WHAT ARE THE OPTIMAL TREATMENT STRATEGIES IN PEOPLE OF INCREASED STROKE RISK DUE TO CAROTID STENOSIS: USING CLINICAL TRIAL AND EXTERNAL DATA TO EVALUATE LONG-TERM BENEFITS AND COST-EFFECTIVENESS?

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A THESIS SUBMITTED FOR THE DEGREE OF

Doctor of Philosophy

MICHAELMAS 2018

Acknowledgements

First and foremost, I would like to extend my deepest gratitude to my primary supervisor Associate Prof. Borislava Mihaylova for going over and beyond her call of duty in continuously supporting and guiding me throughout the course of my DPhil. I am eternally grateful for the time she has dedicated towards me, the knowledge she has shared with me, and for consistently pushing me to achieve high standards in my research. I would also like to thank my other supervisors Prof. Alastair Gray, Prof. Alison Halliday and Dr. Richard Bulbulia for making time to meet and advise me despite their numerous commitments, and providing valuable feedback and guidance.

A special mention to my college, St Edmund Hall and its students and staff. As an international student coming to the UK, it provided me with a second home, a second family and memories to last a lifetime, in the midst of my DPhil.

If not for the financial support I received via the Nuffield Department of Population Health (NDPH) studentship, this thesis would not have been a possibility. I feel blessed to have had the chance to pursue my DPhil under such fortunate circumstances.

There are many others to whom I would like to extend my thanks for helping me throughout the past four years. In particular Dr. Dylan Morris for his expertise on treatment methods for carotid stenosis and related randomised control trials, Dr. Djurre de Waard for being the second reviewer of the systematic review performed in chapter 4, Elinor from the NDPH admin team, the Health Economics Research Centre (HERC) admin team of Barbara, Luke

and Mandy for their continuous support, and all my other colleagues at HERC for facilitating such an enjoyable and supportive working atmosphere.

I would also like to thank the countless number of lifelong friends I have made during my time at Oxford. Their continuous support and company has helped me get through many highs and lows during the course of my DPhil. I've always felt that Oxford was more than just a degree, it was an experience. An experience not just defined by the history, traditions, and aura of it, but to a much larger extent by the people from around the world that Oxford brings together.

And finally and most importantly I would like to thank my parents Ruwan and Taranga Lokuge for their selfless love and care, for giving me the independence to make my own decisions in life from the very beginning, for being the two people I can always count on when the chips are down, and for the sacrifices they have made to bringing me to where I am today. No words will suffice to explain how grateful I am to them. If not for their continuous support, none of this would have been possible.

Publications and Presentations

Publications related to DPhil:

- Lokuge K. et al *Meta-analysis of the procedural risks of carotid endarterectomy and carotid artery stenting over time*. The British Journal of Surgery. 2018;105(1):26-36.

Other publications:

- Clayton GL. et al *The INVEST project: investigating the use of evidence synthesis in the design and analysis of clinical trials*, Trials, 2017 May 15; Vol. 18(1):P219.

Conference abstracts:

- Lokuge K. et al *Systematic review of randomised and observational evidence of effects of treatments of carotid stenosis to prevent stroke.* Trials. 2015; Vol. 16(Suppl 2): P164.
- Lokuge K. et al *Procedural risks of carotid endarterectomy and carotid artery stenting have improved since 2005: Results from a systematic review of observational studies.* International Journal of Stroke 2016, Vol. 11(4S) S6–S63

Poster presentations:

- International Clinical Trials and Methodology Conference, Glasgow, 2015
- UK Stroke Forum, Liverpool, 2016
- NDPH DPhil student's poster competition – 2015, 2016
- Nuffield Department of Population Health (NDPH) Symposium – 2016, 2017

Seminar presentations:

- July 2018: **Health Economics Research Centre internal seminar series**, Oxford "*Cost-effectiveness analysis of treatments methods for carotid stenosis in patients with symptomatic and asymptomatic carotid stenosis*".
- June 2018: **Carotid research fellows group**, Oxford "*Cost-effectiveness analysis of treatments methods for carotid stenosis in patients with symptomatic and asymptomatic carotid stenosis*".
- May 2016: **Carotid research fellows group**, Oxford "*Procedural effects of treatment methods for carotid stenosis in observational studies: a comparison over time and geographic regions*".
- February 2016: **Carotid research fellows group**, Oxford "*Procedural and long-term effects of treatment methods for carotid stenosis: a systematic review of randomised and observational evidence*".

Abstract

Introduction: Stroke, a major cause of disability and death worldwide, can be caused by carotid artery stenosis. Detection and treatment of carotid stenosis has substantial health and economic impact worldwide. It is therefore important to evaluate the long-term effects and cost-effectiveness of treatment methods for carotid stenosis, namely medical therapy (MT), carotid endarterectomy (CEA) in addition to MT, and carotid artery stenting (CAS) in addition to MT.

Methods: The literature was systematically reviewed for economic evaluations comparing treatment methods for carotid stenosis, to summarise current evidence and identify limitations of available economic evaluations. Randomised Controlled Trials (RCTs) and large observational cohort studies were systematically reviewed to summarise information on the clinical effectiveness of treatment methods. Information from this evidence was then combined with information from the literature on quality of life and healthcare costs relevant to carotid stenosis patients, to inform a new decision analytical model, evaluating the cost-effectiveness of all available treatment methods for carotid stenosis patients in the UK.

Results: There was a clear need in the literature for an economic evaluation comparing all available treatment methods for carotid stenosis in a single framework. Other limitations were identified relating to model structure, input parameters used, and reporting of results. Results synthesised from RCTs show that CEA has lower procedural stroke/death risks and lower overall stroke risks when compared to CAS, with differences mostly attributable to the larger number of minor strokes following CAS. When compared to MT alone, CEA reduced

the risk of the combined endpoint of any stroke or procedural death. Observational studies showed that procedural stroke/death risks of CEA have decreased overtime, whilst procedural stroke/death risks of CAS patients appear to be stable. Results from the cost-effectiveness framework comparing all treatment methods show that, at willingness to pay for a quality adjusted life year (QALY) of £20,000, CEA in addition to MT is the most cost-effective strategy in patients up to the age of 75 years. MT alone was the most cost-effective option for patients 75 years or older. Treatment decisions based on the cost-effectiveness analysis remained the same when considered by gender or symptomatic status of patients. The value of information analysis indicated that further information about the relative post-procedural stroke risks of CEA plus MT vs MT alone is most valuable to reduce uncertainty in treatment decisions.

Conclusion: The cost-effectiveness framework and evidence developed in this thesis addresses directly the limitations in the literature. It used information about procedural CEA risks in recent observational cohort studies and relative treatment effects from meta-analysis of RCTs, showing that optimal treatment decisions depend on the age of patients, with CEA plus MT being cost-effective in patients up to the age of 75 but MT alone likely to be more cost-effective in older people. These findings should be highly relevant in the development of future treatment guidelines.

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List of Abbreviations

ACAS	Asymptomatic Carotid Atherosclerosis Study
ACST	Asymptomatic Carotid Surgery Trial
ACT	Asymptomatic Carotid Trial
Asymp	Asymptomatic
CAS	Carotid artery stenting
CAVATAS	Carotid and Vertebral Artery Transluminal Angioplasty Study
CEA	Carotid endarterectomy
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence Intervals
CDN$	Canadian Dollars
CNI	Cranial Nerve Injuries
CRD	Center for Reviews and Dissemination
CREST	Carotid Revascularization Endarterectomy versus Stenting Trial
CSTC	Carotid Stenting Trialists' Collaboration
ECST	European Carotid Surgery Trial
EPD	Embolic Protection Devices
EVA-3S	Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis
EVPI	Expected Value of Perfect information
EVPPI	Expected Value of Partial Perfect Information
HRG	Healthcare Resource Group
HRQoL	Health Related Quality of Life
HSE	Health Survey England
HTA	Healthcare Technology appraisal
ICA	Internal Carotid Artery
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental Cost-effectiveness Ratio
ICSS	International Carotid Stenting Study
ICU	Intensive Care Unit
IPD	Individual Participant Data
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat
MeSH	Medical Subject Headings
MI	Myocardial Infarction
MINAP	Myocardial Ischaemia National Audit Project
MT	Medical Therapy
N/A	Not applicable
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NHS	National Health Service

NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OECD	Organisation for Economic Cooperation and Development
OR	Odds Ratio
OxVasc	Oxford vascular study
p.a.	per annum
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity analysis
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCTs	Randomised Controlled Trials
SAPPHIRE	Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy
SE	standard error
SPACE	Stent-Protected Angioplasty versus Carotid Endarterectomy
Swedvasc	Swedish National Registry for Vascular Surgery
Symp	Symptomatic
TIA	Transient Ischemic Attack
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
US$	United States Dollars
VA	Veterans Affair
VOI	Value of information
vs	versus

1

Introduction

1.1 Carotid stenosis and its treatments

Carotid stenosis is defined as narrowing of the carotid artery caused by the build-up of cholesterol, fat and other substances travelling through the bloodstream such as inflammatory cells, cellular waste products, proteins and calcium. Build-ups of these substances inside the carotid artery are commonly referred to as plaque. Pieces of plaque can break off, enter the bloodstream and lodge in smaller intra-cerebral arteries, interrupting the blood flow and thereby resulting in a stroke[1] or a Transient Ischemic Attack (TIA)[2]. Strokes and TIAs can also be caused by the clotting of blood in the carotid artery due to roughened irregular areas inside the carotid artery, a result of plaque deposits, thereby reducing the blood flow to the brain.

Screening for carotid artery stenosis uses an ultrasound imaging technique. There are two main methods commonly used to measure the degree of stenosis in the carotid artery, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method, and the European Carotid Surgery Trial (ECST) method,(1) explained in more detail in **appendix text 1.1.** Patients with evidence of carotid stenosis can be symptomatic, defined as patients having experienced a stroke or TIA within 6 months (e.g. prior to procedure), or asymptomatic (without recent such symptom or without symptom). Asymptomatic patients in the UK are identified if a patient undergoes a test (such as a duplex ultrasound scan, CT scan, etc) irrespective of the reason for test, and the doctor notices that the patient's arteries are narrowed.(2)

[1] Defined as a neurological deficit caused by an interruption of blood flow to the brain, and can result in fatalities

[2] Defined as a temporary (less than 24 hours) neurological dysfunction caused by an interruption of blood flow to the brain

There are three methods of treating carotid stenosis to reduce stroke risk in patients: medical therapy (MT) alone, carotid endarterectomy (CEA) in addition to MT (CEA plus MT), and carotid artery stenting (CAS) in addition to MT (CAS plus MT). However, during a CEA or a CAS procedure the patient may experience a stroke due to pieces of plaque breaking off. In addition, during a CEA or a CAS procedure the patient may also experience a myocardial Infarction (MI) if a piece of plaque breaks off and blocks a smaller artery leading to the heart. Both strokes and MIs can be fatal. These events, if they occur within 30 days of a CEA or CAS procedure, are referred to as procedural risks

Medical Therapy (MT)

MT refers to treatment with a combination of drug therapies usually including antiplatelet, antihypertensive, and lipid-lowering therapies, to reduce the risks of stroke and MI. A breakdown of the types of medical therapies typically used and their purpose is given below.

- Antiplatelet therapy - Used to decrease platelet aggregation.
- Antihypertensive therapy – Used to lower blood pressure.
- Lipid-lowering therapy – Used to reduce low-density lipoprotein cholesterol in the blood.

There has been an increase in the availability and use of lipid lowering therapies after the year 2000 with results from Asymptomatic Carotid stenosis Trial (ACST)-1 reporting that the use of statins among study participants increased from less than 10% in 1993 to more than 80% when trial follow up ended in 2007.(3) Comparatively the prescription of antiplatelet and antihypertensive therapies have remained steady over time, with the majority

of patients in both older trials such as ECST,(4) and newer trials such as Asymptomatic Carotid Trial-1 (ACT-1)(5) often receiving both antiplatelet and antihypertensive therapies.

Carotid endarterectomy (CEA)

CEA is a surgical procedure to remove the plaque in the carotid artery, under local or general anaesthesia. It is carried out by performing an incision on the neck, thus exposing the narrowed internal carotid artery (ICA). The ICA is then opened using either the conventional CEA technique where a longitudinal incision is made (**appendix text 1.2**) or using the eversion technique where an oblique division of the ICA is performed at its origin (**appendix text 1.3**). Prior to opening the artery, the blood flow of the narrowed artery may be re-routed by placing a silicon tube (known as shunting) above and below the area of stenosis, thereby reducing the time the blood flow to the brain is interrupted during CEA (**appendix text 1.4**).

Further procedural risks stemming specifically from undergoing CEA include cranial nerve injuries (i.e. nerves encountered during the CEA process are damaged with injuries to specific nerves resulting in issues such as vocal cord paralysis, swallowing problems,(6) and hematoma) and risks associated with blood thinning medications used during CEA, which can cause bleeding post-procedure due to the blood still being thin, resulting in a blood clot in the surrounding neck tissues and swelling, redness and pain in the surrounding area.

Carotid Artery Stenting (CAS)

CAS is performed by inserting an expandable tubular metal frame known as a stent into the carotid artery. This is done by initially inserting a catheter into a large artery (in most cases this is the femoral artery in the groin) and threading it through other arteries to the carotid artery. A guidewire is then used to convey a device with a balloon and a stent to the narrowed ICA. The balloon may then be placed inside the stent and inflated at the blockage site, thus expanding the stent and pushing it against the artery wall. Afterwards the balloon is deflated and removed, leaving the stent in place. The procedure pushes the plaque against the artery walls, and aims to prevent pieces of plaque from breaking off. Note that some CAS procedures are performed without the use of balloon angioplasty, due to operators using self-expanding stents. Stents used during the CAS procedure can be either open cell, closed cell, or a hybrid of both (**appendix text 1.5**). Operators may also place a protection device above the area in which the stent it placed to stop embolic particles released from causing blockages in smaller arteries in the brain (**appendix text 1.6**).

Further procedural risks, stemming specifically from the CAS procedure, include bleeding at the point of catheter insertion, damage to the blood vessel at the site of catheter insertion and infections. Potential benefits of CAS when compared to CEA include shorter hospital stays, faster recovery periods, minimal scarring and a very low risk of cranial nerve injuries.

Note that patients intervened with either CEA or CAS will continue to be treated with a combination of MT after intervention. To reflect this, the three treatment strategies are referred to as “MT alone”, “CEA plus MT” and “CAS plus MT” in the cost-effectiveness framework in **chapter 5**.

Treatment practise in the UK

The current NICE (National Institute for Health and Care Excellence) guideline states that immediate CEA is recommended for symptomatic patients with a degree of stenosis 50% to 99% (NASCET methods of measurement),(7) while not making recommendations with regard to CEA for asymptomatic patients. CAS could be performed in symptomatic patients if CAS is preferred to CEA in a particular case and patients are advised with respect to that decision,(8) while in asymptomatic patients the evidence on the efficacy of CAS is deemed inadequate to make recommendations.(9) Guideline recommendations do not differ by age or gender of patients. CEA is a more established procedure in the UK, with the first ever recorded case in medical literature performed in 1954 at St Mary's Hospital, London in 1954, and the first RCT comparing CEA vs MT beginning recruitment in 1981.(4) CAS is a newer procedure, with the first RCT comparing CEA vs CAS beginning recruitment in 2001.(10) Recent hospital episode statistics' data from the National Health Service in the England notes 3,800 CEA and 460 CAS procedures performed in 2017/18.(11)

1.2 Justification, aim of research and outline of thesis

Stroke is one of the leading causes of disability(12) and accounts for around a third of all cardiovascular deaths in Europe.(13) It is estimated that stroke costs the UK National Health Service (NHS) and social care services about £1.7 billion a year.(14) Add to that informal care costs; loss in potential income due to individuals in the working population experiencing stroke; and the benefit payments to stroke survivors, and the societal cost of stroke may add up to £9 billion a year in the UK.(15)

Carotid artery stenosis accounts for around 20% of all ischaemic strokes in the UK.(16) Hence, carotid stenosis can have a significant economic impact on a country's healthcare system due to the cost of managing adverse outcomes such as stroke and the costs of the interventions to treat it. Randomised control trials (RCTs) comparing treatment methods for carotid stenosis provide clinicians and policy makers with information about which interventions are most favourable when considering stroke risks of patients and procedural risks of CEA and CAS. However, while results from RCTs remain the gold standard for clinical effectiveness, they do not take into account the cost involved, and the impact that treatments and adverse events have on people's quality of life and post-trial survival.

The costs of managing carotid stenosis patients undergoing treatment may differ from one intervention to another. The initial cost of treatment differs between interventions, whilst costs for the management of patients after intervention may also differ, with randomised evidence showing that rates of adverse events such as strokes post intervention can depend on the type of intervention.(17-19)

In addition to increasing the risk of death, strokes also have an impact on the quality of life (QoL) of patients[3]. Results from the Oxford Vascular study (OxVasc) indicate that the average QoL of patients a year after stroke is 0.70, whereas the average QoL of similar individuals in the absence of stroke is 0.85 (QoL life measured using EQ-5D instrument).(20) The impact stroke has on the QoL of patients in the study differed depending on stroke severity.(20) Results from ICSS have also shown that the QoL of symptomatic patients (those

[3] Measured by quality adjusted life years (QALY), a measurement of disease burden by taking into account both the quality and quantity of life lived. One QALY is equal to a year of perfect health, whereas when an individual's health is less than perfect health, it would equate to a QALY of less than 1.

who have experienced a stroke or TIA up to 6 months prior to randomisation) at baseline was 0.758 in patients randomised to CEA and 0.775 in patients randomised to CAS when measured using the EQ-5D instrument.(21)

These issues concerning effectiveness and cost illustrate the need for formal cost-effectiveness analysis of the treatment methods for carotid stenosis. An economic evaluation via a cost-effectiveness framework allows lifetime costs and health outcomes of alternative treatment methods for a particular disease or disease event to be evaluated. Health outcomes in cost-effectiveness analyses take into account the health related quality of life of patients in addition to life expectancy and allow the calculation of the incremental cost-effectiveness ratio (ICER) or the additional cost per an additional QALY. The ICER of an intervention A compared to an intervention B is calculated by the formulae below where $\boldsymbol{Cost_A}$ refers to the lifetime cost of a patient treated with intervention A, $\boldsymbol{QALYs_A}$ refers to QALYs experienced by a patient treated with intervention A, $\boldsymbol{Cost_B}$ refers to the lifetime cost of a patient treated with intervention B, and $\boldsymbol{QALYs_B}$ refers to QALYs experienced by a patient treated with intervention B. Note that that patients treated with intervention A or B would be reflective of the target patients and have similar risk factors and characteristics ensuring comparability between groups in all other respect besides the respective treatment A or B.

$$\boldsymbol{ICER_{AvsB} = \frac{Cost_A - Cost_B}{QALYs_A - QALYs_B}}$$

Healthcare systems often have an implicit or explicit threshold monetary value (or a range of values) they would be willing or able to pay per an additional QALY, above which interventions are less likely to be recommended. For the NHS this is set at £20,000 by the National Institute for Health and Care Excellence (NICE).(22) Comparing ICERs to a

country's threshold of willingness to pay-per-QALY can help interpret whether the intervention is cost-effective.

Cost-effectiveness frameworks can be extended to include a probabilistic sensitivity analysis accounting for the uncertainty in data and/or model parameters. Results from the probabilistic sensitivity analysis summarise this uncertainty, informing stakeholders about the probability that an intervention is cost-effective (for particular values of the willingness-to-pay per QALY), as well as highlighting what further information is needed to reduce this uncertainty.(23)

Cost-effectiveness analysis plays an important role in the UK at a national policy level, with economic evaluations based on cost-effectiveness frameworks, integrated into the decision making process of NICE.(24) With carotid stenosis being a risk factor of stroke, which has a large financial impact on both the NHS and UK society, as mentioned above, an economic evaluation considering all available treatment methods for carotid stenosis will be important in providing further information for UK policy makers.

In this thesis I aim to identify the optimal treatment methods for carotid stenosis, by evaluating the long-term net benefits and cost-effectiveness of treatment methods for carotid stenosis. The literature is reviewed firstly for current economic evaluations on treatment methods for carotid stenosis, and, secondly, for information on the clinical effectiveness of treatment methods for carotid stenosis. Information from these reviews is combined with external data to develop a modelling framework to evaluate the long-term net benefits and cost-effectiveness of treatment methods for carotid stenosis.

To determine whether the evidence in the literature is sufficient to identify the cost-effective treatment method for carotid stenosis, a systematic review of economic evaluations comparing treatment methods for carotid stenosis was undertaken (**chapter 2**). Input parameters and modelling approaches, health benefits (e.g. QALYs) and lifetime costs of patients undergoing each intervention were summarised. The input parameters and modelling approaches in existing cost-effectiveness evidence were critically appraised to assess whether the data and methods was adequate to inform the cost-effectiveness of treatment methods for carotid stenosis in contemporary clinical practise.

RCTs provide valuable information on comparative clinical effectiveness of treatments, which can inform cost-effectiveness analysis. Participants in RCTs are randomly assigned to treatment arms, resulting in patients in each treatment arm being similar with regard to both observed and unobserved factors that may influence outcomes, hence reducing any potential bias. In comparison, observational studies are likely to have some selection bias associated with the choice of interventions for patients, resulting in differences in risk factors of patients in each intervention arm. This can result in the calculation of comparative effects between treatments being biased. Therefore, evidence from RCTs was systematically reviewed for comparative procedural, post-procedural and overall effects between carotid stenosis interventions, and this information was then synthesised for a number of endpoints using meta-analytical techniques (**chapter 3**). This synthesised information summarises all randomised evidence to-date and informs input parameters for comparative effects between interventions in the new cost-effectiveness framework.

While RCTs remain the gold standard when informing the comparative effects between interventions, absolute stroke risks from RCTs may not be reflective of typical patients and

clinical practise. RCTs employ strict inclusion criteria when recruiting patients, with patients at high risk for one or both interventions or with significant comorbidities sometimes being excluded from trials. Furthermore, most RCTs comparing treatment methods for carotid stenosis finished recruitment before the year 2008, barring the Asymptomatic Carotid Trial-1 (ACT-1) which compared CAS vs CEA in asymptomatic patients, finishing recruitment in 2013.(25) With evidence suggesting that the in-hospital stroke/death risks of both CEA and CAS patients have decreased in recent years,(26) absolute procedural risks from existing published RCTs may not be reflective of contemporary patients and practise. Thus, a systematic review of large observational studies reporting procedural risks of CEA and CAS was carried out (**Chapter 4**), with meta-analytical and meta-regression techniques used to identify how procedural risks of CEA and CAS have changed over time, and to inform the procedural risks of CEA and CAS in contemporary practise.

Information from the systematic reviews of RCTs and observational studies, combined with information from other sources in the literature, was used to develop a new cost-effectiveness model to compare all three treatment methods for carotid stenosis in a single unified framework for the UK, using a probabilistic Markov decision analytical model (**chapter 5**), to address the main research question of this thesis. The projected life years, QALYs and lifetime costs are reported for categories of patients by age, gender and symptomatic status. This new framework was developed to address the limitations in previous cost-effectiveness frameworks identified in **chapter 2**. The model was used to project the quality-of-life adjusted survival and lifetime costs of patients undergoing each of the three treatment methods for carotid stenosis and in turn evaluate the interventions' cost-effectiveness. A value of information analysis was performed to calculate the cost of uncertainty to society

given the uncertainty in model input parameters. In addition, the expected value of partial perfect information was calculated to identify which model input parameters contributed most to decision uncertainty, thus helping identify areas in which future research will be valuable in reducing decision uncertainty.

The final chapter (**chapter 6**) summarises the findings of the thesis, highlighting its contribution to the literature, its value in informing policy decisions, and its recommendations for further research.

The appendix is divided into five sections, one for each of the chapters 1, 2, 3, 4 and 5. These sections contain additional information on the methods used in each of the chapters, along with additional results, which have not been reported in the main body of the thesis.

2

A systematic review and critical appraisal of cost-effectiveness studies comparing treatment methods for carotid stenosis

2.1 Introduction

In the United Kingdom (UK), stroke is estimated to cost the society about £8.9 billion each year.(15) Approximately half of these are direct healthcare costs, 27% informal care costs inclusive of costs of care for patients provided for by family members, friends and professional carers, and 24% indirect costs such as loss of earnings in the working population due to stroke morbidity and mortality.(15) Around 20% of all ischaemic strokes in the UK are caused by carotid stenosis.(16) Carotid stenosis can be treated to reduce the risk of stroke using one of three modalities: medical therapy (MT) (a combination of medical therapies including antihypertensive, antithrombotic and lipid lowering therapies), carotid endarterectomy (CEA) (in addition to MT), and carotid artery stenting (CAS) (in addition to MT). However, costs for interventions, their procedural risks and stroke risks of patients post intervention differ by the method of intervention.

Randomised Control Trials (RCTs) have shown that, compared to patients randomized to MT alone, patients randomized to CEA have lower long-term stroke risks in both symptomatic(18) and asymptomatic(17) patients. Furthermore, compared to symptomatic patients randomized to CAS, symptomatic patients randomized to CEA have lower procedural stroke/death risks and lower overall stroke risks.(19)

However, when developing relevant guidelines and advising healthcare professionals on which interventions to use, both clinicians and policy makers must take into account the economic burden an intervention will pose on the healthcare system in addition to the safety and effectiveness of an intervention, justifying the need for cost-effectiveness analysis. In the cost-effectiveness analyses, costs and health outcomes of alternative treatment methods for a disease are evaluated and incremental costs and benefits (eg: quality adjusted life year

(QALY)) calculated between alternative interventions. This allows calculation of the incremental cost-effectiveness ratio (ICER), the ratio of the incremental costs and the incremental benefits. The ICER allows decision makers to determine whether an intervention is cost-effective, based on the respective cost-effectiveness threshold.

In this chapter, I systematically review the literature on economic evaluation studies reporting cost-effectiveness results for treatment methods for carotid stenosis; summarise their key parameters and cost-effectiveness results, critically appraise the parameters and modelling approaches used, and the totality of available cost-effectiveness evidence to determine if available evidence is sufficient to inform on the cost-effectiveness of treatment methods for carotid stenosis in a contemporary setting.

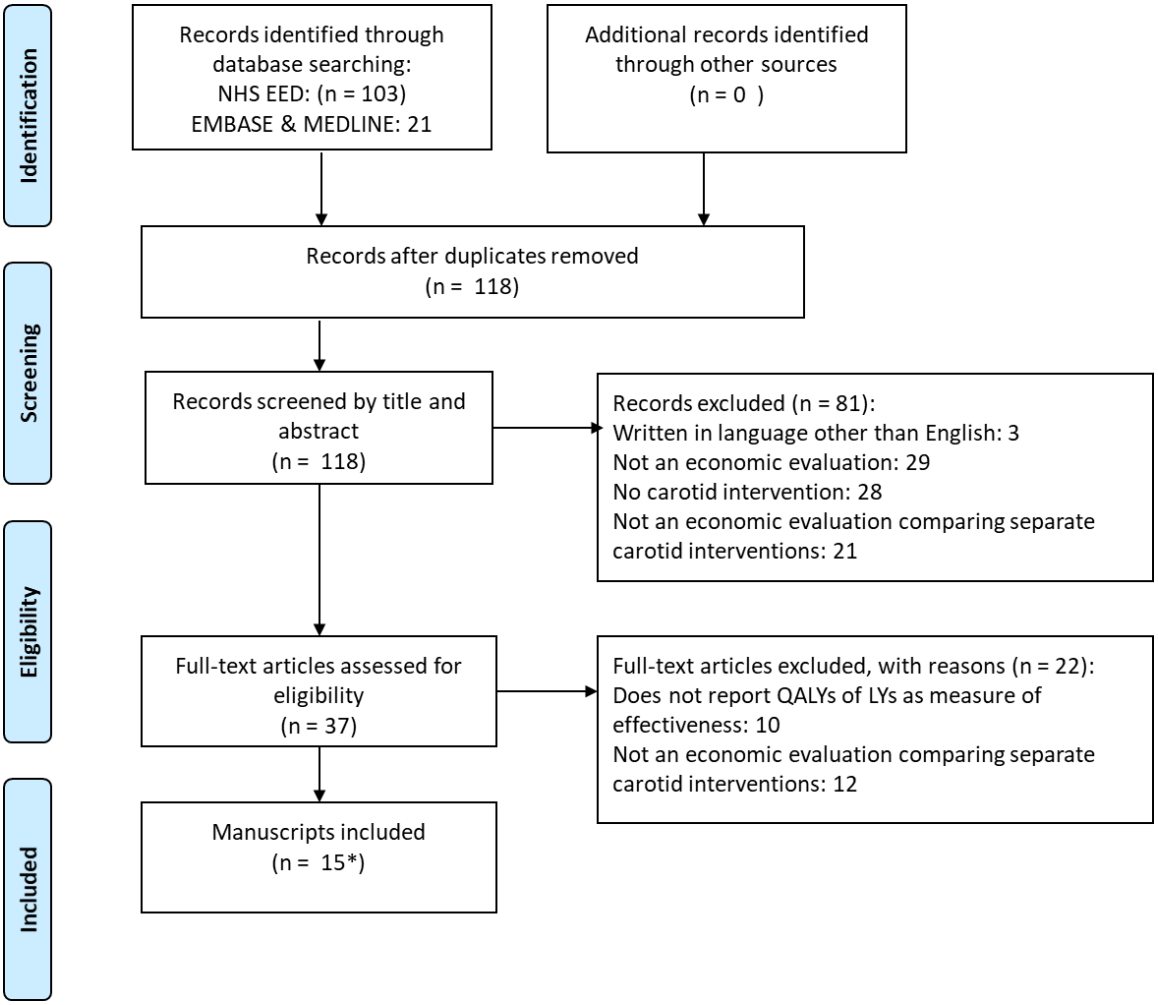
2.2 Methods

Study Selection

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(27), a 27-item checklist and four-phase flow diagram (**figure 2.1**) outlining the minimum set of items for reporting in a systematic review, were followed. The National Health Service Economic Evaluation Database (NHS EED), a database maintained by the Centre for Reviews and Dissemination (CRD), University of York which systematically identified economic evaluations of medical interventions in MEDLINE, Embase, CINAHL, PsycINFO and PubMed(28) from inception of these databases to 31st December 2014, was searched for the duration of its maintenance (from 1994 to December 2014) for cost-effectiveness studies comparing treatment methods for carotid stenosis under the search term

"carotid" in the category "any field". Both bibliographic and full abstract records were searched.

Figure 2.1: PRISMA flow Diagram – Study selection



**One Manuscript, Featherstrone et al(21) was a HTA report of the economic evaluation published in Morris et al(29) and thus was used in data extraction.*

As the NHS EED database was not updated after 31st December 2014, MEDLINE and Embase were also searched from 1st January 2015 to 12th February 2018 for cost-effectiveness studies comparing treatment methods for carotid stenosis using the following search criteria:

((carotid ADJ3 stenosis) OR (carotid ADJ3 artery)) AND ((exp "cost benefit analysis"/), where *"cost-benefit analysis",* the MeSH (Medical Subject Headings) term for economic evaluations, was expanded to include all entry items under it.

Articles were screened by title and abstract, followed by full-text review to identify studies which reported results on the cost-effectiveness of treatment methods for carotid stenosis. Studies which reported stroke risks of patients as the measure of effectiveness but not life years and/or quality adjusted life years as the measure of effectiveness, studies published in a language other than English, studies which did not include a carotid intervention, and studies which compared two variations of the same intervention were excluded.

Reference lists of all selected articles were checked for further relevant studies.

Assessment for reporting bias

All selected studies were assessed for reporting bias using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist for reporting economic evaluations of health interventions.(30) Each assessed item was graded and scored as: reported (score: 1), partially-reported (score: 0.5), not-reported (score: 0).

Data extraction

Characteristics of the economic evaluations including interventions compared, study setting (e.g. healthcare system or region), study time horizon, source data used, type of modelling techniques used, model inputs and model outputs were extracted. When the study setting was not reported, the study setting was determined by sources of input parameters for costs. In the extraction of model inputs, parameter values, data sources and characteristics of data source populations for key model inputs such as procedural and post-procedural risks, health-related quality of life (HRQoL), and costs were extracted. In the extraction of model outputs, incremental costs, incremental benefits, ICERs, and their confidence intervals were extracted. In addition, cost-effectiveness results reported for categories of patients by age, gender and symptomatic status were also extracted.

Reported results for interventions were interpreted as cost-effective or not using willingness to pay per QALY in the study setting location. We used a willingness to pay per QALY of £20,000 - £30,000 for the UK,(31) US$50,000 - US$100,000 for the USA, CDN$ 20,000 – 100,000 for Canada.(32) Sweden did not have a set willingness to pay per QALY threshold based on the national healthcare budget, instead focusing on an individuals' willingness to pay per QALY.(33)

2.3 Results

118 non-duplicate manuscripts were identified from the search strategy outlined above (**figure 2.1**). After reviewing titles and abstracts, 37 manuscripts qualified for full-text review. Of the manuscripts included in the full-text review, 10 were not considered further

due to them not reporting life years or quality adjusted life years as an effectiveness outcome measure, while 12 were excluded due to the economic evaluation not comparing two or more distinct carotid interventions. 15 manuscripts reporting 14 economic evaluations were included in the review, the quality assessment for reporting bias and data extraction. One manuscript, Featherstone et al,(21) was a healthcare technology appraisal (HTA) report from which the economic evaluation in Morris et al(29) originated. The HTA report in this case aided in identifying further key input parameters used in the economic evaluation in Morris at al.(29)

The mean score of economic evaluations when assessed for reporting bias was 20 (range: 15.5 to 24), where the maximum score for an economic evaluation was 24 (**appendix table 2.1**). Economic evaluations scored lowest in the sections for reporting study setting and location (5 out of 14), and for reporting the population and methods used to elicit preferences for outcomes (8.5 out of 14) due to economic evaluations not reporting the methods used to measure the quality of life in different health states.

Heterogeneity was evident between the methodologies used in the 14 economic evaluations, with economic evaluations differing in terms of study setting, interventions compared, time horizon, modelling techniques and symptomatic status of target population (**table 2.1**). Of the 14 economic evaluations, eight had a study setting in the United States, two in the United Kingdom, one in Canada, one in Sweden and one in the Netherlands. In one economic evaluation, (34) the country from which perspective the study was developed was unclear but was assumed to be in Europe by looking at input parameters used for costs. Five economic evaluations studied the cost-effectiveness of CEA vs MT and nine the cost-effectiveness of CAS vs CEA. There were no economic evaluations studying the cost-effectiveness of CAS

vs MT, nor studies comparing all three treatment methods in a single study. Nine of the 14 economic evaluations used Markov state transition decision analytical models with four of these(35-38) having no event, death, major stroke, minor stroke and MI as health states, while the remaining five(39-43) had no event, death, major stroke and minor stroke as health states. Luebke et al(34) used a decision analytical model with two health states: an experience of a fatal/disabling stroke and without an experience of a fatal/disabling stroke. In the remaining four economic evaluations(29, 44-46), Morris et al(29) compared the mean costs and quality adjusted life years (QALYs) of patients treated with CEA versus CAS in the International Carotid Stenting Study (ICSS) at 5-year follow-up, Khan et al(44) compared the mean costs and QALYs of patients treated with CEA versus CAS in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) at 4-year follow-up, and Maud et al(46) compared the mean costs and QALYs of patients treated with CEA versus CAS in the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial at 1-year follow-up. Mahoney et al(45) projected the life expectancy of patients in various health states at 1-year follow-up in SAPPHIRE to obtain lifetime costs and QALYs for patients treated with CEA versus CAS.

Table 2.1: Summary of characteristics of cost-effectiveness studies of interventions for carotid stenosis

Study	Target population & subgroups	Setting and location	Comparators	Currency& Price date	Discount rate	Time horizon	Health outcomes	Key study analytical method
Henriksson M. (2008)(40)	Asymptomatic patients Base case: 65-75 year old males and females	Sweden	CEA vs MT	2006 Euros 1 Euro = 9.5 Swedish Kronor	3%	Lifetime	QALYs and lifetime costs	Markov state transition model: 30 days then annual cycles Markov states: No event, Disabling stroke, non-disabling stroke, death
Patel S. (1999)(41)	Base case: 66 year old symptomatic patients (50% to 69%)	NOT REPORTED Assumed as United States from inputs for costs	CEA vs MT	1997 US Dollars	3%	NOT REPORTED Assumed as lifetime due to reporting of lifetime costs	QALYs and lifetime costs	Markov state transition model: 30 days then annual cycles Markov states: Perfect Health, Minor Stroke, Major Stroke, Death
Cronenwett J. (1997)(39)	Base case: 67 year old asymptomatic patients (>=60%); 66% Male	NOT REPORTED Assumed as United States from inputs for costs	CEA vs MT	1996 US Dollars	5%	NOT REPORTED Assumed as lifetime due to reporting of lifetime costs	QALYs and lifetime costs	Markov state transition model: 30 days then annual cycles Markov states: Well post CEA, Major stroke post CEA,
Thapar A. (2013)(42)	68 year old asymptomatic patients	United Kingdom	CEA vs MT	Jan 2010 UK GBP	3.5%	Lifetime	QALYs and lifetime costs	Markov state transition model: 30 days then annual cycles Markov states: No event, Disabling stroke, non-disabling stroke, death
Young K. (2010)(38)	Symptomatic patients Base case: 70 year olds	NOT REPORTED Assumed as United States from inputs for costs	CAS vs CEA	2007 US Dollars	3%	Lifetime	QALYs and lifetime costs	Markov state transition model: 30 days then annual cycles Markov states: No event, Major stroke, Minor stroke, MI and Death

Study	Target population & subgroups	Setting and location	Comparators	Currency& Price date	Discount rate	Time horizon	Health outcomes	Key study analytical method
Almekhlafi M. (2014)(35)	65 year old symptomatic patients	Canada	CAS vs CEA	2012 Canadian dollars	5%	Lifetime	QALYs and lifetime costs	Markov state transition model: 30 days then annual cycles Markov states: No event, Major stroke, Minor stroke, MI and Death
Kilaru M. (2003)(36)	70 year old symptomatic (>70%) & asymptomatic (>80%) patients	NOT REPORTED Assumed as United States from inputs for costs	CAS vs CEA	1997 US dollars	3%	NOT REPORTED Assumed as lifetime due to reporting of lifetime costs	QALYs and lifetime costs	Markov state transition model: 30 days then annual cycles Markov states: No event, Major stroke, Minor stroke, MI and Death
Morris S. (2016)(29)	Symptomatic patients (>=50%) from ICSS	United Kingdom	CAS vs CEA	Calculated in 2013/14 GBP; Presented in 2013/14 USD	3.5%	5 years	QALYs and mean costs	Single study based evaluation: Comparing mean costs and QALYs at 5 years in ICSS
Mahoney E. (2011)(45)	Symptomatic & Asymptomatic patients from SAPPHIRE (Mean age:72 years)	NOT REPORTED Assumed as United States from inputs for costs	CAS vs CEA	2002 US dollars	3%	Lifetime	QALYs and mean costs	Single study based evaluation: Using SAPPHIRE results at 1 year, and projecting life expectancy (see study parameters section). Account for repeated vascularization (both CEA and CAS)
Khan A. (2012)(44)	Symptomatic and asymptomatic patients from CREST (mean age: 69.1 years).	NOT REPORTED Assumed as United States from inputs for costs	CAS vs CEA	2010 US dollars	NR	4 years	QALYs and mean costs	Single study based evaluation: The mean costs and QALYs at 4 years were evaluated to calculate cost-effectiveness
Luebke T. (2016)(34)	Asymptomatic patients Base-case: 65 to 75 year-olds	NOT REPORTED Assumed as Europe based on sources in	CEA vs MT	2012 Euros	3%	5 years	QALYs and 5 year costs	Observational decision analytical model with patients having either a fatal/disabling stroke or surviving.

Study	Target population & subgroups	Setting and location	Comparators	Currency& Price date	Discount rate	Time horizon	Health outcomes	Key study analytical method
		literature review						
Maud A. (2010)(46)	Symptomatic and Asymptomatic patients from SAPPHIRE (mean age: 72)	NOT REPORTED Assumed as United States from inputs for costs	CAS vs CEA	2006 US dollars	NR	1 year	QALYs and mean costs	Mean costs and QALYs in CEA and CAS arm of SAPPHIRE trial were estimated using clinical information from SAPPHIRE and cost and QALY information from other sources
Vilain K. (2012)(37)	Symptomatic and asymptomatic patients from CREST (mean age: 69.1 years).	USA	CAS vs CEA	2008 US dollars	3%	10 years	QALYs and 10 year costs	A Markov chain transition model with model inputs from CREST at 1 year, projected to 10 years
Janssen M. (2008)(43)	Symptomatic patients	Netherlands	CAS vs CEA	2003 Euros	4%	Not reported	QALYs and costs	A Markov model with healthy (symptomatic), major stroke, minor stroke and death as health states

CEA: Carotid Endarterectomy; CAS: Carotid Artery Stenting; MT: Medical Therapy; QALY: Quality adjusted life year

Procedural event risks of CEA and CAS

Four economic evaluations, studying the cost-effectiveness of CEA vs MT in **asymptomatic** patients, sourced the procedural risks of CEA from RCTs and observational cohort studies with recruitment periods in the period 1988 - 2003 (**table 2.2**). Henriksson et al(40) employed a CEA procedural stroke risk of 1.2% in men and 3.4% in women as informed by the Swedvasc registry data;(47) Cronenwett et al(39) used a CEA procedural stroke/death risk of 2.3% from the ACAS study,(48) and Thapar et al(42) used information from ACST-1 to inform CEA procedural stroke/death risks which was 2.9% as reported in the 10 years results(3) (**figure 2.2**). Luebke et al(34) used a CEA procedural fatal/ disabling stroke risk of 1.42% based on a review of the literature (exact source unclear).

