Cost-effectiveness of carotid endarterectomy as a stroke prevention strategy

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Declaration

I, Maria M Benade-Treadwell, hereby certify that this thesis:

(a) has been composed by myself

and

(b) that the work contained herein is my own, excepting in those areas where the help of others is acknowledged.

Signed

Date

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Abstract

Following the publication of two large-scale randomised controlled trials in the early 1990s, little doubt remains about the efficacy of carotid endarterectomy as a means of preventing stroke in selected sub-groups of patients. However, the effectiveness and cost-effectiveness of this intervention as a stroke prevention strategy are uncertain, as are the public health implications when this strategy is applied to a population.

This thesis focuses on the effectiveness and cost-effectiveness of carotid endarterectomy as a stroke prevention strategy in the Scottish population. The variation in uptake of carotid endarterectomy by hospital and region between 1981 - 1996 is described by analysing a unique set of patient linked data on hospital use and outcome following carotid surgery for 2892 patients. Stroke-free survival and overall survival before and after the publication of the trial results for this cohort are also assessed. A systematic overview of studies addressing the costs and benefits of carotid endarterectomy is conducted by critically appraising the methodology and interpretation of previous cost and cost-effectiveness estimates. Unlike previous studies, this thesis considers the resource implications of carotid endarterectomy by estimating not only the procedure cost of carotid endarterectomy, but also the overall NHS work-up costs for a large cohort of patients with transient ischaemic attack referred to a Scottish teaching hospital for carotid endarterectomy assessment, investigation and surgery. Finally, as part of the analysis of cost-effectiveness estimates for Scottish patients, a novel use of the European Carotid Surgery Trial data has enabled assessment of the transferability of efficacy results obtained in a randomised controlled trial to a setting outside trial conditions.

CHAPTER ONE: INTRODUCTION

Carotid endarterectomy as a strategy for stroke prevention has evolved over many decades since the first successful removal of a stenosed segment of the carotid artery reported in 1954 (Eastcott et al., 1954). Two large randomised controlled trials (European Carotid Surgery Trialists' Collaborative Group, 1991; (ECST) North American Symptomatic Carotid Endarterectomy Trial Steering Committee, 1991 (NASCET) have showed that in selected patients with symptomatic internal carotid artery stenosis of 70% or more, carotid endarterectomy (CEA) in addition to best medical therapy is associated with a significant reduction in the rate of stroke compared with best medical therapy alone. The number needed to treat to prevent one stroke of any kind is estimated at seven to ten patients over a two to three year follow-up.

Patients who have experienced a transient ischaemic attack (TIA) are at an increased risk of stroke (Dennis et al., 1990). Some TIAs are due to carotid stenosis and as mentioned, ***carotid endarterectomy*** has been shown to reduce the risk of stroke in carefully selected symptomatic patients with carotid stenosis of 70% or more. The identification and management of patients with TIAs is one of many strategies, which might reduce the number of strokes further. Estimates suggest that if carotid endarterectomy were performed on all eligible patients with transient ischaemic attack in England, the annual incidence of first-ever strokes would decrease only by 0.5% (Dennis et al., 1991). Estimates of the economic implications of performing carotid endarterectomy as a stroke prevention strategy are however not available.

Though there is now little doubt concerning the efficacy of carotid endarterectomy for some selected subgroups, the cost implications and the outcome of this procedure outside trial conditions have not yet satisfactorily been addressed.

1.1 Stroke

Stroke is the second most common cause of death worldwide accounting for nearly 4.5 million deaths per year (Murray and Lopez, 1997a), and the sixth most common cause of premature disability (Murray and Lopez, 1997b). In Scotland about thirteen percent of all deaths annually are attributed to stroke (Information and Statistics Division, National Health Service, Scotland, 1995). This is the third most common cause of death in Scotland after heart disease (30%) and cancer (25%) and one of the most common causes of physical disability (Secretary of State for Health, London: HMSO, 1991). The management of patients who have had a stroke is estimated to consume about 4% of National Health Service resources in Scotland (Isard and Forbes, 1992).

The epidemiology of stroke.

With the exception of the available mortality statistics, very little is known about the epidemiology and incidence of stroke in Scotland. Stroke is defined as a clinical syndrome characterised by "rapidly developing symptoms and/or signs of focal and at times global loss of cerebral function, lasting longer than 24 hours or leading to death, with no apparent cause other than that of vascular origin" (Aho et al., 1980). Stroke events can be classified as major, disabling, fatal or minor strokes. A major

stroke is defined as symptoms lasting longer than seven days; a disabling stroke is a stroke that after six months is still associated with disability as recorded on the modified Rankin Scale of 3, 4 or 5. A fatal stroke is considered to have caused the death of the patient (ECST Trialists' Collaborative Group, 1998) and a minor stroke refers to an acute disturbance of focal neurological function with symptoms lasting more than 24 hours and less than seven days. A minor stroke is by definition not disabling after one week of onset.

The incidence of a disease quantifies the number of new cases that develop in a population of individuals at risk during a specified time interval. The incidence of stroke however appears to be relatively similar for Caucasians in most developed countries where it has been studied. Stroke incidence rates rise exponentially with increasing age, from about 30 per 100 000 population in the third and fourth decades to almost 3000 per 100 000 in the eighth and ninth decades (Bonita, 1992; Malmgren et al., 1987). The age-and-sex standardised incidence of first-ever stroke appears to be somewhere between 200 and 400 per 100 000 per year in those aged between 45 and 84 years (Sudlow et al., 1997). The annual age-and-sex standardised incidence reported in the Oxford Community Stroke Project, 1981 - 1985, the only true incidence study from the United Kingdom, was 200 per 100 000 persons (Bamford et al., 1988). Using these incidence rates as reference, between 10 000 and 20 000 first-ever strokes per year can be expected in the Scottish population of about five million.

The economic burden of stroke.

The economic burden of stroke can be defined in terms of the direct cost of providing medical care to patients and the indirect cost associated with lost productivity and other intangible costs. A third of all strokes are fatal and another third will recover and remain relatively independent. The remaining third however will be dependent and will require long-term care. Murray and Lopez ranked cerebrovascular disease as the sixth most common cause of premature disability worldwide using disability-adjusted life-years (DALYs). The burden of premature mortality and disability attributed to stroke and quantified in terms of DALYs is not available for the Scottish population neither is the economic impact of this disability. A fatal stroke may incur a small cost. Those who recover will require acute stroke care and probably some form of rehabilitation for a short period, but those left dependent will be using a considerable amount of available health care resources. Hence the need to estimate the lifetime cost of stroke using an incidence-based approach. Several early studies using an incidence-based approach have estimated the lifetime cost of stroke (Mills et al., 1978; Hartunian et al., 1980). More recent studies from the United States and the Netherlands have been published estimating the economic burden of stroke both with regards to the individual and society and also distinguishing between the acute care cost and the life-time cost of stroke (Taylor et al., 1996; Bergman et al., 1995). Similar studies from the United Kingdom or Scotland have not been identified. Only once the lifetime cost of stroke has been quantified, will it be possible to determine the "total" economic burden of stroke and the cost-effectiveness of stroke prevention strategies such as carotid endarterectomy.

Prevalence-based studies estimating the cost of treating stroke in a given year have been reported from Canada, Sweden, the United Kingdom, The Netherlands, New Zealand and the United States (Smurawska et al., 1994; Terént et al., 1994; Asplund et al., 1993; Persson et al., 1990; Isard and Forbes, 1992; Evers et al., 1997; Alberts et al., 1996; Scott et al., 1994; Matchar et al, 1996). The cost of stroke using a prevalence-based approach accounted for about 4.3 % of the total National Health Service expenditure in Scotland (Isard and Forbes, 1992). Prevalence-based studies are valuable in identifying the costs of stroke at a given time, however they provide little insight into the lifetime cost associated with stroke incident cases.

The management of stroke

One of the national targets in the United Kingdom is to reduce the mortality for stroke in people between 65 and 75 years of age by at least 40% by the year 2000. (Secretary of State for Health. HMSO, 1991). A more recently published Green Paper on the future of the public health strategy, proposed to reduce the mortality from heart disease and stroke and related illness amongst people younger than 65 years by at least one-third, from 66.2 to 44.1 per 100 000 population, by 2010. (*"Our Healthier Nation – A contract for Health" 1998)* Two alternatives could be considered to achieve this objective. Firstly strategies to prevent stroke and secondly treatment of acute stroke to prevent the consequences of this disease.

Treatment of acute stroke.

Optimal pharmacological treatment for acute stroke is not yet available, although various treatment modalities are being investigated. The treatment of stroke patients during the acute phase in dedicated stroke units has however showed benefits to a "wide range of stroke patients in a variety of different ways" including a reduction in death and a reduction in the need for institutionalised care as result of a reduction in disability (Stroke Unit Trialists' Collaboration, 1997; Langhorne et al., 1995).

Stroke prevention, the decline of stroke and the contribution of risk factors.

Time trends in stroke incidence have been observed, and it is possible that stroke is becoming less common. These changes in the stroke incidence began more or less at the same time as the control of hypertension improved in the community. Although hypertension control in residents in Rochester, Minnesota continue to improve during the 1970s and 1980s, the stroke incidence rates stabilised or even increased (Broderick et al., 1989). Changes in potential risk factors, other than hypertension, could be contributing factors to the initial decline observed.

Data on trends in stroke incidence are limited. Small community-based cohort studies have been identified in which incidence trends were studied over time (Broderick et al., 1989; Terent, 1988; Ueda et al., 1981; Tuomiletho et al., 1991). From published data, it is apparent that trends in stroke incidence in different countries do not follow a similar pattern. The time trend information most widely quoted comes from Rochester, Minnesota where the stroke incidence declined remarkably during the 1950s and 1960s. An overall average annual decline (3.1 per 100 000) in the

incidence rate, adjusted for age and sex has been observed over time (1945 - 1949 to 1955 - 1959) in Rochester, Minnesota (USA), (Garraway et al., 1979). However, this trend did not continue into the 1980s, instead an increase in stroke incidence has been reported (Broderick et al., 1989). The Framingham Study beginning in 1953 and investigating the secular trends in stroke incidence, prevalence and fatality found a significant decline in stroke severity over the three decades but no change in the incidence of stroke. (Wolf et al., 1992). These two studies however, are not representative of the American population as a whole. No overall decline was reported in the incidence rate from Auckland over the study period of 1981 - 1991 (Bonita et al., 1993).

Studies from Denmark reported conflicting results: one study between 1972 and 1990 reported an increase in men (Jorgenson et al., 1992). A second study found no significant change in men or women for the period 1976 to 1988 (Lindenstrom et al., 1993). A decline in the stroke incidence in men and women aged 65 to 84 years was reported in another study from Denmark for the period 1976 to 1993, but the decline was only significant in men (Truelsen et al., 1997).

No change in stroke incidence was reported from one study in Goteborg Sweden (Harmsen et al., 1992). An increase in the stroke incidence has however been reported from Soderhamn, Sweden in women, but the over 85-year age group was responsible for most of the increase. A decline in stroke incidence has been reported from studies in Finland and Japan (Tuomiletho et al., 1991; Ueda et al., 1981). It is important to note that the study years for these studies reporting the incidence rates of stroke were more or less during the same time periods except for a more recent

study in a well-defined population in France which reported relatively stable incidence rates over the period 1985 - 1994 (Lemesle et al, 1999).

Other possible reasons associated with the changes in stroke incidence include:

- the improved management of modifiable risk factors (Wolf, 1993)
- differences in the decline in the incidence of specific stroke subtypes with a high case-fatality and
- an increased awareness and recognition of transient ischaemic attacks by the general population as well as by physicians;
- the availability of computed tomography (CT scanning) during the latter half of the 1970s which appears to have increased the detection of less severe stroke cases which would have otherwise not have been diagnosed as a stroke event (Broderick et al, 1989; Wolf et al., 1992).

The end of a decline in the incidence of stroke might be considered artefactual, due to increased case ascertainment by computed tomography. It could be argued that all incidence rates before the advent of CT scanning were under estimations; though this is contentious as the probability of a definite diagnosis of stroke on clinical examination is high (Broderick et al., 1989; Shahar et al., 1995; Barker and Mullooly, 1997).

Risk factors for stroke.

There are several well-recognised risk factors for stroke. Increasing age and increasing blood pressure are the two factors most strongly associated with stroke,

followed by symptomatic vascular disease (ischaemic heart disease, transient ischaemic attack and peripheral vascular disease), carotid stenosis and cervical bruit. Cigarette smoking, diabetes mellitus, valvular heart disease and a high plasma fibrinogen are all moderately associated with stroke (Hankey et al., 1994).

Although carotid stenosis of 70% or more in symptomatic patients is associated with a high relative risk of stroke, as a risk factor it may have very little impact on the overall incidence of stroke if the prevalence of carotid stenosis in the population is low.

Patients who have had a TIA are at an increased risk of stroke as well as other serious vascular events. (Dennis et al., 1990). In addition to the treatment of hypertension the risk of stroke in TIA patients can also be reduced by about 25% by using aspirin, (Antiplatelet Trialists' Collaboration, 1988) and by about 12% by performing carotid endarterectomy for *appropriately selected patients*. (European Carotid Surgery Trialists' Collaborative Group, 1991; North American Symptomatic Carotid Endarterectomy Trial, 1991). While carotid endarterectomy has been shown to reduce the risk of stroke in the medium term in selected patients, the impact of this strategy on the overall incidence of stroke is very small representing only a 0.5% reduction in the incidence of first stroke (Dennis and Warlow, 1991). Although aspirin and carotid endarterectomy have been found to reduce the risk of stroke neither is likely to prevent more than 4% of all strokes nor will the reduction of blood pressure in hypertensive TIA patients prevent many strokes. (Warlow et al., 1996)

1.2 Transient ischaemic attack and carotid stenosis.

Only about 15% of strokes are preceded by TIAs and only a small proportion are as result of severe carotid stenosis (Warlow et al., 1996). Strokes can present so soon after a TIA not allowing time for the implementation of treatment. Treatment is furthermore not 100% effective, is also associated with risks and patient compliance with treatment is not always optimal. The majority of TIA-patients are eligible for aspirin and/or hypertension control. This is not the case for carotid endarterectomy, which is only indicated, in recently symptomatic patients with stenosis of more than 70% and who are fit for surgery "perhaps only 10% of all hospital referred TIA cases" (Hankey et al., 1992). Persons who have experienced a carotid territory transient ischaemic attack (TIA) or minor non-disabling stroke within the previous six months might be considered suitable candidates for carotid endarterectomy.

Incidence of Transient Ischaemic Attack. (TIA)

A transient ischaemic attack is an acute disturbance of focal neurological or mononuclear function with symptoms lasting less than 24 hours and (after adequate investigation) assumed to be due to vascular disease of an embolic or thrombotic kind (UK-TIA study group, 1991). The true incidence rate of TIA is difficult to determine for various reasons. Patients experiencing a TIA do not always present to a health care professional and even when they do, their symptoms may not be diagnosed correctly. Patients often present to medical practitioners with only the history of the event and with very little, if any clinical signs still present. Since the clinical histories described are often vague and non-specific, an appropriate diagnosis

is only possible if the medical practitioners have a high index of suspicion of the disease.

Transient ischaemic attack incidence studies have been performed in several countries. A total of 25 studies have been identified over a 30 - year period. The earliest study was by Acheson and others in the United Kingdom in 1968 (Acheson et al., 1968) and the most recent study describing the incidence of transient ischaemic attacks was from Spain in 1996 (Sempere et al., 1996). Six studies were reported from the United States of America from 1969 to 1990 (Friedman et al., 1969; Karp et al., 1973; Whisnant et al., 1973; Rhoads et al., 1980; Alter et al., 1985; Lai et al., 1990). Three studies each were reported form Sweden (Terent et al., 1979; Mettinger et al., 1984; Terent et al., 1988) and Italy (Fratiglioni et al., 1989; Ricci et al., 1991; Lauria et al., 1996). Four countries, each reported two studies. These countries were the United Kingdom (Acheson et al., 1968; Dennis et al., 1989) Denmark (Liddegaard et al., 1986; Uggerhoj Anderson et al., 1988), Australia (Stewart-Wynne et al., 1992; Shah et al., 1995) and Spain, (Matias-Guiu et al., 1994; Sempere et al., 1996). The studies form Australia and Spain were also the most recent studies reported. One study each was reported from the five countries: Estonia (Zupping and Roose 1976), China (Li et al., 1985), Norway (Johnson and Skre, 1986), France (Giroud et al., 1986) and Japan (Ueda et al., 1988). Of the 25 studies, 19 were primarily incidence studies, and six (Karp et al., 1973; Whisnant et al., 1973; Li et al., 1985; Ueda et al., 1987; Fratiglioni et al., 1989; Matias-Guiu et al., 1994) also reported on the prevalence of the disease.

Criteria for "ideal" stroke incidence studies have been previously outlined. (Malmgren et al., 1987, Sudlow et al., 1996). These criteria, although primary developed for stroke incidence studies, are also applicable and relevant to all studies determining disease incidence. Discrepancies in the methodology used in the TIA incidence studies restrict the potential for comparison in most instances. The main concerns regarding the TIA incidence studies can be summarised as follows:

1) These studies were not representative of the total population for which an incidence rate was calculated;
2) The lack of a standard definition used in these studies is regarded as a major main constraint;
3) Case ascertainment was either by:
    a) retrospective review of case notes (Friedman et al., 1969; Alter et al., 1970; Whisnant et al., 1973; Zupping and Roose, 1976)
    b) hospital discharges (Mettinger et al.,1984; Alter et al., 1985; Lai et al., 1990; Liddegaard et al., 1986; Shah et al., 1995
    c) survey techniques (Karp et al., 1973; Rhoads et al., 1980; Li et al., 1985; Johnson and Skre, 1986; Urakami et al.,1987; Fratiglioni et al., 1989; Matias-Guiu et al., 1994 and
    d) prospective registers (Acheson et al., 1968; Terent et al., 1979; Giroud et al., 1986; Terent et al., 1988; Uggerhoj Anderson et al., 1988; Dennis et al., 1989; Ricci et al., 1991; Stewart-Wynne et al., 1992; Shah et al., 1995; Lauria et al., 1996; Sempere et al.1996;
4) Small populations – less than20 cases (Karp et al., 1973; Johnson and Skre, 1986; Ueda et al., 1987; (Matias-Guiu et al., 1994);

5) Rates were also reported only for selective age groups with different age bands in the different studies. Crude incidence rates instead of age and sex adjusted rates were reported in these studies.

The crude annual TIA incidence rate in Western countries derived from these prospective community studies prior to 1989, is about 5 per 100 000. (Dennis et al., 1989). A more recent study by Sempere (1992-1994) reported a crude annual incidence rate of 35 per 100 000 comparable with the rate reported by Dennis and others. "Amaurosis fugax accounts for about 20% of all TIAs." (Uggerhoj Anderson et al., 1988; Dennis, 1989) with a crude incidence rate of 6 per 100 000. Notwithstanding all these inconsistencies, the crude incidence rates reported from the various countries are very similar. The age-sex adjusted annual incidence rate of TIA in the UK is estimated at about 42 per 100 000, (Oxfordshire Community Stroke Project: 1981-1986, Dennis et al., 1989). It should however be mentioned that the data from the OCSP relate to the 1980's, almost 20 years ago and also to an area geographically and demographically different to Scotland where the morbidity and mortality is likely to have been lower than that observed in Scotland. The average annual risk of stroke during the first year after a TIA is about 11.6% and approximately 5.9% per annum over the first five years after the TIA (Dennis et al., 1990;Whisnant and Wiebers, 1987).

Prevalence of Transient ischaemic attack.

The prevalence of a disease is defined as the proportion of individuals in a population who have the disease at a specific time interval. The prevalence, therefore refers to

the status of the disease in the community and is usually more appropriate for the description of chronic stable conditions such as TIA. The estimation of period prevalence is considered a more suitable measure for acute transient conditions, which are episodic than the estimation of point prevalence. There is considerable variation in the prevalence of TIA. It increases with advancing age and differences exist between whites and blacks and also between males and females.

Twelve community-based surveys (Ostfeld et al., 1973; Karp et al., 1973; Whisnant et al., 1973; Boysen et al., 1979; Wilkinson et al., 1979; Li et al., 1985; Urakami et al., 1987 (Daisen, Japan); Urakami et al., 1987 (Ama, Japan) Ueda et al., 1987; Fratiglioni et al., 1989; Matias-Guiu et al., 1994; Bots et al 1997) in five countries have estimated the prevalence of TIA between the years 1965 to 1984. More recent studies include a study from Spain (Matias-Guiu et al., 1994) and Rotterdam, the Netherlands (Bots et al, 1997). Four studies (Ostfeld et al., 1973; Karp et al., 1973, Li et al., 1985, Matias-Guiu et al., 1994) applied door-to-door survey methods in selected populations and three studies (Wilkinson et al., 1979; Urakami et al., 1987; Fratiglioni et al., 1989) used questionnaires. The numbers in these study populations were small and not representative of the general population.

Prevalence of carotid stenosis

Carotid stenosis is defined as the narrowing of the carotid artery and is almost always artherothrombotic in nature. The stenosis is at or near the bifurcation of the common carotid artery into the external and internal carotid artery. The degree of stenosis is expressed as the maximum percentage reduction in the diameter of the relevant

carotid artery. The stenosis may be mild (defined as less than 30%), moderate (30 – 69%) or severe (70 –99%) (European Carotid Surgery Trialists' Collaborative Group, 1991). Although carotid stenosis of 70% or more in symptomatic patients is associated with a high relative risk of stroke, as a risk factor it may have very little impact on the overall incidence of stroke if the prevalence of carotid stenosis in the population is low.

Four studies (Balow et al., 1966; Pessin et al 1977; Thiele et al., 1980; Bogousslavsky et al., 1986) were identified estimating the prevalence of carotid stenosis in symptomatic populations. TIAs were the presenting symptom in all four of the studies, TIA and stroke in one study and TIA, stroke and amaurosis fugax in another study. These studies were relatively small, ranging from 95 cases to 250 cases in the most recent study (Bogousslavsky et al., 1986). These four studies display methodological differences, which hamper comparison. The modality used to determine the percentage stenosis was angiography in all four of the symptomatic populations. For stenosis of 75% or more the reported prevalence varies from 20% (Bogousslavsky et al., 1986) to 39% (Pessin et al., 1977). The prevalence of carotid occlusion is estimated at 5% based on all four studies. (Balow et al., 1966; Pessin et al., 1977; Thiele et al., 1980; Bogousslavsky et al., 1986). Since these populations from whom these rates were obtained were not representative of the general population and were in most instances selected high-risk populations, prevalence rate of 1% seems reasonable for the general population (Whittey et al., 1998). When including only individuals 65 years and older a prevalence of 2 - 7% for severe stenosis seems acceptable based on community studies (Whittey et al., 1998).

The reported prevalence of carotid stenosis in asymptomatic patients varies from 32.5% (Hennerici et al., 1981) to 3.8% (Pujia et al., 1992). The populations from whom these rates were obtained were again not representative of the general population. A more recent study estimated the prevalence of asymptomatic carotid atherosclerosis in a general population of 25.4% in men and 26.4% in females. (D' Alessando et al., 1992) All the studies determining the stenosis in asymptomatic populations are more recent (1981 - 1995) than the studies concerned with symptomatic populations (1966 - 1986). Doppler ultrasound was used as the investigating modality for the asymptomatic populations, and this non-invasive assessment tool became available for assessing the carotid arteries, bifurcation about 20 years ago. (Blackshear et al, 1979)

A value of 20% is usually applied for stenosis greater or equal to 60% for asymptomatic populations, with a high prevalence. In the case of low prevalence asymptomatic populations (stenosis 60% or more), 5% is usually regarded as the reference value (Chamber and Norris, 1985; Alexandrax et al., 1995; Ahn et al., 1991; Hennerici et al., 1981; Luisiani et al., 1990; Pujia et al., 1992)

Identifying patients with extracranial internal carotid artery stenosis

Three methods can be used to detect extracranial internal carotid artery stenosis in patients presenting with transient ischaemic symptoms. In the first instance it may be inferred clinically through cervical auscultation for the presence of an arterial bruit (though this is not an essential, and bruits may be present for reasons other than internal carotid stenosis). A second method of detecting internal carotid stenosis is by

means of non-invasive imaging techniques (ultrasonography, computed tomography angiography, or magnetic resonance angiography.) Thirdly, internal carotid stenosis may be detected by means of invasive imaging, which includes intra-arterial or intravenous digital subtraction angiography or conventional cerebral angiography (Hankey et al., 1990).

Before carotid surgery is considered, the carotid bifurcation must be imaged. The peri-operative evaluation of potential candidates for carotid endarterectomy includes duplex ultrasound and conventional carotid angiography or a combination of Duplex ultrasound and magnetic resonance angiography supplemented by conventional angiography. The majority of cases presenting with TIAs are assessed by taking a proper history and doing a clinical examination. Most of the patients are then referred for duplex examinations and only patients identified having stenosis more than 70% and who are medically fit for surgery are referred for a conventional angiogram prior to CEA.

Carotid angiography is currently regarded as the "gold standard" for examining the carotid arteries and is considered to be 100% sensitive and specific. However, the investigation is invasive and carries a risk of stroke or death of 1 - 2%. (ACAS, 1995). Duplex ultrasound is largely used as the first "tool" in the evaluation to assess the degree carotid of stenosis in symptomatic patients. The procedure is overall well tolerated and inexpensive, it is safe and the sensitivity and specificity range from approximately 81% to 90% and 82% to 95% (Feussner et al., 1988; Blakeley at al., 1995). The sensitivity increases to 94 - 99% for detecting stenosis more than 50%, and in instances of occlusion the sensitivity and specificity of duplex sonography can be between 91 - 99% and 84 - 96% respectively. The sensitivity and specificity

however is highly dependent on the skill and experience of the operator and range from 72 – 97% for sensitivity and from 83 – 95% for specificity. (Khaw, 1997). In the hands of experienced, trained operators, adhering to validated duplex criteria, carotid duplex imaging is safe, highly sensitive and specific.

The proportion of patients who have a TIA before their stroke.

Three methods were described of ascertaining the proportion of patients with stroke who have a TIA before their stroke (Hankey, 1986). The first method is to determine the annual incidence of TIA and the prognosis of TIA over the average lifetime of a TIA patient. The second is to describe the prevalence of TIA and the prognosis of TIA based on the actuarial average annual rate of stroke and the third is to estimate the proportion of people with a first-ever stroke who recall a previous TIA.

Incidence and prognosis of Transient Ischaemic Attack

The age-and-sex adjusted annual incidence rate of TIA in the UK is estimated at about 42 per 100 000 (Oxfordshire Community Stroke Project: 1981-1986) (Dennis et al., 1989). The average annual risk of stroke during the first year after a TIA is about 12% and approximately 6% per annum over the first five years after the TIA or 30% at five years (Dennis et al., 1990; Whisnant and Wiebers, 1987). Though reliable community-based data regarding the long-term prognosis of people with TIA for stroke are lacking, it is accepted that the probability of surviving ten years after a TIA is about 55%. Since the long-term mortality rate after TIA is slightly greater

than the long-term stroke rate, it is expected that 50% of people with TIA would have suffered a stroke after 10 - 15 years (Dennis et al., 1990).

Applying these prognostic data to the Scottish population of five million, about 2500 incident TIA cases would be expected and about 300 (12%) would suffer a stroke within the first year and about 1250 (50%) after 10 - 15 years. In any one year in Scotland it is expected that 1250 (12.5%) of the 10 000 first strokes would have occurred in patients who had a TIA in the preceding 10 - 15 years.

Prevalence and prognosis of Transient Ischaemic Attack.

It is suggested that a formula should be used to estimate the prevalence of TIA since surveys conducted to determine the prevalence of TIA are all extremely unsatisfactory and are unlikely to reflect the actual number of cases in the community (Hankey, 1986). Prevalence is the product of incidence and survival and since incidence and survival data are more accurate than prevalence data, it is regarded that an estimate of the prevalence of TIA using this formula will be more reliable. Though the long-term (beyond five-years) prognosis of people with TIA for stroke is not known, the probability of surviving ten years after a TIA is about 55%, and 40% in surviving 15 years (Goldner et al., 1971). Using this formula it is possible to estimate the prevalence of TIA in Scotland at about 15 000 or 300 per 100 000. If these 15 000 people who have previously experienced a TIA are to suffer a stroke at the actuarial average annual rate of stroke of 6.5% per year over the first five years, it would be expected that 975 (6.5%) of the 15 000 prevalent people with TIA would

suffer a stroke each year making up 9.8 % of the 10 000 first strokes in Scotland each year.

The proportion of people with a first-ever stroke who recall a previous TIA.

About 10 -15% of people who suffer a stroke recall having a TIA before their stroke, and only half report these events to a doctor (Dennis et al., 1989). This suggests that each year in Scotland 1000 to 1500 people with a first-ever stroke recall having a prior TIA and 500 - 750 of the 10 000 people with a first-ever stroke each year have consulted their doctor about it.

Based on the three methods, the proportion of people with a first-ever stroke in Scotland who had a TIA prior to the stroke is estimated at about 10 - 15% of the 10 000 annual incident strokes. The population attributable risk of transient ischaemic attacks as a risk factor for stroke appears then to be about 10 – 15%. Transient ischaemic attack is thus one of the risk factors for stroke that might be responsible for 1000 -1500 of strokes in the Scottish population.

Applying the annual TIA incidence of 42 per 100 000 population and assuming that 25% of first-ever stroke (incidence of first-ever stroke 400 per 100 000) are non-disabling strokes (Dennis et al., 1989) to the Scottish population of five million people, we can expect about 2500 Transient Ischaemic Attacks (TIAs) per annum and about 2500 (25%) first-ever non-disabling strokes. This will result in about 5000 patients who might be possible candidates for CEA. Of these 5000 Transient ischaemic attacks and non-disabling strokes, 80% or about 4000 are in the carotid territory and only 20% (800) have carotid stenosis of 70 to 99% and are eligible for

carotid endarterectomy. If all of these 800 patients receive a carotid endarterectomy, 80 strokes might be prevented, less than 1% of the 10 000 strokes occurring annually in Scotland.

It appears then that carotid endarterectomy has a small but significant role to play in preventing disabling strokes, however this intervention might be quite costly and certainly will not change the stroke burden. Since stroke is considered to be a preventable disease the economic assessment of carotid endarterectomy as a stroke prevention strategy, which might be of benefit to some patients, is long overdue.

From within this multifaceted and complex setting, this thesis aims to assess the costs and benefits of carotid endarterectomy (CEA) in Scotland as a stroke prevention strategy and the implications for the health care delivery system.

This objective will be achieved firstly by describing carotid endarterectomy in Scotland with specific reference to the observed changes over time; the geographical distribution of the procedure; survival of the CEA cohort over time and the influence of the published randomised controlled trials and the cost implications using generic cost measures such as bed days as proxy for cost.

Secondly, by performing a systematic review of the economic literature on carotid endarterectomy, with special emphasis on the cost estimates and the cost-effectiveness of carotid endarterectomy in Scotland.

Thirdly, by prospectively estimating the cost of carotid endarterectomy in three hospitals in Scotland. And finally by assessing the transferability of the results from a randomised controlled trial to a "real-life" population, by assessing the cost-

effectiveness of carotid endarterectomy based on actual ("real-life") cost estimates and by describing the lifetime cost associated with this procedure.

1.3 Thesis structure.

A chapter will be dedicated to each of these aspects and the structure of the thesis will be as follows.

Chapter Two describes the carotid endarterectomy procedure in Scotland from 1981 to 1996. This situation analysis of CEA is the largest historical cohort analysed to date in the United Kingdom and probably worldwide over the longest time period and in excess of 12 500 patient-years of observation. The geographical distribution of CEA, the hospital volume of CEA, the patients' characteristics and survival of the Scottish CEA patients over time are discussed in relation to the findings of a published randomised controlled trial. The cost of carotid endarterectomy is estimated using generic measures such as bed days. The implications of prediction models on the number of CEA needed to be performed are assessed as well the recommendations from the randomised controlled trials on preferred centres.

Chapter Three presents the first systematic review of the studies on the costs and benefits of carotid endarterectomy and pre-operative investigations prior to carotid surgery as identified in the literature. This review has been conducted using a standard evaluation protocol recommended to authors, referees and editors for the review of economic submissions to journals. I have identified inconsistencies in the

published economic literature and formulated possible explanations for the discrepancies observed.

Chapter Four reports on the programme cost of carotid endarterectomy where the *"programme"* is defined as the *"work-up"* cost of a cohort of patients who might be considered for potential carotid endarterectomy and the CEA *"procedure"* cost in hospital. This is the first study reporting on the total direct programme cost of CEA and also the cost in the "work-up" of a cohort of patients for possible carotid endarterectomy. This is also the first study reporting on the total direct procedure cost of carotid endarterectomy in Scotland using patient specific cost data in a prospective study obtained from two Scottish centres. The uncertainties that apply to the cost estimates are discussed in terms of a sensitivity analysis. The "work-up" of potential candidates from initial assessment at a neurovascular clinic to carotid endarterectomy is described as well as implications of associated time delays. Based on the proportions of patients investigated prior to CEA, a transition ratio from first consultation to CEA was determined which will provide invaluable information in estimating *need* for developing services such as "one-stop" transient ischaemic attack clinics.

Chapter Five assesses the transferability of results from the randomised controlled trial, the European Carotid Endarterectomy Trial, to a "real life" Scottish carotid endarterectomy population. Only modelling studies have been identified investigating the transferability of the efficacy of trial results to hypothetical populations. This investigation is unique since the efficacy data from a randomised

controlled trial and cost data from a study population representing a "real life" surgical and medical population were investigated. The cost effectiveness of carotid endarterectomy as it relates to data obtained from "real life" cohorts is evaluated in terms of stroke prevention. Several null hypotheses related to the transferability of trial results are tested in this chapter. The uncertainty associated with the cost effectiveness of this procedure is assessed in a sensitivity analysis. The lifetime cost of carotid endarterectomy is assessed using an incidence-based approach.

Chapter Six summarises the findings of this thesis and puts forward suggestions to improve the delivery of health services and subsequently the cost-effectiveness of carotid endarterectomy. Recommendations for future related research and conclusions are formulated.

CHAPTER TWO: BACKGROUND

CAROTID ENDARTERECTOMY IN SCOTLAND.

2.1 Introduction

There has been a marked increase in the number of carotid endarterectomies performed in one centre in Scotland over the eight-year period, 1985 – 1993 (John et al., 1993). A similar trend in the number of carotid endarterectomies within Great Britain and Ireland has been documented over the past decade with a sharp rise in the number of CEA during 1992, twice as many as during 1984 and 1989 respectively (Murie et al., 1994). McCollum and others found similar frequencies when extrapolating audit data (McCollum et al., 1997). This phenomenon has also been observed in other countries (Tu et al., 1998; Gillum, 1995). The onset of this increase coincided to a large degree with the publication of the results from the two large randomised controlled clinical trials (RCTs) during the early 1990s (ECST Collaborative Group, 1991; NASCET Steering Committee, 1991). Guidelines on the management of patients with carotid stenosis based on these trial results have subsequently been published (Moore et al., 1995, Findlay et al., 1997, Scottish Intercollegiate Guidelines Network, 1997).

More recently a six-fold increase in the number of carotid endarterectomies being performed in Scotland has been described for the period 1989 to 1995. The geographical inequality in the provision of CEA has also been highlighted in this report, with the CEA rate per 100 000 resident population varying between 0 (two

regions) and 19 (one region) (Adam et al., 1998). Despite the increase in the number of carotid endarterectomies and the geographical inequality described, the cost implications of this procedure, as a stroke prevention strategy has not been assessed in Scotland, neither have the recommendations from the trials regarding the number needed to treat to prevent one stroke been assessed.

The cost of carotid endarterectomy in Scotland is not known. Current data sources in Scotland do not allow for an accurate cost estimation. The length of hospitalisation for the procedure is a variable routinely collected in the national database of the National Health Service (NHS) in Scotland, which can be used to estimate the cost of carotid endarterectomy. Although this database incorporates Healthcare Resource Groups (HRGs) based on the International Classification of Diseases (ICD) and on the surgical operations and procedures of the Office of Population Censuses and Surveys (OPCS) classification, HRG costs for Scotland are not available.

The routinely collected variables for patients who have had a carotid endarterectomy include demographic variables, the presenting diagnosis according to ICD 9 classification, the operation code, prior admissions for transient ischaemic attacks (Transient ischaemic attacks) and stroke, length of hospital stay, any admissions following the procedure and cause of death by ICD 9 code (WHO; Geneva, 1989). Mortality statistics are linked with the Government Statistical Services from the General Registrars' Office. It is also possible to describe the frequency of carotid endarterectomy over time from this database and examine how practice has changed in relation to the publication of the large randomised controlled clinical trials. Furthermore, routinely collected variables in this comprehensive database allow for

the generation of many additional variables, which can be utilised in time to event analysis, or survival analysis.

The objectives of this study are:

1. to describe the carotid endarterectomy procedure in Scotland from 1981 to 1996;
2. to assess the geographical and hospital variation in utilisation of CEA over time in Scotland using routinely generated data;
3. to assess the characteristics and survival of the Scottish CEA patients over time in relation to the findings of a published randomised controlled trial and
4. to estimate the cost of carotid endarterectomy using bed days as a proxy for cost.

At the outset of this chapter the national database, the ISD database, and how the study population for this investigation was compiled from this database is briefly discussed. A description of the study population and carotid endarterectomy over the last sixteen years in Scotland follows. I describe and justify why the data set, the Scottish ISD-CEA data set, has been divided into three almost equal five-year periods. I perform time-to-event analyses for these three almost equal five-year periods and compare the survival curves for different variables. The survival curves obtained are subsequently compared to the survival reported from the randomised controlled European Carotid Surgery Trial in Chapter five.

2.2 Methods

2.2.1 Description of the study population

The study population included a cohort of Scottish patients who had a carotid endarterectomy procedure during the period 1981 to 1996 and were followed-up till March 1997 (Scottish ISD-CEA data set). These patients were identified by means of the Scottish Record Linkage System from the Information and Statistics Division (ISD) of the Scottish Health Service. ISD was formed when the NHS (Scotland) Act came into effect on 1 April 1974 and is responsible for the collection, processing and dissemination of statistical information. A total episode of care is defined as the time between an admission to a hospital and discharge from the health service, regardless of intermediate transfers to other institutions. Computerised medical records at national level in Scotland contain information about episodes of care by consultants. Heasman described the potential to link these records on a patient specific basis at an International Symposium in Oxford during 1967 (Heasman, 1968). Procedures have been developed linking these episodes of care for individual patients, thereby creating a comprehensive record for each patient containing all episodes of care received (Heasman and Clarke, 1979).

The study population was thus identified through record linkage with the index event specified as carotid endarterectomy, coding positions 0.828, L294 and L295 (Kendrick and Clarke, 1993). These codes were from the Tabular List of the classification of surgical operations and procedures of the Office of Population Censuses and Surveys 3 (OPCS 3) and the Office of Population Censuses and Surveys 4 (OPCS 4) codes for the period 1981-1996 and were used to identify

carotid endarterectomy patients (HMSO, London 1975 and 1990). OPCS 3 codes were in use during the period 1981 to 1988 and the code 082.8 for operations of arteries in the neck, NEC (endarterectomy) applies to this period. The OPCS 4 coding system which came into effect in 1989 and is still applicable, includes the codes L29.4 (Endarterectomy of carotid artery and patch repair of carotid artery) and L29.5 (Endarterectomy of carotid artery NEC).

Once the index event was identified, additional variables were extracted to inform the proposed survival analysis. These additional variables were grouped into three distinct categories. Variables related to the event itself, variables related to subsequent episodes and variables related to diagnoses in the three months prior to the carotid endarterectomy. The main events or end points of interest included any subsequent hospitalised cerebrovascular event (stroke and TIA) and death from any cause after the carotid endarterectomy.

Not all Scottish patients who were randomised to the European Carotid Surgery Trial could be successfully identified in the database. Investigation of this led to the discovery that other 082 codes were also used for the coding of carotid endarterectomy. These additional codes for *Operations of arteries in the neck, (NEC)* included 082.3 (resection with graft), 082.4 (bypass graft) and 082.5 (implantation with graft). These codes were therefore added to the specifications of the database to ensure the identification of "all" or the majority of the patients in Scotland who had carotid endarterectomy during the study period. It was judged that the additional OPSC 3 codes (082,3, 082.4, 082.5) with the specific carotid endarterectomy OPCS 3 code (082.8) would identify the majority of carotid endarterectomy procedures

during the study period. It was assumed that these OPCS 3 codes were similar and equivalent to the OPSC4 codes (L29.4 and L29 5) used from 1989 onwards.

2.2.2 Defining the data sets

The study population in the main data set, the Scottish ISD-CEA data set, was divided into three almost equal five-year periods for analysis purposes, because of the documented change of the procedure over time (John et al., 1993; Murie et al., 1994; Adam et al., 1998). This allowed comparisons to be made between the three different time periods. The first period or the *early period* of the study included the five years from January 1981 to December 1985. The second or *middle period*, January 1986 to June 1991, *referred* to the five and a half years prior to the publication of the two large randomised controlled trials. The third period or *most recent period*, July 1991 to December 1996, referred to the five and a half years after the publication of the findings from ECST and NASCET. The survival analysis for the most recent period also included the first three months of 1997 and follow-up was for five years and nine months, until 31 March 1997. It is acknowledged that the follow-up for the cohort for the most recent period was incomplete and that any differences observed in comparing the final cohort to the earlier cohorts are most likely due to incomplete follow-up rather than real differences.

An alternative would have been to divide the study population into two periods on the basis of the OPCS classification, which changed at the beginning of 1989. However, it was decided that having only two and a half years prior to the publication of the results of the RCTs might not provide sufficient data to compare

with a much longer period after publication of trial results. Although it was also felt that it would not be wise to compare the very early years to the more recent years in the study, when the procedure has been well established, it was done nevertheless to emphasise the evolving nature of the procedure over time. Since one of the objectives of this study was to determine whether results from the randomised controlled trials (RCTs) could be transferred to "real life" populations, the period prior to and the period after the publication of RCTs will be highlighted. For the purpose of this study "real life" referred to everyday practice and clinical situations encountered in the health care setting.

2.2.3 Estimation of carotid endarterectomy cost.

Using the length of stay in hospital (expressed as the number of bed days) for the carotid endarterectomy procedure, the "cost" of carotid endarterectomy for the three periods was estimated. The cost of one surgical bed day was estimated at £300. This cost assigned to a bed day was calculated using the Scottish Health Services Costs 1996/97 as reference. Allocated costs as published in the Scottish Health Services Costs 1996/1997 include overheads as well as capital charges and was used for all capital and overhead cost estimations in the study.

2.2.4 Volume of carotid endarterectomies per hospital.

The classification of hospitals where carotid endarterectomies were performed into low, medium and high volume hospitals was data driven and endorsed by work previously performed by Edwards and others. Low volume hospitals were defined as

hospitals performing between one and 12 carotid endarterectomies per year, medium volume hospitals doing 13 to 49 carotid endarterectomies per year and high volume hospitals performing more than 50 carotid endarterectomies per year (Edwards et al., 1991). The number or volume of carotid endarterectomies performed per "vascular" surgeon per year was not investigated.

2.2.5 Defining the analyses.

Statistical analysis.

The choice of statistical methods was determined by the nature of the variables in the ISD-CEA data set compiled from the routinely collected data. Most of the variables are categorical or nominal. Continuous variables include time to event variables and length of hospital stay. Time-to-event variables have been computed using the date of carotid endarterectomy procedure as the date of entry into the study.

Normal probability plots were used to assess any departure from normality. The inter-quartile ranges were defined as $Q_{0.25}$ - $Q_{0.75.}$ The interquartile range (IQR) is the difference between the first and third quartiles; this difference indicates the range of the middle half of the data set (Levin and Rubin, 1991). All categorical variables were compared by means of chi-square statistics. All p-values reported are two-sided. Time-to-event variables are analysed using Kaplan-Meier survival curves. The log-rank statistic and the Breslow tests are used to compare the survival curves obtained for the groups. All analyses compare survival between patients during the three time intervals, between men and women and between age categories with

respect to the length of time to any subsequent stroke event and to death of any cause.

The log-rank test emphasises the tail of the survival curve and gives equal weight to each failure time whereas the Breslow test weighs deaths according to the number at risk at the time of death, placing more weight on early deaths. An alternative test, the Peto-test, which also places more emphasis on the information at the beginning of the survival curve where the number at risk is large, could also have been used in the analysis. According to Kleinbaum (1996) these tests give similar results in practice, hence the use of the Breslow test.

The main time-to-event outcomes in this cohort were subsequent hospitalised cerebrovascular events and death from any cause after carotid surgery. Cerebrovascular events included stroke and transient ischaemic attack and were defined in this study according to the ICD9 classification, using codes 430 – 438 for stroke and transient ischaemic attack. All cause mortality was defined as a death from any cause including a fatal stroke and it is a reflection overall *survival.* The cause of death as classified by ISD was used to determine whether a death was stroke related or not.

Survival analyses were performed for these events occurring from date of operation up to 1826 days or five years after the procedure, thus determining the risk of having a "stroke" event or death during the five years after carotid endarterectomy in a cohort of patients having this operation. ***"Stroke-free" survival*** was defined as surviving for a total period of five years after successful carotid surgery, without experiencing any *hospitalised* stroke event.

Mean survival times with 95% confidence intervals and standard errors are reported. The mean survival time is not the average of the observed survival times, since it does not make sense to compute the usual arithmetic average if all of the cases have not experienced the event. "Special techniques are used to estimate mean survival time when there are censored observations. If the largest observed survival time is for a censored observation, the estimate of the mean survival time is said to be restricted to the largest observed survival time" (Norušis, 1994). The median survival time is the time point by which half of the cases are expected to experience the event (either stroke or death) and is not reported. To minimise the effect of confounding of dissimilar follow-up times for the three periods, a five-year assessment of survival is investigated for each period instead of survival over the entire period thereby comparing relative similar periods of survival (i.e. comparing like with like). Using the entire period will result in different lengths of follow-up. Patients operated on during the period 1981 -1985 can effectively have 10 to 16 years of follow-up, patients in the middle period, five to 10 years of follow-up and the most recent group at the most only five years.

2.3 Results.

Validity of carotid endarterectomy coding.

The specific code for carotid endarterectomy procedures in the OPCS 3 classification in use during the period 1981 to 1988 was 082.8. It was recognised that the codes 082.3, 082.4 and 082.5 were also used for coding of the procedure when patients from the ECST could not be linked to the specific CEA codes (082.8). Using these

additional codes in combination with the appropriate CEA codes (082.8, L29.4 L29.5), the CEA extracting procedure form the ISD National database was again performed. Only 74 (2.6%) cases were identified as being erroneously coded. Forty of these cases (7.5%) were during the early period and 34 (7.4%) during the middle period. No carotid endarterectomy coding errors were observed for the most recent period *(Table 2.6).* Of the 74 additional CEA identified, 12 more CEA patients who were randomised to surgery in the ECST could be identified. The five patients who crossed-over to medical treatment were also subsequently identified in the ISD database. Fourteen CEA trial patients could not be linked or identified resulting in 92% (172/186) linkage accuracy including the 5 patients who crossed-over to medical treatment. It is however necessary to mention that the initial linkage without the additional OPCS 3 codes secured only an 83% linkage (155/186).

2.3.1 Baseline characteristics of the study population.

Number of patients, age and sex distribution.

A total of 2892 carotid endarterectomies were performed over the 16-year study period from January 1981 to December 1996. When the Scottish ISD-CEA data set was divided into the three periods a total number of 536 (18.5%) carotid endarterectomies were performed during the early period, 476 (16.2%) during the middle period. The majority of operations 1880 (65%), were performed during the period after the publications of the two large randomised controlled clinical trials *(Table 2.1).* The age distribution for this study population exhibits a normal distribution with the mean age of 64.1 yearsand standard deviation of 8.71 *(Table*

2.1, Figure 2.1). The mean age of the early and middle period was 61 years and 66 years for the most recent period. Considering the entire data set the majority of patients 1413 (48.9%) were in the age category 50 to 65 years and 1268 (43.8%) of patients were between the ages of 66 to 80 years. *(Table 2.2).*

Of these operations 1719 (59%) were done in men and 1173 (41%) were in women *(Table 2.3, Figure 2.2).* The ratio of about 60 men to 40 women was observed over all the years studied, with the exception of 1988 when the frequency of the operation (38) was similar in men and women (50%) *(Table 2.4).* The frequency of the operation in men for the other years ranged from a low of 55% in 1985 to a high of 68% during 1989

Patient-years of observation.

The total years of observation for the 16-year study period was 12547 years with a mean survival time for the entire study period of 9.9 years (95% C.I. 9.6; 10.2, Standard Error 0.3). Considering only the five-year follow-up period the mean survival time was 4.39 years (95% C.I. 4.34; 4.44, Standard error 0.03).

Preceding events.

There were 1295 (45%) documented hospitalised stroke and TIA events in the three months before carotid endarterectomy in this ISD cohort of 2892 CEA patients. Of these, 1000 (77%) were hospitalised stroke events, 588 in men and 412 in women. The difference observed in hospitalised stroke events between men and women was not significant ($p = 0.63$). Of the 1000 strokes 468 (46.8%) were between the ages of 50 - 65 years and 455 (45.5%) in the age group 66 to 80 years. It was not

possible to distinguish between "minor" and major stroke events in this Scottish ISD-CEA cohort. The proportion of hospitalised strokes prior the CEA in the Scottish ISD-CEA cohort was 35% (1000/2892). This was considerably higher than the proportions of "minor" stroke lasting less than seven days reported in the ESCT (23% for the surgery group 21% for the medical group) *(Table 2.5).* This finding emphasised the difficulty to differentiate between stroke severity in this routinely collected data source.

In the entire study population 295 patients (10.2%) had a documented (hospitalised) transient ischaemic event in the three months prior to the carotid endarterectomy. Of these patients, 186 were males and 109 were females ($p = 0.19$). Assessing the frequency of prior transient ischaemic events for the three subgroups, there were 7% (37/536) documented TIAs for the early period, 9% (44/476) for the middle period and 11% (214/1880) for the third or most recent period ($p = 0.01$). Only 10% of cases (295/2892) had a preceding transient ischaemic attack prior to carotid surgery. This proportion of 10% was considerably less than the proportion of TIAs (52%) reported in the ECST cohort. It must however be recognised that all these TIAs in this study population were documented or hospitalised events whereas the TIAs reported in the ECST were self reported incidents not necessarily requiring hospital admission. The differences observed between the four age categories concerning preceding TIAs were non-significant.

2.3.2 Frequency of the procedure over the 16-year study period.

A total of 98 operations were performed during 1981. A gradual increase was observed from 1981 till 1985 when 121 patients had a CEA. A gradual decline in the number of operations was observed from 1986 to 1989, with a minimum of 60 operations during 1989. From 1990 a steep increase in the number of carotid endarterectomies occurred, with 68 operations in 1990 to a total of 443 procedures during 1996. This represents more than a six-fold increase *(Table 2.4, Figure 2.3).*

2.3.3 Geographical distribution of carotid endarterectomy and hospital volume.

Over the study period of 16 years, all 2892 carotid procedures could be linked to a specific *health board of residence.* The health board resident population for 1995 ranged from a high of 912 500 in Greater Glasgow to a low of 19 870 in Orkney. Though the health board of residence is not coded on the linked database from 1981-1985, the health board of residence for the 536 operations performed during the early period of investigation could be derived through local government district or postcode of residence. *(Table 2.7).* The frequency of the procedure according to *health board of residency* varies from a minimum of 2 operations in Orkney health board to a maximum number of 626 operations in the Greater Glasgow health board *(Table 2.7, Figure 2.4).*

The CEA rate per 100 000 of the Scottish population has increased steadily from an all time low of 1.2 per 100 000 (1989) to a maximum of 8.6 per 100 000 (1996). The CEA rate per 100 000 population per health board of residence varied from zero in two health boards (Shetland and Orkney) to a maximum of 19 per 100 000 in the

Tayside health board during 1994. The CEA rate per 100 000 population per health board has been consistently higher in Tayside compared to the other 14 health boards, ranging from 6.1/100 000 in 1986 to 17 /100 000 in 1996. Similar increases were observed in the health board of Argyll and Clyde, Ayrshire and Arran, Dumfries and Galloway, Grampian and Greater Glasgow. The CEA rate per 100 000 residents in the Lothian health board has remained relatively stable varying between 4.5 /100 000 (1992) and 3.9 (1996) *(Table 2.8, Figure 2.5).*

Over the 16 years, the operation was performed in 20 hospitals in 11 of the 15 health boards in Scotland *(Table 2.9).* Using the hospitals where these early operations were performed as reference to classify all the procedures with a specific *health board of operation*, the maximum number of 1193 (41.2%) operations were also associated with the Greater Glasgow health board and the minimum of four (0.14%) CEA with the health board of the Western Isles *(Table 2.9).* Between 1981 and June 1991 carotid endarterectomy was performed in nine (Greater Glasgow, Tayside, Lothian, Grampian, Dumfries and Galloway, Lanarkshire, Highland, Forth Valley and Western Isles) of the 15 health Boards, and since July 1991 also in two additional health boards, Ayrshire and Arran and Argyll and Clyde. The operation was never performed in the four Health Boards of the Borders, Fife, Orkney and Shetland *(Table 2.9, Figure 2.6).*

Hospital volume.

