Patients with NIHSS scores lower than 3 had significantly ($p<0.001$) lower disability levels (18%) than those with scores of between 3 and 10 (49%) and than those with scores above 10 (91%).

Significant differences were found amongst patients in terms of previous disability ($p<0.001$). Patients who suffered a recurrent stroke between index event and 24-month follow-up were also more likely to be disabled (41% vs. 26%; $p=0.007$) as were those suffering a recurrent CHD event (50% vs. 27%; $p=0.019$). Significant differences in 2-year disability levels between patients were still identified depending on their marital (<0.001) and employment status ($p=0.010$).

APPENDIX 14:

UNIVARIATE PREDICTORS OF QUALITY OF LIFE

Quality of life one month after the cerebrovascular event

One month after index cerebrovascular event, stroke patients reported significantly lower EQ-5D quality of life than TIA patients ($p<0.001$). Significant differences in quality of life were also identified for: age (0.74, 0.75 and 0.65 for those aged <65, 65-74 and >74, respectively; $p<0.001$); gender (females 0.66 vs. males 0.74; $p<0.001$); being previously disabled (0.48 vs. 0.73; $p<0.001$); history of stroke (0.62 vs. 0.71 for those without; $p=0.003$); history of atrial fibrillation (0.64 vs. 0.71 for those with no history; $p=0.018$); history of hypertension (0.67 vs. 0.74; $p=0.002$); history of PVD (0.64 vs. 0.71 for those without; $p=0.002$); event severity (0.76, 0.59 and 0.12 for those with NIHSS scores of <3, 3-10 and >10; $p<0.001$); and probability of event, which ranged from 0.80 for those being coded as having suffered a probable event to 0.68 for those suffering a definite event ($p=0.006$).

Patients suffering a recurrent stroke or recurrent CHD event within their index event and one-month follow-up had significantly lower quality of life than those suffering no further events (0.56 vs. 0.71; $p<0.001$ and 0.45 vs. 0.70; $p=0.023$, respectively). Many of these significant differences were also observed when quality of life was measured using the EQ-VAS, except for history of atrial fibrillation ($p=0.084$) and PVD ($p=0.108$); and probability of event ($p=0.167$).

In terms of socio-economic characteristics, significant differences in EQ-5D quality of life estimates were identified across patients' living arrangements before the event, marital status, education levels, socio-economic class and employment status.

Patients living in their own homes at the time of event reported significantly higher quality of life than those living in warden or care home accommodation (0.71 vs. 0.55 and 0.59, respectively; p=0.007). Those living alone at time of event also reported worse quality of life than those living accompanied (0.64 vs. 0.73; p<0.001). Patients in higher socio-economic groups reported significantly higher quality of life estimates (p=0.046), ranging from 0.75 for those in socio-economic group II to 0.64 for those in group V. Finally, quality of life estimates by employment status ranged from 0.80 for those in full-time employment to 0.54 for the unemployed (p<0.001).

As before, many of these significant differences across patient groups were observed for EQ-VAS scores. However, no differences were identified across patients in terms of education levels (p=0.116) and socio-economic class (p=0.150). By contrast, significant differences in EQ-VAS scores were identified across patients depending on deprivation levels, with patients living in the most deprived areas reporting scores of 61 compared to 74 for those in the least deprived areas (p=0.019).

Quality of life six months after the cerebrovascular event

Six months after index cerebrovascular event, no significant differences in EQ-5D quality of life were identified between stroke and TIA patients (0.70 vs. 0.75, respectively; p=0.056). Furthermore, for the EQ-VAS, TIA and stroke patients reported very similar quality of life estimates (74 vs. 75; respectively; p=0.692). However, significant differences in EQ-5D quality of life were identified for: age (0.76, 0.75 and 0.69 for those aged <65, 65-74 and >74, respectively; p<0.001); being previously disabled (0.49 vs. 0.75; p=0.014); history of hypertension (0.70 vs. 0.75 for those without; p=0.024); history of diabetes (0.65 vs. 0.73 for those with no

history; p=0.023); history of PVD (0.64 vs. 0.73 for those without; p=0.047); and event severity (0.75, 0.66 and 0.39 for those with NIHSS scores of <3, 3-10 and >10; p<0.001).

Patients suffering a recurrent stroke within the first 6 months after the event reported lower EQ-5D quality of life estimates than those who did not (0.60 vs. 0.74; p=0.001). The only significant differences in EQ-VAS scores observed across patients' clinical characteristics were: previous disability (p<0.001), history of PVD (p=0.041) and event severity (p=0.042)

In terms of socio-economic characteristics, significant differences in EQ-5D quality of life estimates were identified across patients' living arrangements before the event (p=0.001), marital status (p=0.021), and employment status (p<0.001). For EQ-VAS scores significant differences across patient groups were only identified for employment status (p<0.001) and living arrangements (p<0.001) at time of event.

Quality of life one year after the cerebrovascular event

One year after index cerebrovascular event, significant differences in EQ-5D quality of life were identified between stroke and TIA patients (0.69 vs. 0.78; p<0.001). However, as at the 6-month follow-up, for the EQ-VAS TIA and stroke patients reported similar quality of life estimates (76 vs. 74; respectively; p=0.156). Significant differences in EQ-5D quality of life were identified for: age (0.77, 0.76 and 0.69 for those aged <65, 65-74 and >74, respectively; p<0.001); gender (females 0.69 vs. males 0.77; p<0.001); being previously disabled (0.49 vs. 0.76; p<0.001); history of hypertension (0.70 vs. 0.77 for those without; p=0.001); history of diabetes (0.64 vs. 0.74 for those with no history; p=0.003); event severity (0.76, 0.67 and 0.44 for those

with NIHSS scores of <3, 3-10 and >10; p<0.001); and the probability of the event (0.72, 0.77 and 0.84 for definite, probable and possible events, respectively; p=0.019). In addition patients suffering a recurrent stroke or recurrent CHD event within the one-year follow-up had significantly lower quality of life than those suffering no further events (0.62 vs. 0.75; p<0.001, and 0.57 vs. 0.74; p=0.006, respectively).

For EQ-VAS scores, significant differences were also observed in: age (p<0.001); gender (p<0.001); previous disability (p<0.001); history of stroke (p=0.015); history of hypertension (p=0.023); history of PVD (p=0.005); event severity (p=0.010); and suffering a recurrent stroke within one year of event (p=0.002). In terms of socio-economic characteristics, significant differences in EQ-5D and EQ-VAS quality of life estimates were identified across patients' living arrangements before the event, marital status, and employment status. Although significant differences across patients were identified in EQ-5D estimates for socio-economic status and education levels, no such differences were identified in EQ-VAS scores.

Quality of life two years after the cerebrovascular event

Two years after the index cerebrovascular event significant differences were found between TIA and stroke patients in terms EQ-5D quality of life (0.75 vs. 0.67; p=0.003, respectively). Significant differences in EQ-5D quality of life were also identified for: age (0.77, 0.72 and 0.65 for those aged <65, 65-74 and >74, respectively; p=0.001); gender (females 0.66 vs. males 0.75; p=0.002); previous disability (0.47 vs. 0.73; p<0.001); history of diabetes (0.60 vs. 0.71 for those with no history; p=0.009); and event severity (0.74, 0.60 and 0.46 for those with NIHSS scores of <3, 3-10 and >10; p<0.001). In addition, patients suffering a recurrent

stroke or recurrent CHD event within the 2-year follow-up had significantly lower quality of life than those suffering no further events (0.61 vs. 0.72; p=0.002 and 0.48 vs. 0.71; p<0.001, respectively).