Of the five economic evaluations on **symptomatic** patients (one CEA vs MT; four CAS vs CEA), procedural stroke risks of CEA ranged from 2.8% to 5.4% and procedural stroke risks of CAS from 3.96% to 7.02% (**table 2.2; figure 2.2**). Janssen et al(43) did not report the procedural risks used for CEA patients. Procedural risks of CEA in Patel et al(41) was sourced from the North American Symptomatic Carotid Endarterectomy Trial (NASCET), in Morris et al(29) from ICSS, and in Janssen et al(43) from the European Carotid Surgery Trial (ECST). Procedural risks of CAS in Morris et al(29) was informed from ICSS, and in Janssen et al(43) from the Global CAS registry.(49) Almekhlafi et al(35) and Young et al(38) sourced procedural risks of CEA and CAS from a meta-analysis of 12(50) and five RCTs respectively,(51) and did not differentiate procedural risks by symptomatic status, with procedural risks from a population of both symptomatic and asymptomatic patients used in an economic evaluation targeted at symptomatic patients. The recruitment periods in RCTs and observational studies from which procedural risks in economic evaluations on

symptomatic patients were sourced ranged from 1987 to 2008, with the most recent source, ICSS (study recruitment period 2001 – 2008) used in Morris et al.(29)

Five economic evaluations studied the cost-effectiveness of CAS vs CEA in a **mixed symptom** population with procedural stroke risks of CEA ranging from 0.9% to 3.1% and of CAS from 2.3% to 5% (**table 2.2; figure 2.2**). Mahoney et al(45) and Maud et al(46) sourced procedural risks of CEA and CAS from SAPPHIRE,(10) Khan et al(44) and Vilain et al(37) from CREST. Kilaru et al(36) sourced procedural CEA risks from an observational cohort study in the New Presbyterian Hospital while procedural risks of CAS were obtained by averaging across four non-randomised prospective studies(52-55) and one retrospective study.(56) Study recruitment periods ranged from 1997 to 2008 (**table 2.2**), the most recent being CREST (study recruitment period: 2000 – 2008). Vilain et al(37) differentiated procedural risks by symptomatic status, reporting results in their sub-group analysis while three economic evaluations did not differentiate procedural risks by symptomatic status, only reporting outcomes for a mixed symptom population.

Table 2.2: Summary of data on procedural risks of CEA and CAS used in economic evaluations

Economic Evaluation	Symptomatic status of study population in Economic Evaluation	CEA				CAS				Relative risks CAS vs CEA
		Procedural risks	Data Source	Study recruitment period	Different risk by symp status?	Procedural risks	Data Source	Study recruitment period	Different risk by symp status?	
Henriksson M. (2008)(40)	Asymptomatic	Stroke Men: 0.012 Women: 0.034	SWEDVASC	1994 - 2003	YES	N/A				N/A
Cronenwett J. (1997)(39)	Asymptomatic	Stroke/Death: 0.023	ACAS	1988 - 1993	YES	N/A				N/A
Thapar A. (2013)(42)	Asymptomatic	Stroke/Death: 0.029	ACST-1	1993 - 2003	YES	N/A				N/A
Luebke T. (2016)(34)	Asymptomatic	Disabling stroke/death: 0.0142	Unclear	Unclear	Unclear	N/A				N/A
Patel S. (1999)(41)	Symptomatic	Stroke: 0.054	NASCET	1987 -	YES	N/A				N/A
Morris S. (2016)(29)	Symptomatic	Stroke: 0.033[1]	ICSS	2001 - 2008	YES	Stroke: 0.07[1]	ICSS	2001 - 2008	YES	2.13[1]
Young K. (2010)(38)	Symptomatic	Stroke: 0.0468	Meta-analysis of Wallstent, Kentucky, SAPPHIRE, SPACE, EVA-3S(51)	2000 - 2006	NO	Stroke: 0.0702	Meta-analysis of Wallstent, Kentucky, SAPPHIRE, SPACE, EVA-3S(51)	2000 - 2006	NO	1.5

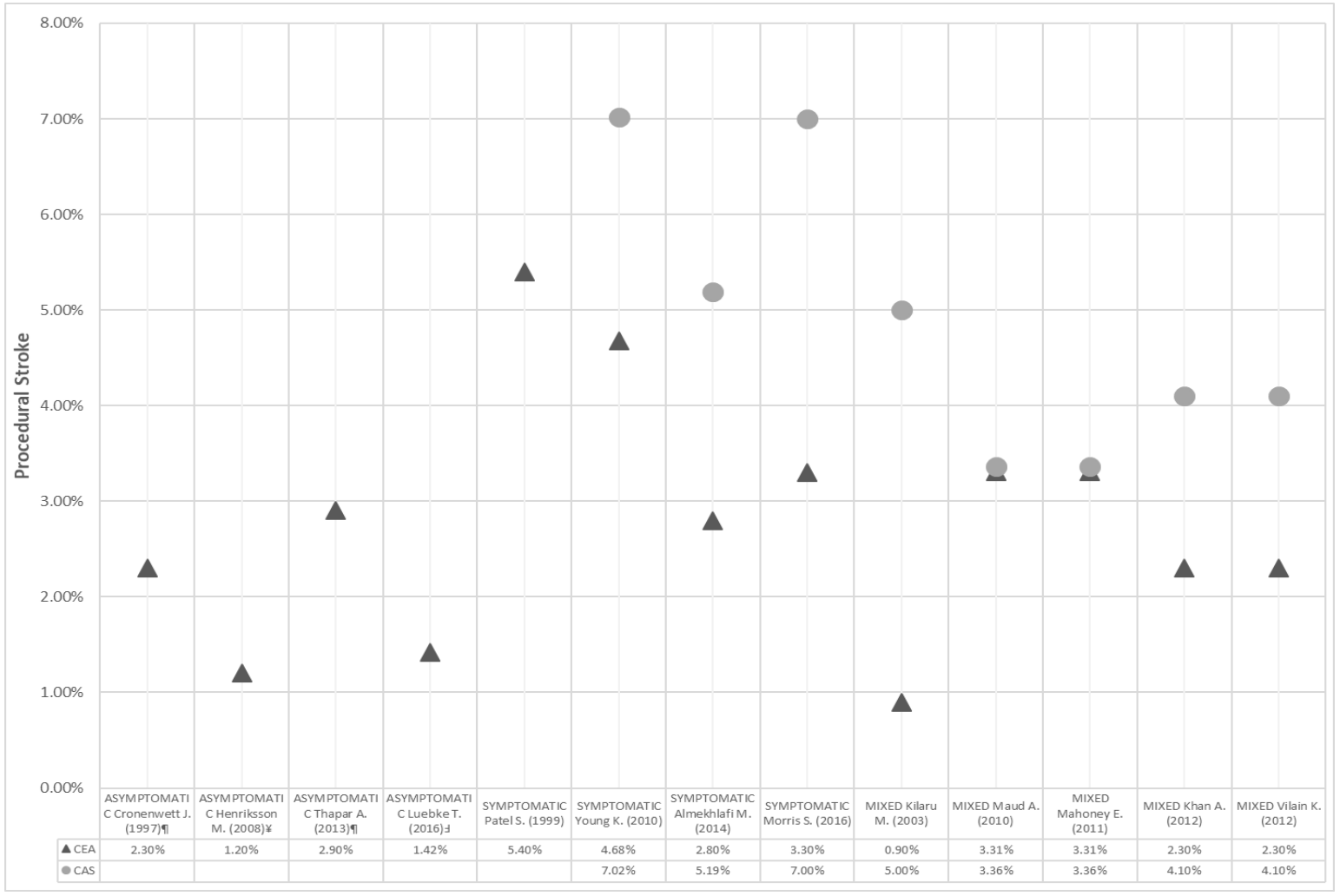
Economic Evaluation	Symptomatic status of study population in Economic Evaluation	CEA				CAS				Relative risks CAS vs CEA
		Procedural risks	Data Source	Study recruitment period	Different risk by symp status?	Procedural risks	Data Source	Study recruitment period	Different risk by symp status?	
Almekhlafi M. (2014)(35)	Symptomatic	Stoke: 0.028	Published Meta-analysis of 12 RCTs(50)	Unclear - 2008	NO	Stroke: 0.0519	Published Meta-analysis of 12 RCTs	Unclear - 2008	NO	1.85
Janssen M. (2008)(43)	Symptomatic	Not reported	ECST	1981 – 1994	YES	Not reported	Global CAS Registry	1997 - 2002	Not reported	N/A since 2 different sources used for procedural risks of CEA and CAS
Kilaru M. (2003)(36)	Symptomatic & Asymptomatic	Stroke: 0.009	New York Presbyterian Hospital	1997 – 2001	NO	Stroke: 0.05	Averaged across 4 non randomised studies	1998 - 1999	NO	N/A since 2 different sources used for procedural risks of CEA and CAS
Mahoney E. (2011)(45)	Symptomatic & Asymptomatic	Stroke: 0.031[2]	SAPPHIRE	2000 - 2002	Not clear	Stroke: 0.036[2]	SAPPHIRE	2000 - 2002	Not clear	1.16¥
Khan A. (2012)(44)	Symptomatic & Asymptomatic	Stroke: 0.023[3]	CREST 4 year follow-up	2000 - 2008	NO	Stroke: 0.041[3]	CREST 4 year follow-up	2000 - 2008	NO	1.79[3]
Maud A. (2010)(46)	Symptomatic & Asymptomatic	Stroke: 0.031[2]	SAPPHIRE	2000 - 2002	NO	Stroke: 0.036[2]	SAPPHIRE	2000 - 2002	NO	1.16¥

Economic Evaluation	Symptomatic status of study population in Economic Evaluation	CEA				CAS				Relative risks CAS vs CEA
		Procedural risks	Data Source	Study recruitment period	Different risk by symp status?	Procedural risks	Data Source	Study recruitment period	Different risk by symp status?	
Vilain K. (2012)(37)	Symptomatic & Asymptomatic	Stroke: Mixed: 0.023[3] Symp: 0.032[4] Asymp: 0.014[4]	CREST 1 year follow-up	2000 - 2008	YES	Stroke: Mixed: 0.041[2] Symp: 0.055[4] Asymp: 0.025[4]	CREST 1 year follow-up	2000 - 2008	YES	Mixed Symp: 1.74[4] Asymp: 1.88[4]

CEA: Carotid Endarterectomy; CAS: Carotid Artery Stenting; N/A: not applicable; Symp: symptomatic; Asymp: Asymptomatic

[1]Source from related HTA(21); [2]Procedural risks not reported in economic evaluation, and thus sourced from of SAPPHIRE(10); [3]Procedural risks not reported in economic evaluation, and thus sourced from publication of CREST(57); [4]Procedural risks not reported in economic evaluation, and thus sourced from publication of CREST(58); ¥Relative risks calculated using procedural risks reported for each treatment arm, since relative risks were not reported

Figure 2.2: Procedural stroke risk in economic evaluations



Note: Studies within categories ordered by date of publication. ¥Only Men; ¶Procedural Stroke/Death; ǂProcedural Disabling stroke/death

Relative risks of procedural events of CAS vs CEA

Almekhlafi et al(35) used relative risks of 1.85 for CAS vs CEA from a meta-analysis of 12 RCTs to calculate procedural risks of CAS.(50) Six economic evaluations(29, 37, 38, 44-46) studying the cost-effectiveness of CAS vs CEA used information from the same RCTs to inform the procedural risks of both CEA and CAS, thereby incorporating the relative risks between treatment arms from the respective RCTs. Morris et al(29) had a relative procedural stroke risk from CAS vs CEA of 2.13 from ICSS, Khan et al(44) and Vilain et al(37) 1.79 from CREST,(57) Young et al 1.5(38) from a meta-analysis(51) of Wallstent, Kentucky, SAPPHIRE, Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) and Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trials, Mahoney et al(45) and Maud et al(46) 1.16 from SAPPHIRE.(10) Two economic evaluations(36, 43) sourced procedural risks of CEA and CAS from different RCTs or observational studies.

Post-procedural/ long-term stroke risks

Post-procedural stroke risks in three economic evaluations comparing CEA vs MT(39, 40, 42) in **asymptomatic** patients were sourced from ACAS (study recruitment period: 1988 – 1993) and ACST-1 (study recruitment period 1994 – 2003), with none of the three economic evaluations differentiating differences in long-term stroke risks of CEA vs MT by stroke severity (**table 2.3; figure 2.3**). Luebke et al(34) sourced post-procedural risks from a review of the current literature (exact source unclear). Only Cronenwett et al(39) used increased non-stroke related mortality risks in asymptomatic carotid stenosis patients when compared to the general population, adding a rate of 0.5% to age and sex specific mortality rates in the UK.

All economic evaluations of **symptomatic** patients sourced post-procedural stroke risks from RCTs with recruitment periods from 1981 to 2008 (**table 2.3; figure 2.3**). As with procedural risks, Almekhlafi et al(35) and Young et al(38) did not differentiate post-procedural risks by symptomatic status. Young et al(38) did not account for differences of post-procedural stroke risks between treatment methods by stroke severity. Patel et al(41) accounted for increased non-stroke related mortality risks by assuming a mortality risk of 7.7% in major stroke survivors and 6.3% in symptomatic patients. Morris et al,(29) Almekhlafi et al,(35) and Young et al(38) obtained post-procedural mortality risks from RCTs whose patient populations had symptomatic carotid stenosis, thus accounting for increased non-stroke related mortality risks in patients who had experienced stroke.

Post-procedural stroke risks in economic evaluations of CAS vs CEA in **mixed symptom** populations were sourced from RCTs with recruitment periods between 2000 and 2008, with the exception of Kilaru et al(36) who did not report the source of post-procedural stroke risks (**table 2.3; figure 2.3**). Vilain et al,(37) Khan et al,(44) Mahoney et al(45) and Maud et al(46) sourced post-procedural mortality risks from RCTs and thus it was assumed that they accounted for increased non-stroke mortality risks in patients who have experienced stroke. Khan et al(44) and Maud et al(46) did not differentiate post-procedural stroke risks by symptomatic status.

Table 2.3: Summary of data on post-procedural/long-term stroke risks used in economic evaluations

Economic Evaluation	Symp status of study population	Stroke risks defined as	MT		CEA		CAS		Relative risks¥	Stratified by Symp status	Account for stroke severity	Accounts for non-stroke related mortality	Accounts for increased mortality risks
			Parameter Values	Data Source & Study recruitment period	Parameter Values	Data Source & Study recruitment period	Parameter Values	Data Source & Study recruitment period					
Henriksson M. (2008)(40)	Asymp	Annual (excluding procedural events)	Stroke: Men: 0.0281 Women: 0.0168	ACST-1 1994 - 2003	RR: 0.345	ACST-1 1994 - 2003	N/A		CEA vs MT: 0.345	YES	NO	YES	NO
Cronenwett J. (1997)(39)	Asymp	Annual (excluding procedural events)	Ipsilateral Stroke: 0.023	ACAS 1988 - 1993	Ipsilateral Stroke: 0.006	ACAS 1988 - 1993	N/A		CEA vs MT: 0.261	YES	NO	YES	YES
Thapar A. (2013)(42)	Asymp	Annual (excluding procedural events)	Stroke/Death: 0-5 years: 0.021; 0-10 years: 0.016	ACST-1 1994 - 2003	Stroke/Death: 0-5 years: 0.009; 0-10 years: 0.014	ACST-1 1994 - 2003	N/A		CEA vs MT: 0-5: 0.429 5-10: 0.875	YES	NO	YES	NO
Luebke T. (2016)(34)	Asymp	Annual	0.012	Unclear	Disabling/ fatal stroke: 0.004	Unclear	N/A		Unclear	Unclear	YES	YES	Unclear
Patel S. (1999)(41)	Symp	Annual (excluding procedural events)	Year 3 onwards*: Minor Stroke (0.021), Major	NASCET 1987 -	Year 3 onwards*: Minor Stroke (0.016), Major Stroke (0.004)	NASCET 1987 -	N/A		CEA vs MT: 0.067	YES	YES	YES	YES

Economic Evaluation	Symp status of study population	Stroke risks defined as	MT		CEA		CAS		Relative risks¥	Stratified by Symp status	Account for stroke severity	Accounts for non-stroke related mortality	Accounts for increased mortality risks
			Parameter Values	Data Source & Study recruitment period	Parameter Values	Data Source & Study recruitment period	Parameter Values	Data Source & Study recruitment period					
			Stroke (0.009)										
Morris S. (2016)(29)	Symp	Cumulative 5-year stroke risks			5-year stroke: 0.058¶	ICSS 2001 - 2008	5-year stroke: 0.089¶	ICSS 2001 - 2008	CAS vs CEA: 1.53¶	YES	YES	YES	YES
Young K. (2010)(38)	Symp	Annual (excluding procedural events)	N/A		Stroke: 0.0210	2-year SPACE, 3-year SAPPHIRE, and 4-year EVA-3S results 2000 - 2006	Stroke: 0.04	2-year SPACE, 3-year SAPPHIRE, and 4-year EVA-3S results 2000 - 2006	CAS vs CEA: 1.905	NO	NO	YES	YES
Almekhlafi M. (2014)(35)	Symp	Annual (excluding procedural events)	N/A		Minor Stroke: 0.0515 Major Stroke: 0.013	Published Meta-analysis of 12 RCTs(50)	Minor stroke: 0.067 Major stroke: 0.0143	Published Meta-analysis of 12 RCTs(50)	CAS vs CEA: 1.26	NO	YES	YES	YES

Economic Evaluation	Symp status of study population	Stroke risks defined as	MT		CEA		CAS		Relative risks¥	Stratified by Symp status	Account for stroke severity	Accounts for non-stroke related mortality	Accounts for increased mortality risks
			Parameter Values	Data Source & Study recruitment period	Parameter Values	Data Source & Study recruitment period	Parameter Values	Data Source & Study recruitment period					
Janssen M. (2008)(43)	Symp	Annual (excluding procedural events)	N/A		Minor Stroke: 0.0066 Major Stroke: 0.0043	ECST 1981 - 1994	Not reported		Not reported	YES	YES	NO	NO
Kilaru M. (2003)(36)	Symp & Asymp	N/A	N/A		Not reported		Not reported		Not reported				
Mahoney E. (2011)(45)	Symp & Asymp	One-year stroke risks	N/A		Minor Stroke: 0.033 Major Stroke: 0.04	SAPPHIRE 2000 - 2002	Minor Stroke: 0.05 Major Stroke: 0.006	SAPPHIRE 2000 - 2002	CAS vs CEA: 0.767	YES	YES	YES	YES
Khan A. (2012)(44)	Symp & Asymp	Cumulative 4-year stroke risks	N/A		Stroke: 0.086	CREST 4-year follow-up 2000 - 2008	Stroke: 0.108	CREST 4-year follow-up 2000 - 2008	CAS vs CEA: 1.26	NO	Unclear	YES	YES

Economic Evaluation	Symp status of study population	Stroke risks defined as	MT		CEA		CAS		Relative risks¥	Stratified by Symp status	Account for stroke severity	Accounts for non-stroke related mortality	Accounts for increased mortality risks
			Parameter Values	Data Source & Study recruitment period	Parameter Values	Data Source & Study recruitment period	Parameter Values	Data Source & Study recruitment period					
Maud A. (2010)(46)	Symp & Asymp	One-year stroke risks	N/A		Major Stroke†: 0.04 Minor Stroke†: 0.02	SAPPHIRE 2000 - 2002	Major Stroke†: 0.01 Minor Stroke†: 0.04	SAPPHIRE 2000 - 2002	CAS vs CEA: 0.976	NO	YES	YES	YES
Vilain K. (2012)(37)	Symp & Asymp	One-year stroke risks	N/A		Major Stroke: 0.015 Minor Stroke: 0.006	CREST 1-year follow-up 2000 - 2008	Major Stroke: 0.016 Minor Stroke: 0.014	CREST 1-year follow-up 2000 - 2008	CAS vs CEA: 1.43	YES	YES	YES	YES

CEA: Carotid Endarterectomy; CAS: Carotid Artery Stenting; MT: Medical Therapy; N/A: not available

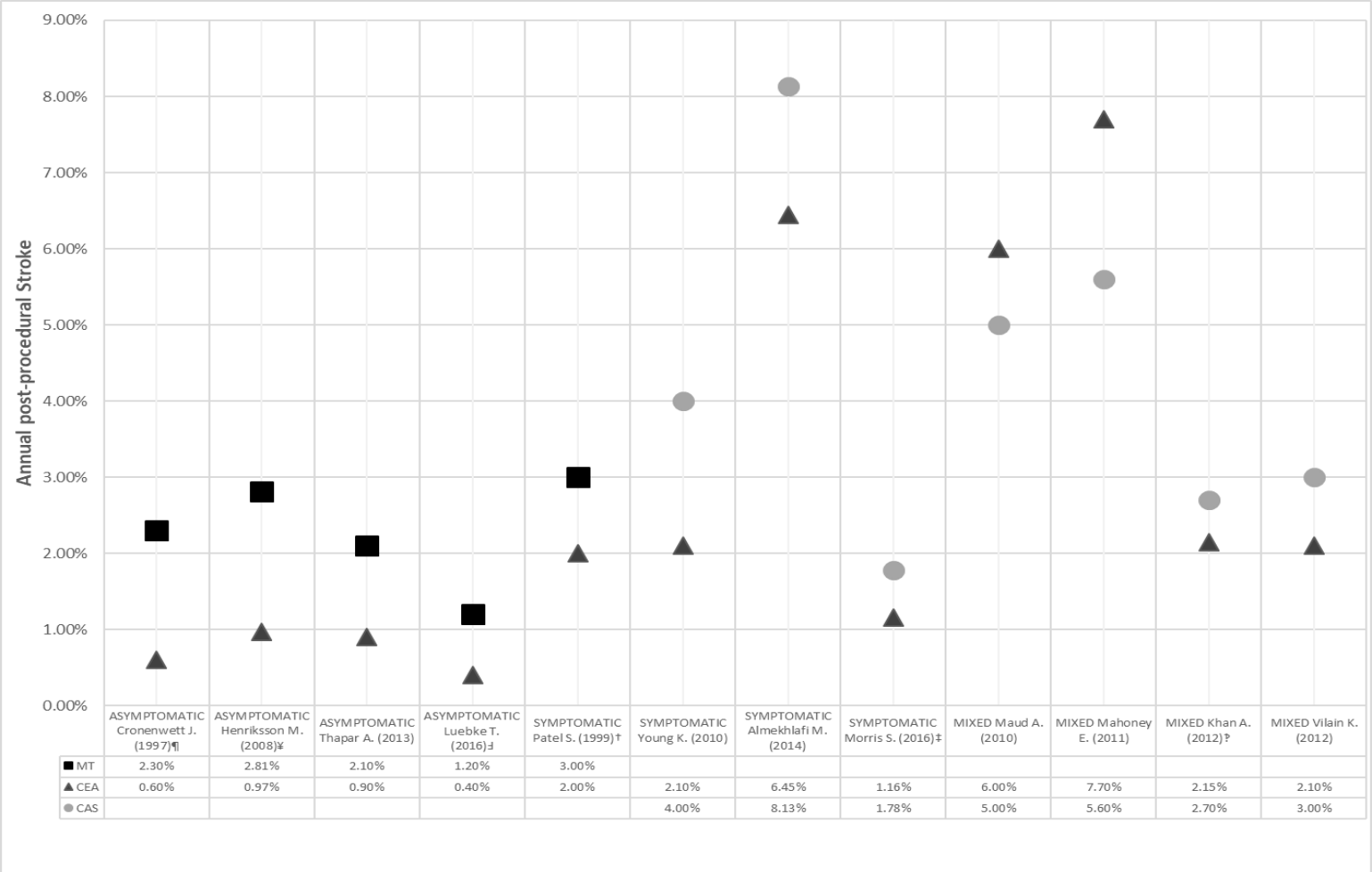
**Post-procedural risks in years 1 and 2 are listed in Appendix Table 2.2*

¶Obtained from HTA report on study(21)

†Only ipsilateral strokes (Includes 30-day procedural stroke risks

¥Only Henriksson et al, Almekhlafi et al and Morris et al (via HTA report(29)) reported relative risks/ hazard ratios between interventions. In other studies, relative risks were calculated by using long-term stroke risks reported for each separate intervention

Figure 2.3: Post-procedural/long-term stroke risks in economic evaluations



Note: Studies within categories ordered by date of publication. ¶Only Ipsilateral Stroke; †Annual stroke risks third year onwards; ¥Only Men; ǂDisabling stroke/ Fatal Stroke; ‡5-year cumulative stroke risks annualised;ŧ4-year stroke risks annualised

Relative risks of post-procedural stroke

Henrikkson et al(40) used the relative post-procedural stroke risk of 0.345 for CEA vs MT from ACST-1 and the post-procedural stroke risks of patients treated with MT in ACST-1 to calculate the post-procedural stroke risks of patients undergoing CEA. Similarly, Almekhlafi et al(35) used a relative minor stroke risk of 1.3 and a relative major stroke risk of 1.1 for CAS vs CEA from a meta-analysis of 12 RCTs to calculate the post-procedural stroke risks of CAS. Morris et al(29) was reported to have a cumulative 5-year stroke hazard ratio of 1.53 for CAS vs CEA,(59) with stroke risks informed from ICSS.

Eleven economic evaluations did not report relative post-procedural stroke risks nor mentioned that such were used in the calculation of absolute post-procedural stroke risks. However, in eight of these economic evaluations (3 comparing CEA vs MT,(39, 41, 42) 5 comparing CAS vs CEA) it was clear that post-procedural stroke risks of both interventions were sourced from the same RCTs, thereby incorporating relative post-procedural stroke risks between interventions from the respective RCTs. Cronenwett et al(39) used information from ACAS, (48) Thapar et al(42) information from ACST-1,(3) and Patel et al(41) information from NASCET(60) to inform of relative long-term relative risks of CEA vs MT. Young et al(38) synthesised information from SPACE, SAPPHIRE and EVA-3S using meta-analysis techniques, Mahoney et al(45) and Maud et al(46) information from SAPPHIRE,(61) Khan et al(44) and Villain et al(37) information from four year and one year follow-up of CREST(57) to inform of relative post-procedural stroke risks of CAS vs CEA.

Health Related Quality of Life (HRQoL)

Of nine economic evaluations using Markov state transition decision analytic models, Henrikkson et al(40) and Thapar et al(42) reported a HRQoL of 0.7 for patients in the 'no event' health state, sourcing this information from a cross-sectional postal public health survey in Stockholm County (n = 4950, 20-88 years) in 1998 which administered EQ-5D.(62) Kilaru et al(36) did not report the HRQoL of patients who had not experienced an event, but assumed that CEA patients had a decrement of 2 weeks of QoL, and CAS patients a decrement of 2 days of QoL immediately after procedure. Vilain et al(37) reported using a HRQoL of 0.704 for CEA patients and 0.708 for CAS patients at baseline as per information collected from a mixed symptom population in CREST. Almekhlafi et al(35) reported a HRQoL of 0.86 at baseline as per information from the Beaver Dam Health outcomes study which included 5,925 participants aged 43-84 years. Four economic evaluations(38, 39, 41, 43) using Markov state transition models did not report the HRQoL used for "no event" model state. All economic evaluations based on Markov state transition models sourced information on the decrements in HRQoL after a major stroke, minor stroke and MI from external sources including systematic reviews, previously published cost-effectiveness studies, and a combination of single centre studies (**appendix table 2.3**). The characteristics of populations from which this information was sourced was not clear due to either them not being reported, or the values calculated using two or more sources. Luebke et al(34) who used a decision analytical model with two health states did not cite where HRQoL inputs were sourced from.

In four economic evaluations, prospectively collected patient data was used.(29, 44-46) Morris et al(29) reported a HRQoL of 0.758 for CEA patients and 0.775 for CAS patients at

baseline in symptomatic patients in ICSS using the EQ-5D questionnaire. HRQoL data collected for each patient in ICSS at yearly intervals up to five years, with the average HRQoL of patients a year after procedure being 0.745 and 0.743 for CEA and CAS patients respectively, and 0.564 and 0.575 five years after procedure. Mahoney et al(45) evaluated the HRQoL of CEA and CAS patients using data in SAPPHIRE with HRQoL of each patient collected at two weeks, four weeks, six months and 12 months. Khan et al(44) and Maud et al(46) assumed the HRQoL of patients prior to intervention to be 0.815, post disabling stroke to be 0.718, post MI to be 0.744 while HRQoL post minor stroke was not reported. The characteristics of the population from which this information was sourced were unclear.

Costs of CEA and CAS procedures

The costs of the CEA and CAS procedures in the studies reviewed were calculated using either resource use and costs from RCTs(29, 37, 45), data from single centres(35, 36, 40, 41, 43), or reimbursement records from national sources(39, 42, 44, 46) (**appendix table 2.4**). Young et al(38) assumed no differences between the costs for CEA and CAS, though the source from which this information was derived was not reported. Luebke et al(34) reported that the cost of CEA was sourced from the literature, though the exact source from which this information was derived was unclear. Procedural costs in six economic evaluations(29, 35, 36, 41, 43, 45) included equipment, theatre times and professional fees. In the remaining six economic evaluations (37, 39, 40, 42, 44, 46) it was evident that equipment and theatre time costs were included in the hospital charges in the model inputs for procedural costs of CEA and/or CAS. However, it was not clear whether the hospital charges also included the clinicians' fees.

Cost of managing stroke

Six economic evaluations(29, 35, 39, 40, 44, 46) included both inpatient and follow-up costs when calculating the costs of managing stroke. Follow-up costs included costs recorded in hospital billing data such as accident and emergency care visits, day case or hospitalization costs and physician services and costs not reported in hospital data such as non-hospital primary and social care costs, homecare costs and social services costs (**appendix table 2.4**). Two other economic evaluations, Mahoney et al(45) and Vilain et al(37), also included inpatient and follow-up costs when calculating the cost of managing stroke, but follow-up costs were limited to only those recorded in hospital billing data. The duration of follow-up when calculating costs of managing stroke in economic evaluations ranged from one to five years. Sources for cost of managing stroke were not reported in two economic evaluations.(36, 38) It was not clear as to what costs were included when calculating the costs of managing stroke in three economic evaluations(41-43) due to the model inputs being sourced from either a literature review or from multiple sources. However, Thapar et al(42) reported that community, social services and informal care costs after disabling stroke were included. Luebke et al(34) sourced the cost of CEA and cost of managing stroke from the literature, but the actual studies from which costs were sourced were unclear.

Cost-effectiveness of treatment strategies for carotid stenosis in Europe

Three economic evaluations in the review studied the cost-effectiveness of CEA vs MT in a European setting (**table 2.4**). Henrikkson et al(40) reported an ICER per QALY gained with CEA compared to MT of €34,557 in 65-year-old asymptomatic men, and €311,133 for 65-year-old asymptomatic women. Luebke et al(34) reported an ICER per QALY gained with

CEA compared to MT of €90,230 in 65 to 75-year-old asymptomatic patients, showing that CEA was not cost-effective at a willingness to pay per QALY of €50,000. Thapar et al(42) reported an ICER per QALY gained from CEA compared to MT of £7,584 in 68-year-old asymptomatic patients, which was cost-effective at a willingness to pay per QALY of £20,000.

Two economic evaluations studied the cost-effectiveness of CAS vs CEA in a European setting. Morris et al(29) reported that CAS cost US$ 736 more than CEA despite resulting in 0.01 less QALYs than CEA over five years in symptomatic patients (**table 2.4**), hence showing the CAS was dominated by CEA. Janssen et al(43) did not report incremental results but stated that CAS was preferred to CEA (not statistically significant) in symptomatic patients, when using information from the Global CAS registry and ECST to inform procedural risks, and CEA was preferred to CAS (statistically significant) when using information from a Cochrane review(63) to inform procedural risks.

Table 2.4: Summary of cost-effectiveness results in economic evaluations in Europe

Study	Target population & subgroups	Country	Comparators	Cost	QALYs	Incremental Results	PSA performed	VOI analysis performed	Reports by Symp status	Reports by age	Reports by gender
Henriksson M. (2008)(40)	Base case: 65 and 75 year old asymptomatic males and females	Sweden	CEA vs MT	65 year-old men: CEA: €18,733; MT: €13,898 75 year-old men: CEA: €14,852; MT: €9,201 65 year-old women: CEA: €19,238; MT: €11,804 75 year-old women: CEA: €15,378; MT: €8,044	65 year-old men: CEA: 8.477; MT: 8.338 75 year-old men: CEA: 5.929; 5.838 65 year-old women: CEA: 8.378; MT: 8.54 75 year-old women: CEA: 5.97; MT: 5.961	65 year-old men: ICER: €34,557 75 year-old men: ICER: €58,930 65 year-old women: ICER: €311,133 75 year-old women: ICER: €779,776	YES	YES[1]	YES	YES	YES
Thapar A. (2013)(42)	68 year old asymptomatic patients	United Kingdom Europe	CEA vs MT	CEA: £8,496 MT: £7,855	CEA: 9.627 MT: 9.537	ICER = £7584	YES	NO	YES	YES	YES
Luebke T. (2016)(34)	Asymptomatic patients	Europe	CEA vs MT	Inc Cost: €2,946.49	Inc QALYs: 0.03	ICER: €90,230.12	YES	NO	YES	NO	NO
Morris S. (2016)(29)	Symptomatic patients (>=50%) from ICSS	United Kingdom	CAS vs CEA	CEA: £6,499 CAS: £6,820	CEA: 3.228 CAS: 3.247	Inc Cost: US$736* Inc Benefit: -0.01*	YES	NO	YES	YES	YES

Study	Target population & subgroups	Country	Comparators	Cost	QALYs	Incremental Results	PSA performed	VOI analysis performed	Reports by Symp status	Reports by age	Reports by gender
Janssen M. (2008)(43)	Symptomatic patients	Netherlands	CAS vs CEA	Costs and QALYs not reported Scenario 1 (ECST and Global CAS registry) shows CAS preferred (results not statistically significant) Scenario 2 (Cochrane review) shows CEA preferred (results statistically significant).			YES	NO	YES	NO	NO

CEA: Carotid Endarterectomy; CAS: Carotid Artery Stenting; MT: Medical Therapy; QALY: Quality Adjusted Life Year; PSA: Probability Sensitivity Analysis; VOI: Value of Information; Inc: Incremental; Symp: Symptomatic status

** Incremental results adjusted for potential confounders*

[1]VOI analysis had previously reported information in an accompanying VOI analysis in asymptomatic patients in Sweden(64)

Cost-effectiveness of treatment strategies for carotid stenosis in North America

Two economic evaluations studied the cost-effectiveness of CEA vs MT in a North American setting (**table 2.5**). Patel et al(41) reported an ICER of US$4,462 per QALY gained with CEA in 66-year-old symptomatic patients and Cronenwett et al(39) reported an ICER of US$8,004 per QALY gained with CEA in 67-year-old asymptomatic patients. In both studies CEA was cost-effective at a willingness to pay per QALY of US$50,000.

Seven economic evaluations studied the cost-effectiveness of CAS vs CEA in a North American setting (**table 2.5**). Two of these economic evaluations were based on only symptomatic patients, with both Young et al(38) and Almekhlafi et al(35) reporting that CEA dominated CAS in symptomatic patients, having lower cost and higher QALYs. Five economic evaluations studied the cost-effectiveness of CAS vs CEA in a mixed symptom population. Vilain et al(37) reported that CEA dominated CAS. Mahoney et al(45) reported an ICER of US$6,555 per QALY suggesting that CAS was cost-effective. Maud et al(46) and Khan et al(44) reported ICERs of US$67,891 and US$229,429 per QALY gained with CAS, respectively (**table 2.5**).

Table 2.5: Summary of cost-effectiveness results of economic evaluations in North America

Study	Target population & subgroups	Country	Comparators	Cost	QALYs	Incremental Results	PSA performed	VOI analysis performed	Reports by Symp status	Reports by age	Reports by gender
Patel S. (1999)(41)	Base case: 66 year old symptomatic patients (50% to 69%)	USA	CEA vs MT	CEA: US$16,269 MT: US $15,869	CEA: 6.75 MT: 6.62	ICER: US$4,462	NO	NO	YES	YES	NO
Cronenwett J. (1997)(39)	Base case: 67 year old asymptomatic patients (>=60%)	USA	CEA vs MT	CEA: US$14,448 MT: US$12,407	CEA: 8.12 MT: 7.87	ICER: US$8,004	NO	NO	YES	YES	NO
Young K. (2010)(38)	Symptomatic patients Base case: 70 year olds	USA	CAS vs CEA	CEA: US$35,200 CAS: US$52,900	CEA: 9.64 CAS: 8.97	Inc Cost: US$17,700 Inc Ben: -0.67	YES	NO	YES	NO	NO
Almekhlafi M. (2014)(35)	65 year old symptomatic patients	Canada	CAS vs CEA	CEA: CDN$24,624; CAS: CDN$30,731	CEA: 6.83 CAS: 6.71	Inc Cost: CDN$6,107 Inc Ben: -0.12	YES	NO	YES	NO	NO
Kilaru M. (2003)(36)	70 year old symptomatic (>70%) & asymptomatic (>80%) patients	USA	CAS vs CEA	CEA: US$28,772 CAS: US$35,789	CEA: 8.36 CAS: 8.20	Inc Cost: US$7,017 Inc Ben:-0.16	NO	NO	NO	YES	NO
Mahoney E. (2011)(45)	Symptomatic & Asymptomatic patients from SAPPHIRE (Mean age:72 years)	USA	CAS vs CEA	CEA: US$57,187 CAS: US$60,528	CEA: CAS:	ICER: US$6,555	YES	NO	YES	NO	NO

Study	Target population & subgroups	Country	Comparators	Cost	QALYs	Incremental Results	PSA performed	VOI analysis performed	Reports by Symp status	Reports by age	Reports by gender
Khan A. (2012)(44)	Symptomatic and asymptomatic patients from CREST (mean age: 69.1 years).	USA	CAS vs CEA	CEA: US$13,276 CAS: US$18,335	CEA: 0.702 CAS: 0.712	ICER: US$229,429	YES	NO	NO	NO	NO
Maud A. (2010)(46)	Symptomatic and Asymptomatic patients from SAPPHIRE (mean age: 72)	USA	CAS vs CEA	CEA: US$8,916 CAS: US$12,782	CEA: 0.701 CAS: 0.753	ICER: US$67,891	YES	NO	NO	NO	NO
Vilain K. (2012)(37)	Symptomatic and asymptomatic patients from CREST (mean age: 69.1 years).	USA	CAS vs CEA	CEA: US$79,617 CAS: US$80,141	CEA: 4.849 CAS: 4.841	Inc Cost: US$524 Inc Ben: -0.008	YES	NO	YES	NO	NO

CEA: Carotid Endarterectomy; CAS: Carotid Artery Stenting; MT: Medical Therapy; QALY: Quality Adjusted Life Year; PSA: Probability Sensitivity Analysis; VOI: Value of Information; Inc: Incremental; Symp: Symptomatic status

Probabilistic Sensitivity analysis (PSA)

Three out of five economic evaluations studying the cost-effectiveness of CEA vs MT performed PSAs to account for uncertainty in input parameters. Henrikkson et al(40) reported that CEA had a 70% probability of being cost-effective in 65-year-old asymptomatic men and <10% in 65-year-old asymptomatic women at a willingness to pay per QALY of €52,500. Luebke et al(34) reported that CEA had 71.8% probability of being cost-effective at a willingness to pay per QALY of €50,000 for 65 to 75 year-old asymptomatic patients. Thapar et al(42) only reported 95% confidence intervals of incremental results, indicating that differences in both costs and effects between CEA and MT are not statistically significant in 68-year-old asymptomatic patients.

Seven out of nine economic evaluations of CAS vs CEA reported PSAs. Young et al(38) reported that CEA had a probability above 59% of being cost-effective in 70-year-old symptomatic patients at willingness to pay per QALY thresholds up to US$20,000. In a mixed symptom population with a mean age of 72 years, Mahoney et al(45) reported that CAS had a probability of 98.3% of being cost-effective at a willingness to pay per QALY of US$50,000 and Maud et al(46) a probability of less than 40% at willingness to pay per QALY of $67,891. Khan et al(44) reported that CAS only had a probability of 0.11% of being cost-effective at a willingness to pay per QALY of US$68,000 in a mixed symptom population with a mean age of 69 years. Morris et al(29) reported that at willingness to pay per QALY ranging from US$0 to US$50,000 the probability of CAS being cost-effective was less than 0.4%. Almekhlafi et al(35) only reported 95% confidence intervals for incremental results, showing that the differences between both costs and effects (QALYs) of CEA vs CAS were not statistically significant in symptomatic patients. Janssen et al(43) did not report 95%

confidence intervals, but stated that differences between CEA and CAS were not statistically significant in symptomatic patients, except when they sourced procedural and post-procedural risks from a Cochrane review meta-analysis.(63)

Value of information (VOI) analysis

None of the economic evaluations reported results from a VOI analysis. However, Henrikkson et al(40) had previously reported information in an accompanying VOI analysis in asymptomatic patients in Sweden(64) noting that the long-term stroke rates in the MT group was the biggest contributor towards uncertainty in cost-effectiveness results.

Heterogeneity in cost-effectiveness by age and gender

In economic evaluations studying CEA vs MT, Henrikkson et al(40) used both gender-specific procedural and post-procedural risks, and age- and gender-specific non-stroke related mortality risks and concluded that CEA is cost-effective in men aged 73 or below, while it is unlikely to be cost-effective in women or older men, with it being reported that lower long-term stroke risks in women being the main reason behind CEA not being cost-effective in women.

Thapar et al(42) used age- and gender-specific non-stroke related mortality risks and reported that CEA is likely to be cost-effective in both men and women aged below 75 when compared to MT. Two other economic frameworks studying CEA vs MT differentiated non-stroke related mortality risks by age. Cronenwett et al(39) used age-specific non-stroke related mortality risks and reported that while CEA is cost-effective in the base-case scenario of 67-year-old asymptomatic patients, it does not appear cost-effective in older patients with an ICER > US$100,00 in patients aged 79. Similarly, Patel et al(41) used age-specific non-

stroke related mortality risks and reported CEA not being cost-effective for patients aged above 83 at a willingness to pay of US$60,000 per QALY.

Morris et al(29) evaluated the cost-effectiveness of CAS vs CEA within categories of patients by age and gender using participant data in ICSS. They calculated mean costs and QALYs at 5-years and reported that the probability that CAS is cost-effective was lower in men compared to women, and lower in patients aged >=70 years compared to those aged <70 years. Kilaru et al,(36) evaluated the cost-effectiveness of CAS vs CEA in categories of patients by age and reported that while CEA is cost-effective in patients up to the age of 90, the probability of CEA being cost-effective was highest in patients aged below 70 years. It was not clear as to how Kilaru et al(36) accounted for differences by age in their analysis.