The number of operations performed per hospital per year for the five years after the publication of the RCTs is summarised in table 2.10. For the period 1992 to 1996 a

minimum of three operations were performed in Western Isles Hospital, Stornoway and a maximum of 368 in the Western Infirmary Glasgow. Nine of the 20 hospitals performed between 46 and 368 Carotid endarterectomies over the five-year period assessed. Only three hospitals (Royal Infirmary Edinburgh, Ninewells Dundee, and Western Infirmary Glasgow) performed more than 45 carotid endarterectomies per year over three consecutive years (1994 -1996).

Classifying the hospitals into low, medium and high volume hospitals it was found that 25% of hospitals performing Carotid endarterectomies were considered being high volume hospitals during 1995 and 1996. The lowest proportion of operations in high volume hospitals was 8% in 1992 and the highest proportion of 27% in 1996. More than 50% of hospitals performing carotid endarterectomies between 1992 and 1996 were in hospitals defined as low volume hospitals (1-12 CEA per year) *(Table 2.11, Figure 2.7).* Of the 15 hospitals performing 443 carotid endarterectomies in 1996, four hospitals were high volume hospitals, doing 294 (66%) of the Carotid endarterectomies for that year. One hundred (23%) operations were in three medium volume hospitals and 49 (11%) of the carotid endarterectomies were in eight low volume hospitals.

2.3.4 Length of hospital stay.

Examining the distribution of the length of hospital stay for the entire population, a minimum stay of zero days were observed for five patients, and a maximum stay of 582 days for one patient. The five patients with no recorded hospital stay were from the Royal Infirmary Edinburgh (1982), Glasgow Royal Infirmary (1995,1996)

Southern General hospital, Glasgow (1995) and from Ninewells hospital (1994). Two of these patients subsequently died, one within a week of the procedure and the other suffered a stroke event one week after the procedure, but the recorded date of death was during 1993 and coded as a non-stroke related death. Discussions with ISD did not provide any plausible explanations other than that the patients might have been transferred to another institution of care and might still be there and hence "not discharged" from the hospital or National Health Service.

The mean number of days in hospital was 7.98 with a standard deviation of 20.7. The $IQR_{0.25 - 0.75}$ was four to eight days with a median length of stay of five days. It was not possible to distinguish between type of hospital stay, that is intensive therapy, high dependency and general ward stay from the routinely collected data. The length of hospital stay for the three periods shows a reduction in overall length of stay from the early period to the most recent period, indicating the change in the procedure over time. The maximum length stay of 582 days appears unacceptably long. This is likely to be explained by the fact that the total length of hospital stay recorded in this study population is from admission for the carotid procedure to (eventual) discharge and thus including transfers to other institutions (hospitals or convalescence centres) when required by patients who suffered any complications. A truer reflection of the length of hospital stay for carotid endarterectomy is probably found using the inter-quartile range, reflecting the length of hospital stay for 50% of the study population *(Table 2.12, Figure 2.8).* A 38.5% decrease in the mean length of hospital stay was observed from the early period to the most recent period and a 44.8% decrease in days in hospital from the middle period to the most recent period, again suggesting a change in the management of these cases.

2.3.5 Estimation of CEA cost using bed days as proxy for cost.

The mean cost for CEA for the period 1981 - 1996 based on the mean number of bed days was £2396 (median 1500; IQR 1200 – 2400). The mean cost of CEA for the period 1981 -1985 was £3110 compared to £1926 for the most recent period 1991 - 1996 *(Table 2.13).*

2.3.6 Outcome events: Subsequent cerebrovascular events and all cause mortality.

Subsequent cerebrovascular events (stroke and transient ischaemic events).

Subsequent stroke events in this cohort included hospitalised transient ischaemic attacks and stroke events. It was however not possible to distinguish between ipsi- and contra lateral stroke as well as major strokes events in this Scottish ISD cohort.

Among the 2892 patients who had surgery over the 16-year study period, there were 128 (4.4%) a strokes or TIAs within 30-days of the carotid surgery and 652 (22.5%) were reported over the entire16-year study period *(Table 2.14).* Of these, 175 were stroke related deaths, 161 patients suffered a stroke prior to death and 316 patients who suffered an event after the carotid endarterectomy were either still alive or were lost to follow-up at the end of the study period. A decrease of 60% in subsequent stroke events was observed from the early period to the most recent period.

Over a five-year period after CEA, 545 cerebrovascular events were documented hospitalised events and it appears that the majority (84%; 545/652) of these subsequent events occurred within five years after the carotid surgery. However, since the follow-up for the cohort during the most recent period was incomplete,

inferences can not be drawn on the differences observed between the entire study period and the five-year period of follow-up. Only crude rates for cerebrovascular events, which present the actual experiences of the three cohorts, were therefore reported (*Table 2.14).*

For the analysis of any fatal or non-fatal stroke event, the overall five-year failure rate was 19%. The failure rates for the three periods were 27% for the early period, 21% for the middle period and 16% for the most recent period – a percentage difference of 33% between the early period and the most recent period. However, the incomplete follow-up of the most recent period should be recognised. These failure rates were well in excess of those reported in the randomised controlled trials. NASCET reported an estimated 9% cumulative risk of any ipsilateral stroke at two years in the surgical group and ESCT reported an overall risk of non-fatal major stroke or death of 9.6 %.

Cumulative survival to any subsequent stroke event in the five years after carotid endarterectomy is summarised in table 2.15. Kaplan-Meier estimators for any subsequent stroke events for patients operated on during the three intervals are shown in figure 2.9. The log-rank tests for differences in the survival form any subsequent stroke event between these three time intervals, were significant ($p = 0.005$). The Breslow-test, which places more weight on the early events, was highly significant ($p<0.001$). No significant difference in the five-year risk of any subsequent cerebrovascular event between men and women was observed (Log-rank: $p = 0.14$ and Breslow: $p = 0.11$) *(Figure 2.10).* Differences in five-year risk of any subsequent stroke for the four age categories were also significant with a p-value of 0.001 for both the Log-rank and Breslow tests *(Figure 2.11).* Over the 16-year period a total of

259 (9%) subsequent carotid endarterectomies were documented in this study population (Scottish ISD-CEA cohort) *(Table 2.14).*

All cause mortality.

A total of 783 deaths were reported over the 16-year study period. Of these deaths, 175 (22%) were reported to be stroke related and 608 were reported as non-stroke deaths. Of the 608 deaths due to other causes, 161 (26.5%) patients suffered a subsequent stroke after the carotid endarterectomy and prior to death, resulting in 447 (57%) reported deaths assumed not to be associated with stroke. Sixty-six patients (2.3%) died within 30 days after carotid surgery. A total of 484 deaths were reported during the five years of follow-up after CEA, 135 (27.9%) for the early period, 118 (24.4%) during the middle period and 231 (47.7%) deaths in the most recent period *(Table 2.16).* The 5-year crude mortality rate for the entire CEA cohort was 167 per 1000. The five-year crude mortality rates for the three periods were 252 per 1000 for the early period, 248 per 1000 for the middle period and 123 per 1000 for the most recent period. Although the differences observed between the number of deaths during the three periods were statistically highly significant ($p < 0.001$) for both the entire period and the five-year follow-up period it should be borne in mind that the follow-up for the final cohort was incomplete influencing any inferences drawn. The difference observed in overall survival for the three periods was not significant (Log rank $p = 0.67$; Breslow $p = 0.71$)*(Table 2.19, Figure 2.12).* Of the 783 reported deaths for the entire period, 489 were in men and 294 in women. Considering only the five-year period of follow-up, 312 deaths occurred in males and 172 in females. The difference observed between men and women was statistically significant ($p =$

0.05) for the entire period as well as for the five year follow-up (p = 0.015) *(Table 2.17, Figure 2.13).* Data about the outcome events were available in all patients for the early and middle periods and were assumed to be "complete" since no censoring was observed during the five year period investigated The five-year risk of *all cause mortality* was assessed for the three time periods. For the primary analysis of *all cause mortality* the overall five-year failure rate was 16.7%. The failure rates for the three periods were 25% for the early and middle period and 12% for the most recent period – a percentage difference of 52% between the two periods before publication of the randomised trials and the most recent period. Comparing the five year overall survival between men and women in this study population, a statistical significant difference was observed (p = 0.016) using the log-rank test statistic *(Figure 2.13).* Statistical significance between males and females was not reached (p= 0.07) with the Breslow test, which places more weight on the early deaths. The mean survival time for women (4.5 years; 95% C.I. 4.37, 4.54) was slightly longer than for the men (4.3 years; 95% C.I. 4.27, 4.41). A similar trend was observed when men and women were compared during the different time periods using the Log-rank statistic *(Table 2.17).* Comparing the five-year overall survival for the four age categories, highly significant differences with both the log-rank and Breslow tests were obtained (p < 0.001). The mean survival time for patients less than 50 years of age was 4.8 years (95% C.I. 4.65 - 4. 92) compared with 3.2 years (95% C.I. 2.56 - 3.93) in the age category older than 80 years *(Table 2.18, Figure 2.14).*

2.4 Discussion.

The CEA rate per 100 000 population in Scotland has increased steadily over the years 1985 to 1993 from 1.2 per 100 000 to 8.6 per 100 000 in 1996. The CEA rate in Scotland in 1993 of 5.9/100 000 was also higher than the CEA rate of 3.5 per 100 000 for England and Wales and considerably higher than the CEA of 0.7/100 000 observed in Northern Ireland (Irvine et al., 1996). Despite the higher CEA rates in Scotland, significant regional variation in the provision of CEA per health board of residence has again been highlighted in this report with the CEA per 100 000 residence per health board varying between zero to 19 per 100 000 population for one specific year. Though extensive variation in the CEA rates was seen during the years investigated in three of the fifteen health boards, these three health boards are notably the smaller health boards with a different population composition. The population rates for carotid endarterectomy reported were crude rates only, which represent the actual experiences of the population and provide data for the allocation of health care resources. Although these crude rates are easy to calculate and are widely used for comparisons, the values may be confounded by the underlying population structure. Age and sex standardised rates might therefore provide more precise rates for comparison, however standardisation of rates was not performed in this study.

The majority of hospitals performing carotid endarterectomies after the publication of the randomised controlled trials were considered to be low-volume hospitals. However most of the carotid endarterectomies performed after the publication of the trial results were in a small number (3.3%) of high-volume hospitals. In 1996 11% of

carotid endarterectomies were performed in eight low-volume hospitals, 23% in three medium-volume hospitals and 66% of operations in four high-volume hospitals.

The assessment of this routinely collected data on CEA over a 16-year period in Scotland illustrated the influence of the publication of the results of the two large randomised controlled trials during the early 1990s on the practice of carotid endarterectomy. The years preceding the publication of the trial results saw a decrease in the number of carotid endarterectomies in Scotland. A marked and sustained increase was found from 1992 onwards. This study provides confirmation that the frequency with which this operation is performed has changed as result of published clinical evidence from the two large randomised clinical trials demonstrating the efficacy of CEA but that practice might not have been altered.

The limitations of this data set, obtained from a routinely collected data source, should be recognised before drawing definite conclusions from the results obtained in this study. The absence of clinical variables in this data set, the selected nature of the population studied and the incomplete follow up for the final cohort compounded the inferences drawn from this study.

The study showed that the "stroke-free" survival of patients not associated with the trial was not comparable with the "stroke-free" survival of patients in the ECST. The "stroke-free" survival of the surgical patients in the ECST at three years was estimated at about 88% (the percentage without any stroke that lasted more than seven days or surgical death) (ECST, 1991). The corresponding estimates for the ISD cohort were 82%, 83% and 76% for the most recent, middle and early period respectively *(Table 2.14)*. These results also suggested that clinical practice might

have changed from the early period to the later periods. This investigation further demonstrated the reduction in the use of health care resources based solely on length of hospital stay. The use of bed days as a proxy for cost appears to be an extremely crude measure of the cost of CEA when compared to the cost estimates from Newcastle and the Wessex study (Radestock, 1992; Smithies et al., 1997).

In the context of the Scottish population the maximum number of carotid endarterectomies performed during 1995 continues to be within the limits (450 – 700) of the number of CEA we would expect, based on suggestions from the Association of British Neurologists (Brown et al., 1992) and estimates, using the incidence rates of TIA and of minor non-disabling strokes (Hankey et al., 1996, Smithies et al., 1997). Based on these estimates the number of patients eligible for CEA in Scotland is expected to be somewhere between 450 and 700 per year. The increase observed in the number of carotid endarterectomies in Scotland over the last couple of years from 68 (1990) to 443 (1996) can be considered as still within the expected volume of CEA for Scotland. What is however alarming is the huge variation observed in the volume of operations performed between the hospitals. Three operations were performed in one hospital (Western Isles) and a total of 368 operations in another (Ninewells) for the five year period after the publication of the trials results. It is evident from the results presented in tables 2.10 and 2.11, that the 50% of hospitals in Scotland where carotid endarterectomies were performed were in low-volume hospitals performing one to 12 carotid procedures per year. This demonstrates a very low carotid endarterectomy activity in the majority of hospitals. Although carotid endarterectomies were performed mainly in low and medium

volume hospitals, just over half (51%) of all carotid endarterectomies over the period 1992 to 1996 was in high volume hospitals. It also suggests that the recommendations from the trials and subsequent guidelines of about 50 CEA per surgeon per year are not implemented or alternatively might not be appropriate for Scotland. If the delivery of carotid endarterectomies and the benefits from the procedure are to be optimised, these findings need to be further investigated (NASCET Collaborators, 1991; SIGN guidelines, 1994; Moore et al., 1995).

Reliability and validity of routine collected data with special reference to ISD .

The data used for this analysis were obtained from a routinely collected data set. Routinely collected hospital discharge statistics or administrative data sets have become widely used for epidemiological studies, quality assessment and medical effectiveness research, mainly because these data sets provide large samples at low cost. The use of these sets however remains controversial based on concerns that such data is inaccurate and lacks especially physiological variables. The findings of this study should therefore be interpreted against the background of all the limitations of data collected in this manner.

Prerequisites for data quality include completeness, validity, accuracy, availability as well as timeliness (Wyatt, 1995). The analysis of routinely collected data have always been open to criticism, since these data sources are usually dependent on hospital and district returns. Variation of data collection between institutions is not unexpected considering the multiple steps involved to submit a "return". Data should be reliable and valid for analysis to allow inferences to be drawn from the results

obtained. Reliability addresses the issues of accuracy, consistency and completeness and whether it provides consistent results. Validity of the data set relates to the degree to which the analysis performed on collected data will measure what it intended to measure. Aspects to consider here include the role of chance, the effect of bias and confounding. Data validity, in the case of ISD data is restricted mainly to data feasibility, e.g. checking age and sex against a particular diagnosis.

Accuracy of SMR1 and OPCS coding.

The Scottish Morbidity Record 1 (SMR1) is an episode-based record capturing all inpatients and day cases discharged from Scottish hospitals, excluding psychiatric and obstetric wards. The main reason for admission is entered onto the SMR1, which is essential for statistical analysis, audit and contracting. Discharge summaries are generally used by coding personnel to determine ICD or OPCS codes. When these summaries are not available, case notes are examined or the doctor in charge of the case is contacted to obtain relevant information. If the information available is still insufficient, the National Health Service Centre for Coding and Classification (NHSCCC) at Loughborough is contacted. This process is known as terming and also defines Read codes, which contains a range of variables other than diagnoses and procedures. Only once sufficient information is obtained, are ICD or OPCS codes established by referring to the appropriate code books. Codes are then entered into Patient Administration Database (SMR1) from which contract allocations, Healthcare Resource Groups (HRGs) and pricing are carried out on a monthly basis. The data are submitted quarterly to the Department of Health or Scottish Office. Considering

all the different steps involved in the data collection, it is not surprising that errors occur, especially taking into account the variation in recording practice and coding policy between different hospitals. However, the accuracy of hospital discharge data depend to a large degree on the willingness and conscientiousness of medical staff to supply the information (Galland et al., 1998; McKee and James, 1997; Harley and Jones, 1996; Davenport et al., 1996).

The accuracy of ICD and OPCS codes produced by Hospital Activity analysis were assessed as far back as 1980 and reported to be 20% inaccurate. Although the time period studied, pertained to general surgery only, it was also observed that the situation in subspecialties is no better. The disagreement was more pronounced when a patient had more than one diagnosis or operative procedure (Gough et al., 1980; Romano and Mark, 1994). More recently Galland and others reported on the accuracy of OPCS coding with specific reference to vascular surgery in the United Kingdom and found that OPCS codes considerably underestimate (31%) the actual amount of vascular activity, with endovascular procedures less well documented than surgical reconstructions (Galland et al., 1998). Though error rates of between 20 - 40% have been described using different criteria, (Mukherjee et al., 1991; Smith et al., 1991) it is suggested that these reports of data inaccuracy may be an overestimation due to publication bias (Sellar et al., 1990). The Quality Assessment and Accreditation Unit (QAA) of the Information and Statistics Division (ISD) is responsible for monitoring the quality of SMR data against national standards. According to Harley and Jones an improvement of 5.4% in the accuracy of main operation coding has been observed between 1992 (85.3%) and 1994 (90.7%) (Harley and Jones, 1996). This study however found that the accuracy of main

operation and second operation coding for carotid endarterectomy was only 83% with the first identification process using the patients who were in the ECST data set as the "gold" standard. It was assumed that it would be possible to identify all patients who were randomised to the surgical arm of the ECST in the CEA cohort from ISD for the period 1981 to 1996. This was clearly not the case since only 83% (155/186) of the Scottish patients in the surgical arm of the ECST could be identified. Re-examining the ECST data it was discovered that ten patients who were in the ECST were incorrectly coded using codes 082.3 and 082.5, and a further two were identified when the link numbers were consolidated. The identification of the additional 12 CEA patients and five patients who crossed over to medical care increased the accuracy of identifying patients who were known to be randomised to CEA in the ECST and should have been coded as such by 9% to 92% (172/186). This increase in accuracy of identifying a surgical procedure was only possible since data from the surgical arm of the Scottish cohort of the ECST data set was available. The identification of incorrect OPCS codes resulted in a "re-run" of the computer programme with the additional codes on the ISD data base, to ensure that "all" the CEA in Scotland over the period 1981 to 1996 would be accounted for.

Left and right censoring in survival analysis.

Though information was collected on documented TIAs and non fatal strokes during the three months prior to CEA, time to event analysis, i.e. time from presenting stroke or TIA to carotid endarterectomy was not performed since the issue of left censoring could not be satisfactorily addressed. Furthermore, information of events

prior to CEA was incomplete. Only documented hospitalised TIAs/stroke events are known and no record exists of transient events patients had, but did not report to their doctor. The information on preceding events leading to carotid surgery is thus incomplete and even when reported, the onset of the event recorded may or may not have been the first transient ischaemic episode. The exact survival time on the left was thus in most instances unknown. The measures of survival analysis however have been primarily developed to deal with data that are right censored *(Figure 2.15)*.

Results and the implications of the randomised controlled trials.

The ECST and NASCET reported an absolute risk reduction of major stroke and/or death 9.6 % and 16.5% respectively in-patients with severe stenosis. Based on the findings from these trials the number needed to treat (NNT) with a CEA to prevent one stroke is between six and 10 over a 3- and 2-year period respectively. If all the patients eligible for a CEA in Scotland were to receive a CEA about 800 patients will have a carotid endarterectomy and 80 strokes might be prevented, less than 1% of the 10 000 strokes occurring annually in Scotland.

CEA lowers the overall risk of ischaemic stroke by about 50% over the next three years in patients with 70 - 99% stenosis. Only about 20% of such patients have a major stroke on medical treatment alone. Whether an operation will be beneficial for an individual depends on the risk of stroke and death with surgery and the risk of stroke without surgery. Prognostic models have been developed to assist clinicians to identify those patients who will benefit the most form surgery.

The risk-factor modelling suggested that the NNT might be as low as three carotid endarterectomies to prevent one stroke or as many as a 100 carotid endarterectomies to prevent one stroke when the risk profile of patients is taken into consideration (Rothwell et al., 1999). To reduce the NNT to as low as three, suggests that only patients in the high risk category might be considered for the procedure, and might at the same time deprive patients who might be considered having a lower risk from the operation and the associated benefit. Identifying the three patients who would benefit most from carotid endarterectomy, and result in the prevention of one stroke, might be very costly and might have far-reaching implications for carotid endarterectomy in Scotland.

2.5 Summary

This was the largest historical cohort analysed to date over the longest time period and in excess of 12500 of patient-years of observation for the entire study period of 16 years. This study showed that CEA rates in Scotland have increased over time and that the variation seen by health board might indicate over or under utilisation of the procedure. The accuracy of routinely collected data for CEA was found to be between 83% and 92%. The study further showed that the cost of CEA decreased over time, mainly because of the reduction in hospitals stay during the letter years. It was clear from this investigation that the use of routinely collected data for epidemiological studies and quality assessment of health care delivery remains an area of concern and that determining needs and provision of health services based on routinely collected data might result in an underestimation of services required

both with regards to human resource need, physical facilities and financial resources.

The influence of the publication of the results of the two larger randomised trials was evident in this study with a marked increase of CEA from 1992 onwards. The study demonstrated that the majority of hospitals in Scotland performing carotid endarterectomies after the publication of the trials are defined as low-volume hospitals, suggesting that current recommendations regarding hospitals where these operations should be performed are inappropriate for Scotland. The study showed that the stroke-free survival of CEA patients in Scotland not in a trial was not comparable with the stroke-free survival of Scottish patients randomised to surgery in the ECST.

The use of routinely collected data for epidemiological studies and quality assessment of health care delivery remains an area of concern. Results from randomised controlled trials might have influenced some aspects of practice, but recommendations based on trial results appeared not to be fully implemented.

This investigation representing the largest historical CEA population being studied to date provided the unique opportunity of linking the study population to patients in a randomised controlled trial conducted almost over the identical time period. Results obtained also questions the transferability of trial results to other settings. Definitive conclusions will however only be possible once more comparable cohorts are assessed.

Table 2.1: Baseline characteristics for Scottish ISD-CEA patients: 1981 – 1996.

	Males	Females
The entire period: 1981 – 1996 *(n = 2892)*		
Number	1719 (59%)	1173
Mean age (SD)	64.1 (8.68)	64.0 (8.75)
Preceding events	588	412
Subsequent "stroke" events*	309	236
Deaths	312	172
The early period: 1981 – 1985 *(n = 536)*		
Number	324 (60%)	212
Mean age	60.6	61.3
Preceding events	97	63
Subsequent "stroke" events*	89	55
Deaths	93	42
The middle period: 1986– June 1991 *(n = 476)*		
Number	283(59%)	192
Mean age	61.4	60.7
Preceding events	84	48
Subsequent "stroke" events*	60	40
Deaths	81	37
The most recent period: July 1991 – 1996 *(n = 1880)*		
Number	1112 (59%)	768
Mean age	65.7	65.5
Preceding events	407	301
Subsequent "stroke" events*	160	141
Deaths	138	93

* Strokes and TIA during five-year follow-up period

Table 2.2: Age distribution for the Scottish ISD-CEA patients for the three five-year periods investigated: 1981 -1996.

	Three five-year periods			
Age category	**1981 – 1985**	**86 -Jun 1991**	**Jul 91- 1996**	**1981- 1996**
< 50 years	54 (10%)	40 (8.4%)	65 (3.5%)	159 (5.5%)
50 – 65 years	322 (60.1%)	293 (62.7%)	798 (42.4%)	1413 (48.9%)
66 – 80 years	157(29.3%)	142 (30.5%)	969 (51.5%)	1268 (43.8%)
> 80 years	3 (0.6%)	1 (0.2%)	48 (2.5%)	52 (1.8%)
Total	536 (18.5%)	476 (16.5%)	1880(65%)	2892

Table 2.3: Age and sex distribution for the three five-year study periods and for the Scottish ISD-CEA cohort: 1981 - 1996.

	Age categories in years				
	< 50	50 – 65	66 – 80	> 80	All ages
1981 - 1985					
Males	35 (11%)	197 (61%)	89 (27%)	3 (1%)	324 (60.4%)
Females	19(9%)	125 (59%)	68 (32%)	0	212(39.6%)
1986 - June 1991					
Males	16 (5.7%)	184 (65%)	83(29.3%)	0	283 (59.5%)
Females	24 (12%)	109(56%)	59(31%)	1(0.5%)	193(40.5%)
July 91 - 1996					
Males	34 (3%)	483 (43%)	567 (51%)	28 (3%)	1112 (59%)
Females	31(4%)	315 (41%)	402(52%)	20 (3%)	768 (41%)
1981 - 1996					
Males	85 (5%)	864 (50%)	739 (43%)	31 (2%)	1719(59.4%)
Females	74 (6%)	549 (47%)	529 (45%)	21 (2%)	1173(40.6%)

Table 2.4: Number of carotid endarterectomies per year for males and females and the crude CEA rate per 100 000 population in Scotland: 1981 - 1996.

Year	Males (%)	Females	Total	CEA rate / 100 000
1981	58 (58%)	40	98	2.0
1982	59 (63%)	34	93	1.9
1983	67 (63%)	40	107	2.1
1984	73 (62%)	44	117	2.3
1985	67 (55%)	54	121	2.4
1986	67 (57%)	47	114	2.3
1987	58 (59%)	41	99	2.0
1988	38 (50%)	38	76	1.5
1989	41 (68%)	19	60	1.2
1990	44 (65%)	24	68	1.4
1991	77 (59%)	54	131	2.6
1992	168 (63%)	98	266	5.3
1993	178 (59%)	123	301	6.0
1994	220 (56%)	176	396	7.9
1995	243 (60%)	159	402	8.0
1996	261 (59%)	182	443	8.9
Total	1719 (59%)	1173	2892	3.6*

* Cumulative rate

Table 2.5: Preceding cerebrovascular events (strokes and transient ischaemic attacks) according to study period for the Scottish ISD - CEA cohort: 1981 - 1996.

	Study periods			
Preceding Events	**1981 -1985 (n = 536)**	**1986 - June 1991 (n = 476)**	**July 1991- 1996 (n = 1880)**	**1981- 1996 (n = 2892)**
TIA	37 (7%)	44 (9%)	214 (11%)	295 (10%)
Strokes	160 (30%)	132 (28%)	708 (38%)	1000(35%)
All events	197 (37%)	176 (37%)	922 (49%)	1295(45%)

Table 2.6: Carotid endarterectomy coding according to OPCS 3 and OPCS 4 classification for the three study periods for the Scottish ISD-CEA cohort.

	CEA code correct		
Period	**Yes**	**No**	**Total**
January 1981 - December 1985	496 (92.5%)	40 (7.5%)	536
January 1986 - June 1991	441 (92.6%)	34 (7.4%)	476
July 1991 – December 1997	1880 (100%)	0	1880
January 1981 – December 1997	2818 (97.4%)	74 (2.6)	2892

Table 2.7: Health Board of residence for males and females for the Scottish ISD-CEA cohort: 1981 - 1996.

Health Board of Residence	Males	Females	Number	Percent
Argyll and Clyde	144	110	254	8.8
Ayrshire and Arran	154	117	271	9.4
Borders	21	9	30	1.0
Dumfries and Galloway	59	37	96	3.3
Fife	105	52	157	5.4
Forth Valley	53	37	90	3.1
Grampian	120	71	191	6.6
Greater Glasgow	362	264	626	21.6
Highland	28	9	37	1.3
Lanarkshire	137	106	243	8.4
Lothian	187	120	307	10.6
Orkney	1	1	2	0.1
Shetland	2	2	4	0.1
Tayside	344	234	578	20.0
Western Isle	2	4	6	0.2
Total	**1719**	**1173**	**2892**	**100**

Table 2.8: CEA rate per 100 000 in Scotland per health board of residence for the period 1986 –1996.

Years	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996
SCOTLAND	2.2	1.9	1.5	1.2	1.3	2.6	5.2	5.9	7.7	7.8	8.6
Argyll and Clyde	1.8	2.0	0.7	0.2	0.9	2.1	6.7	5.3	9.2	10.6	9.3
Ayrshire and Arran	1.6	0.8	1.9	0.5	0	1.3	5.6	10.6	13.8	12.2	9.8
Borders	4.9	2.0	0	1.0	0	1.0	3.8	4.7	1.9	1.9	2.8
Dumfries and Galloway	2.8	0.7	0.7	2.7	1.4	2	8.8	10.1	8.1	6.8	8.8
Fife	3.2	1.7	1.2	0.6	1.1	2.9	3.4	2.8	4.8	6.8	7.7
Forth Valley	0.7	0.7	1.1	0.7	1.5	1.5	2.2	3.7	5.1	3.7	5.5
Grampian	1.2	1.0	1	0.6	0.8	2.7	2.1	2.5	5.3	5.3	8.1
Greater Glasgow	2.3	2.2	1.5	1.6	1.4	2.9	6.5	7.8	9.6	8.8	12.4
Highland	1.0	0.5	0	0	0.5	0.5	1.0	1.4	3.9	2.9	3.8
Lanarkshire	1.6	2.1	1.2	0.7	0.7	2.1	2.7	5.2	5.2	6.2	8.0
Lothian	2.0	1.3	1.3	1.6	1.9	2.8	4.5	4.2	3.8	5.5	3.9
Orkney	0	0	0	0	0	0	0	5.1	0	0	5.1
Shetland	0	4.5	0	0	0	8.9	0	0	0	0	4.3
Tayside	6.1	6.7	5.4	3.6	4.6	5.6	14.7	12.4	19.0	18.5	17.0
Western Isles	0	0	3.3	0	0	0	3.4	0	6.8	0	0

Table 2.9: Health Board of operation and hospital for the Scottish ISD-CEA cohort: 1981 - 1996.

Health board of operation	Hospital of operation	Frequency (%) per hospital	Total (%) per health board
Western Isles	Western Isles, Stornoway	4 (0.1)	4 (0.1)
Argyll and Clyde	Inverclyde, Royal, Greenock	6 (0.2)	6 (0.2)
Highlands	Raigmore	25 (0.9)	25 (0.9)
Lanarkshire	Monklands	26 (0.9)	26 (0.9)
Forth	Stirling Royal	9 (0.3)	33 (1.2)
	Falkirk and District	24 (0.8)	
Dumfries and Galloway	Dumfries and Galloway	66(2.2)	66 (2.2)
Ayrshire and Arran	Isle of Arran Memorial	1 (0.03)	171(5.9)
	Ayr Hospital	170 (5.9)	
Grampian	Aberdeen Royal Infirmary	195 (6.8)	195 (6.7)
"Lothian"	Western General, Edinburgh	4 (0.1)	4 (0.1)
	Royal Northern Infirmary	4 (0.1)	4 (0.1)
	Royal Infirmary, Edinburgh	456 (15.7)	464 (16)
Tayside	Dundee Royal Infirmary	116 (4.0)	709 (24.7)
	Ninewells	593 (20.5)	
Greater Glasgow	Southern General, Glasgow	37 (1.3)	1193(41.2)
	Stobhill	54 (1.9)	
	Gartnaval, Glasgow	284 (9.8)	
	Western, Infirmary	369 (12.8)	
	Glasgow Royal Infirmary	449 (15.5)	
Total		2892 (100)	2892

Table 2.10: Health Board of operation and hospital for the period 1981 - 1996 prior to and after publication of the randomised controlled trials.

Hospital of operation	1981 - 1991	1992	1993	1994	1995	1996	1992 - 1996	Total
Western Isles, Stornoway	1			3			3	4
Inverclyde, Royal, Greenock	-	-	-	-	-	6	6	6
Raigmore	4	2	3	4	5	7	21	25
Monklands	8	2	2	3	9	2	18	26
Stirling Royal				2	3	4	9	9
Falkirk and District	17	1		2	1	3	7	24
Dumfries and Galloway	13	9	11	12	9	12	53	66
Isle of Arran Memorial	1	-	-	-	-	-	0	1
Ayr Hospital	1	19	38	46	43	23	169	170
Aberdeen Royal Infirmary	70	12	12	30	27	44	125	195
Western General, Edinburgh	4	-	-	-	-	-	0	4
Royal Northern Infirmary	4	-	-	-	-	-	0	4
Royal Infirmary, Edinburgh	203	48	44	46	59	56	253	456
Dundee Royal Infirmary	70	16	12	5	8	5	46	116
Ninewells	273	47	45	78	78	72	320	593
Southern General, Glasgow	4	-	-	-	-	33	33	37
Stobhill	28	2	3	4	7	10	26	54
Gartnaval, Glasgow	161	67	56	-	-	-	123	284
Western, Infirmary	1		20	126	116	106	368	369
Glasgow Royal Infirmary	221	40	55	36	37	60	228	449

Table 2.11: The number of carotid endarterectomies in Scotland over the period 1992 – 1996 classified according to hospital volume

	Years					
Number of CEA in:	**1992**	**1993**	**1994**	**1995**	**1996**	**Total CEA (n)**
Low volume hospitals:	28	43	35	42	49	197(11%)
Medium volume hospitals:	170	147	158	107	100	682(38%)
High volume hospitals:	67	111	204	253	294	929 (51%)
Total CEA (n)	**265**	**301**	**397**	**402**	**443**	**1808**

*** low volume: 1-12 operations; medium volume:13 -49 operations; high volume > 50 operations**

Table 2.12: Length of hospital stay of ISD-CEA cohort: 1981 - 1996.

(Minimum, maximum, mean, standard deviation, and interquartile range.)

Length of hospital stay	1981-1985	1986-June '91	July '91 - 96	1981 -1996
Minimum	0	1	0	0
Maximum	533	582	357	582
Mean	10.4	11.6	6.4	7.98
IQR	5 - 10	5 - 9	3 - 7	4 - 8
Median	7	7	5	5

Table 2.13: Estimated cost (£) of carotid endarterectomy for the ISD-CEA cohort (1981 - 1996) based on the number of days hospitalised for carotid surgery.

	1981-1985	**1986 - June '91**	**July '91 – Dec 96**	**1981 -1996**
Mean (£)	3110	3448	1926	2396
Median (£)	2100	2100	1500	1500
IQR (£)	1500 – 3000	1500 - 2700	900 - 2100	1200 - 2400

Table 2.14: Subsequent cerebrovascular events (stroke and TIA) within 30 days of carotid surgery, all subsequent cerebrovascular events from date of surgery for the 16-year period of follow-up, the five-year period of follow-up and subsequent CEA.

Subsequent events after CEA	**1981-1985** *n = 536*	**1986-1991** *n = 476*	**1991-1996** *n = 1880*	**1981 - 1996** *n = 2892*
"Stroke" events				
0 days - 30 days	28(5.2%)	16(3.4%)	84(4.5%)	128(4.4%)
0 days - 16 years	215(40%)	132 (28%)	305(16%)	652(22.5%)
0 days - 5 years	144 (27%)	100 (21%)	301(16%)	545 (18.8%)
Subsequent CEA	97 (18%)	45 (9.5%)	117 (6%)	259 (9%)

Table 2.15: Survival tables for subsequent stroke events in the five years after carotid endarterectomy for the Scottish ISD-CEA cohort: 1981 - 1996.

Time	**1981 - 1985**		**1986 – June 1991**		**July 1991 –1997**	
Time months	*Cumulative survival*	*Number remain*	*Cumulative survival*	*Number remain*	*Cumulative survival*	*Number remain*
0	.9981	535	.9979	475	.9910	1863
6	.8489	455	.9076	432	.9133	1621
12	.8209	440	.8824	420	.8874	1379
18	.7948	426	.8592	409	.8702	1152
24	.7780	417	.8508	405	.8524	993
30	.7649[1]	410	.8382	399	.8354	811
36	**.7575[2]**	**406**	**.8256**	**393**	**.8175**	**626**
42	.7481	401	.8214	391	.8082	481
48	.7407	397	.8067	384	.8019	331
54	.7388[3]	396	.8025	382	.7869	200
60	.7313	392	.7899	375	.7819[4]	156

[1]25 months; [2] 38 months; [3] 56 months; [4]57 months

Table 2.16: Mean survival time with 95 % confidence intervals and standard error for the ISD-CEA cohort over the 16-year study period and for a five-year follow-up period.

	0 –16.3 years	0 - 5 years
1981 – 1985	***n= 536***	***n= 536***
Deaths (d)	***d = 345***	***d = 135***
Mean (95% C.I.)	9.78 (9.31-10.25)	4.35 (4.23 , 4.47)
Standard error	0.24	0.06
1986 – June 1996	***n = 476***	***n = 476***
Deaths (d)	***d = 198***	***d = 118***
Mean (95% C.I.)	9.92 (9.39 - 10.46)	4.39 (4.27, 4.51)
Standard error	0.27	0.06
July 91 – March 97	***n = 1880***	***n = 1880***
Deaths (d)	***d = 240***	***d = 231***
Mean (95% C.I.)	7.85 (7.41 - 8.30)	4.41 (4.34, 4.48)
Standard error	0.23	0.04
1985 – March 97	***n= 2982***	***n = 2982***
Deaths (d)	***d=783***	***d= 484***
Mean (95% C.I.)	9. 9 (9.6 - 10.2)	4.39 (4.34 - 4.44)
Standard error	0.3	0.03

Table 2.17: Mean survival time (years), 95 % confidence intervals and standard error for men and women in the ISD-CEA cohort: 1981 - 1996.

	Years of follow-up	
	0 - 16.3 years	**0 - 5 years**
All deaths (d)*	***d = 783***	***d = 484***
Males	***d= 489***	***d = 310***
Mean (95% C.I.)	9.6 (9.2 , 10.0)	4.34 (4.27, 4.41)
Standard Error	0.2	0.04
Females	***d = 294***	***D = 172***
Mean (95% C.I.)	10.3 (9.8, 10.8)	4.45 (4.37, 4,53)
Standard Error	0.2	0.04

d = deaths

Table 2.18: Mean survival time in years by age category for the Scottish ISD-CEA cohort over a five-year follow-up period.

Age category	Patients (n)	Deaths (d)	Mean survival (95% C.I.) (years)
<50 years	159	14	4.8 (4.65 - 4.92)
50 - 65 years	1413	208	4.5 (4.44 - 4.58)
66 -80 years	1268	245	4.2 (4.12 - 4.3)
> 80 years	52	17	3.2 (2.56 - 3.93)

Table 2.19: Survival tables for all cause mortality for the Scottish ISD-CEA cohort for the three periods: 1981 - 1996.

	1981 – 1985		**1986 - June 1991**		**July 1991 - March 1997**	
Time months	*Cumulative survival*	*Number remain*	*Cumulative survival*	*Number remain*	*Cumulative survival*	*Number remain*
0	0.9981	531	0.9979	466	.9979	1889
6	0.9474	504	0.9679	452	.9602	1727
12	0.9229	491	0.9465	442	.9428	1477
18	0.9117	485	0.9208	430	.9243	1226
24	0.8891	473	0.9015	421	.9034	1049
30	0.8722	464	0.8887	415	.8806	858
36	0.8477	451	0.8528	402	.8654	658
42	0.8289	441	0.8330	389	.8388	492
48	0.8083	430	0.8030	375	.8209	355
54	0.7838	417	0.7772	363	.7971	222
60	0.7462	397	0.7537	352	.7728	131

Figure 2.1: Age distribution in five-year intervals for the Scottish ISD-CEA study population (n = 2982;mean age = 64 years; Standard deviation = 8.71).

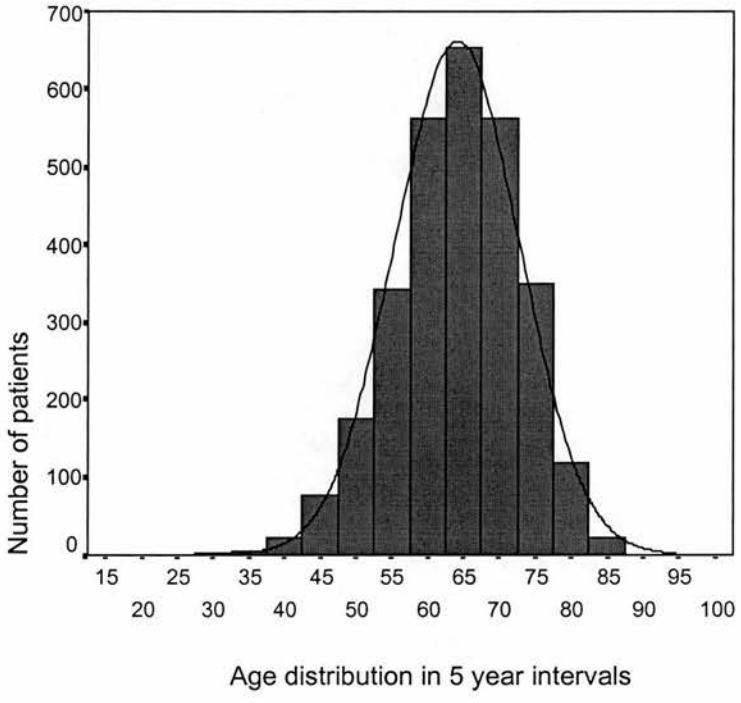


Figure 2.2: Number of carotid endarterectomies by gender in Scotland for the three study periods, 1981 -1996.

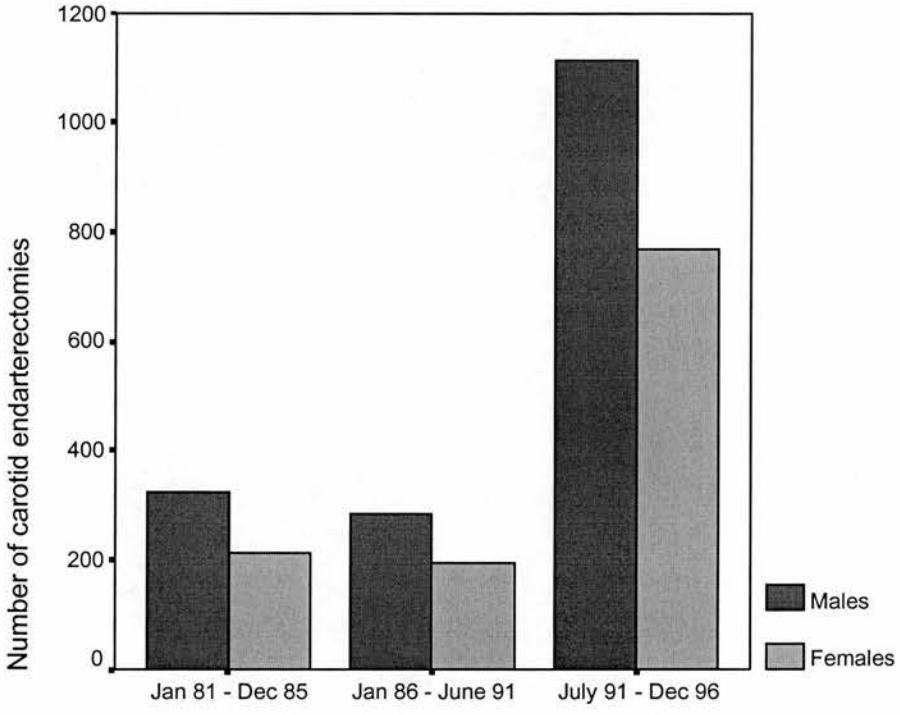


Figure 2.3: Number of carotid endarterectomies by year in Scotland: 1981 - 1996.

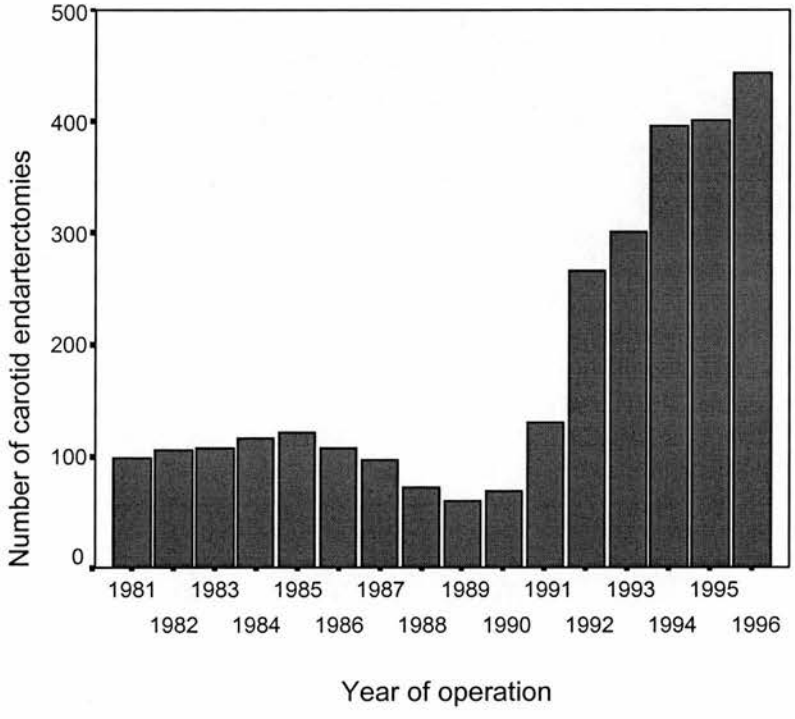


Figure 2.4: Carotid endarterectomies in Scotland by health board of residence: 1981 - 1996.

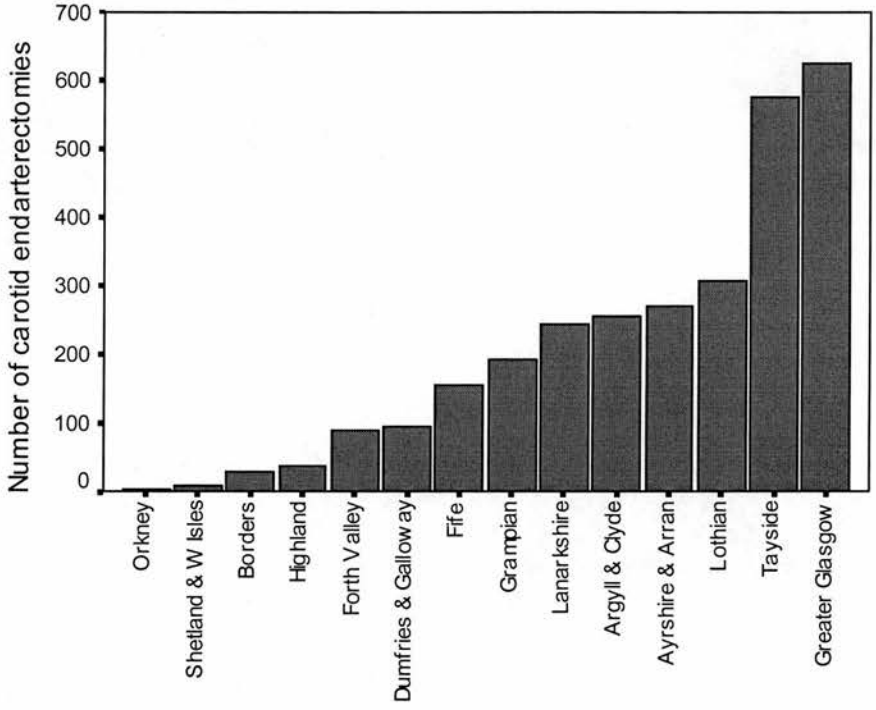


Figure 2.5: CEA rate per 100 000 in Scotland per health board of residence for the period 1986 - 1996.

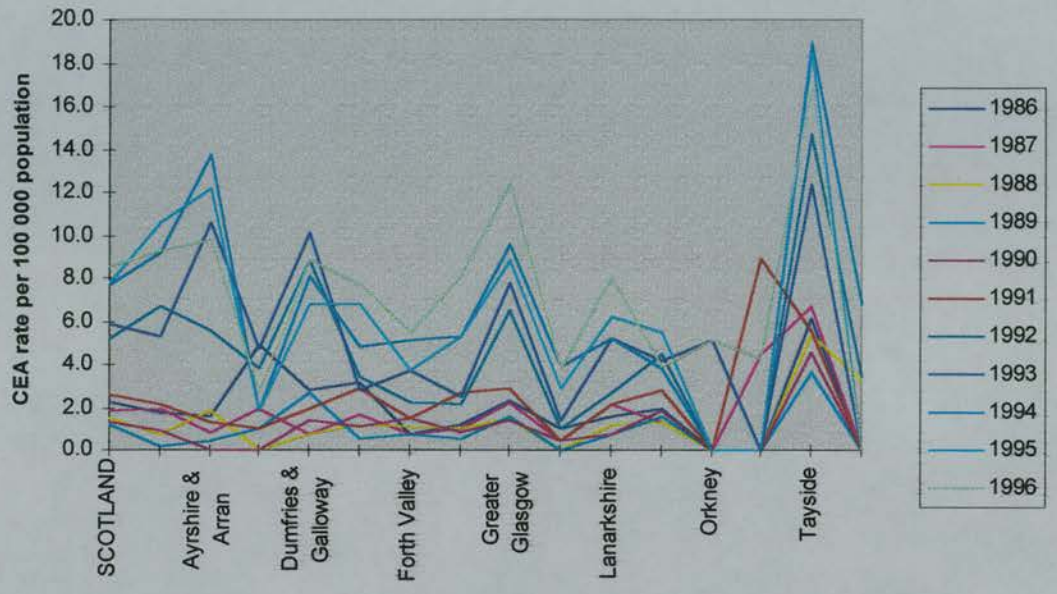


Figure 2.6: Carotid endarterectomies in Scotland by hospital: 1981- 1996.

(Western General Hospital and Royal Northern Infirmary illustrated together)

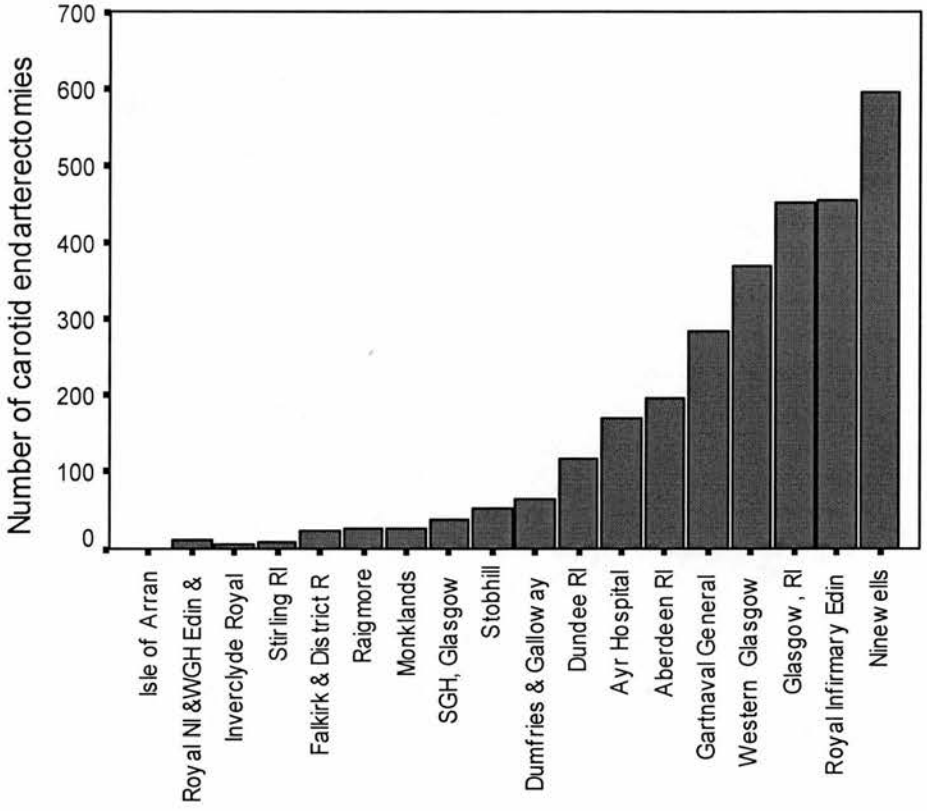


Figure 2.7: Carotid endarterectomy hospital volume (%) in Scotland for the 5 years (1992 - 1996) after the publication of the randomised controlled trials.