For EQ-VAS scores, as with the 6- and 12-month follow-ups, no significant differences were observed between TIA and stroke patients (76 vs. 75; p=0.660). Significant univariate predictors of 2-year EQ-VAS scores included: age (p=0.005); gender (p<0.001); previous disability (p=0.003); history of hypertension (p=0.037); history of PVD (p=0.011); and suffering a recurrent CHD event (p=0.003). For the first time in a follow-up, event severity was no longer a significant univariate predictor of EQ-VAS scores (p=0.060).

In terms of socio-economic characteristics, significant differences in EQ-5D and EQ-VAS quality of life were identified across patients' living arrangements before the event; marital status; socio-economic status; education levels; and employment status.

APPENDIX 15: MULTIVARIATE PREDICTORS OF EQ-VAS SCORES

Predictors of EQ-VAS quality of life: complete-case analysis

Variable	1 month		6 months		1 year		2 years	
	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z
Age (years)								
<65	0.91	0.733	-0.64	0.838	3.53	0.181	-1.62	0.665
65 to 74	2.47	0.206	1.42	0.537	2.59	0.188	2.47	0.306
≥75	Reference case		Reference case		Reference case		Reference case	
Gender								
Female	Reference case		Reference case		Reference case		Reference case	
Male	5.42	0.002	0.70	0.728	4.83	0.008	7.47	0.002
Previously disabled	-6.49	0.023	-12.78	<0.001	-7.30	0.027	-3.76	0.387
History of stroke	-1.82	0.450	3.30	0.184	-3.94	0.113	-0.94	0.770
History of TIA	-2.49	0.225	-1.58	0.522	-0.43	0.851	-0.32	0.906
History of AF	-1.86	0.390	-0.36	0.890	0.16	0.944	-0.05	0.984
History of hypertension	-0.97	0.563	0.03	0.988	-2.07	0.192	-1.08	0.599
History of angina	0.32	0.890	-2.37	0.360	-2.69	0.250	-0.60	0.831
History of MI	-1.61	0.589	1.17	0.691	-3.87	0.229	1.27	0.699
History of diabetes	1.76	0.533	-1.77	0.560	0.19	0.944	-2.23	0.475
History of PVD	-4.57	0.124	-4.20	0.245	-4.37	0.178	-5.46	0.236
Smoking status								
Never	Reference case		Reference case		Reference case		Reference case	
Previous	-0.21	0.904	-1.70	0.385	-0.19	0.919	-4.67	0.040
Current	1.08	0.633	-2.31	0.431	-3.73	0.116	-0.20	0.950
Event type								
TIA	Reference case		Reference case		Reference case		Reference case	
Stroke	-3.48	0.040	1.73	0.349	-1.36	0.447	-0.11	0.958
Event severity (NIHSS)								
<3	Reference case		Reference case		Reference case		Reference case	
3 to 10	-5.43	0.009	-3.71	0.170	-3.79	0.110	-6.14	0.043
>10	-19.28	<0.001	-9.01	0.135	-2.05	0.660	-1.23	0.797
Probability of event								
Definite	Reference case		Reference case		Reference case		Reference case	
Probable	-0.36	0.896	-6.26	0.038	-4.96	0.140	-8.82	0.215
Possible	-0.04	0.990	-4.41	0.297	-5.85	0.069	-0.97	0.848
Not coded	-6.64	0.310	-4.23	0.503	-2.61	0.724	-25.28	0.081
Recurrent stroke	-3.92	0.145	-3.32	0.224	-6.28	<0.001	-1.03	0.623
Recurrent TIA	-0.04	0.992	0.48	0.743	0.47	0.709	0.95	0.490
Recurrent CHD	-6.67	0.564	-5.26	0.452	-1.14	0.729	-6.38	0.042
Recurrent PVD	N/A	N/A	20.2	0.061	-7.99	0.521	-2.64	0.713
Residence before event								
Own home	Reference case		Reference case		Reference case		Reference case	
With relative	5.65	0.324	-7.52	0.333	-6.59	0.365	0.11	0.994
Warden housing	-5.41	0.260	-1.99	0.664	-7.36	0.124	-6.51	0.184
Care home	3.76	0.569	-5.25	0.668	-0.90	0.906	-9.37	0.169
Other	-5.74	0.437	12.93	0.454	-0.74	0.959	N/A	N/A
Lived alone	-2.52	0.376	-0.61	0.873	-1.48	0.577	-2.22	0.565
Marital status								
Married	Reference case		Reference case		Reference case		Reference case	
Widow	1.57	0.586	1.56	0.703	-0.26	0.923	1.27	0.755
Single	-2.13	0.559	-5.37	0.259	-1.39	0.708	-3.69	0.473
Separated	-1.97	0.630	-4.36	0.417	-5.86	0.209	3.55	0.541
Partnered	-5.76	0.166	-4.81	0.434	-8.50	0.128	1.30	0.885

Predictors of EQ-VAS quality of life: complete-case analysis (cont.)

Variable	1 month		6 months		1 year		2 years	
	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z
Age left education	0.25	0.235	0.17	0.457	-0.12	0.624	-0.01	0.995
Socio-economic class								
I	-0.56	0.860	-2.49	0.516	1.50	0.656	7.26	0.088
II	-1.69	0.424	-2.78	0.286	-0.35	0.879	4.14	0.194
III-N	-0.23	0.925	1.50	0.561	2.92	0.226	6.89	0.012
III-M	Reference case		Reference case		Reference case		Reference case	
IV	-3.40	0.255	-4.58	0.190	-3.91	0.215	-2.06	0.570
V	0.99	0.726	4.76	0.187	4.99	0.076	-0.37	0.930
Employment status								
Full-time	3.14	0.255	10.70	0.001	4.28	0.112	9.20	0.013
Part-time	-1.33	0.618	4.42	0.104	1.19	0.691	9.76	0.006
Home carer	-4.75	0.412	1.60	0.818	-3.05	0.609	-1.83	0.691
Unemployed	-12.06	0.239	-7.99	0.531	-19.26	0.094	19.43	0.385
Cannot work	-3.66	0.548	-6.14	0.430	-3.52	0.661	-9.84	0.151
Retired	Reference case		Reference case		Reference case		Reference case	
Deprivation (IMD score)	-0.19	0.147	-0.15	0.319	-0.01	0.945	0.09	0.568
Constant	69.93	<0.001	76.14	<0.001	76.39	<0.001	65.27	<0.001
	No. 715 $p>\chi^2$ <0.001 Adj. R^2 0.006		No. 558 $p>\chi^2$ <0.001 Adj. R^2 0.001		No. 630 $p>\chi^2$ <0.001 Adj. R^2 0.005		No. 406 $p>\chi^2$ <0.001 Adj. R^2 0.002	