Heterogeneity by symptomatic status

Five economic evaluations comparing CEA vs MT were based only on either asymptomatic(34, 39, 40, 42) or symptomatic(41) patients Similarly four economic evaluations(29, 35, 38, 43) comparing CAS vs CEA were based on only symptomatic patients, with results reported in previous paragraphs. Procedural and post-procedural stroke risks used in these studies were applicable to the symptomatic status of the study population in each of these studies, except in the case of Lubke et al(34) where sources for procedural and post-procedural stroke risks were unclear.

Of the five economic evaluations which studied the cost-effectiveness of CAS vs CEA in mixed symptom populations, only two reported results by symptomatic status. Mahoney et al(45) looked at the costs and QALYs of patients in the SAPPHIRE separately by symptomatic status and reported an ICER of US$2,667 for CAS in asymptomatic patients

and US$204,229 in symptomatic patients. The difference in results between symptomatic and asymptomatic patients were driven by the 1-year SAPPHIRE results which reported a significant clinical benefit for CAS when compared to CEA in asymptomatic patients, while no differences were observed between CEA and CAS in symptomatic patients. Similarly, Vilain et al(37) calculated mean costs and QALYs of patients in CREST by symptomatic status of patients. CEA was the dominant strategy in symptomatic patients, whilst in asymptomatic patient an ICER of US$277,249 per QALY gained was estimated. All results in sub-groups by symptomatic status, age and gender are reported in **appendix table 2.5**.

2.4 Discussion

Five economic evaluations studied the cost-effectiveness of CEA vs MT (three in Europe, two in North America). CEA was shown to be cost-effective in a European setting in asymptomatic patients, and in a North American setting in symptomatic patients. There were no economic evaluations studying the cost-effectiveness of CEA vs MT in symptomatic patients in Europe or asymptomatic patients in North America. Henrikkson et al(40) reported that the cost-effectiveness of CEA depends on the age and gender of patients, with CEA reported to be cost-effective in younger asymptomatic men, and unlikely to be cost-effective in women or older men. Results from economic evaluations of CAS vs CEA varied. In Europe, Morris et al(29) reported that CAS was dominated by CEA though differences of costs and effects between CEA and CAS were not statistically significant, while Janssen et al(43) reported CEA to be cost-effective in symptomatic patients with statistically significant differences between CEA and CAS when using information from a Cochrane review meta-analysis to source procedural and post-procedural stroke risks. In North America, CEA dominated CAS in symptomatic patients(35, 38), while in mixed symptom populations

results varied with Vilain et al(37) reporting that CEA dominated CAS, and three other economic evaluations(44-46) reporting CAS having probabilities ranging from 0.11% to 98.3% of being cost-effective at willingness to pay per QALY levels ranging from US$50,000 to US$68,000. Cost-effectiveness results of CAS vs CEA differed by symptomatic status, age and gender of patients. There were no economic evaluations studying the cost-effectiveness of CAS vs MT, nor of all three treatment strategies in a single study setting.

The majority of economic analyses in our review sourced the data for procedural risks of CEA and CAS from RCTs, which recruited before 2008. Exceptions to this were two studies using observational registry data for procedural risks. Henrikkson et al(40) used procedural risks from SWEDVASC with recruitment period until 2003, and Janssen et al(43) sourced CAS procedural risks from the Global CAS Registry with recruitment period from 1997 to 2002. Evidence suggests that in-hospital risks of CEA and CAS,(26) and procedural stroke/death risks in asymptomatic patients undergoing CEA(65) have decreased in recent times. Thus, procedural risks employed in the economic evaluations studying the cost-effectiveness of treatment methods for carotid stenosis may not reflect contemporary practice. Furthermore, while RCTs remain the gold standard for relative procedural risks between interventions, the absolute procedural risks of interventions in RCTs may not reflect the typical clinical practice due to use of patient inclusion criteria in RCTs. For example, SAPPHIRE required patients to have at least one condition which increased the risk of CEA complications(10), a scenario that does not mimic real world practice. Data on procedural risks of interventions in more recent observational cohort studies could help alleviate this limitation.

Six economic evaluations(29, 34, 37, 44-46) had a limited time horizon much shorter than patients' lifetime. Of these six economic evaluations, four compared mean costs and QALYs up to a specific time point (ranging from one to five years), one used a decision tree with no Markov state transitions and a time horizon of 5 years, and one used a Markov chain decision analytical model with a time horizon of 10 years. It is good practice for economic evaluations to have a time horizon which captures all differences in costs and health outcomes between interventions,(23) and this often requires a lifetime horizon. Results from ACST-1 show that post-procedural stroke risks of asymptomatic patients differ between those allocated to CEA and MT at 10-year follow-up,(3) while results from CREST show that patients allocated to CAS had a statistically significantly higher overall stroke risk or procedural death when compared to patients allocated to CEA at 10-year follow-up.(66) Hence an economic framework with a limited time horizon may not account for differences in stroke risks between treatment strategies over the patient's lifetime.

One economic analysis studying the cost-effectiveness of CAS vs CEA in mixed symptom populations based on a Markov decision analytic model did not differentiate procedural and post-procedural risks by patient's symptomatic status. Similarly, three economic analyses which studied the cost-effectiveness of CAS vs CEA in mixed symptom populations by calculating mean costs and QALYs of patients groups in a RCT with both symptomatic and asymptomatic patients did not report results by symptomatic status. Results from RCTs have shown that relative procedural and post-procedural stroke risks do not differ statistically significantly by symptomatic status.(19) However, it has been shown that symptomatic patients have higher procedural stroke risks with both CEA and CAS,(67) while post-procedural stroke of patients randomized to CEA differ in RCTs in symptomatic patients(54,

61, 68, 69) and asymptomatic patients.(3, 70) Only two economic evaluations looking at mixed symptom populations in our literature review and reported results by symptomatic status, suggesting that the cost-effectiveness of CAS vs CEA differed by symptomatic status with Mahoney et al(45) reporting CAS having an ICER of US$2,667 compared to CEA in symptomatic patients and a much higher ICER of US$204,229 in asymptomatic patients while Vilain et al(37) reported CEA dominating CAS in symptomatic patients and CAS having an ICER of US$277,249 compared to CEA in asymptomatic patients. Thus, not accounting for differences in risks between symptomatic and asymptomatic patients can be considered a significant limitation in economic evaluations when studying the cost-effectiveness of treatment methods for carotid stenosis in mixed symptom populations.

Three economic evaluations reported results by gender, and six by age, showing that the cost-effectiveness of treatment methods for carotid stenosis are dependent on both age (with CEA being more cost-effective compared to MT when patients are intervened at a younger age) and gender of patients. Morris et al(29) reported results by age and gender by estimating mean 5-year costs and QALYs of CEA and CAS patients by gender and age groups though, given the time horizon of five years, this analysis would not have fully captured stroke risks of patients and their survival over their lifetime. Two other economic evaluations based on Markov decision analytical models reported results by gender of patients, of which only Henrikkson et al(40) used gender-specific estimates of procedural and post-procedural stroke risks. Five economic evaluations employing Markov decision analytical models reported cost-effectiveness results by age, but none of these analyses used age-specific procedural or post-procedural stroke risks, instead only accounting for heterogeneity in patients by age via non-stroke related mortality risks. With sub-group analysis of ECST and

NASCET indicating that overall stroke risks of symptomatic carotid stenosis patients vary significantly by age,(71) the small number of economic evaluations which have reported cost-effectiveness results by age is a limitation.

Of nine economic analyses employing Markov chain decision analytical models, four did not account for differences in procedural and post-procedural stroke risks between treatment methods by stroke severity. Of five economic analyses which did, only Almekhlafi et al(35) did so by employing relative risks between treatment methods, differentiated by stroke severity. One of the largest RCTs comparing CAS vs CEA, ICSS, reported that while patients randomized to CEA have statistically significantly lower procedural and post-procedural minor stroke risks compared to patients randomized to CAS, there were no statistically significant differences of procedural and post-procedural major risks between CEA and CAS.(68) Results from other smaller RCTs are more varied, with synthesis of evidence from RCTs likely to give a more conclusive result.

The majority of economic analyses included in this review (10 out of 14) performed a PSA, with its importance being highlighted by the National Institute for Clinical Excellence (NICE) which recommended evaluating the uncertainty in economic evaluations in their guidelines in 2014.(72) Results in our literature review underlie the importance of PSAs, with uncertainty in data and input parameters leading to non-statistically significant differences between treatment methods, both in terms of costs and effects. Large degrees of uncertainty can be put down to economic analyses sourcing model input parameters informing procedural and post-procedural stroke risks from a single RCT with small patient populations compared to observational studies. Large observational cohort studies may help reduce uncertainty in absolute procedural or post-procedural stroke risks in economic analyses, though information

from observational studies may be subjected to selection and outcome measurement bias. Using information from a meta-analysis of RCTs instead of a single RCT when obtaining relative procedural and post-procedural risks can further help reduce the uncertainty in results from economic analyses.

No economic evaluations reported results from a VOI analysis, although Henrikkson et al(40) referred to a previously performed VOI analysis on treatment of carotid stenosis in asymptomatic carotid stenosis in Sweden. VOI analysis is not currently required by NICE in economic evaluations though it's potential contribution to informing future research priorities has been noted by NICE.(73) Given the degree of uncertainty involved in cost-effectiveness results, there is a cost to society from an incorrect decision. A VOI analysis can be used to calculate the expected cost of uncertainty in results from a cost-effectiveness analysis(74) and hence determine whether spending on further research is justified. VOI for particular input parameters (i.e. expected value of partial perfect information) can point to particular areas of uncertainty future research should prioritize.

Economic evaluations were assessed for reporting bias in accordance with the CHEERS checklist. While a large number of economic evaluations did not report study setting, the setting was identifiable from the input parameters used for costs (except in Luebke et al(34)). Most economic evaluations employing Markov decision analytic models sourced model input parameters for HRQoL from external sources, but did not clearly describe the populations from which these estimates were derived. Similarly, costs involved in the management of stroke were not reported in two economic evaluations and not clearly reported in three others thus not making it possible to identify what components of costs were used, the follow-up period post stroke over which costs were calculated, and the

characteristics of the population from which cost were sourced. Inconsistencies in the reporting of input parameters for HRQoL and costs made it difficult to critically evaluate these economic evaluations and decide whether the input parameters used were appropriate for the study population of the economic evaluation. Input parameters for procedural and post-procedural stroke risks were well reported across the majority of economic evaluations included in the review, with sources of input parameters from procedural and post-procedural stroke risks only being unclear in Luebke et al(34) and Kilaru et al.(36) Reporting of results from economic evaluations was consistent, with all economic evaluations except Janssen et al(43) reporting incremental costs and effects. Of the nine economic evaluations which included PSAs, two reported 95% confidence intervals, four reported results from cost-effectiveness acceptability curves, and three reported both 95% confidence intervals and results from cost-effectiveness acceptability curves.

Our analysis was also hindered by the difficulties in comparing input parameters for costs of managing stroke and CEA and CAS procedures across economic evaluations which were reported in different currencies, and costed at different time points. This also affected the comparison of incremental results of economic analyses. Comparisons of incremental results across economic evaluations were also hampered by differences between analytical frameworks with regard to time horizon and modelling techniques. The economic evaluations included in this review differed with regard to interventions compared, study setting, model structure, and symptomatic status of patients.

In summary, evidence suggests that while CEA is likely to be cost-effective when compared to MT in both Europe and North America, results from economic evaluations of CAS vs CEA are mixed. Cost-effectiveness findings for CEA and CAS are likely to depend on a patient's

age, gender and symptomatic status. All economic evaluations which performed a PSA showed considerable uncertainty surrounding costs' and QALYs' differences between treatment strategies. A number of limitations were identified in the economic evaluations included in the literature review. These included use of information from a single RCT to inform relative procedural and post-procedural stroke risks, thereby not taking into account all the evidence in the literature and resulting in large degrees of uncertainty. Therefore, systematically reviewing RCTs of treatment methods for carotid stenosis, and synthesizing the evidence using meta-analysis techniques can help strengthen this evidence (**chapter 3**). Furthermore, procedural risks used in economic evaluations included in this review may not reflect contemporary practice, with the majority of economic evaluations sourcing procedural risks from RCTs which recruited patients many years ago (the latest by 2008). Evaluating how procedural risks of CEA and CAS in symptomatic and asymptomatic patients have changed over time, and identifying contemporary procedural risks in more recently published observational cohort studies (**chapter 4**) aims to address this issue. Other limitations in the economic evaluations identified in this literature review include not accounting for heterogeneity in procedural and post-procedural stroke risk by age, gender and symptomatic status, not accounting for differences in procedural and post procedural risks by stroke severity between treatment methods, not accounting for uncertainty in input parameters, having too short a time horizon to reflect all differences in procedural and post-procedural stroke risks between treatment methods, and not performing a VOI analysis. Given the limitations in economic evaluations studying the cost-effectiveness of CEA vs MT and CAS vs CEA, and the absence of an economic evaluation studying the cost-effectiveness of all three interventions in a single study setting, there appears to be a gap in the literature for a

new economic evaluation. **Chapter 5** presents a new economic analysis which addresses the limitations identified in the literature and studies the cost-effectiveness of all three interventions for carotid stenosis in a contemporary setting, accounting for heterogeneity between patients and uncertainty in key parameters, and reporting cost-effectiveness and VOI results by age, gender and symptomatic status of patients.

3

Systematic review and meta-analysis of randomised evidence of procedural, post-procedural and overall effects of CEA and CAS

3.1 Introduction

With stroke being one of the major causes of death and carotid stenosis one of its risks factors as outlined in **chapter 1**, identifying effective treatment methods for carotid stenosis to reduce stroke risks has been of great scientific interest. Current treatment methods include medical therapy (MT) alone, carotid endarterectomy (CEA) added to MT; and carotid artery stenting (CAS) added to MT

Evidence of comparative effects of different treatments (eg, relative risks or odds ratios) is an integral part in the development of a cost-effectiveness framework, with randomised control trials (RCTs) recognised as the gold standard when comparing effectiveness of healthcare interventions, due to it minimising the possibility of biases affecting the results.(75) In this chapter evidence from RCTs of procedural, post-procedural and overall effects of treatment methods for carotid stenosis are reviewed, and this evidence synthesised across a number of endpoints using meta-analysis and network meta-analysis techniques.

3.2 Methods

Published results of RCTs comparing treatment methods for carotid stenosis (ie, MT alone, CEA (in addition to MT) or CAS (in addition to MT)) were included in the review if 100 participants or more were randomly allocated in each treatment arm. Eligible RCTs were identified by initially searching the Cochrane Central Register of Controlled Trials for publications related to interventions for carotid stenosis under the MeSH term “carotid stenosis”, and identifying RCTs included in these publications. Furthermore, the following international registers of clinical trials, the clinicaltrials.gov registry (search term used: “carotid”, limited to trials which reported results) and the international standard randomised

controlled trials number (ISRCTN) registry (searched under condition: “carotid stenosis”), were also searched for RCTs comparing two or more treatment methods for carotid stenosis. Manuscripts of these RCTs were identified through a combination of reference lists of Cochrane reviews; publications listed in clinicaltrials.gov; and the websites of individual RCTs. These sources were also used to identify long-term follow-up data of the identified trials. The selected studies were reviewed by a single reviewer (Kusal Lokuge) and data extracted.

The quality of RCTs (**text 3.1**) was evaluated using a Cochrane collaboration’s tool based on a set of criteria.(76) The criteria included the method of randomisation (selection bias), blinding of outcome assessment (detection bias), loss in follow-up of patients (attrition bias), and reporting bias. RCTs were not graded on blinding of participants and personnel, as the nature of the intervention made it not possible for the surgeon/ operator or patient to be blinded to it. The criteria are described in **text 3.1**.

Text 3.1: Criteria for RCTs quality assessment

Scoring method: One star (*) would be given for each criteria, if no bias was evident.

- **Selection bias:**

  Method of randomisation used when allocating patients to treatment arms – whether sequence generation process used to randomised patients and allocation concealment lead to a risk of selection bias, which compromised the randomisation process.

- **Detection bias - Blinding of outcome assessment:**

  Whether patients were followed up by neurologists or clinicians not involved in procedures; whether outcomes were assessed blinded to treatment or not.

- **Attrition bias - Incomplete outcome data:**

  Proportion of patients excluded from the analysis; proportion of patients lost due to attrition.

- **Reporting bias - Selective reporting:**

  Whether trials reported outcomes as stated in study protocol, or reported major outcomes (stroke, death).

Outcomes were analysed using Intention to Treat (ITT) populations in RCTs. Outcomes of interest were: a) procedural outcomes defined as those occurring between randomisation and 30 days after procedure (for CAS vs CEA studies only), b) overall outcomes defined as those occurring from randomisation to end of follow-up, and c) post-procedural outcomes defined as those occurring after the procedural period (with participants experiencing procedural stroke/death outcomes excluded). The main procedural outcome of interest was procedural stroke/death. Procedural major stroke (Modified Rankin Score of ≥3), procedural minor stroke (Modified Rankin score of <3) and procedural myocardial infarction (MI) were further outcomes of interest summarised. The main overall outcome of interest in trials comparing CAS vs CEA was total strokes. Total major strokes and total minor strokes were further outcomes of interest summarised. In trials comparing CEA vs MT, the main overall outcome of interest was "total strokes including procedural deaths". In the network meta-analysis, an indirect comparison was made using information from CEA vs MT trials and CAS vs CEA trials for the outcome "total strokes and procedural deaths". The main post-procedural outcome of interest was long-term stroke, with post-procedural major strokes and post-procedural minor strokes being further outcomes of interest.

All outcomes were summarised by symptomatic status of patients with symptomatic patients defined as those who have experienced a stroke or transient ischemic attack within 6 months prior to randomisation. In RCTs with both asymptomatic and symptomatic patients where outcomes were not reported by participants' symptomatic status, relative risks were pooled for "mixed" (ie, symptomatic and asymptomatic) populations. Outcomes were also summarised separately by age and gender categories where such results were reported.

Statistical Methods

The fixed effects Mantel Haenzel method(77) was used to synthesise event odds ratios from included RCTs across all endpoints. While follow-up periods between studies differed, creating doubts about potential bias when synthesising long-term end points, synthesis of relative risk measures such as odds ratios are more robust to this at least within the ranges of follow-up times studied, as long as the follow-up period in each treatment arm within a study was the same. A random effects network meta-analysis(78) was used to obtain an indirect comparison of the effects of CAS vs MT by using information available from RCTs comparing CEA vs MT, and CAS vs CEA, as no RCTs compared CAS vs MT directly. Heterogeneity between studies was investigated using Cochrane's I^2 statistic,(76) while heterogeneity between pooled estimates in symptomatic and asymptomatic patients and between age and gender subgroups was tested using the two sided t-test. (79)

3.3 Results

Ten RCTs meeting the inclusion criteria were identified from three systematic reviews(17, 18, 80) published in the Cochrane central register for controlled trials, with a further trial identified from the clinicaltrials.gov registry. The published manuscripts of all trials comparing CEA vs MT alone were identified from the two Cochrane systematic reviews(17, 18) and one further manuscript from the ACST-1 trial published after the publication of these systematic reviews was identified from the ACST-2 website.(23) The published manuscripts of trials comparing CAS vs CEA were identified initially from the Cochrane systematic review,(80) and then by reviewing the trial specific pages on clinicaltrial.gov registry.

In five of the included RCTs (**table 3.1**) CEA was compared with MT alone, 3 trials were in asymptomatic patients (5,226 participants) and 2 in symptomatic patients (5,250 participants). More than 90% of patients in these trials were prescribed antithrombotic drugs (mainly aspirin). The trials were carried out between 1981 and 1995, except for the Asymptomatic Carotid Surgery Trial (ACST)-1 whose recruitment period ended in 2003. Prescription of lipid lowering drugs was uncommon in the earlier trials, with it being prescribed to less than 20% of patients at recruitment in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) (study recruitment: 1987-1996) and European Carotid Surgery Trial (ECST) (study recruitment: 1981-1994) trials. In ACST 11% of CEA patients and 8% of MT patients were prescribed lipid lowering drugs at recruitment in 1993, but this increased to 80% and 82% by later follow-up in 2007. No information was reported on the type of lipid-lowering drugs prescribed to patients in the Asymptomatic Carotid Atherosclerosis Study (ACAS)(48) and Veterans Affair (VA)(81) trials. CEAs in the trials were performed using customary techniques (ie, longitudinal incision or evasion technique). Study populations in all RCTs were similar in terms of age and gender except for the VA trial which included only males.

Six RCTs comparing CAS vs CEA were identified (**table 3.1**); 3 in symptomatic patients, 2 in mixed symptomatic/asymptomatic patients and 1 in asymptomatic patients. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was excluded from the analysis of relative risks between CEA and CAS as only 26% patients in the endovascular treatment arm, underwent CAS.(82) While all trials in mixed symptom populations had randomisation stratified by symptomatic status, outcomes by patients' symptomatic status were not reported for the Stenting and Angioplasty with Protection in Patients at High Risk

for Endarterectomy (SAPPHIRE) trial. All trials except the Asymptomatic Carotid Trial (ACT)-1 had more than half of their quoted recruitment period prior to year 2005.

Table 3.1: Randomised Controlled Trials of carotid stenosis interventions included in the systematic review

Trial	Interventions	Symptomatic Status (NASCET method)	Recruitment period	Location	Median follow-up	Participants	Male (%)	Mean Age (years)	Primary endpoints	Secondary endpoints
ECST(18, 54)	CEA vs MT	Symptomatic (>0%)¶	1981-1994	Europe & Australia	6.1 years*	3024	72%	63	• Fatal or disabling ipsilateral ischaemic stroke	• major stroke or surgical death, any major stroke, death from any cause, any major stroke or death, disabling/fatal stroke or surgical death, fatal stroke or surgical death.
VA (17, 81)	CEA vs MT	Asymptomatic (>50%)	1983-1993	North America	4 years*	444	100%	65	• Ipsilateral neurological events	• Any stroke; death
NASCET(18, 60, 83)	CEA vs MT	Symptomatic (>0%)¶	1987-1996	North America	5 years*	2226	69%	66	• Ipsilateral stroke	• ipsilateral stroke; death; death or stroke; ipsilateral fatal stroke; ipsilateral major stroke; fatal stroke; major stroke; death or major stroke
ACAS (17)	CEA vs MT	Asymptomatic (>60%)	1988-1993	North America	2.7 years	1662	66%	67	• Ipsilateral stroke or any perioperative stroke or death	• Ipsilateral TIA; any stroke; major ipsilateral stroke; any major stroke; death
ACST (3, 17, 84)	CEA vs MT	Asymptomatic (>60%)[3]	1993-2003	Mainly Europe	9 years	3120	66%	68	• Perioperative stroke or death; non-perioperative stroke	• Non perioperative fatal or disabling stroke; non-perioperative carotid territory ischaemic stroke
SAPPHIRE(10, 80, 85)	CEA vs CAS	Symptomatic (>=50%)	2000-2002	USA	3 years[a]	334	67%	73	• Procedural Stroke/Death/ MI	• **Procedural:** Stroke, Death, MI, Stroke/Death, Major Stroke,

Trial	Interventions	Symptomatic Status (NASCET method)	Recruitment period	Location	Median follow-up	Participants	Male (%)	Mean Age (years)	Primary endpoints	Secondary endpoints
		Asymptomatic (>=80%)							• Ipsilateral stroke between 31 days & 1 year after treatment	Minor Stroke, Cranial Nerve palsy • Ipsilateral Stroke/Death from neurological causes up 3 years after treatment
EVA-3S(61, 80, 86)	CEA vs CAS	Symptomatic (>=60%)	2000-2005	France	3.6 years	524	75%	70	• Procedural Stroke/Death • Procedural stroke/death or ipsilateral stroke up to 4 years after treatment	• **Procedural:** Stroke, Death, MI, Disabling Stroke, Cranial Nerve palsy, access site haematoma • Any stroke, and death or any stroke up to 4 years after treatment • Carotid restenosis up to 3 years after treatment.
CREST(57, 58, 66, 80)	CEA vs CAS	Symptomatic (>=50%) Asymptomatic (>=60%)	2000-2008	North America	7.4 years	2502	65%	69	• Procedural Stroke/Death/ MI • Ipsilateral stroke up to 4 years after randomisation	• **Procedural:** Stroke, Death, MI, Major Stroke, Cranial nerve palsy, access site haematoma • Degree of stenosis of relevant carotid artery 6 and 12 months after treatment
SPACE(69, 80)	CEA vs CAS	Symptomatic (>=50%)	2001-2006	Europe	2 years[a]	1214	72%	69	• Procedural Ipsilateral Stroke/Death	• **Procedural:** Death, Stroke, Stroke/ Death, Disabling Stroke/Death

Trial	Interventions	Symptomatic Status (NASCET method)	Recruitment period	Location	Median follow-up	Participants	Male (%)	Mean Age (years)	Primary endpoints	Secondary endpoints
									• Ipsilateral stroke up to 2 years after randomisation	• Stroke/Death or carotid restenosis within 2 years after randomisation
ICSS(80, 87, 88)	CEA vs CAS	Symptomatic (>=50%)	2001-2008	International[1]	4.2 years	1713	70%	70	• Stroke/Death/ MI within 120 days after randomisation • Long-term rate of fatal or disabling stroke in ay territory	• **Within 120 days after randomisation**: Death, Stroke, MI, Disabling stroke, Cranial Nerve Palsy and access site haematoma requiring surgery or prolonging hospital stay
ACT-1(5)	CEA vs CAS	Asymptomatic (>=70%)	2005-2013	USA	5 years[a]	1453	60%	68	• Procedural Stroke/Death/ MI or ipsilateral stroke within 1 year. • 5 year stroke free survival	• Composite of cranial-nerve and peripheral-nerve injury, vascular injury, noncerebral bleeding, wound complications related to the neck incision or femoral puncture site, and other complications, 30 days after procedure.

*[1]Europe, Australia, New Zealand, Canada, [2]Europe, Australia, Canada; [4]Measured using Common Carotid Artery method; *Mean follow-up period; [a]Maximum follow-up period up to which results were reported; ¶Only patients with >50% degree of stenosis were included in the analyses.*

Study quality

No trials were scored down for selection bias, with all randomisation processes carried out by a central randomisation service. The outcomes in all trials were assessed by an independent team; independent neurologists or surgeons in CAS vs CEA trials, independent external review teams in NASCET and ECST, and blinded review teams in VA, ACAS and ACST-1. Thus no trials were scored down for detection bias. Loss in follow-up across all trials remained minimal, except for the VA trial which was scored down under attrition bias for having a 7.9% loss during follow-up. With the exception of SAPPHIRE, which did not report outcomes by symptomatic status as mentioned in their trial protocol, all other trials reported outcomes stated in the initial trial protocol. All RCTs comparing CAS vs CEA classified procedural strokes by stroke severity, with the International Carotid Stenting Study (ICSS), Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) and SAPPHIRE also classifying post procedural strokes by stroke severity. The study population in SAPPHIRE was at higher surgical risk than in other RCTs due to the inclusion criteria, which specified that patients should have at least one condition considered to potentially increase the risk of surgical complications. However, this was not seen as a reason for downgrading the trial's study quality score. A breakdown of how each RCT scored on study quality is shown in **table 3.2**.

Table 3.2: Summary of quality assessment in RCTs

Trial	**Selection bias**	**Detection bias**	**Attrition bias**	**Reporting bias**
ECST	*	*	*	*
VA	*	*		*
NASCET	*	*	*	*
ACAS	*	*	*	*
ACST	*	*	*	*
SAPPHIRE	*	*	*	
EVA-3S	*	*	*	*
CREST	*	*	*	*
SPACE	*	*	*	*
ICSS	*	*	*	*
ACT-1	*	*	*	*

Procedural outcomes

Results from RCTs comparing CAS vs CEA show that symptomatic patients allocated to CAS have a statistically significant higher risk of procedural stroke/death compared to symptomatic patients allocated to CEA (OR: 1.71 (1.33, 2.20); **figure 3.1 and appendix figure 3.1**). The procedural stroke/death risks of CAS versus CEA were higher but not statistically significantly different in asymptomatic patients (OR: 1.81 (0.97, 3.36); **figure 3.1**). There were no statistically significant differences observed in odds ratios of procedural stroke/death for CAS vs CEA between symptomatic and asymptomatic patients (heterogeneity p = 0.88), with an overall OR of 1.73 (1.37 to 2.18) across all patient populations (**figure 3.1**). No important heterogeneity was observed across odd ratios of procedural stroke/death for CAS vs CEA in individual trials (**appendix figure 3.1**).

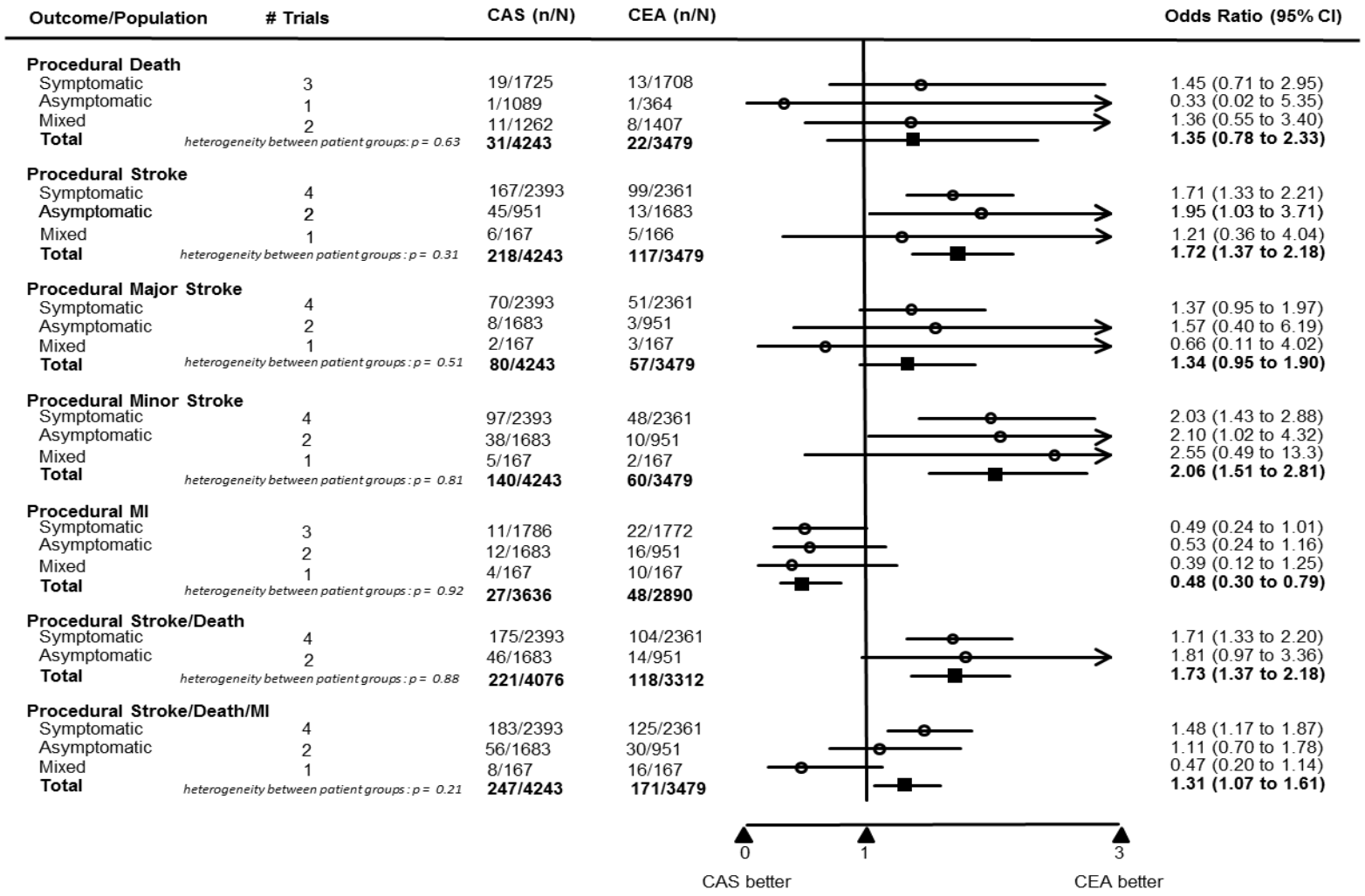
Results in categories of patients by age were reported for three RCTs with symptomatic patients. Odds ratios of procedural stroke/death risks of CAS versus CEA differed significantly between patients aged below 70, and those aged 70 or more, with CAS shown to have significantly higher procedural stroke/death risk when compared to CEA in patients aged above 70 (OR: 2.30 (1.57, 3.35)), while there were no significant differences in procedural stroke/death risks between CEA and CAS in patients aged below 70 with an OR of 1.05 (0.69, 1.61); **appendix figure 3.2**). Procedural stroke/death risks of CAS vs CEA did not differ between males (OR: 1.79 (1.32, 2.43)) and females (OR: 1.60 (1.04, 2.47)); **appendix figure 3.3**). Results by participants' age or gender were not reported in RCTs of asymptomatic patients.

Procedural major stroke risks of CAS vs CEA were not statistically different (Total OR: 1.34 (0.95, 1.90); **figure 3.1 and appendix figure 3.4**) with similar odds ratios observed in symptomatic, asymptomatic and mixed populations (heterogeneity p = 0.51). CAS had a statistically significant higher procedural risk of minor stroke when compared to CEA (OR: 2.06 (1.51, 2.82); **figure 3.1**), with similar odds ratios in symptomatic, asymptomatic and mixed patient populations (heterogeneity p = 0.81).

Procedural MI risk was lower in CAS vs CEA (OR: 0.48 (0.30, 0.79); **figure 3.1 and appendix figure 3.6**) with similar effects observed in symptomatic, asymptomatic and mixed symptom populations (heterogeneity p = 0.92; **figure 3.1**).

Other evaluated procedural outcomes include procedural deaths, where no differences were observed when comparing CAS vs CEA patients (OR: 1.35 (0.78, 2.33); **figure 3.1 and appendix figure 3.7**), procedural stroke risks which were statistically significantly higher in CAS vs CEA (OR: 1.72 (1.37, 2.18); **figure 3.1 and appendix figure 3.8**), and the composite outcome of procedural stroke/death/MI risks which was also statistically significantly higher in CAS vs CEA (OR: 1.31 (1.07, 1.61); **figure 3.1 and appendix figure 3.9**). Relative effects across symptomatic, asymptomatic and mixed patients populations were similar in all three outcomes.

Figure 3.1: PROCEDURAL outcomes in RCTs comparing CAS versus CEA



Overall outcomes

In trials comparing CEA vs MT, CEA had a lower risk of any stroke or procedural death (OR: 0.66 (0.59, 0.75)), with similar relative risks in symptomatic and asymptomatic patients (heterogeneity p = 0.15; **figure 3.2a**; and **appendix figure 3.10**). Note that procedural strokes or deaths could only occur in the CEA arm.

In trials comparing CAS vs CEA, symptomatic patients had a higher risk of any stroke with CAS, when compared to CEA (OR: 1.48 (1.22, 1.80)). While differences in overall stroke risks were not significantly different between CEA and CAS in asymptomatic and mixed symptom patient groups, no heterogeneity was observed in odds ratios across patients of different symptomatic status (heterogeneity p = 0.63; total OR 1.43 (1.20, 1.70); **figure 3.2b**). No heterogeneity was observed between odds ratios in individual trials (p=0.35; **appendix figure 3.11)**.

The risk of any major stroke was similar between CAS and CEA and did not differ between populations by stroke symptomatic status (heterogeneity p= 1.00; total OR=1.07 (0.77 to 1.48); **figure 2b and appendix figure 3.12**). Risk of minor stroke increased with CAS versus CEA **(figure 3.2b and appendix figure 3.13**). While there was clear evidence showing that CAS had higher overall minor stroke risks when compared to CEA in symptomatic patients (OR 1.74 (1.34, 2.27)), the increase in risk was not statistically significant in trials of mixed symptom populations (OR: 1.29 (0.87, 1.77)).

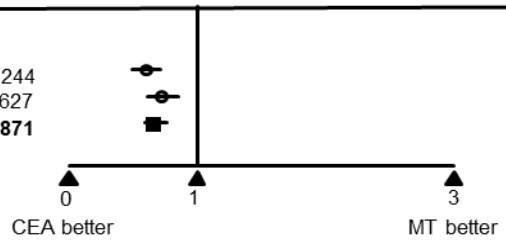
No differences in overall death risks were observed when comparing CAS vs CEA (OR: 1.12 (0.95, 1.33); **figure 3.2b and appendix figure 3.14**), with similar effects observed between symptomatic and mixed patients categories (p = 0.53).

There were no differences in any stroke or procedural death risks between CAS and MT patients (OR:0.97 (0.78, 1.18) for CAS vs MT) in the network meta-analysis. Here information from five trials comparing CEA vs MT (NASCET, ECST, ACST-1, ACAS, VA) and four comparing CAS vs CEA (ICSS, EVA-3S, SPACE, CREST) (**appendix table 3.1**) to create an indirect comparison between CAS and MT and obtain estimates of odds ratios for CAS vs MT.

Figure 3.2: OVERALL outcomes in RCTs

a) CEA vs MT

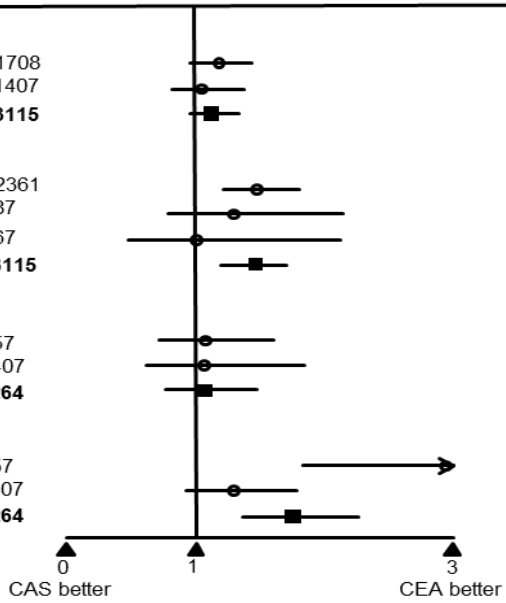
Outcome/Population	# Trials	CEA (n/N)	MT (n/N)	
Any Stroke or Procedural Death				
Symptomatic*	2	260/1483	333/1244	0.60 (0.50 to 0.72)
Asymptomatic	3	294/2596	395/2627	0.72 (0.61 to 0.85)
Total	*heterogeneity between patient groups : p = 0.15*	**554/4079**	**728/3871**	**0.66 (0.59 to 0.75)**



**Only patients with greater than 50% degree of stenosis have been included.*

b) CAS vs CEA

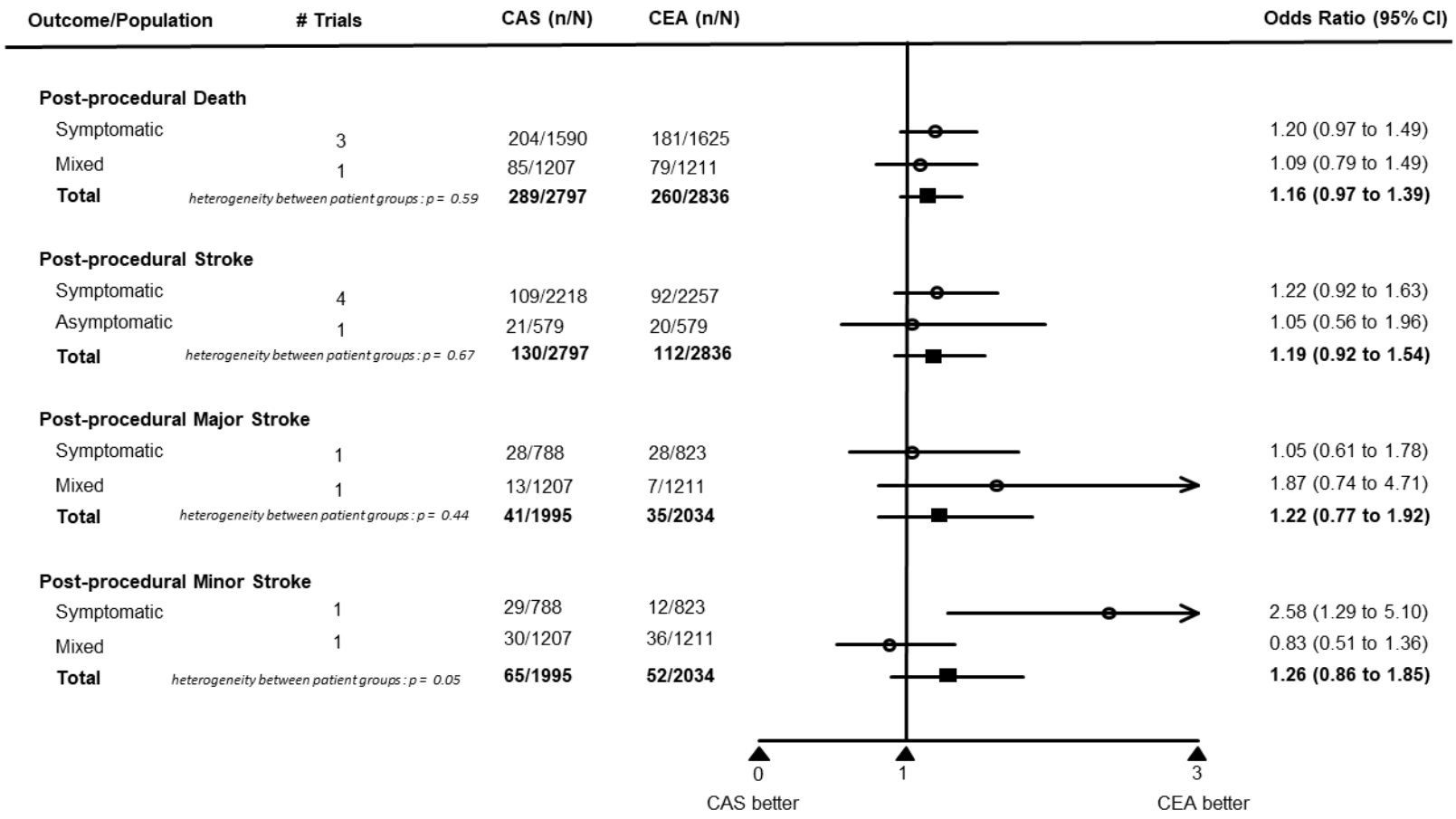
Outcome/Population	# Trials	CAS (n/N)	CEA (n/N)	
Any Death				
Symptomatic	3	223/1725	194/1708	1.17 (0.95 to 1.44)
Mixed	2	125/1429	118/1407	1.05 (0.81 to 1.37)
Total	*heterogeneity between patient groups : p = 0.53*	**348/3154**	**312/3115**	**1.12 (0.95 to 1.33)**
Any Stroke				
Symptomatic	4	276/2393	191/2361	1.48 (1.22 to 1.80)
Asymptomatic	1	36/594	28/587	1.29 (0.78 to 2.14)
Mixed	1	15/167	15/167	1.00 (0.47 to 2.12)
Total	*heterogeneity between patient groups : p = 0.63*	**327/3154**	**234/3115**	**1.43 (1.20 to 1.70)**
Any Major Stroke				
Symptomatic	1	52/853	49/857	1.07 (0.72 to 1.60)
Mixed	2	27/1429	25/1407	1.07 (0.62 to 1.85)
Total	*heterogeneity between patient groups : p = 1.00*	**79/2012**	**74/2264**	**1.07 (0.77 to 1.48)**
Any Minor Stroke				
Symptomatic	1	67/853	23/857	3.09 (1.91 to 5.01)
Mixed	2	84/1429	65/1407	1.29 (0.93 to 1.80)
Total	*heterogeneity between patient groups : p = 0.02*	**157/2282**	**92/2264**	**1.74 (1.34 to 2.27)**



Post-procedural outcomes

There were no statistically significant differences in post-procedural stroke risks in patients allocated to CAS versus CEA in the four RCTs reporting sufficient information to calculate this outcome (total OR 1.19 (0.92, 1.54); heterogeneity between symptomatic and asymptomatic patients p=0.67; **figure 3.3 and appendix figure 3.15**). Only ICSS and CREST reported sufficient information to enable calculation of post-procedural long-term risks separately for major and minor strokes. Major stroke risks were similar for CAS vs CEA (pooled OR: 1.22 (0.77, 1.92); heterogeneity between symptomatic and mixed symptom populations p=0.44; **figure 3.3 and appendix figure 3.16**). Post-procedural minor stroke risks too were similar between CAS and CEA (pooled OR: 1.26 (0.86, 1.85), heterogeneity between symptomatic and mixed symptom populations p = 0.05; **figure 3.3 and appendix figure 3.17**). Non-procedural death risks were also similar when comparing CAS vs CEA (OR: 1.16 (0.97, 1.39); **figure 3.3 and appendix figure 3.18**).