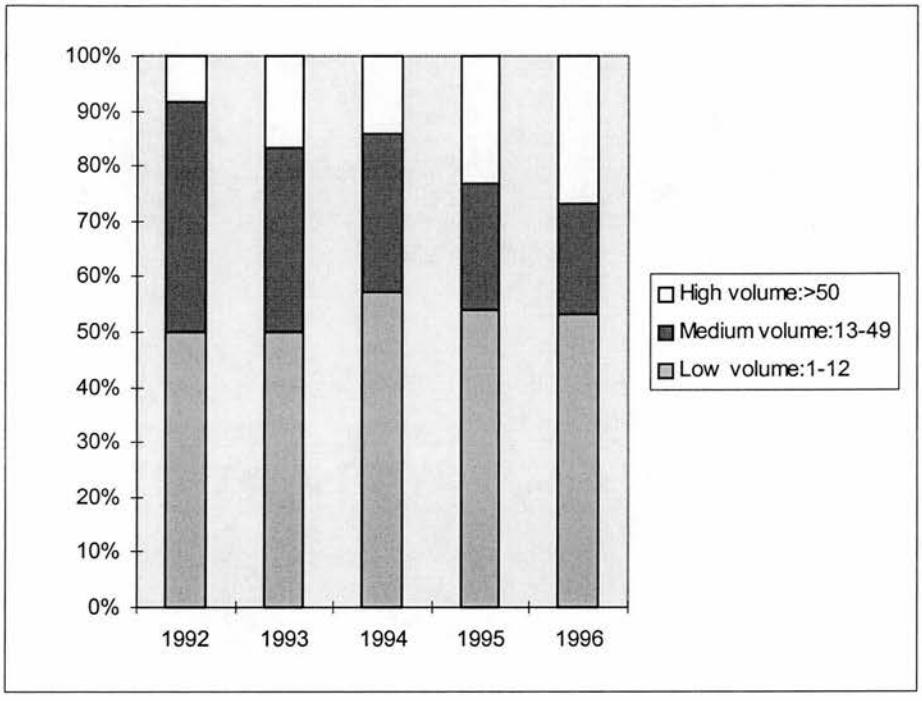


Figure 2.8: Hospital stay for the Scottish ISD-CEA study population over the 16-year period: 1981 - 1996.

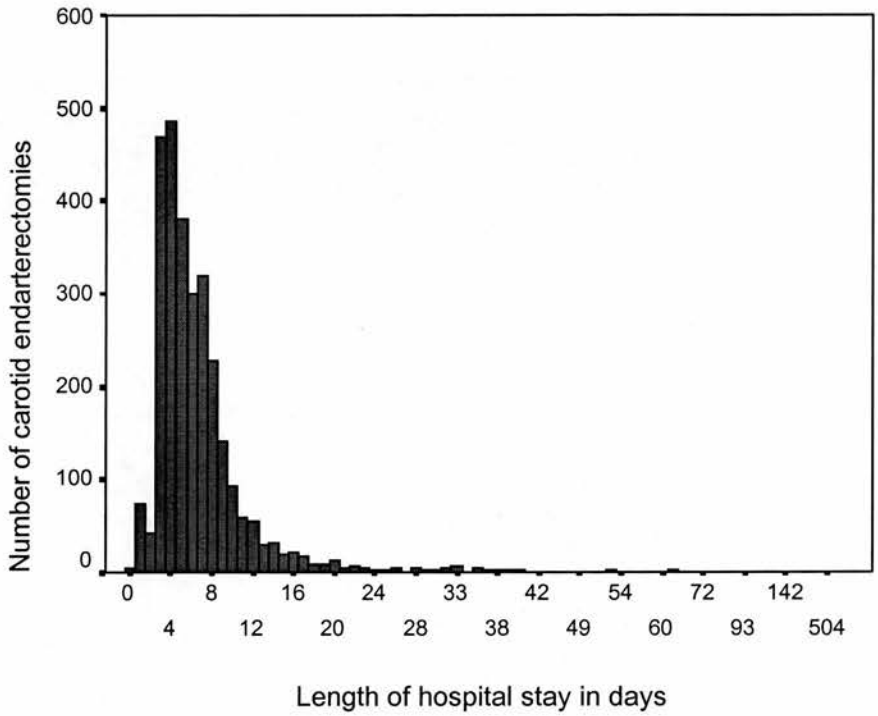


Figure 2.9: Kaplan-Meier five-year survival estimates for any subsequent stroke for the three time periods for the Scottish ISD-CEA cohort: 1981 - 1996.

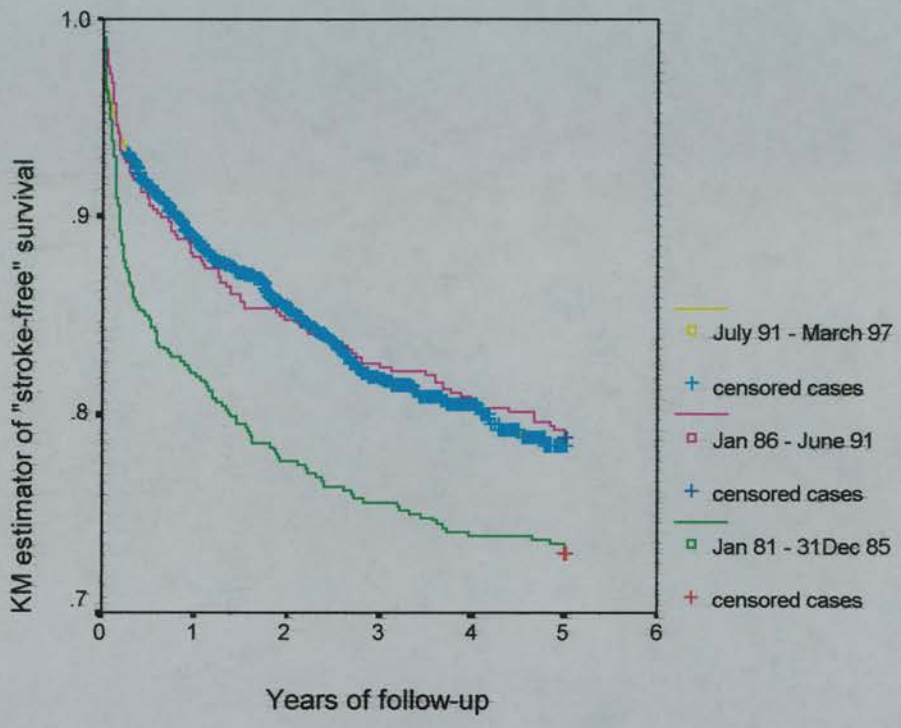


Figure 2.10: Kaplan-Meier five-year survival estimates for any subsequent stroke for males and females in the Scottish ISD-CEA cohort: 1981 - 1996.

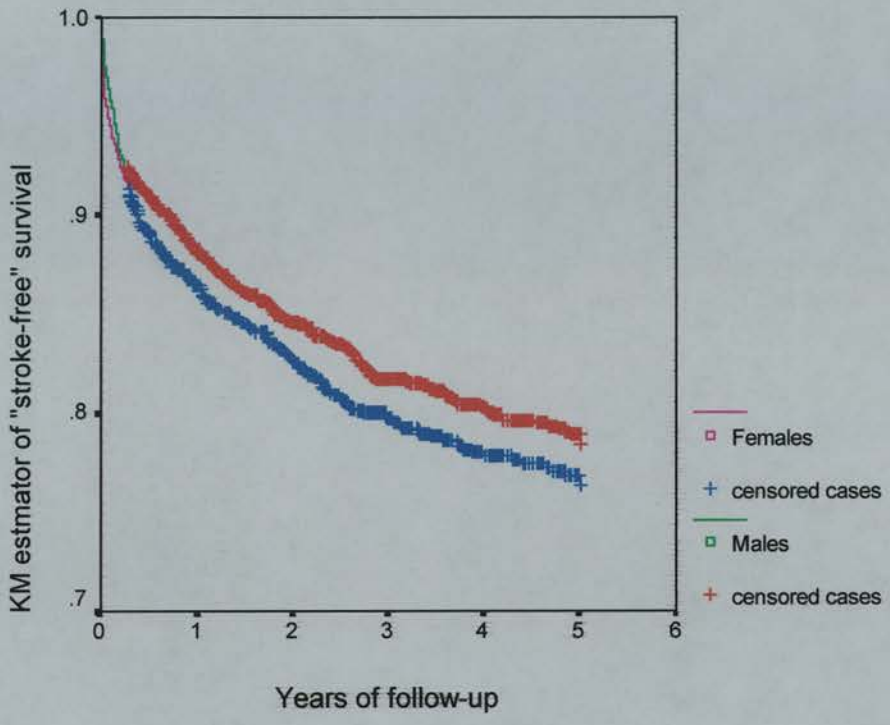


Figure 2.11: Kaplan-Meier five-year survival estimates for any subsequent stroke by age category for the Scottish ISD-CEA cohort: 1981 - 1996.

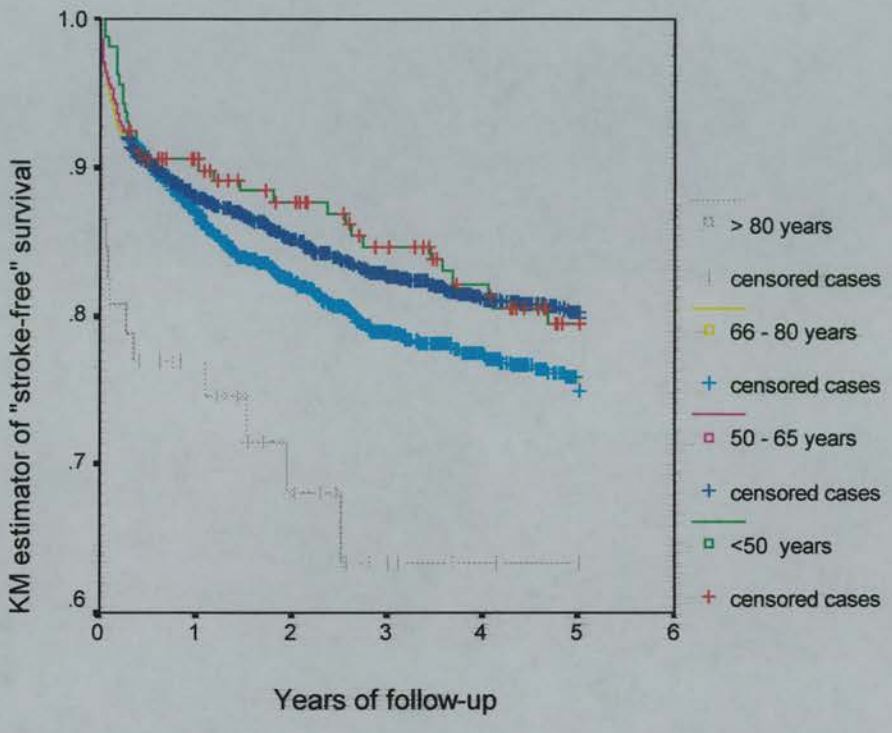
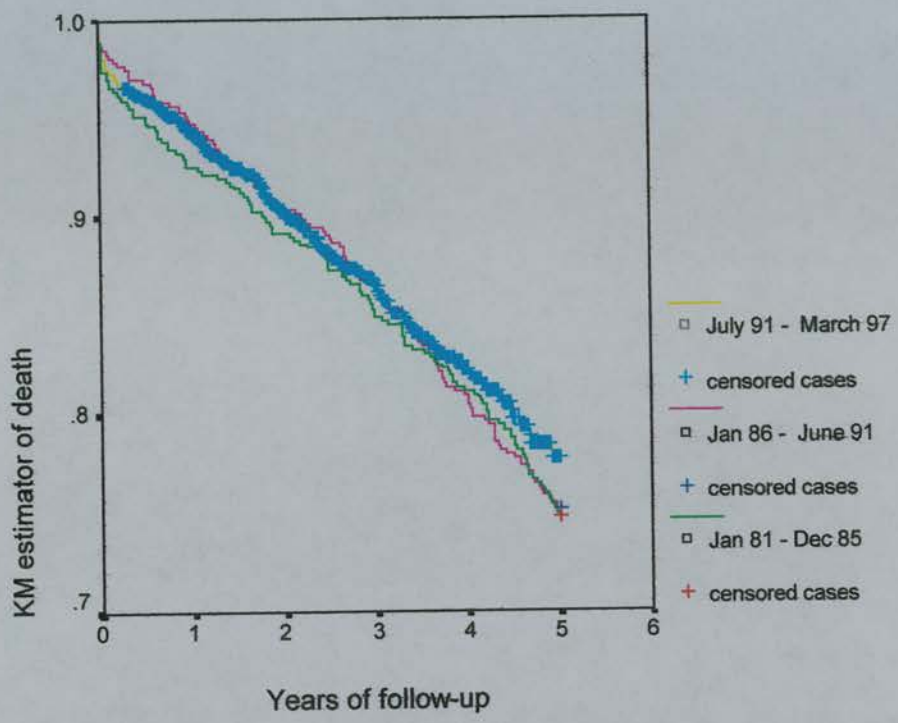
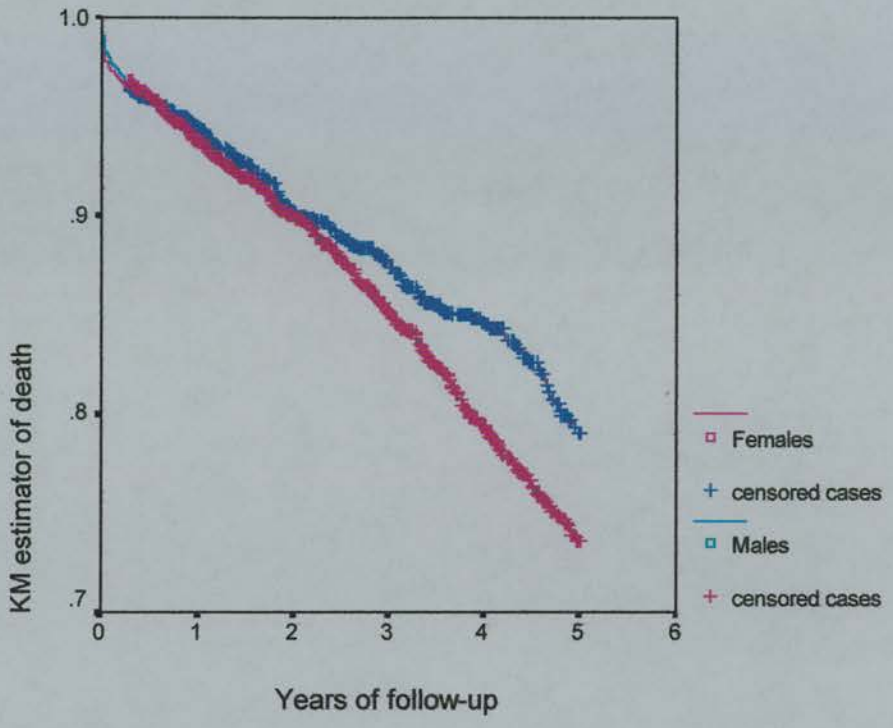


Figure 2.12: Kaplan-Meier five-year survival estimates of death from any cause for the three time periods for the Scottish ISD-CEA cohort: 1981 - 1996.



No at risk:	2892	2411	1943	1511	1161	880
No deaths:	8	169	262	340	414	484

Figure 2.13: Kaplan-Meier five-year survival estimates for death from any cause for males and females in the Scottish ISD-CEA cohort: 1981 - 1996.



Females:						
No at risk:	1171	984	793	615	482	366
No deaths:	2	64	105	126	145	172
Males:						
No at risk:	1798	1432	1150	899	688	498
No deaths:	2	105	157	213	268	312

Figure 2.14: Kaplan-Meier five-year survival estimates of death from any cause by age category for the Scottish ISD-CEA cohort: 1981 - 1996.

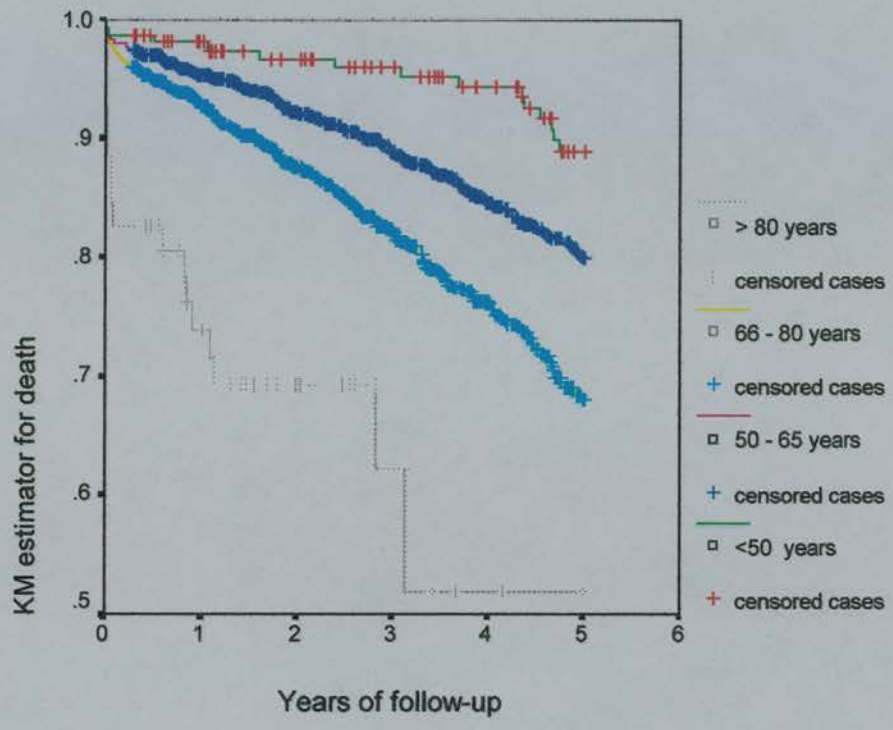
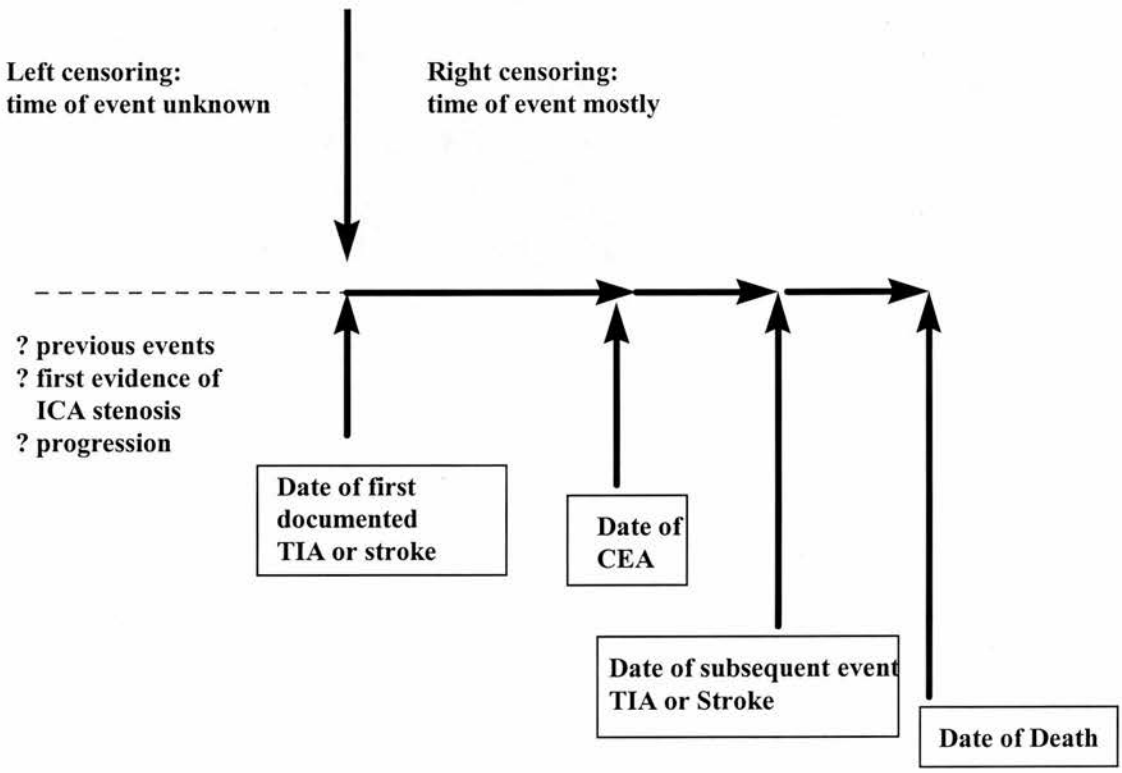


Figure 2.15: Schematic presentation of the effect of left and right censoring in the time-to-event analysis for carotid endarterectomy.



CHAPTER THREE: A SYSTEMATIC REVIEW OF THE LITERATURE EXAMINING THE COSTS AND BENEFITS OF CAROTID ENDARTERECTOMY AND THE ASSOCIATED PRE-OPERATIVE INVESTIGATIONS.

3.1 Introduction.

The systematic review of available literature on the proposed topic of investigation is regarded by some as secondary research and not a very exciting activity. This however constitutes an important and necessary element of any research project and may not be neglected (Greenhalgh, 1997). A systematic review constitutes an overview of primary studies that used explicit and reproducible methods. A meta-analyis on the other hand is a mathematical synthesis of the result of two or more primary studies addressing the same hypothesis (Greenhalgh, 1997). As this review is a systematic review and not a meta-analysis no attempt will be made to weight the different studies or synthesise the results mathematically. In order to present this review in a more interesting manner I assessed and discussed the studies identified in the literature on the resource implications of carotid endarterectomy and the pre-operative investigations prior to carotid endarterectomy using a set of recommended guidelines for the review of economic submissions to journals.

Costs and consequences are the essential components of any economic evaluation, irrespective of the activities of interest. These two components each need to be addressed when studies on economic evaluations are assessed and two key questions need to be answered: Is there a comparison between two or more alternatives? and

are both the costs (inputs) and consequences (outputs) of the alternatives examined? The consequences of carotid endarterectomy have been assessed in two large randomised controlled trials (European Carotid Surgery Trialists' Collaborative Group, (ECST) 1991; North American Symptomatic Carotid Endarterectomy Trial (NASCET) Steering Committee, 1991). There is conclusive evidence that carotid endarterectomy reduces the risk of stroke in symptomatic patients with more than 70% stenosis of the internal carotid artery. The cost implications of this procedure however, have not yet been satisfactorily addressed. Since the health care environment has become much more cost conscious in the last decades and is moving more and more into settings with limited resources, there is an increasing interest in the application of economics to this intervention.

The essential elements of economic evaluations were listed as far back as 1974 by Williams. More recently Drummond et al created a structure which captures all the important and relevant methodological criteria for assessing economic studies (1997). Drummond and Jefferson on behalf of the British Medical Journal Economic Evaluation Working party also produced a set of guidelines for the evaluation of "economic submissions", a "checklist" for use by referees, authors and editors (Drummond and Jefferson, 1996; Drummond, 1985).

Eastcott and colleagues in London introduced carotid endarterectomy, or rather carotid reconstruction for symptomatic cerebrovascular disease in 1953 (Eastcott et al., 1954). Since then, five randomised controlled trials (RCTs) of carotid endarterectomy for patients with symptomatic carotid stenosis have been conducted. Two of these trials (Fields et al., 1970; Shaw et al., 1984) were launched in the 1960s, but neither demonstrated any benefit for this procedure. The number of

carotid endarterectomies nevertheless escalated, and many inappropriate endarterectomies were performed generating concerns both in Europe and North America, resulting in three larger RCTs being set up: The European Carotid Surgery Trial (ECST) in 1981, the Veterans Affairs Co-operative Studies program (VACS) in 1986 and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) in 1987. Patients in these trials were randomised to carotid surgery in addition to best medical treatment versus best medical treatment alone. Medical treatment included the control of modifiable vascular risk factors such as hypertension, (Collins et al., 1990) and advice to stop smoking (Shinton and Beevers 1989). The risk of stroke in patients with symptomatic carotid stenosis can also be reduced by long term antiplatelet therapy such as aspirin or ticlopidine (UK-TIA study group, 1991; Hass et al., 1989).

The ECST and NASCET trials demonstrated carotid endarterectomy to have a definite and statistically significant benefit in terms of stroke risk reduction to individuals with transient ischaemic events and mild ischaemic stroke originating from the carotid artery territory. The VACS Study was terminated prematurely when the results from ECST and NASCET became available (Hobson et al., 1993).

The cost-effectiveness of carotid endarterectomy (CEA), however, has not been critically and extensively assessed. A recent systematic review of the cost-effectiveness research of stroke evaluation and treatment identified only modelling studies assessing cost-effectiveness and expressed concern about the divergent conclusions drawn from studies addressing similar questions (Holloway et al.,

1999). Holloway et al suggested that it might be premature to use results from current cost-effectiveness research in policy and practice guidelines.

In order to perform cost-effectiveness analysis the cost of the procedure must be compared with the cost of medical treatment and related to the effectiveness gains of the respective alternatives. Many studies have been performed to determine the cost of carotid endarterectomy. Comprehensive assessment of the cost of medical care as an alternative to carotid endarterectomy has not been undertaken. Most studies refer only to the cost of antiplatelet therapy and do not consider the cost of regular visits or the cost of managing adverse effects such as gastrointestinal haemorrhage (Oster et al., 1994). Though a number of studies were identified in the literature, addressing the costs and cost-effectiveness of the CEA and the associated pre-operative investigations, the requirements for a proper economic evaluation of the procedure or associated investigations are not satisfied by any of them.

3.2 Methodology.

3.2.1 Objective

The objective of this systematic review was:

- to critically appraise the studies identified in the literature addressing the economic implications of carotid endarterectomy and the pre-operative investigations in symptomatic and asymptomatic persons with carotid stenosis prior to carotid endarterectomy and
- to discuss any implications for future research.

3.2.2 Inclusion and exclusion criteria

I sought to identify all published studies assessing the cost implications of carotid endarterectomy and studies assessing the cost implications of preoperative investigation modalities for carotid stenosis in both symptomatic and asymptomatic patients. I excluded all carotid endarterectomy studies and preoperative imaging investigation studies for carotid stenosis not concerned with cost or economic evaluation. I excluded all studies not in the English language.

3.2.3 Search strategy

A systematic search strategy was developed to identify research papers specifically related to the evaluation of the costs and benefits of carotid endarterectomy and of the preoperative investigations associated with carotid surgery (Appendix 1). In developing a search strategy, the Cochrane Stroke Group MEDLINE search strategy was examined for possible use to identify studies related to the costs and benefits of carotid endarterectomy. This search strategy has as its main objective the identification of stroke related studies and although used in one of the preliminary searches, was found to generate many inappropriate studies to the proposed review. A novel search strategy was developed to detect possible studies for the review.

The following databases were searched: 1) electronic searches of MEDLINE, (1966 - 1997) EMBASE (1974 - 1997) and BIOSIS (1982 - 1997); 2) reference lists from relevant studies and reviews; 3) personal communications with experts in this field.

A total of 381 papers concerned with cost issues were identified in Medline using the electronic search strategy for the period 1966 to 1997 Of the 381 potential papers

only 37 were considered relevant to the research question. To identify the 37 most appropriate papers the titles, abstracts and keywords of the 381 potential papers were searched for specific words. The following words were used in truncated form: cost; cost-effectiveness; economic; carotid surgery; carotid endarterectomy; carotid stenosis. Of the 37 papers identified for further evaluation 30 out of 213 possible studies were published during the period 1993 to 1997 and seven of 90 possible studies during 1984 to 1992. For the period 1966 to 1986, a total of 78 possible studies were identified, but none of them were considered relevant for purpose of this review. (For the years 1981 –1986: 65 studies, for 1976 – 1980: 11 studies and for 1966 – 1975 only two studies).

Searching EMBASE yielded 432 possible studies for the period 1980 to 1998 with a total of 27 papers relevant to the systematic review. The search of EMBASE did not identify additional studies not already identified using the MEDLINE database.

A hand search of journals was not undertaken, hence sensitivity and specificity of the electronic searching was not performed.

3.2.4 Methodological quality

Published studies were identified and assessed, and a decision made whether to include or exclude a specific study. The characteristics of each study collected, included: 1) type of study (randomised controlled trial, observational or modelling); 2) study design (prospective or retrospective); 3) study method; (partial or full economic evaluation); 4) study objective 5) study population (size, age and gender);

6) cost elements (costs or charges); 7) study centre (United Kingdom, Europe, or USA)

The methods used to critically appraise these studies followed the guidelines for an economic evaluation proposed by Drummond and Jefferson. These guidelines address ten distinct aspects which were discussed under three separate headings: 1) *study design* including the study question, the selection of alternatives and the form of evaluation applied, 2) *data collection* incorporating effectiveness data, benefit measurement and valuation, costing and modelling, and 3) *analysis and interpretation of results* which encompass the adjustments for timing of costs and benefits, allowing for uncertainty and the presentation of results. I applied this "check-list" by Drummond and Jefferson to the studies concerned with the resource implications for diagnostic modalities in selecting patients for carotid surgery patients as identified in the literature (Appendix 2).

3.2.5 Outcome measures:

I defined the following outcomes I would consider relevant for the purpose of this review:

i. *For carotid endarterectomy*

1) Cost per life-year gained, 2) incremental cost-effectiveness ratios and 3) cost per carotid endarterectomy.

ii. For pre-operative investigations prior to carotid endarterectomy

1) Number of cases with internal carotid stenosis of ≥ 70% detected, and

2) The cost of the imaging procedure to identify these cases suitable for carotid endarterectomy.

3.3 Results

For the purpose of this review a brief description of the characteristics of the published studies will be given. This is followed by a brief description of the requirements of each of the ten criteria, against which these studies were assessed, before discussing the results of the individual studies.

3.3.1 Studies assessing the cost consequences of carotid endarterectomy.

3.3.1.1 Study characteristics

A total of twenty-three reports, addressing the economic implications of carotid endarterectomy, were identified in the literature over a 30-year search period *(Figure 3.1).* Twenty of these were published studies of which three were miscellaneous publications, (a cost management algorithm (Ricotta et al., 1998), a short report (Baird, 1995), and one letter (Mead, 1995)) *(Table 3.1).* Eighteen of these studies were published studies and were identified using MEDLINE, EMBASE and BIOSIS databases. The remaining two studies were unpublished reports. All the studies identified were however conducted and reported on during the last 10 years. These studies were divided into full and partial economic evaluations. The full economic evaluation being studies assessing the cost and benefits of CEA and the partial economic evaluation referred to studies assessing only the cost of CEA.

Of the twenty studies, (18 published and 2 unpublished), three (Cronenwett et al., 1997; Kuntz et al., 1996; Nussbaum et al., 1996) were full economic evaluations, which used modelling techniques based on published RCT data and one (Lavender et al., 1998) applied cost data to their model to assess the effectiveness of CEA. The remaining sixteen studies (Smurawska et al., 1998; Back et al., 1997; Mellisano et al., 1997; Garrard et al., 1997; Dardik et al., 1997; Ballard et al., 1997; Pollard et al., 1997; Smithies et al., 1996 (unpublished); Hirko et al., 1996; Ammar, 1996; Kriass et al., 1995; Luna et al., 1995; Patel et al., 1995; Radestock 1992 (unpublished); Maini et al., 1990; Green et al., 1987) were partial economic evaluations using retrospective observational data for their research. Three of the studies (Back et al., 1997; Mellisano et al., 1997; Ammar, 1996) used a combination of retro-and prospective observational data. None of these studies were randomised controlled trials.

a) Type of study.

Cost-effectiveness analysis: modelling studies:

Three of the studies (Cronenwett et al., 1997; Kuntz et al., 1996; Nussbaum et al., 1996) applied Markov modelling techniques based on published randomised controlled trial data to perform cost-effectiveness analyses. The modelling study by Lavender used SIMULA simulation language to perform an effectiveness analysis. The study by Kuntz considered symptomatic and asymptomatic populations, two studies (Lavender et al., 1998; Nussbaum et al., 1996) considered symptomatic

populations, and one (Cronenwett et al., 1997) considered an asymptomatic population only.

Retrospective cost analysis and cost description studies.

Eight studies (Back et al., 1997; Mellisano et al., 1997; Garrard et al., 1997; Dardik et al., 1997; Ballard et al., 1997; Pollard et al., 1997; Ammar, 1996; Kraiss et al., 1995) were retrospective studies, using observational data to compare alternatives in their cost analyses. Eight (six published and 2 unpublished) of the studies (Smurawska et al., 1998; Smithies et al., 1997; Hirko et al., 1996; Luna et al., 1995; Patel et al., 1996; Radestock 1992; Maini et al., 1990; Green et al., 1987) were cost description studies. In the majority of the retrospective studies, symptomatic as well as asymptomatic patients were considered. The published studies by Patel, Pollard, Kraiss, the unpublished reports by Smithies and Radestock and the short report (Baird) did not describe their study populations in terms of being symptomatic and/or asymptomatic. The smallest percentage of asymptomatic patients assessed was 14% in one study (Maini et al., 1990) and 53% was the largest proportion of asymptomatic patients (Back et al., 1997) in studies with both symptomatic and asymptomatic patients. The average proportion of asymptomatic patients assessed in all these studies was 32%.

One study (Ricotta et al., 1998) investigated global pricing and capitation models as cost management strategies for carotid endarterectomy. Although the authors referred to the unit costs of the CEA procedure as well as charges associated with the pre-operative diagnostic testing, this study was not critically assessed and is not discussed in this review.

b) Study length.

The shortest study period was 12 months in three (Garrard et al., 1997; Ammar, 1996; Green et al., 1987) of the sixteen CEA cost studies. One of these three studies (Ammar, 1996) being a prospective study. The study of Maini (1990) having the longest study period was a retrospective review of case notes over a 10-year period. The mean length of the study period for all the studies was 39.2 months.

c) Size of studies.

The maximum number of patients was 343 reported from Italy in a prospective study (Melissano et al., 1997). The minimum number was 49 cases in a retrospective review of patient notes from the Department of Vascular Surgery, Royal North Shore Hospital Sydney, Australia (Patel et al., 1995). The mean number of cases in these studies was 168. Only one study (Nussbaum et al., 1996), applying modelling techniques, described the number of patients used in the modelling; three groups with 100 patients in each of the hypothetical groups.

d) Age and sex distribution.

The mean age of the patients in these studies was 68 years with the youngest study population having a mean age of 64.5 (Nussbaum et al., 1996) and the study population with the oldest mean age being 76 years (Ammar, 1996). The study populations were predominantly male, (70%), with only one study (Ballard et al., 1997), a retrospective review of case notes of symptomatic and asymptomatic patients, having almost equal numbers of male (53.1%) and female patients. All but

three of the published studies were reported from the United States of America. The three exceptions included one study from the United Kingdom (Lavender 1998), one from Northern Italy (Melissano et al., 1997), and one from Australia (Patel et al., 1995). The two unpublished reports (Smithies et al., 1997; Radestock 1992) were both from the United Kingdom.

3.3.1.2 Study design

The study design includes the (a) study question, (b) the selection of alternatives and (c) the form of evaluation applied.

a) Study question

The question should be economically important in terms of its resource implications and should be phrased in such a way that considers both the costs and consequences of the alternative treatment(s), service(s) or programme(s). The question should clearly state and justify the viewpoint for the evaluation.

Cost-effectiveness analysis: modelling studies:

Only two papers (Cronenwett et al., 1997; Kuntz et al., 1996) formulated satisfactory research questions addressing the three elements needed for economic studies described by Drummond and Jefferson. Their research questions assessed both the costs and consequences of two alternatives, medical therapy versus carotid endarterectomy. Though the economic importance in terms of the resource implications of the relevant choices was not explicit in their questions this was discussed in the introduction sections of the papers. Their questions were framed

against the background of NASCET and ACAS (Executive Committee of the Asymptomatic Carotid Atherosclerosis Study, 1995), which showed significant risk reductions for carotid endarterectomy, but did not consider the cost-effectiveness of carotid endarterectomy.

The study question by Nussbaum and others (1996) was considered reasonable, though not clearly formulated and the research objective was not immediately apparent. In assessing the paper the research objective was forthcoming in the phrase: "we evaluated the long term, societal cost-benefit ratio of carotid endarterectomy using a decision analysis model". These three modelling studies assessed the lifetime cost of patients treated with CEA or best medical care. The primary objective of the study by Lavender and others was not to evaluate the cost-effectiveness of CEA and the research question in terms of an economic assessment was not relevant.

Retrospective cost analysis studies. (Comparing cost of alternatives)

Eight studies (Back et al., 1997; Pollard et al., 1997; Melissano et al., 1997; Garrard et al., 1997; Dardik et al., 1997; Ballard et al., 1997; Ammar, 1996; Kraiss et al., 1995) were primarily concerned with methods or alternatives to reduce the cost of carotid endarterectomy. Only the research question by Kraiss in these eight studies was regarded as satisfactory. The research questions in remaining seven studies (Back et al., 1997; Pollard et al., 1997; Melissano et al., 1997; Garrard et al., 1997; Dardik et al., 1997; Ballard et al., 1997; Ammar, 1996) were considered reasonable in terms of economic evaluation since two of the elements required for a well formulated question were considered.

Retrospective cost description studies (Describing only the cost of the procedure).

Published studies.

Six studies (Smurawska et al., 1998; Hirko et al., 1996; Luna et al., 1995; Patel et al., 1995; Maini et al., 1990; Green et al., 1987) described the cost of the procedure. Three studies (Smurawska et al., 1998; Hirko et al., 1996; Maini et al., 1990) described the cost of carotid endarterectomy over time and how it has changed due to changes in management. Of the six *cost description studies* (Smurawska et al., 1998; Hirko et al., 1996; Luna et al., 1995; Patel et al., 1995; Maini et al., 1990; Green et al., 1987) ***only two*** (Maini et al., 1990; Green et al., 1987) formulated satisfactory questions. The research questions in the other four studies were reasonable. Two studies compared the cost of carotid endarterectomy between institutions (Luna et al., 1995; Green et al., 1987).

Unpublished studies.

The research questions in the unpublished reports (Smithies et al., 1997; Radestock 1992) were considered reasonable since two of the three elements for a proper question were addressed.

b) The selection of competing alternatives.

The rationale for the choice of the alternatives should be given and also whether a "do-nothing" alternative was considered. The alternative interventions should be properly described, i. e. *Who did what, to whom, where and how often?*

Cost-effectiveness analysis: modelling studies:

The alternatives in the modelling studies (Lavender et al., 1998; Cronenwett et al., 1997; Kuntz et al., 1996; Nussbaum et al., 1996) were carotid surgery versus medical treatment. Nussbaum also considered a *do-nothing* alternative.

Cost analysis studies.

The alternatives were sufficiently described in all eight studies concerned with methods to reduce costs by comparing conventional protocols with alternative protocols (Back et al., 1997; Pollard et al., 1997; Melissano et al., 1997; Garrard et al., 1997; Dardik et al., 1997; Ballard et al., 1997; Ammar, 1996; Kraiss et al., 1995). The alternative protocol allows only duplex investigation preoperatively, preoperative work-up on an outpatient basis, same day admission, regional anaesthesia, and selective admission to intensive care units and early hospital discharge. Angiography was only to be performed selectively in cases where duplex results were inconclusive. The rationale for the choices was explained and justification given for their inclusion in the relevant studies.

Cost description studies.

Alternatives were not discussed in the six cost description studies (Smurawska et al., 1998; Hirko et al., 1996; Luna et al., 1995; Patel et al., 1995; Maini et al., 1990; Green et al., 1987). The elements responsible for the change in practice over time and their associated influence on the costs were referred to in these studies.

Both the unpublished studies (Smithies et al., 1997; Radestock, 1992) did not refer to the alternatives that would be investigated. These studies, although having the word cost-effectiveness in the title, were not considered to be cost-effectiveness analyses

but were more in line with cost-outcome description studies. Though the investigators set out to produce cost-effectiveness analyses, the essential principles were ignored. No reference to a cost-effectiveness ratio was made in either of these studies. These reports did not discuss alternatives to be compared and did not mention alternatives in terms of their observational data though used the effectiveness data from the RCT published studies in their analyses. The Newcastle study (Radestock, 1992) referred to alternative stroke prevention strategies by discussing the cost of hypertension treatment and the cost of screening for hypertension. The study from Wessex (Smithies et al., 1997), in addition to the cost per stroke prevented by treating hypertension, also referred to the cost per stroke prevented with aspirin treatment, treatment of hypercholesterolaemia and the number of persons who need to stop smoking, based on the literature.

c) Form of Evaluation

The forms of evaluation should be stated i.e. cost minimisation, cost effectiveness, cost benefit and cost utility analysis. *"Is it worth achieving this goal?"* for cost benefit analyses and *"What is the most efficient way of spending a given budget?"* when assessing cost minimisation and cost effectiveness studies. Cost-effectiveness analysis can for all practical purposes be one of two types. In the first instance, the health effects of the alternatives are known to be equal and therefore only the costs need to be analysed. The least costly alternative is the most efficient and this is often referred to as cost-minimisation analysis. When the alternatives may differ in both

cost and effect, a cost-effectiveness ratio (cost per unit of health effect) needs to be calculated for each.

The three modelling studies (Cronenwett et al., 1997; Kuntz et al., 1996; Nussbaum et al., 1996) applied cost-*effectiveness analyses* and estimated the "lifetime cost" of CEA. Cost analysis and cost description analysis were used in all the other studies. The unpublished studies (Smithies et al., 1997; Radestock, 1992) were cost-outcome description studies. The cost description studies (Smurawska et al., 1998; Hirko et al., 1996; Luna et al., 1995; Patel et al., 1995; Maini et al., 1990; Green et al., 1987) *described the use of resources for carotid endarterectomy.* These studies were mainly concerned with the direct costs of the procedure. The group of studies (Back et al., 1997; Dardik et al., 1997; Melissano et al., 1997; Garrard et al., 1997; Ballard et al., 1997; Pollard et al., 1997; Ammar, 1996; Kraiss et al., 1995) concerned with methods or alternatives to reduce the cost of carotid endarterectomy can be classified as *cost analysis studies* and not cost minimisation studies. Since the outcome of the procedure using different clinical pathways has not been established yet.

Of the eighteen studies concerned with the cost of carotid endarterectomy, eleven had the word *cost-effectiveness* in the title or in the abstract, but only in four were the basic principles of a cost-effectiveness analysis applied. However, as pointed out by Drummond et al, the distinction between *cost-effectiveness, cost-benefit and cost-utility analyses* are often made purely for instructional or academic reasons, and the distinctions in real life are often blurred.

The "modelling" study by Lavender et al can not be regarded as a "true" cost-effectiveness analysis, since the computer simulation techniques were applied to

estimate the effectiveness of CEA in the first place and not the cost implications. The investigators however acknowledged the importance to include costs in the development of a model assessing the effectiveness of CEA and "investigated" the cost-effectiveness of CEA in their discussion (Lavender et al., 1998).

Six of these eighteen studies (Mellisano et al., 1997; Back et al., 1997; Ballard et al., 1997; Ammar, 1996; Luna et al., 1995; Kraiss et al., 1995) with cost-effectiveness in the title or abstract could not be regarded as either cost-effectiveness, cost-benefit or cost-utility analyses. Eight studies (Mellisano et al., 1997; Back et al., 1997; Ballard et al., 1997; Garrard et al., 1997; Pollard et al., 1997; Dardik et al., 1997; Ammar, 1996; Kraiss et al., 1995) are considered cost analysis studies. Eight studies (Smurawska et al., 1998; Smithies et al., 1997; Hirko et al., 1996; Luna et al., 1995; Patel et al., 1995; Radestock, 1992; Maini et al., 1990; Green et al., 1987) were retrospective and concerned primarily with the description of just the costs of carotid endarterectomy. The study by Pollard et al requires some clarification since this is a study not primarily concerned with carotid endarterectomy but with the cost-savings resulting from same-day admissions for two "comparable" procedures i.e. lower extremity revascularisation and carotid endarterectomy. This study is thus different from all the other studies where carotid endarterectomy was the procedure of main interest.

3.3.1.3 Data collection

The data collection incorporates the elements: 1) Effectiveness data; 2) Benefit measurement and validation; 3) Costing and 4) Modelling.

a) Effectiveness data

Details of the design and the results of the study from where the effectiveness data were obtained and which are to be used in the economic evaluation should be given. It should state clearly whether the effectiveness data were from the results of a single study or from a meta-analysis. The gold standard for assessing the efficacy of interventions is the randomised double blind controlled trial, which has the highest internal validity and is most free from bias. Failing the gold standard an overview of clinical studies for establishing effectiveness or observational data or modelling techniques can be used. Generalisability of the study population is important in assessing the results, as is the transferability of the findings.

Cost-effectiveness analysis: modelling studies:

The results from the randomised controlled trials, the NASCET (North American Symptomatic Carotid Endarterectomy Trial Steering Committee, 1991) and ACAS (Executive Committee of the Asymptomatic Carotid Atherosclerosis Study, 1995) were applied as the effectiveness data in the three studies (Cronenwett et al., 1997; Kuntz et al., 1996; Nussbaum et al., 1996) using modelling techniques to assess the cost-effectiveness of carotid endarterectomy. Since the cost-effectiveness of CEA was not formally assessed by Lavender, this study will not be assessed with the other modelling studies.

The effectiveness measure applied in these studies is defined as "stroke-free" life years after CEA. A "stroke-free" life year is defined as surviving "stroke-free" for a total period of two years (NASCET), three years (ECST) and five years (ACAS) after successful carotid surgery.

Kuntz evaluated symptomatic and asymptomatic populations, Cronenwett evaluated an asymptomatic population and Nussbaum evaluated a symptomatic population. Nussbaum et al also used observational data in addition to published data in their modelling study. Kuntz and Cronenwett did not specify the sizes of their hypothetical cohorts. Nussbaum reviewed the results of 150 carotid endarterectomies performed at an academic centre and applied a Markov model comparing three cohorts of patients, each with 100 subjects, who had experienced transient ischaemic attack. One cohort was observed, one cohort received aspirin therapy and the third cohort had carotid surgery.

Cost analysis and cost description studies.

The remaining sixteen studies were observational cost analysis and cost description studies (*Published:* Smurawska et al., 1998; Back et al., 1997; Dardik et al., 1997; Melissano et al., 1997; Garrard et al., 1997; Pollard et al., 1997; Ballard et al., 1997; Ammar, 1996; Hirko et al., 1996; Patel et al., 1995; Luna et al., 1995; Kriass et al., 1995; Maini et al., 1990; Green et al., 1987; *Unpublished:* Smithies et al., 1997; Radestock, 1992).

b) Benefit measurement and valuation

Primary outcome measures for the economic evaluation should be clearly stated, i.e. cases detected, life-years gained or cost-effectiveness ratios in the case of carotid endarterectomy. Details should be given of the methods used to value health benefits. These methods include time-trade off and standard gamble. It is also important that the subjects from whom valuations were obtained should be stated, for example

patients, members of the general public, or health professionals. Since measuring preferences for health outcomes as described above is a very time consuming and complex task, pre-scored multi-attribute health-status classification systems are preferred. Benefits are measured in natural units such as life-years gained, mmHg reduction in hypertension control *in cost-effectiveness analysis*, in monetary units in *cost-benefit analysis* and in healthy years or quality adjusted health years in cost-utility analysis. The use of an overall ratio or index e.g. cost-effectiveness ratio (i.e. the difference in costs divided by the difference in life-years) is the preferred and accepted manner to report cost-effectiveness analysis.

Cost-effectiveness analysis: modelling studies.

Only the modelling studies by Kent, Nussbaum and Cronenwett referred to benefit measurements. Kent et al and Cronenwett calculated cost-effectiveness as the "incremental cost of surgery per quality adjusted life year gained" when compared with medical treatment. Nussbaum and Kent expressed the lifetime cost in terms of "quality adjusted life expectancy". The outcome measures in the unpublished reports were the estimated cost per stroke prevented.

c) Costing.

Costing involves the estimation of resources used. Unit costs of the resources should be reported separately from the quantities of the resources used. Estimation methods for both quantities and unit costs should be explained, as well as recording the currency and price date.

Cost-effectiveness analysis: modelling studies.

Kuntz, Nussbaum and Cronenwett described the cost estimates used in the construction of their decision analytic models. These estimates were based on the average allowable reimbursements for professional fees and hospital charges for diagnostic related groups *(Table3.2)*. Estimates of all cost variables were given in the three modelling studies. The costs in the modelling studies were expressed in US$, the reference years were 1993 (Kuntz et al., 1996) and 1996 (Cronenwett et al., 1997). Nussbaum failed to mention the year to which the cost in his study referred. Cronenwett also reported the undiscounted rate, allowing the reader to recalculate results using different discount rates.

Cost analysis and cost description studies.

The retrospective studies all used charges with the exception of Smurawska, Garrard and Patel who used costs in their calculations. The study by Patel was a cost description study with itemised costing on all investigations before and during hospitalisation. Only one (Ammar, 1996) of these retrospective studies mentioned the reference year for which calculations were done. Two retrospective/prospective studies (Back et al., 1997; Ammar, 1996) reported costs in US$ and one study reported costs in ECUs (European Currency Unit) (Melissano et al., 1997).

The cost of CEA in four similar cost analysis studies (Back et al., 1997; Dardik et al., 1997; Ballard et al., 1997; Kraiss et al., 1995) varied from a minimum of US$ 7608 (Ballard et al., 1997) to a maximum of US$ 11 546 (Back et al., 1997) for the conventional protocol. The cost of CEA over time reported by Smurawska (1998) demonstrated a decrease from US$ 10 394 ± 7821 during 1994 to US$ 6857 ± 3014 in 1996.

The unpublished studies (Smithies et al., 1997; Radestock, 1992) were reported in pound sterling but a reference financial year was not specified. Radestock reported a cost of £3300 per CEA based on retrospective data and Smithies et al estimated the cost of CEA based on HRG cost between £1890 and £4670. The study from Wessex (Smithies et al., 1997) used a standardised approved approach as outlined in "The Costing for Contracting Manual" (NHSE Leeds 1995). Applying a consultation process with health care professionals an aggregate Healthcare Resource Group (HRG) cost for Routine Vascular Surgery which included CEA was produced. The CEA "costs" estimates for the individual studies are summarised in Table 3.2.

d) Modelling

In assessing economic evaluations, details of any modelling used should be given e.g. decision tree model, regression modelling, epidemiology model as well as justification of the type of model and key parameters applied. Different types of decision modelling methods can be applied, for example: 1) decision tree modelling, 2) Markov modelling, 3) Monte Carlo simulation models and 4) Standard life tables. Modelling may be applied to: a) extrapolate the progression of clinical outcomes, b) transform final outcomes from intermediate measures, c) examine the relation between inputs and outputs in production function models, d) use data from a variety of sources to undertake a decision analysis and e) use evidence from trials or systematic reviews to "predict" what might happen in different clinical settings or populations.