Predictors of EQ-VAS quality of life: multiple imputation

Variable	1 month		6 months		1 year		2 years	
	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z
Age (years)								
<65	3.19	0.275	-2.73	0.248	2.20	0.394	-0.94	0.753
65 to 74	3.09	0.113	0.59	0.773	1.55	0.442	1.55	0.446
≥75	Reference case		Reference case		Reference case		Reference case	
Gender								
Female	Reference case		Reference case		Reference case		Reference case	
Male	5.99	<0.001	-0.18	0.912	3.66	0.029	6.98	<0.001
Previously disabled	-7.24	0.001	-8.89	0.001	-7.07	0.012	-4.59	0.223
History of stroke	-0.41	0.838	3.54	0.064	-3.68	0.124	-1.48	0.602
History of TIA	-3.40	0.136	-1.23	0.495	-0.86	0.664	-0.52	0.825
History of AF	-1.21	0.672	-1.53	0.422	-0.66	0.785	-0.72	0.742
History of hypertension	-1.20	0.477	-1.02	0.475	-2.85	0.041‡	-0.98	0.560
History of angina	0.23	0.921	0.01	0.998	-2.65	0.276	-0.01	0.996
History of MI	-2.11	0.418	0.35	0.880	-4.73	0.082	0.63	0.834
History of diabetes	1.90	0.471	-0.84	0.736	0.30	0.896	-2.23	0.442
History of PVD	-4.80	0.184	-6.01	0.048‡	-3.27	0.308	-5.61	0.140
Smoking status								
Never	Reference case		Reference case		Reference case		Reference case	
Previous	0.20	0.908	-1.69	0.280	-0.93	0.549	-4.60	0.014
Current	1.72	0.479	-3.14	0.165	-3.87	0.075	-0.94	0.722
Event type								
TIA	Reference case		Reference case		Reference case		Reference case	
Stroke	-3.71	0.029	2.60	0.095	-0.54	0.741	0.63	0.767
Event severity (NIHSS)								
<3	Reference case		Reference case		Reference case		Reference case	
3 to 10	-5.43	0.013	-1.18	0.591	-2.86	0.175	-5.49	0.034
>10	-19.27	0.002	-1.00	0.799	-0.90	0.830	-0.59	0.872
Probability of event								
Definite	Reference case		Reference case		Reference case		Reference case	
Probable	0.30	0.923	-6.90	0.003	-4.18	0.221	-12.31	0.027‡
Possible	0.45	0.895	-1.76	0.482	-4.33	0.125	0.79	0.791
Not coded	-6.90	0.370	-6.47	0.185	0.64	0.917	-16.79	0.076
Recurrent stroke	-3.82	0.116	-1.82	0.391	-5.14	0.005	-1.09	0.585
Recurrent TIA	0.21	0.948	1.01	0.459	0.42	0.739	1.26	0.276
Recurrent CHD	-6.11	0.545	-2.01	0.693	-1.11	0.695	-2.97	0.227†
Recurrent PVD	N/A	N/A	32.02	0.212	-0.63	0.960	-1.68	0.764
Residence before event								
Own home	Reference case		Reference case		Reference case		Reference case	
With relative	3.27	0.528	-5.60	0.336	-5.75	0.336	2.28	0.799
Warden housing	-6.57	0.116	-2.66	0.490	-6.97	0.107	-7.03	0.144
Care home	0.21	0.983	-12.28	0.032‡	-3.80	0.557	-1.64	0.803
Other	-5.89	0.435	10.64	0.209	3.62	0.790	N/A	N/A
Lived alone	-3.17	0.254	-0.82	0.753	-1.67	0.494	-0.72	0.799
Marital status								
Married	Reference case		Reference case		Reference case		Reference case	
Widow	3.73	0.197	1.47	0.616	-0.58	0.853	-0.77	0.801
Single	0.16	0.963	-7.65	0.030‡	-1.12	0.741	-6.51	0.103
Separated	-1.55	0.683	-3.20	0.386	-6.35	0.166	1.07	0.820
Partnered	-5.99	0.187	-3.46	0.541	-10.60	0.029	-1.76	0.803

Predictors of EQ-VAS quality of life: multiple imputation (cont.)

Variable	1 month		6 months		1 year		2 years	
	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z	Coeff.	P>z
Age left education	0.18	0.409	0.30	0.301	-0.09	0.699	0.01	0.982
Socio-economic class								
I	-0.32	0.919	-1.65	0.622	1.36	0.650	6.38	0.088
II	-1.86	0.384	-2.41	0.262	-0.59	0.790	4.02	0.143
III-N	-1.06	0.611	1.52	0.473	2.24	0.292	6.07	0.021
III-M	Reference case		Reference case		Reference case		Reference case	
IV	-3.77	0.179	-2.07	0.472	-3.27	0.255	-1.57	0.616
V	0.72	0.792	2.43	0.349	4.00	0.127	-1.63	0.645
Employment status								
Full-time	2.14	0.465	11.21	<0.001	3.93	0.173	7.59	0.030
Part-time	-3.19	0.341	6.22	0.008‡	0.36	0.897	8.34	0.017
Home carer	-3.43	0.629	2.34	0.665	-3.88	0.480	-2.74	0.609
Unemployed	-7.83	0.379	-2.47	0.727	-19.17	0.035‡	10.69	0.154
Cannot work	-5.23	0.378	-4.36	0.452	-3.13	0.685	-12.50	0.126
Retired	Reference case		Reference case		Reference case		Reference case	
Deprivation (IMD score)	-0.20	0.142	-0.14	0.224	-0.01	0.943	0.05	0.751
Constant	69.34	<0.001	74.99	<0.001	78.86	<0.001	66.63	<0.001
	No. 1085 $p>\chi^2$ <0.001 Adj. R^2 0.017		No. 999 $p>\chi^2$ <0.001 Adj. R^2 0.008		No. 870 $p>\chi^2$ <0.001 Adj. R^2 0.009		No. 582 $p>\chi^2$ <0.001 Adj. R^2 0.011	

†Variables found to be significant (p<0.050) in the complete-case analysis.
‡Variables not found to be significant (p≥0.050) in the complete-case analysis.

APPENDIX 16: PRIMARY CARE RESOURCE USE PROFORMA

Patient number ☐☐☐☐☐ Date ☐☐/☐☐/☐☐

Date of event ☐☐/☐☐/☐☐

Previous resource use ☐☐/☐☐/☐☐ to ☐☐/☐☐/☐☐

Nurse home visit		
Nurse surgery visit		
Nurse telephone		
GP home visit		
GP surgery visit		
GP telephone		

Year one resource use ☐☐/☐☐/☐☐ to ☐☐/☐☐/☐☐

Nurse home visit		
Nurse surgery visit		
Nurse telephone		
GP home visit		
GP surgery visit		
GP telephone		

Year two resource use ☐☐/☐☐/☐☐ to ☐☐/☐☐/☐☐

Nurse home visit		
Nurse surgery visit		
Nurse telephone		
GP home visit		
GP surgery visit		
GP telephone		

Year three resource use ☐☐/☐☐/☐☐ to ☐☐/☐☐/☐☐

Nurse home visit		
Nurse surgery visit		
Nurse telephone		
GP home visit		
GP surgery visit		
GP telephone		

Year four resource use ☐☐/☐☐/☐☐ to ☐☐/☐☐/☐☐

Nurse home visit		
Nurse surgery visit		
Nurse telephone		
GP home visit		
GP surgery visit		
GP telephone		

Year five resource use ☐☐/☐☐/☐☐ to ☐☐/☐☐/☐☐

Nurse home visit		
Nurse surgery visit		
Nurse telephone		
GP home visit		
GP surgery visit		
GP telephone		