Figure 3.3: POST-PROCEDURAL outcomes in RCTs comparing CAS versus CEA



3.4 Discussion

In this meta-analysis of randomized evidence of effects of CEA and CAS, CAS had significantly higher procedural stroke/death risks compared to CEA. While this holds when considering procedural minor stroke risks, the odds for procedural major stroke risks did not differ statistically significantly between CEA and CAS patients. Similarly, CAS had higher overall stroke and overall minor stroke risks when compared to CEA, while no statistically significant differences were observed in overall major stroke risks. No statistically significant differences in post-procedural long-term stroke risks were observed between CEA and CAS. Only two trials reported sufficient information to evaluate post-procedural long-term stroke risks by stroke severity, with no statistically significant differences observed between CEA and CAS. CEA reduces the risk of overall stroke or procedural death when compared to MT alone.

Other systematic reviews(89, 90) which have synthesised information from RCTs comparing CAS vs CEA have also shown CEA to have lower procedural and overall risks compared with CAS, while Bangalore et al(90) state that after excluding procedural events, CEA and CAS risks were similar. However, these reviews did not distinguish the relative risks of major and minor strokes. Furthermore, both previous reviews included data from the CAVATAS trials, in which only 26% of patients under the endovascular treatment arm actually underwent CAS, with the rest receiving balloon angioplasty, which may have influenced the results in favour of CEA.(82) Another meta-analysis of RCTs comparing CAS vs CEA by Sardar et al(91) excluded both CAVATAS and SPACE, with SPACE being excluded due to only 26% of CAS patients having a protection device during the procedure. This review showed CAS to have lower procedural death, stroke, MI or cranial nerve palsy risks when compared to CEA. However, this result was largely driven by the high number of cranial nerve palsy injuries

in the CEA when compared to CAS (135 of 2890 vs 9 of 3636). Other results from this meta-analysis remain similar to our analysis, with CEA shown to have lower procedural and overall stroke risks largely due to the high number of minor strokes associated with CAS, while there were no differences in long-term post-procedural fatal or disabling stroke risks between CEA and CAS. The most recent systematic review of RCTs comparing treatment methods for carotid stenosis Barkat et al(92) focuses only on asymptomatic patients, including all relevant RCTs irrespective of the number of patients randomised to a treatment arm, and reported that CEA reduces the odds of long-term mortality (differences not significant) and ipsilateral stroke (differences statistically significant) when compared to MT, and perioperative stroke and mortality when compared to CAS with differences not being statistically significant. Barkat et al(92) is to the best of my knowledge the only other systematic review of RCTs comparing treatment methods for carotid stenosis which reports relative risks of CAS vs MT by performing a network meta-analysis, reporting no statistically significant differences in post-procedural long-term risks between CAS and MT, with a relative long-term ipsilateral stroke risk of 0.58 (0.32, 1.05) and relative mortality risk of 0.84 (0.38, 1.84) for CAS vs MT.

CAS has been found to have higher procedural stroke/death risks and overall stroke risks compared to CEA. However, it is evident that a large number of stroke events in CAS patients are minor strokes, with no statistically significant differences in both procedural and overall major stroke risks between CEA and CAS. Major stroke has a greater negative impact on health related quality of life than minor stroke.(20) Therefore, any further analysis of overall impact of different treatment methods for carotid stenosis on quality-adjusted survival and cost-effectiveness, need to take into account the separate effects of CAS and CEA on major and minor strokes (see **chapter 5)**, given that, compared to minor

strokes, major strokes have both a greater impact on health related quality of life,(20) and a higher health and social care costs.(93) It is worth noting that the calculation of odds ratios for both procedural risks and overall stroke risks may be biased in favour of CAS by the inclusion of results from the SAPPHIRE trials where all patients had at least one medical complication which increased the risk of surgery. However, the sample size of SAPPHIRE was much smaller compared to other RCTs, thus having a limited impact on results pooled using fixed-effects meta-analysis techniques.

No differences in post-procedural long-term stroke risks were observed between CEA and CAS, implying that differences in overall stroke risks between CEA and CAS stem mainly from lower procedural risks of CEA. This could be due to CAS being a relatively new procedure when compared to CEA, thus not benefitting from increased operator experience. However, it is worth noting that in our analysis individuals with procedural events were removed from the number at subsequent risk, thus violating the principle of intention to treat analysis and possibly introducing some bias. Thus, the individual patient data meta-analysis of trials comparing CAS vs CEA from collaborations such as Carotid Stenting Trialists' Collaboration (CSTC) is likely to provide further useful data.

Our results indicate statistically significant lower procedural stroke/death risks, and lower overall stroke risks for symptomatic patients undergoing CEA, when compared to those undergoing CAS. No statistically significant differences in these risks were observed in asymptomatic patients. This could be due to limited information available on asymptomatic patients, which may have hindered the statistical strength of our analysis as indicated by the large confidence intervals of ORs. Only CREST and ACT-1 reported results for asymptomatic patients, with SAPPHIRE not reporting results by symptomatic status. Pooling information from mixed symptom populations shows that CEA has lower risk of procedural stroke/death, and of overall stroke risks in the combined population.

While pooling information from both patient groups can be justified by the lack of heterogeneity observed between ORs of symptomatic and asymptomatic patients, critics may argue that this absence of heterogeneity itself may have stemmed from the uncertainty surrounding ORs from asymptomatic populations. Thus a need for further RCTs comparing CAS vs CEA in asymptomatic patients remains, with large trials in the pipeline such as ACST-2 expected to provide more information on the effectiveness of interventions in asymptomatic patients, adding much needed statistical strength to a meta-analysis of this nature.

When stratifying patients by age, it was noted that, compared to CAS, CEA had lower procedural stroke/death risks in symptomatic patients 70 years or older, while no differences were observed in those aged below 70. No information was available on how relative procedural stroke/death risks of CAS vs CEA differed by age in asymptomatic patients. Differences in relative procedural stroke/death risks of CAS vs CEA between age groups could be pivotal in informing policy makers, especially when incorporated to a cost-effectiveness framework looking at a case by case scenario based on a patient's risk factors. Thus, this information has been taken into account in a sensitivity analysis in the new cost-effectiveness framework studying cost-effectiveness of treatment methods for carotid stenosis (**chapter 5**).

When compared with patients randomised to MT alone, both asymptomatic and symptomatic patients randomised to CEA had lower overall stroke or procedural death risk. In the analysis of symptomatic patients, only those with a degree of stenosis greater than 50% (NASCET measurement) were included in the analysis, with a previous analysis of the ECST and NASCET trials showing relative risks of overall stroke or procedural death differing significantly between patients with a degree of stenosis less than 50%, and greater than 50%.(18) This analysis(18) showed that symptomatic patients

with less than 50% stenosis have lower risks with MT than with CEA, leading to most guidelines recommending that only symptomatic patients with greater than 50% degrees of stenosis undergo operation. While our results are in support of the use of CEA in both symptomatic and asymptomatic patients due to achieving lower overall stroke rates, it is worth noting that the majority of the patients included in these trials were recruited prior to the year 2000, and thus the studies did not take into account advances made in medical therapy in recent years, particularly in the use of more intensive statin therapy. Only 16% of patients in NASCET and 8% in ECST, two of the oldest trials, were on lipid-lowering therapy. Patients receiving lipid-lowering therapy in ACST-1 increased from around 10% in the beginning of the trial to more than 80% in 2007, highlighting the rapid increase in use of lipid-lowering therapy.(3) While advances in MT are likely to favour long-term stroke rates, these are likely to be found for both CEA and MT in the long run, thus having a minimal effect on stroke odds ratios after excluding procedural events. Improvements in MT may also have an impact on procedural risks of CEA (and CAS), due to the role it plays in controlling risk factors of patients prior to intervention. This may favour CEA (in CEA vs MT) and thereby affect the cost-effectiveness of CEA vs MT. Changes in procedural risks of CEA and CAS over time are further examined using large observational studies in **chapter 4**. Results from the network meta-analysis suggest that there are no differences in overall stroke risks between CAS and MT, with the uncertainty in the odds ratios reflecting the lack of information required to perform an indirect comparison of this nature. More concrete evidence on how treatment of patients with CEA or CAS compares with MT alone in contemporary practise will be helpful once the results of trials in the pipeline are available.

A number of new RCTs have been initiated in the past decade. ACST-2, which looks at CAS vs CEA in asymptomatic patients had a recruitment target of 5,000 patients(94),

now revised to 3,600, and is currently on track to complete recruitment by early 2020 and is closest to completion.(23) CREST-2 consists of 2 independent parallel trials, one comparing CEA vs MT alone and the other CAS vs MT alone, and has currently recruited 1,191 patients(95), having estimated to recruit 2,480 patients by 2020.(96) SPACE-2 however, which initially started as a three armed trial of MT alone vs CEA vs CAS, changed its trial design to two parallel trials of MT alone vs CEA and MT alone vs CAS (similar to CREST-2), before stopping due to slow recruitment.(97) While difficulties in recruiting patients for RCTs may be partly attributed to strict inclusion criteria, patients may also be reluctant to enrol in trials with MT alone when previous RCTs have shown CEA to have lower stroke risks. Therefore, other approaches can be considered to overcome limitations in current evidence from available RCTs', when developing the analytical framework for the cost-effectiveness analysis of treatment methods for carotid stenosis.

There are limitations to our analysis. Identification of trials and manuscripts was not performed by searching the underlying literature de novo, and so it is in theory possible that some trials or manuscripts were missed. However, given the limited number of trials with more than 100 patients in each trial arm which have compared interventions for carotid stenosis as identified in previously published systematic reviews, and the compulsory registration of RCTs in online registers of trials, the chances of this are very small. A further limitation of this systematic review was that it was performed by a single reviewer, which might have increased the probability of missing studies in the study identification or data extraction process. Secondly, this meta-analysis was based on published results data, with many RCTs not presenting results for separate endpoints (eg, stroke risks by stroke severity). Third, when calculating relative post-procedural major and minor stroke risks between interventions, patients who have experienced an event in

the procedural period were excluded from the analysis, which can create a small bias due to the randomisation process being hindered as not all patients randomised to an intervention were included in the analysis. Other limitations stem from a large proportion of patients in these trials (with the exception of ACT-1) having been recruited prior to the era of intensive statin therapy, thus bringing into question their validity in a contemporary care setting. These limitations, together with generally limited information in asymptomatic patients, highlight the value of and the need for the completion of ongoing trials.

Our results suggest that compared to MT alone, CEA reduces overall stroke risks (inclusive of procedural deaths) and, compared to CAS, CEA has lower procedural stroke/death risks and lower overall stroke risks. Most difference in outcomes between CAS and CEA however are due to a higher rate of procedural minor strokes with CAS. Post-procedural long-term stroke risks are not statistically different between CEA and CAS. Given the possibility of procedural risks of CAS falling with time due to technical advances and increased operator experience, and the considerable uncertainty in relative value of different treatments in the current more intensive practice of MT, trials in the pipeline will prove crucial in providing much needed data on comparative effectiveness of interventions to treat carotid stenosis in a contemporary care setting.

4

Have procedural and overall risks of CEA and CAS changed over time? A systematic review and meta-analysis of observational cohort studies

4.1 Introduction

Clinical guidelines and cost-effectiveness analyses of carotid endarterectomy (CEA) and carotid artery stenting (CAS) (**chapter 2**) are based on randomised controlled trial (RCT) data although these trials' patients were mostly recruited some years ago as noted in **chapter 3**. While RCTs remain the gold standard for comparative analysis between treatment methods for carotid stenosis, absolute procedural risks of CEA and CAS patients may have changed since these trials were conducted. Control of vascular risk factors has intensified and the widespread use of statins may play a pivotal role in reduction of stroke risk.(3, 98) Patient selection for CEA and CAS has also improved(99) with patients considered unfavourable for CEA due to hostile anatomy or co-morbidities more likely to be referred for CAS. Furthermore, emerging evidence suggests that both in-hospital and procedural stroke/death risks of CEA and CAS might have decreased with improved patient selection, better operator skills and technological advancements cited as possible contributors.(3, 26, 65) A decrease in procedural risks may put into question the results from economic evaluations which have been developed to evaluate the cost-effectiveness of treatment methods for carotid stenosis, with information from either RCTs or observational cohort studies prior to the year 2005 being used to inform procedural risks of CEA and CAS patients (**chapter 2**).

This chapter systematically reviews procedural risks of CEA and CAS in large observational cohort studies to study the variation of risks over time in order to obtain estimates of contemporary procedural risks of CEA and CAS.

4.2 Methods

Study selection

MEDLINE and EMBASE were searched from inception to 20th May 2016 for observational cohort studies reporting procedural risks in patients undergoing CEA and CAS. A combination of terms related to the presence of carotid stenosis, CEA and CAS interventions, and outcomes made up the core search criteria, which were then combined with terms identifying observational cohort studies **(appendix table 4.1).** Manuscripts were initially screened by title and abstract, followed by full text review to identify observational cohort studies with a population of greater than 1000 patients diagnosed with carotid stenosis, who had undergone CEA or CAS. Studies were only considered if they reported outcomes by symptomatic status (ie, recent history of stroke or transient ischemic attack (TIA)) and if they had a follow-up period of at least 30 days from procedure. Studies also had to report at least one of the following procedural outcomes: stroke, death, myocardial infarction (MI), sub-categories of stroke, or a composite endpoint of any of these outcomes. When populations overlapped across eligible manuscripts, only the most recent study population was included. The reference lists of recent systematic reviews(100-103) were checked for further relevant studies.

Quality assessment

An adapted version of the Newcastle quality assessment scale(104) was used to evaluate risk of bias (**appendix text 4.1**) based on patient selection (representativeness, description of risk factors, ascertainment of exposure) and outcome evaluation (method of outcome assessment, length and adequacy of follow-up). Maximum score was 8 with higher scores indicating better quality.

Procedural events were defined as events occurring within 30 days from the procedure. The primary procedural outcome was stroke or death. Other outcomes of interest included death, stroke, myocardial infarction (MI), stroke/death/MI, major stroke (Modified Rankin Score of ≥3), and minor stroke (Modified Rankin score of <3).

Outcomes were summarised by participants' symptomatic status at study entry. Event rates were also summarised according to whether study recruitment periods ended before the year 2005, or thereafter, because of the substantial increase in use of statins and other stroke prevention treatments in later years.

Partial second review

Kusal Lokuge reviewed all manuscripts. A second reviewer (Djurre De Waard) screened a random sample of 20% of the manuscripts(105) by title and abstract and then by full text. The second reviewer also assessed the risk of bias and extracted data from 20% of the included studies. Concordance was calculated by calculating the percentage of manuscripts which were selected by both first AND second reviewer from the same random sample, when compared to the total number of manuscripts selected by the first OR second reviewer.

Statistical methods

The restricted maximum likelihood random effects method(77) with Freeman-Tukey (double arcsine) transformation(106, 107) was used to synthesise the event rates in observational cohort studies. The analyses were executed in R Studio v0.99.903, with package Metaphor version 1.9-9. Heterogeneity between studies was assessed using p-values from I^2 heterogeneity statistic(108), while heterogeneity between pooled estimates of pre- and post-2005 studies was assessed using two-sided t-tests, after the logarithmic

transformation of event rates. A 95% level of significance was used. Random effects logistic meta-regressions(109) were performed with year of completion of study recruitment as an explanatory variable to assess annual trends in procedural event rates.

Sensitivity analysis

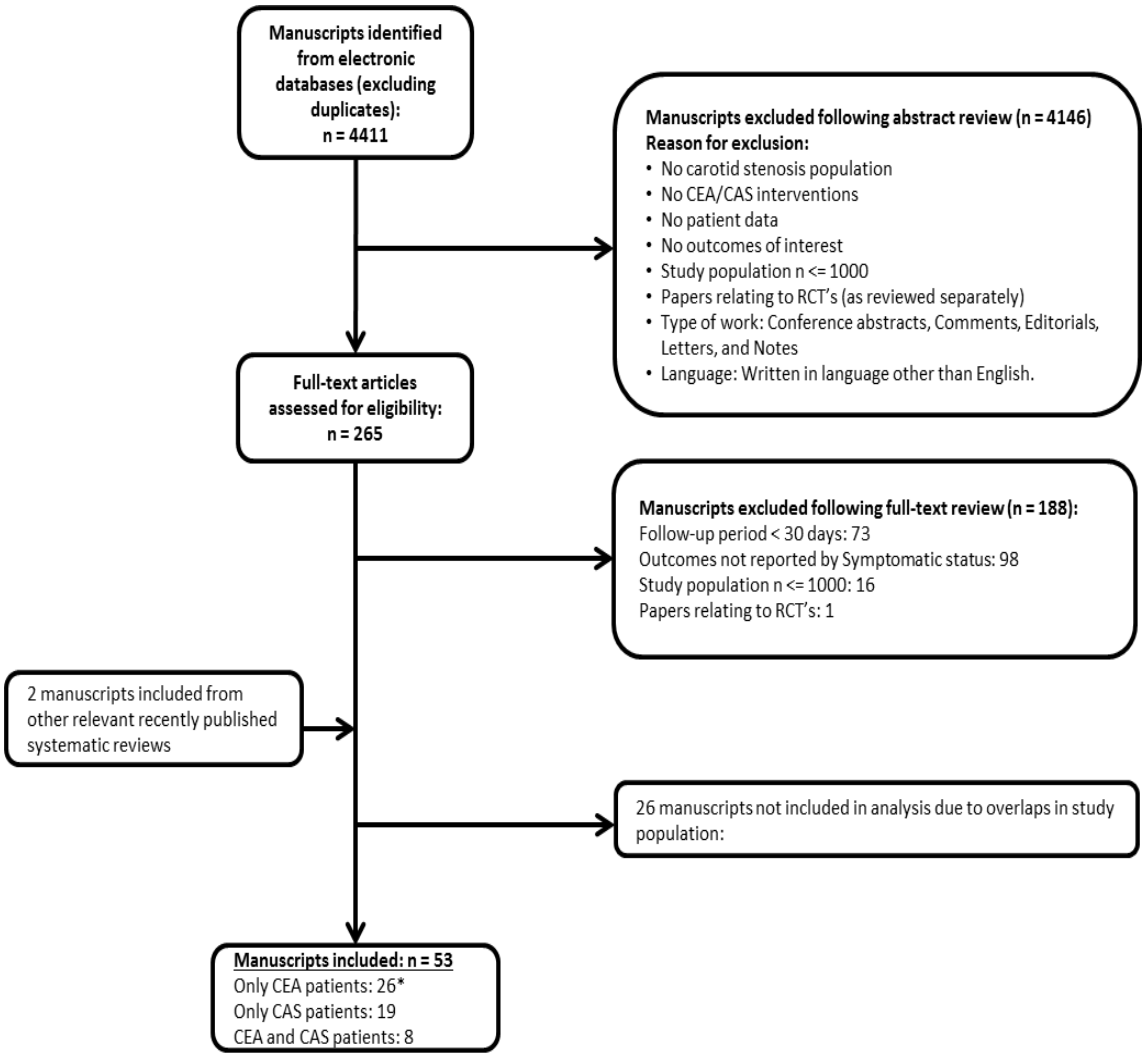
In a further sensitivity analyses, studies with a quality assessment score of less than 6 were excluded to assess the robustness of the results to study quality. Observational cohort studies were also further stratified by method of outcome assessment (whether assessed by an independent neurologist or not), and by geographic region (Europe or Northern America) which had been identified as possible reasons for heterogeneity.

4.3 Results

Study selection

4,411 manuscripts were screened by title and abstract by the first reviewer (KL) with 265 of them progressing to full-text review (**figure 4.1**). 77 manuscripts fulfilled the eligibility criteria, but 26 of these had study populations overlapping with populations in other eligible manuscripts (**appendix table 4.2**). Two further manuscripts(110, 111) were added following review of references from recent reviews. The second reviewer screened 883 manuscripts (20%) by title and abstract. There was 98% concordance between the two reviewers in the judgement of eligibility of studies; any disagreement was resolved by discussion. Thus, 53 manuscripts (**appendix table 4.3**) were included in the review and underwent quality assessment and data extraction.

Figure 4.1: Selection of studies for inclusion in the systematic review



*Vikatmaa P. et al (2012) contributed data for 8 separate study populations. Kresowik T. et al (2004) contributed data for 2 separate study populations.

CEA, carotid endarterectomy; CAS, carotid artery stent procedure; RCT, randomised controlled trial.

Study quality assessment

The average quality score of included studies was 6.6 (**appendix table 4.4**). Nine studies were scored down by one point because the study population was not representative of usual carotid stenosis populations, either due to the average age of the cohort being above 75 years or due to population characteristics not being reported. Nineteen were scored down because of a lack of a description of the definition of "symptomatic" patients. When explicit, the majority of studies defined symptomatic patients as those with stroke or TIA within 6 months prior to procedure. However, larger retrospective databases defined symptomatic patients as those experiencing "stroke or TIA any time before procedure". Twenty-two studies were scored down due to their method of outcome assessment. Although outcome assessment by independent neurologists is the gold standard, such studies are rare. Therefore, studies in which outcomes were assessed through record linkage or by consultant neurologists/surgeons or trained nurses but not by an independent neurologist received the highest score on this indicator; where outcomes were self-reported by the patient or the method of outcome assessment was not stated, the score was reduced. The second reviewer (DW) also extracted data from and assessed the risk of bias in 10 manuscripts (20% of those included in systematic review), with results matching those of the first reviewer.

Procedural stroke/death was the most commonly reported outcome, reported in 29 CEA studies (8 pre-2005, 21 post-2005) and 13 CAS studies (2 pre-2005, 11 post-2005). Period of study recruitment ranged from 1976 to 2014 in CEA studies, and from 1989 to 2011 in CAS studies. Only 7 CEA studies and 5 CAS studies reported procedural MI event rates. 3 CEA studies and 7 CAS studies reported results for major and minor strokes separately.

Procedural risks of CEA (Symptomatic patients)

The procedural stroke/death risk following CEA in symptomatic patients across the 24 studies was 3.44% (95% CI 2.70% - 4.23%) (**figure 4.2**). However, procedural stroke/death risk in studies where the recruitment period ended after 2005 (2.68% (95% CI 2.12% - 3.31)) was significantly lower (p = 0.002) than in studies completing recruitment before 2005 (5.11% (3.48% - 7.06%); **figure 4.2**). Substantial heterogeneity in rates was observed across individual studies (**appendix figure 4.1**). The meta-regression analysis assessing annual trend over time indicated a 6.1% per annum reduction in CEA procedural stroke/death rate in symptomatic patients (**figure 4.3a**). When considered separately, the rates of procedural deaths and strokes were lower in later studies, however the differences were not statistically significant (**figure 4.2**), and data on procedural major and (separately) minor strokes, are limited (**appendix figure 4.2**). There was no heterogeneity between rate of procedural MI in studies completing recruitment before or after 2005 (heterogeneity p=0.94; overall risk 0.96% (95% CI 0.71% - 1.25%); **figure 4.2**).

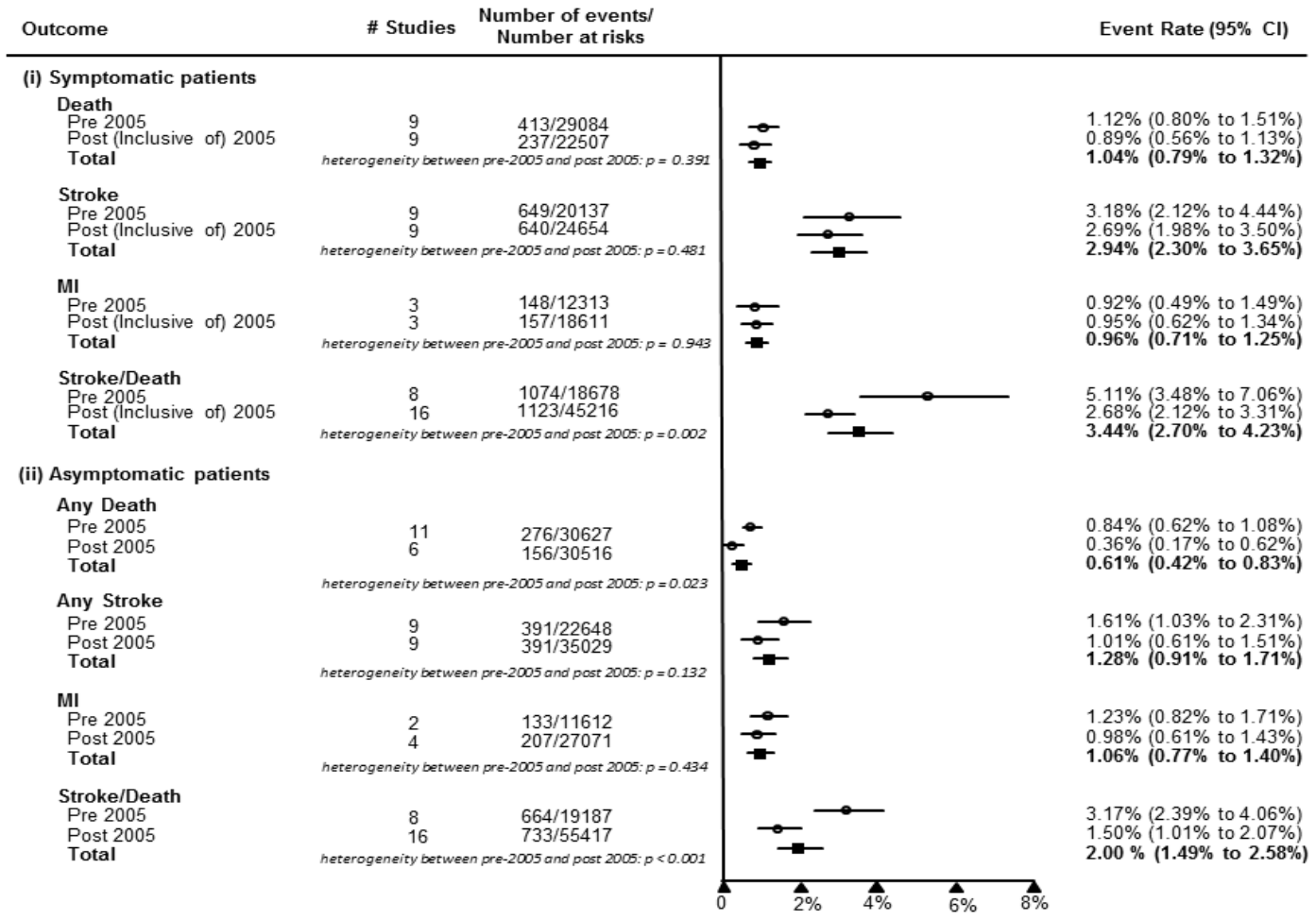
Three studies in the review reported procedural outcomes by delay of procedure from symptoms(112-114) suggesting higher procedural stroke/death rates with an earlier procedure but mixed results as to the time period over which procedural risks might be increased. Two studies reported procedural outcomes by type of symptom(112, 115) suggesting higher rate with increased symptom severity.

Procedural risks of CEA (Asymptomatic patients)

In asymptomatic patients, the overall CEA procedural stroke/death risk across the 24 studies was 2.00% (95% CI 1.49%-2.58%) (**figure 4.2**), with combined procedural risks in post-2005 studies (1.50% (1.01% - 2.07%)) being significantly lower (p = 0.0001)

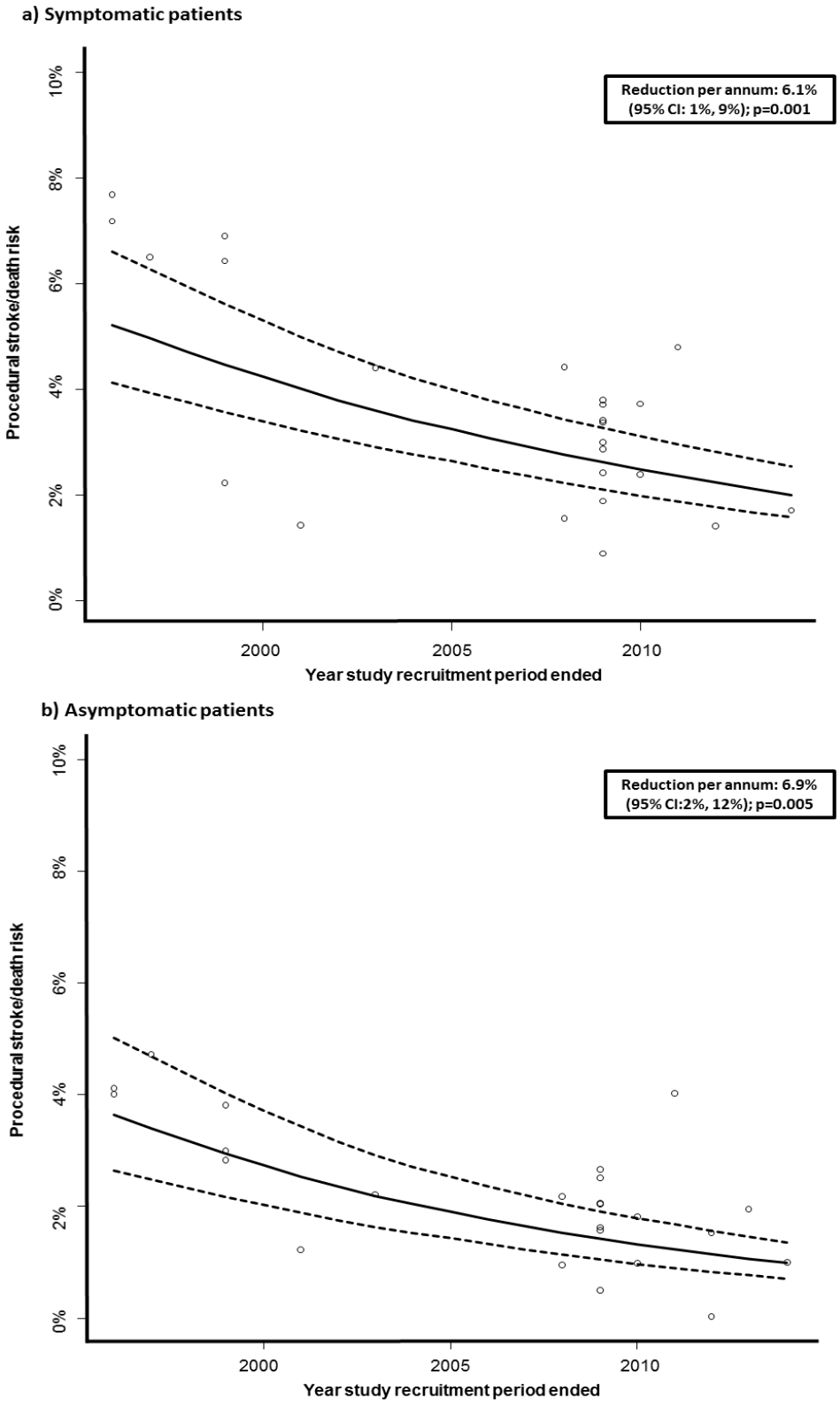
when compared with corresponding risks in pre-2005 studies (3.17% (2.39% - 4.06%)) (**figure 4.2**). Substantial heterogeneity in rates was observed across individual studies (**appendix figure 4.3**). In the meta-regression analysis, there was 6.9% per annum reduction in CEA procedural stroke/death rate (**figure 4.3b**). Procedural deaths and strokes, separately, were lower in later studies, with the differences in death rate significantly lower in post-2005 studies (**figure 4.2**). Data on procedural major and, separately, minor strokes is very limited (**appendix figure 4.2**). There was no heterogeneity in procedural MI rates between studies completing recruitment before or after 2005 (heterogeneity p=0.43) and the combined rate across all studies was 1.06% (95% CI 0.77% - 1.40%) (**figure 4.2**).

Figure 4.2: CEA procedural risks in patients classified by symptomatic status



Adverse event rates summarised across all studies and separately for studies completing recruitment before year 2005 ("Pre 2005") or thereafter ("Post 2005").CEA, carotid endarterectomy; MI, myocardial infarction; CI, confidence interval

Figure 4.3: Meta-regression of CEA procedural stroke/death rates over time, classified by symptomatic status



Procedural risks of CAS (Symptomatic patients)

The procedural stroke/death risk of CAS in symptomatic patients did not change significantly over time (heterogeneity p=0.74 between pre- and post-2005 studies) with an overall rate across the 13 studies of 4.77% (95% CI 3.67% - 5.99%) **(figure 4.4**). Substantial heterogeneity in procedural risk was observed across individual studies (**appendix figure 4.4**). In the meta-regression analysis, there was a non-statistically significant 2.7% (95% CI: -3%, 8%) per annum reduction in CAS procedural stroke/death rate in symptomatic patients (**figure 4.5a**). There were no differences between the rates of procedural deaths and strokes, separately, before and after 2005 (**figure 4.4**). The ratio between rates of procedural major to procedural minor strokes was about 2:3 (1.54% vs 2.38%; **appendix figure 4.5**). The combined rate of procedural MI across the five contributing studies, all completing recruitment post 2005, was 0.92% (95% CI 0.44% - 1.54%) (**Figure 4.4**).

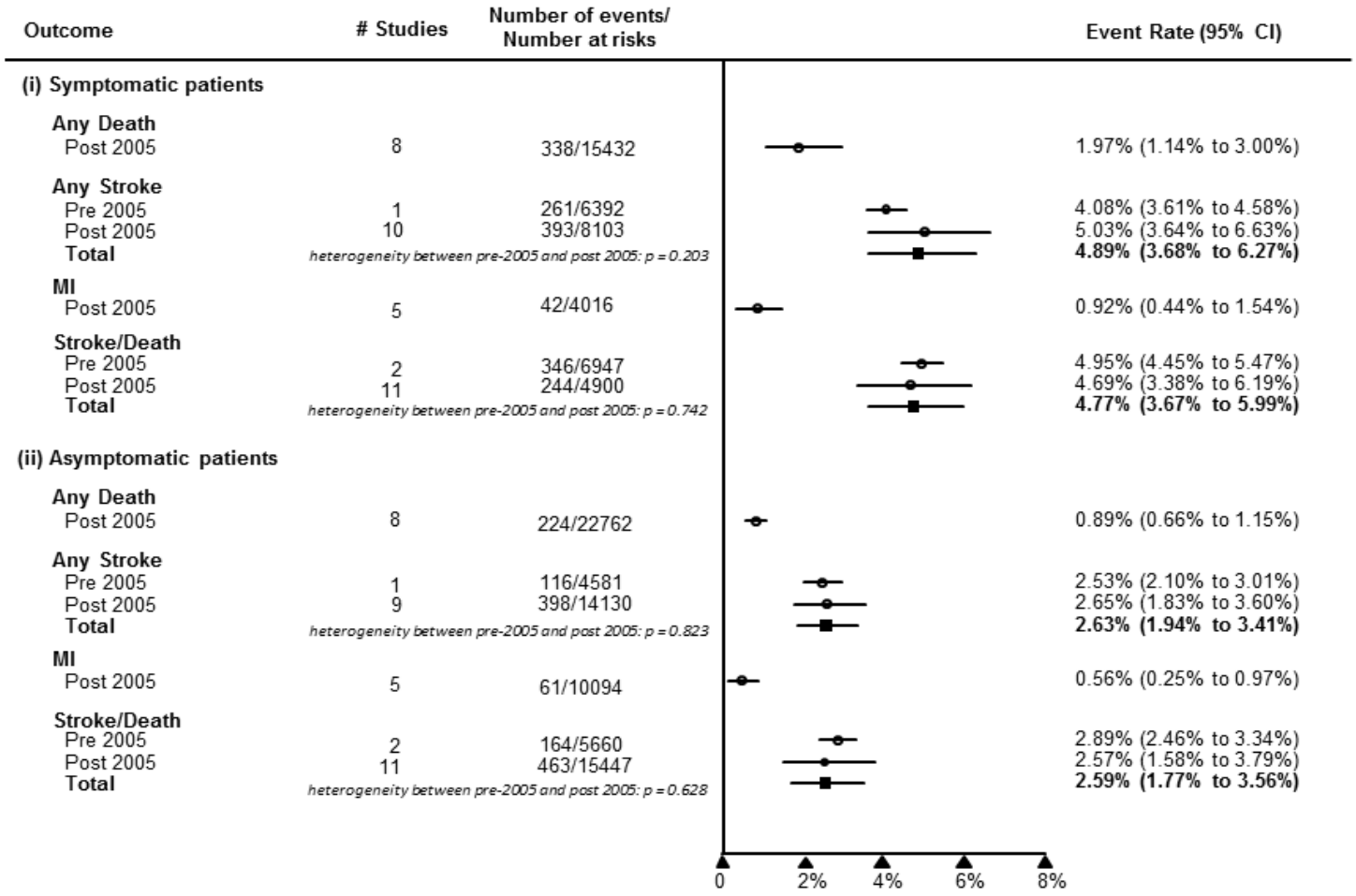
Procedural risks of CAS (Asymptomatic patients)

The procedural stroke/death rate of CAS also did not change significantly in asymptomatic patients (heterogeneity p = 0.63 between pre- and post-2005 studies), with an overall risk of 2.59% (95% CI 1.77% - 3.56%) across the 13 contributing studies (**figure 4.4**). Substantial heterogeneity was observed across the individual studies (**appendix figure 4.6**). In the meta-regression analysis, there was a non-statistically significant 1.8% (95% CI: -8%, 11%) per annum reduction in procedural CAS stroke/death rate in asymptomatic patients (**figure 4.5b**). There were no differences in the rates of procedural CAS deaths and strokes, separately, before and after 2005 (**figure 4.4**) and the ratio between rates of procedural major to procedural minor strokes was about 2:3 (0.87% vs 1.46%; **appendix figure 4.5**), The

combined rate of procedural MI across the five contributing studies, all completing recruitment post 2005, was 0.56% (95% CI 0.25% - 0.97%) (**figure 4.4**). The data from studies used to calculate results in asymptomatic CEA patients are summarised in **appendix table 4.8**.