Cost-effectiveness analysis: Modelling studies in symptomatic patients.

Kuntz et al constructed decision analytic models to calculate the lifetime costs and quality adjusted life expectancy for two separate hypothetical cohorts treated either with carotid endarterectomy or with medical treatment. They based their analysis primarily on the results from the NASCET and the ACAS. Nussbaum also constructed a Markov model comparing three cohorts of 100 patients each who experienced a transient ischaemic attack and were managed by observation, aspirin or carotid endarterectomy to calculate the lifetime cost of CEA to society. Separate outcomes for carotid endarterectomy were determined on operative results from their own institution as well as from the NASCET.

Cost-effectiveness analysis: Modelling studies in asymptomatic patients.

Cronenwett et al performed a cost-effectiveness analysis using a Markov decision model in which the probabilities for the base case analysis were based on data from ACAS and used NASCET data for patients who crossed over, i.e. became symptomatic and calculated the incremental lifetime cost.

3.3.1.4 Analysis and interpretation of results

The analysis and interpretation of result section summarises (a) adjustments for timing of costs and benefits, (b) allowance for uncertainty and (c) the presentation of results.

a) Adjustments for timing of costs and benefits

It is important that the time horizon over which costs and benefits are considered is given. The time horizon should preferably extend over the entire anticipated life of the treated individuals to capture all the effects of the alternatives. Discount rates should be given and if not considered, an explanation should be given as to why not. Discounting means that the money we spend now is worth more at present than it would be in the distant future. Discounting can be defined as follows: costs that are incurred at different points in time need to be "weighted" or discounted to reflect the fact that those costs which occur in the immediate future are of more importance than those costs which accrue in the distant future.

Cost-effectiveness analysis: Modelling studies. (Table 3.2)

The three modelling studies in asymptomatic patients addressed adjustments for timing of costs and benefits by applying a discount rate of 3% (Kuntz et al., 1995) and 5% (Cronenwett et al., 1997; Nussbaum et al., 1996).

b) Allowance for uncertainty.

Sensitivity analysis should be applied when there is uncertainty about the costs and effectiveness of different procedures. This investigates the extent to which results are sensitive to alternative assumptions about key variables.

Uncertainty can be related to the observed data inputs, the extrapolation of the data and to the analytical methods. Details should be given of the statistical tests used and

the confidence intervals when stochastic data are reported. Details should be given of the approach used when a sensitivity analysis is performed.

Sensitivity analyses were done in the modelling studies; one-way analysis in all three studies and a three-way analysis in one study (Kuntz et al., 1996). Kuntz and others reported that the cost-effectiveness of CEA in symptomatic patients were not very sensitive to wide variations in baseline assumptions. In asymptomatic patients, however, the cost-effectiveness of CEA were sensitive to a number of variables, most importantly the operative risk associated with carotid endarterectomy and the cost of the procedure. Cronenwett and others found that age was the variable that most significantly influenced cost-effectiveness of CEA and the second most important variable was stroke rate during medial management. This translated to carotid endarterectomy being cost-effective when the patient was younger (< 70 years) and the stroke rate was high. This finding is in keeping with clinical expectations.

Sensitivity analyses were applied in both the unpublished studies. A one-way sensitivity analysis was applied in the study from Newcastle, this was however not a modelling study where this technique to address uncertainty is best used. The analyses performed in the Newcastle and Wessex studies were more appropriate as a scenario analyses. (Best case, worst case scenario)

Uncertainty was accounted for with standard statistical tests in the retrospective and prospective studies with two exceptions, Patel and Melissano.

d) Presentation of results.

Presentation of results should ideally refer to incremental analysis, major outcome measures, comparisons with other health care interventions and should of course answer the original study question.

The modelling studies presented their results as cost-effectiveness ratios or as quality adjusted life expectancy expressed as the average lifetime cost to society. The two unpublished studies reported on the cost per stroke prevented. The results of the cost description and cost analysis studies were presented as the cost of CEA in monetary units.

Cost-effectiveness analysis: Modelling studies

The modelling studies (Cronenwett et al., 1997; Kuntz et al., 1996) presented their results as cost-effectiveness ratios. Nussbaum presented his results as quality adjusted life expectancy expressed as the average lifetime cost to society of either observation or aspirin therapy or CEA after TIA.

Kuntz et al found that for a typical symptomatic NASCET patient carotid endarterectomy provides a benefit of 0.35 discounted QALYs compared with medical treatment at an incremental cost per QALY gained of $4100. For a typical asymptomatic ACAS patient carotid endarterectomy provides a benefit of 0.15 discounted QALYs compared with medical treatment at an incremental cost of $52700 per QALY gained.

Nussbaum estimated the average life expectancy among TIA patients with no intervention to be 7.18 years, 7.26 years with aspirin treatment, 7.63 years based on

the NASCET results and 7.69 years when results from his own centre was used. QALYs were estimated to be 6.03 without treatment, 6.25 years with aspirin, 7.18 years with carotid endarterectomy based on NASCET data and 7.35 years when data from their own centre was used. This translated to a gain of 1.15 QALYs (7.18 - 6.03) in favour of surgery where no treatment was given or 0.93 QALYs, or 11.2 months in favour of surgery in the group where aspirin was given (7.18 - 6.25).

Cronenwett reported for the base case an undiscounted quality adjusted life expectancy in the medical group of 11.1 years versus 11.6 years in the surgical group. Discounting at 5% yielded 7.87 QALYs in the medical group and 8.12 QALYs in the surgical group, resulting in a difference of 0.25 QALYs (three months) in favour of the surgical group. Cronenwett concluded that the incremental cost-effectiveness ratio of $8004 calculated, compared favourably with other commonly accepted medical practices.

Unpublished studies reporting on cost-effectiveness of CEA.

Radestock used the number needed to treat (NNT) from the NASCET and the ECST results to prevent one stroke and multiply the cost estimate from the observational data with the NNT to calculate the cost to prevent one stoke. Using these reference values, a cost of £37 570 was estimated to prevent one stroke, based on NASCET data. The cost of stroke as obtained in the literature was briefly discussed in the report, but it was not related to the cost of carotid endarterectomy.

Smithies and others used the cost estimated from the 203 carotid endarterectomies in their retrospective data set and applied the NASCET and ECST data to it. They calculated the number of disabling or fatal strokes that could be avoided at 2 -3 years

for the 203 carotid endarterectomies. The calculated cost of carotid endarterectomy was then multiplied with the estimated number of strokes avoided.

Though comparisons with other health care interventions in terms of relative cost effectiveness were made in these modelling studies it is a prerequisite that this should be done *only* "when close similarity in study methods and settings can be demonstrated". Neither of the studies refer to methods and settings; references are given which can be follow to verify whether methods and settings were comparable. This was however considered outside the scope of this study was not pursued.

3.3.2. Studies assessing the cost consequences of carotid imaging - Pre-operative investigations prior to carotid endarterectomy.

3.3.2.1 Study characteristics

Seven studies and an *Editorial* were identified in the literature addressing the resource implications of imaging strategies for carotid endarterectomy in both symptomatic patients and asymptomatic populations using the search strategy described. Four of the studies (Lavenson et al., 1996; Vanninen et al., 1995; Kent et al., 1995; Hankey et al., 1990) considered symptomatic populations. The remaining three studies (Yin et al., 1998; Lee et al., 1997; Derdeyn et al., 1996) assessed the cost implications of screening for carotid stenosis in asymptomatic persons.

The *Editorial* "Cost-effective investigation of patients with suspected transient ischaemic attacks" should be regarded as a protocol or a set of recommended

guidelines on how to manage a particular group of patients with a description of costs attached to the proposed investigations. Since this paper was an *Editorial* it was not considered appropriate to evaluate it using the suggested criteria for economic evaluations, and was therefore not considered in this review.

The baseline characteristics of these studies are summarised in table 3.3.

Symptomatic populations.

Only two (Kent at al., 1995; Vanninen et al., 1995) of the four studies in symptomatic populations reported the mean age of their study populations and the percentage males in the study population. The mean number of patients in these four studies (Lavenson et al., 1996; Kent et al., 1995; Vanninen et al., 1995; Hankey et al., 1990) were 132 with 45 the smallest number of patients (Vanninen et al., 1995) and 296 patients the largest study population (Hankey et al., 1990). One study (Kent et al., 1995) used Markov modelling, two (Vanninen et al., 1995; Hankey et al., 1990) described various scenarios and one study (Lavenson et al., 1996) described the cost effect of duplex examination on strokes avoided.

Asymptomatic populations.

The three studies (Yin et al., 1998; Lee et al., 1997; Derdeyn et al., 1996) investigating the cost-effectiveness of screening asymptomatic populations for CEA all applied Markov modelling techniques. The mean age of these three study populations was 62.5 years. Two (Lee et al., 1997; Derdeyn et al., 1996)

of the three studies investigated all-male populations and only one (Derdeyn et al., 1996) referred to the number of patients investigated.

3.3.2.2 Study design

Seven studies (Yin et al., 1998; Lee et al., 1997; Lavenson et al., 1996; Derdeyn et al., 1995; Kent et al., 1995; Vanninen et al., 1995; Hankey et al., 1990) were identified reporting on the "cost" of pre-operative investigations. When evaluating these studies against the requirements for an "ideal" research question, five (Yin et al., 1998; Lee et al., 1997; Derdeyn et al., 1995; Kent et al., 1995; Vanninen et al., 1995) satisfied the criteria outlined by Drummond and Jefferson, but only two studies (Kent et al., 1995, Vanninen et al., 1995) were in symptomatic patients. Though neither of the studies, both in symptomatic and asymptomatic populations, formulated the outcomes of interest in the research question per se, the outcome measurements were described and referred to in six of the studies, the exception being the study by Lavenson et al.

a) Research question

Symptomatic patients.

Two (Kent et al., 1995; Vanninen et al., 1995) of the four studies investigating symptomatic patients formulated their research questions in such a manner which addressed the economic importance in terms of resource implications and the relevant choices or alternatives. Kent and co-workers considered both the costs of the screening modalities as well as the outcome objective in their study question. Both

these studies discussed and justified their viewpoint for the analysis In the case of Vanninen the outcome measure of interest became only apparent in the results section of their paper.

Two studies (Lavenson et al., 1996; Hankey et al., 1990) did not address the aspects considered necessary elements in a research question for the economic evaluation of health care interventions. The study by Lavenson failed to satisfy the requirements needed for an adequately formulated research question. Duplex ultrasound was the only alternative considered and the outcome of interest was not incorporated in the study design section, but became apparent only in the result section.

The economic implications in terms of resource implications concerning the alternative choices were not clearly formulated in the paper by Hankey and co-worker. The viewpoint of the economic evaluation was also not implicitly stated, though the perspective of provider organisation became apparent. This study is regarded as methodologically unsound to be assessed in terms of the requirements for an economic evaluation.

Asymptomatic patients

All three studies (Yin et al., 1998; Lee et al., 1997; Derdeyn et al., 1995) investigating screening of asymptomatic populations satisfied the requirements for a well formulated question.

b) The selection of competing alternatives.

Two studies (Kent et al., 1995; Vanninen et al., 1995) in symptomatic patients compared three alternatives duplex sonography, magnetic resonance angiography and

contrast angiography and in one study (Kent et al., 1995) a combination strategy of these three imaging modalities was also assessed. One study in symptomatic patients (Hankey et al., 1990) compared clinical methods against duplex ultrasound. The three studies assessing "cost-effectiveness" in asymptomatic populations (Yin et al., 1998; Lee et al., 1997; Derdeyn et al., 1996) compared duplex sonography against a "do-nothing" alternative. They also described the rationale for the selection of the alternatives with justification for their choices and evaluated the cost-effectiveness of screening in terms of resource implications.

The alternative interventions (imaging modalities) as well as the rationale for their selection were described in sufficient detail by Kent and Vanninen. Hankey investigated the "safest, most cost-effective way of selecting patients for angiography" by comparing clinical examination methods and duplex ultrasound to identify patients for angiography. The alternatives considered by Hankey and co-worker, clinical methods versus duplex ultrasound, were only discussed towards the latter part of their paper. The study design is described as a *prospective cohort study,* but that is only true with respect to the evaluation of the 485 consecutive patients with TIA who were referred and evaluated for a possible conventional carotid angiogram and not regarding the proposed cost-effectiveness evaluation. During the prospective study period, duplex ultrasound was also not available as an imaging modality in the settings where these patients were assessed. This study design is more in keeping with a type of modelling where "modelling techniques enable an evaluation to be extended beyond what has been observed in a single set of direct observations". This study could more appropriately be considered as an example of

"retrospective" modelling or a scenario analysis. The study by Lavenson et al did not compare alternatives and was classified as cost-description study.

c) Form of Evaluation

Seven of the eight studies refer to *cost-effectiveness* in the title, but in only four (Yin et al., 1998; Lee et al., 1997; Kent et al., 1996; Derdeyn et al., 1995) was a cost-effectiveness analysis performed. Vanninen and others refer to cost effectiveness of the imaging procedures, but fail to do an appropriate analysis to determine cost effectiveness. Drummond and Jefferson emphasise that the methodology used in a given study should be examined to determine whether it suits the problem under review. In assessing the methodologies used in the studies, only the four studies referred to already qualify as cost effectiveness analyses.

Hankey used the term cost-effectiveness inappropriately in terms of economic evaluations and did not perform a cost-effectiveness analysis. They analysed "cost-effectiveness" by using estimated costs of several imaging strategies that might be used to investigate a hypothetical sample of patients with symptomatic stenosis. This study, though comparing two alternatives, is more in keeping with a cost-outcome description study. The study by Lavenson et al referred to *cost savings* in the title and in the methodology discussed the cost implications or cost effect of duplex examination.

3.3.2.3 Data collection

a) Effectiveness data

None of the identified studies in symptomatic patients were randomised controlled trials. Three studies (Kent et al., 1995; Vanninen et al., 1995; Hankey et al., 1990) evaluating symptomatic patients were observational studies. Sensitivities and specificities for the imaging techniques were based on the observational data and used as baseline results for the models in symptomatic patients in two (Kent et al., 1995; Vanninen et al., 1995). Hankey et al assumed the sensitivity for Duplex ultrasound to be 100% in their "model". In asymptomatic patients, one study (Derdeyn et al., 1996) generated Doppler sensitivities and specificities locally by reviewing carotid bifurcation examinations over a two-year period at their institute. Two studies (Yin et al., 1998; Lee et al., 1997) performed a meta-analysis to obtain estimates of sensitivity and specificity of duplex ultrasound.

The prevalence of carotid stenosis in two studies (Vanninen et al., 1995; Hankey et al., 1990) in symptomatic patients was obtained from their observational data. Kent and others referred to a prevalence used in their sensitivity analysis, but did not describe its source.

In the asymptomatic populations (Yin et al., 1998; Lee et al., 1997; Derdeyn et al., 1996) estimates of carotid stenosis prevalence were obtained through a literature review. The angiographic complication rate, surgical risk, stroke risk and mortality rate, and benefit of CEA reported in ACAS (1995), were the rates used for the asymptomatic populations. For symptomatic populations corresponding rates reported from NASCET were used in the modelling. The 30-day to two-year

probabilities of stroke among symptomatic patients were estimated from NASCET and used in the subsequent modelling by Kent et al. The three studies (Yin et al., 1998; Lee et al., 1997; Derdeyn et al., 1996) assessing asymptomatic populations developed decision models to evaluate the effect of screening or no screening on QALY and cost. Yin, Lee and Derdeyn applied the results from the NASCET and the ACAS in the modelling studies.

b) Benefit measurement and valuation

Four studies, only one (Kent et al., 1995) being in symptomatic patients, assessed the outcome measures in economic terms e.g. "incremental cost per quality-adjusted life year gained" (Derdeyn et al., 1996; Kent et al., 1995), "quality-adjusted-life-years", and "costs and marginal cost effectiveness ratios" (Yin et al., 1998; Lee et al., 1997). Cases detected and the cost effect of carotid surgery in terms of strokes prevented were the main outcome measures in the studies by Vanninen, Hankey and Lavenson. Kent used time-trade-off and assumed that the quality weight for one year of life after a major stroke was 0.4 and a disutility of 0.25 years for a minor stroke. Only Lee, Derdeyn and Yin valued health benefits. Both Lee and Derdeyn used time-trade-off methods to measure preferences of patients at risk for stroke. Yin derived quality of life adjustments from earlier studies. The degree to which minor and major stroke decreases quality of life was adjusted with a factor that ranged from zero for death and one for complete health. Kent referred to health-related weights in a similar fashion than Yin, and assumed a disutility following a major stroke of 0.4 and after a minor stroke of 0.25 years (utility meaning preference). Similar to the studies

assessing the cost consequences of carotid endarterectomy, no reference to standard accepted methods to measure benefits was made. No details were given on how the benefits were measured, and I assumed that these benefits were obtained from the literature.

c) Costing.

Quantities of resources, estimated unit costs and costing details were reported adequately in all the studies evaluating cost-effectiveness in symptomatic patients. In the asymptomatic population studies, unit costs were reported for all the cost variables. All these studies on cost-effectiveness of screening for carotid surgery used estimated costs rather than charges with the exception of Lee who used charges as a proxy for cost. Six studies reported costs in US dollars (1994 -1995), five of these studies (Yin et al., 1998; Lee et al., 1997; Derdeyn et al., 1996; Lavenson et al., 1996; Kent et al., 1995) were from the United States and one from Finland (Vanninen et al., 1995). The cost in the study by Hankey et al was reported in pounds sterling.

All the studies reported in US dollars refer to the year on which the costs were based. In the study by Kent et al all costs were converted to 1993 dollars. Kent and co-workers did not include the cost of duplex ultrasound investigations because it was assumed that all patients were initially screened with Doppler and that it would therefore be a constant. By not incorporating this cost, the overall cost of the preoperative investigations would have been reduced, resulting in a more favourable cost-effectiveness ratio. Considering, however the unit cost of preoperative

investigations, Duplex ultrasound is the least costly. It can thus be argued that since an ultrasound investigation is needed anyway to decide whether a patient will be further investigated, this cost should not be included in the cost to estimate a cost-effectiveness ratio.

The study reported in pounds sterling from the UK (Hankey et al., 1990) reflected probably 1989 - 1990 prices, although it was not apparent. The financial year, on which all the cost calculations to the NHS were based, was not specified in the paper. Private consultant fees were based on the recommendations of the British Medical Association's fees working party in 1989.

d) Modelling

Four (Yin et al., 1998; Lee et al., 1997; Derdeyn et al., 1996; Kent et al., 1995) of the seven papers applied modelling according to acceptable economic simulation techniques using Markov modelling. Two of these studies (Derdeyn et al., 1996; Kent et al., 1995) used results from observational data in subsequent modelling. Two other studies (Vanninen et al., 1995; Hankey et al., 1990) used a "type" of modelling, but not a proven recognised modelling approach. Markov models were developed in the case of all three studies (Yin et al., 1998; Lee et al., 1997; Derdeyn et al., 1996) evaluating the cost-effectiveness of screening versus no screening in asymptomatic populations based on evidence from clinical trails (ACAS, 1995; NASCET, 1991; and ECST, 1991).

Symptomatic populations.

The three studies (Kent et al., 1995; Vanninen et al., 1995; Hankey et al., 1990) assessing symptomatic patients were observational studies that applied modelling techniques to extend their evaluation beyond the set of observations. Data from their observational studies were used to describe the baseline characteristics of the hypothetical cohorts for the subsequent modelling. Kent and others used the results from their observational data in subsequent Markov modelling. Vanninen and co-workers also used observational data and constructed several hypothetical models based on theoretical population of 1000 patients, but did not use a recognised modelling technique. Hankey did not specify a specific model either or referred to the term modelling in their paper. In the study conventional angiography and duplex ultrasound were extrapolated to a 1000 patients in different scenario settings, which can for all practical purposes be considered as a form of modelling. The assumptions by Hankey et al are unrealistic regarding Duplex sensitivity as 100% and angiographic complication rate the same for all degrees of stenosis. That only patients with carotid ischaemic symptoms who were likely to proceed to carotid angiography would be referred is however reasonable. Bearing these assumptions in mind these findings are not generalisable to other populations and create a potential for bias. Since Duplex ultrasound was not available at the time at the centre where Hankey conducted the prospective study, the study can be considered as a "form of retrospective modelling". No reference is however made to any of the economic modelling techniques considered appropriate in economic evaluations of this nature.

Asymptomatic populations

In the asymptomatic populations, the two studies (Lee et al., 1997; Derdeyn et al., 1996) assumed the two cohorts to be men older than 65 years and 60 years, whereas one study (Yin et al., 1998) modelled a population of people 60 years and older. Derdeyn developed a computer model to simulate the cost-effectiveness of screening an asymptomatic cohort of 1000 men during a 20-year period. Two populations were evaluated: a population with a low prevalence (4%) of ≥ 60% stenosis, representative of the general population and a population with a high prevalence (20%) of ≥ 60% stenosis and associated vascular risk factors.

Restricting the hypothetical population to men 65 years and older (Lee et al., 1997; Derdeyn et al., 1996) seems appropriate, since the stroke rate and carotid disease in men are higher than in women (about two thirds of participants in ACAS were male) and the risk of stroke increases rapidly between the age of 60 and 70 years (Barnett et al., 1992). It was therefore assumed that screening would have the greatest benefit when done in 65-year old men, and if screening were not cost-effective for this group it would be unlikely to have any benefit in other groups. These models, which combined published data of the accuracy and cost of duplex ultrasound and carotid angiography and of the risks, benefits and costs for hypothetical cohorts, could create further bias.

Lee and Yin explicitly defined Markov states. In the case of Yin seven well-defined Markov states were described, whereas Lee described only three Markov states. Although it must be recognised that Lee described these three possible states only with regards to major complications of angiography, Yin described seven Markov

states for screening. The three Markov states, minor stroke, major stroke and death due to angiography used by Lee are the major outcome events of interest and are the same as those described by Yin for angiography. Yin, by using more Markov states ensured that "all" possibilities were accounted for from the point of screening, but then these additional Markov states as defined by Yin could be regarded as transition probabilities.

Kent and Derdeyn did not provided a schematic presentation for their decision analysis and although not considered essential a diagram on the decision tree helps to describe the various probabilities. Lee and Yin provided suitable diagrams. Derdeyn and Lee used transition probabilities of one-year, and Yin used one-month probabilities. Though one-year periods as time points are chosen usually for pragmatic reasons and to simplify decision analytic models, one-month periods are more appropriate for Markov modelling.

3.3.2.1 Analysis and interpretation of results (Table 3.4).

a) Adjustments

Of the studies concerned with symptomatic patients, only one (Kent et al 1995) referred to a time horizon and allowed for discounting both with regards to costs and benefits. The studies assessing asymptomatic populations all discussed a time horizon and discounting. In three studies (Yin et al., 1998; Lee et al., 1997; Kent et al., 1995) the lifetime cost and quality-adjusted life expectancy of patients were estimated and one study considered a period of 20 years (Derdeyn et al., 1996).

Kent et al (symptomatic patients) and Yin (asymptomatic patients) used discount rates for both costs and utilities (QALYs) of 5% and Derdeyn and Lee (asymptomatic populations) used a rate of 3%. It was not explicit in the paper by Derdeyn whether the discount rate of 3% also applied to utilities. Yin also provided a sensitivity analysis within a range of 0 - 10%, which is a sensible approach since the choice of a discount rate is arbitrary.

b) Allowance for uncertainty.

Standard statistical analyses were performed in two studies (Kent et al., 1996; Vanninen et al., 1996) investigating symptomatic patients and then only with regards to the stochastic data.

The uncertainty inherent to extrapolation has been reasonably handled by the application of Markov decision analysis modelling in the studies by Kent, Derdeyn, Lee and Yin. Base case variables with appropriate ranges were tested in three studies (Yin et al., 1998; Derdeyn et al., 1996; Kent et al., 1995). Lee and Yin applied sensitivity analysis to their models to address aspects of uncertainty intrinsic in hypothetical cohort populations. The effect on marginal cost-effectiveness was examined by Kent et al by changing the prevalence of carotid stenosis, the cost of screening and surgery, the complication rates as a result of the procedures and the stroke risk reduction from carotid endarterectomy. A sensitivity analysis was performed to determine the robustness of the baseline results to variations in the model parameters with good effect since this allowed for the data to be interpreted not only as point estimates. The model by Yin assessed similar parameters compared

with the other studies, but included also the starting age of screening and thereby accounted for the effects of ageing and the progression of the disease. This was considered a sensible approach, since the risk of stroke increases with increasing age. The prevalence of carotid stenosis used in these modelling studies range from 2 - 20%. Derdeyn who modelled a high risk of stenosis as well as a low risk population with suitable prevalence rates made this distinction between populations with different carotid stenosis prevalence rates. Kent et al did not refer to a prevalence rate of carotid stenosis, but since they studied symptomatic patients and applied modelling to their observational data, reference to a prevalence rate of carotid stenosis was considered unnecessary. Kent and Derdeyn assessed the effect of change for each variable over a wide range in a one-way analysis. Kent also performed a three-way sensitivity analysis of the effect of the sensitivity and specificity of duplex ultrasound and the acceptable cost-effectiveness threshold on the choice of contrast angiography versus duplex ultrasound as a preoperative test. Though Yin did not specify the form of sensitivity analysis used, it is assumed that he also performed a one-way sensitivity analysis, since one-way sensitivity analysis is the simplest and most common form of this type of analysis. Sensitivity analysis, however, has three major limitations: 1) since the researcher has discretion as to which variables and what values are included, this can create selection bias; 2) as no guidelines exist on what degree of variation in results is acceptable proof that the analysis is robust, interpretation of a sensitivity analysis is considered arbitrary and 3) the interactions between parameters may not be reflected when uncertain parameters are varied one at a time. These limitations are therefore extremely relevant and applicable to the

sensitivity analyses performed in these four studies (Yin et al., 1998; Lee et al., 1997; Derdeyn et al., 1996; Hankey et al., 1990).

c) Presentation of results.

Symptomatic populations.

Most of the studies comply with the requirement in reporting on the main components of cost and benefit, direct cost, indirect costs, life years gained and improvements in quality of life in a disaggregated form.

Kent et al reported on the incremental cost per quality adjusted life year gained in evaluating symptomatic patients. Kent found that the combination strategy of duplex ultrasound and MRA followed by conventional angiography (CA) for dissimilar findings resulted in the greatest quality adjusted life expectancy. Taking the cost of CA and MRA as well as the cost of carotid endarterectomy into consideration, neither of these strategies was cost-effective. The combination strategy was found to be more effective than Duplex, but also more expensive at $22 400 per QALY gained compared with Duplex at $9000 per QALY gained. The use of duplex ultrasound was found to be less expensive than CA, but was associated with a greater lifetime morbidity and mortality. If conventional angiography is preferred to duplex ultrasound, Kent et al estimated an additional cost of $99 200 for each QALY gained which is higher than many of the cost effectiveness ratios reported for other medical interventions.

Vanninen reported on the imaging cost per patient and on the cost per stroke prevented. *Lavenson reported* only on the cost per stroke prevented. *Hankey found*

that to detect stenosis of 75% or more it is "most cost effective" to screen with Duplex irrespective of the presence of a carotid bruit. The word "most" is not defined and quantified by an acceptable cost-effectiveness ratio neither expressed in units to allow comparison for example cost per QALY gained. Cost consequences were expressed in terms of the cost per number of disabling strokes, addressing the outcome measure of interest, but not satisfying a cost-effectiveness analysis.

Asymptomatic populations.

The three studies assessing the cost-effectiveness of screening asymptomatic populations reported on the incremental cost per quality adjusted life year gained and also compared the options available.

Lee et al evaluated the cost-effectiveness of screening under the assumption that surgery has prolonged benefits over a lifetime, and found that screening resulted in an additional cost of $1553 per person. It generated 0.013 QALY or 4.75 days more than no screening at a cost of $120 000 per QALY. When the complication rate of angiography reached 2%, the non-screening strategy however, generated more QALYs and was less expensive than screening. Lee et al found that the marginal cost-effectiveness was receptive to the disease prevalence in the screening population. Lee used the recommendations of Laupacis and others to assess cost-effectiveness (Laupacis et al., 1992).

Derdeyn et al found a one time screening programme of a population with a high prevalence (20%) of ≥ 60% cost $35 130 per incremental QALY gained. One time screening in a low prevalence population of ≥60% stenosis produced an incremental

discounted cost of $52 588 per incremental QALY. Derdeyn concluded that a one-time screening programme for an asymptomatic population with a high prevalence of carotid stenosis might be cost-effective, but that annual screening of populations with a low prevalence of carotid stenosis is detrimental since more QALYS were lost in the screened population than by natural progression of carotid stenosis using limits of cost-effectiveness ratios as published in the literature. These limits are however controversial. Derdeyn followed the limits as proposed by Goldman and Kupersmith and co-workers (Goldman et al., 1992; Kupersmith et al., 1995).

Yin et al concluded that for 60-year old patients with asymptomatic stenosis of 60 - 99% and a prevalence of 5%, duplex screening increased the quality adjusted life years gained, decrease the lifetime cost of care under baseline assumptions. The incremental cost per QALY gained or the cost effectiveness ratio was $39 495. Yin et al derived their screening strategies from duplex ultrasound with and without angiography and did not study MRA as a supplement to ultrasound. Referring to the characteristics of a screening modality, which should be non-invasive having a low procedural risk, considering angiography in the context of screening is regarded as inappropriate. Yin used the recommendations by Laupacis et al. and concluded that one time screening is more cost effective than screening every five years provided a 4.5% or more carotid stenosis prevalence is present in the population to be screened and that the specificity of Duplex of at least 91%.

From these published limits it is obvious that there is little consensus regarding what is considered very cost-effective or borderline, with the exception of the expensive category where agreement exists.

3.4 Critique of published studies.

The methods and economic data upon which these studies assessing the economic implications of carotid endarterectomy and the pre-operative investigations prior to the procedure are based, need to be improved if robust conclusions regarding the cost-effectiveness of carotid endarterectomy are to be formulated. Although the essential elements for structured economic evaluations have been described first in the early 1970s by Williams and again more recently by Drummond, only reasonable adherence to these recommendations were noted in these studies evaluated. It is important that the conduct and reporting of studies assessing economic implications of interventions should be standardised "to ensure that those performing such studies are held accountable for their study methods and interpretation" (Holloway et al., 1999). The more recent studies however suggest a better adherence to the recommended guidelines and recommendations for economic publications, though this could still be improved upon.

The use of a checklist for critically appraising the studies assessing the cost and benefits of carotid endarterectomy provided a structure for evaluation, which protect against sources of bias (Drummond et al., 1996; Oxman 1994).

The basic requirements for sound cost-effectiveness analyses were not adhered to in any of these studies. It is evident in reviewing these studies examining the costs and benefits of carotid endarterectomy and pre-operative imaging investigations that the term "cost-effectiveness" is used indiscriminately by investigators, authors and also by editors who published the manuscripts. The distinction between cost-effectiveness analyses and cost-utility analyses, which often becomes blurred, was not evident in

these studies (Drummond et al., 1997). Reported outcome measures were used inappropriately to the type of analysis performed. Outcomes were reported in measurements associated with cost utility analyses in studies where the investigators set out to perform cost-effectiveness analyses. Though the form *of economic evaluation* was alluded to in the title of all these studies, Drummond and Stoddart pointed out that "the titles of studies are notoriously bad guides to their contents" (Drummond and Stoddart, 1985). This was reaffirmed in the assessment of these. I acknowledged however that cost-utility analysis is a special form of cost-effectiveness analysis where the effectiveness is measured in the number of life-years gained adjusted for quality of life or similar measures of utility. Although it might be argued that much of my criticisms are levelled at terminology and semantics, inappropriate use of terminology leads to confusion when evaluating the literature. It is however debatable whether studies should be invalidated purely because of the inappropriate use of terminology, which was clearly the case in most of these studies. On the other hand if terminology is used out of the acceptable context in scientific literature, comparison between studies will prove to be more difficult.

The majority of the studies identified that investigating the cost implications of carotid endarterectomy are studies from the United States from America. The studies can be classified into two broad categories: studies assessing the cost implications of carotid endarterectomy and studies assessing the cost-implications of the pre-operative investigations for CEA. The studies investigating the cost implications of CEA can be divided into studies assessing the cost-effectiveness of carotid endarterectomy or modelling studies (full economic evaluation) and studies

evaluating cost minimisation strategies or CEA cost description studies (partial economic evaluation).

All the studies investigating cost-effectiveness of CEA or pre-operative investigations were modelling studies, applying the same effectiveness data from the NASCET and ACAS. The heterogeneity in study methods and results reported however makes it difficult to compare the cost-effectiveness of these studies. All the modelling studies applied an incidence-based approach estimating the lifetime cost of patients treated either surgically with carotid endarterectomy or medically with aspirin. Only one study (Nussbaum et al., 1996) reported on the average lifetime cost to society using different treatment strategies. These modelling studies estimating the lifetime cost of CEA included the cost of stroke, but did not include the cost of the "work-up" of a patient population who might be considered for carotid surgery. Ignoring the cost of identifying the CEA patients from a cohort of potential carotid surgery candidates might underestimate the total cost of carotid surgery resulting in cost-effectiveness ratios favouring carotid surgery.

Effectiveness measure or "stroke-free" life years gained.

It is disturbing that the results of the base-case cost-effectiveness ratios reported from the different studies, assessing the same interventions are so divergent, considering the similarities in the models. Not only was the same effectiveness measure, "stroke-free" life expectancy used in the modelling studies, but in assessing the outcome of patients after CEA or medical treatment, similar 30-day probabilities of stroke and death and annual stroke rates were also applied in the these studies. Nevertheless

different results were obtained. While this discordance might be mainly due to the variation in the CEA cost estimates, some of it might be attributable to the effectiveness measures expressed differently in the individual studies. The life expectancy gained was either reported in terms of undiscounted or discounted QALYs. However, different discount rates were used, and life-years gained were not always quality adjusted, which obviously impede on meaningful comparisons. Since the same efficacy data from the published RCTs, the NASCET and ACAS were used one would expect the effectiveness data to be of the same magnitude. The reported life expectancy gains, applied in these studies, for a typical NASCET patient or ACAS patient were 4.2, 4.4 and 3 months respectively regardless of the qualification of the effectiveness measure used. This finding might however indicate that the methods used to discount life expectancy could be inappropriate.

Cost measures of CEA, medical treatment and stroke.

The estimated cost of CEA was derived from Medicare reimbursements for professional fees and hospital charges for the relevant diagnosis-related group in all these studies. The differences in the cost of carotid endarterectomy might be because Medicare reimbursements from different geographical areas were used to determine the cost of the procedure resulting in different estimates.

To assess the lifetime cost of these patients, the cost of stroke had to be considered. The cost estimations used in these three studies for the acute care of stroke, annual care of stroke and the cost for the first year of stroke were also very different

(Table3.2). The cost estimates for stroke in these studies were obtained from the literature in all instances.

Comparing the "cost" estimates for CEA between the various observational studies were difficult, since cost or charges were used in the individual studies. "Charges represent the highest level mix of local and distant institutionalised cost, transferred among sites that generated revenues and losses" (Back et al., 1997). Using charges can thus overinflate the costs incurred, making the procedure more costly and seemingly less cost-effective, but probably giving a more accurate estimate. None of the authors however indicated to what extent the use of charges might have biased their estimates.

The cost description studies all identified hospitalisation costs as one of the major contributors to escalating health care cost. Reducing the length of hospital stay seems a sensible way to decrease the cost of the procedure. The use of duplex ultrasound as a "reliable" imaging modality to determine carotid stenosis is gaining support and routine use of conventional angiography might therefore soon be unnecessary contributing to the overall cost reduction of CEA. It was generally found that selective use of angiography, avoiding routine ITU admission and discharging the patient from hospital on the first postoperative day could reduce the cost of carotid endarterectomy by almost 50%.

Benefit measurements.

It is important to value health benefits and this can be done either through time-trade-off or standard gamble methods. Since cost-effectiveness analysis deals with effects

measured in natural units, valuing these effects in terms of their monetary benefit or utility is not applicable. However, the majority of the studies concerned with carotid endarterectomy and preoperative investigations applied utility measurements from the literature to their findings, which might be responsible for the differences, observed in the reported outcome measures. They failed to describe how these benefit measurements were determined and used preference scores from the literature in their calculations. They did not apply or refer to any of the existing pre-scored multi-attribute health status classification systems: Quality of Well-Being (QWB), Health-Utility Index (HUI) and EuroQol neither were the Short Form (SF) 36, the Nottingham Health Profile and the Sickness Impact Profile which are comprehensive measures of health-related quality of life (Drummond et al., 1996). As an extensive discussion of utility measures was considered outside the scope of this investigation, valuing health benefits and associated problems were not pursued.

Discounting.

The different discount rates as well as the application of discounting in these studies might explain some of the variation in the reported outcome measures. Controversy still exists in health care on discounting. It is generally agreed that costs should be discounted in any study if the time horizon is longer than one year and current recommendations vary between 3 - 6%. Discounting was only applied in the three modelling studies. The rates of 3 and 5% used are considered within the acceptable proposed range. It is suggested that a single discount rate should apply to both costs and health benefits, even when health benefits are expressed in non-monetary units

such as life years gained. In discounting only costs and not health benefits as well, the health gain over time can appear more favourable than what it really is. Discounting costs and utilities at the same rate appears methodologically sound since it provides consistency between cost-effectiveness and cost-benefit analysis. Discounting costs and utilities at the same rate however underwrites the notion that it is possible to transform resources into health at any time, which might be unrealistic.

Study population.

The reported outcome measures might also be biased. All-male populations or predominantly male populations were used in the modelling studies, but the effectiveness result measures from the NACSET and the ACAS that were applied were derived from both males and females in the trials. Since the modelling was predominantly based on the results from the NASCET and ACAS trials, the gender mix from those studies should ideally have been used in the modelling. Modelling based on a 100% male population might be unrealistic and not representative of the gender mix encountered in normal everyday practice. Although the justification given by the authors for including only men in their modelling studies was reasonable, it remains possible that substantial bias was introduced since an all-male study population does not represent the general population.

Modelling.

The application of modelling techniques using published data from clinical trials in hypothetical cohorts is also a matter of concern. Hypothetical cohorts are not actual or verifiable study populations. Many assumptions are required in subsequent modelling, thus creating a huge potential for bias. As mentioned, predominantly male populations were used in these modelling studies, but the effectiveness measure was from a mixed population and was not adjusted to be gender specific.

Limitations of Markov modelling can be summarised as follows: 1) strict assumptions are required about "zero memory" meaning that the transition probabilities only depend on the health state patients are in now, and not how long they had been in that state or how they got there; 2) comorbidity is only indirectly assessed and 3) estimates of costs and event probabilities are used.

The primary concern about these modelling studies relates to the patient cohorts used. It is important that a study cohort simulates an identifiable patient population before the conclusions of the analysis can be applied clinically.

Models must be interpreted with caution and these results are usually not generalisable to genuine populations for whom disease progression might be very different from what is expected. Markov modelling has distinct advantages to decision tree models, since decision tree models do not specify when events occur in contrast with the Markov modelling which assumes that the patient is always in one of a finite number of states of health referred to as Markov states. The structure of the decision tree model also implies that an event may occur only once. In the case of Markov modelling all events are modelled as transitions from one state to another and each state is assigned a utility. The time horizon of the analysis is divided into

equal increments of time, referred to as Markov cycles. Markov modelling also makes provision for events occurring more than once which is obviously true in the case of transient ischaemic attacks (Sonnenberg and Beck, 1993). Since the progression of arteriosclerosis in the carotid arteries might be rapid in some individuals, one-year periods for modelling transitions are regarded as inappropriate, thus the one-month period used by Yin is considered more realistic. Nevertheless modelling remains a prediction of possible events based on probabilities in hypothetical cohorts, which might explain the variation seen between these studies. Modelling studies can thus only be regarded as the " best alternative" in the absence of "real" life populations.

3.5 Summary

From the limited published evidence available, the cost-effectiveness of carotid endarterectomy remains unclear for several reasons. Considerable variation was observed between the studies. An incremental cost of $4100 per quality adjusted life year gained for symptomatic patients was reported. The cost-effectiveness of carotid endarterectomy in asymptomatic patients varied from $8000 to $52 700 per quality adjusted life year gained. The cost effectiveness of the pre-operative investigations varied from $35 100 per QALY in symptomatic patients to $120 000 in asymptomatic patients. The cost of carotid endarterectomy varied from $7608 to $11 546 and from £1800 to almost £5000. The lack of agreement among studies addressing the same intervention reduces confidence that these analyses are reliably estimating the cost-effectiveness they

purport to measure. The main reason for these inconsistencies is probably related to the study design used in the different studies. Although the variation in cost estimates used was not considered to be enormous, it contributed to the inconsistencies observed. After critically appraising these studies it is apparent that a study other than a modelling study, is needed to assess the economic consequences of carotid endarterectomy and of the imaging procedures prior to carotid endarterectomy. The differences in the model structure as well as differences in the input variables may explain the divergent conclusions. The variation in input variables, which was identified as the major contributing factor resulting in different conclusions, needs to be reduced if the results from cost-effectiveness analysis are to be used by health care policy makers. The quality of the studies assessing the cost and benefits of carotid endarterectomy and the associated pre-operative investigations need to be improved if robust conclusions regarding the cost-effectiveness of carotid endarterectomy are to be formulated.

An accurate estimate of the cost of CEA, the cost of medical treatment for TIA patients not having surgery and of the lifetime cost of stroke for Scotland is needed, if the cost-effectiveness of CEA as stroke prevention is to be critically assessed.

Table 3.1: Study characteristics of the studies assessing the costs and benefits of carotid endarterectomy:

MARKOV MODELLING STUDIES – COST-EFFECTIVENESS ANALYSIS.

Author(s)	Kuntz et al.	Nussbaum et al.	Cronenwett et al.	Lavender et al.
Year and Country	1996, USA	1996 USA	1997, USA	1998, UK
Original currency	Cost in 1994 US$	Cost in ? US$	Costs in 1996 US$	Costs in 1992 £ sterling
Patient population	Symptomatic & asymptomatic	Symptomatic & asymptomatic	Asymptomatic ≥ 60-99% stenosis	Symptomatic > 70% stenosis
Number				
Age (mean) years	65	65	67	65
Male	100%	70%	66%	100%
Study period				
STUDY DESIGN:				
Alternatives considered	CEA vs. medical treatment	CEA vs. aspirin vs. observation	CEA vs. medical treatment	CEA vs. medical treatment
Evaluation form	Cost-effectiveness	Cost-effectiveness	Cost-effectiveness	Effectiveness of CEA as QALM and marginal cost /QALY
DATA COLLECTION:				
Effectiveness data sources	NASCET; ACAS	NASCET and own data	ACAS , NASCET	ECST; NASCET
Outcome measures	Incremental cost-effectiveness ratio for CEA, QALYs	Life expectancy Cost-benefit ratio of CEA	Incremental cost-effectiveness ratio for CEA	Marginal l cost per QALY
Cost data sources	1993 Medicare Reimbursement	Medicare Reimbursement and DRGs	Medicare Reimbursement and DRGs	CEA cost reported in Newcastle study
ANALYSIS AND INTERPREATION OF RESULTS:				
Time horizon & discount rate	"Life-time" Costs & life expectancies at 3%	"Life-time" to age 99. Costs & life expectancies at 5%	Costs & life expectancies at 5%	QALM discounted at 6%
Sensitivity analysis	Peri-operative risk, stroke risk, CEA risk reduction, Cost of CEA, Cost of stroke.	Cost of CEA on overall life-time cost , cost of peri-operative complications, stroke rate	Age, stroke rate during medical care, peri-op event rate, costs	Age, stroke rate with and without CEA, CEA costs

Table 3.1: Study characteristics of the studies assessing the costs and benefits of carotid endarterectomy: *(Continue)*
RETROSPECTIVE STUDIES, OBSERVATIONAL DATA, COST ANALYSIS.

Author(s)	Back et al	Dardik et al.	Mellissano	Kraiss et al
Year & Country	1997, USA	1997, USA	1997, Italy	1995, USA
Original currency	US$; 1996	US$; 1995	ECU; 199?	US$; 199?
Patient population	Symptomatic asympt. (53%)*	Symptomatic asympt. (33%)*	Symptomatic asympt. (27%)*	_
Number	60 ; 42	201	343	196
Age (mean) years	69	72	68	_
Males	_	63%	80%	_
Study period	55 months	32 months	?12 months	24 months
STUDY DESIGN:				
Alternatives considered	CEA pathways: Conventional **or** • Duplex; • Regional anaesthesia; • Selective ICU; • Early discharge	CEA pathways: Conventional **or** • Angiogram day pre-op • Selective ICU; • Early discharge	CEA pathways: Conventional **or** • Duplex; • Regional anaesthesia; • Selective ICU; • Early discharge	CEA pathways: Conventional **or** • Duplex; • Regional anaesthesia; • Selective ICU; • Early discharge
Evaluation form	Cost analysis	Cost analysis	Cost analysis	Cost analysis
DATA COLLECTION:				
Effectiveness data sources	_	_	_	_
Outcome measures	Cost of CEA Outcome after CEA	Reduce LOHS, Outcome		Cost reduction Outcome of CEA
Cost data sources	Office of clinical resource management	Hospital charges		Hospital charges
ANALYSIS AND INTERPREATION OF RESULTS:				
Time horizon & discount rate	_	_	_	_
Sensitivity analysis	_	_		_

* % asymptomatic patients in study population.

Table 3.1: Study characteristics of the studies assessing the costs and benefits of carotid endarterectomy: *(Continue)*
RETROSPECTIVE STUDIES: OBSERVATIONAL DATA, COST ANALYSIS.

Author(s)	Garrard et al	Pollard et al.	Ballard et al.	Ammar.
Year & Country	1997, USA	1997, USA	1997, USA	1996 USA
Original currency	US$; 1995	US$; 199?	US$; 199?	US$; 199?
Patient population	Symptomatic asympt (51%)*	CEA, (83) LER, (39) CABG (177)	Symptomatic asympt. (45%)*	Symptomatic asympt (38%)*
Number	97	83	194	237
Age (mean) years	68	70	74	76
Males	_		53%	66%
Study period	12 months	24 months	30 months	12 months
STUDY DESIGN:				
Alternatives considered	• CEA ± angiogram +duplex	Pre-operative evaluation: hospital vs. outpatient clinic	• CEA ± angiogram +duplex	Various variables assessed to reduce cost of CEA; preoperatively in theatre and postoperatively
Evaluation form	Cost analysis	Cost analysis	Cost analysis	Cost analysis
DATA COLLECTION:				
Effectiveness data sources	_	_	_	_
Outcome measures	Cost of CEA based on duplex only	Reduce LOHS,	Surgical outcome, resource cost	Cost reduction Outcome of CEA
Cost data sources	Medicare 1995; CPT[1], DRG[2]	_	Medicare 1995	Charges Own institution
ANALYSIS AND INTERPREATION OF RESULTS:				
Time horizon & discount rate	_	_	_	_
Sensitivity analysis	_	_	_	_

* % asymptomatic patients in study population.

Table 3.1: Study characteristics of the studies assessing the costs and benefits of carotid endarterectomy: (*Continue)*
RETROSPECTIVE STUDIES: OBSERVATIONAL DATA, COST DESCRIPTION.

Author(s)	Smurawska et al	Hirko et al.	Luna et al.	Patel et al
Year & Country	1997, Canada	1996, USA	1995 USA	1995, Australia
Original currency	US$; 1995	US$; 199?	US$; 199?	Aus$; 199?
Patient population	Symptomatic asympt. (25%)*	Symptomatic asympt. (26%)*	Symptomatic asympt (28%)*	_
Number	757	284	57	49
Age (mean)	68±9	67	70	70
Male	_	61%	_	67%
Study period	36 months	48 months	18 months	12 months
STUDY DESIGN:				
Alternatives considered	_	_	_	_
Evaluation from	Cost description	Cost description	Cost description	Cost description
Effectiveness data sources	_	_	_	_
DATA COLLECTION:				
Outcome measures	Cost of CEA over time	Cost of CEA over time. Outcome of CEA	Cost of CEA over time. Outcome of CEA	Cost reduction Outcome of CEA
Cost data sources	_	_	Charges own institution and state billing #	Hospital charges
ANALYSIS AND INTERPREATION OF RESULTS:				
Time horizon & discount rate	_	_	_	_
Sensitivity analysis	_	_	_	_

% asymptomatic patients in study population.
#Medical Consumer Price Index

Table 3.1: Study characteristics of the studies assessing the costs and benefits of carotid endarterectomy: *(Continue)*
RETROSPECTIVE STUDIES: OBSERVATIONAL DATA, COST DESCRIPTION.

Author(s)	Maini et al	Green et al	Smithies et al	Radestock.
Year & Country	1990, USA	1987, USA	1997 UK (Wessex)	1992, UK (Newcastle)
Original currency	US$; 199?	US$ 1985	£; 1996	£; 1992?
Patient population	Symptomatic asympt (15%)*	_		? symptomatic
Number	215	157		77
Age (mean) years	67	67		59
Male	63%			76%
Study period	10 years	12 months		?5 years
STUDY DESIGN				
Alternatives considered	Describing CEA over two 5-year periods	University vs. Community hospital	Describing CEA cost in different NHS trusts	Comparing CEA cost with that of alternative stroke prevention strategies from literature
DATA COLLECTION:				
Outcome measures	Outcome & cost over time	Cost of CEA	Cost of CEA	CEA cost description
Effectiveness data sources	_	_	_	_
Cost data sources	Hospital charges MCPI 1978#	Hospital financial data	HRG costs	NHS costs
ANALYSIS AND INTERPREATION OF RESULTS				
Time horizon & discount rate	_	_	_	_
Sensitivity analysis	_	_	_	One-way

* % asymptomatic patients in study population.
#Medical Consumer Price Index

Table 3.2: Results and conclusions of the studies assessing the costs and benefits of carotid endarterectomy:
MARKOV MODELLING STUDIES – COST-EFFECTIVENESS ANALYSIS.

Author(s)	Kuntz et al.	Nussbaum et al	Cronenwett et al	Lavenson et al.
Year & Country	1996, USA	1996 USA	1997, USA	1998, UK
CEA cost	11 390	12 495	8 500	3 300
Stroke cost:				
acute	8 550	7 026	9 000	
Annual	24 820	21 233	18 000	
Baseline results	For typical NASCET patient CEA provides benefit of 0.35 discounted QALYs at incremental cost of $4100 per QALY gained.	Life expectancy 7.18 years for observation; 7.26 for aspirin; 7,63 for NASCET; 7.69 UMHC. Lifetime cost: with aspirin = 24 070 CEA NASCET: 23 538	Average life expectancy in medical 11.6 vs. 11.9 in surgical group. QALYs of 7.87 for medical and 8.12 for surgical treatment.	Costs in £ sterling
Sensitivity analyses	In symptomatic patients: not very sensitive to wide variations in baseline variables.	Model relatively insensitive to small variations in individual parameters		Most sensitive to age changes and stroke risk.
Best	Incremental CER[1] of CE vs. medical therapy: $400/ QALY[2] gained for a 50-year man and $33 800 for an asymptomatic 50-year male patient.	Observe & aspirin treated groups: highest % of strokes, lifetime costs of observation and aspirin most sensitive to changes in cost. Very high stroke rate CEA more cost-effective.	Younger patient with lower stroke rate during medical care resulted in best outcome.	45 year old ; low 1-month stroke risk post-op; high stroke risk without CEA. CEA cost £3224, gave 10.3 QALM[3] Cost of £3800/QALY
Worst	Incremental CER for CEA= $11 300/ QALY gained in 75 year old male with symptoms. $89 500/ QALY in 75 year old asymptomatic male	If peri-operative stroke rate exceeds 12% the benefit of CEA becomes very small	Age variable influenced cost-effectiveness the most. Stroke rate during medical care second.	85 year old; high 1-month stroke risk post-op; low stroke risk with no CEA. CEA cost £4993; Generated 0.6 QALM*. Cost: £90000/QALY
Conclusions	Symptomatic patients: CEA efficient use of resources. No symptom patients: CE not efficient.	CEA less expensive than either observation or aspirin and also results in increased QALYs	Asymptomatic ≥ 60-99% stenosis	

[1] CER = Cost-effectiveness ratio [2] QALY = Quality Adjusted Life Year [3] QALM = Quality Adjusted Life Months

Table 3.2: Results and conclusions of the studies assessing the costs and benefits of carotid endarterectomy: *(Continue)*

RETROSPECTIVE STUDIES: OBSERVATIONAL DATA, COST ANALYSIS.