APPENDIX 17. OUTPATIENT VISITS AND UNIT COSTS

Speciality	Number of visits (n=8807)	% of total visits	Mean unit cost, £
Anaesthetics	28	0.32	93
Audiological medicine	30	0.34	164
Breast surgery	71	0.81	91
Cardiac surgery	8	0.09	146
Cardiology	341	3.87	120
Clinical haematology	16	0.18	135
Colorectal surgery	32	0.36	85
Dermatology	331	3.76	83
Diabetic retinal screening	212	2.4	26
Diabetic medicine	240	2.75	103
Dietetics	16	0.18	47
Electrocardiogram (ECG)	119	1.35	27
Electromyography (EMG)	27	0.31	100
Ear, nose and throat	146	1.66	79
Echocardiogram	109	1.24	58
Electroencephalograph	46	0.52	100
Endocrinology	37	0.42	115
Exercise test	10	0.11	59
Gastrointestinal surgery	4	0.05	105
General medicine	306	3.47	121
General surgery	259	2.94	112
Geriatric medicine	556	6.31	155
Gynaecology	74	0.84	106
Haematology	145	1.65	117
Health visiting services	3	0.03	45
Infectious diseases	6	0.07	177
Intensive care	2	0.02	88
Medical gastroenterology	105	1.19	104
Medical oncology	26	0.30	128
Nephrology	87	0.99	122
Neurology	2308	26.21	139
Neurosurgery	58	0.66	149
Occupational therapy	11	0.12	75
Ophthalmology	1020	11.58	67
Oral surgery	44	0.50	90
Orthoptics	168	1.91	57
Paediatric neurology	5	0.06	241
Pain management	3	0.03	101
Palliative medicine	17	0.19	327
Physiotherapy	33	0.37	30
Plastic surgery	52	0.59	77
Podiatry	7	0.08	31
Psychotherapy	54	0.61	147
Radiotherapy	128	1.45	134
Renal surgery	4	0.04	115
Restorative dentistry	5	0.06	97
Thoracic medicine	168	1.91	122
Transplantation surgery	3	0.03	283
Trauma & Orthopaedics	141	1.61	87
Urology	141	1.61	87
Vascular medicine	1041	11.82	120
X-ray	4	0.04	28

APPENDIX 18: INPATIENT RESOURCE USE AND UNIT COSTS

	Hospital Length of Stay (S.D.)			Costs	
Ward	**All patients**	**Hospitalised patients**	**Users**	**Unit cost, £**	**Source**
Dialysis	0.01 (0.09)	0.01 (0.11)	3.00 (-)	103	233
Radiology	0.02 (0.49)	0.02 (0.62)	9.00 (11.31)	132	233
Elderly rehabilitation	1.99 (12.56)	3.19 (15.79)	46.84 (40.47)	185	233
Cardiac day care	1.21 (6.63)	1.94 (8.31)	14.95 (18.46)	192	233
Geriatric medicine	0.05 (1.29)	0.08 (1.63)	31.50 (3.53)	194	235
Community hospital	8.96 (29.71)	14.36 (36.59)	64.30 (52.85)	212	235
General medicine	3.85 (11.88)	6.17 (14.56)	14.38 (19.41)	249	236
Medical short stay	0.43 (1.54)	0.68 (1.91)	3.55 (2.95)	249	236
Pain management	0.01 (0.09)	0.01 (0.11)	3.00 (-)	250	233
Palliative care	0.07 (1.29)	0.11 (1.63)	17.2 (11.37)	250	233
Diabetic medicine	0.01 (0.26)	0.02 (0.33)	6 (2.83)	259	233
Endocrinology	0.01 (0.03)	0.01 (0.04)	1.00 (-)	259	233
Stroke rehabilitation	1.71 (10.78)	2.75 (13.55)	54.05 (29.27)	262	233
Emergency medicine	0.08 (0.68)	0.13 (0.85)	1.60 (2.62)	284	236
Thoracic medicine	0.27 (3.60)	0.44 (4.55)	18.11 (23.85)	286	236
Medical assessment	0.87 (3.42)	1.39 (4.24)	2.59 (5.52)	288	233
Dermatology	0.01 (0.16)	0.01 (0.21)	4.00 (0.00)	297	236
Gastroenterology	0.14 (1.96)	0.22 (2.48)	11.07 (17.69)	350	236
Infectious diseases	0.20 (2.72)	0.32 (3.44)	11.29 (17.69)	353	236
Stroke unit	3.90 (12.24)	6.25 (15.02)	20.08 (21.16)	354	173, 237
Nephrology	0.17 (3.13)	0.28 (3.95)	29.86 (30.26)	357	236
Urology	0.11 (0.94)	0.17 (1.18)	4.20 (4.30)	408	236
Neurology	0.33 (3.51)	0.53 (4.44)	10.13 (16.95)	419	236
Paediatric neurology	0.01 (0.12)	0.01 (0.15)	4.00 (-)	419	236
General surgery	0.36 (3.14)	0.58 (3.96)	8.68 (12.92)	443	236
Coronary care unit	0.04 (0.42)	0.06 (0.53)	8.82 (2.24)	450	233
Obstetrics	0.01 (0.09)	0.01 (0.11)	3.00 (-)	474	236
Intensive rehabilitation	2.43 (26.36)	3.91 (33.30)	153.74 (147.28)	455	233
Trauma	0.65 (4.08)	1.04 (5.13)	16.62 (12.75)	475	236
Oncology	0.07 (1.10)	0.11 (1.40)	11.29 (9.79)	486	236
Haematology	0.05 (1.25)	0.09 (1.58)	21.33 (16.04)	512	236
Colorectal surgery	0.01 (0.29)	0.01 (0.37)	10.00 (-)	513	236
Specialist surgery	0.01 (0.03)	0.01 (0.04)	1.00 (-)	513	236
Surgical emergency	0.03 (0.38)	0.05 (0.48)	4.25 (2.05)	513	236
Vascular surgery	0.59 (4.34)	0.95 (5.46)	6.81 (13.26)	513	236
Gynaecology	0.06 (0.67)	0.10 (0.84)	4.28 (3.53)	540	236
Cardiology	0.09 (1.28)	0.14 (1.62)	6.44 (9.31)	569	236
Interventional radiology	0.01 (0.03)	0.01 (0.04)	1.00 (-)	580	233
Plastic surgery	0.03 (0.62)	0.05 (0.79)	6.80 (7.66)	650	236
Neurosurgery	0.57 (5.12)	0.92 (6.46)	22.16 (23.49)	669	236
Oral surgery	0.01 (0.12)	0.01 (0.15)	4.00 (-)	695	236
Ear, nose and throat	0.05 (0.69)	0.09 (0.88)	4.33 (4.61)	716	236
Ophthalmology	0.03 (0.40)	0.05 (0.51)	2.69 (2.90)	743	236
Breast surgery	0.02 (0.48)	0.04 (0.61)	9.83 (7.57)	769	233
Cardiothoracic surgery	0.04 (0.52)	0.06 (0.66)	5.75 (3.06)	963	236
Urology transplant	0.01 (0.06)	0.01 (0.07)	2.00 (-)	1099	236
Intensive treatment unit	0.05 (0.67)	0.09 (0.85)	4.64 (4.31)	1412	233