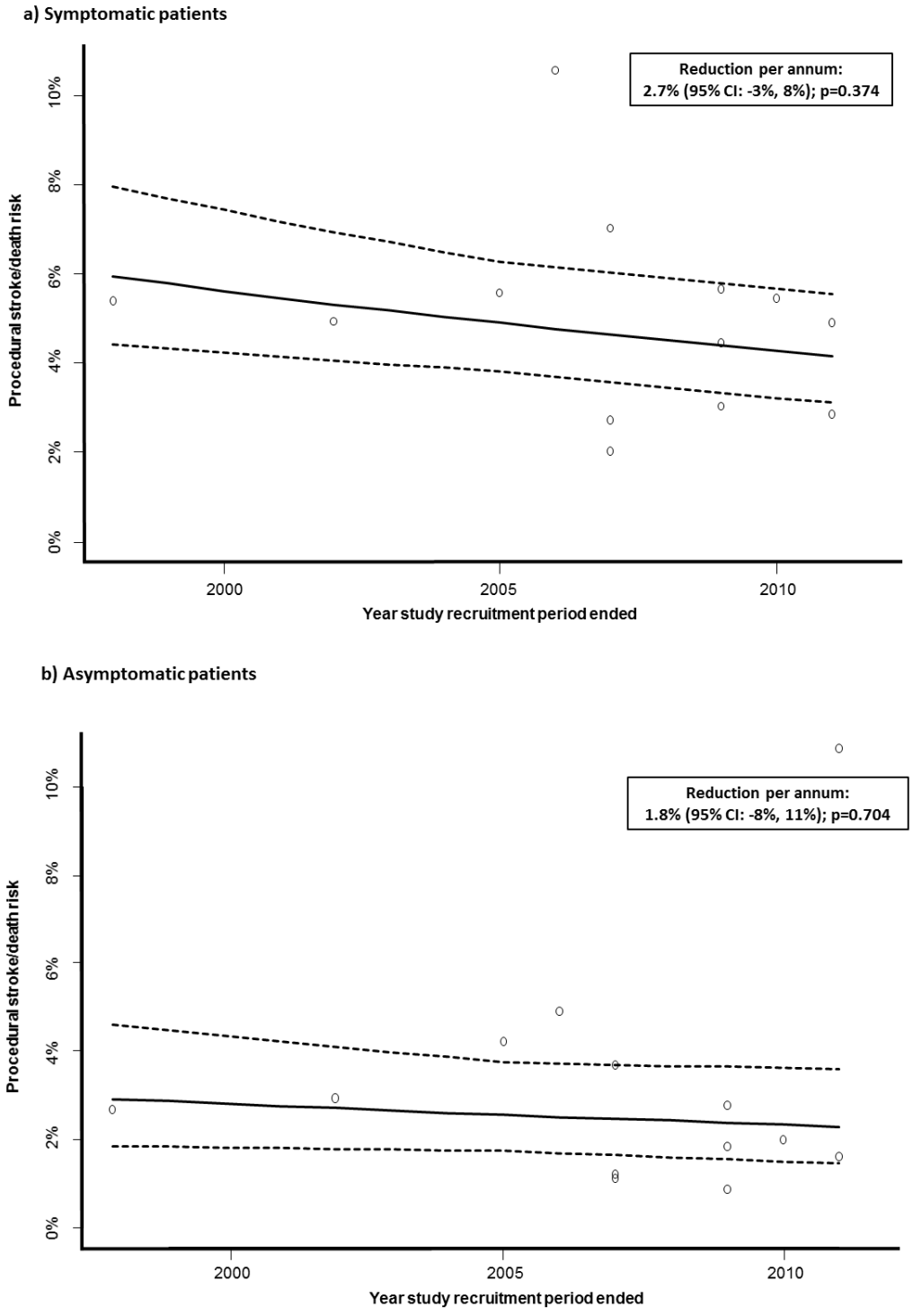
There were no studies in the review reporting procedural outcomes by time since symptoms or by type of symptoms.

Figure 4.4: CAS procedural risks in patients classified by symptomatic status



Adverse event rates summarised across all studies and separately for studies completing recruitment before year 2005 ("Pre 2005") or thereafter ("Post 2005").CAS, carotid artery stent procedure; MI, myocardial infarction; CI, confidence interval.

Figure 4.5: Meta-regression of CAS procedural stroke/death rates over time, classified by symptomatic status



Sensitivity analyses

Similar trends in differences of procedural stroke/death risks between pre- and post-2005 studies were observed in studies with a quality score of 6 or more, with post-2005 procedural stroke/death risks being significantly lower than pre-2005 procedural stroke/death risks in symptomatic ($p = 0.03$) and asymptomatic ($p = 0.02$) CEA patients, while no differences were observed in symptomatic ($p = 0.52$) and asymptomatic ($p = 0.95$) CAS patients (**appendix table 4.5)**. There were no clear differences in procedural risks between studies in which outcomes were assessed by an independent neurologist and studies in which no assessment was performed by independent neurologist (**appendix table 4.6)**. In a sensitivity analysis of procedural stroke/death separately for North America and Europe, however, there were some notable differences with higher procedural CEA stroke/death rates observed in pre-2005 studies conducted in North America, while procedural CEA rates in post-2005 studies were similar in the two regions. This resulted in larger reductions in CEA procedural stroke/death rates observed from pre- to post-2005 among studies conducted in North America compared to those in Europe (**appendix table 4.7**). The rates of procedural CAS stroke/death were also somewhat higher in North America than in Europe and remained so in later years (**appendix table 4.7**).

4.4 Discussion

The procedural risks of CEA and CAS over time were systematically reviewed. Data from 54 studies, including nearly 300,000 patients suggests that procedural stroke/death risk following CEA has decreased in recent years for both symptomatic and asymptomatic patients. While post-2005 procedural risks were similar between studies conducted in Europe

and North America, post 2005 procedural risks were somewhat higher in studies conducted in North America pre 2005. Risks of CAS appear to have remained more stable over time with an insignificant decrease in recent years and, again, somewhat higher risks reported for studies conducted in North America. Only one study reported overall stroke risks in patients, a year or more from procedure, thus not allowing for comparisons to be made across time periods for overall stroke risks.

Some of the decrease in procedural risks could be due to improvements in medical treatment, with statin treatment in patients prior to intervention probably important. Since 2003, the use of statins has increased dramatically, with the use of lipid-lowering therapy in the ACST-1 trial increasing from less than 10% in 1993 to more than 80% when trial follow up ended in 2007.(3) A sub-group analysis in ACST-1 suggested that patients on lipid-lowering therapy had lower perioperative risks.(3) McGirt et al. found that, in 1566 patients undergoing CEA, preoperative statin therapy was associated with lower procedural stroke risk (1.2% vs 4.5%), TIA (1.5% vs 3.6%) and mortality (0.3% vs 2.1%).(98) ACST-1 data also indicated that some procedural CEA strokes are caused by thrombosis or thrombotic occlusion of the ipsilateral carotid artery(116) with diastolic blood pressure a possible risk factor of procedural stroke/death.(117) A better understanding behind causes of procedural stroke in CEA patients from trials such as ACST-1 may also have contributed towards a fall in procedural risks of CEA over time.

Our results suggest that CEA procedural risks have decreased over time, but those of CAS appear to be more stable. A trend towards centralization of CEA in high-volume facilities with specialist anaesthetists, neurology and intensive care support and high-volume vascular centres and surgeons(118) may have contributed to this. Furthermore, patients considered

"high-risk for CEA" are increasingly being referred to CAS which might explain the lower risk profile for CEA-treated patients in cohort studies.(119) However the effect of such patient selection is expected to be more limited in large studies such as those included in this review.

There has been somewhat less time to establish procedural norms and quality assurance standards for CAS when compared to CEA, with the first RCT to include only CAS as one of the treatment arms, publishing results in 2004.(10) Thus with CAS being a relatively newer procedure CAS's operators might be in an earlier part of the learning curve. With increased operator experience and a better understanding on how best to make use of technological advancements in stenting, procedural CAS risks might fall in the future. For example, it has been suggested that when operators gain experience, embolic protection devices (EPDs) result in fewer adverse events(120). However, whilst overall, EPDs may reduce procedural risks(121), evidence remains mixed, as distal EPDs have been shown to cause more ischemic lesions compared with proximal EPDs.(122)

Procedural risks for symptomatic CEA and CAS in post-2005 observational studies were lower than those for symptomatic per protocol populations in randomised trials: SPACE (CEA: 6.5%; CAS: 7.7%)(123), EVA-3S (CEA: 3.9%; CAS: 9.6%)(123) and ICSS (CEA: 3.4%; CAS: 7.5%).(87) Comparable per protocol stroke/death risks data were not available from asymptomatic clinical trial populations. Intention-to-treat procedural stroke/death risks in asymptomatic patients in earlier trials were > 2.5% for CEA(3, 70, 81) but recent trials have reported procedural risks similar to those from post-2005 observational studies reported here: asymptomatic patients in CREST-1 (CEA: 1.4%; CAS 2.5%)(58) and ACT-1 (CEA: 1.7%; CAS: 2.9%).(5) However results from the logistic meta-regression report that

procedural risks of asymptomatic CEA patients post-2010 fall below 1.4%, and those of asymptomatic CAS patients fall below 2.5% post-2006 showing that procedural risks of even the most recent RCTs may not reflect contemporary practise. Post-2005 procedural risks may better represent contemporary practice and contribute to the ongoing debate about appropriateness of carotid intervention in the context of better contemporary medical treatment. Procedural risks after 2005 are much lower than current guideline thresholds for acceptable CEA practice (symptomatic: 6%; asymptomatic: 3%),(124) but these also need to be reviewed in conjunction with more intensive medical treatment and long-term stroke risk.

In due course, pooled results from several completed and ongoing large randomised trials directly comparing CEA with CAS (CREST-1, ACT-1 and ACST-2(125)) and CEA/CAS vs MT (ECST-2(126) and CREST-2(127)) will provide reliable contemporary randomised evidence. Until newer RCTs are complete, results from older RCTs remain the gold standard for a comparative analysis between treatment methods. While observational data cannot provide reliable direct evidence for comparative procedural risks, it can inform absolute risks of particular interventions in categories of patients.

Health policy decisions are informed by cost-effectiveness studies. However, most cost-effectiveness studies(29, 35, 37-39, 41-46) have used older data from RCTs where the majority of patients were recruited prior to 2005, or from earlier observational cohort studies to inform procedural risks Without recent randomised data, contemporary observational data together with relative risk estimates from randomised trials could be used to improve analyses for current clinical practice, as shown in **chapter 5**. Observational data could also help inform long-term stroke risks in carotid stenosis patients in the context of cost-effectiveness frameworks. However, despite the search criteria of our systematic review including search

terms to identify observational cohort studies reporting long-term stroke risks, there was only 1 post-2005 CEA study(128) and 2 post-2005 CAS(128) (129) studies reporting long-term stroke risks by symptomatic status. The majority of studies did not report post-procedural long-term outcomes by symptomatic status, reported results on sub-categories of stroke such as ipsilateral strokes, or in most cases only reporting deaths as the sole long-term outcome. Thus other sources of information will need to be looked at to inform on long-term stroke rates in cost-effectiveness frameworks in a contemporary framework. These include sub-group analysis from RCTs limited to patients who have been treated with contemporary methods of medical therapy post intervention.

A number of possible limitations should be noted. First, whilst the inclusion of large observational studies ensured that robust estimates of procedural rates are included, the lengthy study recruitment periods in some of the included studies (60% of studies had recruitment periods longer than 4 years) might have limited our ability to capture changes in procedural risk over time. Second, only limited data was available on procedural MI and major and minor stroke separately, which diminishes our ability to consider the relative importance of different adverse events profiles for CEA and CAS over time. Third, some of the data in the review came from selective carotid registries which may not have systematically included patients from underperforming centres, instead focusing on better-performing high volume centres. However, this bias is unlikely to have materially influenced the results reported here. Fourth, there was limited data on procedural outcomes by type of symptoms and time delay from symptoms which limited our ability to discuss the value of procedure timing with respect to symptoms; reliable evidence on these will be useful to guide recommendations. Fifth, a large number of observational cohort studies of CAS patients, and

a smaller proportion of CEA patients have had their outcomes assessed by an independent neurologist. This leads to concerns about a larger number of minor neurological deficits detected in these studies and underreporting of such events in studies where outcomes were not assessed by an independent neurologist. However, no significant differences in procedural stroke/death risks were observed between these types of studies suggesting that our findings are robust to this variation in outcome assessment. Finally, data from observational studies can be subject to selection bias due to patients who are considered high risk for CEA being referred to CAS. However, selection bias is likely to minimal in our review where only studies with a study population of greater than 1000 were included.

In this systematic review, we report a decrease in procedural stroke/death risk of CEA patients in recent years. The decrease was somewhat higher in studies conducted in North America, with pre 2005 procedural risks of CEA patients being higher in North America compared to Europe, while in post-2005 studies CEA procedural risks were similar between Europe and North America. Procedural risks of CAS appear to have remained stable over time with an insignificant decrease in recent years and, again, somewhat higher risks reported in studies in North America. These results suggest that policy guidelines and cost-effectiveness frameworks sourcing procedural risks from older data may not reflect contemporary practice. With ongoing trials still recruiting, recent observational data, allowing for potential bias, may help inform policy. Results from this systematic review have been used in developing the cost-effectiveness framework in **chapter 5**.

5

Cost-effectiveness of treatment methods of carotid stenosis in symptomatic and asymptomatic patients

5.1 Introduction

As discussed in **chapter 2,** previous economic analyses of carotid endarterectomy (CEA) and carotid artery stenting (CAS) are limited by a number of factors including (1) use of older data for procedural and post-procedural stroke risks which are not reflective of a contemporary practise; (2) not accounting for uncertainty in input parameters; (3) not differentiating parameter values for procedural and post-procedural stroke risks by symptomatic status of carotid stenosis patients; (4) not accounting for non-stroke related mortality and increased non-stroke vascular mortality risks in patients following stroke events; (5) using analytical frameworks which do not include all three treatment methods for carotid stenosis (and potentially missing an appropriate comparator); and (6) using analytical frameworks which do not evaluate the interventions' effects over the patient's life span. The systematic review of randomised controlled trials' data (**chapter 3**) indicated the importance of considering procedural adverse events of CAS and CEA separately for major and minor strokes, with CEA shown to have lower procedural minor stroke risks when compared to CAS and lower, though not statistically significant, procedural major stroke risks. Data from RCTs also suggested that post-procedural stroke risks were lower in CEA-treated patients but not statistically different from those in CAS-treated patients. The systematic review of data from large observational cohort studies (**chapter 4)** indicated that the procedural risks of CEA have decreased in recent years.

In this chapter I present a new probabilistic Markov decision-analytic model to evaluate the net effects and cost-effectiveness of CEA and, separately, CAS added to medical therapy in asymptomatic and symptomatic carotid stenosis patients, in categories by age and gender. This framework uses findings from the previous chapters of this thesis, as well as further data

sourced from the literature with the aim of addressing the main limitations found in previous cost-effectiveness models of carotid stenosis. The model is used to evaluate the health-related quality of life-adjusted survival, healthcare costs and cost-effectiveness of treatment options for carotid stenosis in categories of patients with the aim of informing future treatment guidelines and decisions.

5.2 Methods

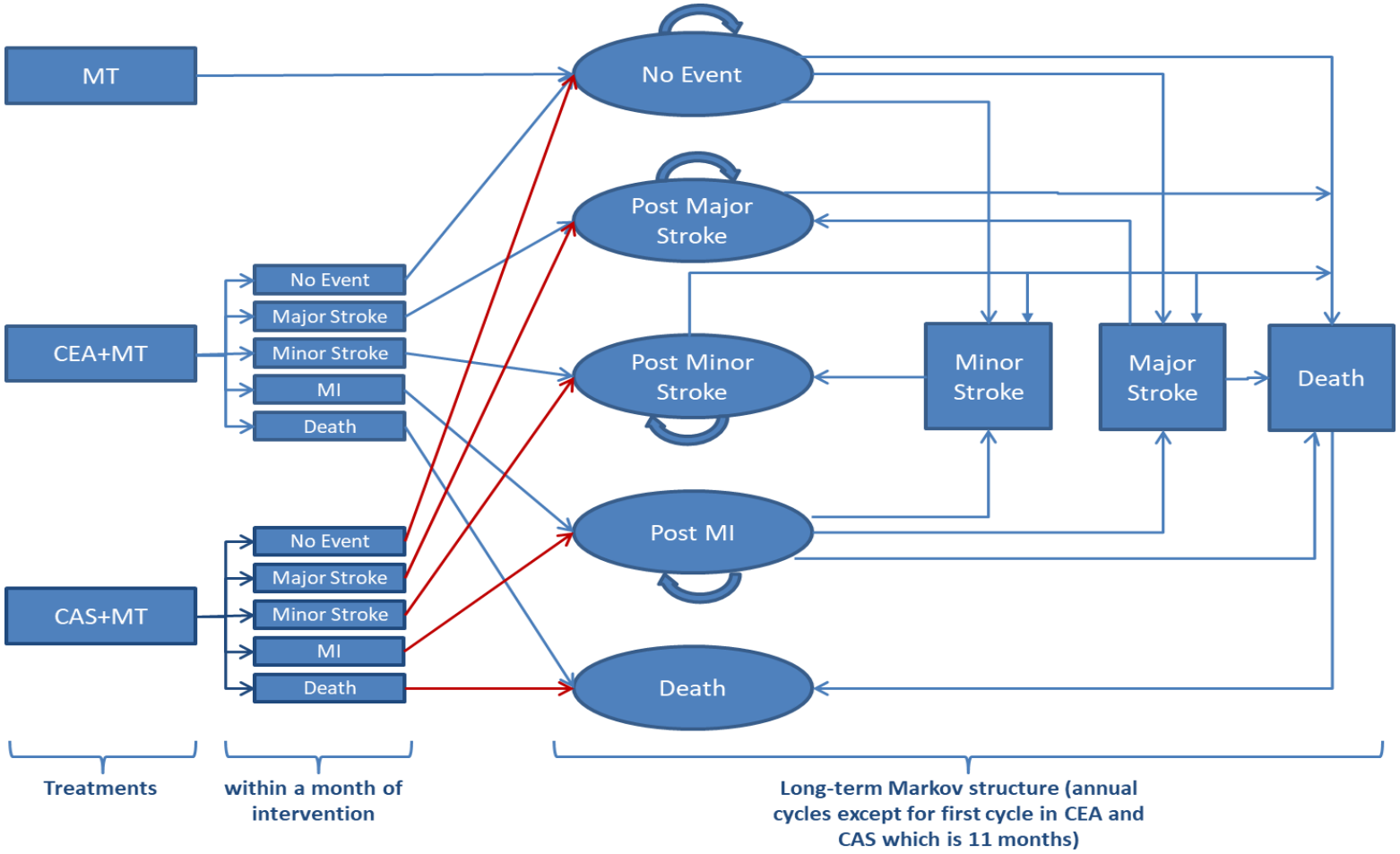
A cost-effectiveness framework was developed to evaluate lifetime costs and quality-adjusted life years (QALYs) of carotid stenosis patients treated with medical therapy (MT) alone (defined as a combination of aspirin, statin, clopidogrel and anti-hypertensive medications), CEA added to MT, or CAS added to MT. The model evaluates healthcare costs and QALYs from the United Kingdom (UK) health and personal social services perspective.

Model inputs were informed by recent relevant data with costs standardized to year 2015/16 prices using the UK National Health Service (NHS) Hospital and Community Services Index.(130) The choice of recent data sources when informing model input parameters aimed to acknowledge the increased use of medical therapies and decreased disease risks under the use of such therapies. The overall costs and QALYs are summarized for each treatment option and for categories of patients by age, gender and symptomatic status. Future (after the first year) healthcare costs and QALYs in the model were discounted at a rate of 3.5% per annum as recommended by the National Institute for Health and Care Excellence.(73)

Model structure

A Markov state transition model with an annual cycle was developed to estimate QALYs, and lifetime costs of patients treated for carotid stenosis with patients progressing annually through a number of health states until death or 95 years of age. These health states include minor stroke, non-fatal major stroke, (procedural only) MI, or death (due to stroke or procedural MI, or non-stroke vascular or non-vascular causes) (**figure 5.1**). In the first annual cycle, patients in the CEA plus MT and CAS plus MT groups undergo their index CEA or CAS procedure and can experience procedural adverse events (i.e. stroke, death or myocardial infarction (MI) within the first month following CEA or CAS). Annual risks (transition probabilities in the model) of minor, major and fatal strokes, and of non-stroke mortality are specified by symptomatic status, age and gender of patients and take into account the previous medical history of patients. Patients' health related quality of life (QoL) is specified by age, gender, symptomatic status and previous experiences of adverse events. Age- and gender-specific non- stroke vascular and non-vascular mortality risks are derived from UK population data(131) and dependent on prior history of stroke or transient ischemic attack (TIA) of patients. Health states in the model were decided by identifying the major risks of carotid stenosis as reported in RCTs and observational cohort studies identified in **chapter 3** and **4**. The model structure was also informed by other economic evaluations of treatment methods for carotid stenosis based on decision analytical models,(35, 36, 40-42) and was developed under the supervision of advisors including clinical expert.

Figure 5.1: Markov state transition cost-effectiveness model of treatment methods for carotid stenosis



*****Note: Patients in MT arm enter directly into the long-term Markov structure***; boxes in figure refers to events/ outcomes which occur; ellipses in figure refer to health states***

Procedural risks of CEA and CAS

The systematic review of observational cohort studies (see **chapter 4**) informed procedural stroke, death, and procedural MI risks of symptomatic and asymptomatic patients treated with CEA plus MT. The procedural stroke/death risks, and MI risks from post-2005 studies in the review were employed as reflecting current clinical practice (**table 5.1**). Information from RCTs reporting procedural outcomes by stroke severity (see **chapter 3**) was used to calculate the proportion of major and minor stroke in procedural stroke/death rates as described in more detail in **appendix text 5.1**. Results from the SVS Vascular registry(67) reported no statistically significant differences in procedural risks between categories of patients by age and gender. Procedural risks were therefore not differentiated by age or gender of the patient.

Procedural risks following CAS (**table 5.1**) were estimated by applying the relative risks of procedural major stroke, procedural minor stroke and procedural MI for CAS vs CEA from the meta-analysis of RCTs (**chapter 3; further** detail in **appendix text 5.2)** to the absolute procedural major stroke, minor stroke and MI risks of similar patients treated with CEA as described above.

Table 5.1: Procedural risks of CEA and CAS in the cost-effectiveness model

	Procedural risks (CI)		Statistical distribution in PSA	Data Source
	Symp	**Asymp**		
CEA				
Stroke/Death	0.0268 (0.0212, 0.0331)	0.015 (0.0101, 0.0207)	A Log Normal distribution was used to generate values for stroke/death rates which were then split major, minor or fatal.	Systematic review of observational cohort studies (**chapter 4**)
Major stroke[1]	0.0109	0.0061		
Minor stroke[1]	0.0145	0.0081		
MI[1]	0.0095	0.0098	A Log Normal distribution was used to generate values for MI rates which were then split into fatal and non-fatal MIs	
CAS				
Major stroke	0.0146	0.0081	A Log Normal distribution was used to generate values for relative procedural risks between CAS vs CEA which were then used to calculate procedural risks of CAS patients.	Calculated by multiplying procedural CEA risks with pooled relative risks from RCTs[2] (**chapter 3**)
Minor stroke	0.0298	0.0167		
MI[1]	0.0046	0.0047		

** Symp: Symptomatic; Asymp: Asymptomatic; CI: Confidence Interval; PSA: Probability Sensitivity Analysis; CEA: Carotid Endarterectomy; CAS: Carotid Artery Stenting; MI: Myocardial Infarction*

[1]Proportions of major strokes (including fatal) (0.41 (0.26, 0.56)) and minor strokes (0.54 (0.38, 0.70)) were based on information from ICSS, EVA-3S, SPACE and CREST (see Appendix Table 1) and applied to stroke/death rates from post-2005 CEA large observational studies. Proportion of fatalities (13%) obtained from proportion of fatalities in strokes in patients admitted to hospitals in England and Wales in 2013 – 14 plus information from the OxVasc which gave the proportion of major strokes in all strokes in a UK setting.

*[2]Relative risks of CAS vs CEA used are **major stroke (RR: 1.34 (0.95, 1.90)** and **minor stroke (2.06 (1.51, 2.81))**, obtained from ICSS, EVA-3S, SPACE, CREST, ACT-1 and SAPPHIRE, and MI (0.48 (0.30, 0.79)) obtained from ICSS, EVA-3S, CREST, ACT-1 and SAPPHIRE*

Post-procedural risks of stroke following CEA plus MT

Post-procedural stroke risks were derived from populations of carotid stenosis patients, the majority being prescribed statin therapy (**appendix text 5.3)**. Annual post-procedural minor and major stroke rates for asymptomatic patients receiving CEA in addition to MT were obtained from combining data from the Asymptomatic Carotid Atherosclerosis Study (ACAS), Veteran Affair (VA), and Asymptomatic Carotid Surgery Trial (ACST)-1 trials' patients who were using statin therapy at recruitment and underwent CEA procedure (personal communication) (**table 5.2**). The annual post-procedural major and minor stroke rates of symptomatic CEA patients were informed by the ICSS trial where 81% of patients randomized to CEA were reported to be using statin therapy a month after intervention.(21)

An individual participant data (IPD) meta-analysis of the ECST and NASCET trials reported that symptomatic patients aged 75 years or older had 1.38 times higher ipsilateral ischemic stroke risk compared to those aged between 65 and 75 years.(71) Using this information and linear interpolation techniques, post-procedural stroke risks (major and minor) in symptomatic patients in the model were assumed to increase by 3.27% for each year of age between 65 and 75 years, after which post-procedural stroke risks were assumed constant.

Results from the pooled analysis of ECST and NASCET trials reported a relative risk of ipsilateral stroke for women vs men of 0.79 (0.64, 0.97).(71) The post-procedural stroke risks of symptomatic patients in the model were, therefore, also adjusted by gender. Given that 71% of patients in the CEA arm of ICSS were men and 30% were women, post-procedural stroke risks of symptomatic men were adjusted upwards 1.07 times and of symptomatic women downwards 0.84 times. With 66% of patients treated with CEA and prescribed with statins in ACAS, ACST-1 and VA trials being men and 34% being women, post-procedural

stroke risks of asymptomatic men were adjusted upwards 1.08 times and of asymptomatic women downwards 0.85 times. Adjusted post-procedural stroke risks of men and women by age are shown in **appendix table 5.1** for asymptomatic patients and **appendix table 5.2** for symptomatic patients.

Post-procedural stroke risks following CAS plus MT and MT alone

Relative risks of post-procedural major stroke risks and post-procedural minor stroke risks for CAS plus MT vs CEA plus MT were calculated by combining results from the two largest relevant RCTs; ICSS and CREST (**see chapter 3**), which were the only trials reporting sufficient information to calculate effects on post-procedural long-term strokes by stroke severity. These relative risks were applied on respective post-procedural major and minor stroke risks of CEA plus MT patients to calculate annual absolute post-procedural major and minor stroke risks in patients treated with CAS in addition to MT (**table 5.2**).

Relative post-procedural major stroke risks and relative post-procedural minor stroke risks of CEA vs MT were obtained from the IPD meta-analysis of ACAS, VA and ACST-1 (personal communication). These were the only RCTs with available data on post-procedural stroke risks by stroke severity. While these trials were all in asymptomatic patients, no significant differences were observed between pooled post-procedural relative stroke risks (including procedural deaths) of CEA vs MT between symptomatic and asymptomatic patients, nor was there any heterogeneity across individual trials for this endpoint as shown in **chapter 3**. These relative risks were then applied (inverted into MT vs CEA comparisons) to respective post-procedural major and minor stroke risks of CEA treated patients to obtain the absolute post-procedural major and post-procedural minor stroke rates of patients treated with MT alone.

Table 5.2: Post-procedural risks in the cost-effectiveness model

	Stroke risks (SE)		Statistical distribution in PSA		Data source
	Symp	**Asymp**	**Symp**	**Asymp**	
Annual post-procedural stroke risk after CEA plus MT					
Major Stroke	0.0098 (0.00167)	0.0042 (0.0007)	Beta(34, 3447)	Beta(33, 7790)	Symp: ICSS; Asymp: IPD meta-analysis of ACAS, VA and ACST-1
Minor Stroke	0.0046 (0.0012)	0.0035 (0.0007)	Beta(16, 3465)	Beta(27, 7796)	
Annual post-procedural stroke risk after CAS plus MT			A Log Normal distribution was used to generate values for relative procedural risks between CAS vs CEA[2] which were then used to calculate non-procedural stroke risks of CAS patients.		Calculated by multiplying post-procedural stroke risks of CEA with relative risks from RCTs[2] comparing CAS plus MT vs CEA plus MT (**chapter 3**)
Major Stroke	0.0119	0.0049			
Minor Stroke	0.0059	0.0051			
Annual stroke risk with MT alone			A Log Normal distribution was used to generate values for relative procedural risks between CEA vs MT[3] which were then used to calculate stroke risks of MT patients.		Calculated by multiplying post-procedural stroke risks of CEA with relative risks from RCTs[2] comparing CAS plus MT vs CEA plus MT [3] (**chapter 3**)
Major Stroke	0.0174	0.0072			
Minor Stroke	0.0085	0.0073			

** Symp: Symptomatic; Asymp: Asymptomatic; p.a: per annum; SE: Standard error; PSA: Probability Sensitivity Analysis; CEA: Carotid Endarterectomy; CAS: Carotid Artery Stenting; MT: Medical Therapy; IPD: Individual Patient Data; ICSS: International Carotid Stenting Study; ACAS: Asymptomatic Carotid Atherosclerosis Study; VA: Veterans Affair; ACST: Asymptomatic Carotid Surgery Trial; p.a: per annum*

[1] Proportion of fatalities (13%) obtained from proportion of fatalities in strokes in patients admitted to hospitals in England and Wales in 2013 – 14 plus information from the OxVasc which gave the proportion of major strokes in all strokes in a UK setting.

*[2]Relative risks of CAS vs CEA used are **major stroke (RR: 1.23 (0.77, 1.92**)) and **minor stroke (1.26 (0.86, 1.85))** obtained from ICSS and CREST trials.*

Recurrent stroke risks

The long-term risks of having a recurrent major or minor stroke amongst patients with minor stroke were assumed to be the same as those of symptomatic carotid stenosis patients in each treatment arm. Long-term annual stroke risks of patients following a MI was assumed to be 1.57% as obtained from 14,703 patients (not necessarily with carotid stenosis) who experienced an acute MI in the VALIANT trial (recruited from 1998 to 2001 from 24 countries), 463 of whom experienced strokes within a median follow-up of 24.7 months.(132)

Proportion of fatal strokes and MIs

Thirteen percent of all strokes (not necessarily in patients with carotid stenosis) in patients admitted to hospitals in England and Wales in 2013 – 14 were fatal.(133) Given that about 40.3% of all strokes in the UK are major(134), and assuming that only major strokes can be fatal, 32.3% of all major strokes were estimated to be fatal and this estimate was used in the decision model.

The proportion of fatal procedural MIs was calculated using information from the Myocardial Ischaemia National Audit Project (MINAP) registry for 2012 – 13 (not necessarily in carotid stenosis patients) in 211 hospitals in England and Wales. This data included 118,075 patients and showed a 30-day MI mortality rate of 2.7%.(135)

Non-stroke related mortality

All deaths in the UK by gender and age category (65-69, 70-74, 75-79, 80-84, 85-89, 90 and over) were obtained from Mortality Statistics: Deaths Registered in England and Wales (2014).(131) These were divided by the total population in England and Wales in 2014 in the

relevant age/gender groups to calculate the all-cause mortality rate in each age- and gender-specific category.

Similarly, stroke related deaths were obtained from mortality statistics in the UK as deaths classified under International Statistical Classification of Diseases and Related Health Problems (ICD)-10 codes I60 - I61 and I63 - I64.

Non-stroke vascular mortality rates were calculated by deducting stroke-related deaths (I60 - I61 and I63 - I64) from those due to diseases of the circulatory system (ICD-10 codes I00-I99). Non-vascular annual mortality rate for each age and gender category was calculated by using the following formulae:

$$\frac{\text{total deaths} - \text{vascular deaths}}{\text{total number at risk}}$$

The annual non-stroke vascular and non-vascular mortality rates for each age and gender group are shown in **table 5.3.** Given that mortality statistics in England and Wales are reported in 5-year age groups,(131) linear interpolation methods were used to approximate changes in mortality rates with each year of age.

Non stroke vascular mortality in patients aged between 65 and 69 was 0.32% in men and 0.12% in women (**table 5.3**) with a combined non-stroke vascular mortality in men and women of 0.22%. The results from ECST showed that in patients with unilateral arterial disease the 5-year non-stroke vascular mortality risk was 2.7%, resulting in a per annum rate of 0.54%. Therefore, it was estimated that patients in the model who had experienced a stroke had 2.45 times (0.54/0.22) increased non-stroke vascular mortality risk (**appendix text 5.5**).

Table 5.3: Annual mortality rates in England and Wales, 2014

		65-69	70-74	75-79	80-84	85-89	90+
All-cause mortality	**Men**	1.42%	2.37%	3.96%	7.02%	12.47%	22.74%
	Women	0.92%	1.53%	2.72%	5.12%	9.54%	19.90%
Stroke mortality	**Men**	0.04%	0.08%	0.18%	0.35%	0.66%	1.21%
	Women	0.03%	0.06%	0.14%	0.33%	0.67%	1.33%
Non-stroke mortality	**Men**	*1.38%*	*2.29%*	*3.78%*	*6.67%*	*11.82%*	*21.53%*
	Women	*0.89%*	*1.47%*	*2.58%*	*4.80%*	*8.87%*	*18.57%*
Non-vascular mortality	***Men***	*1.04%*	*1.72%*	*2.82%*	*4.91%*	*8.63%*	*15.99%*
	Women	*0.75%*	*1.20%*	*2.03%*	*3.68%*	*6.60%*	*13.89%*
Non-stroke vascular mortality	***Men***	*0.34%*	*0.57%*	*0.96%*	*1.76%*	*3.19%*	*5.54%*
	Women	*0.14%*	*0.26%*	*0.55%*	*1.12%*	*2.27%*	*4.68%*

Health-related Quality of Life (QoL) at entry into the model

Information from the Oxford vascular study (OxVasc), including 748 survivors of stroke recruited in the period 2002-07 in Oxfordshire, UK with a mean age of 75 years and matched control patients (ie, without previous stroke drawn from the English population taking part in 2006 Health Survey for England (HSE)), was used to inform the QoL of symptomatic and asymptomatic patients aged 75 years.(20) Health related QoL in OxVasc was measured using the eq-5d 3 level (EQ 5D 3L) questionnaire where patients were required to report problems across five domains, with questionnaire responses converted to QoL utilities using UK population tariff.(136) Symptomatic patients aged 75 to 80 years were assigned a QoL of 0.76 (standard error (SE) 0.014), as reported for patients who experienced a minor stroke or TIA (same estimates reported) in the past 6 months in the OxVasc population.(20) QoL of asymptomatic patients aged 75 to 80 years was derived from the control sample in OxVasc

(**appendix text 5.6**).(20) While the OxVasc population had only a few patients diagnosed with carotid stenosis, the QoL of patients in OxVasc who had experienced a minor stroke or TIA was similar to the QoL of symptomatic patients in ICSS(21) (**appendix text 5.7**). No information of the QoL of asymptomatic carotid stenosis patients was available, with SAPPHIRE, where 70% of participants were asymptomatic not reporting QoL of patients by symptomatic status (**appendix text 5.7**)

No significant differences in QoL of patients were reported between baseline and immediately after CEA or CAS procedure as per results from CREST(137) and SAPPHIRE(138) trials (**appendix text 5.8**).

Since the utility values quoted above from OxVasc were for patients with a mean age of 75 years, they were only applied for patients aged 75 to 80 years. For age groups 65 to 70, 70 to 75, 80 to 85 and 85 years and older, the QoL of patients as reported in OxVasc was adjusted based on how QoL varied proportionally between age groups in the general UK population (**appendix table 5.4)**. Adjusted utility values for each age group are summarized in **table 5.4**. Health-related QoL EQ-5D-3L data from HSE in years 2003,(139) 2006,(140) and 2011(141) were analysed to investigate the age and gender-specific quality of life of middle-aged and older adults in the UK (**appendix table 5.4**). There were no important differences in the QoL of men and women for age groups above 55 years and therefore the same utility values were used for both.

Health-related QoL after stroke

OxVasc also reported the mean QoL of 106 patients who had experienced a major stroke (0.60 (standard error (SE) 0.025)) and mean QoL of 302 patients who had experienced a

minor stroke (0.74 (0.014)) after 1 year of post stroke follow-up. Note that the QoL of major strokes was calculated by weighting the QoL of moderate strokes (0.65 (0.027) and severe strokes (0.41 (0.063) using proportions based on number of patients in each of these stroke categories in OxVasc. Using the QoL utility of controls in OxVasc (**appendix text 5.6**), a 0.25 (0.028) lower utility is seen at 1 year after a major stroke and a 0.11 (0.019) lower utility after a minor stroke, respectively (**table 5.4**). Health related QoL after stroke in OxVasc was measured using the EQ 5D 5L questionnaire with patient responses converted to utilities using the UK population tariff.(136)

To check the reliability of this data, we compared post stroke decrements in QoL in OxVasc with other published sources (**appendix text 5.9**).

Health-related QoL after recurrent stroke

In our model, patients with a major stroke are assumed not to experience a further decrement in QoL when experiencing either a recurrent major or minor stroke. For patients with previous minor stroke, we have assumed that a recurrent minor stroke is assumed not to have further effect on their QoL. However, a subsequent major stroke is assumed to lead to a QoL decrement of 0.14 (**table 5.4)**, bringing their total stroke-related QoL decrement to the overall decrement of those experiencing a first major stroke.

Health-related QoL after procedural MI

While there is some evidence to suggest that the QoL of patients who had experienced a MI is lower in the month following the MI(142), the effect of MI on long-term QoL is less clear. Kent et al reported that, while a decrement in QoL of 0.05 (0.028) is observed during the year in which the MI occurred, the longer-term impact of MI on QoL of patients is negligible.(143)

Similarly Alva et al report a 0.07(0.035) reduction in QoL in the event the MI had occurred the year before, and no statistically significant differences in QoL when the MI had occurred more than a year ago.(144) Following these studies, we assume a 0.05 (0.028) decrement in QoL for the year in which a MI is experienced, with no reductions in QoL in subsequent years.

Table 5.4: Health-related Quality of life (QoL)

Patient category	Utility (SE)	Statistical distribution in PSA	Population details as per data source	Data Source
Symp patients (65 – 69 years)	0.79 (0.02)	Beta (566, 122)	65-69 year old patients post stroke/TIA in OxVasc	OxVasc study(20): 748 survivors of stroke recruited in from 2002-07 in Oxfordshire, UK; mean age: 75. Age specific adjustments[1] made by information from HSE. HRQoL measured using eq-5d questionnaire.
Symp patients (70 - 74 years)	0.78 (0.02)	Beta (501, 143)	70-74 year old patients post stroke/TIA in OxVasc	
Symp patients (75 - 79 years)	0.76 (0.016)	Beta (540, 171)	75-79 year old patients post stroke/TIA in OxVasc	
Symp patients 80 - 85 years)	0.73 (0.015)	Beta (617, 232)	80-85 year old patients post stroke/TIA in OxVasc	
Symp patients (85+ years)	0.70 (0.015)	Beta (682, 296)	85+ year old patients post stroke/TIA in OxVasc	
Asymp patients (65 – 69 years)	0.90 (0.015)	Beta (411, 52)	65-69 year old patients of control group for OxVasc population	Control group from English population taking part in 2006 HSE survey with matched risk factors for OxVasc population. Age specific adjustments[1] made by information from HSE. HRQoL measured using eq-5d questionnaire.
Asymp patients (70 - 74 years)	0.87 (0.014)	Beta (474, 71)	70-74 year old patients of control group for OxVasc population	
Asymp patients (75 - 79 years)	0.85 (0.014)	Beta (545, 96)	75-79 year old patients of control group for OxVasc population	

Patient category	Utility (SE)	Statistical distribution in PSA	Population details as per data source	Data Source
Asymp patients 80 - 85 years)	0.81 (0.013)	Beta (682, 158)	80-85 year old patients of control group for OxVasc population	
Asymp patients (85+ years)	0.78 (0.013)	Beta (800, 226)	85+ year old patients of control group for OxVasc population	
Reduction in QoL post-major stroke	0.25 (0.028)	Beta(60,179)		OxVasc study(20)
Reduction in QoL post-minor stroke	0.11 (0.019)	Beta(30,240)		
Reduction in QoL post MI (only in year of MI event)	0.05 (0.028)	Beta(3,57)		25 673 European patients aged 50 to 80 years with a history of cardiovascular disease.(143) HRQoL measured using eq-5d questionnaire.
Reduction in QoL of recurrent major stroke in patients with a minor stroke	0.14 (0.031)	Beta(17,107)		OxVasc study(20)

**PSA: Probability Sensitivity Analysis; OxVasc: Oxford Vascular Study; QoL: Quality of Life; MI: Myocardial Infarction; Symp: Symptomatic; Asymp: Asymptomatic; HSE: Health Survey England.*

*[1] QoL of patients as reported in OxVasc was adjusted based on how QoL of patients differed between age groups in the general UK population (**appendix table 5.4**).*

Cost of stroke

We used information from OxVasc,(93) a population based study in 485 TIA (mean age: 73) and 729 stroke (mean age: 75) survivors registered in 9 general practices in Oxfordshire, UK recruited between 2002 and 2007 for the costs of major and minor strokes. Costs included emergency visit, emergency transport, outpatient care visit, day case, or hospitalization, nursing and residential care costs. The calculation of costs of major and minor stroke in the OxVasc population is detailed in **appendix text 5.10**.

Costs of major and minor strokes a year after the index TIA/stroke event, and 2 years after the index event in OxVasc(93) were used to inform costs in the model in the first and subsequent years, respectively, for patients experiencing either a major or minor stroke, as shown in **table 5.5** (unpublished data obtained by personal communication with the author Dr. Ramon Luengo-Fernandez).

The cost of fatal stroke in the UK was obtained from post-trial monitoring data (1997 – 2007) of the United Kingdom Prospective Diabetes Study (UKDPS)(145) in which 5102 type 2 diabetes patients with a mean age of 52.4 at recruitment (recruitment period: 1997 – 1992) were studied. This study reported a cost of £3,954 for a 60-year-old man (2012 prices; standardized to 2015/16 prices in **table 5.5**). Costs in the UKPDS were calculated by assigning each hospital episode of patients in UKPDS to a healthcare resource group, and using information from health resource group to calculate the costs incurred in each hospital episode. Costs outside of inpatient and day stays were calculated by giving patients a maximum of seven resource use questionnaires during clinic visits (patients who did not attend clinic visits were sent the questionnaire by post). In the case of fatal strokes, costs were limited to inpatient costs. A NICE (National Institute for Health and Care Excellence)

guidance report on detection of atrial fibrillation during diagnosis and monitoring of hypertension reported a cost of £3,315 (2011 prices; standardized to 2015/16 prices in **table 5.5**) for a fatal stroke, similar to that reported in the UKPDS study.(145)

Cost of MI

Post-trial monitoring (1997 – 2007) of the UKPDS(145) was also used to inform costs of non-fatal MIs in the model. In the study, the authors used Healthcare Resource Group (HRG) hospital episode costs and information for non-inpatient costs from patient resource use questionnaires and reported an inpatient cost of £6,379 and non-inpatient cost of £963 in the year the MI occurred and an inpatient cost of £1,154 and non-inpatient cost of £671 in subsequent years (2012 prices; standardized to 2015/16 prices in **table 5.5**). The cost of fatal MI was also informed from the UKPDS which reported mean inpatient cost of £1,521 per fatal MI.