Author(s)	Back et al	Dardik et al.	Mellissano et al.	Kraiss et al
Year & Country	1997, USA	1997, USA	1997, Northern Italy	1995, USA
Sensitivity analysis	–	–	–	–
CEA cost	Mean cost	Mean cost	Mean cost	Charges
Conventional	11 456 ± 4072	9508 ± 724	6 764 ECU	11 140 ± 729
Alternative	9 739 ± 4151	8572 ± 246	3 036 ECU	5 861 ± 229
Results & Conclusions	Cost associated with CEA reduced by introducing a critical pathway, without increased risk if patients managed according to approved protocol	A critical pathway can reduce CEA cost but it is important to establish an accurate control group	Selective use of angiography, ICU, routine use of regional anaesthesia & reduced hospital stay lower cost of CEA without compromising quality	CEA can be safely performed without routine protocol. Using the alternative protocol, charges significantly reduced

[1]GA = General anaesthesia

Table 3.2: Results and conclusions of the studies assessing the costs and benefits of carotid endarterectomy: (*Continue)*

RETROSPECTIVE STUDIES: OBSERVATIONAL DATA, COST ANALYSIS.

Author(s)	Garrard et al	Ballard et al.	Pollard et al.	Ammar.
Year & Country	1997, USA	1997, USA	1997, USA	1996 USA
Sensitivity analysis	–	–	–	–
CEA cost	Total charges	Mean cost	Cost p.a.	Charges over time
Conventional	20 203	7 608	74 000 p.a.	23 000
Alternative	14 174	5 534	15 000 p.a.	13 000
Results & Conclusions	Angiograms 43% of total costs of CEA. Non-routine use of angiogram does not increase post-op risk of stroke or LOHS.[2]	Agreement between duplex and angiogram in detecting stenosis > 45% No difference between stroke & death rate for CEA based solely on duplex. CEA performed on duplex results is "cost-effective" and appropriate	Outpatient preoperative evaluation & same day admission associated with a decrease in length of hospital stay which led to cost savings	Cost containment strategies to reduce CEA charges. Reported on % use of angiogram, ECGs, blood tests, X-rays, carotid shunts, ICU stay. Cost-cutting strategies can reduce charges while maintaining patient safety

[1]GA = General anaesthesia

Table 3.2: Results and conclusions of the studies assessing the costs and benefits of carotid endarterectomy: (*Continue)*
RETROSPECTIVE STUDIES: OBSERVATIONAL DATA; COST DESCRIPTION

Author(s)	Smurawska et al	Hirko et al.	Luna et al.	Patel et al
Year & Country	1997, Canada	1996, USA	1995 USA	1995, Australia
Sensitivity analyses	–	–	–	–
CEA cost	Over time	Charges over time	Mean charges	Mean costs
	10 394 ± 7821 (1994)	14 378 (1990)	11 750 (other facilities)	7 053 (with non-productive expenditure)
	6 857 ±3 014 (1996)	10 436 (1994)	8 060 (community hospital)	5 865 (without non-productive expenditure)
Results & Conclusions	LOHS decrease due to pre-op outpatient evaluation. Lower complication rates, but more asymptomatic CEA. Changes in management of patients having CEA with decrease in hospital stay and decrease in ICU[1] stay reduce costs	Angiography prior to CEA decreased over time. LOHS decreased over time, also decrease in ICU stay. Decrease in CEA charges (1990 – 1994) Study documented changing nature of CEA and documents that changes have not adversely affected safety of CEA.	Limited use of ICU and short post-operative stays reduce overall hospital costs. Cost saving measures can be implemented without adversely affecting patient outcome.	Areas of "non-productive" expenditure, which does not contribute to patient care, but increase cost of CEA. These areas include prolonged pro-op stay, omitted or repeat investigations and ICU use post-op. Removing these cost would reduce cost of CEA.

[1] ICU = Intensive Care Unit; [2] LOHS = Length of hospital stay *Medical Consumer Price Index

Table 3.2: Results and conclusions of the studies assessing the costs and benefits of carotid endarterectomy: (*Continue)*
RETROSPECTIVE STUDIES: OBSERVATIONAL DATA, COST DESCRIPTION.

Author(s)	Maini et al	Green et al.	Smithies et al	Radestock.
Year & Country	1990, USA	1987, USA	1997 UK (Wessex)	1992, UK (Newcastle)
Sensitivity analyses	–	–	–	–
CEA cost	Charges over time 3 113 (1987 -1983) 2 620 (1984 – 1988)	CEA cost at two hospitals 6126 (University hospital) 3918 (Community hospital)	"Estimation" of CEA cost based on HRGs from health professionals. 1890 - 4672	Mean cost 3 300
Results & Conclusions	LOHS and costs decreased over time Reduced LOHS and cost of CEA can be reduced without negative effects on peri-operative morbidity and mortality rates.	Results obtained at a community hospital are comparable to results at a university hospital.	CEA although costly offers health gain equal with many other procedures on the NHS tariff.	

Table 3.3: Study characteristics of pre-operative investigations for carotid endarterectomy in symptomatic populations and asymptomatic populations: *SYMPTOMATIC POPULATIONS:* COST-EFFECTIVENESS ANALYSIS.

Author(s)	Kent et al.	Vanninen et al.	Lavenson et al.	Hankey et al.
Year & Country	1995, USA	1996 USA	1996, USA	1990, UK
Original currency	Cost in 1993 US$	Cost in ? US$	Costs in 1996 US$	Costs in 1992 sterling
Number	88	45 (1000)[3]	100 (48 symptomatic; 52 asymptomatic)	296 (1000)[3]
Age (mean) years	70	58	_	_
Male	66%	84%	_	_
Study period	19 months	12 months	_	10 years
STUDY DESIGN:				
Alternatives considered	Duplex, MRA[1], CA[2], Combination	Duplex, MRA[1], CA[2], Combination	Duplex	Clinical evaluation vs. Duplex
Evaluation form	Cost effectiveness analysis	Cost effectiveness analysis	Cost savings/duplex performed Cost of stroke avoided/duplex performed.	
Modelling	Markov	Scenario setting	_	Scenario setting
DATA COLLECTION:				
Effectiveness data sources	NASCET ; ECST	Own centre	NASCET;ACAS	Published data
Outcome measures	Incremental cost-effectiveness ratio for CEA, QALYs	Number of strokes prevented	Cost effect of duplex examination on strokes avoided	Costs & number of disabling strokes after CA
Cost data sources	1993 Medicare Reimbursement	Local hospital, Kuopio University Hospital. Finland	_	NHS cost estimates; BMA fees; BUPA
ANALYSIS AND INTERPREATION OF RESULTS:				
Time horizon & discount rate	Cost & life expectancy at 5%	_	_	_
Sensitivity analysis	Multi-way	Scenario setting	_	_

[1] magnetic resonance angiography; [2] conventional angiography; [3] number in modelling

Table 3.3: Study characteristics of pre-operative investigations for carotid endarterectomy in symptomatic populations and asymptomatic populations: *(Continue)*

SCREENING *ASYMPTOMATIC POPULATIONS* FOR CAROTID STENOSIS; MARKOV MODELLING STUDIES; COST-EFFECTIVENESS ANALYSIS.

Author(s)	Derdeyn et al.	Lee et al.	Yin et al
Year & Country	1996, USA	1997, USA	1998, USA
Original currency	US$; 1996	US$; 1994	US$; 1994
Number	215 (1000)	–	–
Age (mean) years	60	65	60
Males	100%	100%	
STUDY DESIGN			
Alternatives considered	Duplex screening: Population with high prevalence of carotid stenosis vs. low prevalence population.	Duplex screening vs. no screening.	Duplex screening vs. no screening.
Effectiveness data sources	Published data; NASCET; ACAS.	ACAS.	Published data; NASCET; ACAS.
Outcome measures	Incremental cost/ incremental QALY; cost-effectiveness ratio.	QALY; costs; marginal cost-effectiveness ratio.	QALYs & lifetime costs of care.
Cost data sources	Medicare 1995.	California Office of Statewide Health Planning and Development.	Medicare 1994.
Time horizon & discount rate	20 years.	30 years; 3% costs & utilities.	Costs & QALYs discounted at 5%.
Sensitivity analysis	Probabilistic; multi – way.	Probabilistic; multi – way.	Probabilistic; multi – way.

Table 3.4: Results and conclusions of pre-operative investigations for carotid endarterectomy in *symptomatic and asymptomatic populations.*

***SYMPTOMATIC POPULATIONS:* COST-EFFECTIVENESS ANALYSIS**

Author(s)	Kent et al.	Vanninen et al.	Lavenson et al.	Hankey et al.
Year & Country	1995, USA	1994 USA	1996, USA	1990, UK
Sensitivity analyses				–
Best	For pre-op detection of 70 –99% stenosis combination of duplex & MRA supplemented by CA is associated with greater morbidity & mortality.	Duplex & MRA with sensitivity of 100% resulted in 27.9 strokes prevented	–	–
Worst	Using Duplex alone less expensive, but performing CA alone resulted in unacceptable high costs	CA only, complication rate of angiography of 0.5%; sensitivity of 100% resulted in 23.3 strokes prevented	–	–
Conclusions	Combination strategy of duplex & MRA reserving CA for disparate results more cost effective than CA alone.	Both models, which included duplex before CA, were cheaper than when CA is routinely performed on all patients. Combination of Duplex & confirmatory MRA/CA most cost-effective	Cost savings from the use of duplex examinations to identify carotid artery lesions for CEA and thus prevent "costly" strokes	Patient selection prior to CEA should consist of clinical evaluation and Duplex. Performing Duplex on all clinically suitable patients before CA is recommended

[1] CER = Cost-effectiveness ratio [2] QALY = Quality Adjusted Life Year [3] QALM = Quality Adjusted Life Months

Table 3.4: Results and conclusions of pre-operative investigations for carotid endarterectomy in *symptomatic and asymptomatic populations*: *(Continue)*
SCREENING *ASYMPTOMATIC POPULATIONS* FOR CAROTID STENOSIS; MARKOV MODELLING STUDIES; COST-EFFECTIVENESS ANALYSIS.

Author(s)	Derdeyn et al.	Lee et al.	Yin et al.
Year & Country	1996, USA	1997, USA	1998, USA
Baseline results	Annual screening of a population with a high prevalence of carotid stenosis gained 30 QALYs at incremental cost of £35 130 and $52 588 in low prevalence populations.	Over a lifetime, screening resulted in an additional cost of $1553 per person and generated 0.013 QALY (4.75days) more than no screening at a cost of $120 000 /QALY	Screening of a hypothetical population increased average QALYs and lifetime cost. Incremental cost /QALY gained was $39 495. Linking age & prevalence likely to increase the cost-effectiveness of screening for asymptomatic populations
Sensitivity analysis			
Best	One-time screen of asymptomatic population with high prevalence of carotid stenosis with duplex followed by arteriography and surgery if indicated is cost-effective.	Marginal cost-effectiveness sensitive to disease prevalence. Cost-effectiveness ratio decreased to $50 000/QALY with population carotid stenosis prevalence of 40%	Screening was more sensitive when performed once in high disease prevalence populations
Worse	One time screening of low prevalence populations was borderline cost-effective, annual screening produced negative QALYs.	With a CEA complication rate of 3%-4 % marginal cost-effectiveness ratio $196000 and $318 000	Combination of changes in the rate of peri-operative mortality & complications, cost of duplex, patients age and interval between examinations made screening more costly and less effective.
Conclusions	One-time screening of high prevalence populations might be cost-effective and annual screening was very expensive. Annual screening of low prevalence populations was detrimental	Screening approaches acceptability only under implausible conditions (free screening instrument with perfect test characteristics, asymptomatic population with 40% prevalence of carotid stenosis)	Screening for asymptomatic carotid stenosis can be cost-effective when both screening and CEA are performed in centres of excellence.

Figure 3.1: Schematic presentation of studies examining cost and benefits of CEA.

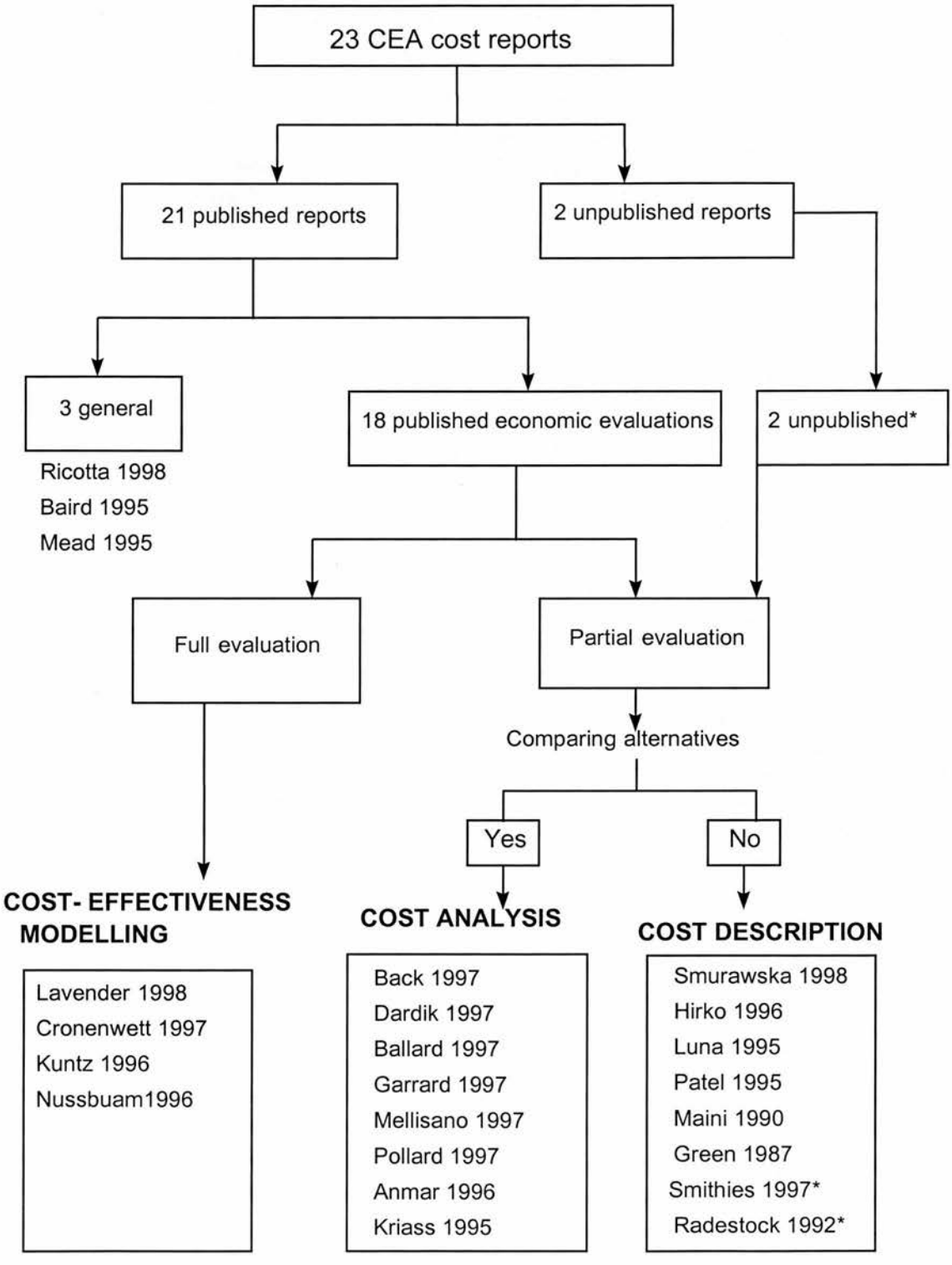
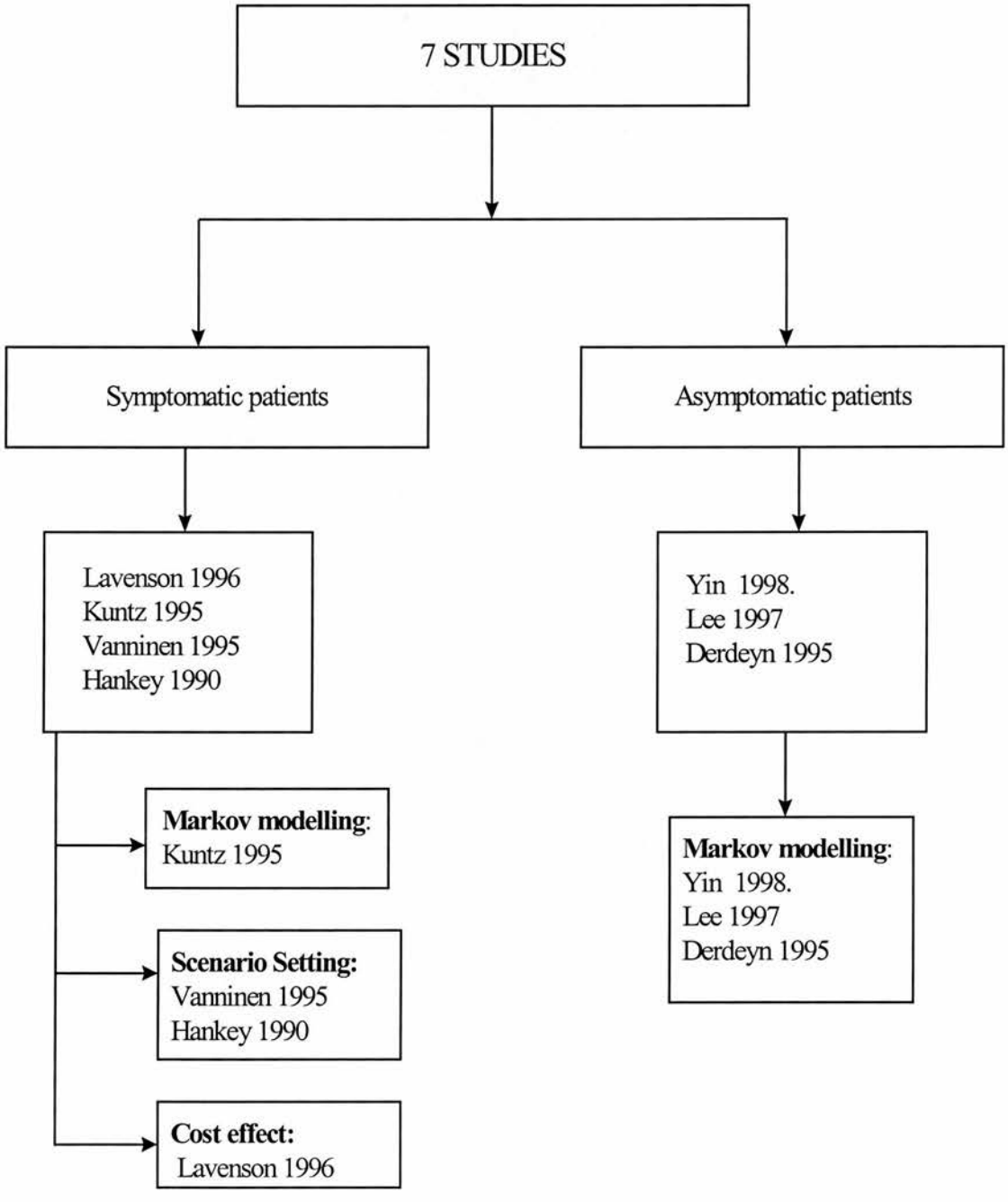


Figure 3.2: Schematic presentation of studies examining the cost and benefits of the peri-operative investigations associated with carotid endarterectomy.



CHAPTER FOUR: THE PROGRAMME COST OF IDENTIFYING PATIENTS FOR CAROTID ENDARTERECTOMY.

4.1 Introduction

The cost of carotid endarterectomy (CEA) reported in the literature has considered only the cost of the pre-operative investigations (Lavenson et al., 1996; Kent et al., 1995; Vanninen et al., 1995; Hankey et al., 1990) and the cost of the surgical procedure for the individual patient (Smurawska et al., 1998; Back et al., 1997; Mellisano et al., 1997; Garrard et al., 1997; Ballard et al., 1997; Pollard et al., 1997; Hirko et al., 1996; Smithies et al., 1996; Ammar, 1996; Kriass et al., 1995; Luna et al., 1995; Patel et al., 1995; Radestock, 1992; Maini, 1990; Green et al., 1987). The cost incurred in selecting patients from the potential "pool" of referred patients has been largely ignored in these studies. In order to estimate the total direct cost of this procedure, it is necessary to include the cost incurred at the different levels of investigation prior to carotid endarterectomy, since the cost of investigating a large "pool" of potential patients is not inconsequential and can not be ignored.

The "pool" of potential patients is those experiencing symptoms suggestive of a transient ischaemic attack (TIA) and minor non-disabling stroke associated with the distribution of the carotid artery. These patients are usually assessed clinically by a neurologist, geriatrician, stroke physician or vascular surgeon. If the patient is considered clinically to have a transient ischaemic attack originating in the carotid territory and is fit for surgery, the patient is referred for a duplex investigation to determine the degree of internal carotid stenosis. Patients with stenosis of more than

about 70%, who are deemed medically fit for probable carotid surgery are then usually referred for carotid angiography to obtain a more precise estimate of the degree of stenosis. Once stenosis of 70% or more is confirmed the patient is prepared for a carotid endarterectomy. This investigation pathway or "work-up" for patients suffering a TIA is only applied to patients who have suffered a recent ischaemic event to ensure that carotid surgery is performed within a maximum time period of six months from most recent symptoms (Humphrey, 1994; Brown et al., 1992; ECST, 1991; Brown et al., 1994).

The aim of this study was to estimate the "total direct" programme cost of carotid endarterectomy to the National Health Service (NHS) as applied to a cohort of patients with transient ischaemic attack and non-disabling stroke referred to a teaching hospital for CEA assessment, investigation and carotid endarterectomy. The "total direct" programme cost of carotid endarterectomy incorporates the cost incurred during the "work-up" of a potential "pool" of carotid endarterectomy patients as well as the cost of the carotid endarterectomy "procedure". Only the "direct" cost as estimated in two independent study populations is reported.

The cost of identifying patients from a cohort of potential candidates who might be suitable candidates for a carotid endarterectomy was described as the "work-up" cost. The "work-up" for CEA was defined as the assessment at the neurovascular clinics, the duplex examination and the carotid angiogram. The cost associated with the "work-up" was estimated as a deterministic value, (Barber and Thompson, 1998) or alternatively described as a top-down approach estimating the unit cost for a neurovascular attendance, a duplex investigation and a carotid angiogram.

The CEA "procedure" is defined as the episode of care in hospital and includes the bed days and the theatre component. The cost of carotid endarterectomy, the "procedure" cost, was estimated using "patient specific" cost data which were prospectively collected in consecutive patients. The use of patient specific cost data to estimate cost is also known as a bottom-up approach (Barber and Thompson, 1998; Whynes and Walker, 1995). Applying the "procedure" cost to the number of patients identified for carotid endarterectomy in the "work-up" of the "pool" of patients a total direct "programme" cost was estimated. Costs are estimated by measuring the quantities of resources utilised and by assigning a unit cost or price to the resources used (Drummond, 1996).

Since economic evaluations of health care procedures are costly and can not always be performed when necessary and in all settings, a sensitivity analysis was performed. The cost estimates obtained in this study were used to address the uncertainty encountered with economic evaluations associated with these programmes. A sensitivity analysis involves three steps. Firstly, the identification of the uncertain parameters for which a sensitivity analysis is required, secondly the specification of the plausible ranges over which uncertain factors are thought to vary, and thirdly the calculation of study results based on combinations of the best guess.

4.2 Methods

4.2.1 Setting

The cost description study estimating the total "programme" cost of CEA was performed in three hospitals in Scotland. Two of the three hospitals are large general major teaching hospitals (Royal Infirmary, Edinburgh and the Western General Hospital, Edinburgh) covering a full range of services and one a general hospital (Southern General Hospital, Glasgow) with some teaching units.

Data were collected at the Western General Hospital to estimate the "work-up" cost of CEA. Itemised cost data were prospectively collected on a consecutive number of carotid endarterectomy patients operated on at the specialised vascular surgery unit at the Royal Infirmary, Edinburgh and at the vascular unit at the Southern General Hospital, Glasgow, to estimate the procedure cost of CEA.

4.2.2 Description of the two study populations.

To estimate the "work-up" cost of carotid endarterectomy a cohort consisted of patients identified from the Neurovascular clinic attendance book (July 1997 to June 1998) and the Lothian Stroke Register (July 1996 to June 1997) at the Western General Hospital, Edinburgh was studied over a one-year period. The Lothian Stroke Register (Appendix 3 and 4) is a hospital-based stroke register with the aim to collect information on stroke, transient ischaemic attack and retinal artery occlusion in patients presenting at the Western General Hospital whether admitted or not. Both the neurovascular clinic attendance book and LSR were used, since these two data sources complement each other. The LSR provided detailed information on the

number of patients with carotid territory transient ischaemic attack, the number of duplex investigations and number of angiograms performed on the cohort, whereas the neurovascular clinic attendance book provided essential information on the number of patients who might be considered for possible CEA.

The cohort of patients studied to determine the "procedure" cost, comprised of consecutive patients operated on at the Royal Infirmary in Edinburgh and Southern General hospital in Glasgow for whom patient specific cost data were collected during the period 15 December 1997 to 15 July 1998 at the Royal Infirmary, Edinburgh and during the period 1 January 1998 to 17 July 1998 at the Southern General hospital in Glasgow.

4.2.3 Defining the programme.

The programme is defined as the "work-up" to CEA and the CEA "procedure" itself (Figure 4.1). Using the selection criteria described in Section 4.2.4, the "pool" of patients who might be potential candidates in the work-up to CEA was identified. Patients referred to the neurovascular clinics at the Western General Hospital with transient ischaemic attack (TIA)-like symptoms and clinically assessed as having carotid territory ischaemic events were considered suitable candidates for further investigation. The degree of stenosis in the internal carotid artery was then determined using the non-invasive duplex imaging technique. Based on a duplex finding of stenosis in the internal carotid artery of 70% or more, probable candidates for carotid endarterectomy were identified. These candidates were then evaluated using conventional carotid angiography, the current "gold standard" to determine the

degree of stenosis more accurately. Only patients who displayed internal carotid artery stenosis of 70% or more, not having an occluded vessel or any complications associated with the angiography were regarded suitable candidates for carotid endarterectomy and were referred for surgery.

4.2.4 Selection criteria at each level of investigation to estimate the "work-up" cost of CEA.

Inclusion and exclusion criteria *(Figure 4.2).*

Neurovascular clinic: (NVC)

Inclusion criteria.

- Patients with symptoms suggestive of transient ischaemic attacks, minor and major non-disabling stroke, Amaurosis Fugax, retinal artery occlusion as well as other non-specific "neurological" symptoms.
- Appointments of longer than 30 minutes, since 30-minute or longer appointments are allocated to all "new patients" to allow sufficient time for a thorough clinical assessment.

Exclusion criteria.

- Appointments of less than 30 minutes duration ("follow-up visits").

Lothian Stroke Register: (LSR)

The modified Rankin Scale (Oxford Handicap Scale) of clinical prediction of outcome at one year was used to select patients with a diagnosis of TIA or stroke. The values, 0 to 5, in the Modified Rankin Scale are defined as follows:

- 0 indicates no symptoms;
- 1 refers to minor symptoms which do not interfere with lifestyle;
- 2 means some restriction to lifestyle, but patients can look after themselves;
- 3 is defined as significant restriction to lifestyle, which prevent total independence;
- 4 refers to a severe handicap preventing independent existence, though not requiring constant attention and
- 5 means patients are severely handicapped, totally dependent and requiring full-time attention (Bamford et al., 1989).

Inclusion criteria.

- All patients with probable and definite anterior territory carotid ischaemic attacks and retinal artery occlusion were included provided:
  i. *The Rankin Scale of clinical prediction of outcome at one year was 0, 1 or 2, and*
  ii. *That the Oxford Handicap Scale before the stroke was not 3, 4, or 5.*
- These patients were regarded as a minor stroke patients and were included in the group of "possible patients" suitable for further investigation for CEA.

Exclusion criteria.

- Patients with a disabling stroke and a previous stroke were excluded if the Oxford Handicap Scale of clinical prediction of outcome at one year were 3, 4 or 5 regardless of the Oxford Handicap Scale before the event.
- Patients with posterior circulation transient ischaemic attacks were also excluded since the benefit of carotid endarterectomy is specifically for the anterior circulation ischaemic events, i.e. carotid arteries.
- Patients with epilepsy, migraine, tumours, syncope, dizziness, hypoglycaemic, hyperventilation and other non-specific symptoms seen at the clinics.
- Patients with atrial fibrillation.

Duplex investigation

Inclusion criteria.

Patients with internal carotid artery stenosis of 70% or more detected with duplex ultrasound examination were included for further investigation since the benefit of CEA in reducing the risk of stroke in patients with stenosis of 70% or more has been shown in two large randomised controlled clinical trials (ECST Collaborative Group, 1991; NASCET Steering Committee, 1991).

Exclusion criteria.

Patients with internal carotid artery stenosis of less than 70% detected with duplex ultrasound examination were excluded from this cohort.

Conventional carotid angiography.

Inclusion criteria.

- Internal carotid artery stenosis of 70% or more.

Exclusion criteria.

- Internal carotid artery stenosis of less than 70%.
- Any complications during and immediately after angiography.
- Internal carotid artery occlusion of the symptomatic artery.
- Medically "unfit" for surgery due to other comorbidities.

4.2.5 Measurement of the resource quantities in the programme.

4.2.5.1 Resource quantities to select patients for carotid endarterectomy from a "potential cohort" of candidates, the "work-up" cost.

The resource quantities at each level in the work-up for a typical uncomplicated patient who proceeded to carotid endarterectomy included *one attendance* as a "new" patient at the neurovascular clinic, *one carotid duplex ultrasound* investigation, *one follow-up consultation* after the duplex investigation to inform the patient of the findings of the duplex and *one conventional carotid angiography* before the carotid endarterectomy.

4.2.5.2 Resource quantities used in performing carotid endarterectomy, the "procedure" cost.

Resource quantities used in performing carotid endarterectomy included the resources used for one episode of care in hospital for the CEA from admission to discharge. An episode of care included the peri-operative period, the time in theatre and the hospital stay after the procedure in theatre. The episode of care in hospital included peri-operative and post-operative bed days and resources used in theatre. Data collected on the resources used for these patients having CEA during the pre-operative stage, prior to the hospital admission, were deterministic in nature, whereas data collected during the episode of care were patient specific cost data.

4.2.5.3 Resource quantities used for the carotid endarterectomy after discharge from hospital, the post-operative cost.

The resources used during the post-operative period included one follow-up visit at the vascular surgery outpatients department with the vascular surgeon approximately six weeks after the procedure and one post-CEA duplex investigation performed at that time.

4.2.6 Assignment of prices or unit costs.

4.2.6.1 Neurovascular clinic consultation unit cost.

The average unit cost per "new" neurovascular attendance was based on costs published in the Scottish Health Service Costs (SHSC) 1996/1997. These costs are produced by the Scottish Office of the Department of Health and include direct and allocated costs associated with an attendance at an outpatient department. The direct cost per attendance includes medical and nursing staff, and laboratory cost. The allocated costs incorporate all other costs not included as direct costs.

The arithmetic mean of the cost per neurovascular outpatient attendance at the Western General Hospital, the Southern General hospital and the Royal Infirmary Edinburgh was estimated at £99 per outpatient attendance (Neurology outpatient departments: Western General Hospital (£63), Southern General Glasgow (£113) and Royal Infirmary Edinburgh (£120)). Though patients with symptoms suggestive of transient ischaemic events are routinely assessed at neurovascular outpatients clinics, divisions of the neurology departments, these patients are not routinely seen at the Department of Neurology at the Royal Infirmary but at the Vascular Surgery Outpatient Department at the Royal Infirmary, Edinburgh. This outpatient department at the Royal Infirmary, Edinburgh however is not separately accounted for in the Scottish Health Services Costs Book.

All vascular outpatients' consultations are incorporated with general surgery outpatient consultations, which consist of a completely different case-mix than those patients assessed at a neurovascular clinic. The vascular surgery outpatient

department attendances are assumed to be incorporated in the attendance figures of general surgery outpatients at a cost per attendance of £46. This cost of £46 is considered an underestimation of a neurovascular clinic consultation when compared to the cost estimates from the Neurology departments at the Western General hospital and the Southern General hospital. The calculation of an arithmetic mean for an outpatient attendance at the two hospitals with neurovascular clinics was considered as the most appropriate alternative in estimating the cost for a "new" patient's visit at an outpatient department. The average unit cost per "new" neurovascular attendance at an outpatient department was therefore estimated at £88 and a follow-up consultation at the clinic was estimated at half the cost of a "new" neurovascular attendance at £44. The follow-up visits are usually of shorter time duration than a "new" neurovascular clinic attendance and the cost for such a visit was therefore adjusted to £44 per follow-up visit.

In determining the cost of haematological and biochemistry investigations for the CEA cost description cohort prior to carotid endarterectomy, the unit cost estimates were based on the Pricing Index of Investigations from the National Health Service. All radiological examinations and other radiological investigations were determined using assigned costs form the Department of Radiology at the Royal Infirmary, Edinburgh which include allocated costs and human resource costs.

4.2.6.2 Unit costs assigned for duplex ultrasound.

The total cost of one duplex investigation was estimated at about £70. The cost of the duplex ultrasound equipment and consumables was calculated using the capital cost of the room, the depreciated current value of the machine, the annual maintenance and consumables, totalling a cost £26.60 per duplex investigation. The human resource cost was estimated at £38.67 per examination and includes the salary of a full-time Superintendent III radiographer and 30% of a consultant radiologist's annual remuneration. The estimated overhead cost inclusive of electricity, heating and administration was estimated at £5.17 (Appendix 5).

4.2.6.3 Unit cost per carotid angiography.

The direct cost of equipment and consumables used for a carotid angiography was calculated from existing sources at the Department of Radiology at the Royal Infirmary, Edinburgh. Hourly remuneration for human resources was calculated using published pay scales for the medical staff involved and includes superannuation and National Insurance. Hospitalisation or bed day cost was calculated using the Health Service Cost 1996/1997 of the Information and Statistics Division of the NHS in Scotland. The equipment and consumable cost for both the selective and non-selective (arch) intra-arterial digital subtraction angiogram was estimated at £280 per investigation. The total human resource cost of a radiologist, two radiographers and an auxiliary nurse performing a carotid endarterectomy was estimated at about £74. The total direct procedure cost was thus estimated at £354 not including the overnight hospitalisation.

Overnight accommodation is usually required when performing a carotid angiogram. The length of hospital stay is usually regarded as two bed days resulting in an additional cost of £596 for hospitalisation using the mean estimated bed day cost of £298. The total direct and allocated cost of a carotid angiogram was estimated at £950 per angiogram.

A unit cost estimate of any other radiological procedures carotid endarterectomy patients might have had, was based on cost estimates from the Departments of Radiology and Directorate of imaging at the Western General Hospital and the Royal Infirmary, Edinburgh. A chest X-ray was estimated at £20 and a computed tomography (CT) scan at £121.

4.2.6.4 Unit costs for the resources used during carotid endarterectomy procedure.

The Scottish Health Service Costs (SHSC) 1996/1997 was used to describe all costs associated with the hospitalisation of a patient for the carotid surgery. Cost is analysed between direct and allocated costs. Direct cost includes medical, dental and nursing staff, and the cost of professions allied to medicine. Direct cost, as published in the SHSC, was used for the hospitalisation of each individual in the prospective CEA costing study with the exception of the direct theatre costs, which were collected during the study (Appendix 6). The theatre cost and the laboratory cost components of the direct cost per surgical case were adjusted using the cost estimations from the itemised data collection (Appendix 6). The costs for all anaesthetic equipment and medications as well as all surgical materials and equipment were obtained from the Purchase Order Details from the

Procurement Department for the Royal Infirmary Edinburgh, National Health Trust, published April 1998. The cost assigned to bed days was calculated using the Scottish Health Services Costs 1996/97 as reference. Allocated costs as published in the Scottish Health Services Costs 1996/1997 include overheads as well as capital charges and was used for all capital and overhead cost estimations in the study.

4.2.7 Sensitivity analysis: Deterministic/ probabilistic.

Sensitivity analyses were performed for the programme cost of a cohort of potential patients investigated for possible carotid endarterectomy and for the procedure cost of carotid endarterectomy.

4.2.7.1 Programme cost sensitivity analysis: deterministic analysis.

In the case of the programme cost, point estimates for the parameters in the work-up to carotid endarterectomy were applied to determine the cost (a top down approach). The sensitivity analysis performed on these point estimates is considered to be deterministic in nature. A base transition ratio model was constructed using the proportions in the transition progression from a consultation as a "new" patient to duplex investigation, to a subsequent follow-up consultation, to a carotid angiogram and to the carotid surgery. The point estimates used in the study were applied to the observed transition ratio observed in the work-up to CEA in this study to estimate the cost incurred at each transition level.

Sensitivity analyses for the programme cost were thus performed from two perspectives by:

- altering the transition progression ratio observed in the programme.
- and alternatively varying the individual cost parameters in the programme.

The key variables or parameters, which might affect the overall programme cost of carotid endarterectomy, include:

- the number/proportion of "new" consultations of all the consultations at the NVC;
- number / proportion of duplex investigations of the "new" consultations;
- number / proportion of follow-up consultations after duplex investigations;
- an angiogram performed or not done;
- Magnetic Resonance Angiography (MRA) performed instead of digital subtraction angiography (DSA) (conventional carotid angiography) and
- the cost estimates for each of the individual parameters.

4.2.7.2 Procedure cost sensitivity analysis: probabilistic analysis.

Patient specific cost data collected in the prospective costing study allow for a probabilistic sensitivity analysis. The key parameters for this sensitivity analysis include:

- the cost of the peri-operative investigations with and without an angiogram;
- the cost of the hospitalisation divided into bed days and theatre cost and
- the cost of the post-operative stage.

The plausible ranges are specified using the 95% confidence interval around the mean for these key parameters.

4.2.8 Measurement of time intervals in the work-up to CEA.

Since the optimum benefit derived from carotid endarterectomy is soon after a person has experienced a transient ischaemic event, (Humphrey, 1994; Brown et al., 1992; ECST, 1991) time-to-event variables in the work-up to carotid endarterectomy were collected from the Lothian Stroke Register and CEA cost description study. The data collected on these time-to-event variables were only analysed to describe the time delays that might occur in the referral of these patients for appropriate health care.

Data were collected on the time intervals from most recent transient ischaemic attack to first visit with the health care system; from first visit with the health system to first appointment with either a consultant neurologist, stroke physician or vascular surgeon; from consultation with a consultant neurologist or vascular surgeon to duplex investigation; from duplex investigation to carotid angiography and from angiography to carotid endarterectomy.

These variables include:

- Time in days from most recent transient ischaemic attack to first assessment at the neurovascular clinics and or vascular clinic;
- Time in days from assessment at neurovascular clinics to duplex investigation;
- Time in days from duplex investigation to carotid angiogram and
- Time in days from carotid angiogram to carotid endarterectomy.

4.3 Data management and analysis

Data recorded on data collection forms for the carotid endarterectomy cost description study were punched, verified and stored using Microsoft, Excel Version 5. All cost calculations were done using Microsoft Excel version 5. Separate files for demographic variables, time to event variable, pre-operative investigations, hospitalisation, human resources in theatre, surgical equipment and instruments, anaesthetic equipment and medications were merged using SPSS version 7 for Windows.

Policy makers, purchasers and providers need to know the total cost of implementing a treatment. The fundamental information for cost data is therefore the arithmetic mean since it is possible to estimate the total cost of an intervention from the arithmetic mean. Measures such as the median, mode and geometric mean cannot provide an estimate of the total cost. Although the distribution of costs is often highly skewed, it does not imply that the use of the arithmetic mean is inappropriate. Because of the skewness of the data the standard deviation alone is not the best way to present the spread of costs between individuals. Describing the variability in costs between individual is however important and it is useful to present the interquartile range.

The arithmetic means, as measure of location, and interquartile ranges are reported. The inter-quartile ranges (IQR) were defined as $Q_{0.25}$ - $Q_{0.75}$ The median cost, which can be interpreted as the most "typical" cost for individual patients are also reported. P-values or confidence intervals are not reported since costs between alternative treatments are not compared. Standard errors and

confidence intervals are not reported. Although they reflect the precision of the estimated mean, these measures are not considered appropriate ways to describe how costs differ between individuals (Altman et al., 1983; Barber and Thomson, 1998). Normal probability plots were used to assess the empirical distributions for evidence of departure from normality. The mean, median and IQR for the time-to-event variables in the work-up to CEA are reported.

All statistical analyses were performed using SPSS for Windows (Professional and Advanced Statistics options) and all the sensitivity analyses were performed using MS Excel version 5.

4.4 Results

4.4.1 The total direct "work-up" cost of a cohort of patients for potential CEA.

The Neurovascular clinic appointment book.

A total number of 964 patients were seen at the neurovascular clinics during the one-year period studied. Of these attendances, 790 appointments were 30 minutes or longer and were regarded as first time attendances for "new" neurological patients. The 790 patients identified represented the "pool" of potential CEA candidates who might be considered suitable candidates for CEA and might be entered into the LSR depending on the clinical assessment findings. (*Table 4.1*)

The Lothian Stroke Register.

Baseline characteristics.

Of 790 first or "new" consultations at the neurovascular clinics, 660 patients were entered into the register for the study year investigated, 412 (52%) patients were entered in the Lothian Stroke Register as having had a carotid territory ischaemic event and having a modified Rankin score of less than three. Four hundred and one (97.3%) duplex investigations were performed on the 412 patients identified with carotid territory ischaemia. Eleven patients did not have a duplex investigation for a variety of reasons. The main reasons were subsequent ischaemic events prior to the duplex investigation, which rendered them unsuitable for further investigations for possible CEA *(Table 4.1).*

Of the 412 patients identified, 244 (59%) were male and 168 (41%) were female. The age distribution of these patients was not normal and displayed a distribution curve that was slightly skewed to the left. The majority (47%) of patients was between 66 and 80 years of age (193/412), with 33% (136/412) being between 50 and 65 years of age. Ten percent of the study population was represented in the under 50 year age group as well as the above 80 years age categories, but with more (52%) females in the over 80 group compared to 42% females in the under 50 age group. The age group 50 to 65 years had the lowest percentage of female patients at 35% *(Table 4.2 and Figure 4.3).*

Of the 401 patients having carotid duplex investigations, a total of 237 (59%) patients did not have any degree of stenosis reported in either of the internal carotid arteries. "No" stenosis was defined as not having any degree of stenosis

(0%) reported, based on the findings of the carotid duplex investigation. Twenty-four (6%) patients had "no" stenosis reported in one artery and stenosis less than 70% reported in the other artery. Twenty-five (6%) patients had stenosis less than 70% in the both arteries reported. A combination of "no" stenosis in one artery with stenosis of 70% or more was found in 28 (7%) patients. Twenty-five patients (6%) had stenosis less than 70% in the one artery with 70% or more in the other artery. Stenosis of 70% or more was reported for both the internal carotid arteries in 19 (5%) patients. Seventeen patients (4.2%) had "no" stenosis in one artery with occlusion in the other artery. Occlusion on the one side with less than 70% stenosis on the other side was reported in 19 patients (5%). Six patients (1.5%) had stenosis of 70% or more on the one side with occlusion on the other side. Occlusion of both the right and left internal carotid artery was reported in one patient. Of the 401 patients, 286 (71%) had "no" stenosis or stenosis of less than70% with duplex examination (*Table 4.3 and Figure 4.4*).

Of the 401 patients, 78 (19.5%) had had stenosis more than 70%. Nineteen (5%) had stenosis of 70% or more reported for both internal carotid arteries. For the remaining 59 with stenosis of more than 70% in one artery, 28 were found to have "no" stenosis in the other artery and 25 had less than70% stenosis in the other internal carotid artery. Six patients had a combination of an occluded artery and more than 70% stenosis in the other artery. Only 26 (33%) of these 78 patients with stenosis of 70% in either internal carotid artery were referred for carotid angiography. Sixteen patients, who had stenosis of 70% or more but did not have an angiogram, had documented existing comorbidities, which rendered them unsuitable for carotid surgery. For the remaining 36 patients explanations as

to why angiograms were not performed could only be postulated and ranged from patient's preference, time period from most recent transient ischaemic symptoms to assessment by a consultant too long to derive any benefit from CEA *(Figure 4.4)*.

Fifteen of the 26 patients (58%) who had an angiogram proceeded to carotid surgery. The reasons why nine patients who had an angiogram performed, but did not have carotid surgery ranged from stenosis less than 70% determined with angiography, occlusion of the symptomatic artery, transient ischaemic complications suffered during the angiogram procedure, patient's preference not to proceed with surgery and anatomical difficulties.

Of the cohort having carotid transient ischaemic attacks 97% (401/412) had a duplex investigation, 6.3% (26/412) had an angiogram and 4.4 % (18/412) eventually had a carotid endarterectomy. Three of the eighteen patients from this cohort who had carotid endarterectomy performed, did not have an angiography prior to carotid surgery. Considering all patients with symptoms suggestive of transient ischaemic attacks or the "pool" of patients referred to the neurovascular clinic for investigation for possible carotid endarterectomy, only 2.3% (18/790) were operated on *(Figure 4.2)*.

The work-up cost of the study cohort of patients who might be suitable candidates for carotid endarterectomy was subsequently determined by applying the deterministic cost estimates from published data sources to the proportions of patients found at each of the levels using the data from the neurovascular appointment book and the LSR. These levels include the preoperative

consultations, duplex investigations, follow-up consultation and carotid angiograms.

The total cost for the pre-operative consultations and investigations was estimated by multiplying the number of neurovascular clinic consultations (790) with the *unit cost of a visit of £88.* A total cost of £69 520 was estimated identifying patients for possible carotid endarterectomy from a "pool" of potential candidates. The total cost of duplex investigations for this cohort was calculated at £28 070. The patients referred for a duplex investigation usually have a follow-up consultation visit for a discussion of the findings of the duplex investigation. The total cost of the follow-up visits was estimated at £17 644. The total cost of "all" the consultations for this cohort was estimated at £87 164. The total cost of the 26 angiograms performed was £24 700. The "work-up" cost for this cohort from consultation at a neurovascular clinic to duplex, to follow-up visit to angiography was estimated at a total cost of ***£139 934*** (*Table 4.4*).

4.4.2 The total direct CEA procedure cost.

Carotid endarterectomy cost description study.

4.4.2.1 Baseline characteristics (Table 4.5).

The total direct procedure cost of 64 consecutive carotid endarterectomy patients at two centres was estimated. Forty-two (66%) of the patients were investigated and operated on in the Royal Infirmary in Edinburgh. Twenty-two (34%) patients in Glasgow had all their pre-operative investigations and were admitted for surgery, but only 19 (30%) were operated on. Of the three patients who did not

have surgery, one suffered a stroke the day before the scheduled surgery, one could not give informed consent because of cognitive impairment and the third patient suffered a fatal myocard infarction on the eve of the operation.

The age distribution of the study population represented a normal distribution with the mean age of 67 years and a standard deviation of 8.1 *(Figure 4.5).* The majority of patients, 39 (64%), operated on was in the 66 to 80 year age category. 75% of the patients in the study population were men.

The work-up cost of this CEA cohort was estimated based on data from all 64 patients who were prepared for surgery. The procedure cost was based only on the 61 patients who had surgery.

4.4.2.2 Resources used during the pre-operative stage.

The resources used during the work-up of the patient, *the pre-operative stage*, to carotid endarterectomy included medical consultations, haematology and biochemistry investigations, carotid ultrasound and carotid angiography. The mean total cost estimated for this cohort during the work-up prior to CEA was £1359 (IQR 857 – 1976; median cost £1416) *(Table 4.6).* A total of 128 duplex investigations were performed on these 64 patients. Fifty-five of these patients had had two duplex investigations, one during the work-up to carotid endarterectomy and the second duplex the day prior to carotid endarterectomy. Six of the patients had only one duplex performed, but two patients had three duplex examinations and another patient had a total of four duplex investigations

during the period of assessment prior to surgery. Angiograms were performed in 66% of the patients prior to the carotid endarterectomy *(Table 4.7).*

Itemised costing of all haematology and biochemistry investigations were expressed per unit using the NHS scale and included the total cost of the equipment, overheads and human resource cost with a mean of cost £54 (median £51; IQR: £40 - £71).

The mean cost of the duplex investigations, the carotid angiography (procedure only) and computed tomography for the 64 patients was estimated at £533 with the interquartile range (IQR) £310 to £658. The mean total cost of the angiogram (bed days and procedure) for this cohort was £890 with a median cost of £950 (IQR: £354 - £950) *(Table 4.8).*

4.4.2.3 Hospitalisation.

The resources used during hospitalisation included hospital stay or number of bed days, resources used in theatre and medication prescribed during the period after surgery.

a) Resources used in theatre.

The four main variable cost components in theatre included the human resource component, anaesthetic drugs and equipment, surgical instruments and materials and theatre overheads. The cost of the first three components has been prospectively collected (Appendix 6), while the theatre overhead cost was estimated using data from five comparable hospitals where the CEA procedure is performed (Aberdeen Royal Infirmary, Gartnaval Hospital, Glasgow, Glasgow

Royal Infirmary, Southern General hospital Glasgow, Ninewells Hospital Dundee).

The mean cost per carotid endarterectomy for the human resources in theatre was estimated at £443 (median £422; IQR: £295 - £564); £124 (median £134; IQR: £71 - £162) for anaesthetic drugs and equipment and for surgical instruments and materials £204 (median £179; IQR: £151 - £209). Theatre overheads, using data from the five comparable hospitals, were estimated at £88 per hour, resulting in a mean cost of £265 per CEA (median £258; IQR: £212 - £328) *(Table 4.9).*

The cost of all complications following surgery or complications during the period immediately after surgery, which required surgical intervention, was added to the hospitalisation cost. Two subjects required surgical intervention post carotid endarterectomy, both these patients were from the centre in Edinburgh. One patient developed a wound haematoma on the second post-operative day and was returned to theatre. The second patient suffered an intracerebral haemorrhage four days after the carotid procedure, was transferred to the Western General Hospital where a Burr hole was performed and intraventricular catheter was inserted. He was subsequently admitted to intensive therapy unit at the WGH where he stayed till his death 18 days after the initial carotid surgery. One patient from the centre on Glasgow suffered a major disabling stroke 24 hours after carotid surgery and died seven days after the carotid endarterectomy.

b) Bed days

Bed days contributed the greatest proportion to the cost of hospitalisation, with a mean cost of days in intensive therapy unit of £819 (median £0; IQR: £0 - £967),

a mean cost of £399 (median £517; IQR: £259 - £776) in the high dependency unit *(Table 4.8)*. The mean cost in the general surgical ward inclusive of the days prior to surgery, the days after surgery and medications used after surgery was estimated at £1101. (median £914; IQR: £761 - £1068) *(Table 4.10)*. The mean length of stay was 5.16 days (median of four days), a minimum of three bed days and a maximum of 23 days *(Table 4.11)*.

4.4.2.4 Resource use during the post-operative stage.

The postoperative stage of care contributed the least to the cost of the procedure at only £154 (median £158; IQR: £158 - £158). It included only the human resource component during the postoperative follow-up visit with the vascular surgeon usually six weeks after the procedure and the carotid ultrasound performed at that time. All cost incurred immediately after the carotid procedure were accounted for in the surgical bed day cost and the medications during hospitalisation *(Table 4.8)*. The proportional breakdown of the cost for carotid endarterectomy is presented in Table 4.12.