APPENDIX 19: HOSPITAL DAY CASES AND UNIT COSTS

	Day cases (S.D)			Costs	
Ward	**All patients**	**Day case patients**	**Users**	**Unit costs, £**	**Source**
Dialysis	0.12 (3.04)	0.39 (5.35)	74.50 (3.53)	103	233
Radiology	0.01 (0.10)	0.02 (0.17)	1.40 (0.55)	132	233
Cardiac day care	0.04 (0.23)	0.11 (0.39)	1.22 (0.54)	192	233
General medicine	0.01 (0.05)	0.01 (0.09)	1.00 (0.00)	249	236
Medical short stay	0.01 (0.05)	0.01 (0.09)	1.00 (0.00)	249	236
Pain management	0.01 (0.04)	0.01 (0.07)	1.00 (0.00)	250	233
Endocrinology	0.01 (0.10)	0.02 (0.18)	1.40 (0.89)	259	233
Emergency medicine	0.07 (0.30)	0.21 (0.50)	1.19 (0.50)	284	236
Thoracic medicine	0.01 (0.09)	0.02 (0.16)	1.14 (0.38)	286	236
Medical assessment	0.04 (0.20)	0.12 (0.34)	1.04 (0.21)	288	233
Dermatology	0.02 (0.14)	0.05 (0.25)	1.11 (0.32)	297	236
Gastroenterology	0.01 (0.03)	0.01 (0.05)	1.00 (-)	350	236
Stroke Unit	0.01 (0.03)	0.01 (0.05)	1.00 (-)	354	173, 237
Nephrology	0.01 (0.46)	0.04 (0.81)	8.50 (10.61)	357	236
Urology	0.02 (0.19)	0.06 (0.33)	1.32 (0.75)	408	236
Neurology	0.01 (0.10)	0.03 (0.18)	1.00 (0.00)	419	236
Paediatric neurology	0.01 (0.06)	0.01 (0.10)	2.00 (-)	419	236
General surgery	0.01 (0.07)	0.02 (0.12)	1.00 (-)	443	236
Oncology	0.04 (0.92)	0.12 (1.62)	6.86 (10.75)	486	236
Day surgery	0.02 (0.14)	0.05 (0.24)	1.20 (0.41)	489	233
Endoscopy	0.13 (0.46)	0.41 (0.74)	1.34 (0.72)	489	233
Haematology	0.01 (0.29)	0.04 (0.51)	4.00 (3.46)	512	236
Vascular surgery	0.01 (0.10)	0.03 (0.17)	1.00 (0.00)	513	236
Gynaecology	0.01 (0.05)	0.01 (0.09)	1.00 (0.00)	540	236
Cardiology	0.02 (0.14)	0.05 (0.25)	1.19 (0.40)	569	236
Interventional radiology	0.01 (0.06)	0.01 (0.10)	1.00 (0.00)	580	233
Plastic surgery	0.01 (0.10)	0.03 (0.17)	1.00 (0.00)	650	236
Neurosurgery	0.01 (0.04)	0.01 (0.07)	1.00 (0.00)	669	236
Oral surgery	0.01 (0.03)	0.01 (0.05)	1.00 (-)	695	236
Ear, nose and throat	0.01 (0.06)	0.01 (0.11)	1.50 (0.71)	716	236
Ophthalmology	0.08 (0.39)	0.26 (0.66)	1.52 (0.83)	743	236
Breast surgery	0.01 (0.09)	0.01 (0.15)	3.00 (-)	769	233

APPENDIX 20: MEDICATION USAGE BY FOLLOW-UP

Baseline				1 month				6 months				12 months				24 months			
Medication	**BNF**	**No.**	**%†**	**Medication**	**BNF**	**No.**	**%†**	**Medication**	**BNF**	**No.**	**%†**	**Medication**	**BNF**	**No.**	**%†**	**Medication**	**BNF**	**No.**	**%†**
Aspirin	2	499	43	Aspirin	2	638	75	Aspirin	2	575	74	Aspirin	2	520	74	Aspirin	2	299	71
Atenolol	2	238	21	Simvastatin	2	536	63	Simvastatin	2	493	63	Simvastatin	2	458	65	Simvastatin	2	262	62
Simvastatin	2	207	18	Atenolol	2	199	23	Atenolol	2	182	23	Bendro‡	2	164	23	Atenolol	2	109	26
Bendro‡	2	185	16	Bendro‡	2	197	23	Bendro‡	2	180	23	Atenolol	2	160	23	Ramipril	2	93	22
Frusemide	2	132	11	Clopidogrel	2	184	22	Ramipril	2	170	22	Ramipril	2	141	20	Bendro‡	2	91	22
Lisinopril	2	109	9	Ramipril	2	164	19	Omeprazole	1	106	14	Omeprazole	1	91	13	Frusemide	2	61	15
Ramipril	2	104	9	Paracetamol	4	106	12	Paracetamol	4	104	13	Lisinopril	2	86	12	Warfarin	2	59	14
Lansoprazole	1	85	7	Lansoprazole	1	99	12	Lisinopril	2	103	13	Paracetamol	4	85	12	Lisinopril	2	56	13
Amlodipine	2	81	7	Lisinopril	2	96	11	Warfarin	2	97	12	Warfarin	2	85	12	Amlodipine	2	55	13
Omeprazole	1	76	7	Warfarin	2	95	11	Clopidogrel	2	96	12	Frusemide	2	82	12	Paracetamol	4	53	13
Salbutamol	3	75	6	Omeprazole	1	92	11	Dipyridamole	2	92	12	Clopidogrel	2	79	11	Omeprazole	1	52	12
Levothyroxine	6	73	6	Dipyridamole	2	83	10	Frusemide	2	92	12	Lansoprazole	1	78	11	Atorvastatin	2	50	12
Metformin	6	66	6	Frusemide	2	78	9	Lansoprazole	1	82	11	Dipyridamole	2	75	11	Clopidogrel	2	45	11
Paracetamol	4	65	6	Amlodipine	2	77	9	Amlodipine	2	74	9	Amlodipine	2	72	10	Lansoprazole	1	41	10
Digoxin	2	62	5	Levothyroxine	6	65	8	Levothyroxine	6	65	8	Atorvastatin	2	62	9	Dipyridamole	2	37	9
Beclomethasone	3	57	5	Lactulose	1	57	7	Atorvastatin	2	59	8	Leveothyroxine	6	56	8	Levothyroxine	6	33	8
Amitriptyline	4	55	5	Coversyl plus††	2	53	6	Metformin	6	51	7	Losartan	2	42	6	Calcium	9	30	7
Enalapril	2	55	5	Atrovastatin	2	51	6	Perindopril	2	49	6	Calcium	9	40	6	Citalopram	4	29	7
Gliclazide	6	53	5	Metformin	6	51	6	Citalopram	4	47	6	Digoxin	2	40	6	Digoxin	2	25	6
Nifedipine	2	46	4	Digoxin	2	48	8	Amitriptyline	4	45	6	Perindopril	2	39	6	Losartan	2	25	6
Calcium	9	44	4	Perindopril	2	48	8	Digoxin	2	40	5	Amitriptyline	4	38	5	Metformin	6	25	6
Losartan	2	43	4	Amitriptyline	4	43	5	Gliclazide	6	40	5	Metformin	6	38	5	GTN‡‡	2	24	6
Cocodamol	4	42	4	Gliclazide	6	42	5	Calcium	9	39	5	Citalopram	4	37	5	Doxazosin	2	23	5
ISMN*	2	42	4	Senna	1	42	5	Losartan	2	38	5	GTN‡‡	2	36	5	Enalapril	2	23	5
Atorvastatin	2	40	3	Enalapril	2	41	5	GTN‡‡	2	36	5	Bisoprolol	2	34	5	ISMN*	2	23	5
Alendronate	6	37	3	Calcium	9	40	5	Bisoprolol	2	34	4	Enalapril	2	33	5	Gliclazide	6	22	5
Bisoprolol	2	37	3	Citalopram	4	40	5	ISMN*	2	34	4	Felodipine	2	32	5	Ferrous sulphate	9	21	5
Doxazosin	2	37	3	Losartan	2	40	5	Enalapril	2	33	4	Gliclazide	6	31	4	Perindopril	2	21	5
Lactulose	1	37	3	Bisoprolol	2	33	4	Lactulose	1	31	4	ISMN*	2	30	4	Cocodamol	4	20	5
Citalopram	4	36	3	GTN‡‡	2	32	4	Felodipine	2	30	4	Doxazosin	2	28	4	Amitriptyline	4	19	5

†Percentage of patients taking particular medication; ‡Bendroflumethiazide; *Isosorbide mononitrate; ††Combination of perindopril and indapamide; ‡‡Glyceril trinitrate