Cost of CEA and CAS

A detailed calculation of the costs of CEA and CAS was presented by Featherstone et al(21) who report a cost of £4,501 for CEA and £4,724 for CAS in the UK at 2013 prices (standardized to 2015/16 prices in **table 5.5**). These costs, used in the base case analysis, were calculated by evaluating resources used in the ICSS trial (including surgeon and radiologist time; operating theatre time, including nursing staff, drugs, consumables and overheads; anaesthesia; materials and devices including stents, shunts, patches, cerebral protection devices, catheters, wires and sheaths; and length of hospital stay in the intensive care unit (ICU) and inpatient ward). Resources used were multiplied by unit costs from published sources, including anaesthetic costs from the GALA trial, stent material costs from

the University College London Hospitals NHS foundation trust, unit costs of surgeon, radiologist, registrars, anaesthetist theatre costs from the Unit costs of Social and Health Care(146) and ICU and ward stay costs from HRG National Schedule for Reference costs 2011-12 data.

In a sensitivity analysis, costs of CEA and CAS reported in the 2014-15 HRG National Schedule for Reference costs data(147), including costs only related to the hospital admission for CEA and CAS, were used (**appendix text 5.11**).

Cost of MT

In the model, it was assumed that medical therapy for patients with carotid stenosis included a single antiplatelet therapy (aspirin 75mg daily), an anti-hypertensive (Amlodipine – 10mg) and high-intensity statin (Atorvastatin 80mg daily). In addition, CAS patients were assumed to be on dual antiplatelet therapy, taking 75mg of clopidogrel daily in addition to the medical therapies stated above in the initial 6 months after procedure, and on the same medical therapies as patients following the other two treatment options thereafter. Prices of these drug therapies were based on the 2017 edition of the British National Formulary(148) (**appendix table 5.7)**.

Table 5.5: Healthcare costs in the model

	Cost[1] (SE) (UK£)	Statistical distribution in PSA	Data Source
Fatal Strokes	3674 (1152)	Gamma (10,361)	United Kingdom Prospective Diabetes Study (UKDPS)(145): 5102 type 2 diabetes patients had been recruited from 1977 – 1992, with a mean age of 52.4 at recruitment
Major Stroke (annual costs)			
First year	16,460 (1,153)	Gamma(204,81)	OxVasc study(93): 729 stroke survivors (mean age: 75) in Oxfordshire, UK recruited from 2002-07. Costs include in-hospital, nursing and residential care costs.
Subsequent years	2,322 (459)	Gamma(26,91)	
Minor Stroke (annual costs)			
First year	7,388 (626)	Gamma(139,53)	OxVasc study(93)
Subsequent years	2,181 (354)	Gamma(38,57)	
MI (annual costs)			
First year	6,844 (1,062)	Gamma(42,165)	UKDPS(145)
Subsequent years	1849 (47)	Gamma(213,3)	
CEA(procedure)	4528 (148)	Gamma (931,5)	Featherstone et al(21): Resource use data from ICSS and unit costs from published UK sources
CAS(procedure)	4752 (129)	Gamma (1358,3)	
MT (annual costs)[2]	89		British National Formulary(148) MT included aspirin (75mg), Amlodipine (10mg) and Atorvastatin (80mg) [2] for 365 days

**SE: Standard Error; PSA: Probability Sensitivity Analysis; MI: Myocardial Infarction; CEA: Carotid Endarterectomy; CAS: Carotid Artery Stenting; MT: Medical Therapy; UKPDS: United Kingdom Prospective Diabetes Study; OxVasc: Oxford Vascular Study*

[1]Note: Costs were standardized to 2015/16 prices using the NHS hospital and Community services index(130). Costs as in original source (with cost year) is given is ***supplementary table 5.***

[2]Annual costs of CAS+MT patients for 1st year was £100 due to the prescription of 75mg of Clopidogrel for the first 6 months.

Reporting of results

Life years, QALYs and total costs estimated by the model for MT, CEA plus MT, CAS plus MT are reported, and were used to calculate incremental life years, QALYs, and costs between treatment strategies. When one intervention was not dominated by another, the Incremental Cost-Effectiveness Ratio (ICER) between interventions was calculated using the formulae (given as an example for CEA plus MT vs MT alone):

$$ICER_{CEAvsMT} = \frac{Cost_{CEA} - Cost_{MT}}{QALYs_{CEA} - QALYs_{MT}}$$

The projected rates of first within the study minor, non-fatal major and fatal stroke are also reported for each intervention at 1, 5, 10 and 15 years in the cost-effectiveness model. All results are reported by age, gender and symptomatic status of patient.

Probabilistic sensitivity analysis

Probability distributions were fitted around all major parameters in the model, parametrized using the underlying uncertainty in source data (**table 5.1, 5.2, 5.4, and 5.5**). Monte Carlo simulation was used to sample all parameter values simultaneously from the respective distributions and evaluate the resulting uncertainty in cost-effectiveness results using probabilistic sensitivity analysis. One thousand simulations were performed. Simulated values were ordered and the 2.5^{th} percentile and 97.5^{th} percentile taken to form 95% confidence intervals. Cost-effectiveness acceptability curves(149) and cost-effectiveness frontiers were used to summarize the results at thresholds of willingness to pay ranging from £0 to £50,000 per QALY, and to report the probability that an intervention is cost-effective at each level of willingness to pay. When calculating cost-effectiveness acceptability curves,

at each level of willingness to pay-per-QALY ranging from £0 to £50,000, 1000 Monte Carlo simulations were performed and the incremental net monetary benefit calculated for each simulation. This was used to calculate the probability an intervention was cost-effective at each level of willingness to pay-per-QALY, which were then used to plot the cost-effectiveness acceptability curves.

Deterministic sensitivity analysis

Key model input parameters were varied in one-way and scenario sensitivity analyses. Firstly, CEA and CAS costs were sourced from the 2014-15 HRG National Schedule for reference costs data(147), instead of using costs reported by the ICSS. Second, post-procedural stroke risks of asymptomatic patients were adjusted for age and gender of patients by using results from the individual patient data meta-analysis of ACAS, ACST-1 and VA studies where patients above the age of 75-years had 1.78 times post-procedural stroke risks compared to patients aged 65-75 years (base case: 1.38), and there were no differences in post-procedural stroke risks by gender of asymptomatic patients (base case: women vs men = 0.79). Third, the relative risk of overall post-procedural stroke for CAS vs CEA from meta-analysis of the EVA-3S, ICSS, SPACE and CREST RCTs (**chapter 3**) (OR: 1.19 (**appendix figure 3.15**)) was used instead of separate relative risks for major and minor strokes, due to concerns of bias (because only 2 RCTs (ICSS and CREST) reported sufficient data to calculate separate relative risks for major and minor strokes). Fourth, the model input parameters for relative procedural and post-procedural minor stroke risks of CAS vs CEA was set to 1 instead of the base case of 2.25 for relative procedural minor stroke risks and 1.39 for relative post-procedural minor stroke risks. Fifth, the relative procedural stroke/death risks for CAS vs CEA from EVA-3S, SPACE and ICSS which reported results by age groups

(**chapter 3**) (Age<70 OR: 1.05; Age>=70 OR: 2.30 (**appendix figure 3.2**)) was used instead of separate relative risks for procedural major and minor strokes to check the impact of possible difference in relative procedural stroke risks of CAS vs CEA by age.

In addition to scenario based deterministic sensitivity analysis, key model inputs were varied to investigate their impact on cost-effectiveness results. First, the procedural stroke/death risks with CEA were set at threshold values in treatment guidelines (Asymptomatic: 3%; Symptomatic: 6%). Furthermore, threshold procedural stroke/death risks were reduced by 10% (Asymptomatic: 2.7%; Symptomatic: 5.4%), 20% (Asymptomatic: 2.4%; Symptomatic: 4.8%), 30% (Asymptomatic: 2.1%; Symptomatic: 4.2%) and 40% (Asymptomatic: 1.8%; Symptomatic: 3.6%) and set as model input parameters. Second, the major stroke mortality risk was varied from 15% to 45% from the base case of 32.35%. Third, the proportional increase in non-stroke vascular mortality risk in patients following a stroke, was reduced to 1 (i.e. no increased non-stroke vascular mortality risks in patients following stroke), 1.5 and 2 times from 2.45 as used in the base case. Third, the long-term stroke risk was reduced by 10% (Asymptomatic: major (0.38%); minor (0.31%); Symptomatic: major (0.88%); minor (0.41%)) and 20% (Asymptomatic: major (0.34%); minor (0.28%); Symptomatic: major (0.78%); minor (0.37%)) to simulate the effect of more intensive medical therapy (e.g. high intensity statin therapy).

Value of Information Analysis

Value of information analysis, while not a requirement under NICE guidelines for economic evaluations, has been suggested by NICE to inform future research recommendations.(73) There is a degree of uncertainty in results of cost-effectiveness analyses, resulting in a probability that an incorrect decision could be made. This, combined with the cost to society

if an incorrect decision is made based on available information, can be used to calculate the expected cost of uncertainty surrounding cost-effectiveness results.(74) Further research into methods to treat carotid stenosis can reduce the expected cost of uncertainty. The expected cost of uncertainty can also be represented as the expected value of perfect information (EVPI), with there being no uncertainty in a decision in the event of perfect information. The EVPI per patient with j alterative interventions and θ unknown parameters can be obtained by subtracting the net benefit given current information ($max_j E_\theta NB(j,\theta)$) from the net benefit given perfect information ($E_\theta max_j NB(j,\theta)$).(23)

Additionally, the EVPI for particular model input parameters or a particular combination of model input parameters, known as the expected value of partial perfect information (EVPPI) can also be calculated using the equation below to help identify which model inputs contributed to decision uncertainty.

$$EVPPI_\delta = E_\delta max_j E_{\mu|\,\delta} NB(j,\delta,\mu) - max_j E_\theta NB(j,\theta)$$

Here δ refers to the input parameter whose EVPI we intend to calculate, μ the remaining unknown parameters such that $\delta \cup \mu = \theta$, with $E_\delta max_j E_{\mu|\,\delta} NB(j,\delta,\mu)$ referring to the expected value of a decision made given perfect information on input parameter δ.(23)

In this analysis, the EVPPI was also calculated at a willingness to pay-per-QALY of £20,000 for the input parameters informing (1) relative procedural stroke/death risks of CAS vs CEA, (2) relative post-procedural minor and major stroke risks of CAS plus MT vs CEA plus MT, (3) relative post-procedural minor and major stroke risks of CEA plus MT vs MT alone, (4) absolute post-procedural stroke risks of CEA patients, and (5) procedural stroke/death risks of CEA patients.

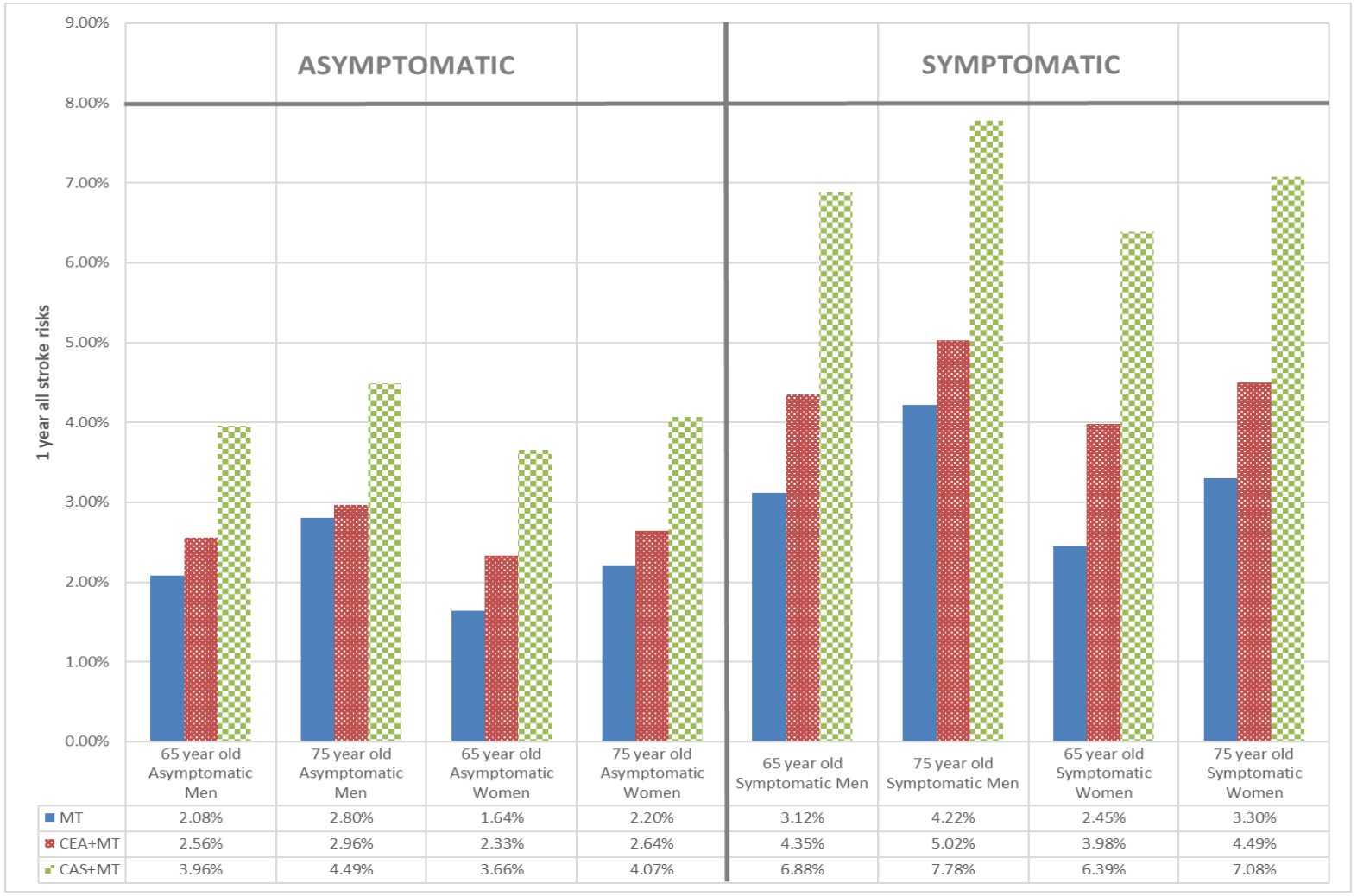
Model checks

The projected undiscounted life years from the model were compared with the life expectancy of men and women in the general UK population across a number of age groups as reported in the UK national life tables 2014-16.(150) The AdVISHE model checklist tool was used throughout the development of the model.(151)

5.3 Results

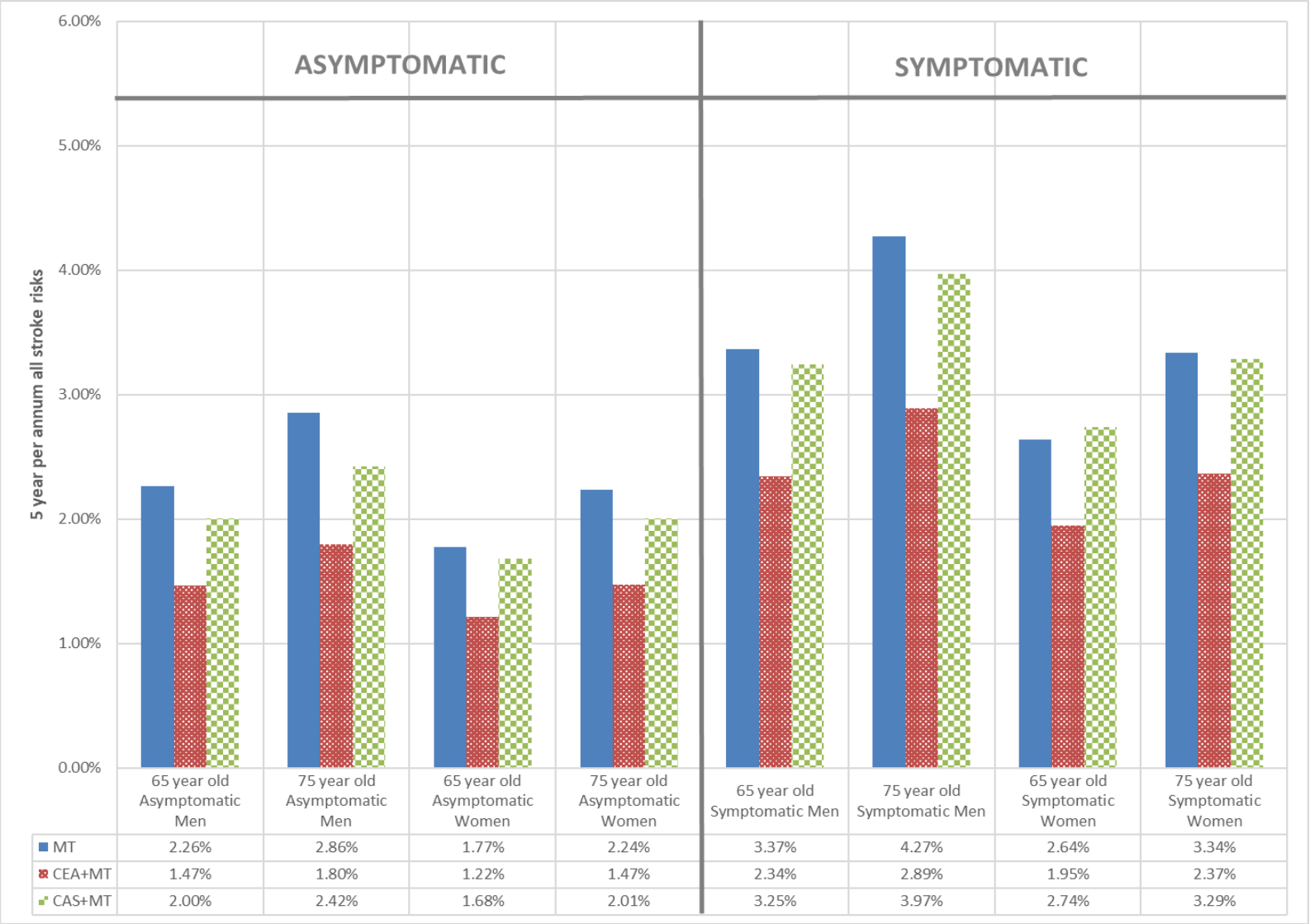
Due to the procedural risks experienced by patients treated with CAS or CEA, the projected minor stroke, non-fatal major stroke and fatal stroke rates of patients at one year were highest among patients treated with CAS plus MT, followed by those treated with CEA plus MT. Patients treated with MT alone had the lowest stroke rate at one year, irrespective of age, gender or symptomatic status (**figure 5.2**). Among 65-year-old symptomatic women, average annual stroke rates in the first five years after treatment initiation were highest in patients treated with CAS plus MT alone, followed by those treated with MT alone, and then those treated with CEA plus MT, while in all other patient groups average annual stroke rates in the first five years after treatment initiation were highest when treated by the MT alone strategy (**figure 5.3**). Annual stroke rates within ten years from treatment initiation were projected to be highest in patients treated with MT alone, followed by those treated with CAS plus MT, and then those treated with CEA plus MT (**figure 5.4**). Similar patterns were observed for annual stroke rates within fifteen years from treatment initiation (**appendix table 5.8**). Benefits from CEA or CAS interventions, compared to MT alone, were evident in the medium to long term in all categories of patient studied.

Figure 5.2: Projected per person stroke rates in the first year after treatment initiation



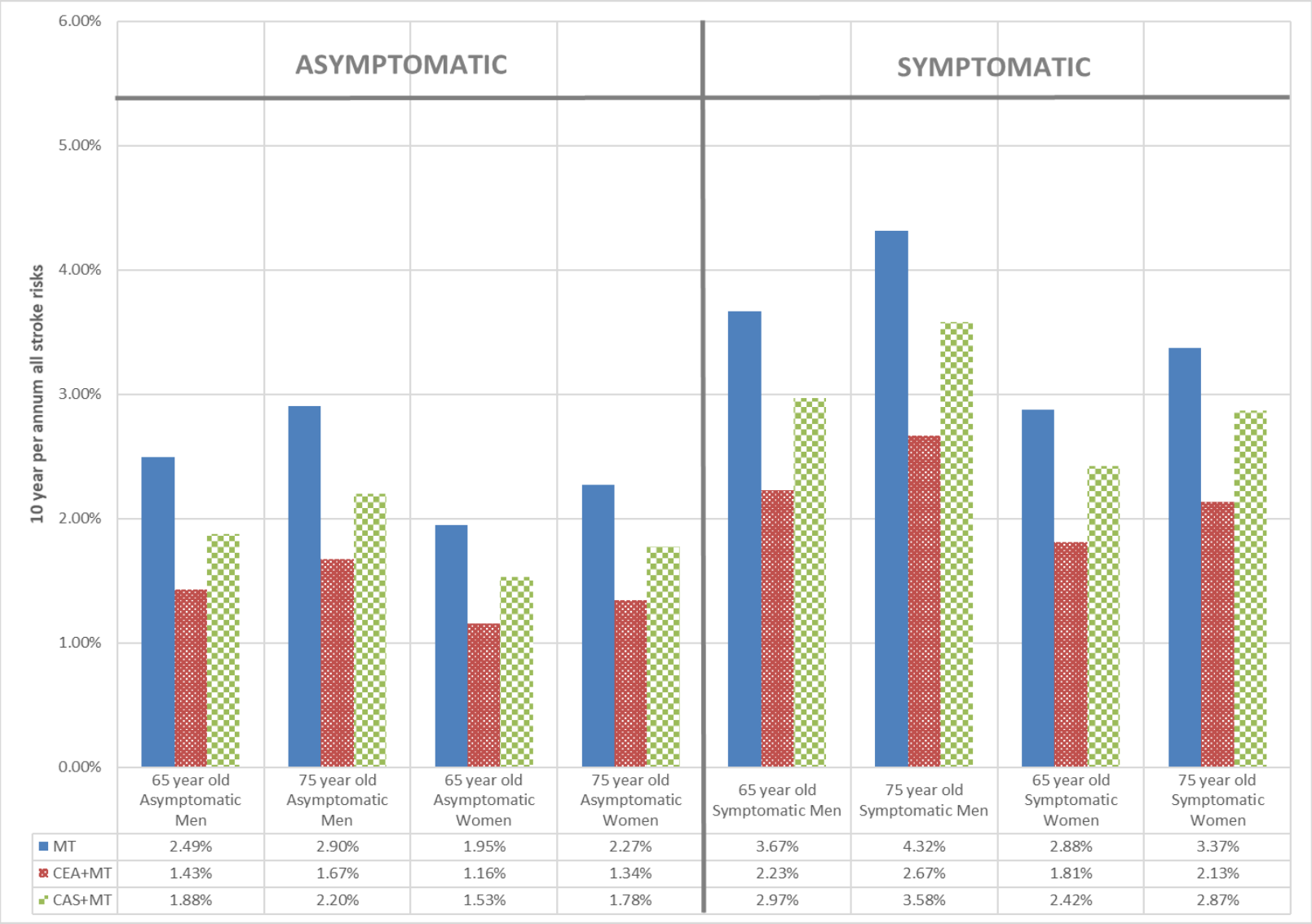
	65 year old Asymptomatic Men	75 year old Asymptomatic Men	65 year old Asymptomatic Women	75 year old Asymptomatic Women	65 year old Symptomatic Men	75 year old Symptomatic Men	65 year old Symptomatic Women	75 year old Symptomatic Women
MT	2.08%	2.80%	1.64%	2.20%	3.12%	4.22%	2.45%	3.30%
CEA+MT	2.56%	2.96%	2.33%	2.64%	4.35%	5.02%	3.98%	4.49%
CAS+MT	3.96%	4.49%	3.66%	4.07%	6.88%	7.78%	6.39%	7.08%

Figure 5.3: Projected per person annual stroke rates during first five-years



	65 year old Asymptomatic Men	75 year old Asymptomatic Men	65 year old Asymptomatic Women	75 year old Asymptomatic Women	65 year old Symptomatic Men	75 year old Symptomatic Men	65 year old Symptomatic Women	75 year old Symptomatic Women
MT	2.26%	2.86%	1.77%	2.24%	3.37%	4.27%	2.64%	3.34%
CEA+MT	1.47%	1.80%	1.22%	1.47%	2.34%	2.89%	1.95%	2.37%
CAS+MT	2.00%	2.42%	1.68%	2.01%	3.25%	3.97%	2.74%	3.29%

Figure 5.4: Projected per person annual stroke rates during first ten-years



	65 year old Asymptomatic Men	75 year old Asymptomatic Men	65 year old Asymptomatic Women	75 year old Asymptomatic Women	65 year old Symptomatic Men	75 year old Symptomatic Men	65 year old Symptomatic Women	75 year old Symptomatic Women
MT	2.49%	2.90%	1.95%	2.27%	3.67%	4.32%	2.88%	3.37%
CEA+MT	1.43%	1.67%	1.16%	1.34%	2.23%	2.67%	1.81%	2.13%
CAS+MT	1.88%	2.20%	1.53%	1.78%	2.97%	3.58%	2.42%	2.87%

Asymptomatic carotid stenosis patients

65-year-old men with asymptomatic carotid stenosis treated with MT alone were projected to live 14.84 years (12.26 QALYs) and incur healthcare and residential care costs of £9,290 (**table 5.6**). If further treated with CEA, they were projected to live an additional 0.35 years (0.43 QALYs) at an extra cost of £1,462 (**table 5.6**). This resulted in an ICER for CEA plus MT vs MT alone of £9,502 (with QALYs and costs discounted). CAS plus MT strategy was dominated by the CEA plus MT strategy in asymptomatic 65 years old men as it cost £1,706 more than CEA plus MT, and was projected to result in 0.13 fewer years of life (0.17 less QALYs) (**table 5.6**). The MT alone strategy had the highest probability of being cost-effective up to a willingness to pay per QALY of £10,000, after which CEA plus MT had the highest probability of being cost-effective (**figure 5.5a**). At willingness to pay for a QALY of £20,000 CEA plus MT had 83.6% probability of being cost-effective, MT alone 12.6% probability, and CAS plus MT 3.8% probability (**figure 5.5a**).

ICERs for CEA plus MT vs MT alone were higher for older asymptomatic men, with the higher non-stroke mortality risks in older patients resulting in less time to benefit from the intervention (**figure 5.6**). Thus, at willingness to pay for a QALY of £20,000, MT alone had the highest probability of being cost-effective for asymptomatic men aged 75 years and above (**figure 5.5e; 5.5g**). CEA plus MT dominated CAS plus MT for asymptomatic men irrespective of age (**appendix table 5.9**).

65 year-old women with asymptomatic carotid stenosis treated with MT alone were projected to live 17.16 years (14.15 QALYs) at a cost of £9,556 (**table 5.6**) to the NHS and social services; the higher projected life expectancy in women being a result of lower non-stroke related mortality risks and post-procedural stroke risks experienced by women.

Asymptomatic 65 year-old women further treated with CEA were projected to live an additional 0.32 years (0.40 QALYs) at an extra cost of £1,464 (**table 5.6**). This resulted in an ICER for CEA plus MT vs MT alone of £11,047 per QALY (with QALYs and lifetime costs discounted); higher than that of 65-year-old asymptomatic men because men have larger differences in 10-year stroke risks between CEA plus MT and MT alone (**figure 5.4**). CAS plus MT strategy was dominated by CEA plus MT in 65-year-old women with asymptomatic carotid stenosis, as costs £1,770 more and is projected to result in 0.12 less years of life (0.16 less QALYs) compared with CEA plus MT (**table 5.6**). MT alone had the highest probability of being cost-effective up to willingness to pay-per-QALY of £10,000, after which CEA plus MT had the highest probability of being cost-effective (**figure 5.5b**). At willingness to pay-per-QALY of £20,000 CEA plus MT had an 81% probability of being cost-effective, MT alone and 15.8% probability, and CAS plus MT a 3.2% probability (**figure 5.5b**).

ICERs of CEA plus MT vs MT alone were higher for older women with asymptomatic carotid stenosis (**figure 5.6)**. At willingness to pay for a QALY of £20,000, CEA plus MT had the highest probability of being cost-effective for 65 and 70 years old asymptomatic females (**figure 5.5b, 5.5d)** while MT alone was the most cost-effective for those aged 75 years or above (**figure 5.5f, 5.5h**). CAS plus MT continued to be dominated by CEA plus MT for women with asymptomatic carotid stenosis, irrespective of their age (**appendix table 5.9**).

Table 5.6: Life expectancy, quality-adjusted life years and lifetime costs

Patient Group	MT*			CEA + MT*			CAS + MT*			CEA + MT vs MT¥		
	Undiscounted LY (95% CI)	Undiscounted QALY (95% CI)	Undiscounted Cost(£) (95% CI)	Undiscounted LY (95% CI)	Undiscounted QALY (95% CI)	Undiscounted Cost(£) (95% CI)	Undiscounted LY (95% CI)	Undiscounted QALY (95% CI)	Undiscounted Cost(£) (95% CI)	Discounted Inc QALYs (95% CI)	Discounted Inc Cost(£) (95% CI)	Discounted ICER(£) (95% CI)
65 year old Asymp Men	14.84 (14.45,15.13)	12.26 (11.8,12.64)	9290 (6812,12446)	15.19 (12.55,12.86)	12.7 (15.07,15.33)	10752 (9489,11901)	15.06 (14.81,15.29)	12.53 (12.25,12.81)	12458 (10370,14530)	0.26 (0.09,0.5)	2446 (740,3623)	9502 (1684,39173)
65 year old Asymp Women	17.16 (16.79,17.45)	14.15 (13.7,14.5)	9556 (7073,12723)	17.48 (14.39,14.71)	14.55 (17.36,17.6)	11020 (9625,12150)	17.36 (17.11,17.57)	14.39 (14.07,14.66)	12790 (10633,14748)	0.23 (0.07,0.48)	2548 (533,3680)	11047 (1161,51996)
75 year old Asymp Men	8.51 (8.34,8.66)	6.82 (6.62,6.98)	4700 (3487,6228)	8.67 (6.94,7.07)	7 (8.62,8.73)	7759 (7052,8262)	8.6 (8.49,8.71)	6.92 (6.8,7.05)	8737 (7705,9607)	0.13 (0.04,0.27)	3377 (2171,4124)	26840 (8115,103224)
75 year old Asymp Women	10.01 (9.83,10.14)	8 (7.8,8.16)	4839 (3598,6425)	10.14 (8.11,8.25)	8.17 (10.09,10.21)	7924 (7176,8437)	10.08 (9.96,10.19)	8.09 (7.96,8.22)	8937 (7795,9915)	0.11 (0.03,0.25)	3437 (2234,4151)	30321 (9525,137508)
65 year old Symp Men	12.84 (12.41,13.15)	9.3 (8.73,9.69)	11019 (7803,15015)	13.12 (9.49,9.88)	9.69 (12.96,13.25)	12183 (10308,13944)	13.02 (12.68,13.24)	9.54 (9.1,9.84)	14294 (11350,17487)	0.26 (0.05,0.57)	2178 (-236,3650)	8367 (-389,67806)
65 year old Symp Women	15.34 (14.9,15.69)	11.1 (10.54,11.55)	11674 (8430,15873)	15.64 (11.31,11.71)	11.51 (15.48,15.77)	12718 (10686,14506)	15.53 (15.19,15.78)	11.34 (10.91,11.68)	14974 (11781,17977)	0.26 (0.05,0.58)	2225 (-164,3712)	8491 (-638,60068)
75 year old Symp Men	6.99 (6.82,7.12)	4.93 (4.71,5.1)	5485 (3936,7510)	7.1 (5.01,5.16)	5.08 (7.04,7.15)	8418 (7516,9092)	7.06 (6.93,7.15)	5.02 (4.86,5.14)	9641 (8145,10839)	0.11 (0.01,0.27)	3248 (1556,4179)	28483 (4512,212691)
75 year old Symp Women	8.53 (8.31,8.68)	6.01 (5.73,6.22)	5804 (4042,8089)	8.64 (6.09,6.25)	6.17 (8.57,8.69)	8714 (7716,9433)	8.59 (8.44,8.69)	6.09 (5.92,6.24)	10016 (8392,11470)	0.12 (0.01,0.29)	3281 (1552,4208)	28452 (2057,189410)

CEA – Carotid Endarterectomy; CAS – Carotid Artery Stenting; MT – Medical Therapy, QALY – Quality adjusted life years, Symp – Symptomatic, Asymp - Asymptomatic

Figure 5.5: Cost-effectiveness acceptability curves for asymptomatic patients, by age and gender

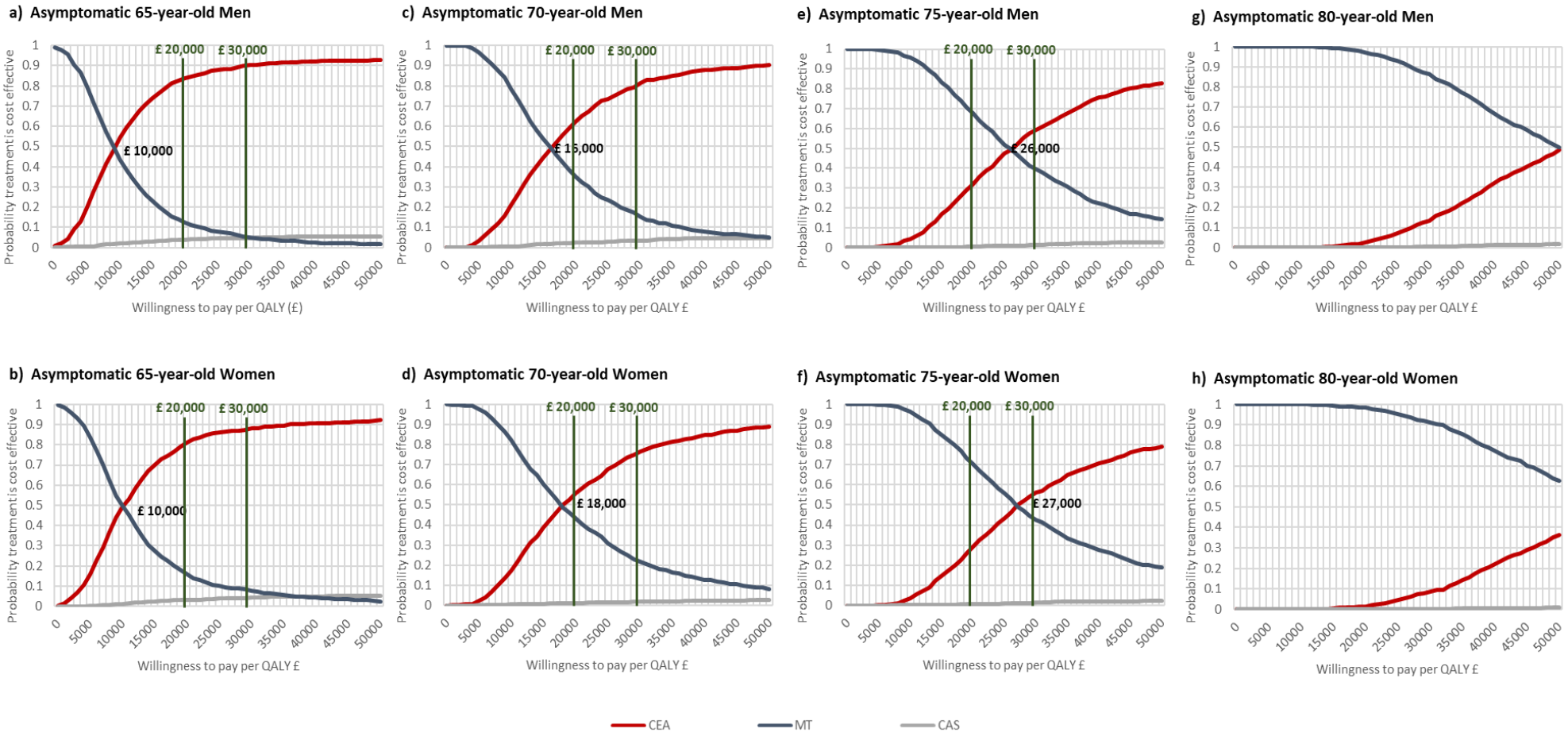
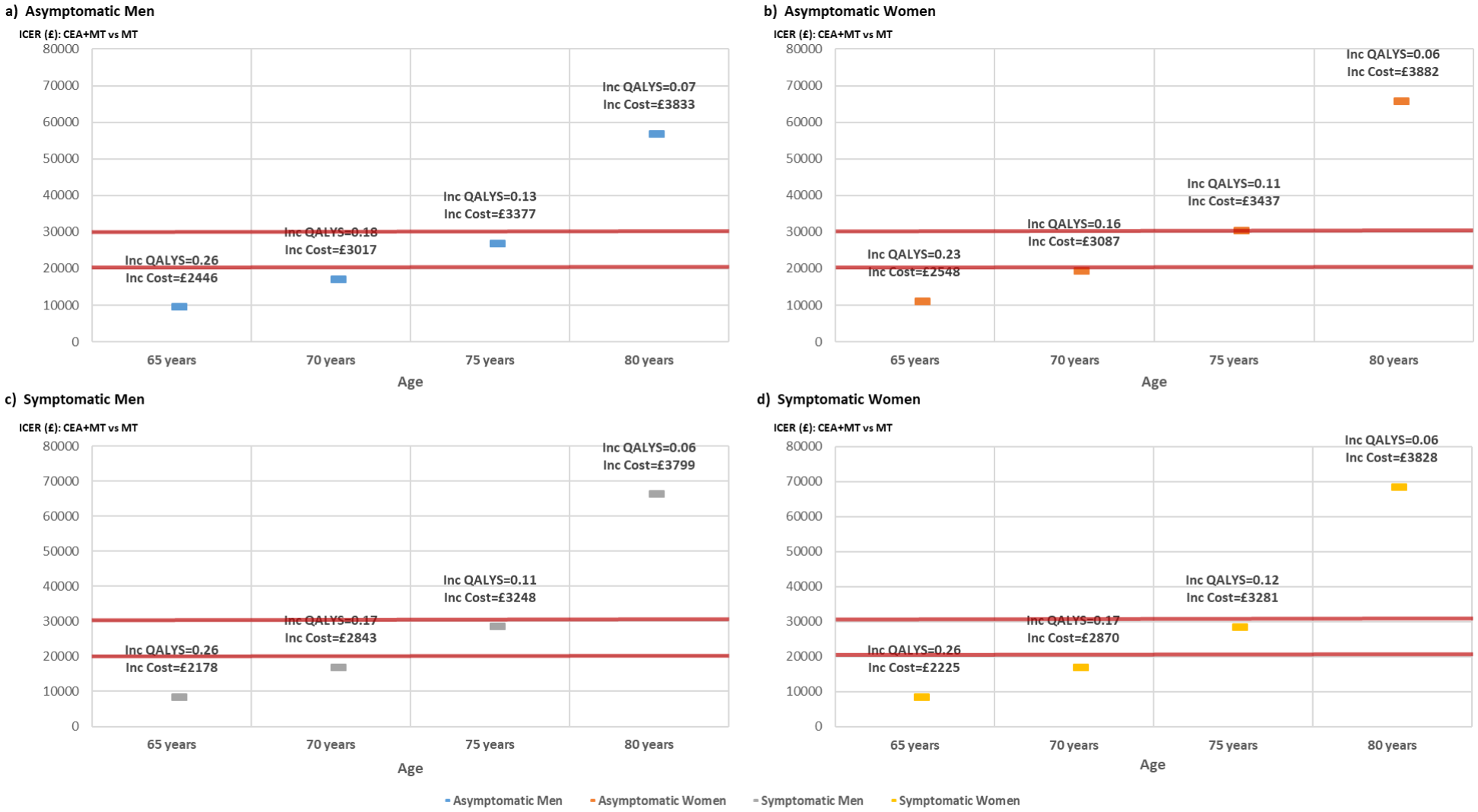


Figure 5.6: Cost effectiveness of CEA plus MT vs MT alone, by age



**Note: With QALYs and Costs discounted in ICERs.*

Symptomatic carotid stenosis patients

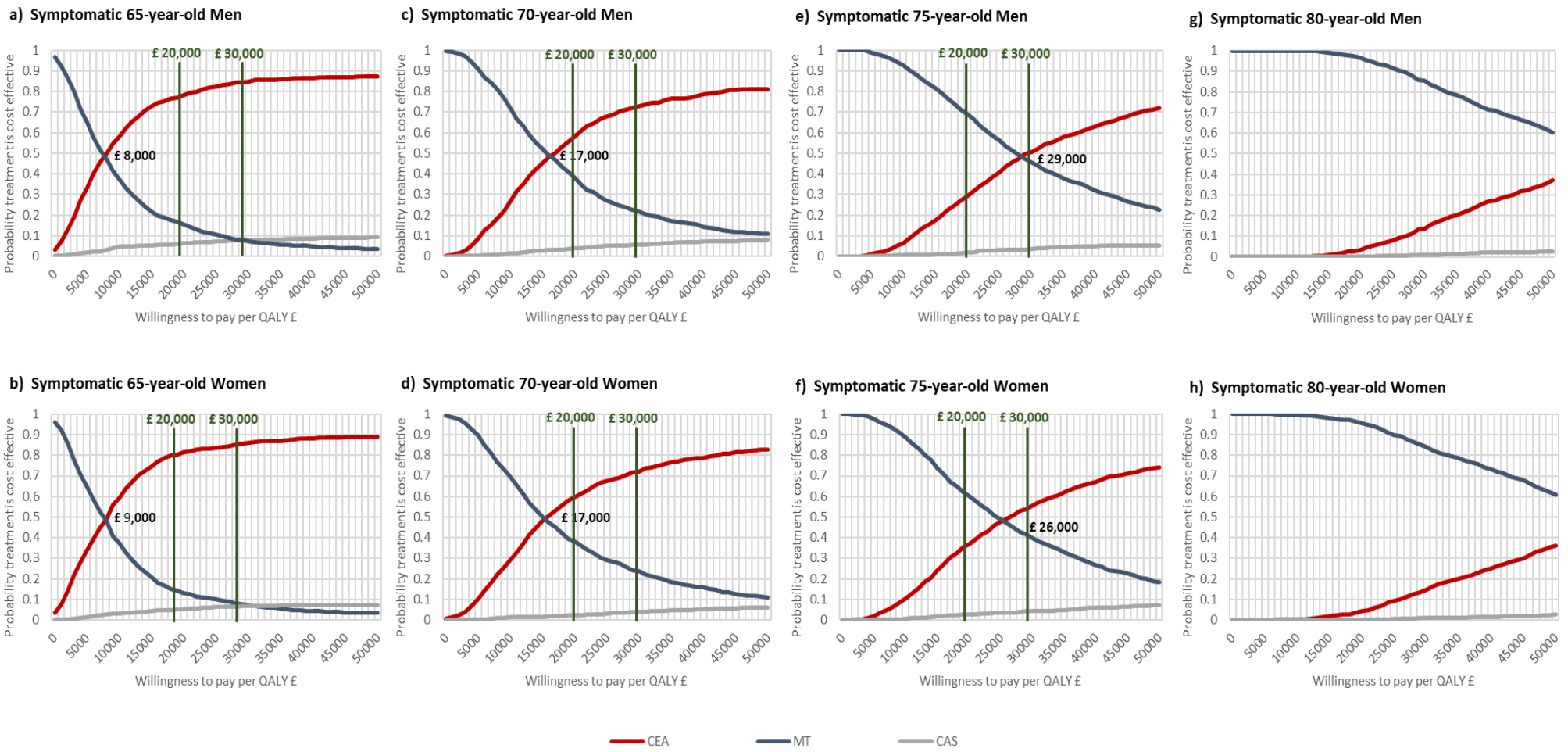
Symptomatic 65-year-old men treated with MT alone were projected to live 12.84 years (9.30 QALYs) at a cost of £11,019 (**table 5.6**) to the NHS and social care services. Life expectancy of symptomatic patients was lower than that of asymptomatic patients due to a combination of higher procedural and post-procedural stroke risks, and non-stroke related vascular mortality risks faced by symptomatic patients. If further treated with CEA in addition to MT, symptomatic 65-year-old men were projected to gain 0.28 additional years of life (0.39 QALYs) at an extra cost of £1,164 (**table 5.6**). This resulted in an ICER of £8,367 per QALY for CEA plus MT vs MT alone (with QALYs and costs discounted). The CAS plus MT strategy was dominated by the CEA plus MT strategy due to patients being projected to live 0.10 years (0.15 QALYs) less than when treated with CEA plus MT and incurring £2,111 extra costs (**table 5.6**). MT alone had the highest probability of being cost-effective up to willingness to pay for a QALY of £8,000, following which CEA plus MT was the most cost-effective option. At willingness to pay per QALY of £20,000 CEA plus MT had an 78.2% probability of being cost-effective, MT alone a 15.5% probability, and CAS plus MT a 6.3% probability (**figure 5.7a**).