4.4.3 Estimation of the "total direct" cost for the carotid endarterectomy programme (work-up and procedure).

The cost distribution of the carotid endarterectomy programme as estimated in this study population does not display a normal distribution and is highly skewed to the right which is frequently the case with cost data. The mean carotid endarterectomy programme cost (work-up and procedure cost) for this cohort was estimated at

£4868 with a median cost of £4300 and an interquartile range (IQR) of £3711 - £5064 *(Table 4.6 and Figure 4.6).* Using a deterministic approach the direct cost incurred in the work-up of a cohort of potential candidates for carotid endarterectomy was estimated at £139 934 *(Table 4.13).*

In the NVC-LSR study cohort consisting of potential carotid endarterectomy patients, 18 patients were identified as having had the procedure. Applying the arithmetic mean cost estimate per carotid endarterectomy obtained from the prospective costing study using patient specific cost data, a direct cost was calculated for the 18 patients who had carotid surgery. The mean cost estimate per carotid endarterectomy of £4868 was adjusted to exclude the cost of £1152 of the pre-operative investigations (already accounted for in the work-up of the cohort, *(Table 4.13),* resulting in a unit cost of £3716 for the actual carotid endarterectomy procedure in hospital. The direct cost of the 18 carotid endarterectomies performed in the cohort investigated was estimated at £66 888. The total direct cost of carotid endarterectomy from selecting a patient from a cohort of potential candidates (790) for a carotid endarterectomy to performing carotid surgery in the few selected patients (18) was estimated at a total cost of ***£206 822*** *(Table 4.13).* ***£139 934 or 68%*** of the total direct programme cost of carotid endarterectomy was incurred before the actual carotid endarterectomy procedure.

4.4.4 Sensitivity analysis.

4.4.4.1 Deterministic sensitivity analysis applying point estimates in the analysis.

Transition ratios.

The transition base case ratio was determined using the study cohort numbers identified from the neurovascular appointment book. For this study, a cohort of 790 patients presented with symptoms suggestive of transient ischaemic attacks for clinical assessment at the neurovascular clinics, 412 patients were clinically assessed as having anterior /carotid territory transient ischaemic symptoms which warranted further investigation, i.e. duplex examination of the carotid bifurcation. 401 patients had a subsequent duplex investigation. All the patients, who had a carotid duplex, had a follow-up consultation to be informed of the duplex findings. Of these 401 patients 26 patients were suitable candidates for a carotid angiography and 18 patients proceeded to carotid endarterectomy. Using these proportions, a transition ratio of 50: 25: 25: 1.5:1 was calculated for this study population. Though only 15 of these 18 patients had a carotid angiogram, the ratio did not change significantly *(Table 4.14)*.

Applying the point cost estimates to this ratio the cost of the base cohort was estimated. The baseline parameters for the sensitivity analysis are presented in table 4.14 and the results of the sensitivity analysis are summarised in table 4.15. The sensitivity analysis was found to be relatively insensitive to small variations in the individual parameters in the base transition ratio model. The parameter that influenced the sensitivity analysis the most was found to be carotid endarterectomy.

Since clinical practice in the work-up to CEA has changed over the last couple of years with selective use of angiography prior to the surgery, a one-way analysis was performed with no angiogram and all other parameters constant. A cost reduction of 12% was found when investigating a cohort for possible carotid surgery under these conditions. This was considered an unrealistic model because if an angiogram is omitted it would either be replaced by an additional duplex investigation or a magnetic resonance angiogram. By substituting an angiogram with either a duplex or MRA investigation or both, a cost reduction of 11% was found for the additional duplex, of 9% for the MRA and of 8% for the combination of a duplex and MRA investigation compared to the base transition ratio model *(Table 4.15).*

Performing a two-way deterministic sensitivity analysis by decreasing the consultation parameter by 25% and by decreasing the angiogram parameter by 50% in the transition ratio model, a 15% decrease in investigating a cohort of patients with TIA-like symptoms for a possible CEA was found. The reduction in programme cost of 15% was the most favourable outcome obtained in addressing the uncertainty associated with the proportions of patients at the different investigation levels. Performing a multi-way analysis by decreasing the duplex and follow-up visit parameter by 25% and angiogram parameter by 50% in the base transition model, and keeping the consultation and CEA parameters constant, a cost reduction of 12% was observed *(Table 4.15).*

Performing two carotid endarterectomies for every 50 patients assessed at the NVC with all the other parameters constant in a one-way analysis a cost increase of 30% was found which was the most costly alternative when investing a cohort

of TIA patients for possible CEA. This investigation pathway of two CEA for every 50 patients assessed did not become more favourable even when the catheter angiogram was substituted for a MRA, one or two duplex investigations. Cost increases of 21% for the MRA and of 19% and 20% when one or two duplex investigations were performed *(Table 4.15).*

Individual parameters. *(Table 4.16: a- f)*

Performing a multi-way analysis on the individual cost parameters in the clinical pathway of carotid endarterectomy with a 25% increase in the base case consultation cost, a 100% increase in the cost of a duplex investigation but with no angiogram cost and with the cost of a CEA procedure at £3716, the most favourable "programme" cost for CEA was found, a difference in real term of £847 or 17% (b) compared to the cost of £4868 for the base case. Repeating the analysis under the same conditions, but increasing the cost of the CEA procedure by 10% a reduction of 10 % (e) was found. Substituting the conventional angiogram for a MRA under the same conditions, resulted also in a cost reduction of 10% (c) compared to the base cohort and even increasing the cost of the CEA procedure resulted in a 2.5% decrease in the base case cost (f).

Applying the 25 % increase in the base case consultation costs, a 100% increase in the cost of a duplex investigation, the procedure cost of CEA remaining constant or even increasing the procedure cost of CEA by 10%, and maintaining the conventional angiography as part of the clinical pathway for CEA, an increase in the base case cost of 2% (a) and 10% (d) was found respectively.

4.4.4.2 Procedure cost sensitivity analysis: probabilistic analysis

Patient specific cost data collected in the prospective costing study allow for a probabilistic sensitivity analysis. The plausible ranges were specified using the 95% confidence interval around the mean for the key parameters *(Table 4.17).* Applying the lower and upper bound of the 95% confidence interval for all the variables identified in the patient specific data set, a difference in overall cost of 20% was observed to either side of the mean cost calculated for the CEA programme for the various scenario settings *(Table 4.18).*

4.4.5 Time to event analyses:

4.4.5.1 Lothian Stroke Register data set (Table 4.19).

The time intervals observed in the clinical work-up or pathway for patients experiencing a transient ischaemic attack through the different transition levels to carotid endarterectomy were expressed in days.

Days between most recent TIA and assessment at NVC.

The mean number of days from the most recent transient ischaemic attack, to assessment by a consultant at the neurovascular clinics at the Western General Hospital for the cohort identified from the LSR was 21 days, with a median time interval of 10 days. The IQR from the most recent transient ischaemic attack to neurovascular clinic assessment was two to 27 days, indicating that a neurologist assessed 50% of the patients within four weeks from onset of the most recent symptom.

Days between assessment at NCV and duplex

The mean number of days between clinical assessment at the neurovascular clinics (NVCs) and duplex ultrasound for the 401 patients identified in the LSR was 5.8 days. A minimum of minus 54 days between clinical assessment at the neurovascular clinics and duplex examination was observed, indicating that some patients had a duplex investigation 54 days or less "prior" to clinical assessment by a consultant. This suggested that the referring general practitioner or physician probably requested the duplex and that the duplex was performed prior to the assessment by the consultant. The maximum number of days observed between assessment at the neurovascular clinic and duplex investigation was 99 days.

Days between Duplex and carotid angiogram.

The mean number of days observed between duplex and carotid angiogram was 33, with a median time interval of 26 days, a minimum of 0 and a maximum of 148 days or almost five months.

Days between carotid angiogram and CEA

The mean number of days between carotid angiogram and carotid endarterectomy for this cohort was 81 days with a median time interval of 51 days, a minimum of 17 and maximum of 410 days, or 13.6 months. However, fifty percent of the patients who had a carotid endarterectomy were operated on between 40 and 75 days or within two and a half-months of the carotid angiogram (IQR: 40 - 75 days) (*Table 4.19).*

Days between NVC and CEA

The mean number of days between assessment at the neurovascular clinics and carotid endarterectomy was 130 days with a median of 85 days, a minimum of eight and a maximum of 521 days. Fifty percent of patients had a carotid endarterectomy between 56 and 134 days or between just less than two months and 4.5 months *(Table 4.21).*

4.4.5.2 CEA cost description study data set (Table 4.20 and 4.21).

Data of the first contact with the health care system after patients had suffered a TIA were also collected in the CEA cost description study. This additional information in the referral chain from most recent transient ischaemic attack to CEA could indicate whether unacceptable time delays occur from the first contact with the health care system to assessment by a consultant. Data were also collected on the time intervals observed in referring patients who have been fully worked-up (i.e. having had a carotid angiogram) by neurologist and then referred to the vascular surgeon for the procedure. Similar data were not available in the LSR data set.

The mean number of days from most recent transient ischaemic attack to first contact with the health care system i.e. the general practitioner in this prospective study was 52 days (median: 7 days; IQR: 1-31).

A mean number of 34 days was found from most recent symptoms to assessment at a neurovascular clinic, with an interquartile range of zero to 52 days. From clinical assessment either by a neurologist or vascular surgeon to duplex

examination, the mean number of days observed was minus one day (IQR: minus 21 to 17 days). The mean number of days between duplex and angiogram was 53 days. (median 26 and IQR of 29 to 70 days). The mean number of days between angiogram and CEA was 29 days (IQR: 7 – 38 days). The minimum number of days between angiogram and CEA was two days and the maximum number of days 109 *(Table 4.20)*. The corresponding figures for the LSR data set from angiogram to CEA were 81 days and 410 days.

The mean number of days from referring a patient (i.e. arranging an appointment) from the neurovascular clinic at the WGH to the vascular clinic at the RIE was 31 (median 22 days; IQR 13 –34days). The mean number of days between the assessment at neurovascular clinic at the WGH and the vascular clinic at the Royal Infirmary, Edinburgh (RIE) for this cohort was 33 days, but with a maximum number of days of 141 days. *(Table 4.20)* The mean number of days from the vascular clinic at the RIE to CEA was 30 days with a median of 27 days and interquartile range of 9 to 47 days *(Table 4.22)*.

4.5 Discussion.

This study reports the results of the programme cost of carotid endarterectomy which was defined as the work-up cost of a cohort of patients who might be considered for CEA and the CEA procedure cost. This total direct carotid endarterectomy programme *cost for this cohort* of 790 cases was estimated at about £207 000 with 68% of the total direct programme cost accounted for before carotid surgery was performed. The total direct CEA *cost per individual patient*

including the work-up cost was estimated at £4868 with only 25% of the total CEA cost attributed to the work-up. This study is likely to be the first study reporting on the programme cost of CEA since studies investigating both the "work-up cost" of identifying patients with carotid territory ischaemic attacks for a probable CEA as well as the "procedure cost" of CEA could not be identified in the published literature. A number of studies (Smurawska et al., 1998; Back et al., 1997; Mellisano et al., 1997; Garrard et al., 1997; Dardik et al., 1997; Ballard et al., 1997; Pollard et al., 1997; Hirko et al., 1996; Smithies et al., 1996; Ammar, 1996; Kriass et al., 1995; Luna et al., 1995; Patel et al., 1995; Radestock, 1992; Maini, 1990; Green et al., 1987) addressed the cost of carotid endarterectomy, but in such a manner that the results obtained are not readily transferable to other settings.

Only one study (Hankey et al., 1990) in which the cost of investigating patients prior to carotid endarterectomy was described, referred to the "programme" cost. Hankey and Warlow concluded that estimating the programme cost to the NHS to identify patients presenting with symptoms, which might justify further investigation for possible treatment, was an extremely difficult task when relying on current available data sources.

This study found that more than half (56%) of the cost of a CEA programme is attributable to the consultations at the neurovascular clinics and duplex investigations in the work-up of a cohort of patients who might be suitable for CEA. The actual procedure contributed only about 32% of the overall cost of the CEA programme.

The consultation cost of patients referred for evaluation of cerebral ischaemia at the neurovascular clinics in this study contributed to 34% of the overall programme cost, making it the highest cost component in the programme with the procedure cost of CEA at 32%. The main reason for this being the large number of patients referred to these clinics for evaluation, only about half of them (52%) having carotid territory related symptoms, and only a small number of patients (2.3%) having carotid surgery. Only one patient out of every 50 patients referred to the neurovascular clinics for evaluation had a CEA. This is considerably higher than the one in 27 patients who were referred for evaluation of cerebral ischaemia and were found to be fit for CEA in a US Veterans Affairs study (Mayberg 1991).

It is however contentious whether the cost of assessing patients referred for a specialist consultation should be added to the overall cost of the programme cost of CEA as it can be argued that this cost should be borne by the health service anyway. Assessing the CEA cost of £4868 for the individual patient, only 25% of the total cost were attributed to the "work-up" cost prior to CEA and 75% of the cost was for the actual procedure.

Fifty percent (69 520/139 934) of the work-up cost (Table 4.4) was attributed to the initial consultation at the neurovascular clinic. This might indicate that patients are being referred "too easily" and that the "gatekeepers" or primary care physicians need to either refine their diagnostic skills in managing patients with symptoms suggestive of transient ischaemia or have easier access to carotid ultrasonography since the cost of a duplex investigation is less than specialist consultation fees and the costs associated with a consultation. Considering also

that only 78 (19%) of the 401 patients referred for duplex investigation were found to have stenosis of 70% or more presents a strong case for primary health care physicians to use duplex ultrasound as a "screening" tool before referring a patient to a consultant. The cost of a duplex investigation is relatively small and the advantage gained by performing this examination in clinical decision making can not be questioned.

The results from this study suggest that the CEA procedure is relatively inexpensive in the context of a CEA programme and that most (68%) of the programme cost is generated during the work-up of a cohort of patients who might be suitable for CEA. The CEA cost estimate (£4868) obtained in this study is similar to the cost estimate based on Healthcare Resource Group (HRG) costs reported by Smithies et al (1997) from one of the NHS Trusts in their study.

Healthcare Resource Groups (HRGs) for the estimation of costs.

HRGs are a way of aggregating patient treatment episodes that are similar in their resource consumption. HRGs further classify case mix by categorising patients into a manageable number of groups which are clinically homogenous, expected to consume similar amounts of resources and based on the ICD classification of diseases. HRGs should be distinguished from Diagnosis Related Groups (DRGs) which is the US counterpart. Though HRGs might assist in cost estimations for specific procedures, these costs are based on aggregates and can thus only be considered as approximations. The huge discrepancies observed in the cost of CEA based on HRGs in the five NHS Trusts investigated by Smithies and others

confirmed the prior belief that cost estimates based on HRG might not be accurate. I acknowledged that HRGs were not primarily designed to estimate procedure specific costs. The cost estimate obtained in this prospective study at the Royal Infirmary Edinburgh and Southern General Glasgow should however provide a more accurate cost estimate for CEA to be used in assessing the cost-effectiveness of a procedure of which the main objective is the prevention of a stroke.

Obtaining accurate information about the direct cost of carotid endarterectomy to the NHS of the investigation of patients with transient ischaemic attacks for possible carotid surgery is not straightforward. Most information for the Scottish Health Services Costs (SHSC) 1996/97 is derived from financial and statistical returns from hospital running costs and community services.

Costs are divided into direct costs and allocated costs. Direct costs being all costs directly associated with medical treatment and care of the patient. Allocated costs include all other costs in providing a service to patients, also known as hotel costs. Indirect and intangible costs are seldom quantified and described, purely because accurate or plausible estimates of these costs are almost impossible to obtain.

The present study reported here, although addressing some of the problems identified in previous studies, acknowledges the difficulties experienced by others investigating this topic. This study is not "pure" since more than one approach was used to determine the cost of carotid endarterectomy. To estimate the programme cost of identifying suitable patients for the procedure, a top-down deterministic approach was employed. Describing the cost of the carotid

procedure patient specific cost data in a bottom-up approach, were predominantly applied. Point estimates were however used for certain resources in the pre-operative stage and for all the resources in the post-operative stage. It should also be mentioned that although necessary measures were taken to avoid double counting in the costing methods, the risk could not be completely eliminated, since routinely collected data sources were used in conjunction with patient specific cost data. Considering these dilemmas encountered in the design of this study, sensitivity analyses were performed to address the uncertainties associated with these estimates.

Routinely collected data sources.

One of the major constraints in this study was the estimation of unit costs for resources used. The Scottish Health Services Costs 1996/97 was used as reference source for many of the calculations. This source does however not, take the different levels of expertise (consultant versus specialist registrar) into account when estimating a cost per attendance at an outpatient department. All "new" consultations are considered to be similar; visits of different time duration (30 - 60 minutes) or by medical personnel with different levels of seniority are regarded as the same. Another concern was the attendance at a dedicated outpatient consultant clinic, which was not accounted for in the SHSC source. The published data in the reference source do not have data on the cost per attendance at neurovascular clinics, but only of neurology and general surgery. The published figure for a neurology outpatient attendance was therefore used. The use of this apparently higher cost per attendance seemed justified since only

one and a half attendance was counted, where in fact most patients for carotid endarterectomy have a minimum of two consultations and some patients have even more.

The published total expenditure in a general surgery ward was used to calculate the cost per bed day. The reasons substantiating this decision were the following: patients were usually admitted for a day post-surgery to the high dependency unit in the Royal Infirmary and for a day to the intensive therapy unit in Glasgow. No direct theatre cost per case was allocated for the bed days in the intensive therapy unit at the Royal Infirmary and the Southern General. Such a cost was however allocated for the Western General hospital, but carotid surgery is not routinely performed at the WGH. The theatre and laboratory costs published for the bed days in intensive therapy unit were considered high for a typical carotid endarterectomy patient since these patients are dissimilar to typical patients being treated routinely in ITU. Data were extensively collected from case notes to account for all direct cost incurred during the intensive therapy and high dependence unit stay. Since the stay in these two units was relatively short, the cost per bed day as calculated from the published SHSC was applied. All these discrepancies described here emphasise the problems associated with the use of routinely collected data.

Operational data from hospitals.

Another constraint in this study was the identification of the potential cohort of patients who might be suitable for carotid endarterectomy. Ideally the "pool" of patients from where the carotid endarterectomy patients originated should include

more than one year of observation. Since the proportion of patients proceeding to carotid endarterectomy is relatively small, observation of more than one year will increase the size of the study population and also account for the influence of unexplained seasonal and year-to-year variation that might occur when studying a one year period only (Personal communication: GD Murray, Professor: Medical Statistics, University of Edinburgh). The major problem in having more than one year of observation was related to the availability of reliable data sources for previous years. Only two data sources, the neurovascular appointment book at the Department of Clinical Neurosciences and the electronic hospital network, HOMER were available to estimate the number of appointments at the neurovascular clinics. Concerns about the accuracy of both these sources have been expressed by the neurology consultants involved in the clinic activities, thus an estimation of the number of neurovascular appointments for both sources was necessary to establish the most reliable source. Although the appointment book was identified as providing a more reliable and accurate reflection of the clinic activity and was used as the data source to estimate the number for the "pool" of patients ("the base of the pyramid") from where patients were selected for carotid surgery, it highlighted the problem of the accuracy of operational data sources for research purposes.

The importance to perform a CEA as soon as possible after a carotid TIA.

The risk of stroke is about 12% in the first year after a TIA and then about 6% per annum for the next four years. It is therefore important that people with transient ischaemic attacks should be identified soon after an attack, preferably

within four to six months, if any benefit conferred by carotid endarterectomy is to be gained. It needs to be mentioned that the most recent recorded transient ischaemic attack before assessment by a neurologist was used in determining the time delays in the work-up to carotid endarterectomy. This obviously has significant implications for performing a carotid endarterectomy during the time window where optimal benefit associated with the procedure might be obtained. A more accurate and reliable entry date in determining the delays in the progress to carotid endarterectomy would have been the very first symptom experienced by patients. Information of this nature was unfortunately not available and it is against this background that patients assessed in this cohort for a possible CEA were evaluated. Identifying these patients form a defined cohort should thus be considered as active case finding since these patients present to the health care systems with symptoms suggestive of transient ischaemic attacks. It is more than likely that a "referred" cohort might not be representative of all potential candidates for CEA in the population who might in some instances benefit more from the procedure than those referred.

For both the LSR cohort and the CEA cost description cohort, 75% of patients were operated on within acceptable time intervals to maximise the potential benefit of a risk reduction in stroke. The maximum time intervals in all these transitions indicate extreme time delays, and it is worrying that 25% of CEA patients did not proceed rapidly to have the procedure. Delays were observed throughout the referral chain and it would be difficult to identify one specific referral transition being responsible for these delays. Referring only to the 25% of patients where unacceptable long time intervals were observed, the delays

found for both cohorts were similar. The CEA cost description cohort's referral pattern appeared to be quicker from assessment at a neurovascular clinic to CEA, but long delays occurred from most recent transient ischaemic attack to CEA. Considering the 18 CEA patients who were referred for CEA from the LSR cohort, only 14 patients might have obtained any "real" benefit in terms of a reduction in stroke risk by having the procedure within the recommended six-month window. Four of these patients were unlikely to have benefited, but contributed to the overall cost. The cost-effectiveness of the procedure in these patients who were operated on after six-months from most recent transient ischaemic attacks is questionable. The time-to-event analyses performed both in the case of the LSR data set and the CEA cost description study indicated that 75% of patients assessed were operated on within five months from presenting with a carotid TIA. This suggested that current clinical practice in the work-up to CEA needs to be improved to derive optimal clinical as well as any cost benefit from this surgical intervention (Brown and Humphrey, 1992). It is apparent form the median times observed for both cohorts that 50% of patients were assessed within reasonable time frames, suggesting that it is possible to obtain optimal referral times for half of carotid TIA patients.

Sensitivity analysis.

Sensitivity analysis has until very recently been the main method used addressing the uncertainty associated with economic evaluations. Although more stochastic data are becoming available to apply classical statistical approaches, the need for sensitivity analysis will not disappear, since some data will always be

deterministic in nature. It is therefore prudent that available results should be applied to the best possible use, whether it is in a sensitivity analysis or whether the results are to be transferred from one setting to another.

The base transition ratio model was found to be relatively insensitive to variations in the individual parameters in the model even varying the individual parameters in the model by performing a one- or multi-way sensitivity analysis. Multi-way analyses, which recognise the uncertainty associated with more than one parameter at a particular point, and are preferred to one-way analyses as it mimics conditions of clinical situations more appropriately, were not found to be more sensitive. Although it was found that the most favourable transition models will be obtained by varying the consultation, duplex and angiogram parameters, the interaction between the ratios of the individual parameters was insensitive to minor variations. The parameter of CEA in the model has been regarded as a constant throughout most of the analyses, since it was assumed that for the purposes of this study and the "programme", that patients are investigated to have one CEA and would not be evaluated for bilateral staged carotid procedures.

However, applying the findings of the US Veterans Affairs Study of one CEA for every 27 patients evaluated of cerebral ischaemia (Mayberg et al., 1991), one could expect to perform two carotid endarterectomies for about every 50 patients with cerebral ischaemia. As demonstrated by the sensitivity analysis, when two carotid endarterectomies were to be performed for every 50 patients with cerebral ischaemia evaluated, the cost of investigating a cohort of patients with cerebral ischaemia increased substantially.

It was also apparent from the sensitivity analysis, addressing uncertainty in the point estimates for the programme cost of investigating patients for probable carotid endarterectomy, that a favourable cost scenario will be obtained if only patients for whom a high index of clinical suspicion of the presence of carotid territory ischaemic events exists, are referred for consultant assessment and evaluation. A high proportion of these "selected" patients with probable carotid stenosis will qualify for duplex investigation thereby increasing the yield of patients with stenosis of 70% or more who might be suitable for carotid surgery. A "programme" to identify suitable candidates for carotid endarterectomy, concentrating only on the most likely candidates for the procedure to be assessed at a neurovascular clinic will however be against the ethos of health care delivery. Such a "programme" would also place an unjust burden on primary health care providers in making decisions outside their domain of clinical expertise ***unless*** access to duplex ultrasound could be given to them. It could be argued that many patients are referred to neurovascular clinics because of pathologies other than carotid stenosis and that access to duplex by general practitioners would not decrease the number of patients evaluated at these clinics as duplex scanning might not be the first line of investigation for these patients. However if general practitioners could refer patients, with a high index of clinical suspicion of transient ischaemic attack, for duplex investigation prior to consultant referral, patients with stenosis less than 70% would not be referred for consultant opinion and patients with other pathologies would be referred anyway. This might reduce the number of outpatients consultant visits and hence the cost,

since only 20%of patients in this study with symptoms suggestive of transient ischaemic attacks were found to have stenosis of more than 70%.

From the transition ratio observed in this study, investigating a 1000 patients with *symptoms **suggestive** of transient ischaemic attacks*, 520 patients will be clinically diagnosed as having carotid related ischaemic attacks. Only 508 of the 1000 patients will have a subsequent duplex examination, 99 will be diagnosed with duplex as having stenosis of 70% or more in one or both carotid arteries. 33 of them will have a carotid angiogram and 23 patients will have a carotid endarterectomy. Or about *45 out of 1000 patients with carotid **related** transient ischaemic symptoms* will have a carotid endarterectomy (or *45 out of about 2000 patients with cerebral ischaemic symptoms* i.e. the "pool" of potential CEA patients). If we then need to perform nine CEA to prevent one stroke, 200 patients with carotid-related symptoms need to be investigated. Or for every 200 patients with carotid-related ischaemic symptoms we can expect to perform nine carotid endarterectomies and thus prevent one stroke at a cost of £103 080 *(Figure 4.7)*.

Though a ratio of one consultation to one duplex to one follow-up visit to one angiogram (1:1:1:1) can be assumed from first consultation to subsequent investigations, this study has shown that these assumptions did not hold absolutely true. A ratio of one consultation to one duplex to 1.5 angiogram to one CEA was found in the work-up of the patients with carotid territory ischaemic attacks identified in the LSR-data set. Thus cost estimates based on a

deterministic approach might either be an underestimation or overestimation of health service and financial requirements as were shown in the sensitivity analyses.

Describing the ratio of duplex to angiography to carotid endarterectomy based on this cohort of 64 patients, it is apparent that the assumed ratio of 1:1:1 was not adhered to for this group of patients either. A ratio of two duplex investigations to 0.66 angiogram investigations to one carotid endarterectomy was observed in the prospective costing study suggesting a changing nature in the "work-up" for carotid endarterectomy. It is however acknowledged that the study population of the CEA cost description study was small and might not be representative of larger cohorts. Based on the observations in the CEA cost description study, it is also anticipated that the frequency of duplex investigations per patient will increase with fewer patients having an angiogram prior to carotid surgery. It is also anticipated that the conventional angiography will be replaced in the future for some patients by non-invasive MRA investigations.

Angiography per se does not contribute much to the overall programme cost of carotid endarterectomy, even in this study where 1.5 angiographies had to be performed for every *one* CEA. More than half (56%) of the programme cost has accrued before patients were referred for angiography. The proportion angiography contributed to the overall cost of investigating a cohort for possible CEA was only 12% and the remaining 32% was for the CEA procedure self.

Angiography however contributed almost 20% to the overall cost of carotid endarterectomy in the case of the individual patient.

Altering the length and type of hospital stay variables in this cohort had little effect on the cost of the procedure, since the overall stay in hospital for these patients was relatively short as well as the stay in intensive therapy units.

Reducing the total length of hospital stay will therefore have no substantial cost implications and was therefore not considered as a key parameter in the sensitivity analysis. From the sensitivity analyses it is apparent that the most favourable cost estimate will be obtained in the absence of a carotid angiogram. Although hospital stay ass relative short (mean of 5.16 days) and was primarily in a general surgery or a ward equivalent to it, bed days contributed much to the overall cost of the procedure.

4.6 Summary.

This study has found that an individual CEA is not too costly and comparable with other similar vascular procedures (Jepson et al. 1997, UK Small Aneurysms Study Group 1998). The cost to prevent one stroke is about £44 000 when the CEA cost estimate of £4868 is applied to the number needed to treat (nine) to prevent one stroke. When the cost of assessing a cohort of patients who might be potential candidates for CEA is considered, the overall cost increases substantially to about £103 000 per stroke prevented. Most of the cost in a CEA programme is spent during the work-up of a potential cohort of patients who might be suitable for CEA resulting in the actual CEA procedure being relatively inexpensive.

It is imperative that the delivery of health care for this selected group of patients who have had a carotid territory transient ischaemic attack should be improved if

the benefit of CEA is to be optimised. One-stop TIA clinics or neurovascular clinics should be given priority and implemented as soon as possible to minimise these delays which are occurring in the current fragmented delivery system thus maximising the potential benefit of this procedure for the selected few (Sandercock, 1998).

Duplex investigation is currently considered the best diagnostic "tool" to determine carotid stenosis since it is safe, non-invasive, with good sensitivities and specificities and is relatively inexpensive. It seems therefore appropriate to recommend primary health care physician access to this investigation to ensure that only patients who would be most likely to benefit from CEA would be referred for specialist consultation.

Developing clinical pathways for the work-up of patients with carotid territory related transient ischaemic attacks to CEA which do not require the routine investigation of carotid angiography, and substituting it for an additional duplex investigation or even a more costly investigating such as MRA compared to the cost of a duplex examination will result in a favourable cost "package".

Table 4.1: Patient proportions from neurovascular clinic to carotid endarterectomy: (Neurovascular clinic appointment book and Lothian Stroke Register.)

	Patient pool	**Carotid distribution symptoms**
Neurovascular clinic	790	412/790 (52%)
Lothian stroke register	660	412/660(62%)
Duplex ultrasound	401/790 (51%)	401/412 (97%)
Carotid angiogram	26/790 (3.3%)	26/412 (6.3%)
Carotid endarterectomy	18/790 (2.3%)	18/412 (4.4%)

Table 4.2: Age and sex distribution: Lothian Stroke Register cohort.

Age category	Male	Female	Total (%)*
< 50 years	25	18	43(10%)
50 - 65 years	88	48	136(33%)
66 - 80 years	108	85	193(47%)
> 80 years	19	21	40(10%)
Total	240	172	412(100%)

* percentage of males and females per age category of the total number of patients

Table 4.3: Carotid stenosis according to duplex investigations for the 401 patients in the LSR data set.

Category	Number of patients
"No" stenosis in either internal carotid artery	237 (59%)
"No" stenosis one artery and stenosis ≤ 70% other artery	24 (6%)
Stenosis ≤ 70% both internal carotid arteries	25 (6%)
"No" stenosis one artery and stenosis ≥ 70%other artery	28 (7%)
Stenosis ≥ 70% one artery and ≤ 70% other artery	25 (6%)
Stenosis ≥ 70%: both internal carotid arteries	19 (5%)
Occlusion on one side with "no" stenosis other artery	17 (4.2%)
Occlusion on one side with stenosis ≤ 70% other side	19(5%)
Occlusion on one side with stenosis ≥ 70% other side	6 (1.5%)
Occlusion "both" sides	1 (0.3%)
Total number of Duplex investigations	**401**

Table 4.4: Baseline parameters and unit costs in the work-up of the study cohort to carotid endarterectomy: Neurovascular clinic and Lothian Stroke Register.

Level of investigation	Patients (n)	Unit cost (£)	Total cost(£)
Neurovascular clinic: new attendance	790	88	69 520
Duplex examination	401	70	28 040
Neurovascular clinic: follow-up visit	401	44	17 644
Carotid angiography	26	950	24 700
Direct "work-up" cost excluding CEA			**£139 934**

Table 4.5: Baseline characteristics of carotid endarterectomy patients in cost description study at the Royal Infirmary, Edinburgh and Southern General Hospital, Glasgow.

Characteristics	**Royal Infirmary, Edinburgh**	**Southern General Hospital, Glasgow**	**Both hospitals**
Number in study	42	22	64
CEA Number	42	19	61
Male (%)	31(73.5%)	17(78.9%)	48(75%)
Mean age	67	70	67.2(65.15; 69.24)
Age category:			
< 50 years	1	2	3
50 -65 years	16	5	21
66 - 80 years	24	15	39
> 80 years	1	0	1
Presenting symptom:			
TIA	16	5	21
Minor stroke	7	6	13
Amaurosis fugax	4	4	8
Combination	14	4	18
Asymptomatic	1	3	4

Table 4.6: CEA cost description study: Resources used during the different stages for the 61 CEA patients at the Royal Infirmary Edinburgh and the Southern General Glasgow.

Resources used during:	**Mean (£)**	**Median (£)**	**IQR (£)**
Work-up to CEA	1359	1416	857 - 1976
Hospitalisation for CEA:	3356	2695	2434 - 3148
(Bed days and theatre)			
Bed days:	2319	1717	1420 - 2291
Theatre:	1037	1018	780 - 1250
Post-operative stage	154	158	158 - 158
Total cost	4868	4300	3711 - 5064

Table 4.7: Number of angiograms performed before CEA at the Royal Infirmary Edinburgh and Southern General Hospital Glasgow.

Angiogram performed	Males	Females	Total
Yes	34(81%)	8(19%)	42(66%)
No	14	8	22(34%)
Total	48	16	64

Table 4.8: Breakdown of the resources (£) used during the different stages for CEA patients at the Royal Infirmary Edinburgh and Southern General Glasgow.

Stage	Arithmetic mean (£)	Median (£)	IQR(£)
Work-up:			
Medical consultation	135	132	132 - 132
Haematology and biochemistry	54	51	40 -71
Ultrasound &Angiography & CT	533	508	310 - 658
ECG & cardiology investigations	75	29	29 - 29
Cost of angiogram: (bed days and procedure)	890	950	354 - 950
Hospitalisation – Procedure:			
Human resources	443	442	295 - 564
Anaesthetic drugs and equipment	124	134	71 - 162
Surgical instruments, materials and sutures	204	179	151 - 209
Theatre overheads	265	258	212 - 328
Total theatre cost	1037	1018	780 - 1250
Hospitalisation – Bed days:			
ITU	819	0	0 - 967
HDU	399	517	0 - 517
Surgical bed days pre –op	340	298	298 - 298
Surgical bed days post –op with medications after CEA	759	611	325 - 910
Total length of hospital stay	2319	1717	1420 – 2291
Post-operative stage			
Human resources and carotid ultrasound	154	158	158 - 158

Table 4.9: Breakdown of procedure cost in theatre at the Royal Infirmary, Edinburgh and Southern General Hospital, Glasgow. Mean, median cost and interquartile range of the human resources, anaesthetics, surgical components and theatre overheads (£).

Hospital	Royal Infirmary, Edinburgh	Southern General Hospital: Glasgow	Both hospitals
Human resources:			
Mean cost (£)	533	243	443
Median (£)	520	223	442
IQR	437 - 586	173 - 281	295 - 564
Anaesthetic drugs and equipment:			
Mean cost (£)	150	67	124
Median (£)	153	67	134
IQR	133 - 170	62 - 72	71 - 164
Instruments and materials:			
Mean cost (£)	214	186	205
Median (£)	170	196	179
IQR	151 – 202	145 - 218	151 – 209
Theatre overheads:			
Mean cost (£)	305	152	264
Median (£)	298	169	258
IQR	257 - 344	120 - 210	212 - 328
Total theatre cost:			
Mean cost (£)	1202	671	1037
Median (£)	1105	633	1018
IQR	1011 - 1308	589 - 777	780 - 1250

Table 4.10: Cost of hospital stay by unit in the carotid endarterectomy cost description study.

Cost of:	Mean (£)	Median (£)	IQR (£)
Days in general ward before surgery	340	298	0
Days in Intensive Therapy Unit	819	0	0 - 967
Days in High Dependency Unit	399	517	0 - 517
Days in general ward after surgery	759	611	325 - 910
Total days in surgical ward	1101	913	901 - 1209
Total length of hospital stay.	2319	1717	1420 - 2291

Table 4.11: Cost description study: Bed days in hospital and time in theatre.

(Minimum and maximum number of bed days, interquartile range, and mean number of bed days with, 95% confidence intervals).

	Minimum	Maximum	IQR	Mean stay
General surgery ward: Before surgery	1	5	0	1.14 (0.99; 1.30)
Intensive Therapy Unit	1	18	1	0.82 (0.18; 1.46)
High Dependency Unit	1	2	1	0.80 (0.62; 0.92)
General surgery ward: After surgery	0	11	2	2.41 (1.97; 2.85)
General surgery ward: Before and after surgery	1	12	1	3.57 (3.14; 4.01)
Total length of hospital stay.	3	23	1.5	5.16 (4.40; 5.93)
Theatre time in minutes	75	330	180	184.4 170.1; 198.4
Theatre time in hours	1.25	1.35	3.00	3.08 2.84; 3.31

Table 4.12 Cost description study: Proportional breakdown of cost.

Resources	**Mean cost (£)**	**Proportion**
Prior to CEA	1359	27%
Bed days and medication	2319	48%
Theatre	1036	21%
After CEA	154	4%
Total	**4868**	**100%**
Hospitalisation:		
Surgical days	1101	32%
ITU days	819	25%
HDU days	399	12%
Theatre	1036	31%
Total	3355	100%

Source: Scottish Health Service Costs1996/97

Table 4.13: The programme cost of investigating a cohort of patients for potential CEA. ***(Number of patients at each level and unit cost per investigation)***

Investigation level	**Patient number**	**Unit cost (£)**	**Total cost(£)**
Neurovascular clinics:	790	88	69 520
LSR entries	412	-	-
Duplex ultrasound	401	70	28 040
Follow-up consultation	401	44	17 644
Angiogram	26	950	24 700
Total "work-up" cost			**£ 139 934**
Total procedure cost	18	3716	**£ 66 888**
*Carotid endarterectomy			
Total programme cost			**£ 206 822**

* excluding work-up; including surgery, hospitalisation and post operative care

Table 4.14: Baseline parameters for transition ratio model using a deterministic sensitivity analysis.

Transition levels	Ratio	Unit cost (£)	Base cohort cost (£)
Consultation	50	88	4400
Duplex	25	70	1750
Follow-up visit	25	44	1100
Angiogram	1.5	950	1425
Carotid endarterectomy	1	3716	3716
Total CEA cost		4868	12 391

Table 4.15: Deterministic sensitivity analysis applied to the transition ratio.

	Consultation (£88)	Duplex (£70)	Follow-up (£44)	Angiogram (£950)	CEA (£3716)	Cohort cost	Impact
Base ratio	**50**	**25**	**25**	**1.5**	**1**	**12 391**	
All parameters in ratio constant; altering only angiogram							
	50	25	25	-	1	10 965	**12%↓**
	50	25	25	0.75	1	11 677	**6%↓**
	50	25	25	Duplex	1	11 035	**11%↓**
	50	25	25	MRA	1	11 319	**9%↓**
	50	25	25	Duplex and MRA	1	11 389	**8%↓**
Increasing and decreasing consultations by 25%; varying angiogram ratio							
	62.5 (25%↑)	25	25	1.5	1	13 490	9% ↑
	62.5 (25%↑)	25	25	-	1	12 066	3%↓
	37.5(25%↓)	25	25	0.75	1	10 579	**15%↓**

Table 4.15: Deterministic sensitivity analysis applied to the transition ratio. (Continue)

Consultation constant; Altering Duplex , follow-up visit and angiogram ratios						
50	31.25 (25%↑)	31.25 (25%↑)	1.5	1	13 104	**6%↑**
50	18,75 (25%↓)	18.75 (25%↓)	1.5	1	11 622	**6%↓**
50	31.25 (25%↑)	31.25 (25%↑)	0.75 (50%↓)	1	12 392	**0%↑**
50	37.5 (50%↑)	37.5 (50%↑)	-	1	12 380	**0%↓**
50	31.25 (25%↑)	31.25 (25%↑)	Duplex	1	11 749	**5%↓**
50	18,75 (25%↓)	18,75 (25%↓)	0.75 (50%↓)	1	10 910	**12%↓**

Table 4.15: Deterministic sensitivity analysis applied to the transition ratio. (Continue)

Increasing consultations, duplex and follow-ups by 25%; altering angiogram transition						
62.5 (25%↑)	31.25 (25%↑)	31.25 (25%↑)	0.75 (50%↓)	1	13 492	9%↑
62.5 (25%↑)	31.25 (25%↑)	31.25 (25%↑)	-	1	12 779	3%↑
75 (50%↑)	31.25 (25%↑)	31.25 (25%↑)	0.75 (50%↓)	1	14 592	18%↑
50	50 (100%↑)	50 (100%↑)	-	1	13 816	12%↑
Consultation, duplex, follow-up visit constant; Altering angiogram with duplex or MRA with two CEA for every 50 patients assessed at the NVC.						
50	25	25	1.5	2	16 105	**30%** ↑
50	25	25	Duplex (x1)	2	14 750	**19%** ↑
50	25	25	Duplex (x2)	2	14 820	**20%** ↑
50	25	25	MRA	2	15 030	**21%** ↑

Table 4.16: Base case parameters and multi-way deterministic sensitivity analyses.

Parameter	Base case cost (£)	Multi-way analyses		
		a.	b.	c.
Consultation	88	110(↑25%)	110(↑25%)	110(↑25%)
Duplex	70	140(↑100%)	140(↑100%)	140(↑100%)
Follow-up	44	55(↑25%)	55(↑25%)	55(↑25%)
Angiogram	950	950	0	0
MRA	(353)	0	0	353
CEA cost	3716	3716	3716	3716
Total CEA cost	4868	4971(↑2%)	4021(↓17%)	4374(↓10%)

Parameter	Base case cost (£)	Multi-way analyses		
		d.	e.	f.
Consultation	88	110(↑25%)	110(↑25%)	110(↑25%)
Duplex	70	140(↑100%)	140(↑100%)	140(↑100%)
Follow-up	44	55(↑25%)	55(↑25%)	55(↑25%)
Angiogram	950	950	0	0
MRA	(353)	0	0	353
CEA cost	3716	4088(↑10%)	4088(↑10%)	4088(↑10%)
Total CEA cost	4868	5343(↑25%)	4393(↓10%)	4746(↓2.5%)

Table 4.17: Baseline parameters for procedure cost: probabilistic sensitivity analysis.

CEA procedure	Base case cost (£)	Lower bound 95%C.I.	Upper bound 95%C.I.
Work-up:			
with angiogram	£ 1359	1165	1552
Without angiogram	£ 599	539	659
Without angiogram and one additional duplex	£ 669	609	729
Hospitalisation:	£ 3355	2632	408
Bed days:	£ 2319	1629	3009
Theatre:	£ 1036	946	1128
Post operative stage	£ 154	147	160
CEA cost with angiogram	£ 4868	4093	5643

Table 4.18: Procedure cost sensitivity analysis.

Work-up with angiogram		**95% Confidence intervals**	
	Base case	**Lower bound**	**Upper bound**
Work-up	1359	1165	1552
Bed days	2319	1629	3009
Theatre	1036	946	1128
Postoperative stage	154	147	160
Carotid endarterectomy cost	4868	3887(↓20%)	5849(↑20%)
Work-up without angiogram		**95% Confidence intervals**	
	Base case	**Lower bound**	**Upper bound**
Work-up without angiogram	599	539	659
Bed days	2319	1629	3009
Theatre	1036	946	1128
Postoperative stage	154	147	160
Carotid endarterectomy cost	4108	3261(↓20%)	4956(↑20%)
Work-up without angiogram but with one additional duplex investigation			
		95% Confidence intervals	
	Base case	**Lower bound**	**Upper bound**
Work-up without angiogram but one additional duplex	669	609	729
Bed days	2319	1629	3009
Theatre	1036	946	1128
Postoperative stage	154	147	160
Carotid endarterectomy cost	4179	3331(↓20%)	5026(↑20%)

Table 4.19: Time referral intervals in days of carotid TIA patients: Lothian Stroke Register data set.

Interval	Mean (Standard error.)	Median	IQR	Minimum	Maximum
Most recent symptoms to Neurovascular clinic	21 (1.5)	10	2 - 27	0	225
Neurovascular clinic to Duplex	5.8 (0.73)	0	0 - 2	-54	99
Duplex to Angiogram	33 (7.5)	26	8 - 39	0	148
Angiogram to CEA	81 (30.4)	51	40 - 75	17	410

Table 4.20: Time intervals in days: CEA work-up in CEA cost description study.

Interval	Mean (Standard error)	Median	IQR	Minimum	Maximum
Most recent symptom to first visit	29 (7.5)	7	1 - 28	0	529
Most recent symptoms to assessment	34 (5.4)	20	0 - 52	-7	52
Neurovascular clinic to Duplex	-1 (5.8)	0	-21 - 17	-117	160
Duplex to Angiogram	53 (5.8)	57	29 - 70	0	151
Angiogram to CEA	29 (4.6)	20	7- 38	2	109

Table 4.21: Summary - Time intervals to carotid endarterectomy costing data set and Lothian Stroke Register data set.

	Mean (Standard Error)	Median	IQR	Minimum days	Maximum Days
CEA Costing data set					
Most recent transient ischaemic attack to CEA*	135 (11.4)	126	93 - 159	9	608
1st health care visit to CEA	107 (6.9)	106	76 - 143	7	268
Neurovascular clinic to CEA	74 (5.6)	63	42 - 99	2	247
LSR data set					
Most recent transient ischaemic attack to CEA	159 (28.1)	118	78 - 186	9	529
Assessment to CEA	130 (29.2)	85	56 - 134	8	521

Table 4.22: Time intervals in days: CEA referral in CEA cost description study.

Interval	Mean	Median	IQR	Minimum	Maximum
First symptom to first visit	29	7	1 - 13	0	529
Referral from Neurovascular clinic to vascular clinic	31	22	13 – 34	0	229
Days from Neurovascular clinic to vascular clinic	33	26	0 - 64	0	141
Vascular clinic to CEA	30	27	9 - 47	1	129
Neurovascular clinic to CEA	63	58	27 - 97	1	196
Assessment to angiogram	45	46	14 - 69	-68	134

Figure 4.1: The carotid endarterectomy programme.

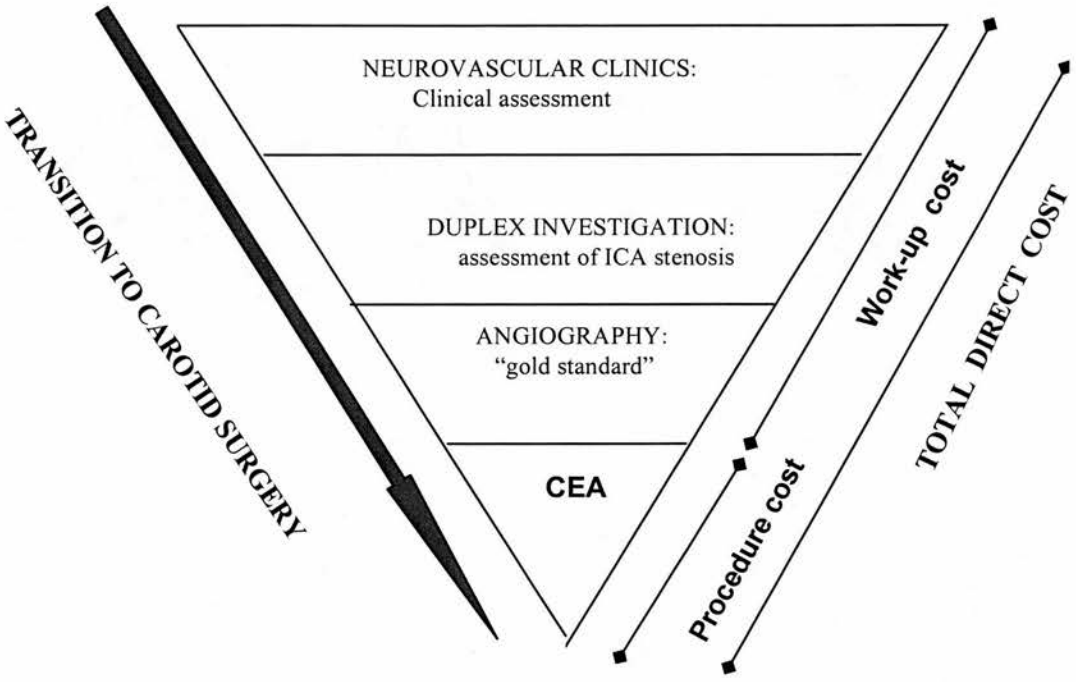


Figure 4.2: Schematic presentation of the progress of patients with Transient Ischaemic Attack-like symptoms to carotid endarterectomy.

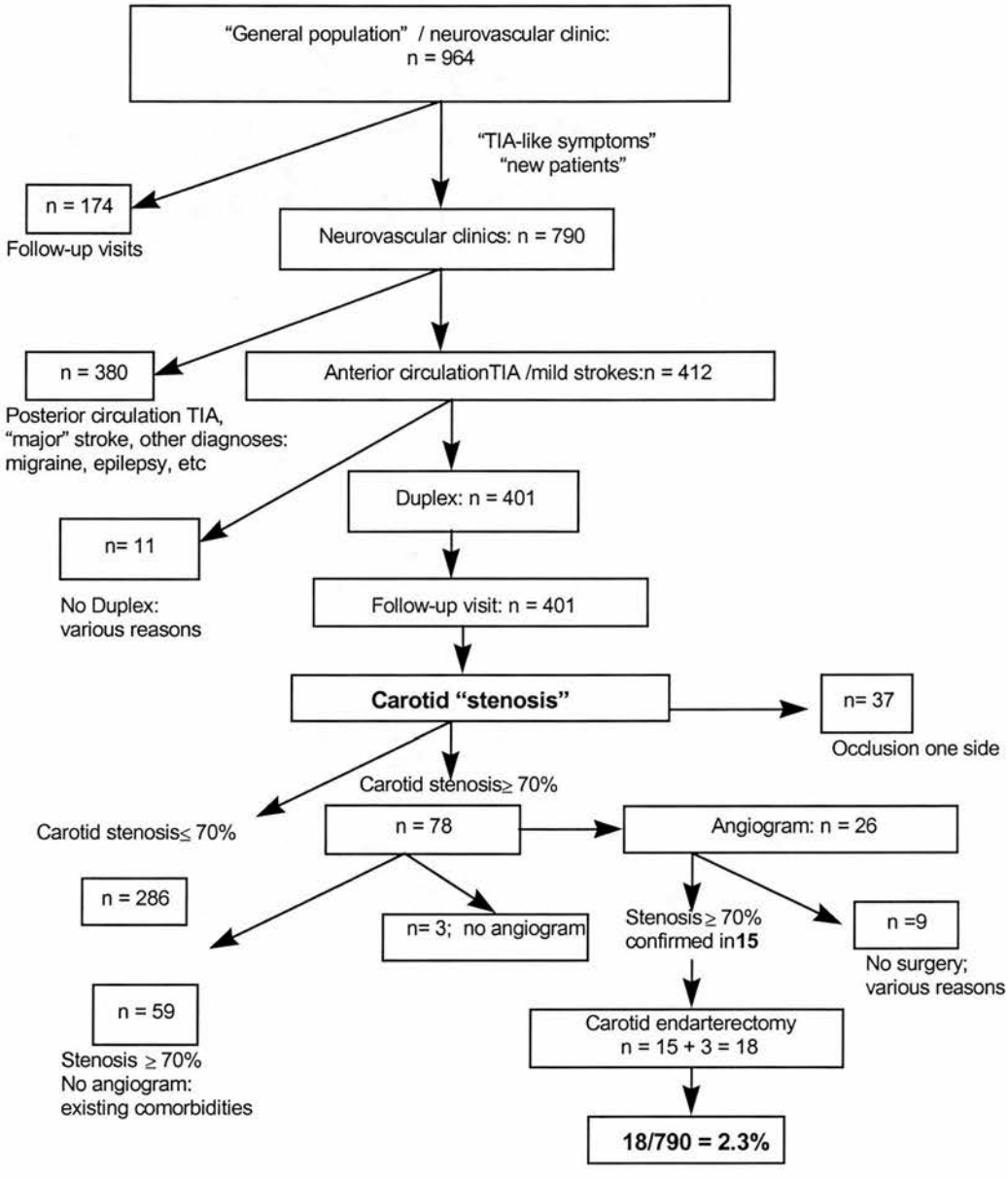


Figure 4.3: Age distribution of probable carotid territory ischaemic attack patients: Lothian Stroke Register. (Standard deviation =12; Mean = 5.8, n= 412)

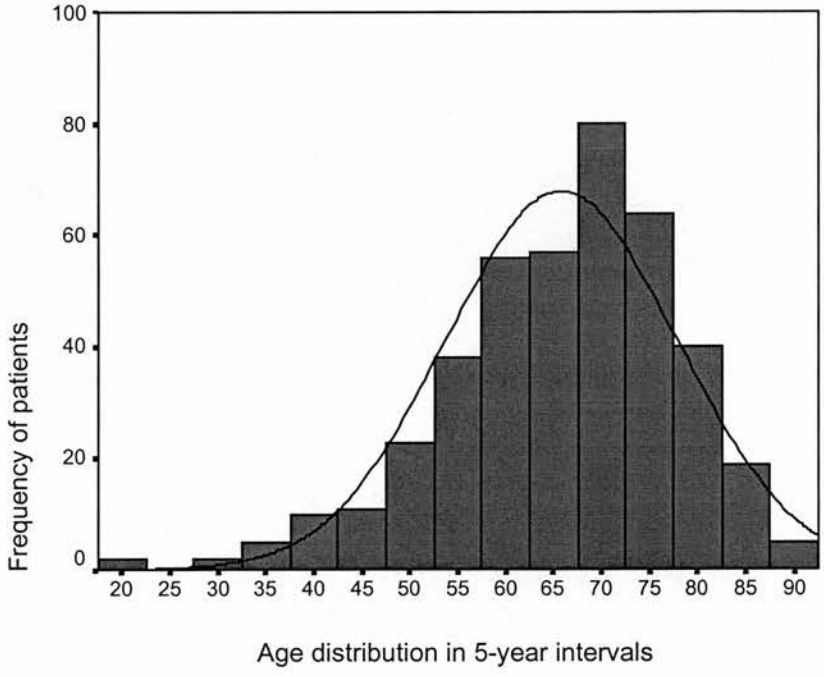


Figure 4.4: Schematic presentation of internal carotid arteries investigated with duplex ultrasound.