APPENDIX 21: UNIVARIATE PREDICTORS OF INPATIENT RESOURCES

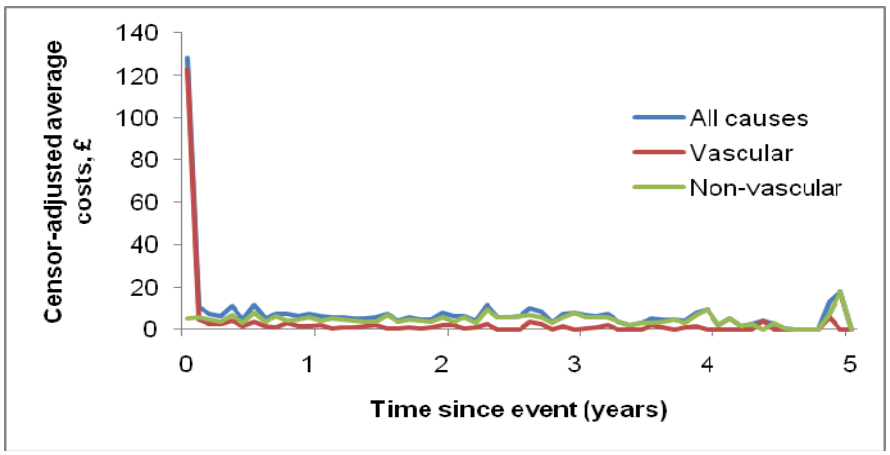
	Day Cases		Hospitalisations		Hospital days, conditional on admission	
	IR (95% CI)	p>z	IR (95% CI)	p>z	Mean (95% CI)	p>z
Age (years)		<0.001		<0.001		0.422
<65	0.22 (0.19 to 0.27)		0.36 (0.31 to 0.41)		48 (34 to 64)	
65 to 74	0.52 (0.47 to 0.57)		0.51 (0.46 to 0.57)		52 (42 to 63)	
≥75	0.29 (0.26 to 0.32)		0.75 (0.70 to 0.80)		65 (58 to 73)	
Gender		<0.001		0.405		0.026
Female	0.28 (0.25 to 0.31)		0.60 (0.56 to 0.65)		67 (57 to 77)	
Male	0.40 (0.36 to 0.44)		0.58 (0.54 to 0.62)		53 (46 to 60)	
Previously disabled		0.022		<0.001		0.941
Yes	0.25 (0.20 to 0.32)		1.10 (0.98 to 1.23)		62 (53 to 73)	
No	0.34 (0.31 to 0.36)		0.51 (0.48 to 0.54)		62 (55 to 70)	
History of stroke		0.944		<0.001		0.366
Yes	0.34 (0.28 to 0.40)		0.77 (0.68 to 0.86)		64 (52 to 77)	
No	0.34 (0.31 to 0.36)		0.56 (0.53 to 0.59)		59 (53 to 67)	
History of TIA		<0.001		0.516		0.408
Yes	0.52 (0.45 to 0.60)		0.61 (0.54 to 0.69)		42 (39 to 64)	
No	0.30 (0.28 to 0.33)		0.58 (0.55 to 0.62)		62 (56 to 70)	
History of AF		<0.001		<0.001		0.243
Yes	0.72 (0.65 to 0.81)		0.82 (0.73 to 0.91)		67 (57 to 78)	
No	0.26 (0.24 to 0.28)		0.54 (0.51 to 0.58)		59 (52 to 66)	
Hypertension history		<0.001		0.002		0.687
Yes	0.39 (0.35 to 0.42)		0.63 (0.59 to 0.67)		64 (56 to 74)	
No	0.27 (0.24 to 0.31)		0.54 (0.49 to 0.58)		55 (47 to 63)	
History of angina		0.808		<0.001		0.452
Yes	0.33 (0.28 to 0.39)		0.76 (0.68 to 0.85)		54 (44 to 64)	
No	0.34 (0.31 to 0.36)		0.55 (0.52 to 0.59)		62 (55 to 69)	
History of MI		<0.001		<0.001		0.082
Yes	0.59 (0.51 to 0.68)		0.87 (0.77 to 0.98)		48 (37 to 60)	
No	0.30 (0.28 to 0.32)		0.55 (0.52 to 0.58)		62 (56 to 69)	
History of diabetes		0.090		<0.001		0.455
Yes	0.39 (0.33 to 0.47)		0.77 (0.67 to 0.88)		59 (45 to 75)	
No	0.33(0.31 to 0.35)		0.57 (0.53 to 0.60)		60 (54 to 67)	
History of PVD		0.368		<0.001		0.131
Yes	0.37 (0.29 to 0.48)		1.16 (1.01 to 1.34)		60 (41 to 79)	
No	0.33 (0.31 to 0.36)		0.55 (0.52 to 0.58)		59 (54 to 65)	
Smoking status		<0.001		0.240		0.137
Never	0.29 (0.26 to 0.32)		0.56 (0.52 to 0.61)		63 (56 to 71)	
Previous	0.40 (0.37 to 0.44)		0.62 (0.57 to 0.67)		60 (50 to 70)	
Current	0.27 (0.22 to 0.33)		0.58 (0.50 to 0.67)		48 (34 to 63)	
Event type		0.704		<0.001		0.077
TIA	0.33 (0.30 to 0.37)		0.45 (0.42 to 0.50)		55 (43 to 68)	
Stroke	0.34 (0.31 to 0.37)		0.70 (0.66 to 0.75)		62 (56 to 69)	
NIHSS score-severity		0.002		<0.001		0.006
<3	0.34 (0.31 to 0.36)		0.47 (0.44 to 0.50)		51 (43 to 60)	
3 to 10	0.33 (0.28 to 0.39)		0.85 (0.77 to 0.93)		69 (59 to 80)	
11 to 20	0.17 (0.11 to 0.26)		1.03 (0.83 to 1.23)		99 (78 to 120)	
>20	0.87 (0.36 to 2.09)		4.88 (3.37 to 7.06)		48 (20 to 80)	
Probability of event		<0.001		<0.001		<0.001
Definite	0.34 (0.31 to 0.36)		0.62 (0.59 to 0.65)		64 (58 to 71)	
Probable	0.63 (0.50 to 0.80)		0.58 (0.45 to 0.74)		25 (15 to 37)	
Possible	0.22 (0.17 to 0.29)		0.35 (0.28 to 0.43)		40 (22 to 60)	
Not coded	0.29 (0.17 to 0.49)		0.55 (0.42 to 0.72)		19 (10 to 30)	

Univariate predictors of inpatient care resource use (cont.)