Symptomatic 65-year-old women treated with MT alone were projected to live 15.34 years (11.10 QALYs) at a cost of £11,674 (**table 5.6**) to the NHS and social care services. If treated with CEA in addition to MT at the age of 65, symptomatic women were projected to gain additional 0.30 years of life (0.41 QALYs) at an extra cost of £1,044 (**table 5.6**). This resulted in an ICER of £8,491 per QALY for CEA plus MT vs MT alone (with QALYs and costs discounted). CAS plus MT strategy was dominated by CEA plus MT strategy, with 65-year-old symptomatic women projected to live 0.11 years (0.17 QALYs) less and incur £2,257

extra costs than if treated with CEA plus MT (**table 5.6**). Up to a willingness to pay-per-QALY of £9,000, MT alone strategy had the highest probability of being cost-effective, after which CEA plus MT was the most cost-effective option (**figure 5.7b**). At a willingness to pay per QALY of £20,000 CEA plus MT had an 81.5% probability of being cost-effective, MT alone a 13.2% probability, and CAS plus MT a 5.3% probability (**figure 5.7b**).

ICERs for CEA plus MT vs MT alone for symptomatic men and women was higher in older patients (**figure 5.6**) with higher non-stroke related mortality risks experienced by older patients resulting in them having less time to benefit from the intervention. Hence at a willingness to pay-per-QALY of £20,000, CEA plus MT strategy was the most cost-effective option for 65 and 70 years old symptomatic patients (**figure 5.7a,5.7b,5.7c,5.7d**), and MT alone for symptomatic men and women aged 75 years and above (**figure 5.7e,5.7f,5.7f,5.7h**). As was the case with 65 years old symptomatic patients, CEA plus MT strategy dominated CAS plus MT for symptomatic patients, irrespective of their age or gender (**appendix table 5.9**).

Figure 5.7: Cost-effectiveness acceptability curves for symptomatic patients, by age and gender



Deterministic sensitivity analysis

Results from the deterministic sensitivity analysis show that sourcing the cost of CEA procedure from HRG 2014-15 HRG National Schedule for reference costs data(147), instead of the cost evaluated in ICSS, did not notably alter the projected ICER of CEA plus MT vs MT alone in all categories of patients irrespective of age, gender and symptomatic status (**appendix table 5.10**).

Results from ACAS, VA and ACST-1 showed that there were no statistically significant differences in post-procedural stroke risks between men and women while asymptomatic patients above the age of 75 had s 79% higher post-procedural stroke risks compared to patients aged between 65 and 75. Using these results to inform how post-procedural stroke risks vary by gender and age in asymptomatic patients led to lower ICERs of CEA plus MT vs MT alone for asymptomatic men and women across all age categories (**appendix table 5.11**).

Using relative post-procedural stroke risks for CAS plus MT vs CEA plus MT reported in the meta-analysis of the EVA-3S, ICSS, SPACE and CREST RCTs (**chapter 3**), instead of relative post-procedural minor and separately major stroke risks for CAS plus MT vs CEA plus as in the base case showed that CAS plus MT was still dominated by CEA plus MT across all patient categories (**appendix table 5.12**). When model input parameters for relative procedural and post-procedural minor stroke risks of CAS plus MT vs CEA plus MT was set to 1, CEA plus MT strategy still dominated the CAS plus MT strategy (**appendix table 5.12**). The results remained similar following the use of relative procedural stroke/death risks of CAS vs CEA of EVA-3S, SPACE and ICSS (which reported results by age) to adjust model

parameters for relative procedural major and minor stroke risks, respectively (**appendix table 5.10**).

If procedural stroke/death risks of CEA were at the threshold level of policy guidelines of 3% in asymptomatic (base case: 1.5%) and 6% in symptomatic (base case: 2.68%) patients, the ICERs for CEA plus MT vs MT alone were higher compared to the base case across all patient groups (**appendix table 5.14**), with the ICERs for 75-year-old patients being above £30,000 (**figure 5.8**) and ICERs for 70-year-old patients above £20,000 (**appendix table 5.14**) irrespective of symptomatic status or gender. ICERs of CEA plus MT vs MT alone remained above £20,000 for asymptomatic 70-year-old men except when procedural stroke/death risks of CEA were at least 30% (procedural stroke/death in asymptomatic patients: 2.1%) below those quoted in policy guidelines and symptomatic 70-year-old men except for when procedural stroke/death risks were at least 40% (procedural stroke/death in symptomatic patients: 3.6%) below policy guidelines levels (**appendix table 5.14**). ICERs of CEA plus MT vs MT alone in 70-year-old women were above £20,000 even when procedural stroke/death risks of CEA patients were 40% below those quoted in policy guidelines, only falling below £20,000 in the base case scenario.

Increasing or reducing the proportion of fatal major strokes in procedural and post-procedural major strokes did not alter projected incremental results and ICERs for CEA plus MT vs MT alone significantly, with the ICERs for all patient groups increasing marginally when fatalities in procedural and post-procedural major strokes were reduced to 15%, and reducing marginally when increased to 45% (**figure 5.9; appendix table 5.15**)

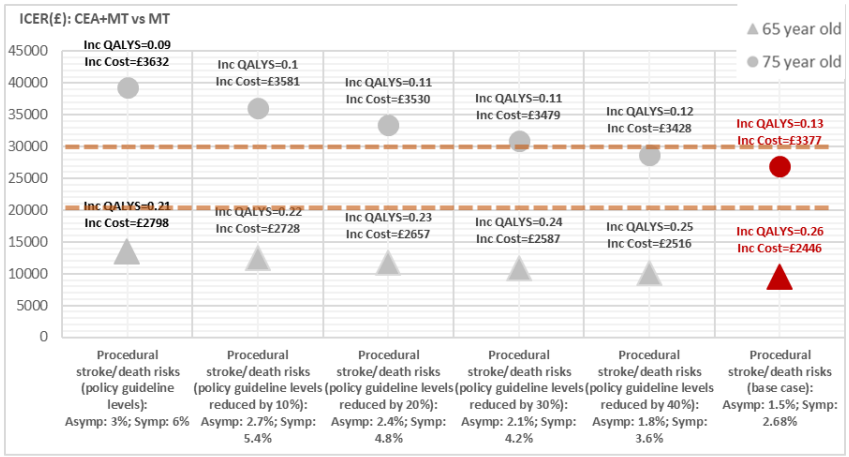
Reducing the proportional increase in non-stroke vascular risks in patients after an experience of stroke to twice (from 2.45 times), 1.5 times and to a scenario where patients having

experienced stroke did not have an increased non-stroke vascular mortality risks, resulted in the ICER for CEA plus MT vs MT alone increasing marginally to £9,840, £10,317, and £10,955, respectively, for 65-year-old asymptomatic men (**figure 5.10**). Similar trends were observed in other asymptomatic patient groups (**figure 5.10; appendix table 5.16**). While reducing the multiple will result in an increase in the life expectancy of patients hence giving them a longer time to benefit from intervention, the absolute increase in life expectancy was higher in patients treated with MT alone due to them having a higher probability of experiencing a major or minor stroke. For 65-year-old symptomatic men, where patients were subjected to increased non-vascular stroke risks due to prior stroke, irrespective of which health state they were in, reducing this multiple to 2x, 1.5x and 1x resulted in the ICER for CEA plus MT vs MT alone decreasing to £7,428, £6,406 and £5,405, respectively (**figure 5.10**). Similar patterns, driven by an increased time to benefit from intervention, were observed across other symptomatic patient groups (**figure 5.10; appendix table 5.16**). It is also worth noting that while in the base case the ICERs of CEA plus MT vs MT alone were similar between symptomatic men and women, reducing the multiple to 1x resulted in lower ICERs for men reflecting the higher post-procedural stroke risks men experience (**appendix table 5.16**).

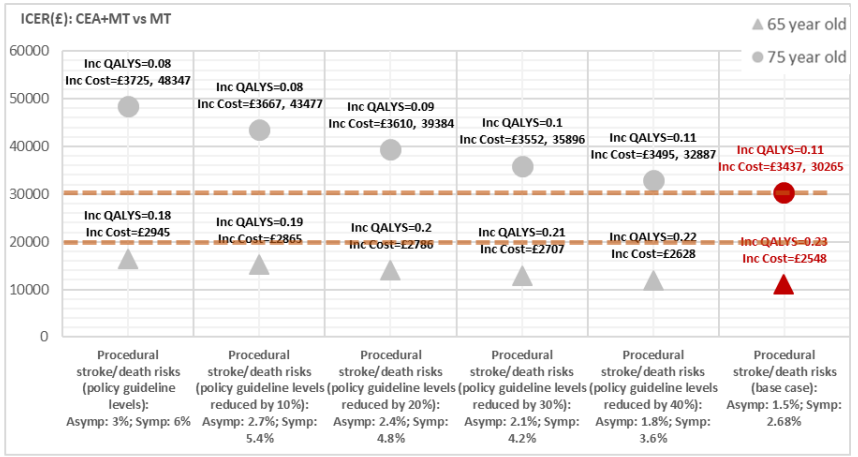
Lower post-procedural minor and major stroke risks in the deterministic sensitivity analysis, led to higher projected ICERs for CEA plus MT vs MT alone in both symptomatic and asymptomatic patients (**figure 5.11; appendix table 5.17**).

Figure 5.8: Deterministic sensitivity on procedural risks of CEA

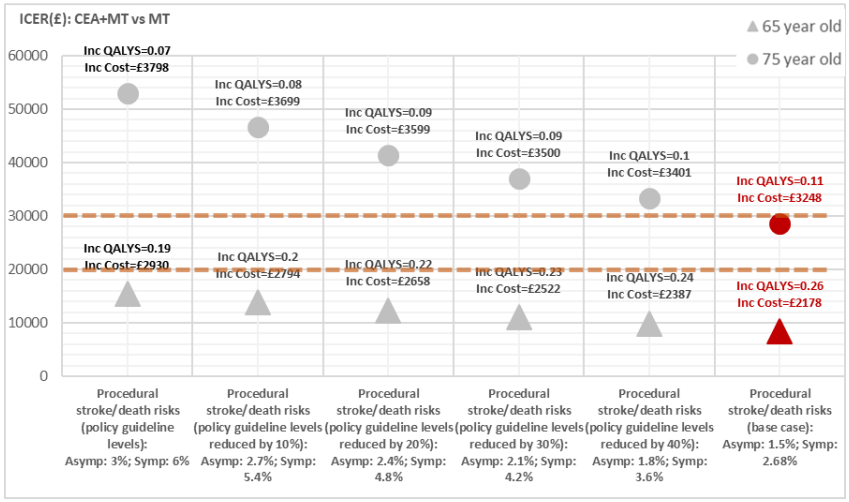
a) Asymptomatic Men



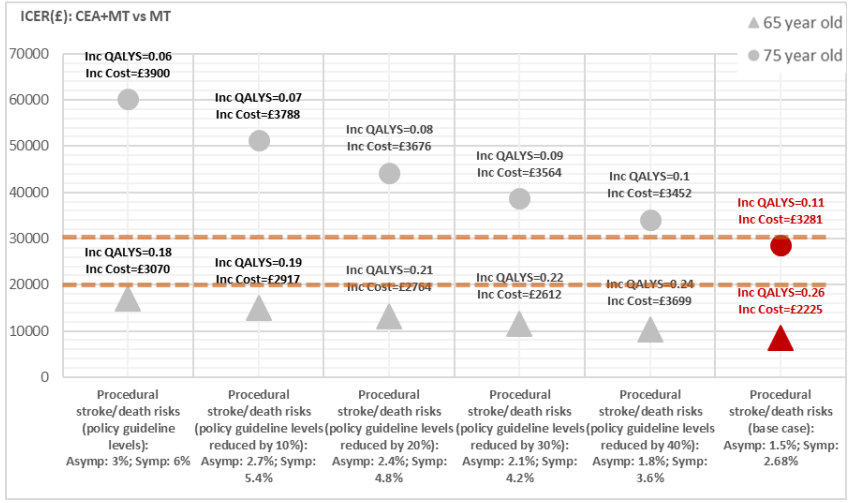
b) Asymptomatic Women



c) Symptomatic Men



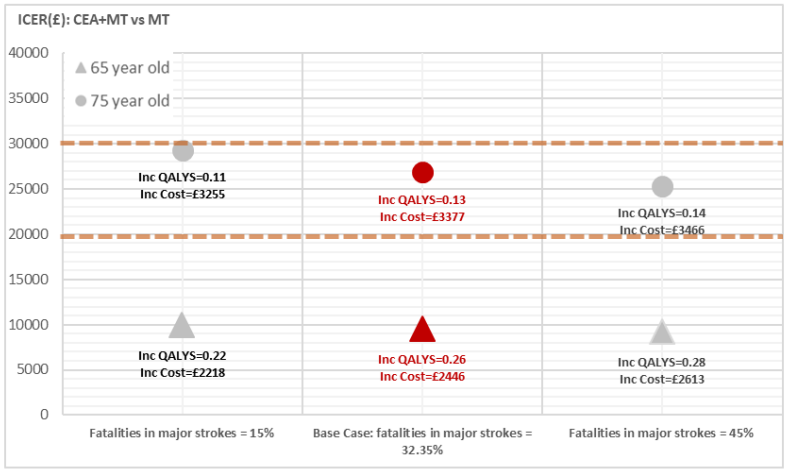
d) Symptomatic Women



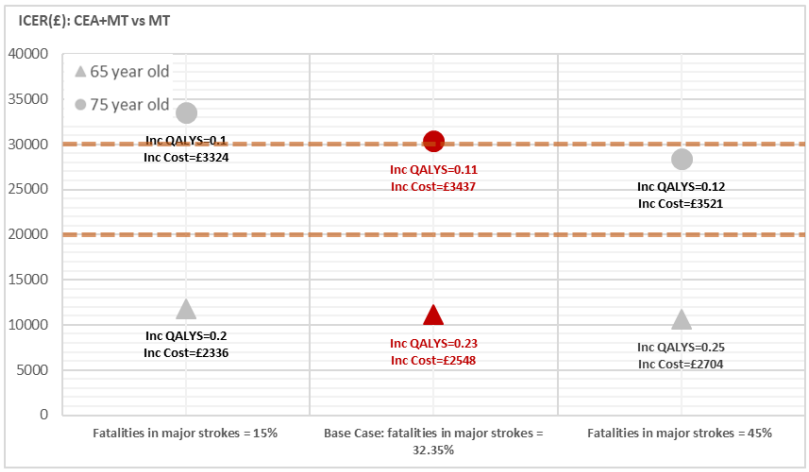
**Note: Results reported in red are base case results*

Figure 5.9: Deterministic sensitivity on fatalities in major strokes

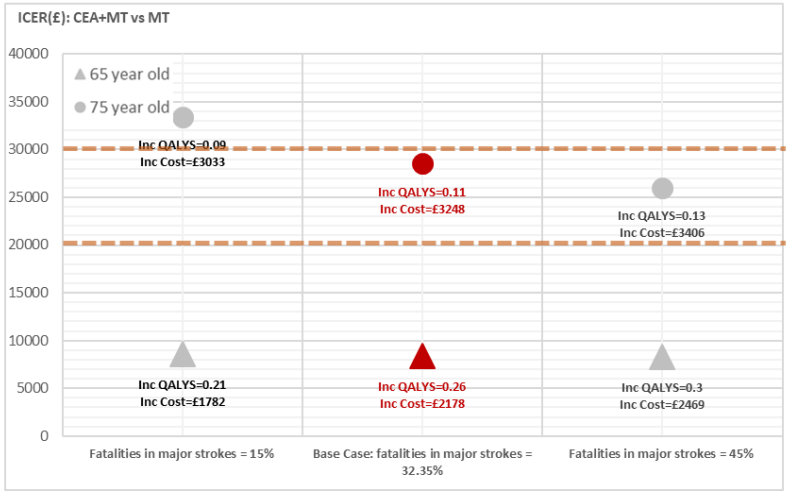
a) Asymptomatic Men



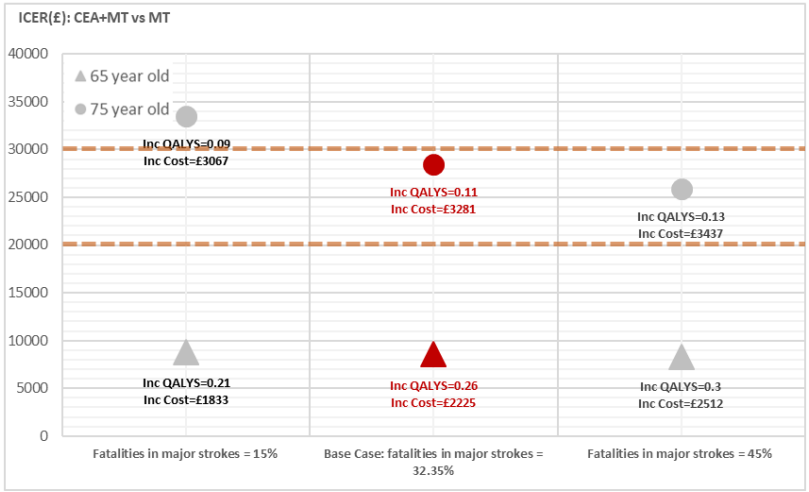
b) Asymptomatic Women



c) Symptomatic Men

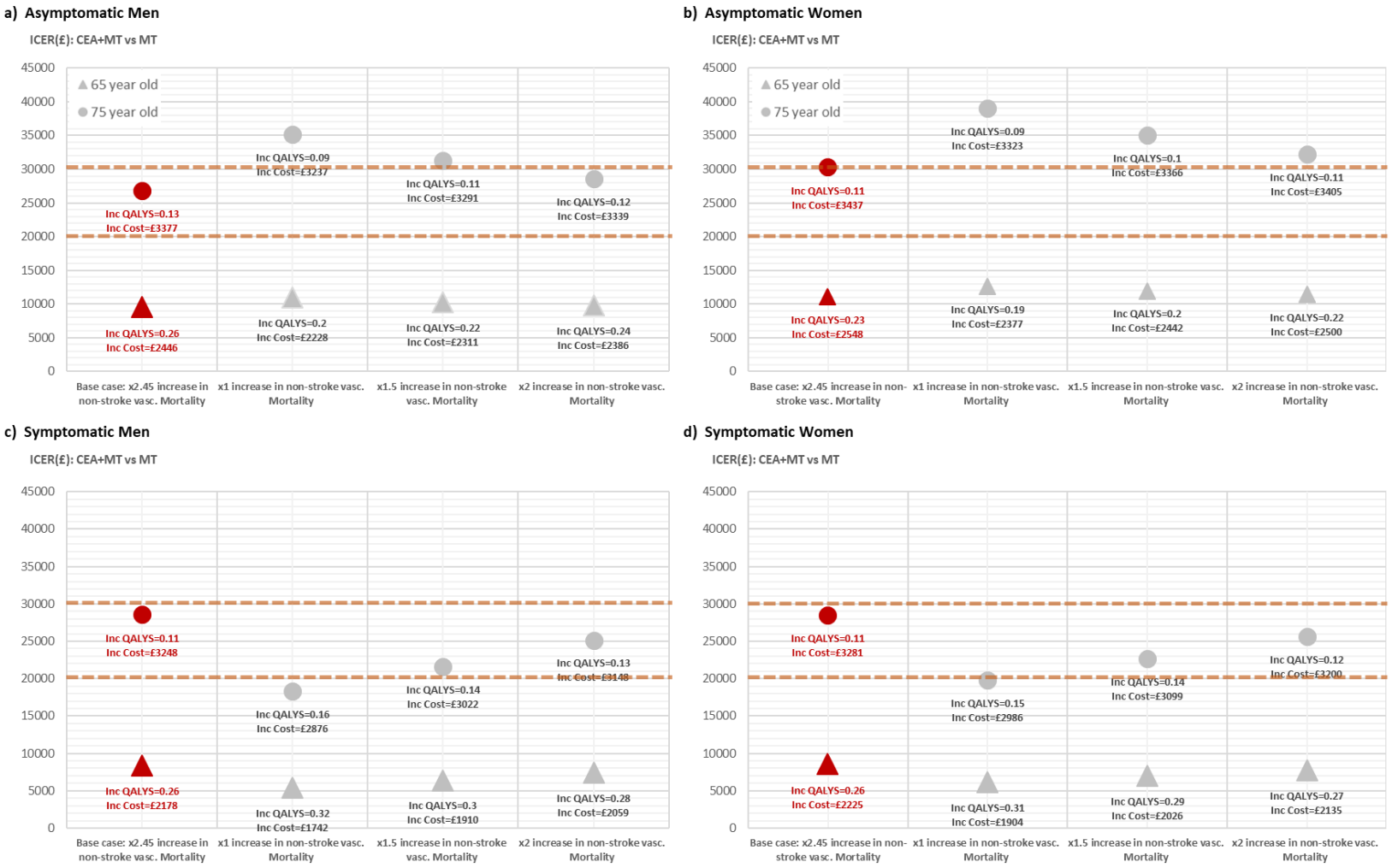


d) Symptomatic Women



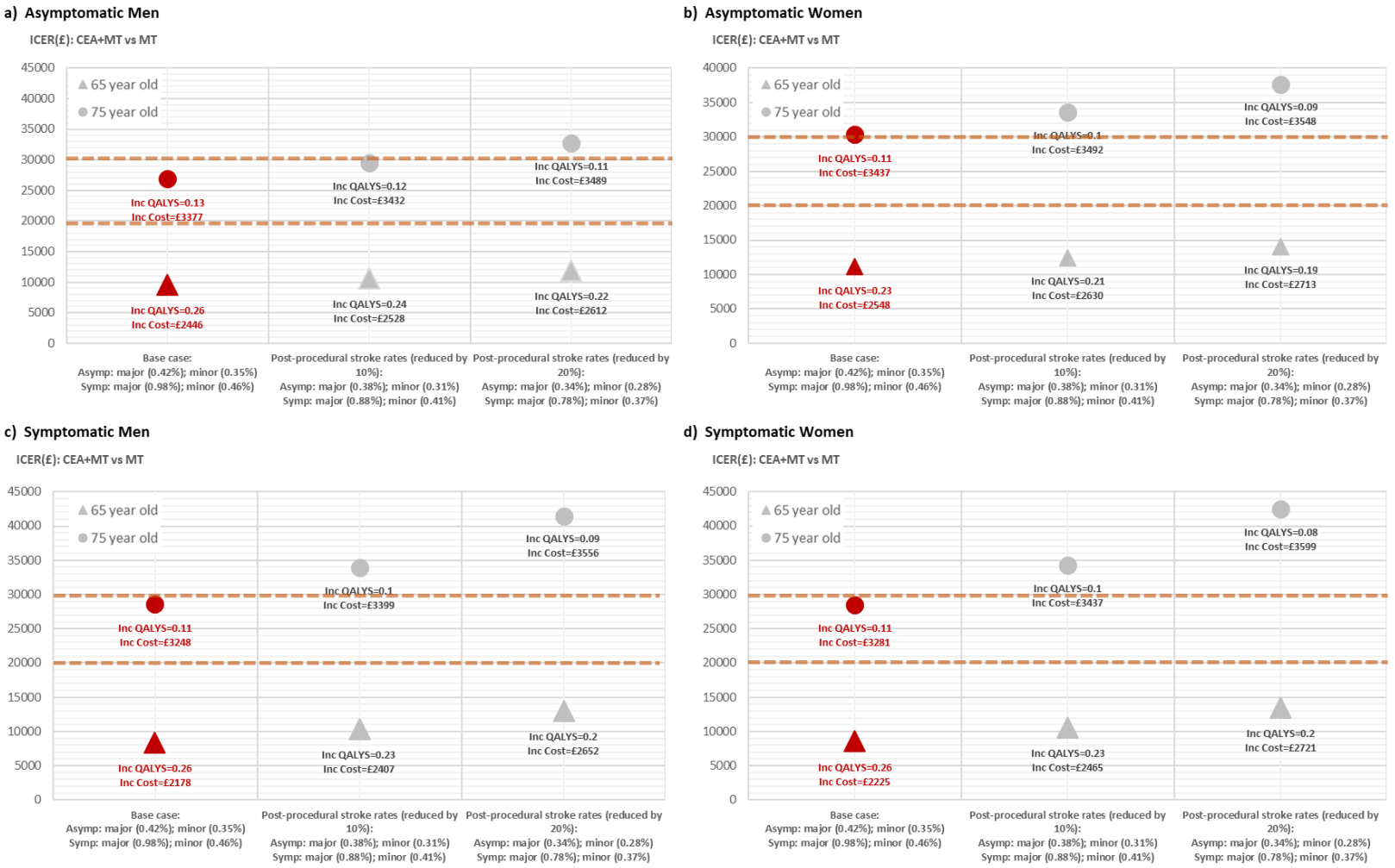
**Note: Results reported in red are base case results*

Figure 5.10: Deterministic sensitivity analysis on increased non-stroke vascular mortality risk



**Note: Results reported in red are base case results*

Figure 5.11: Deterministic sensitivity analysis on post-procedural stroke risks



**Note: Results reported in red are base case results*

Value of information

The EVPI per person for the decision to adopt CEA plus MT for a population of 65 years old asymptomatic men was £149 at a willingness to pay for a QALY of £20,000, and £88 at a willingness to pay for a QALY of £30,000. For 65 years old asymptomatic women, the EVPI per person was £207 and £108 at a willingness to pay for a QALY of £20,000 and £30,000 respectively (**figure 5.12; appendix table 5.11**). At willingness to pay-per-QALY of £20,000 and £30,000 the EVPI per person to adopt CEA for a population of 65-year-old symptomatic men was £285 and £226 respectively. For 65-year-old symptomatic women, these values were similar at £280 and £222 respectively (**figure 5.13; appendix table 5.11)**. For 70-year-old patients, the EVPI per patient for adopting CEA plus MT was higher, ranging between £425 to £662 at a willingness to pay-per-QALY of 20,000 and between £190 and £430 at a willingness to pay-per-QALY of £30,000 (**appendix table 5.11**).

At a willingness to pay per QALY of £20,000 MT alone was the most cost-effective method of treatment for 75-year-old patients with the EVPI per person being £407 and £318 for 75-year-old asymptomatic men and women, and £507 and £597 for 75-year-old symptomatic men and women (**figures 5.12, 5.13**). At a willingness to pay for a QALY of £30,000 the EVPI per person to adopt CEA plus MT was higher for 75-year-old patients when compared to 65-year-old patients, reported at £503 for 75-year-old asymptomatic men and above £600 for a 75-year-old patient in other categories (**figures 5.12, 5.13)**. This was reflective of the projected ICERs of CEA plus MT vs MT alone for 75-year olds ranging from £26,840 to £30,321 **(table 5.6**) in the four 75 years old patient groups, and the uncertainty surrounding these results.

Detailed results from the EVPI analysis for all patient groups at willingness to pay-per-QALY thresholds ranging from £0 to £50,000 are shown in **appendix table 5.18**.

Further analysis showed that the EVPPI per patient of model input parameters for procedural stroke/death risks, and relative procedural stroke/death risks of CAS vs CEA, was zero at willingness to pay-per-QALY of £20,000 (**appendix table 5.19**). For the model input parameters of relative post-procedural minor and major stroke risks of CAS plus MT vs CEA plus MT the EVPPI per patient at a willingness to pay-per-QALY of £20,000 ranged from £40 to £68 in 65-year-old patients, and zero for patients 70 or above (**appendix table 5.19**)

At a willingness to pay-per-QALY of £20,000 the EVPPI per patient of model input parameters for post-procedural stroke risks of CEA patients was zero in 65 years old patients, and varied between £59 and £106 for 75-year-old patients depending on gender and symptomatic status (**appendix table 5.19**). The EVPPI per patient was highest for the model input parameter for relative post-procedural minor and major stroke risks of CAS plus MT vs CEA plus MT, ranging between £200 to £300 in 65-year-old patients, above £600 for 70-year-old patients and above £400 for 75-year-old patients (**appendix table 5.19**).

Figure 5.12: Value of information analysis for asymptomatic patients

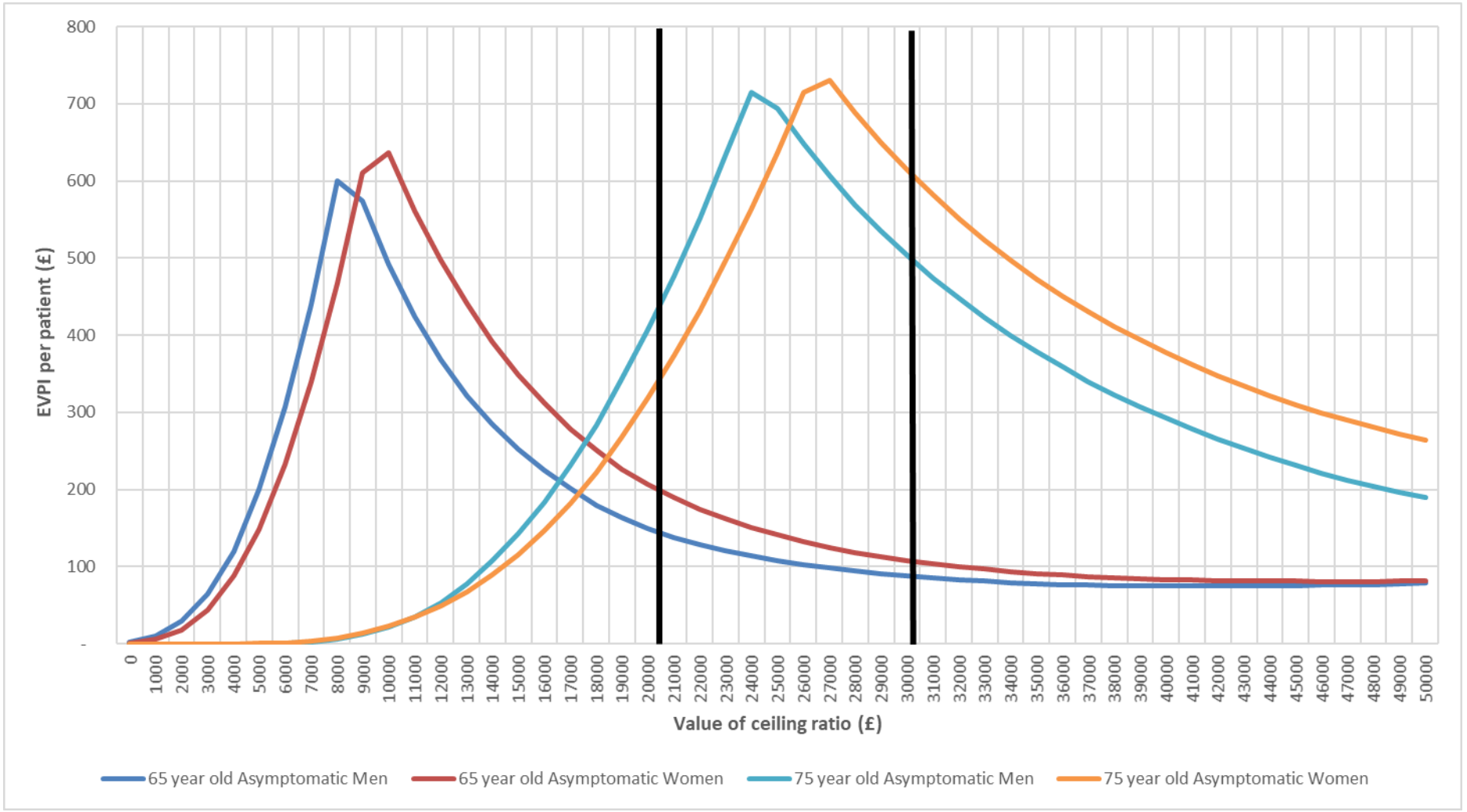
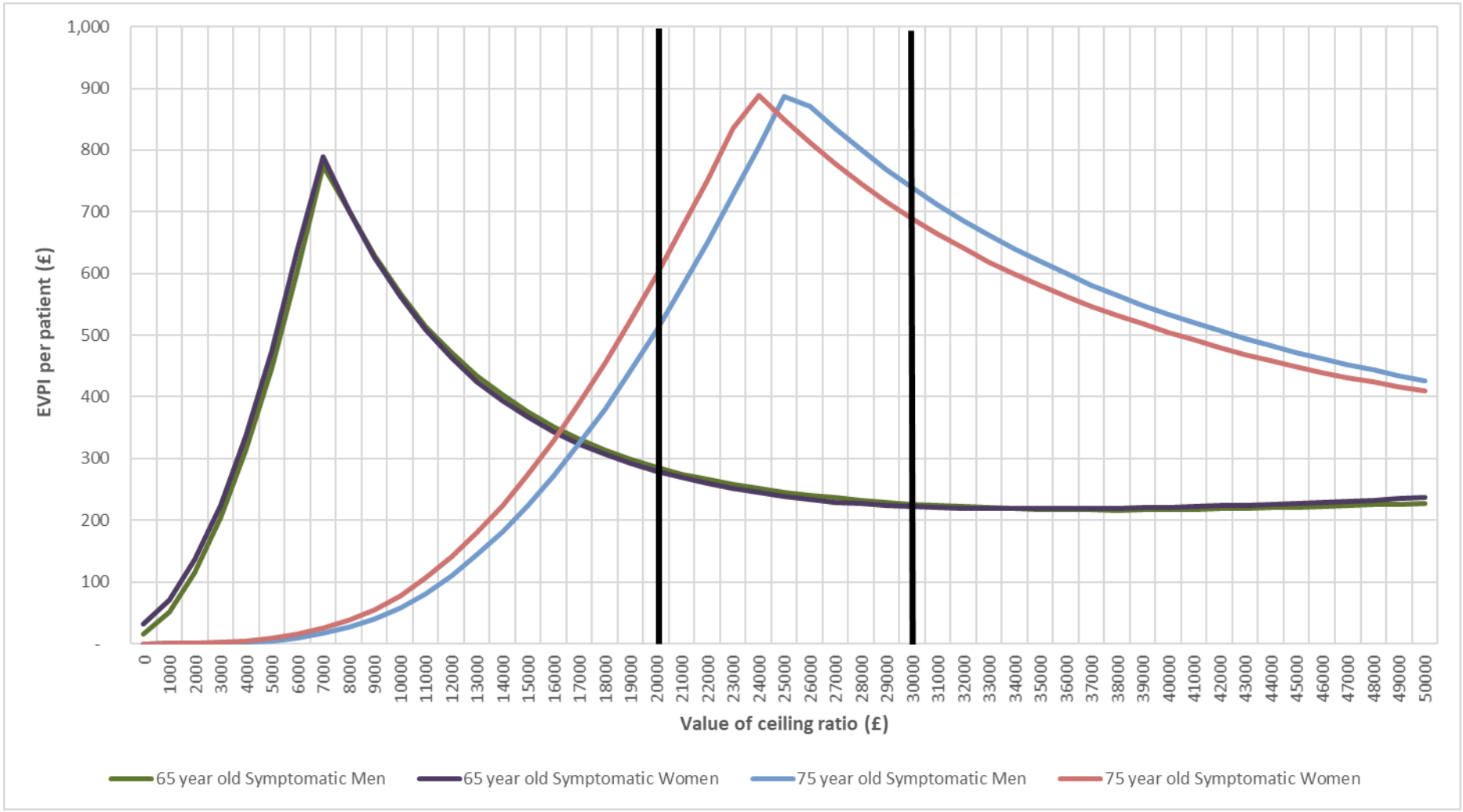


Figure 5.13: Value of information analysis for symptomatic patients



Model checks

Projected undiscounted life expectancy of men (**figure 5.14**) and women (**figure 5.15**) are shown in the respective figures for different ages at which patients are treated, classified by symptomatic status and method of treatment. As expected, projected life expectancy of both asymptomatic and symptomatic carotid stenosis patients were lower than that of the general UK population due to the additional stroke related mortality and other vascular mortality risks faced by carotid stenosis patients. Life expectancy of symptomatic patients were lower than that of asymptomatic patients due to symptomatic patients having a higher non-stroke related vascular mortality and stroke related mortality risks when compared to asymptomatic patients. The steps recommended in the AdVISHE model validation tool were followed where feasible and summarised in **appendix text 5.12.**

Figure 5.14: Predicted life expectancy (undiscounted) for men treated for symptomatic and asymptomatic carotid stenosis and life expectancy of men in the general UK population

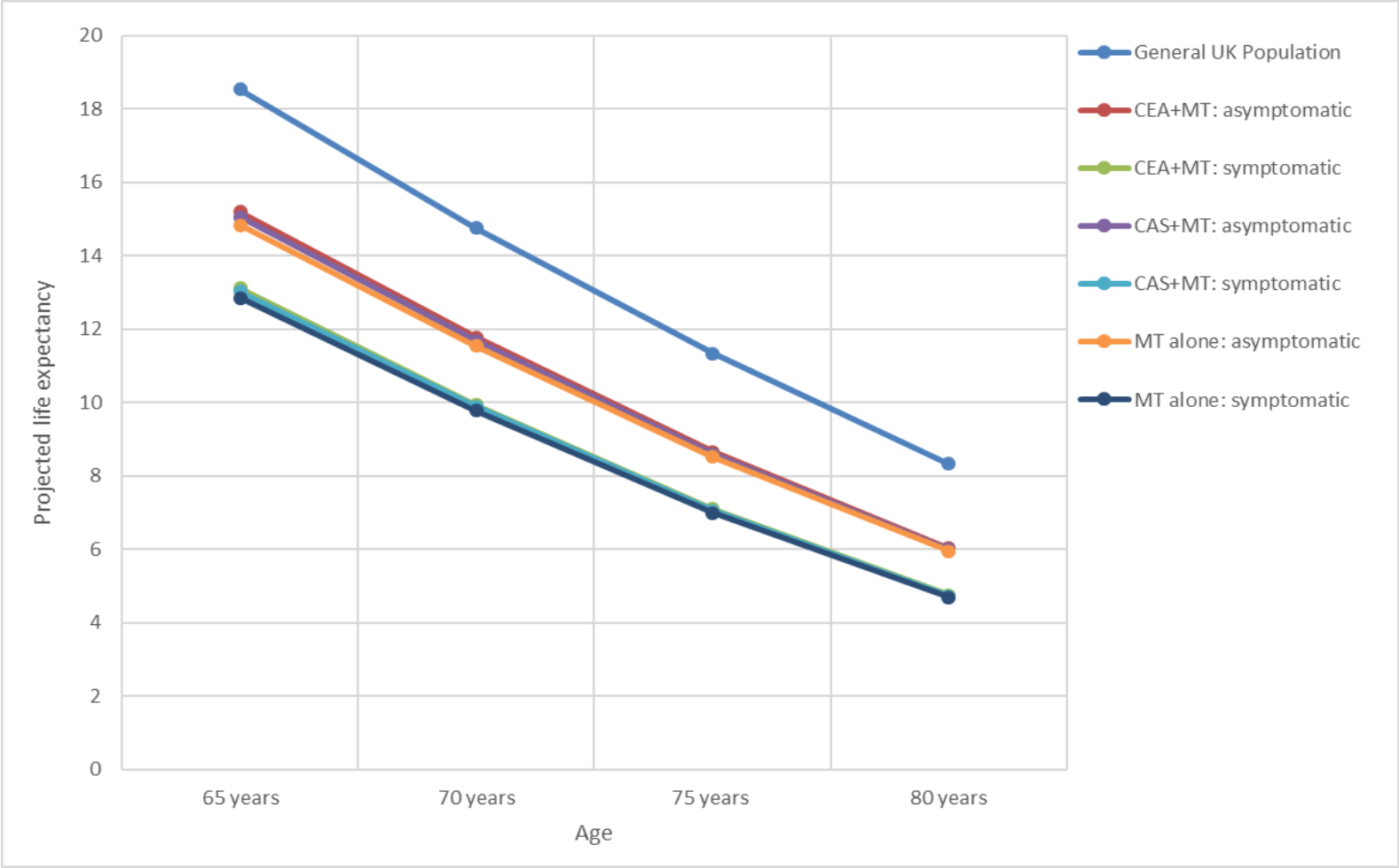
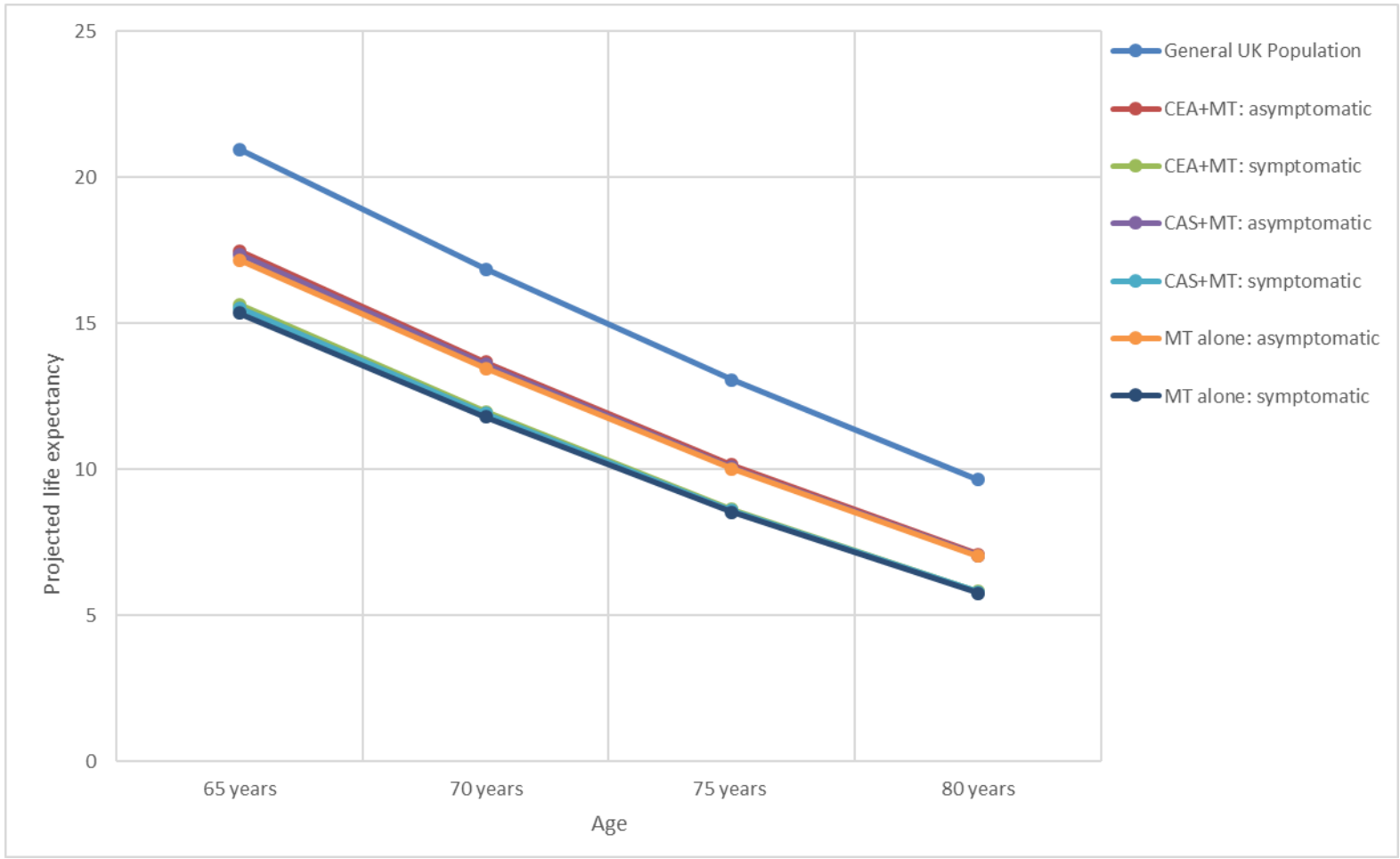


Figure 5.15: Predicted life expectancy (undiscounted) for women treated for symptomatic and asymptomatic carotid stenosis and life expectancy of women in the general UK population



5.4 Discussion

The systematic literature review of economic evaluations studying the treatment methods for carotid stenosis in **chapter 2** identified the need for cost-effectiveness analysis comparing all available treatment methods for carotid stenosis using the same evaluative modelling framework. This economic evaluation attempts to fill this gap and address the limitations identified in previous economic evaluations. The principal finding from our cost-effectiveness analysis is that at willingness to pay for a QALY of £20,000, CEA, added to MT, is the most cost-effective method for treatment for symptomatic and asymptomatic carotid stenosis patients aged up to 75 years, while MT alone is the most cost-effective intervention for both asymptomatic and symptomatic patients aged 75 years and above. CEA plus MT dominated CAS plus MT strategy for both symptomatic and asymptomatic patients, regardless of age and gender.