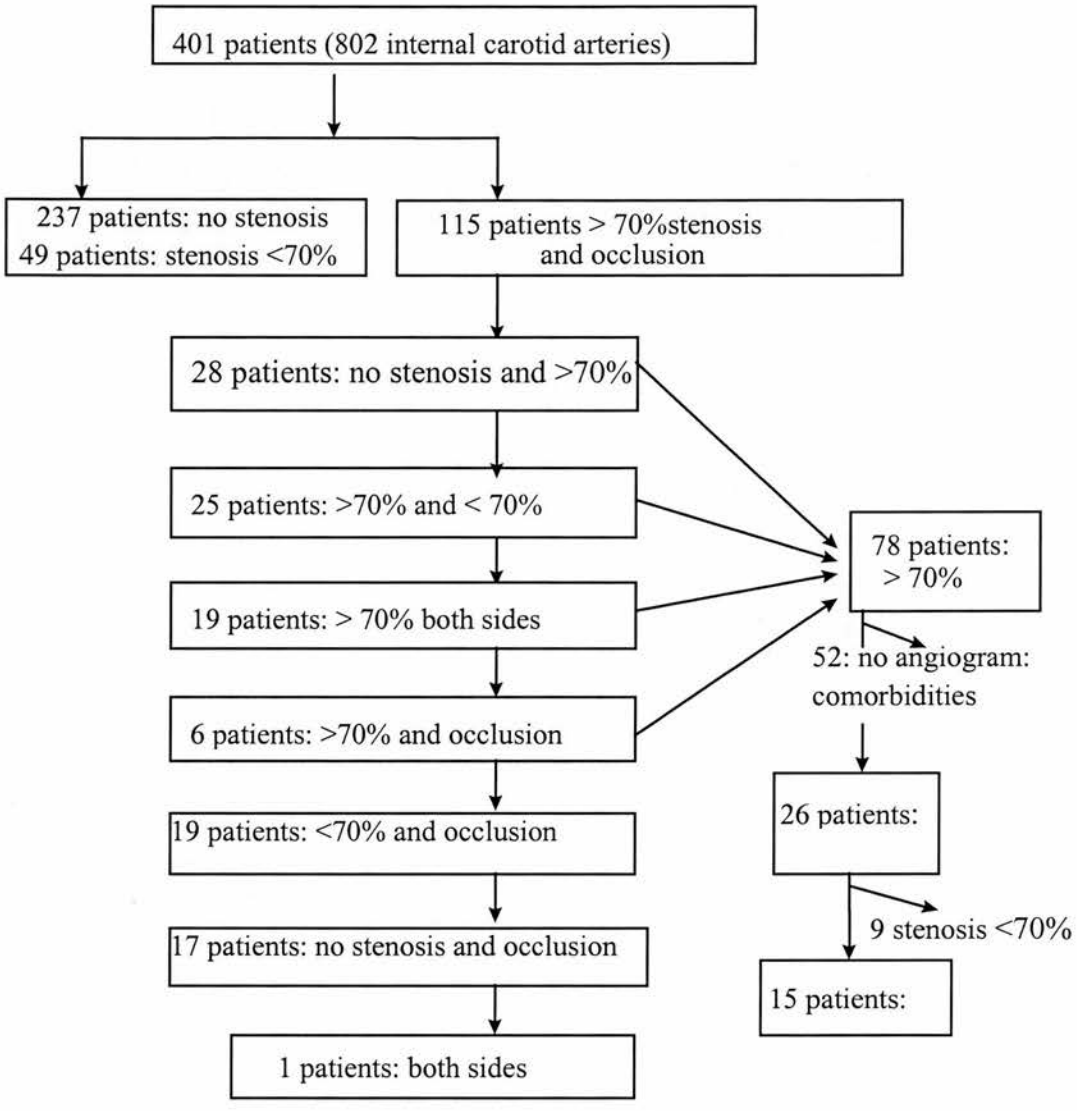


Figure 4.5: Age distribution of patients in the carotid endarterectomy cost description study at the Royal Infirmary Edinburgh and the Southern General Glasgow. (Mean age = 67 years; Standard deviation = 8.1; n = 64)

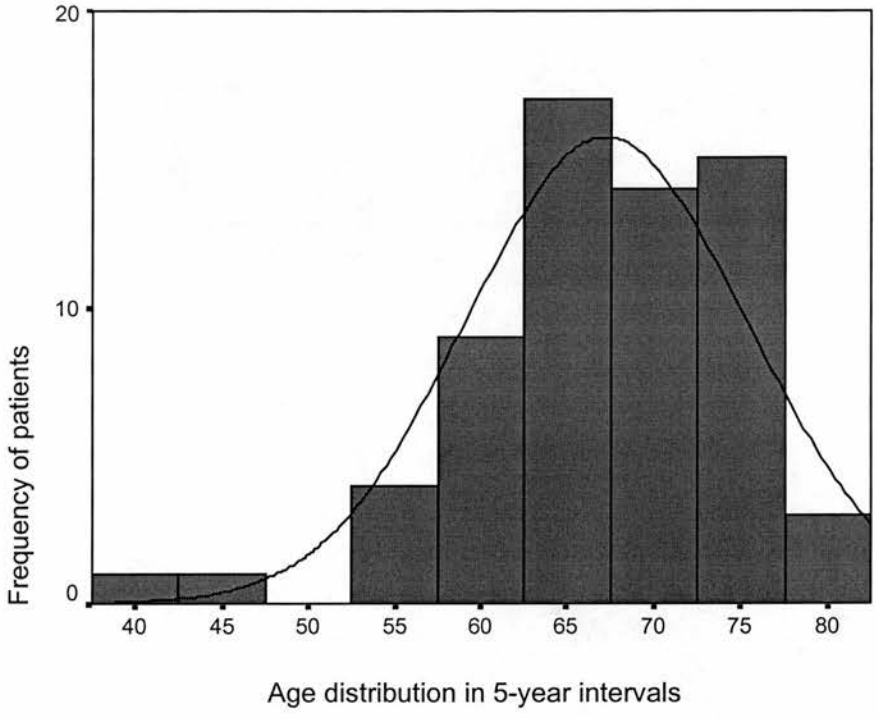


Figure 4.6: The cost distribution for the carotid endarterectomy procedure in the cost description study at the Royal Infirmary Edinburgh and the Southern General Glasgow. (Mean cost = £4868; n= 61)

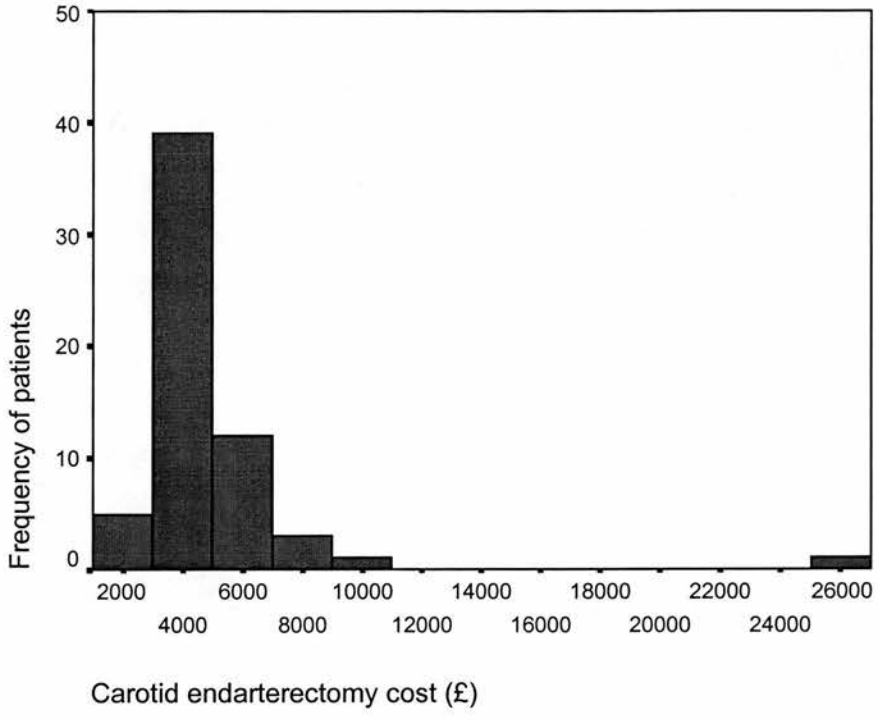
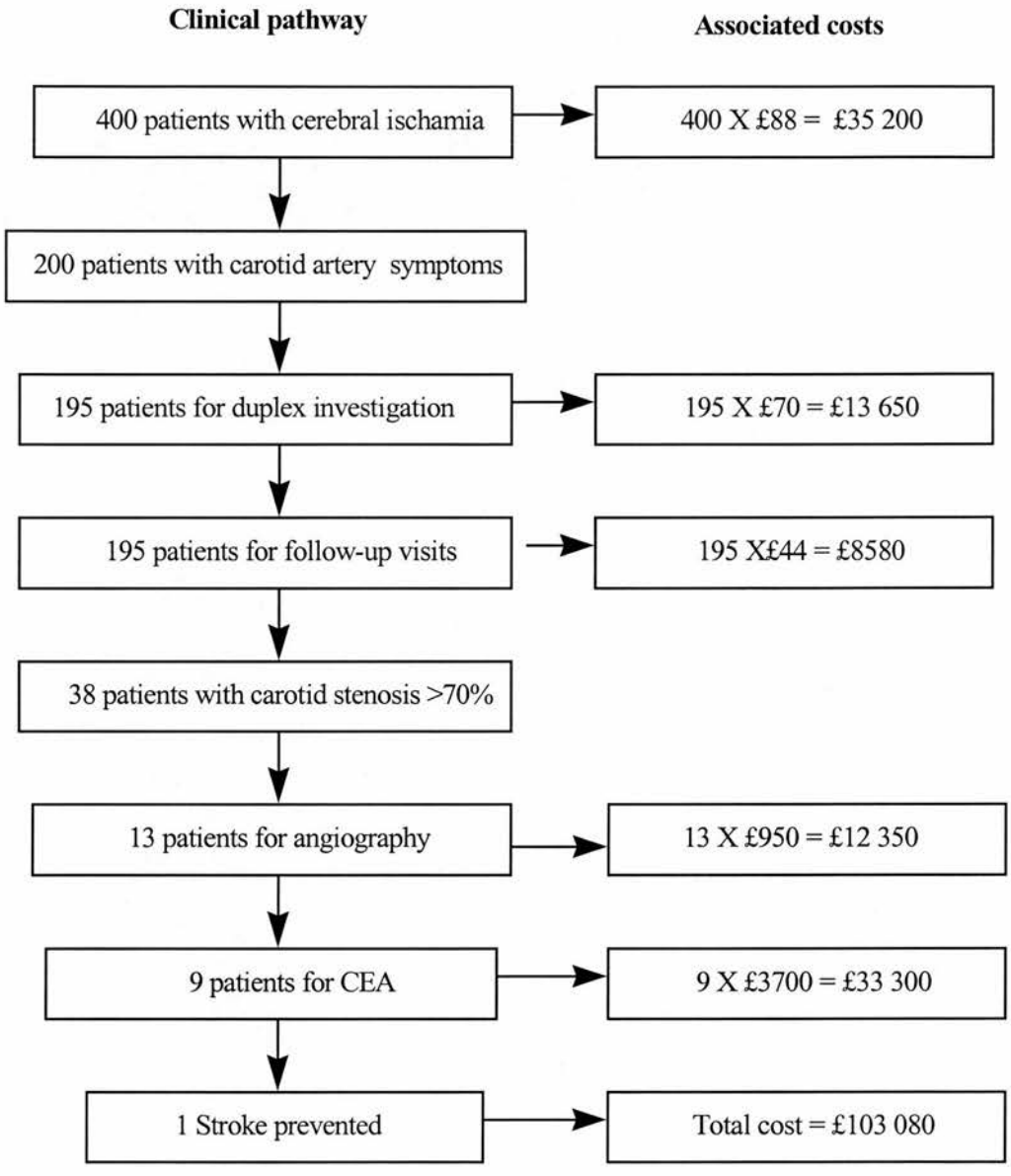


Figure 4.7: Schematic presentation of the clinical pathway of CEA and the associated costs for a CEA programme.



CHAPTER FIVE: CAROTID ENDARTERECTOMY IN SCOTLAND, RANDOMISED CONTROLLED CLINICAL TRIALS AND ASSOCIATED COSTS.

5.1 Introduction

The benefit associated with carotid endarterectomy in terms of "stroke-free" survival for patients with symptomatic carotid artery stenosis of more than 70% has been established by the two randomised controlled trials published during the 1990s (European Carotid Surgery Trialists' Collaborative Group, 1991; North American Symptomatic Carotid Endarterectomy Trial Steering Committee, 1991; ECST Collaborative Group, 1998; NASCET Steering Committee, 1998). Though there is now little doubt concerning the efficacy of this procedure, for some selected subgroups, the cost implications of this procedure has not yet been satisfactorily addressed, neither has the outcome of this procedure in populations representative of "real life" and not associated with a trial, been investigated previously (Brittenden et al., 1999; Hallett at al., 1998).

In this chapter, I firstly compare the outcomes of "stroke-free" survival and overall survival at five years in a Scottish cohort of patients randomised to carotid endarterectomy (CEA) in the European Carotid Surgery Trial (ECST), with the outcomes in Scottish patients operated on outside the trial. ***"Stroke-free" survival*** is defined as surviving for a total period of five years after successful carotid surgery, without experiencing any *hospitalised* stroke event. ***Overall survival*** *is* defined as

surviving for a total period of five years after successful carotid surgery without experiencing a fatal stroke or a death from any cause.

Secondly, I estimate the difference in cost between the Scottish cohort of patients in the ECST randomised to surgical treatment (Scottish-ECST surgical cohort) and those patients randomised to medical treatment (Scottish-ECST medical cohort). The estimated cost difference between the two randomised treatment groups was used, in conjunction with the effectiveness data reported from the ECST and published modelling studies, to calculate a cost-effectiveness ratio.

The proposed objectives were achieved by testing several null hypotheses regarding the "stroke-free" and overall survival in a Scottish-CEA cohort (Scottish ISD-CEA data set). The primary null hypothesis was that there was no difference between the five-year "stroke-free" survival and five-year overall survival of Scottish patients who were randomised to surgery in the European Carotid Surgery Trial (Scottish ECST surgical cohort) and the corresponding survival of all Scottish cases who had a carotid endarterectomy outside the ECST (Scottish ISD-CEA non-ECST cohort) during the same period as the trial (trial patients versus non-trail patients). To reduce bias, in addition to the comparison with all the Scottish CEA cases (ISD-CEA non-ECST cohort), the Scottish patients randomised to surgery in the ECST were also compared with an age-sex-date-of-operation matched control cohort from the ISD-CEA data set (Scottish ISD-CEA non-ECST matched cohort).

The secondary null hypothesis was again of no difference in outcome between the five-year "stroke-free" survival and five-year overall survival, but this time by

comparing the same patients, but using data obtained from two different data sources (ISD-CEA data set versus Scottish-ECST data set).

The cost incurred by the Scottish-ECST cohort, inclusive of all the Scottish patients randomised either to surgery or best medical care into the ECST, was estimated using two approaches. In one method, resource use was assessed by applying findings from the CEA cost description study (Chapter Four) to the episodes of care obtained from routinely collected data. In the second scenario the mean cost estimate of a Healthcare Resource Group (HRG) as defined in the National Schedule of Reference Costs for Elective In-Patients of the Department of Health (1998) was applied to the routinely collected data for each episode of care.

5.2 Methods

5.2.1 Description of the study populations

The study population investigated in this study was described in Chapter Two, and included all patients in Scotland who had a CEA during the period 1981 to 1996. All the Scottish patients who were also randomised to surgery in the ECST during the entire period of the trial were identified (Scottish ECST-surgery cohort). Scottish patients randomised to best medical care were identified in the ISD database (Scottish ECST-medical cohort). Patients in the ECST were randomised between 14 October 1981 and 31 March 1994. The randomisation period (1981 - 1994) for the trial corresponded largely to the period (1981 - 1996) used to identify patients who had a carotid endarterectomy in Scotland from the routinely collected data source of

ISD, the ISD-CEA data set. The Scottish patients randomised into the ECST, the Scottish ECST cohort, were identified from the ECST data set archived at the Department of Clinical Neuroscience at the Western General Hospital. Using the centre code where the operation was performed the centres in Scotland which participated in the trial were identified and consequently the patients from Scotland randomised into the surgery arm in the ECST. Record linked methods were used to link the Scottish patients randomised to surgery in the ECST (Scottish ECST-surgical cohort) to the ISD-CEA data set as discussed in Chapter Two.

Scottish patients randomised to medical care in the ECST were identified through linkage to the national patient database at ISD (Scottish ECST-medical cohort). The linkage was achieved by using the patient's name, date of birth, gender, date of operation, and randomisation centre as key variables. The index event for both the surgical and medical group was the date of randomisation into the trial and information about all subsequent episodes of care from that date onwards up to December 1997 was "collected". The linkage for the Scottish patients randomised to medical care was essential in order to quantify resource use after randomisation in patients treated medically.

5.2.2 Outcomes measures

The primary outcome measures related to the ***"transferability" of trial results*** were five-year "stroke-free" survival and five-year overall survival in a Scottish cohort of patients randomised to surgery in the ECST (Scottish ECST-surgical cohort) compared with non-trial patients in the Scottish cohort having had a carotid

endarterectomy between 1981 to 1996 (Scottish ISD-CEA non-ECST cohort). The outcome variables included not only death associated with a stroke event, *but also "stroke-free" survival* of any type of stroke admitted to hospital and *all cause mortality*. All stroke events identified were hospitalised stroke events only. This applied to both the Scottish ECST-surgery cohort as well as the Scottish ISD-CEA non-ECST cohort. Since data were obtained from the same data source, the ISD data set, any degree of potential bias was minimised.

The outcome measure related to the ***economic evaluation of CEA*** was expressed as in-patient hospital episodes of care of a Scottish cohort of patients randomised to surgery in the ECST (Scottish-ECST surgical cohort) compared with the resource use of the Scottish cohort of patients randomised to best medical care in the ECST (Scottish-ECST medial cohort).

The outcome measure of ***clinical effectiveness of CEA*** defined as "stroke-free" life expectancy was obtained from the final results of the ECST (ECST Collaborative Group, 1998) as well as from a modelling study using NASCET results as reference (Nussbaum et al., 1996). The outcome measures of the economic evaluation and of clinical effectiveness were applied to calculate a cost-effectiveness ratio (difference in cost/ difference in outcome).

5.2.3 Methods used to test the transferability of RCT results.

Primary null hypothesis.

Firstly, the five-year "stroke-free" survival and five-year overall survival of all cases in Scotland who had a carotid endarterectomy outside the ECST (Scottish ISD-CEA

non-ECST cohort) between 1981 and 1996 were compared with the five-year "stroke-free" and five-year overall survival of Scottish patients in the ECST (Scottish ECST-surgical cohort).

Secondly, the five-year "stroke-free" and five-year overall survival of the Scottish patients randomised to surgery in the European Carotid Surgery Trial and identified in the routinely collected ISD-CEA data set, (Scottish ECST-surgery cohort) were compared with a cohort matched for age, sex and date of operation of Scottish patients who had carotid endarterectomy outside the ECST (Scottish ISD-CEA non-ECST matched cohort). An age-sex-date-of-operation cohort of Scottish patients who had a carotid endarterectomy outside the trial, but at the time of the trial was matched to the Scottish surgical participants in ECST on a one-to-one basis. The data set matched for sex, age and year of operation was created using the Scottish patients randomised to carotid surgery in the ECST as reference. The date of birth of patients in the ISD database is not available in order to protect patients' identity. Since the ISD-CEA data set was extracted from the ISD database this variable was not obtainable and the age of the patients who had carotid surgery in the trial was therefore used to identify a similar patient within an age band of plus-minus two years. The date of the operation was known for all Scottish CEA patients, (ECST patients and non-ECST patients) and a more precise matching could be obtained, within a two-month range in most cases, using the operation date. The age-sex-operation-date matched subset survival analysis was considered to be more informative in detecting differences in five-year "stroke-free" and five-year overall survival than comparing the small number of ISD-CEA ECST participants to all the carotid endarterectomy patients in the ISD-CEA non-ECST data set.

Secondary null hypothesis.

The five-year "stroke-free" and five-year overall survival of the Scottish ECST-surgery cohort were compared using data obtained from the routinely collected data source from ISD and data obtained from the randomised controlled trial, the European Carotid Surgery Trial. The data set used for analysis in Chapter Two, the Scottish ISD-CEA data set, was again used here, and all the Scottish participants in the ECST were identified distinguishing between trial patients (Scottish ECST-surgical cohort) and non-trial patients (Scottish ISD-CEA non-ECST cohort). The Scottish patients randomised to surgery in the ECST were extracted from the Scottish ISD-CEA data set, creating a small sub-data set. The Scottish patients randomised to surgery in the ECST were extracted from the ECST data set archived at the WGH, creating another small sub-data set. These two small data sets were merged and an independent data set consisting of two entries for the same patient was created with observed outcomes obtained from two different sources. This data set was used to test the second hypothesis relating to outcomes observed in a trial data set and a routinely collected data set. A binomial variable was created to indicate whether patients' data for analysis were obtained from routinely collected data or whether the data came from the ECST data set.

Since it was not possible to distinguish between ipsi- and contra-lateral stroke events in the routinely collected Scottish ISD-CEA data set, time-to-event analysis was performed, using the time-to-death and time-to-stroke variables as defined in the ECST. Clinical variables are not routinely collected in the ISD database, except for the presenting diagnosis (up to six diagnostic fields) and operation codes (up to four fields). Information on the degree of stenosis and the relation of the ischaemic event

(ipsilateral or contralateral) to the stenotic artery is not available in the routinely collected Scottish ISD-CEA data set. It was thus not possible to compare patients in the two groups with different degrees of stenosis or to test hypotheses related to specific outcomes for the two groups against the degree of stenosis operated on. Thus all analyses performed did not distinguish between low, moderate or severe stenosis as classified in the ECST data set. No assumptions were made on the severity of stenosis in any of the comparisons between the Scottish ECST-surgical cohort and the Scottish ISD-CEA non-ECST cohort. It was however possible to describe the proportions of the different degrees of stenosis for the Scottish ECST-surgical cohort using the ECST data set and to compare these proportions obtained for the Scottish ECST cohort to the proportions of all the ECST patients. The rationale for this was that all outcomes after CEA in the Scottish ISD-CEA data set were evaluated against the results from the ECST on severe carotid stenosis. The proportions of stenosis present in the Scottish ECST-surgical cohort might point to the stenosis-mix of the different degrees of stenosis present in the patients being routinely operated on in Scottish hospitals. For the purpose of this analysis, it was assumed that patients operated on outside the trial could have had any degree of stenosis, but were most likely to have stenosis of 70% or more and were also symptomatic.

5.2.4 Methods used to assess the cost-effectiveness of the procedure.

The cost measure: Cost difference between the surgical and medical cohort.

All episodes of care of the Scottish ECST participants identified in the ISD database were used to determine the resource consequences for the Scottish surgical and

medical cohorts in the ECST. The resource consequences referred only to in-patient care and did not include resources consumed at an outpatient level. All episodes of care from the date of randomisation for a five-year follow up period were included. These episodes of care were obtained from ISD for both the Scottish-ECST surgical and Scottish-ECST medical cohorts. It was assumed that best medical care included the use of aspirin, treatment of hypertension, advice on stopping smoking and treatment of other comorbidities for these patients. The cost of all medications including aspirin was not separately assessed in estimating resource use.

In the first approach the cost difference in resources used between the Scottish-ECST surgical and Scottish-ECST medical cohort was estimated by applying the results from the CEA cost description study, reported in Chapter Four, to the CEA procedure and to the length of hospital stay over the five-year follow-up period. Because the carotid endarterectomy cost estimate from the prospective study reported in chapter four was recent and similar to previous cost estimates from the United Kingdom (Radestock, 1992, Smithies et al., 1997), this estimate was considered to be the most appropriate available estimate and was used in these costing methods. The length of hospital stay was calculated for each patient in both the Scottish-ECST surgical and Scottish-ECST medical cohorts using routinely collected data. The cost of CEA and cost of hospital stay for each patient over the five-year period were estimated for the Scottish-ECST surgical cohort. The cost of hospital stay and of CEA where performed for each patient in the Scottish-ECST medical cohort over the five-year period were also estimated and the difference in cost between the two cohorts was calculated.

The second approach used the mean average cost for 50% of the NHS Trusts as published in the National Schedule of Reference Costs for Elective In Patients (1998) by the Department of Health for the Healthcare Resource Groups (HRGs) to estimate the cost of all procedures and admissions over a five-year period for the 308 Scottish patients randomised into the ECST.

Carotid endarterectomy and its associated costs were considered the main procedure of interest. The corresponding HRG code for the procedure code (OPCS 3 or OPCS 4) of carotid endarterectomy was identified as Q05 (Extracranial or Upper Limb Arterial Surgery) in the National Schedule of Reference Costs for Elective In-Patients. The mean cost for this HRG was found to be £2298 with a minimum cost of £1564 and a maximum cost of £3011. The mean cost of £2298 was applied to all the CEA procedures performed in this cohort. The cost of £2298 was 38% less than cost of £3716 obtained from the patient specific cost data in the CEA cost description study. Where the CEA procedure was coded as an invalid or poorly coded diagnosis, the HRG code was substituted with the more appropriate code of Q05 to estimate an adjusted cost.

The National Schedule of Reference Costs does not include the HRG codes for Invalid Primary Diagnosis or Invalid Dominant Procedures neither for Poorly Coded Primary Diagnosis or Poorly Coded Dominant Procedures. These codes were however used by ISD for the Scottish patients investigated. A pilot study by ISD Scotland, assessing the cost of HRG codes specific for Scotland, based on the National Schedule of Reference Costs, produced costs for both Invalid Primary and Poorly Coded Primary Diagnosis. These mean average costs for both Invalid Primary and Poorly Coded Primary Diagnosis were used in this study in conjunction with the

published costs from the National Schedule of Reference Costs for In-Patients. The mean average cost for an Invalid or Poorly Coded Dominant Procedure was however not available. For the purpose of this study, the arithmetic mean cost of the Invalid Primary and Poorly Coded Primary Diagnosis obtained in the pilot study in Scotland was used as an approximation for mean costs for invalid or poorly coded procedures. Data on all other operations and procedures performed on these patients, as well as other diagnoses for which these patients required a hospital admission during the five years after CEA, were collected. The OPSC code for operations and procedures or ICD9 code for diagnoses was linked to the appropriate HRG code and the mean cost obtained in the National Schedule of Reference Costs. All costs reported, using the HRG code as reference, are adjusted cost estimates.

The arithmetic mean cost of the Scottish-ECST surgical and Scottish-ECST medical cohorts were calculated and the mean cost difference between the two cohorts was obtained. All costs reported reflect 1998 prices as reference year.

The effectiveness measure: Life expectancy difference between the surgical and medical cohort.

The outcome measure of clinical effectiveness of CEA defined as "stroke-free" life expectancy and expressed as life-years gained was obtained from the final results of the ECST and from published modelling studies. (Lavender et al., 1998; Nussbaum et al., 1996; Matchar et al., 1987) Life expectancy was expressed as *life-years gained* and also as *quality adjusted life-years (QALYs)* where available. Using the published final results obtained in the ECST (ECST Collaborative Group, 1998) life expectancy for the surgical and medical cohort in the ECST, curtailed at five years, was

determined by calculating the area under the survival curves to obtain the difference between life-years gained in the two groups. (Gould et al., 1999; Personal Communication: GD Murray, Professor: Medical Statistics, University of Edinburgh). Life-years gained in this instance were not quality adjusted. The findings from the published modelling study by Nussbaum and others who applied the results from NASCET in their simulation models to estimate "stroke-free" life-years and QALYs gained were used in all cost-effectiveness ratio calculations.

5.2.5 Defining the analyses

The choice of statistical methods was determined by the nature of the variables in the data set as well as by the study objectives. Normal probability plots were used to assess any departure from normality. All categorical variables were compared by means of the chi-square test statistic. All p-values reported are two-sided. Continuous variables include time to event variables and length of hospital stay. Variables have been computed using the date of carotid endarterectomy procedure as the date of entry into the study. Arithmetic means are reported for all costs with 95% confidence intervals where appropriate. The inter-quartile ranges were defined as $Q_{0.25}$ - $Q_{0.75}$. All analyses were performed using SPSS version 7 and Microsoft Excel version 5.

5.2.5.1 Time-to-event analyses

The null hypotheses tested were primarily concerned with time-to-event analyses. Thus all analyses comparing "stroke-free" and overall survival in the Scottish ECST

surgical cohort with a "real life" Scottish CEA population not in the trial (Scottish ISD-CEA non-ECST cohort) were performed using Kaplan-Meier product limit estimates of time to calculate years free from carotid stenosis related endpoints ("stroke-free" survival and death). "Real life" referred to everyday practice and clinical situations encountered in the health care setting.

The log-rank statistic and the Breslow tests were used to compare the survival curves obtained for the groups All analyses compared survival between patients in the different ISD-CEA cohorts. These cohorts are defined as the Scottish ECST- surgical cohort; the "real life" Scottish ISD-CEA non-ECST cohort and the age-sex-operation-date matched control group (Scottish ISD-CEA non-ECST matched cohort).

The statistical analysis performed on the ECST data was based on the intention-to-treat principle. Although patients in the medical group who crossed over to surgical treatment after randomisation could be identified in the ISD data set, only patients randomised to surgery and having had a subsequent carotid endarterectomy after randomisation were used to test the null hypotheses.

5.2.5.2 Economic evaluation

An incremental cost-effectiveness analysis was performed in which the *net cost* and *net effectiveness* of the surgical intervention were compared with medical care and expressed as a ratio. An incremental analysis refers to the difference in cost effect observed between two alternatives. A cost-effectiveness ratio was calculated by dividing the difference in the cost of care between the surgical and the medical

groups of the Scottish-ECST cohort by the difference in effect ("stroke-free" survival) between the surgery group and the medical group of patients from the European Carotid Surgery Trial and modelling studies.

The difference in cost was calculated by subtracting the "total direct" cost incurred by Scottish-ECST patients randomised to best medical care from the "total direct" cost incurred by the Scottish-ECST patients randomised to carotid endarterectomy. "Total direct" costs were defined as the cost incurred by every patient from the date of randomisation and including the cost all subsequent episodes of care over the five-year follow-up period.

The effectiveness measures, expressed as the difference in the "stroke-free" life-years between the surgery and medical cohorts, and used in this study were obtained from the final ECST results (ECST, 1998) and from the modelling study based on NASCET results (Nussbaum et al., 1996). The number of life-years gained was used as the denominator in the cost-effectiveness ratio calculations. The cost results used in this analysis have been adjusted using the data from the CEA cost description study reported in this thesis.

5.3 Results

5.3.1 Baseline characteristics of the study populations

A total of 308 patients were randomised into the ECST over the entire trial period in four centres in Scotland. Of these 186 (60%) were randomised to surgical treatment and 122 to best medical care. The 60:40 randomisation ratio for the Scottish-ECST cohort was in keeping with the randomisation ratio in the ECST. This asymmetrical

but unbiased allocation allowed slightly more extensive power to ascertain the adverse effects of surgery (ECST Collaborative Group, 1991). Of the 186 surgical patients, five patients crossed over to medical care after randomisation and 14 patients (7.5%) could not be identified through record linkage. A total of 172 patients (92%) who were randomised to surgery in the ECST were identified, inclusive of the five patients who crossed over to medical care. Of the 186 Scottish-ECST surgical cohort, 167 were identified in the ISD-CEA data set to have had carotid surgery. Two of the 167 carotid endarterectomy patients had a second carotid endarterectomy performed shortly (within 30 days) after the initial carotid surgery for which the patients were randomised *(Table 5.1).*

There were 122 patients from Scotland randomised to medical treatment (Scottish-ECST medical cohort). Only one patient could not be identified using record linkage. Fourteen of these medical patients crossed over to the surgery arm and were all identified, with record linkage, in the ISD database as having had carotid surgery over the entire study period. Five of these patients had carotid surgery within one year from being randomised to medical care in the ECST, while the remaining nine patients were operated on four years or longer after randomisation into the trial. Seven patients had carotid surgery within five years from the date of randomisation. These fourteen carotid endarterectomies were not included in the time to event analysis of the 167 who were initially randomised to surgery *(Table 5.1).*

The baseline characteristics of the ECST patients in Scotland having CEA and the matched control cohort having CEA in Scotland, but outside the trial, are described in Table 5.2. The mean age for the Scottish-ECST surgical cohort was 61.1 years. No departure from normality was observed for the age distribution for either the

surgical cohort of Scottish participants in the ECST or for the matched control group obtained from ISD data ($p = 0.089$) *(Figure 5.1).*

The degree of stenosis as reported from the angiogram results in the ECST for both the Scottish-ECST surgical cohort and the surgical participants from all the other centres are summarised in table 5.3. Of the 186 Scottish-ECST surgical patients 126 (68%) had severe stenosis recorded compared to 699 (43%) with severe stenosis reported for the surgical patients from other centres in the ECST data set. The differences observed for the low, moderate and severe stenosis categories between the Scottish-ECST cohort and the ECST patients from the other participating centres were statistically highly significant ($p < 0.001$).

Early stroke events and all-cause mortality within 30 days of CEA .

Early stroke events within 30 days of CEA (Table 5.4)

A total of 128 (4.4%) hospitalised cerebrovascular events of any kind (major or minor stroke event) was observed during the 30 days after CEA for the Scottish ISD-CEA cohort of 2892 patients. The baseline characteristics of the 2892 patients in the Scottish ISD-CEA cohort were described in Chapter Two. Of these 128 hospitalised cerebrovascular events, 117 (4.3%) occurred in the Scottish ISD-CEA non-ECST cohort having CEA outside the trial and 11 (7%) stroke events occur in the 167 Scottish ECST-surgery cohort. The difference found was statistically not significant. ($p = 0.16$) Only seven strokes were observed for the age-sex-date-of-operation

matched control group, suggesting that cerebrovascular events in the trial patients were more accurately recorded (p = 0.3).

Early all-cause mortality within 30 days of CEA (Table 5.5).

Among the 2892 Scottish ISD-CEA patients who had a carotid endarterectomy between 1981 – 1996, there were 66 (2.3%) deaths within the first 30 days after the surgery, two of which were in the Scottish ECST-surgery cohort. Of the 66 deaths, 44 (67%) were stroke related deaths. Considering only the 167 Scottish patients randomised to surgery in the ECST and identified in the ISD-CEA data set, two deaths (1.3%), one stroke related, were observed during the first 30 days after surgery. For the rest of the Scottish ISD-CEA non-ECST cohort, 64 deaths (2.4%) were recorded of which four were stroke related. The differences observed between these cohorts were not significant (p= 0.3). For the matched control group, five deaths were reported during the 30-day period after CEA. Compared to the Scottish ECST-surgery cohort, this difference was also not significant (p = 0.3).

Late stroke events and all-cause mortality within the five years after CEA.

Late stroke events within the five years after CEA (Table 5.4).

In the Scottish ISD-CEA data set of 2892 a total 545 (18.8%) hospitalised cerebrovascular events of any kind was observed during the five-year period after CEA. For the Scottish ECST-surgery cohort 27(16%) stroke events were observed compared to 518 (19%) stroke events for the Scottish ISD-CEA non-ECST cohort The difference observed between the Scottish ECST-surgery cohort and the Scottish

ISD-CEA non-ECST cohort was not significant (p = 0.36). For the matched control group a total of 49 (29%) stroke events were observed during the five-year period after a CEA. The differences observed between the Scottish ECST-surgery cohort and the Scottish ISD-CEA non-ECST matched cohort was highly significant (p = 0.004). This finding should however be interpreted with caution since only a small number of events were observed.

Late all-cause mortality within the five years after CEA (Table 5.5).

484 (16.7%) deaths were reported for the Scottish ISD-CEA cohort during the five years after CEA was performed. Of these 38 deaths (22.8%) were in the 167 Scottish ECST-surgery cohort, and 446 (16.4%) were in the rest of the Scottish ISD-CEA non-ECST cohort. The difference observed reached statistical significance (p = 0.03). For the matched control a total of 42 (25%) deaths was observed during the five-year period after a CEA. Comparing these deaths with the deaths in the Scottish-ESCT-surgery cohort identified in the ISD-CEA data set, the difference was not significant (p = 0.7).

Resource use expressed as episodes of care (Scottish-ESCT cohort).

A total of 2436 episodes of care were recorded for both the patients in the Scottish-ESCT surgical and medical cohorts for the entire period of follow-up from randomisation. For the surgery group 1627 episodes of care were recorded for the 172 patients identified through record linkage and a total of 809 episodes for the 121 patients in the medical group. The total number of episodes for a five-year period of

follow-up was 1525: 978 (64%) for the surgery group and 547 for the medical group *(Table 5.6)*. These episodes of hospital care were mainly in general surgery and general medicine. With regards to general surgery the frequency for the surgery group was 36% and for the medical group, 27%. For general medicine a frequency of 25% for the surgery group and 27% for the medical group was observed. The episodes of care in Neurology were 6.9% and 8.6% for the surgery and medical groups respectively and in the Intensive Therapy Unit (ITU). 4.5% for the surgery group and 4.4% for the medical group. The remaining episodes of care were associated with "other" specialities (28% for the surgery group and 34% for the medical group) *(Table 5.7)*.

The majority of the patients, 267 (93%) had between one and ten episodes of care over the five-year period of follow-up. Sixteen patients had between 11 and 30 episodes of care and 14 of these 16 patients were in the surgery group. Ten patients had more than 30 episodes of care. The differences observed regarding the episodes of care between the surgery and medical groups were highly significant ($p = 0.007$). Four patients (1.7%) had no record of any episodes of care after the date of randomisation, two being randomised to surgery and two to medical care. Both of these patients randomised to medical care died two years or more after the date of randomisation. Of the two patients randomised to surgery, one crossed over to medical care and died more than two years after randomisation and the other patient died five months after randomisation to surgery. However this patient could not be identified as having had surgery in the ISD-CEA data set, during the five-month period after randomisation.

Of these episodes of care, 33% were for cerebrovascular disease related diagnoses, 28% for cardiovascular related diseases and the remainder (39%) constituted a variety of clinical conditions *(Table 5.8).* The diagnostic categories related to cerebrovascular disease for the episodes of care were 35% for the surgery group and 29% for the medical group. For cardiovascular disease 30% of the episodes of care was for the surgery group and 26% for the medical group. For other diagnostic codes the episodes of care were 37% for the surgery group and 44% for the medical group. The differences observed between the surgical and medical cohorts regarding the admission type by ICD9 diagnosis code were statistically significant ($p = 0.008$).

5.3.2 Findings from hypotheses testing.

Of the total of 2892 CEA performed in Scotland between 1981 and 1996, 167 patients were identified in the ISD-CEA data set as being in the ECST (Scottish ECST-surgery cohort) and 2725 were not operated on under trial conditions. (Scottish ISD-CEA non-ECST cohort) Twenty-seven strokes (16.1%) and 38 (22.7%) deaths were recorded for the 167 patients in the Scottish ECST-surgery cohort for a period of five years. For the Scottish ISD-CEA non-ECST cohort of 2725, 518 (19%) stroke events and 446(16.4%) death events were recorded.

The primary null hypothesis.

i. *Transferability of trial results. Comparing trial patients (Scottish ECST-surgery cohort) and non-trial patients (Scottish ISD-CEA non-ECST cohort).*

The Kaplan-Meier survival estimates comparing the "stroke-free" survival between the ISD-CEA non-ECST cohort and the Scottish ECST-surgery cohort reached statistical significance with the Log-rank test statistic (p = 0.05). The Breslow test, emphasising the early part of the curve, i.e. the period after surgery, was just outside the conventional cut-off point for statistical significance with a p-value of 0.06 *(Table 5.9 and Figure 5.2).* The mean "stroke-free" survival for the Scottish ISD-CEA non-ECST cohort was 4.2 years. (95% C.I. 4.09 - 4.23) The corresponding mean "stroke-free" survival time for the Scottish ECST-surgery cohort was 4.4 years (95% C.I. 4.2 - 4.6). The cumulative "stroke-free" survival for the Scottish ECST-surgery cohort at five years after surgery was 84% and 77% for the Scottish ISD-CEA non-ECST cohort *(Table 5.9).*

The Kaplan-Meier estimates obtained for the Scottish ISD-CEA non-ECST cohort compared to the Scottish ECST-surgery cohort for death were not significant (Log-rank p = 0.8 and Breslow p = 0.5) *(Table 5.10 and Figure 5.3).*

The mean survival time for the Scottish ECST-surgery cohort was 4.48 years (95% C.I. 4.30 - 4.66) and for the Scottish ISD-CEA non-ECST cohort was 4.38 years (95% C.I. 4.33 - 4.44). The cumulative survival from all causes of death ***at five years*** for the Scottish ECST-surgery cohort and for the Scottish ISD-CEA non-ECST cohort was remarkably similar: 76% for the Scottish ECST-surgery cohort and 75.8%

for the Scottish ISD-CEA non-ECST cohort. The overall survival of Scottish ECST-surgery cohort was however better than the survival of the Scottish ISD-CEA non-ECST cohort ***throughout the observation period*** with a cumulative survival of the Scottish ECST-surgery cohort of 86% and the Scottish ISD-CEA non-ECST cohort of 83*% **at three and a half years*** after the carotid procedure. The curves however came together at about four and stayed together thereafter *(Table 5.10 and Figure 5.3).*

ii. <u>Scottish ECST patients and an age-sex-and operation date matched control of Scottish patients not in the trial</u> (Scottish ISD-CEA non-ECST matched cohort).

The number of stroke events in the Scottish ISD-CEA non-ECST matched cohort was 49 (29%) compared to 27 (16%) strokes observed in the Scottish ECST-surgical cohort. A total of 34 (18%) stroke events were recorded for the 186 Scottish patients randomised to surgery in the ECST data set. The mean "stroke-free" survival time for the Scottish ISD-CEA non-ECST matched cohort was 3.9 years (95% C.I. 3.7 - 4.2) and 4.4 years (95% C.I. 4.2 - 4.6) for the Scottish ECST-surgical cohort from the ISD data set. The mean survival time for the Scottish-ECST surgical patients from the ECST data set was 4.3 years (95% C.I. 4.0 - 4.5).

The cumulative "stroke-free" survival for the Scottish ISD-CEA non-ECST matched cohort was 70%. The cumulative "stroke-free" survival for the for the Scottish ECST cohort was 84% and 76% respectively using the ISD-CEA and ECST data set *(Table 5.11 and Figure 5.4).*

The "stroke-free" survival at 30 days after CEA for the Scottish ISD-CEA non-ECST matched cohort, for the Scottish ISD-CEA ECST cohort and for the Scottish-ECST

surgical cohort using ECST data set was almost identical with the cumulative "stroke-free" survival at 96%, 93% and 95% for the respective cohorts. There were only six strokes recorded for the Scottish ISD-CEA non-ECST matched cohort, eleven for the Scottish-ECST surgical cohort using the ISD-CEA data set and ten for the Scottish-ECST surgical cohort using the trial data set.

The fewer number of strokes reported for the matched cohort suggested an underestimation in the identification of stroke events in non-trial patients. The number of strokes observed in each of these cohorts was too small to report on the significance of these differences observed *(Figure 5.5).*

The difference between "stroke-free" survival at five years for the Scottish ISD-CEA non-ECST matched cohort, compared to the Scottish-ECST surgical cohort using the ISD-CEA data set and the Scottish-ECST surgical cohort from the trial data set was highly significant (Log-rank p = 0.005). The difference observed between "stroke-free" survival during the early part of the survival curve (i.e. during the 30 days after the procedure) was significant with the Breslow test statistic (p = 0.006). This significant difference was observed between the matched controlled group and the ECST participants regardless whether data used in the analysis was obtained from the routinely collected data set or from the trial data set.

Among the Scottish ISD-CEA non-ECST matched cohort, 46 (27.5%) death events were observed in the 167 patients. The number of deaths observed in the 167 patients from the Scottish-ECST surgical cohort was very similar at 38 (22.8%) deaths. The mean survival time for all cause mortality was slightly shorter for the matched control group at 4.3 years (95% C.I. 4.1 - 4.5) compared to the mean survival time of 4.5 years (95% C.I. 4.3 - 4.6) for the Scottish-ECST surgical cohort irrespective

whether the data were obtained from the routinely collected data set or the trial data set. These differences observed were not statistically significant (Log-rank p = 0.8, Breslow p = 0.7) *(Table 5.12 and Figure 5.6).*

5.3.3. Resource use estimation using CEA cost description results.

Resource use is reported for the year in which the patient was randomised and for another four years after the year of randomisation, to estimate resource use over a total period of five years. The median follow-up time for the entire Scottish-ECST cohort was 5.7 years with a mean follow-up of 5.6 years and 1589 years of patient observation. The median follow-up time was 5.2 years for the surgical cohort and 5.9 for the medical cohort. The corresponding mean follow-up time was 5.3 and 5.9 respectively.

Resource use in terms of bed days occupied could be estimated for 293 of the 308 Scottish patients randomised into the ECST. Of the 186 patients randomised to surgery, information on health care utilisation based on episodes of care in a hospital, could be determined for 172 patients including the five patients who crossed over to surgery. For the 122 patients randomised to medical care only one patient could not be identified to describe resource use after randomisation.

The total number of bed days used by 293 patients of the Scottish-ECST cohort during the year of randomisation was 3568 days with a mean number of 12.2 bed days. The total number of bed days used by the 172 Scottish ECST-surgical patients was 2628 with mean bed day occupancy of 15.3 days per patient during the year of randomisation *(Table 5.13).* A total of 169 Carotid endarterectomies were performed

during the year of randomisation among the 167 patients identified in the ISD-CEA data set as being randomised to surgery. Two patients had a second CEA within one month of the first procedure. For the 122 randomised to medical care in the ECST, 121 patients had recorded hospital admissions with a total of 940 bed days used, or 7.8 bed days per patient during the year of randomisation. *(Table 5.13)* Five Carotid endarterectomies were performed in the Scottish ECST medical cohort during the year of randomisation and a further two, four years after randomisation. A mean cost of £3716 per CEA was used to estimate the cost of the carotid surgery in the Scottish-ECST cohort and a mean cost of £300 per bed day was used in estimating resource use associated with bed occupancy

The total mean cost for the 293 Scottish-ECST patients, surgical and medical, from the date of randomisation for a five year follow-up period was £13 008 with a median cost of £7316 (IQR 4363 – 12 416). For the surgery group the total mean cost estimated was £ 14 751 (median £9416; IQR 6716 – 15 611) and for the medical group the total mean cost was £10 534 (median 3896; IQR 1196 - 7856). The cost distribution for the Scottish-ECST cohort was not normal *(Table 5.14 and Figure 5.7).* The cost distribution for the Scottish-ECST surgical cohort based on the CEA cost description results also did not exhibit a normal distribution as it was highly skewed to the left (Normal probability plots and Kolmogorov-Smirnov with Liffifors correction: $p = 0.001$) *(Figure 5.8).*

The total mean cost per year based on the CEA cost description results over the five-year follow-up period investigated was the highest (£4934) during the third year after randomisation for the Scottish-ECST medical cohort. High bed occupancy (72 bed

days per patient) for this group contributed to the cost. This high mean cost observed for the medical group during the third year after randomisation was not analysed in terms of speciality utilisation. The corresponding mean cost for the surgical group during the third year was £2505, a difference of 49%. The lowest mean cost per year was seen during the fourth year after randomisation for both the Scottish-ECST medical and surgical cohorts with a mean cost of £541 for the medical group compared with a mean cost of £635 for the surgical group, a cost difference of 15% *(Table 5.15 and Figure 5.9 and 5.10).*

5.3.4 Resource use estimation using HRG reference costs.

Of the 186 patients in the Scottish-ECST surgical cohort, 172 patients were identified including the five patients who crossed over to medical care. Of the 172 identified, only 166 (97%) had an OPCS code that could be linked to a HRG reference code. Of the 166, only 58 (35%) were linked to the appropriate HRG reference code (Q05). Fifty-seven of the 58 carotid procedures were all coded correctly using the OPCS 4 classification, which came into effect after 1988 and one was coded incorrectly using a wrong OPCS 3 code, but an appropriate HRG code. Ninety-five carotid procedures had the correct OPCS 3 code, but displayed an inappropriate HRG reference code, the majority, 93 (95%) being coded as an invalid dominant procedure, for which an associated cost is not published. Eight patients were coded with an OPCS 3 code not associated with the appropriate OPCS 3 code for carotid endarterectomy, and a corresponding HRG code of invalid primary diagnosis. Two patients who had CEA coded with the correct OPCS 3 code, had a HRG reference code associated with

admission for a transient ischaemic attack. Five patients had inappropriate OPSC codes as well as HRG reference codes. For ten of the patients, who had a CEA, the OPCS code was missing and the associated HRG code was also incorrect. Invalid primary diagnosis could be linked to seven cases, invalid dominant procedure to two, and one case was coded as a poorly coded primary diagnosis *(Table 5.16).*

A mean adjusted cost of £7832 was estimated for this cohort of 293 patients using HRG reference costs over a five-year period from the date of randomisation (median 6463; IQR 4221 – 10 419). The mean cost estimated for the surgical cohort of 172 patients was £9128 (median 7832; IQR 5018 – 11 942) and for the medical cohort was £5997 (median 4935; IQR 3176 - 7601) *(Table 5.17 and Figure 5.11).*

Using the total mean cost based on the HRG reference costs, the mean cost per year for the surgery group was higher for each of the five years investigated, with this difference most pronounced during the year of randomisation. The mean cost of the surgical group for the first year was £4088 compared to £1584 for the medical group, a cost difference of 61% *(Table 5.18 and Figure 5.12).*

The cost associated with the HRG for CEA (Q05) is substantially lower (£2298) than the cost estimate obtained in the CEA cost description study. It was expected that the overall resource use based on the national reference cost estimates would be less than the resource cost based on bed days since the cost estimates for HRGs utilise episodes of care as reference instead of bed days. The percentage cost difference between the surgical and medical cohorts based on the CEA cost description study was 29% compared to 36% when HRG reference costs were used.