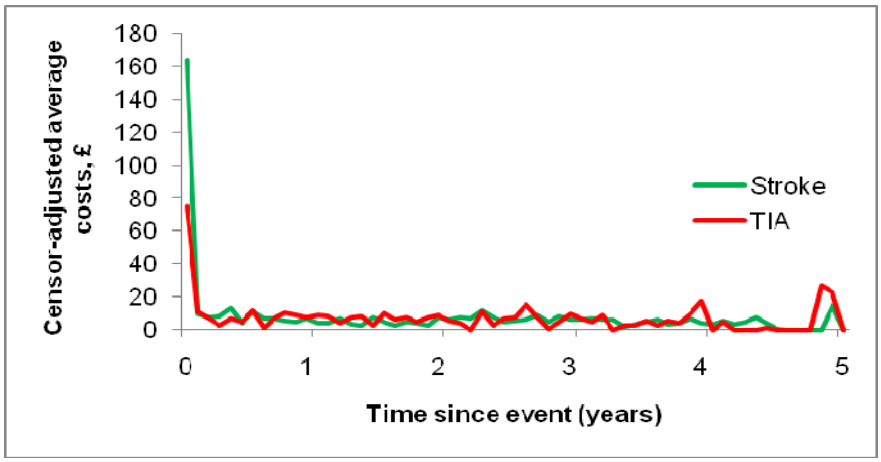
	Day Cases		Hospitalisations		Hospital days, conditional on admission	
	IR (95% CI)	p>z	IR (95% CI)	p>z	Mean (95% CI)	p>z
Recurrent stroke		0.014		<0.001		0.006
Yes	0.28 (0.23 to 0.33)		0.78 (0.71 to 0.87)		80 (69 to 95)	
No	0.35 (0.32 to 0.38)		0.54 (0.51 to 0.58)		54 (48 to 60)	
Recurrent TIA		<0.001		<0.001		0.241
Yes	0.45 (0.39 to 0.51)		0.47 (0.40 to 0.54)		42 (29 to 55)	
No	0.31 (0.29 to 0.34)		0.62 (0.58 to 0.65)		62 (55 to 69)	
Recurrent CHD		<0.001		<0.001		0.123
Yes	0.83 (0.70 to 0.97)		1.30 (1.15 to 1.48)		58 (46 to 70)	
No	0.30(0.28 to 0.38)		0.53 (0.51 to 0.57)		60 (53 to 66)	
Recurrent PVD		0.113		<0.001		0.003
Yes	0.19 (0.09 to 0.40)		1.09 (0.80 to 1.49)		54 (27 to 71)	
No	0.34 (0.32 to 0.36)		0.58 (0.55 to 0.61)		61 (54 to 67)	
Living arrangements		0.253		<0.001		<0.001
Own home	0.33 (0.31 to 0.36)		0.56 (0.53 to 0.59)		65 (58 to 72)	
With relative	0.43 (0.26 to 0.70)		0.61 (0.41 to 0.92)		31 (17 to 50)	
Warden housing	0.30 (0.21 to 0.43)		1.03 (0.85 to 1.25)		78 (60 to 96)	
Care home	0.26 (0.15 to 0.45)		0.70 (0.50 to 0.99)		21 (15 to 29)	
Other	0.11 (0.03 to 0.46)		0.51 (0.27 to 0.99)		28 (11 to 46)	
Lived alone		0.719		<0.001		0.003
Yes	0.33 (0.29 to 0.38)		0.78 (0.71 to 0.84)		79 (67 to 92)	
No	0.32 (0.30 to 0.35)		0.51 (0.48 to 0.54)		53 (46 to 61)	
Marital status		<0.001		<0.001		0.003
Married	0.34 (0.31 to 0.38)		0.48 (0.44 to 0.52)		51 (43 to 59)	
Widow	0.22 (0.19 to 0.25)		0.79 (0.73 to 0.86)		71 (61 to 82)	
Single	0.85 (0.71 to 1.03)		0.65 (0.52 to 0.80)		106 (65 to 143)	
Separated	0.25 (0.18 to 0.35)		0.55 (0.44 to 0.70)		59 (30 to 79)	
Partnered	0.33 (0.22 to 0.51)		0.41 (0.28 to 0.60)		52 (20 to 71)	
Age left education		0.043		<0.001		0.722
<18 years	0.31 (0.29 to 0.34)		0.62 (0.58 to 0.65)		63 (57 to 70)	
≥18 years	0.37 (0.32 to 0.43)		0.46 (0.41 to 0.52)		63 (49 to 80)	
Socioeconomic class		<0.001		0.022		0.412
I	0.63 (0.52 to 0.75)		0.53 (0.44 to 0.64)		68 (43 to 93)	
II	0.24 (0.20 to 0.29)		0.53 (0.47 to 0.60)		58 (46 to 71)	
III-N	0.41 (0.36 to 0.47)		0.61 (0.55 to 0.68)		59 (46 to 73)	
III-M	0.24 (0.20 to 0.29)		0.52 (0.46 to 0.59)		66 (52 to 83)	
IV	0.38 (0.32 to 0.47)		0.63 (0.54 to 0.73)		70 (54 to 86)	
V	0.23 (0.18 to 0.29)		0.68 (0.59 to 0.78)		60 (42 to 72)	
Employment status		<0.001		<0.001		0.048
Full-time	0.18 (0.14 to 0.23)		0.36 (0.30 to 0.43)		35 (22 to 47)	
Part-time	0.26 (0.19 to 0.35)		0.36 (0.28 to 0.47)		79 (34 to 126)	
Home carer	0.17 (0.08 to 0.36)		0.47 (0.30 to 0.73)		60 (25 to 101)	
Unemployed	0.24 (0.12 to 0.45)		0.52 (0.34 to 0.81)		38 (11 to 65)	
Cannot work	0.41 (0.26 to 0.65)		0.55 (0.37 to 0.82)		57 (21 to 78)	
Retired	0.36 (0.34 to 0.39)		0.65 (0.62 to 0.69)		63 (56 to 70)	
Deprivation (quintile)		<0.001		<0.001		0.983
1 – Most deprived	0.37 (0.20 to 0.69)		0.77 (0.51 to 1.16)		55 (26 to 87)	
2	0.39 (0.30 to 0.51)		0.59 (0.48 to 0.74)		57 (29 to 95)	
3	0.67 (0.60 to 0.75)		0.70 (0.63 to 0.78)		59 (49 to 69)	
4	0.22 (0.18 to 0.25)		0.61 (0.56 to 0.67)		67 (55 to 82)	
5 – Least deprived	0.27 (0.24 to 0.30)		0.53 (0.49 to 0.57)		55 (47 to 63)	