CEA plus MT's superiority over MT in patients below the age of 75 was a result of lower post-procedural major and minor stroke risks of CEA plus MT vs MT alone compensating for the procedural risks involved with CEA. For 75-year-old patients MT alone was the most cost-effective option at a willingness to pay for a QALY of £20,000, though at a willingness to pay-per-QALY of £30,000 CEA plus MT was the dominant strategy. Higher non-stroke related mortality risks and post-procedural stroke risks lead to a shorter life expectancy post intervention in older patients, resulting in these patients not benefiting from the lower stroke risks with CEA for as long as younger patients. As a result of this ICERs of CEA plus MT vs MT alone were higher in older patients, with CEA plus MT not being a cost-effective treatment method for patients aged 80 years, irrespective of the willingness to pay for a QALY.

The EVPI per person for adopting the CEA plus MT strategy at a willingness to pay-per-QALY of £20,000 in 65-year-old patients ranged from £149 to £280, but was much higher in 70-year-old patients ranging from £425 to £662, hence showing that a larger degree of uncertainty was associated with the treatment decision in 70-year-old patients. While CEA plus MT strategy was not the most cost-effective method of treatment at a willingness to pay-per-QALY of £20,000 in 75-year-old patients, it was so at willingness to pay-per-QALY of £30,000. However, the degree of uncertainty associated with adopting CEA plus MT in 75-year-old patients at a willingness to pay-per-QALY of £30,000 was highlighted in the value of information analysis, with the EVPI above £500 per asymptomatic patient and above £600 per symptomatic patient for adopting CEA plus MT at a willingness to pay-per-QALY of £30,000. While there is no information available on total number of carotid stenosis patients treated in the UK by age and gender categories, the UK CEA audit reported 4,941 symptomatic patients and 782 asymptomatic patients treated with CEA between October 2011 and September 2012.(152) If 500 75-year-old patients per year were treated for carotid stenosis in the UK with a technology lifespan of 10 years in any of these patient categories, it would result in an EVPI of around £2.5 million, assuming a EVPI per person of £500.

The EVPPI analysis showed that at a willingness to pay-per-QALY of £20,000, additional information would be most valuable for the model input parameters informing relative post-procedural stroke risks of CEA plus MT vs MT alone, while additional information on relative post-procedural stroke risks of CAS plus MT vs CEA plus MT would be also valuable for decisions in 65-year-old patients. This highlights the need for more RCTs comparing CEA plus MT vs MT alone, and to a lesser extent CAS plus MT vs CEA plus MT. CREST-2, a RCT consisting of two independent arms comparing CEA vs MT alone and

CAS vs MT alone is currently in the pipeline having recruited 1,191 patients(95) at present, and target recruitment of 2,480 patients by 2020.(96) However another three arm trial, comparing MT alone vs CEA vs CAS, SPACE-2 was terminated due to slow recruitment.(97) The difficulties faced by SPACE-2 with regard to patient recruitment throws doubt on the success of new trials with MT alone as a treatment arm: it was reported that one of the reasons behind slow patient recruitment in SPACE-2 was due to difficulties in convincing patients who had been admitted to a surgical or interventional radiology departments upon diagnosis, to participate in a RCT where there was a chance of being randomised to MT alone.(97) The EVPPI per person was also high for model input parameters informing post-procedural stroke risks of CEA patients. At present in our analysis, this is informed by ICSS in symptomatic patients (number of CEA patients: 853) and the IPD meta-analysis of ACAS, VS and ACST-1 in asymptomatic patients (number of CEA patients: 1241 CEA patients). Results from the EVPPI analysis highlights the need for larger observational studies reporting long-term stroke risks of patients by symptomatic status. At present, to the best of my knowledge, there are no observational cohort studies reporting long-term minor and major stroke risks in symptomatic and asymptomatic patients treated for carotid stenosis. The lack of such observational studies can partially be due to difficulties in following up patients in large observational studies and the need for an independent neurologist to assess severity of strokes.

Symptomatic patients have higher mortality risks than asymptomatic patients and hence a shorter life expectancy, resulting in symptomatic patients benefiting less from interventions which reduce long-term stroke risks. However, they also have higher post-procedural stroke risks. Therefore, the net benefits with CEA plus MT vs MT alone were larger for

symptomatic patients compared to asymptomatic patients, resulting in symptomatic patients having lower ICERs for CEA plus MT vs MT alone.

ICERs for CEA plus MT vs MT alone were higher in asymptomatic women, compared to asymptomatic men, mainly as a result of higher post-procedural stroke risks in men than women. This resulted in men achieving larger absolute reductions in stroke risks with CEA in the long-run (**table 5.6**). Differences in ICERs for CEA plus MT vs MT alone were less prominent between symptomatic men and women, due to differences in absolute reductions in stroke risks from CEA being minimal between symptomatic men and women as a result of symptomatic patients having a short life expectancy following increased non-stroke vascular mortality risks. Our deterministic sensitivity analysis shows that if the proportional increase in non-stroke vascular mortality risks in post-stroke patients is reduced to 1x (i.e. no increase), ICERs for CEA plus MT vs MT alone were higher in symptomatic women than symptomatic men.

Specific anatomic conditions such as prior neck surgery or radiation make CEA a less viable method of treatment.(153) In such situations the results from this economic evaluation may be used to inform the cost-effectiveness of CAS plus MT compared to MT alone. However, the use of the model to a situation where a patient may not be eligible for a CEA procedure cannot be justified because the model input parameters do not necessary reflect disease risks and treatment effects in such patients. For example, ICSS(154) excluded patients who had contraindications to CEA, ACST-1(84) excluded those with poor surgical risk, and CREST(57) included only patients with anatomical suitability.

Patients treated with CEA gained more QALYs than CAS patients and incurred lower healthcare costs over lifetime, irrespective of their age, gender, or symptomatic status.

Results were driven by relative procedural stroke risks, relative post-procedural minor stroke risks of CAS vs CEA, and relative post-procedural major stroke risks of CAS vs CEA. As shown in **chapter 3,** CAS patients had higher procedural stroke/death risks and post-procedural minor stroke risks than CEA patients with differences being statistically significant, while CEA had lower post-procedural minor and major risks than CAS too, but differences were not statistically significant. Relative post-procedural major and minor stroke risks of CAS vs CEA were calculated using information in ICSS and CREST, the two largest, and barring ACT-1, the most recent trials comparing CAS vs CEA. However, information from 4 RCTs including the most recent RCT comparing CAS vs CEA, ACT-1, are not included in this synthesised information due to these trials not reporting post-procedural stroke risks by stroke severity. Reporting of results from these RCTs by stroke severity in the future or access to evaluate IPD from these RCTs, will enable consideration of information from all RCTs comparing CAS vs CEA, and reduce uncertainty surround input parameters for relative post-procedural minor and major stroke risks.

The European Society of Cardiology guidelines recommend CEA if the documented procedural stroke/death risk is below 6% in symptomatic patients and 3% in asymptomatic patients.(155) However, such thresholds for procedural risks quoted in policy guidelines are based on RCTs with some participants recruited more than two decades ago. As reported in **chapter 4**, the procedural risks of CEA (around 1.5% for asymptomatic patients and 2.68% for symptomatic patients in post-2005 observational studies) have fallen in recent years. If the procedural risks of CEA in the model are at the level of thresholds in guidelines, ICERs for CEA plus MT vs MT alone increase substantially in all patient groups, rising above £20,000 per QALY in patients aged 70 or above regardless of symptomatic status or gender.

Thus, procedural risks of CEA have a pivotal role in deciding which method of treatment is most cost-effective at different ages and policy guidelines should be updated to reflect contemporary practise. At willingness to pay-per-QALY of £20,000, the upper limit procedural CEA risks quoted in guidelines would have to be reduced by at least 30% for CEA to be cost-effective in 70-year-old asymptomatic men, at least 40% in 70-year-old symptomatic men, and more than 40% in 70-year-old symptomatic and asymptomatic women.

Following an increase in use of statins by patients at increased risk of stroke, there is reason to believe that post-procedural stroke risks of patients might be decreasing with time. In our analysis, we sourced post-procedural stroke risks of asymptomatic patients from patients prescribed with lipid-lowering therapy in ACAS, ACST-1 and VA and of symptomatic patient from ICSS where more than 80% of patients were treated with statins. However, study recruitment of ACAS ended in 1993 and ACST-1 in 2003. Statin therapy use has evolved since these times, and thus post-procedural stroke risks may be even lower. To account for this, in the sensitivity analysis post-procedural risks were reduced by 10% and 20% resulting in the ICERs for CEA plus MT vs MT alone increasing, with a 20% decrease in post-procedural stroke risks leading to ICERs above £20,000 for patients aged 70 years or above.

In cost-effectiveness analysis, a healthcare system-wide viewpoint is employed by concentrating on the efficiency of treatment methods across categories of patients, instead of an individual patient,(156) with NICE having integrated national policy level economic evaluations for patient groups with similar risk factors, based on cost-effectiveness frameworks into its decision making process.(24) To factor in how treatment decisions may vary across different types of patients, this cost-effectiveness framework has accounted for

heterogeneity in input parameters by age, gender and symptomatic status of patients, and reported results across different patient categories. However even within these patient categories, the treatment an individual receives may depend on patient preference. In the case of carotid stenosis, situations may emerge where patients ask to be intervened, instead of being managed with MT alone despite being above the age of 75. Patients may also prefer the less invasive CAS instead of CEA, with it being shown that two weeks post-procedure patients treated with CAS plus MT have a higher QoL in terms of physical function and pain when compared to CEA plus MT, though there were no differences in QoL one-year post procedure.(137) The importance of patient preference in the decision making process has been recognised by NICE with research currently being carried out on how to include patient preferences in health technology assessments (HTA).(157)

As outlined in **chapter 2**, two previous economic evaluations compared treatment methods for carotid stenosis in the UK setting.(29, 42) Thapar et al(42) studied the cost-effectiveness of CEA plus MT vs MT alone in 68-year-old asymptomatic patients and reported that when treated with CEA plus MT, patients experienced 0.09 more QALYs than when treated with MT. This was lower than incremental QALYs from CEA plus MT vs MT in both 65-year-old asymptomatic males (0.26 QALYs) and females (0.23 QALYs) in this analysis. Differences in results were mainly due to the fact that procedural risks of CEA which I had employed (see **chapter 4)** were lower than those of CEA patients in ACST-1 as used by Thapar et al.(42) However, Thapar et al(42) reported an incremental cost of £641 for CEA plus MT compared to MT and hence an ICER of £7,584 which was lower than that of asymptomatic men (£9,591) and women (£11,134) as reported in this chapter. This was primarily due to the cost of CEA (£3,345) used by Thapar et al,(42) as sourced from 2010-

11 HRG tariffs, being lower than the £4,528 used by the cost-effectiveness framework in the current chapter.

Morris et al(29) studied the cost-effectiveness of CAS plus MT vs CEA plus MT in symptomatic patients in a 5-year time-horizon analysis in the ICSS study, reporting that CAS plus MT cost US$ 736 more than CEA plus MT, despite resulting in 0.1 less QALYs, with differences in costs and QALYs between CAS plus MT and CEA plus MT not being statistically significant (**appendix table 5.20**). In a sub-group analysis, Morris et al(29) showed CAS plus MT was dominated by CEA plus MT in symptomatic men and all symptomatic patients less than 70 years (**appendix table 5.20**). In symptomatic women and all symptomatic patients above the age of 70 years, CAS plus MT had higher five-year costs than CEA plus MT, but also resulted in a higher number of QALYs (**appendix table 5.20**). While these results differed from those reported here where CEA plus MT dominated CAS plus MT across all symptomatic patient groups, none of the differences in costs and QALYs between CEA plus MT and CAS plus MT reported by Morris et al were statistically significant. Reasons behind differences in results in symptomatic patients between Morris et al, and those reported in the current chapter are outlined in **appendix text 5.13.** When the time horizon in our framework was limited to five years and the model input parameters for relative post-procedural stroke risks of CAS plus MT vs CEA plus MT were sourced only from ICSS, results showed that the CEA plus MT strategy still dominated the CAS plus MT strategy, with five year costs of CAS patients statistically significantly higher than those of CEA patients in all symptomatic patient groups, but there no statistically significant differences observed in QALYs experienced by CEA and CAS patients (**appendix table 5.21**).

Our economic evaluation has a number of limitations. Firstly, given that only two RCTs provided evidence of relative risks of post-procedural major and post-procedural minor strokes between CAS plus MT and CEA plus MT, the uncertainty in these input parameters was large as reflected in our results. Similarly, only three RCTs, all of which were on asymptomatic patients, reported sufficient information to calculate the relative risks of post-procedural major and post-procedural minor stroke between CEA plus MT and MT alone. Therefore, this information had to be used for relative post-procedural major and minor stroke risks for CEA plus MT vs MT alone in symptomatic patients as well. Second, while a framework such as this allows to report cost-effectiveness results for CAS plus MT vs MT alone, given the dominance of CEA, the comparison of CAS versus MT is only relevant in a situation where CEA is not a viable method of treatment. However, given the data informing the analysis, the model may not be reflective of a situation where CEA is not viable as discussed above. Third, health related QoL of symptomatic patients were assumed to be similar to that of the OxVasc population of stroke survivors, and of asymptomatic patients to that of a control group from the general population who had similar risks factors to stroke survivors in OxVasc. The patients in the OxVasc population and their control group do not necessarily have carotid stenosis. However, QoL of the OxVasc population was similar to that of symptomatic patients in ICSS which reported a QoL of 0.76 for symptomatic CEA patients, and 0.78 for symptomatic CAS patients. No information was available with regard to the QoL of asymptomatic carotid stenosis patients in the literature, and thus a cohort with similar risk factors such as age, gender and medical history of diabetes and hypertension was assumed to provide the closest estimate. Fourth, relative post-procedural stroke risks of CAS plus MT vs CEA plus MT was calculated using the intention to treat (ITT) populations of ICSS and CREST where patients who do not undergo the assigned intervention are included

in the analysis. Nevertheless, it is worth noting that only 3.68% (63 out of 1713) patients in ICSS(154) and 7.3% (184 out of 2522) patients in CREST(57) did not undergo the assigned intervention. Fifth, when calculating relative post-procedural major and minor stroke risks, patients who have experienced an event in the procedural period were excluded from the analysis. This is a necessity in a cost-effectiveness framework employing a Markov state transition model with annual cycles, given procedural events are accounted for separately, and relative stroke risks between interventions after the first annual cycle should not incorporate procedural risks. However, this can generate a small bias when calculating relative risks with the randomisation process being hindered due to not all patients randomised to an intervention being considered in the analysis. Sixth, this economic framework does not take into account the risk of cranial nerve injuries, one of the procedural risks of CEA as outlined in **chapter 1**. However, results from CREST have shown that cranial nerve injuries have a minimal effect on health-related QoL in the long-term, adversely affecting only eating/ swallowing functions within two to four weeks from procedure, but not a year after procedure.(158)

In conclusion, this cost-effectiveness analysis of interventions to treat carotid stenosis indicates that CEA plus MT is the most cost-effective treatment method at a willingness to pay for a QALY of £20,000 for patients up to the age of 75 irrespective of gender or symptomatic status. For patients aged 75 years and older, MT is the most cost-effective method of treatment, unless decision makers are willing to increase their willingness to pay-per-QALY to £30,000. MT is the most cost-effective methods of treatment for 80-year-olds irrespective of the willingness to pay for a QALY. CEA plus MT's superiority over MT in under 75-year olds was a result of lower post-procedural stroke risks with CEA plus MT

when compared to MT alone, compensating for the cost of CEA and procedural risks involved. CAS plus MT was dominated by CEA plus MT irrespective of the age, gender, or symptomatic status of the patient, with relative risks of procedural and post-procedural stroke between CAS plus MT and CEA plus MT being the driving factor behind this.

6

Conclusion

6.1 Summary of findings

Stroke has a substantial impact on a country's economy, due to the direct and indirect costs involved in managing patients who have experienced stroke, and the loss in productivity of patients post stroke with many stroke patients having to temporarily or permanently give up employment. Stroke is reported to have an estimated cost to the UK society of £8.9 billion a year.(15) Carotid stenosis is identified as a major cause of stroke, accounting for about 20% of all ischaemic strokes in the UK(16) and, therefore, it can have a substantial health and economic impact. As discussed in **chapter 1,** three treatment strategies can target carotid stenosis to reduce stroke risks: medical therapy (MT) alone, carotid endarterectomy (CEA) plus MT, and carotid artery stenting (CAS) plus MT. Given the economic implications of stroke, it is important to identify which of these treatment strategies are clinically effective and economically feasible.

Economic evaluations in the form of cost-effectiveness analysis, taking into account both the net effects of interventions on individuals' health, and healthcare and other societal resources, play an important role in informing policy makers and healthcare professionals when making treatment decisions. **Chapter 2** presents a systematic review of cost-effectiveness studies comparing treatment methods for carotid stenosis. The findings from the studies comparing CEA plus MT vs MT alone suggested that CEA added to MT is likely to be the cost-effective treatment method in Europe and North America, while the findings from the studies comparing CAS plus MT vs CEA plus MT were mixed.

A number of limitations were identified in economic evaluations included in the literature review. These included (a) obtaining evidence on procedural risks of CEA and CAS from RCTs or studies conducted before the wider use of more intensive medical therapy or at

earlier stages of technology development thereby not reflecting contemporary practice, (b) not accounting for differences in procedural and post-procedural stroke risk by age, gender and symptomatic status hence ignoring a number of important risk factors for carotid stenosis, (c) not accounting for differences in procedural and post procedural risks between treatment methods by stroke severity while recent RCTs evidence suggests that comparative effects between treatment strategies differ for major and minor strokes, (d) having too short a time horizon to be reflective of overall differences in procedural and post-procedural stroke risks between treatment methods, (e) not comparing all available treatment methods in a single framework, (f) not accounting for uncertainty in input parameters as recommended by NICE(72) thereby not capturing the uncertainty involved in making treatment decisions based on cost-effectiveness frameworks, and (g) not performing a value of information (VOI) which could help to identify whether gathering more information to reduce decision uncertainty is worthwhile. The review highlighted the need for further economic evaluations to address these limitations and study the cost-effectiveness of all three interventions for carotid stenosis in a contemporary setting, accounting for heterogeneity between patients and uncertainty in input parameters, and reporting cost-effectiveness and VOI results by age, gender and symptomatic status of patients.

Randomised controlled trials (RCTs) are the gold standard for estimating the comparative effects of different treatments (e.g. in the form of odds ratios, hazard ratios) and informing decision makers of the clinical effectiveness of treatments. Hence they contribute key input parameters to cost-effectiveness analyses. In **chapter 3**, the evidence from RCTs informing procedural, post-procedural and overall outcomes were systematically reviewed and synthesised using meta-analysis techniques. Results from this chapter showed that compared

to MT alone, CEA reduces overall stroke risks (inclusive of procedural deaths). When compared to CAS, CEA had lower procedural stroke/death risks and lower overall stroke risks, with the majority of differences in stroke risks stemming from a higher rate of procedural minor strokes with CAS. There were no RCTs comparing CAS vs MT directly. However, the results from the network meta-analysis suggested no statistically significant differences in long-term stroke risks (including procedural stroke/death risks) between CAS and MT and a large degree of uncertainty around results.

The systematic review of large observational studies of CEA and, separately, CAS in **chapter 4** indicated a significant decrease in procedural risks of CEA over time in both symptomatic and asymptomatic patients. Potential reasons behind this may include improvements in medical therapy, especially in the form of the prescription of statins prior to intervention, centralisation of CEA in high-volume facilities, and improved patient selection. Procedural risks of CAS appear to have remained stable over time with a not statistically significant decrease in recent years. However, given that CAS is a newer technique, there was limited information available on CAS patients in observational cohort studies which recruited patients prior to the year 2005. The findings from this systematic review indicated that policy guidelines and cost-effectiveness frameworks identified in **chapter 2** sourcing procedural risks from older studies may not reflect contemporary clinical practice.

RCTs identified in **chapter 3** which compared CEA with MT completed patient recruitment no later than 2003, while all RCTs comparing CAS with CEA, except ACT-1, had more than half of their quoted patient recruitment period prior to the year 2005. Thus, while RCTs provide important information on the clinical effectiveness of treatment methods in the form of comparative effects, large proportions of patients in RCTs were recruited prior to the era

of wider use of statin therapy, also including more intensive statin therapies. Therefore, absolute procedural risks from the more recent observational studies identified in **chapter 4** are likely to reflect better the procedural risks in contemporary medical practise.

Information from **chapters 3** and **4** was combined with information from other sources in the literature to develop a Markov state transition model with annual cycles to estimate lifetime QALYs and costs of patients treated for carotid stenosis using each of the three treatment strategies. In the model, patients progressed annually through no event, myocardial infarction, minor stroke and major stroke health states until death or 95 years of age. This model was used to evaluate the cost-effectiveness of all available treatment methods for carotid stenosis, and report results by patient's age, gender and symptomatic status. The modelling framework was specifically designed to address the limitations of cost-effectiveness analyses comparing treatment methods for carotid stenosis as identified in the literature (**chapter 2**).

The results showed CEA plus MT to be the most cost-effective treatment method at a willingness to pay-per-QALY of £20,000 for patients up to the age of 75 irrespective of gender or symptomatic status. For patients aged 75, MT is the most cost-effective method of treatment, unless decision makers are willing to increase their willingness to pay-per-QALY to £30,000. MT is the most cost-effective methods of treatment for 80-year olds for all patient categories up to a willingness to pay for a QALY of £50,000 at least. Treatment decision at both willingness to pay-per-QALY of £20,000 and £30,000 were not dependent on symptomatic status or gender of patients.

As reported in **chapter 5**, the **e**xpected value of perfect information (EVPI) per person at willingness to pay-per-QALY of £20,000 for 65-year-old patients ranged from £149 to £285, and was significantly higher in 70-year-old patients. The expected value of partial perfect information (EVPPI) per person showed that additional information would be most valuable for the model input parameters informing relative post-procedural stroke risks for CEA plus MT vs MT alone, highlighting the need for further RCTs comparing these two treatment strategies.

6.2 Contribution to literature and policy implications

The research done in this thesis makes contributions to a number of areas in the literature.

To the best of my knowledge the work presented in **chapter 2** is only the second systematic review of cost-effectiveness studies comparing treatment methods for carotid stenosis. Morris et al(29) reported results from a similar systematic review in their supplementary material, reporting study characteristics and an interpretation of results in a tabular form. However, the review is limited to economic evaluations comparing the cost-effectiveness of CAS vs CEA and did not include the studies comparing CEA vs MT. The systematic review in **chapter 2**, in addition to summarising study characteristics and results, extracted information on the structure of the cost-effectiveness frameworks and their input parameters. These data allowed limitations in published cost-effectiveness studies in the literature to be identified and addressed when developing the cost-effectiveness framework in **chapter 5**.

The systematic review of RCTs comparing treatment methods for carotid stenosis in **chapter 3** took all available evidence across a number of endpoints, and synthesised it using meta-analysis techniques. There have been a number of previously published systematic reviews

identifying RCTs comparing treatment methods for carotid stenosis. Of these, two systematic reviews(89, 90) did not stratify stroke by stroke severity, and included information from the CAVATAS trial where only 26% of patients in the endovascular treatment arm underwent CAS, with the rest receiving balloon angioplasty, which may have influenced the results in CEA's favour.(82) Sardar et al (91) excluded information from SPACE when synthesising information. The systematic review of RCTs comparing CEA vs MT(17, 18) and CAS vs CEA,(19) published by the Cochrane Collaboration, remain the most complete systematic review. However, these reviews were published in the years 2005, 2011 and 2012, and hence excluded more recently published RCTs such as ACT-1, and information from recent publications of long-term follow-up in older RCTs. The systematic review of RCTs, reported in **chapter 3**, addressed these limitations and synthesised information from all RCTs with 100 or more patients randomised to each treatment, and could inform both clinicians and health economists on relative procedural and post-procedural stroke risks between interventions. Given the absence of RCTs comparing CAS vs MT in the literature, the network meta-analysis performed in **chapter 3**, provided information on how long-term stroke risks differ between CAS and MT, with results showing no statistically significant differences in long-term stroke risks (including procedural stroke/death risks) between CAS and MT due to the large degree of uncertainty involved in an indirect comparison. Hence, there remains a need for future trials comparing CAS vs MT. This to my knowledge is the second network meta-analysis performed to analyse differences in stroke risks between CAS and MT, after Barkat et al(92) which concentrates only on asymptomatic patients, and includes RCTs with fewer than 100 patients randomised to a treatment arm.

Findings from **chapter 4** provide evidence on procedural risks of CEA falling significantly over time, while procedural risks of CAS appear to remain more stable with not statistically significant decrease in recent years. Procedural risks of both CEA and CAS in post-2005 observational studies are lower than those of symptomatic patients, and asymptomatic patients in RCTs, except in the case of the two most recent RCTs on asymptomatic patients, CREST and ACT-1. Results from the logistic meta-regression show that post-2010 procedural risks of CEA and post-2006 procedural risks of CAS in asymptomatic patients are lower than those reported in CREST and ACT-1, further emphasising that absolute procedural risks in RCTs may not be reflective of contemporary practise. Given that the majority of economic evaluations identified in **chapter 2** source procedural risks from RCTs, information from post-2005 observational studies can be useful when developing economic frameworks in the future, since it is likely closer to contemporary practise, with all RCTs except ACT-1 ending patient recruitment by 2008. Procedural CEA risks of post-2005 observational studies are also significantly lower than the upper thresholds for procedural risks of CEA for a centre or surgeon, recommended by the European Society of Vascular Surgery,(155) with these thresholds based on RCTs in which patient recruitment ended in 1994. Hence, this threshold may need updating.

Chapter 5 reports to my knowledge the first economic evaluation comparing all three available treatment methods for carotid stenosis in a single framework. Results are reported by patient's symptomatic status, age and gender, thereby informing on how treatment decision may differ based on patient's risk factors. The results suggested that CEA plus MT is the most cost-effective method of treatment at a willingness to pay-per-QALY of £20,000 for patients up to the age of 75 years, irrespective of gender or symptomatic status, with the

probability of CEA plus MT strategy being cost-effective reducing by at least 20% from 65 and 70-year-old patient groups. This may change the perception policy makers have towards CAS, with results showing that CEA plus MT clearly dominates CAS plus MT irrespective of age, gender or symptomatic status, especially since results from previous cost-effectiveness studies comparing CAS plus MT vs CEA plus MT have been mixed.

Current NICE guidelines in the UK state that immediate CEA is recommended for symptomatic patients with a degree of stenosis 50% to 99% (NASCET methods of measurement),(7) while no information was available with regard to the recommendation of CEA for asymptomatic patients. CAS could be performed in symptomatic patients if CAS is preferred to CEA in a particular case and patients are advised with respect to that decision,(8) while in asymptomatic patients the evidence on the efficacy of CAS is deemed inadequate.(9) Results from **chapter 5** based on a cost-effectiveness analysis comparing all three treatment methods for carotid stenosis in the UK, indicated that treatment decisions are dependent on patient's age with CEA plus MT strategy the most cost-effective treatment method for patients below the age of 75, and MT alone most cost-effective in older patients. The cost-effective treatment did not differ by gender or symptomatic status of patient. NICE has recommended asymptomatic patients to be entered to the ACST-2 trial, with guidelines to be reviewed if further evidence is available.(9) Current NICE guidelines refer to efficacy of treatment methods, largely based on stroke risks when choosing treatment methods, with nothing mentioned with regard to whether or not results from economic evaluations have been taken into consideration, despite Thapar et al(42) reporting that CEA is cost-effective compared to MT in asymptomatic patients in the UK and Morris et al(29) reporting that CAS was dominated by CEA, with no statistically significant differences of costs and QALYs

between CAS and CEA in symptomatic patients in the UK. The guidelines do not differentiate treatment decisions by the age of patients.

Chapter 5 also reported results from a VOI analysis, the first on treatment methods for carotid stenosis. Results from this analysis, in particular the results from the EVPPI analysis, help researchers and policy makers identify areas to which resources for future research should be allocated to most efficiently to reduce decision uncertainty. The EVPPI analysis in **chapter 5** highlighted the need for more information on relative post-procedural stroke risks of CEA plus MT vs MT alone and to a lesser extent absolute post-procedural stroke risks.

6.3 Limitations and further research

Limited information on stroke risks by stroke severity

The systematic review of RCTs in **chapter 3** highlighted a lack of RCTs reporting overall and post-procedural stroke risks by stroke severity, with no RCTs comparing CEA vs MT in symptomatic patients, and 2 out of 6 RCTs (4215 out of 7740 randomised patients) comparing CAS vs CEA (one symptomatic; one mixed symptom population) reporting relative post-procedural minor and post-procedural major stroke risks. This lack of information resulted in a greater degree of uncertainty around these model inputs when developing the cost-effectiveness framework in **chapter 5**, with the EVPPI being highest for relative post-procedural minor and major stroke risk of CEA vs MT, highlighting the importance from future research in this area in the form of new RCTs or meta-analysis of individual patient data (IPD) of existing RCTs (if stroke severity available in these studies). Collaboration such as the Carotid Stenosis Trialists' Collaboration (CSTC) have resulted in the IPD from a number of RCTs being pooled, increasing the ability to explore heterogeneity

and reduce uncertainty around input parameters. Information of post-procedural stroke risks by stroke severity from all relevant trials will also help reduce the uncertainty of results from the network meta-analysis in **chapter 3**, with only 5 RCTs at present contributing information towards identifying relative long-term minor and major stroke risks of CAS vs MT.

Heterogeneity by age and gender

The model input parameters for absolute procedural stroke/death risks, post-procedural stroke risks, non-stroke related mortality and quality of life in **chapter 5** are identified for categories of patient by age and gender. However, relative procedural and post-procedural stroke risks were not age- or gender-specific. Results from **chapter 3** show that there were statistically significant differences in relative procedural stroke/death risks of CAS vs CEA between symptomatic patients aged below the age of 70, and symptomatic patients aged above the age of 70, while no significant differences were seen between symptomatic males and females. However, no information was available on how relative procedural minor and major stroke risks of CAS vs CEA, and relative post-procedural minor and major stroke risks of CAS vs CEA and CEA vs MT differed by age and gender. Hence differences in relative stroke risks between interventions by age and gender were not incorporated in the main analysis of the cost-effectiveness framework developed in **chapter 5** (a sensitivity analysis was performed using information on how procedural stroke/death risks changed with age, but stroke severity was not taken into account due to a lack of relevant information). Gaining access to and analysing IPD from completed RCTs to obtain estimates of procedural and post-procedural minor and major strokes by stroke severity and by age and gender could help better inform the heterogeneity (if any) by age and gender in the cost-effectiveness analysis.

Heterogeneity by degree of stenosis

Current guidelines state that treatment decisions are dependent on the degree of stenosis, particularly in symptomatic patients. Accounting for heterogeneity by degree of stenosis was not possible in the cost-effectiveness framework in **chapter 5** due to a lack of information on procedural and post-procedural stroke risks by degree of stenosis. From RCTs, only NASCET and ECST reported results by degree of stenosis, following the reassessment of angiograms by the Cochrane collaboration(18) to recalculate the degree of stenosis in ECST angiograms using the method used in NASCET. Re-analysis of IPD from RCTs where degree of stenosis of individual patients is recorded, and a drive for upcoming RCTs to report results by degree of stenosis will help bridge the gap in lack of information with regard to this area. The systematic review of observational cohort studies in **chapter 4** also indicated a lack of observational studies reporting procedural risks by degree of stenosis, possibly due to observational studies not recording the degree of stenosis of patients.

Observational studies in carotid stenosis patients with long-term follow up

There seems to be a clear gap in the literature with regard to observational studies reporting long-term stroke risks by stroke severity in patients by symptomatic status. This led to the sourcing of input parameters for post-procedural stroke risks in the cost-effectiveness framework in **chapter 5** from RCTs, with an emphasis of having information from patients who have been prescribed with statins. However, this may not be reflective of contemporary practise due firstly to the strict patient inclusion criteria of RCTs, and, secondly to all available RCTs barring ACT-1 completing patient recruitment before 2008. Results from the

deterministic sensitivity analysis in **chapter 5** has shown that reducing absolute post-procedural stroke risks resulted in higher ICERs for CEA plus MT vs MT alone with a 20% reduction resulting in the CEA plus MT strategy not being cost-effective at a willingness to pay-per-QALY of £30,000. Designing an observational cohort study with identified risk factors of patients recorded at baseline, including degree of stenosis, and long-term follow-up for minor and major stroke outcomes or death will be highly informative in future cost-effectiveness analyses.

Extension of cost-effectiveness framework to other geographical areas

At present the cost-effectiveness analysis in **chapter 5** is applicable mostly to a UK healthcare setting, due to the model input parameters for healthcare costs, changes in QoL between age groups, and to a lesser extent procedural and post-procedural stroke risks used in the framework. Modification of these model input parameters to be reflective of other geographical areas will allow for cost-effectiveness results applicable to other geographic settings to be generated.

Sourcing relevant model inputs applicable to Northern American and other western European countries is relatively straightforward, with information from RCTs and large cohort studies likely applicable to these geographic areas, and information from national registries, and national sources for healthcare cost information (e.g. Medicare case-mix based system in the US) being publicly available.

Application of the cost-effectiveness framework to other geographic areas such as Asia, Africa and South America may be more difficult as none of the RCTs comparing treatment methods for carotid stenosis having recruited in these geographic areas, whilst only one

observational cohort study in the systematic review in **chapter 4** was based in Asia. While relative stroke risks between treatment methods may be used from RCTs irrespective of geographic area, with the randomisation process minimising impact of differences in underlying risk factors, the same cannot be said about absolute procedural and post-procedural stroke risks. Procedural risks of CEA and CAS may vary depending on the technology/ equipment available, the quality of training received by surgeons or operators, and their level of experience. For example, it has been shown that with more experienced CAS operators, the use of embolic protection devices in the CAS procedure result in lower adverse events when compared to less experienced CAS operators.(120) Post-procedural stroke risks may also vary depending on the after care available for stroke patients, overall quality of healthcare in the country, and access to relevant medical therapy.

Accounting for procedural and post-procedural risks of CEA and CAS by variations in procedure

As explained in **chapter 1** the CEA and CAS procedures may vary depending on the techniques and equipment used by surgeons and operators. These include the use of traditional or eversion CEA, use of routine or selective shunting during CEA, use of protection devices during CAS procedure, and the type of stents used in the CAS procedure. The cost-effectiveness framework in **chapter 5** does not account for these variations, which can be seen as a limitation. However, it is worth noting that except in the case of using protection devices in the CAS procedure, evidence on whether variations in the CEA or CAS procedure can impact procedural and post-procedural stroke risks remain mixed. It has been shown that CAS patients in whom protection devices were used have a lower rate of stroke or procedural death when compared to those where no device was used(49). However, the majority of patients randomised to CAS in RCTs from which relative procedural and post-procedural stroke risks of CAS vs CEA were sourced from underwent the procedure with a protection device, with 72% of CAS procedures in ICSS(87) and 96.1% of CAS procedures in CREST(57) using protection devices.

Individual patient preferences

Treatment decisions based on the cost-effectiveness framework in **chapter 5** are applicable to categories of carotid stenosis patients classified by age, gender and symptomatic status. Hence it does not take into account individual patient preferences when deciding on the most cost-effective method of treatment. Situations may occur when patients above the age of 75 request to be intervened, instead of being treated with MT alone. Patients may also request

CAS, a less invasive procedure than CEA. NICE has acknowledged the importance of accounting for patient preferences in the decision making process and has commissioned further research on methods and technologies to help capture patient preferences in health technology assessments (HTA).(157) Publication of results from this research when completed may contribute towards extending the cost-effectiveness framework in **chapter 5** to include individual patient preferences.

6.4 Concluding remarks

There seems a clear gap in the literature for a single cost-effectiveness framework comparing all available treatment methods for carotid stenosis, with the existing economic evaluations addressing the cost-effectiveness of treatment methods for carotid stenosis that were identified in the literature all having a variety of limitations. The research carried out in this thesis attempts to fill this gap by taking into account all available clinical information via two systematic reviews and other information from the literature relating to QoL and healthcare costs, to develop a decision analytical framework comparing all available treatment methods for carotid stenosis and evaluate their long-term benefits and cost-effectiveness. Findings showed that at a willingness to pay-per-QALY of £20,000 CEA plus MT was the most cost-effective treatment strategy for patients up to an age of 75, irrespective of gender or symptomatic status, with MT alone being the most cost-effective treatment strategy for patients aged 75 or above. I hope these findings will encourage and inform a revision of current NICE guidelines, in which treatment decisions for carotid stenosis are not currently dependent on the age of patients. This would result in a more efficient use of resources when tackling one of the major causes of stroke, and in turn reduce stroke death and disability in the UK.

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