APPENDIX 22: AVERAGE COSTS OVER TIME

EMERGENCY CARE

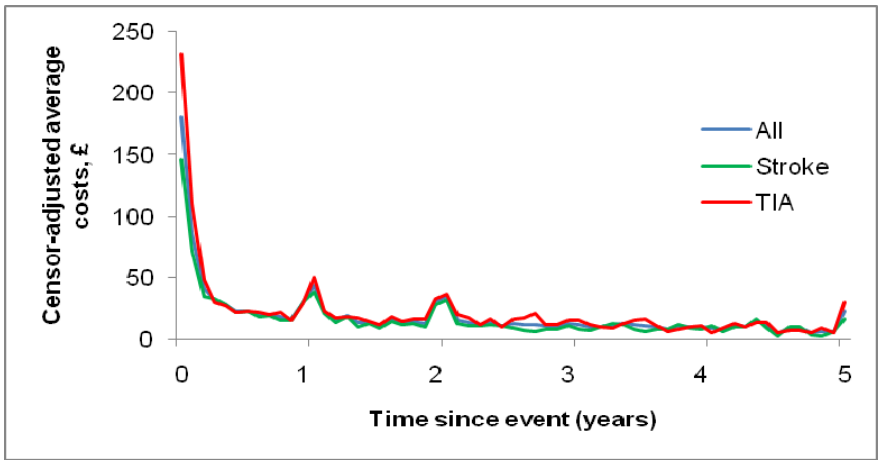


Average emergency care costs over time by cause



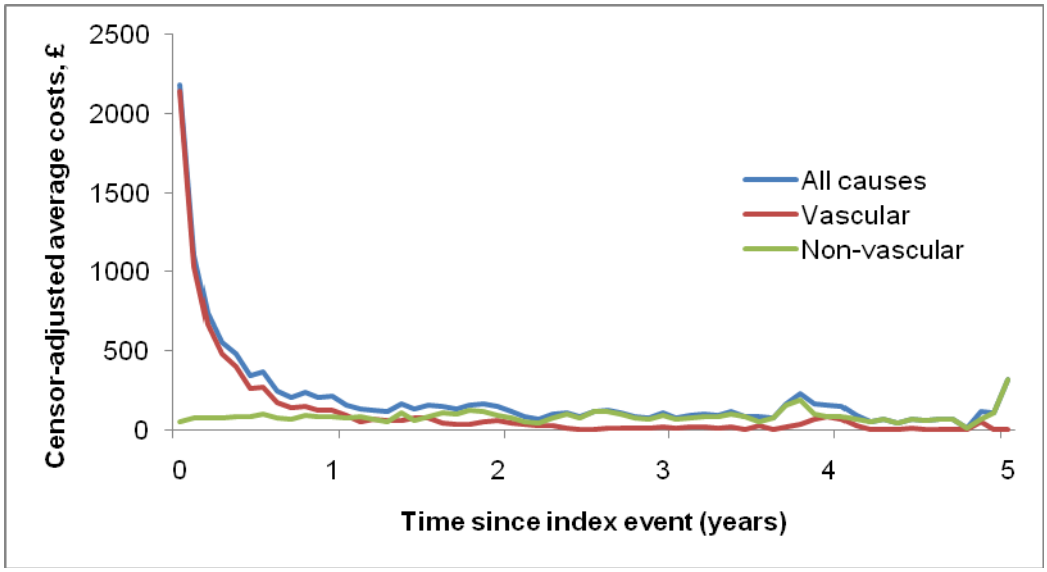
Average emergency care costs over time by event type

OUTPATIENT CARE



Average outpatient care costs over time by event type

INPATIENT CARE



Average inpatient care costs over time by cause

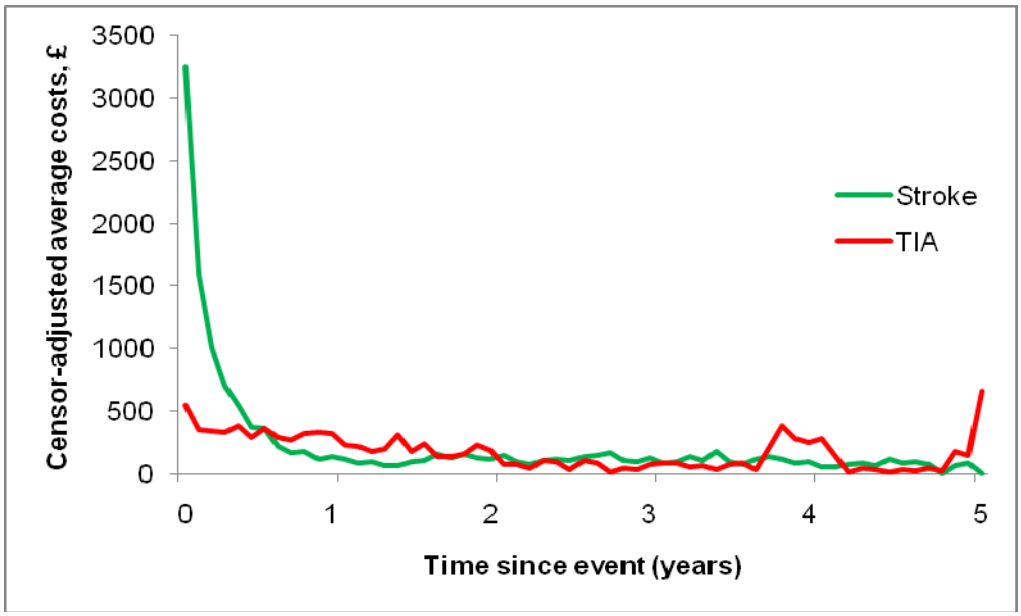


Figure 6.1 Average inpatient care costs over time by event type

APPENDIX 23: UNIVARIATE PREDICTORS OF TOTAL COSTS

Univariate predictors of total costs: all patients

	Mean costs, £ (95% CI)	p>z
Age (years)		0.007
<65	138686 (10219 to 17972)	
65 to 74	13404 (11137 to 15997)	
≥75	17159 (15270 to 19183)	
Gender		0.337
Female	17289 (14637 to 20159)	
Male	14220 (12576 to 16151)	
Previously disabled		0.021
Yes	15979 (13248 to 18948)	
No	16321 (14650 to 18200)	
History of stroke		0.183
Yes	16972 (14360 to 20219)	
No	15554 913723 to 17511)	
History of TIA		0.521
Yes	14426 (11685 to 17412)	
No	16177 (14300 to 18146)	
History of AF		0.009
Yes	18834 (15600 to 22504)	
No	15139 (13350 to 17135)	
Hypertension		0.474
Yes	16409 (14344 to 18807)	
No	14882 (12729 to 17252)	
History of angina		0.999
Yes	15677 (13097 to 18341)	
No	15803 (14075 to 17763)	
History of MI		0.798
Yes	14298 (11544 to 17447)	
No	15995 (14282 to 18059)	
History of diabetes		0.777
Yes	16793 (13533 to 20660)	
No	15676 (13982 to 17638)	
History of PVD		0.127
Yes	18123 (12449 to 23293)	
No	15315 (13850 to 16831)	
Smoking status		0.038
Never	16654 (14513 to 18948)	
Previous	15951(13418 to 18511)	
Current	11964 (9349 to 14754)	
Event type		0.019
TIA	13904 (11488 to 16657)	
Stroke	16923 (15149 to 18858)	
NIHSS-severity		<0.001
<3	12886 (11113 to 14830)	
3 to 10	19860 (17144 to 22854)	
11 to 20	34559 (25412 to 45608)	
>20	11710 (5464 to 19227)	
Probability of event		<0.001
Definite	17164 (15447 to 18939)	
Probable	8345 (6157 to 10846)	
Possible	10370 (6485 to 14871)	
Not coded	5716 (4150 to 7515)	

	Mean costs, £ (95% CI)	p>z
Recurrent stroke		0.020
Yes	23833 (19229 to 28800)	
No	13893 (12422 to 15522)	
Recurrent TIA		0.013
Yes	11899 (8668 to 15546)	
No	16306 (14515 to 18279)	
Recurrent CHD		0.005
Yes	20952 (16935 to 24985)	
No	15147 (13481 to 16837)	
Recurrent PVD		0.096
Yes	21597 (13918 to 28069)	
No	15704 (14188 to 17409)	
Living arrangements		<0.001
Own home	16894 (15047 to 18848)	
With relative	7995 (5693 to 10332)	
Warden housing	22445 (16967 to 28088)	
Care home	5878 (4206 to 7530)	
Other	7893 (3704 to 12710)	
Lived alone		0.007
Yes	20611 (17092 to 24512)	
No	14592 (12883 to 16619)	
Marital status		0.003
Married	13936 (12330 to 15786)	
Widow	18446 (15545 to 21674)	
Single	31891 (18464 to 46747)	
Separated	13406 (8554 to 18161)	
Partnered	16810 (7508 to 20587)	
Age left education		0.965
<18 years	16824 (15176 to 18587)	
≥18 years	15364 (11548 to 19515)	
Socioeconomic		0.863
I	18045 (12022 to 23968)	
II	14890 (11984 to 17781)	
III-N	16800 (12357 to 22104)	
III-M	17155 (13636 to 21277)	
IV	17184 (13845 to 21133)	
V	16159 (13200 to 18992)	
Employment status		<0.001
Full-time	10358 (7501 to 12670)	
Part-time	19132 (9264 to 30176)	
Home carer	14941 (7249 to 22007)	
Unemployed	12506 (5283 to 20195)	
Cannot work	16256 (7823 to 21350)	
Retired	16531 (14881 to 18383)	
Deprivation-quintile		0.507
1 – Most deprived	16462 (7905 to 27063)	
2	17466 (8813 to 31143)	
3	15547 (13061 to 18203)	
4	17285 (14066 to 20989)	
5 – Least deprived	14170 (12481 to 15989)	