5.3.5 Stroke-free life expectancy.

Stroke-free life expectancy curtailed at five years calculated from the final results of the ECST was 4.55 life years in the surgery group compared to 3.94 life-years in the medical group. The difference in stroke-free life expectancy was 0.61 life-years or 7.2 months.

In the modelling study by Nussbaum and others the number of "stroke-free" life-years among patients who received aspirin after TIAs was estimated to be 7.26 years compared with 7.63 years after CEA-NASCET (Nussbaum et al., 1996). A difference of 0.37 life-years (4.4 months) in "stroke-free" life-years for these two cohorts was calculated. Quality-adjusted life expectancy was estimated to be 6.25 with aspirin and 7.18 years after CEA-NASCET resulting in a difference of 0.93 quality-adjusted life-years (QALYs) gained or 11 months of quality adjusted life.

Calculating a cost-effectiveness ratio *(Table 5.19).*

The cost-effectiveness ratio is expressed as cost per life year gained and cost per stroke prevented.

Cost description study results and stroke-free life expectancy from ECST.

Applying the results from the CEA cost description study a mean cost of £14 746 was estimated for Scottish-ECST surgical cohort and a mean cost of £10 534 for the Scottish-ECST medical cohort. The cost difference of £4212 between these two groups divided by the difference in life years gained (0.61) from ECST resulted in a cost-effectiveness ratio of £6905 per life year gained or £62 144 per stroke prevented.

Cost description study results and published stroke-free life expectancy from the literature.

A cost-effectiveness ratio of £11 384 per life year gained was calculated by dividing the difference in cost (£4212) by the difference in life-years gained (0.37) between these cohorts. In terms of stroke prevention however, this ratio increased to £102 454 per stroke prevented, the most expensive alternative. Substituting the QALYs difference of (0.93) in the equation thus dividing the cost difference of £4212 by 0.93, a cost-effectiveness ratio of £4529 per life year gained and £40 761 per stroke prevented was calculated.

HRG results and stroke-free life expectancy from ECST.

The cost difference (£3330) based on the HRGs divided by the difference in stroke-free life expectancy (0.61) as calculated from the ECST findings, resulted in a cost-effectiveness ratio of £5459 per life year gained or £49 131 per stroke prevented.

HRG results and published stroke-free life expectancy from the literature.

Using the cost difference (£3330) between the Scottish-ECST surgical and medical cohorts based on the National Reference Cost schedule and divided by the published stroke-free life expectancy difference (0.37) a ratio of £9000 per life-year gained was calculated or £81 000 to prevent one stroke of any type.

Using the QALYs difference of 0.93 to calculate a cost-effectiveness ratio based on the cost difference (£3330) obtained from the National Reference Schedule of In-

Patient costs, the cost-effectiveness ratio decreased to £3581 per life year gained and the cost to prevent one stroke to £32 226 the most favourable scenario.

By increasing the cost difference (CEA cost description study results) between the surgical and medical cohorts by 20% to £5054 but keeping the number of life-years gained constant (0.37), the cost-effectiveness ratio increased to £13 661 per life-year gained and to £122 945 per stroke prevented. Increasing the number of "stroke-free" life years gained by carotid surgery to 12 months will result in a relative favourable cost-effectiveness ratio of £4212 (£3330) per life year gained and £37 908 (£29 970) per stroke prevented (National Reference costs figures in brackets).

A sensitivity analysis on the cost-effectiveness ratio and the cost-effectiveness in terms of strokes prevented was also performed by using the ranges of the estimated change in total major stroke-free life expectancy in months, published in the final results of the ECST, and the cost differences between surgical and medical cohorts from the CEA cost description study and the HRG reference costs *(Table 5.20 and 5.21).* The most favourable ratio obtained in terms of stroke prevention was £22 836 per unadjusted life-year gained when the "stroke-free" life expectancy gained by CEA was 20 months or 1.66 years. The worst ratio was £114 873 per unadjusted life-year gained when the "stroke-free" life expectancy gained by CEA was only 4 months or 0.33 years.

5.4 Discussion

This study found that the trial results from the ECST were not transferable to Scottish CEA patients who were operated on during the same period as the trial and that

carotid endarterectomy was very expensive in terms of life years gained or the number of strokes prevented if the benefit in clinical effectiveness of the procedure was very small.

This study rejected the primary null hypothesis that there is no difference between the ***five-year "stroke-free" survival*** of all Scottish patients undergoing a carotid endarterectomy outside the ECST compared with the Scottish patients who were randomised to surgery in the ECST during the period 1981 - 1994. The alternative hypothesis of a difference in the *five-year "stroke-free" survival* between trial patients and non-trial patients should therefore be accepted.

The null hypothesis should also be rejected for the cohort of surgical patients matched for age, sex and date of operation to the ECST patients and for the two patient cohorts using a trial data set, the ECST data and a routinely collected data source, the ISD data.

The findings of this study however indicated that the null hypothesis of no difference in the ***five-year overall survival*** between trial patients and non-trial patients should be accepted whether a matched control cohort or all Scottish-CEA non-trial patients are considered regardless of data source used, since the cumulative survival in the three groups (all Scottish ISD-CEA non-trial patients, Scottish ISD-CEA matched control patients and Scottish-ECST CEA patients) was very similar. This finding was not surprising and was expected, since all deaths are registered at the General Register Office for Scotland.

The second objective of this study was to assess the cost-effectiveness of carotid endarterectomy in stroke prevention. We found that carotid endarterectomy was very expensive in terms of life years gained or the number of strokes prevented if the benefit in clinical effectiveness of the procedure was very small. The relative cost-effectiveness of carotid endarterectomy was stronger associated with the benefit of "stroke-free" survival obtained from carotid surgery than with the cost difference between alternative treatments.

Transferability of trial results to the "general" population - the null hypotheses.

The absence of clinical variables in routinely collected data raises questions whether the benefits of carotid endarterectomy in the general population are similar to those reported in clinical trials. Although it is generally assumed that the overall results of clinical trials are generalisable to all patients in the trial and all future similar patients, this assumption has rarely been tested.

Hallett and others (1998) compared the results from NASCET to a geographically defined population and found that the early outcomes were similar to the trial results and also documented the remarkable long-term benefit of CEA. However, the population studied was small (about 100 000) and only 322 carotid endarterectomies were performed over 25 years (1970 – 1995) which reduces the generalisability of their findings. Similar findings were also reported from the Netherlands, though the study periods before and after publication of the trial results were relatively short, in both instances only two years (Dijkema et al., 1998).

Carotid endarterectomy before and after the publication of the randomised controlled trials was also investigated by Brittenden et al (1999) in Scotland. A fourfold

increase was observed in the number of carotid endarterectomies since 1991 and despite an increasing proportion of high-risk patients among those receiving the operation, the results have improved progressively. These findings applied however only to **one** unit in Scotland and were not representative of the overall situation in Scotland.

Reanalysing the results of the ECST by using independently derived and validated prognostic models, it was found that the relative treatment effect varied with the absolute baseline risk of stroke (Rothwell et al., 1996). This suggests that the overall results of the ECST can not be generalised to all symptomatic patients with severe stenosis because of the potential bias in the data and the potential lack of comparability of cases and controls.

The two large RCTs (ECST, 1991; NASCET, 1991) have shown the efficacy of this procedure in certain subgroups of patients, but several caveats apply when these results are extrapolated to patients in the general population with symptoms related to carotid disease. The surgeons participating in these trials were selected for their high level of expertise and excellent track records. Secondly, the results from the RCT might not apply depending on the methods use to measure the stenosis. Also the measurement of stenosis by means other than angiography might not be transferable and thirdly, baseline risk factors appear to have an important effect on peri-operative and long-term outcomes of CEA (Barnett et al., 1998). Although it can be assumed that patients not associated with the trial might have been operated on by different surgeons, it seems unlikely to have been the case in Scotland, since Scotland is a geographically contained area with probably a limited number of vascular surgeons performing this operation.

Trials frequently relate to cohorts of heterogeneous patients for whom costs and outcomes vary. The benefit from an intervention expressed as the absolute or relative risk reduction does not refer to outcomes in terms of life expectancy nor does it attach a cost to the benefit obtained.

A study published by the Rand Corporation in the United States in1988 showed that 32 percent of CEA performed in the United States in Medicare recipients were performed for inappropriate indications (Winslow et al., 1988). Re-assessing their findings in the context of the published RCTs, none of the data from these trials suggested that any of those operations should now be considered appropriate.

Hlatky et al (1984) applied the eligibility criteria of three large randomised controlled trials of coronary bypass surgery to a selected patient population and found that only 4 - 13% of the patients met the eligibility criteria for these trials (European Coronary Surgery Group, 1979; Murphy et al., 1977; CASS principal investigators and their associates, 1983). This suggested that the results of these RCTs apply only to a small proportion of patients "and it is uncertain whether one can extrapolate from the results in a highly selected subgroup to the general population of patients" (Hlatky et al., 1984). These concerns might also hold true for the transient ischaemic attack patient population.

An increase in the number of carotid endarterectomies has been reported after the publication of both the ECST and the NASCET. Tu and others assessed whether patients who had CEA in the early 1990s were selectively referred to regional centres of excellence (high-volume hospitals with low peri-mortality rates) as recommended by NASCET collaborators and whether the increase in the rates of CEA after the publication of NASCET occurred in these centres and found that the publication of

new scientific evidence did not change surgeons and physicians pattern of service (Tu et al., 1998).

Although the findings obtained in my study suggested that the five-year "stroke-free" survival of all Scottish CEA patients who were not in the ECST were less favourable than the "stroke-free" survival of the Scottish CEA patients in the ECST, inconsistencies were noted. Comparing the matched control cohort with the Scottish-ECST cohort, using routinely collected data as source, the five-year "stroke-free" survival of the trial patients appeared "better", as was expected. When the five-year "stroke-free" survival of the Scottish-ECST surgical cohort was compared using data from the trial data set and data from the routinely collected data set, the difference observed in the five-year "stroke-free" survival favoured the routinely collected data source.

Possible explanations for these findings are put forward: The "better" five-year "stroke-free" survival obtained for the Scottish-ECST surgical cohort when routinely collected data were used compared to trial data, suggested that "all stroke events" were probably not recorded in the routine data set (Underreporting of stroke events). This highlight a general concern regarding the accuracy of routinely collected data and the potential source of bias when routinely collected data are investigated.

Assessing the Scottish-ECST surgical cohort and the matched control cohort using the routinely collected ISD data set, the five-year "stroke-free" survival of the trial patients (83.7%) was much more favourable compared to the matched control cohort (70%). This again indicated another source of bias associated with the case-mix and pre-existing comorbidities in these two cohorts, since matching could only be done on the very basic variables such as age, sex and operation date.

Limited clinical variables in routinely collected data sets

In addition to the lack of accuracy associated with routinely collected data, which will be discussed later on, another constraint encountered using the data from a routinely collected data set, was the absence of clinical variables in the data set. The lack of clinical variables hampered any detailed analysis comparing subjects in trial data for whom these variables were recorded with subjects in a routinely collected database where these variables were absent. It is therefore highly likely that those who were not selected for the trial were by definition different. Analyses were thus much curtailed and concentrated on basic variables such as age, sex, death, and hospitalised stroke events. With regards to stroke events, the data available in the Scottish ISD-CEA data set do not distinguish between a minor or major stroke event using the Rankin classification. All stroke events and transient ischaemic events were thus defined as "stroke events", grouped together regardless of severity and analysed as such. This obviously contributed to almost "crude" findings and not as refined, as one would have hoped for.

Clinical variables indicating the degree of stenosis and existing comorbidities would have allowed a much more precise matching. The absence of these variables restricted more definitive comparison between patients in a trial and non-trial patients. Similar concerns were expressed by Tu et al in assessing CEA over time in the United States and Canada. It is also possible that the patients operated on outside the ECST might have been operated on by surgeons who did not have the same skills and expertise as those surgeons participating in the trials.

The five-year "stroke-free" survival results obtained in this study also suggested that the results from randomised clinical trials can not be transferred to "other"

populations and other settings without being conscious of the disparity between a trial population and the general population.

The main limitation in the study population(s) used to compare the trial results with is found in the data source investigated, namely routinely collected data. Although these data sources provide large numbers at relatively low costs, accuracy and completeness of the data remain a big problem. The absence of clinical variables in routinely collected data sets further restricted the comparisons and influenced the validity of the results obtained.

Randomised controlled trials also have certain constraints. Though trials usually relate to cohorts of heterogeneous patients, strict entry criteria into a trial will certainly exclude patients with associated comorbidities who might be at a higher risk of an intervention. Furthermore, the inclusion criteria applicable in these trials might "exclude" many patients outside of trial situations and these criteria might not always be adhered to in "real-life" practice.

Randomisation using the uncertainty principle.

Eligibility into the ECST was determined mainly by the uncertainty principle whereby patients were only randomised to surgical or best medical care when the doctor was "uncertain" which treatment to recommend. Although randomisation based on the uncertainty principle maximises the heterogeneity of the study and also avoids ethical problems, this selection method dilutes the assumption adhered to in this study that patients operated on outside trial conditions were similar and thus comparable with those having carotid surgery in the trial. It was assumed that patients who were operated on outside trial conditions, in "real life", in the Scottish

ISD-CEA data set were patients where the doctor/surgeon was "reasonably certain" that surgery would benefit the patient.

The cost of surgical and medical care for the Scottish-ECST cohort - the cost measure.

Although it was possible to obtain a crude estimate on the cost difference of a cohort of patients treated with CEA compared to a cohort receiving best medical care using results from RCTs, estimating the cost of treatment in everyday practice populations remains difficult. Routinely collected data from this historic Scottish-ECST cohort were used to determine the cost of CEA. The use of resources was only reported for five years since randomisation. Many assumptions were needed, which obviously increased the potential for bias. The cost data on carotid endarterectomy during the 1980s and early 1990s were not available when the majority of these procedures in the trial were performed. Cost specific data as obtained in the current CEA cost description study as well as costs based on the HRG were used to estimate the "total direct" cost of the procedure and costs associated with other admissions.

Although resource use of the activity in Scottish hospitals is classified using HRG-codes in the ISD national database, a Scottish national reference cost for these HRG-codes was not available. A pilot exercise was performed a few years ago to develop national reference costs for the HRG-codes in the NHS in Scotland. This was however not complete and in the absence of a Scottish National Cost Reference the English National Cost Reference, generated and produced by the National Case Mix Office in England, was used to estimate resource use for the Scottish-ECST cohort.

Two methods were used to estimate resource use for a cohort of patients treated either surgically or medically. In the first method, bed days were used as a proxy for cost of all diagnoses and procedures other than the CEA procedure cost that was obtained from the prospective study. Although the use of bed days as a proxy for cost is considered a crude and unrefined approach it appears from the results obtained in this study that it might still be a better approximation of actual resource use than HRGs.

Ninety-eight (59%) of patients who had a CEA had a HRG reference code defined as an Invalid Primary Procedure, for which no reference cost is currently published. Ten patients displayed HRG reference codes associated with a primary diagnosis, which it is considered to substantially underestimate of the cost of the procedure.

Using these reference costs to obtain an estimate of resource use of the surgical Scottish-ECST cohort it was apparent that this would result in an underestimation of resource use, simply because more than half of the CEA had no cost associated with the procedure and in 6% of cases the cost for the procedure was lower than the appropriate reference cost. To arrive at a reasonable estimate for the resource use of the Scottish-ECST cohort when applying the HRG reference cost estimates, it was considered appropriate to apply the cost of a CEA to all cases where the procedure was incorrectly coded. And secondly, to apply the arithmetic mean cost of the Invalid Primary Diagnosis and Poorly Coded Primary Diagnosis to the HRGs coded as Invalid Dominant Procedures for which a reference cost was not published. Consequently all reported costs using the HRGs as reference were adjusted to ameliorate to some extent the effect of underestimation of resources used.

In the second approach the results from the CEA cost description study were applied to the Scottish-ECST cohort. Since the cost of CEA estimated in two previous studies in the UK (Radestock 1992; Smithies et al., 1997) was similar to the results from the CEA cost description study, it seems appropriate and realistic to use the recent CEA cost estimate. Furthermore the estimation of resource use based on HRGs from the National Schedule of Reference Cost produced a much lower estimate, suggesting that the classification of procedures or diagnoses, which are considered to utilise similar resources quantities, might in fact represent an underestimation of the actual amount of resources used. Though the difference between the mean costs was not "significant", it might influence the outcome when used in subsequent calculations to determine incremental cost-effectiveness ratios. Applying these low estimates in equations to assess the cost-effectiveness of procedures might suggest that a procedure is within the acceptable ranges for cost-effectiveness of interventions and thus "affordable" when it is not necessarily true.

The conversion of operations, diagnoses and patients characteristics into Diagnosis-Related Groupings (DRG) or HRGs for use in clinical budgeting has been identified as a potential source of error. The appropriateness of such groupings for use in clinical budgeting has been questioned (Sanderson et al, 1989). This study demonstrated that only 34% of OPCS codes were correctly linked to the appropriate HRG reference code. It needs to be mentioned, however, that the low accuracy obtained was essentially associated with the OPCS 3, which are no longer in use. It is also acknowledged that the accuracy achieved using the OPCS 4 classification was almost a 100% (57/58), which might suggest that more accurate estimations in the future might be obtained using these groupings.

Errors in diagnosis-related groupings (DRG) were found in approximately 24% of joint replacements in three general hospitals in Leicester. These procedures like CEA and other surgical procedures are assumed to be relatively "easy" to code. Most of these errors occurred with the OPCS coding at local hospitals. OPCS codes are converted to HRGs or DRGs, which is converted to the National Reference Cost (Smith et al., 1991). The findings in the present study regarding the OPCS coding errors reflected what was found by Smith and others and might explain the lower cost estimates obtained when the HRG reference costs were applied to the patients in the Scottish-ECST cohort. The need to use two sources to estimate resource use, increased the potential for error, indicated that an accurate and reliable source to estimate resource use is not available at present and that existing sources have many inaccuracies and biases.

To quantify the resource use associated with two alternative therapies with proven efficacy in managing TIAs (CEA and best medical care), the cost of all in-patient admissions for Scottish–ECST surgical and medical cohorts was evaluated and expressed as a cost-effectiveness ratio.

It could be argued that subsequent admissions after randomisation into the ECST could have been totally unrelated to any subsequent ischaemic event and therefore inappropriate to be used in estimating resource use. However, data on all subsequent admissions were collected for both the surgical and medical cohort to estimate resource use after randomisation into the ECST thus reducing any degree of the bias, which might occur. The resource use was not specifically designed to capture only stroke-related events, but to estimate health care resource use over time of a selected

group of patients who presented with similar clinical symptoms, but were managed differently.

Routinely collected data: Accuracy and completeness.

In performing a sensitivity analysis using the number of Scottish participants in the ECST as the reference or *"gold"* standard, a sensitivity of 95% (293/308) was calculated of identifying Scottish- ECST participants in a routinely collected data set. Considering only the 186 patients randomised to surgical treatment in the ECST the sensitivity decreased slightly to 92% (172/186). Though the percentage of the Scottish-ECST surgical patients eventually identified in the routinely collected database is higher than the 90% reported previously for routinely collected data (Harley and Jones, 1996), this relatively high percentage was only attainable because accurate patient information was available from the ECST data set. Achieving this high identification required many consultations with ISD to identify "missing" patients in the ISD-CEA who we knew had had carotid surgery, but were not identified during the first linkage.

It is thus a matter of concern that the capturing of surgical procedures did not perform better and might be as low as 83% (155/186) as was found with the first linkage of Scottish-ECST surgery patients. This suggested that a substantial amount of patient information might be lost when routinely collected data are collated. Though this study did not set out to determine the accuracy of routinely collected data sources, it is evident that a percentage as high as 90% or even 99% as reported recently (Ellis et al., 1999) might be an overestimation of the accuracy of routine data from ISD and might only be attainable under special circumstances.

The benefit associated with this procedure - the clinical effectiveness measure.

The interim results on moderate carotid stenosis published during 1996 showed that the stroke-free life expectancy was shorter in surgery patients than in the non-surgery control groups in patients with moderate stenosis (ECST, 1996). The "stroke-free" life expectancy between surgery and control groups was not published in the final results of the ECST. By calculating the areas under the survival curves this could be calculated and applied in the cost-effectiveness ratio equation.

The final results however suggested that carotid endarterectomy is indicated for most patients with a recent non-disabling carotid-territory ischaemic event when the stenosis is greater than about 80% and that men probably derive more benefit from the procedure than women. A Cox proportional hazards model was used to predict the differences in total major-stroke-free life expectancy between surgery and control groups and is presented as a function of age and of stenosis, and by sex. It is proposed that these prediction models should be used in clinical decision making whether to offer surgery to a particular patient or not. From these graphs it is clear that men derive more benefit from surgery than women, that there was an increased benefit with increasing severity of stenosis and that younger patients displayed distinct benefit over a narrower range of severe stenosis than was the case for older patients. While this model assists in clinical decision making for the individual patient, it does however not translate easily into the overall benefit in terms of stroke-free life years gained for a cohort of CEA patients. These estimated ranges were however applied in a sensitivity analysis to determine the most favourable cost-effectiveness ratio in terms of stroke prevention for a CEA "population".

The absolute risk reduction for major stroke or death reported in the ECST was 11.6%, or expressed as the number needed to treat this suggests that nine carotid endarterectomies need to be performed to prevent one stroke of any type. Analysing the percentage without any disabling or fatal stroke using Kaplan-Meier estimates, it appears that 20 carotid endarterectomies might cause one death or disabling stroke, while preventing two, though the confidence limits on this net benefit were wide. Considering the prediction of benefit from carotid endarterectomy in individual patients using a risk modelling approach, it is suggested that a 100 CEA need to be performed when a relatively low risk score is present (Rothwell et al., 1999). In the case of a high risk score it is suggested that only ***three*** CEA need to be performed to prevent one stroke and when not stratified by risk factors, 14 CEA need to be performed to prevent one stroke. This model used the baseline characteristics of the ECST to predict which patients might benefit the most from carotid endarterectomy. The primary objective of the RCT is to evaluate the efficacy in strictly defined populations. It is not designed to predict the clinical course in individual patients, nor is the best therapy for patients not meeting RCT eligibility criteria well defined. Using baseline characteristics of a highly selected patient population to predict risk in every day clinical practice might therefore be inappropriate (Hlatky et al., 1984). Risk modelling prediction might be more suitable when baseline characteristics of patients from an observational database are used instead. Obviously these extreme numbers needed to treat found by risk modelling will have extensive implications on the cost-effectiveness of this procedure. Using the NNT of three might also exclude patients who might benefit from the procedure which will increase cost over time as more stroke patients would have to be cared for.

Interpretation of the cost-effectiveness ratio calculated.

It is imperative that in settings of limited health care resources those available should be allocated in such a manner as to maximise the health benefit per pound spent. An accurate assessment of the cost-effectiveness of a particular intervention requires knowledge of the cost of the intervention, the cost of the alternatives and the effects of the various interventions on the life-years gained. In assessing the cost-effectiveness of CEA in terms of stroke prevention, the cost of stroke needless to say is closely associated with this assessment.

Comparisons between health care interventions in terms of their relative cost-effectiveness, in cost per life-year or cost per quality-adjusted life-year gained, have become increasingly popular during recent years. Williams, as far back as 1983 published the first "league table" of cost-effectiveness for the United Kingdom. Similar tables were published in North America by Torrance and Zipurski (1984) and Schulman et al (1991) and in Canada, Laupacis and others (1992) classified health technologies into five grades of recommendation based on their incremental cost per QALY.

The two main motivations for league tables are that investigators or analysts can assess their findings in a broader context and also can compare estimates of the cost per life-year gained with other interventions. The exact limits of acceptable cost-effectiveness are controversial. Laupacis et al classified interventions, which cost less than $50 000, or less per QALY as generally acceptable, interventions between $50 000 and $100 000 per QALY as borderline and interventions more than

$100 000 per QALY as not cost-effective. Goldman et al and Kupersmith and co-workers however developed different cost-effectiveness categories. Interventions which cost less than $20 000 per QALY or years of life saved are regarded as highly cost-effective; interventions less the $40 000 as effective; $40 000 to $60 000 as expensive and interventions more than $100 000 as very expensive (Goldman et al., 1992; Kupersmith et al., 1995). As an alternative to these proposed classifications, league tables of cost-effectiveness can be used to assess the cost-effectiveness interventions. For example antihypertensive treatment to prevent stroke costs £940/QALY; coronary artery bypass graft surgery (one vessel, moderate angina) costs £18 830/QALY and neurosurgical intervention for malignant intracranial tumours costs £107 780. All the costs are in pound sterling and reflect 1990 prices (Maynard, 1991; Drummond et al., 1997).

Considering these controversies and discrepancies in these proposed classifications of cost-effectiveness and the criticism directed against the use of cost-effectiveness league tables specifically regarding the use of these tables for the allocation of health care resources, the cost effectiveness of CEA was only crudely assessed in an unrefined manner (Drummond, 1997; Mason et al., 1993).

The sensitivity analysis using estimated ranges of "stroke-free" life expectancy from the ESCT final results, suggested that with an increase in "stroke-free" life expectancy, the cost effectiveness ratio decreased substantially and the cost incurred per stroke prevented put this intervention within the "acceptable published limits" of cost-effectiveness. These cost-effectiveness ratios however might be achievable for only a small minority of selected patients and would certainly not be generalisable to

all carotid endarterectomy patients. A more realistic "stroke-free" life year expectancy gain for the majority of CEA patients to be used in calculating cost-effectiveness ratios, which would be generalisable, would probably be between four and eight months *(Table 5.19 and 5.20).*

The CEA cost-effectiveness ratio in terms of life years gained, expressed as either the cost per life year or QALY gained, were classified with interventions in the middle and lower upper ranges of the cost-effectiveness league table (Appendix 7). For example interventions such as kidney transplant, breast cancer screening, heart transplantation and cholesterol testing and treatment even at the most favourable benefit and cost scenarios.

The most unfavourable cost-effectiveness ratio calculated in terms of stroke prevented was £114 873 when only 4 life months were gained and the cost difference between the alternative treatments was about £4200 which makes CEA as a stroke prevention strategy an extremely expensive option in terms of the published categories for assessing cost-effectiveness of procedures. The best cost-effectiveness ratio in terms of stroke prevented was £18 054 when 20 stroke-free months were gained and the cost difference between the alternative treatments was about £3330 *(Tables 5.21).*

Gaining 12 months or more in "stroke-free" life expectancy will result in highly favourable cost-effectiveness ratios per stroke prevented almost irrespective of the cost differences between surgical and medical cohorts treated over time. Whether benefits of this magnitude could be obtained for the majority of CEA patients remains questionable. It is apparent from the sensitivity analysis that the cost -

effectiveness ratio per stroke prevented is highly sensitive to the "stroke-free" life expectancy gained by CEA and less sensitive to the cost difference between the alternative interventions. Furthermore, a more desirable cost-effectiveness ratio was obtained when life-years gained were quality adjusted.

Carotid endarterectomy and the cost of stroke

The cost of carotid endarterectomy and thus the cost-effectiveness of the procedure can not be discussed without assessing the cost of stroke. Since the primary objective of carotid endarterectomy is the prevention of stroke and the benefit of CEA is expressed in terms of "stroke-free" survival, it is imperative to assess the cost-effectiveness ratio of CEA against the cost of stroke care. The cost of stroke care can essentially be divided into acute care and the long-term stroke care costs. These two cost components constitute the "life-time" cost of stroke. Though the direct cost of the acute care of stroke patients has been estimated (Bergman et al., 1995; Smurawska et al., 1994), few studies have investigated the "life-time" cost of stroke (Jørgenson et al., 1997; Taylor et al., 1996; Terent et al., 1994; Asplund et al., 1993). The average acute care cost per hospital stroke in-patients in Scotland was estimated at about £8500 (Forbes and Dennis, 1995). The lifetime cost of stroke in the United Kingdom has been estimated at £59 000 (Pollock, 1997). The corresponding figure for the lifetime cost in the USA has been estimated at about $100 000 (Kent et al., 1995). In the absence of a more accurate estimate of the life-time cost of stroke, applying the cost of £59 000 per stroke patient over a "life-time" as reference cost in this analysis, it is "evident" that carotid endarterectomy might be quite costly in

preventing stroke and might only be cost-effective under exceptional circumstance for carefully selected patients.

5.5 Summary.

This study found that the five-year "stroke-free" survival of all Scottish patients who had a CEA outside the ECST compared with the Scottish patients who were randomised to surgery in the ECST was not the same. This suggested that trial patients do "better" than patients not associated with a trial. The most favourable cost-effectiveness ratios were between £18 054 and £22 836 per life-year gained when the stroke-free life-years gained was 20 months. These favourable cost-effectiveness ratios appear to be unlikely to be achieved under efficacy outcomes presently obtained. Although is it generally assumed that the overall results of randomised controlled clinical trials are generalisable to all patients in the trial and all future similar patients, this assumption has been shown to be invalid in this study. The relative cost-effectiveness of CEA was stronger associated with the benefit of "stroke-free" survival obtained from carotid surgery than with the cost difference between alternative treatments.

"The great scientific accomplishments of the randomised controlled trials will not be fully realised until we have established mechanisms for ensuring that patients who cannot benefit from carotid endarterectomy do not undergo it and that patients who are appropriately selected receive its full benefit" (Chassin, 1998).

Table 5.1: Breakdown of Scottish ECST cohort randomised to surgery and medical care (1981 -1994).

	Surgery cohort	Medical cohort	Scottish-ECST cohort
Identified in ISD-CEA data set	**172**	**121**	**293**
CEA performed	167	(14*)	181
No CEA	0	107	107
Cross-overs	5	14*	5
Missing	14	1	15
Total	**186**	**122**	**308**

*CEA from medical care cross-overs

Table 5.2: Baseline characteristics of the Scottish ECST-surgery cohort and the Scottish non-ECST matched control cohort from ISD (1981 - 1994).

	Scottish-ECST surgery cohort (n = 172)	**Scottish non-ECST matched cohort (n = 172)**
Males	111 (66%)	111(66%)
Females	56 (34%)	56 (34%)
Mean age (SD)	61.1 (7.74)	61.1 (7.69)
Age categories:		
< 50 years	14	12
50 - 65 years	101	105
66 - 80 years	52	50

Table 5.3: Degree of internal carotid artery stenosis for the surgical patients in the ECST from the reported angiogram findings in the ECST data set.

	ECST surgical participants		
Degree of stenosis	**Scottish cohort (n = 186)**	**Other centres (n= 1621)**	**All ECST participants (n= 1807)**
0 - 29% (Low)	15 (8%)	290 (18%)	305 (17%)
30 - 69% (Moderate)	38 (20%)	557 (34%)	595 (33%)
70 - 99% (Severe)	126 (68%)	699 (43%)	825 (46%)
Not recorded	7 (4%)	75(5%)	82(4%)

Table 5.4: Early and late strokes observed for the different cohorts in the Scottish ISD-CEA data set: 1981 - 1996.

	Stroke events *(s)*		
	< 30 days	*30 days - 5 years*	*0 days - 5 years*
Scottish non-ECST non-matched cohort: (n = 2558)	110 (4.3%)	359 (14%)	469 (18.3%)
Scottish non-ECST matched control: (n = 167)	7 (4.2%)	42 (25%)	49 (29.3%)
Scottish ISD-CEA non-ECST: (n = 2725)	117 (4.3%	401 14.7%)	518 (19%)
Scottish-ECST cohort (n = 167)	11 (7%)	16 (9.6%)	27 (16.2%)
Total events: Scottish ISD-CEA data set: (n = 2892)	**128** (4.4%)	**417** (18.8%)	**545** (18.8%)

Table 5.5: Early and late deaths observed for the different cohorts in the ISD-CEA data set: 1981 - 1996.

	Deaths *(d)*		
	< 30 days	*30 days - 5 years*	*0 days - 5 years*
Scottish non-ECST non-matched cohort: (n = 2558)	59 (2.3%)	345 (13.5%)	404 (15.8%)
Scottish non-ECST matched control: (n = 167)	5 (3%)	41 (24.6%)	42 (25%)
Scottish ISD-CEA non-ECST: (n = 2725)	64 (2.3%)	386 (14.2%)	446 (16.4%)
Scottish-ECST cohort (n = 167)	2 (1%)	36 (21.6%)	38 (22.8%)
Total deaths: Scottish ISD-CEA data set: (n = 2892)	**66** (2.3%)	**418** (16.7%)	**484** (16.7%)

Table 5.6: Number of recorded episodes of care for the Scottish-ECST surgical and medical cohorts by diagnostic group for the entire period and for a five-year period of follow-up.

Episodes of care	Surgery group (n = 172)	Medical group (n = 121)	Scottish-ECST cohort (n = 293)
Entire period of follow-up	1627 (67%)	809	2436
Five years of follow-up	978 (64%)	547	1525

Table 5.7: Breakdown of admission by speciality for the Scottish-ECST surgery and medical cohorts by ICD9 diagnosis code for a five-year period from date of randomisation.

	Surgery cohort (n = 172)	Medical cohort (n = 121)	Scottish-ECST cohort (n = 293)
General surgery	348(36%)	146 (27%)	494
General medicine	246 (25%)	147 (27%)	393
Neurology	68 (6.9%)	47 (8.6%)	115
ITU	44 (4.5%)	24 (4.4%)	68
Other	272 (28%)	183 (34%)	455
Total episodes	978 (64%)	547 (36%)	1525

Table 5.8: Breakdown of admission by type for the Scottish-ECST surgery and medical cohorts by ICD9 diagnosis code for a five-year period from date of randomisation.

	Scottish-ECST cohort (n= 293)		
ICD 9 diagnosis	**Surgery cohort (n= 172)**	**Medical cohort (n = 121)**	**Total (n = 293)**
Cerebrovascular Admissions	345 (35%)	158 (29%)	503 (33%)
Cardiovascular Admissions	276 (28%)	148 (27%)	424 (28%)
Other admissions	357 (37%)	241 (44%)	598 (39%)
Total admissions	978	547	1525

Table 5.9: Cumulative "stroke-free" survival for all the carotid endarterectomy patients in Scotland (1981 -1996) according to ECST status.

	Scottish ECST cohort		**ISD-CEA non-ECST cohort**	
Time (years)	*Cumulative survival*	*Number remaining*	*Cumulative survival*	*Number remaining*
0	0.9934	166	.09938	2708
0.5	0.9341*	156	0.8991	2360
1	0.9222	154	0.8712	2085
1.5	0.8982	150	0.8520	1853
2	0.8802	147	0.8351	1667
2.5	0.8622**	143	0.8208	1477
3.0	_	_	0.8062	1281
3.5	0.8500	138	0.7981	1101
4	0.8438	136	0.7890	993
4.5	_	_	0.7923	845
5	0.8373	129	0.7713	747

*0.78 years **2.6 years

Table 5.10: Cumulative survival for all cause mortality survival tables for all CEA patients in Scotland (1981 -1996) according to ECST status.

	Scottish ECST cohort		**ISD-CEA non-ECST cohort**	
Time (years)	*Cumulative survival*	*Number remaining*	*Cumulative survival*	*Number remaining*
0.1	0.9940	166	0.9941??	2724??
0.5	0.9701	162	0.9580	2514
1	0.9521	159	0.9388	2251
1.5	0.9401	157	0.9205	1994
2	_	_	0.8993	1790
2.5	0.9041	150	0.8796	1586
3	0.8799*	144	0.8587	1366
3.5	0.8615	140	0.8335	1182
4.00	0.8242	132	0.8142	1039
4.5	0.7928	126	0.7880	870
5	0.7610**	118	0.7583	744

*3.26 years; **4.9 years

Log-rank: p= 0.48; Breslow: p = 0.32

Table 5.11: Cumulative *"stroke-free" survival* over five years of the Scottish-ECST surgery cohort from ECST data set and the Scottish ECST-surgical cohort and the Scottish ISD-CEA non-ECST matched cohort from the ISD-CEA data set.

	ECST data set		**ISD data set**			
	Scottish cohort*		**ECST cohort**		**Matched control**	
Time (Years)	*Cumulative survival*	*Number remaining*	*Cumulative survival*	*Number remaining*	*Cumulative survival*	*Number remaining*
0	0.9946	185	0.9940	166	.09940	166
0.5	-	_	_	_	0.8683	145
1	0.8917	161	0.9222	154	0.8323	139
2.5	0.8522[1]	148	0.8622	143	0.7843	130
3	0.8288	141	0.8561[2]	142	0.7478[5]	120
4	0.8161[3]	135	0.8438	136	0.7290	116
5	0.7583[4]	126	0.8373	129	0.7037	110

*Scottish-ECST surgery cohort

[1)] 2.1 years; [2)] 2.7 years; [3)] 3.5 years; [4)] 4.4 years [5)] 3.6 years

Log-rank p = 0.01; Breslow p = 0.015

Table 5.12: Cumulative overall survival over five years of all cause mortality of the Scottish-ECST surgery cohort from ECST data set and the Scottish ECST-surgical cohort and the Scottish ISD-CEA non-ECST matched cohort.

	ECST data set		**ISD data set**			
	Scottish cohort*		**ECST cohort**		**Matched control**	
Time (years)	*Cumulative survival*	*Number remaining*	*Cumulative survival*	*Number remaining*	*Cumulative survival*	*Number remaining*
0	0.9946	185	0.9940	166	0.9940	166
0.5	0.9731	181	0.9701	162	0.9521	159
1	0.9570	178	0.9521	159	0.9341	156
2.5	0.9024	163	0.9101	151	0.8801	146
3	0.8802	158	0.8860	147	0.8318	137
4	0.8268	135	0.8304	133	0.7762	124
5	0.7583	119	0.7670	118	0.7445	116

*Scottish-ECST surgery cohort

Log-rank p = 0.8; Breslow p = 0.7

Table 5.13: Resource use for the Scottish-ECST surgical and medical cohorts expressed in terms of bed days and based on the CEA cost description study results over a five year period from randomisation.

	Surgical cohort (n= 172)		Medical cohort(n = 121)	
	Patients (n)	Bed days Mean	Patients (n)	Bed days Mean
Randomisation year	172 (100%)	15.3	121 (100%)	7.8
Year two	41 (23%)	22	26 (22%)	13.4
Year three	49 (28%)	29	28 (23%)	72
Year four	43 (25%)	8.5	19 (16%)	10
Year five	37 (22%)	12.3	24(20%)	9.5
Over the five years	172	38.0	121	33.4

Table 5.14: Total mean cost (£) for the Scottish-ECST surgical and medical patients from date of randomisation for five years of follow-up based on CEA cost description study results.

	Surgical cohort (n = 172)	Medical cohort (n = 121	Scottish- ECST cohort (n= 293)
Mean (£)	14 751	10 530	13 008
Median (£)	9416	3896	7316
IQR (£)	6716 – 15 611	1196 - 7856	4346 – 12 416

Table 5.15: Total mean cost (£) for the Scottish-ECST surgical and medical cohorts from the date of randomisation for each of the five years of follow-up based on the results of the CEA cost description study.

	Surgical cohort (n = 172)	Medical cohort (n = 121	ECST-Scottish cohort (n= 293)
Randomisation year	8292	2405	5861
Year two	1551	1012	1328
Year three	2505	4934	3508
Year four	635	541	596
Year five	792	683	747

Table 5.16: OPCS coding and HRG coding for the Scottish-ECST surgical cohort.

	OPCS code missing	OPCS 3 code incorrect	OPCS 3 code correct	OPCS 4 code correct	Total
Appropriate HRG	-	1	_	57	58 (35%)
Invalid dominant procedure	2	5	91	-	98 (59%)
Invalid primary diagnosis	8	_	2	-	10 (6%)
Subtotal	10	6	93	57	166
HRG missing	20*	-	-	-	20
Total	30	6	93	57	186

* 20 = 5 cross overs, 14 patients not linked, 1 missing

Table 5.17: Total mean adjusted cost (£) for the Scottish-ECST surgery and medical cohorts from date of randomisation for five years of follow-up based on HRG reference costs.

	Total mean cost (£)		
	Surgical cohort (n = 172)	**Medical cohort (n = 121)**	**Scottish-ECST cohort (n= 293)**
Mean (£)	9128	5997	7832
Median (£)	7832	4935	6463
IQR (£)	5018 – 11 942	3176 - 7601	4221 – 10 419

Table 5.18: Total mean adjusted cost (£) for the Scottish-ECST surgical and medical patients from the date of randomisation for each of the five years of follow-up based on HRG reference costs.

	Total mean adjusted cost (£)		
	Surgical cohort (n = 172)	**Medical cohort (n = 121)**	**ECST-Scottish cohort (n= 293)**
Randomisation year	4088	1584	3054
Year two	652	326	518
Year three	829	581	727
Year four	835	781	813
Year five	867	535	730

Table 5.19: Cost-effectiveness ratios (CER) expressed as cost (£) / life years gained using cost estimates and effectiveness estimates from the final results of the ECST and a modelling study.

Cost estimates:	**CEA cost description results (£4212)**		
Effectiveness data (life-years gained)	**ECST (0.61)**	**Modelling (0.37)**	**QALY (0.93)**
CER per life year gained (£)	6905	11 384	4529
CER per stroke prevented (£)	62 145	102 456	40 671
Cost estimates:	**HRG cost reference (£3330)**		
Effect estimates	**ECST**	**Modelling**	**QALY**
CER per life year gained (£)	5459	9000	3581
CER per stroke prevented (£)	49 131	81 000	32 226

Table 5.20: One-way sensitivity analysis applying the cost difference (δ cost) of the CEA cost description study between the surgical and medical cohorts to the estimated "stroke-free" life expectancy ranges published. (ECST Final results) (δCost = £4212)

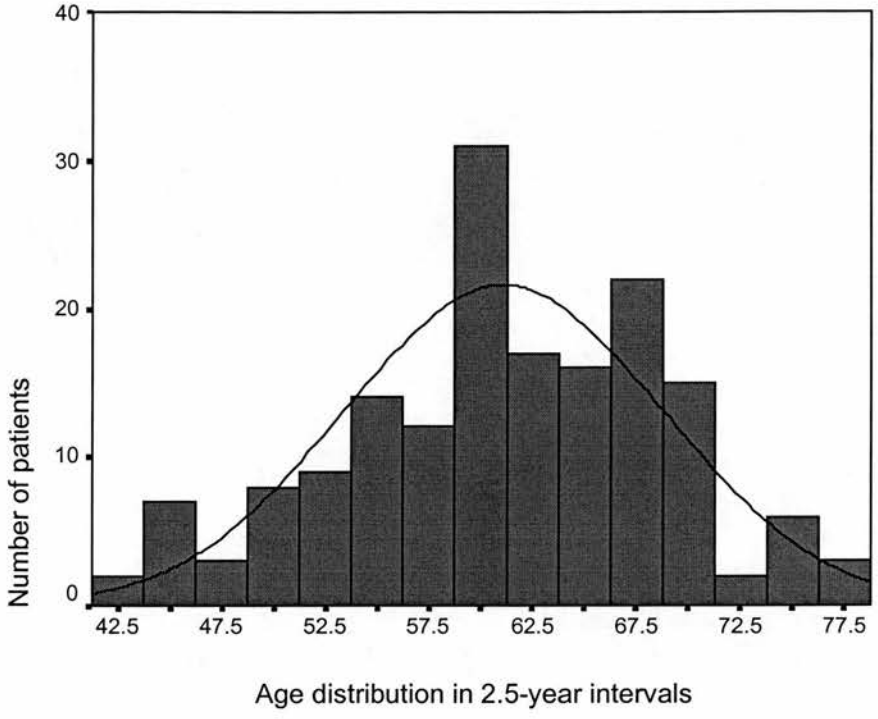
"Stroke-free" life years gained.	Cost /life year gained	Cost / stroke prevented
0.33 (4 months)*	12 764	114 873
0.66 (8 months)*	6 382	57 436
1 (12 months)	4212	37 908
1.33 (16 months)	3167	28 502
1.66 (20 months)	2537	22 836

*females

Table 5.21: Sensitivity analysis applying the cost difference (δ cost) between the surgical and medical cohorts based on the HRG reference costs to the estimated "stroke-free" life expectancy ranges published. (ECST Final results) (δCost = £3330)

"Stroke-free" life-years gained.	Cost /life-year gained	Cost / stroke prevented
0.33 (4 months)*	10 091	90 818
0.66 (8 months)*	5045	45 409
1 (12 months)	3330	29 970
1.33 (16 months)	2504	22 534
1.66 (20 months)	2006	18 054

Figure 5.1: Age distribution in five-year intervals for the surgical cohort of Scottish-ECST participants.



(SD = 7.69; Mean 61.1; n = 167; Kolmogorov- Smirnov statistic = 0.089)

Figure 5.2: Kaplan-Meier estimates of any hospitalised stroke (curtailed at five years) for the Scottish ISD-CEA non-ECST cohort and Scottish ECST-surgical cohort.

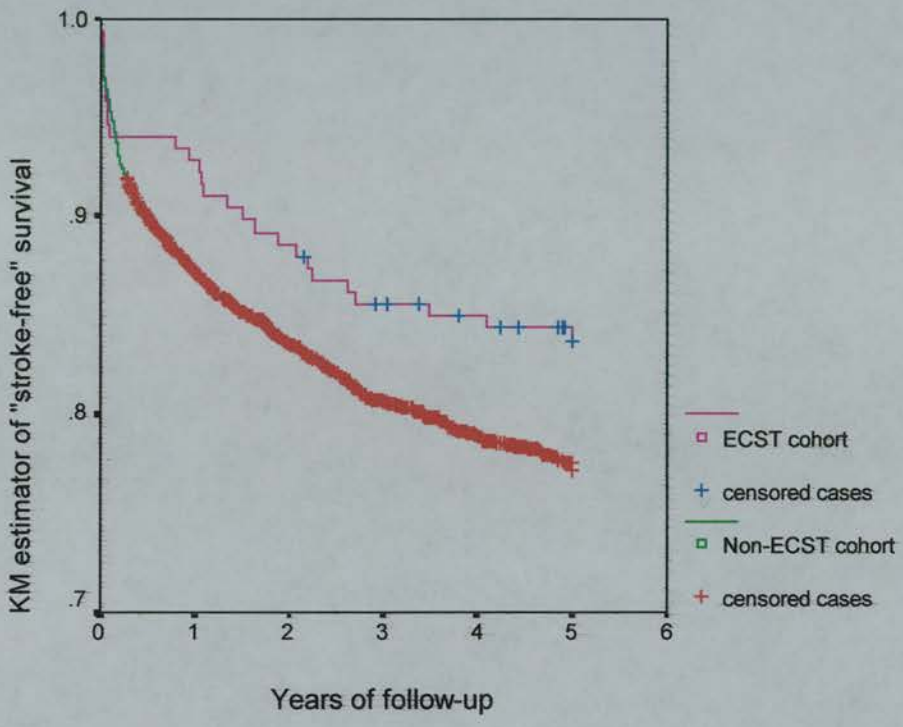


Figure 5. 3: Kaplan-Meier estimates of death for any cause (curtailed at five years) Scottish ISD-CEA non-ECST cohort and Scottish ECST-surgical cohort.

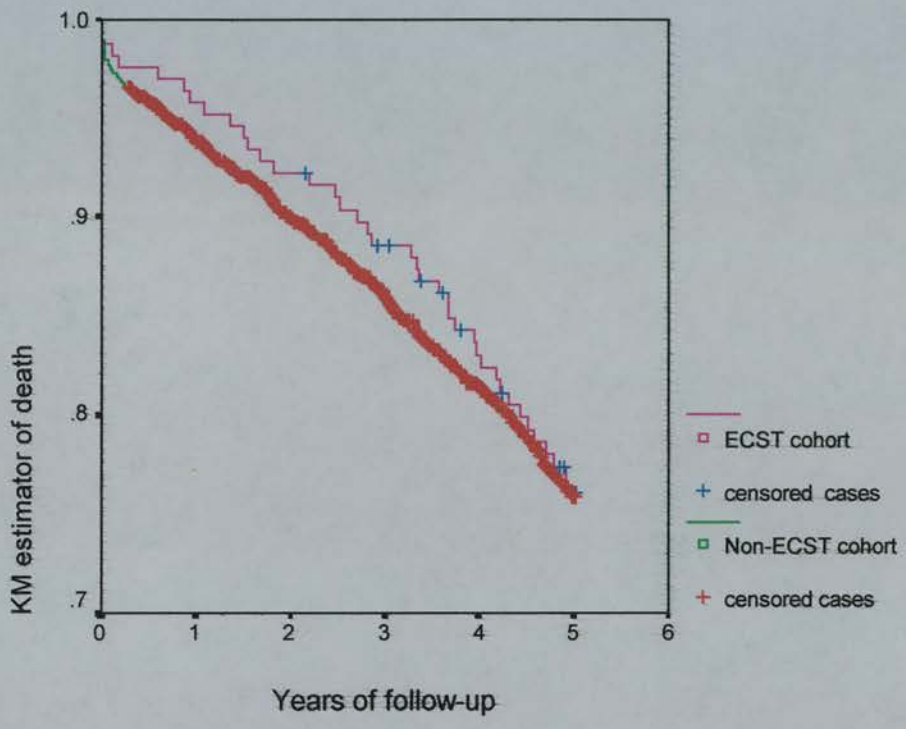


Figure 5.4: Kaplan-Meier estimates of stroke from any cause (curtailed at five years) after CEA for the Scottish-ECST cohort (trial data set); Scottish-ECST cohort (ISD-CEA data set) and Scottish non-ECST matched control cohort (ISD-CEA data set).

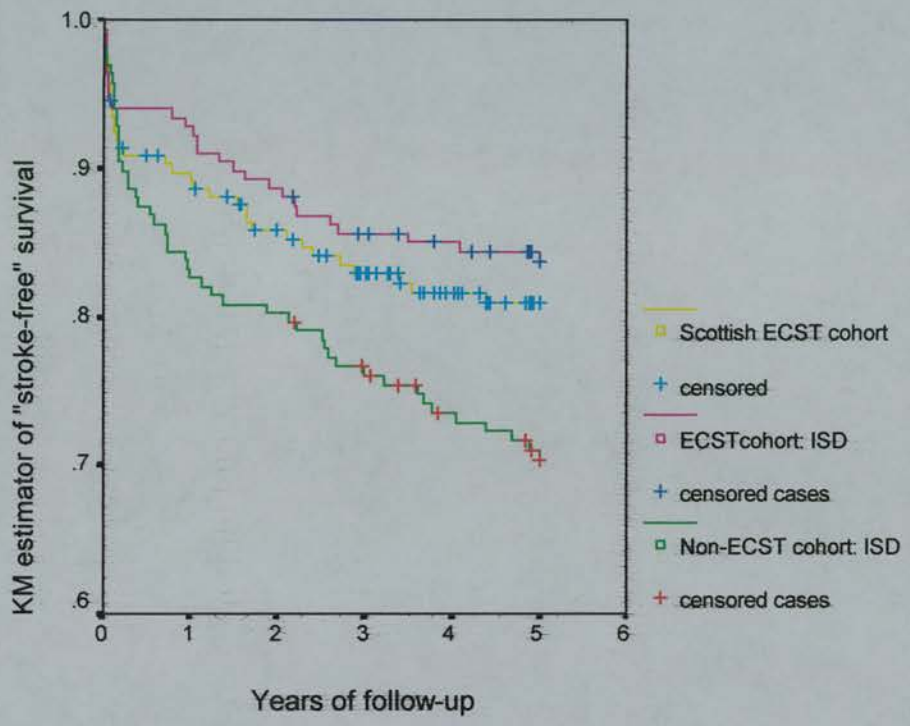


Figure 5.5: Kaplan-Meier estimates of stroke form any cause at 30-days after CEA for the Scottish-ECST cohort (trial data set); Scottish-ECST cohort (ISD-CEA data set) and Scottish non-ECST matched control cohort (ISD-CEA data set).

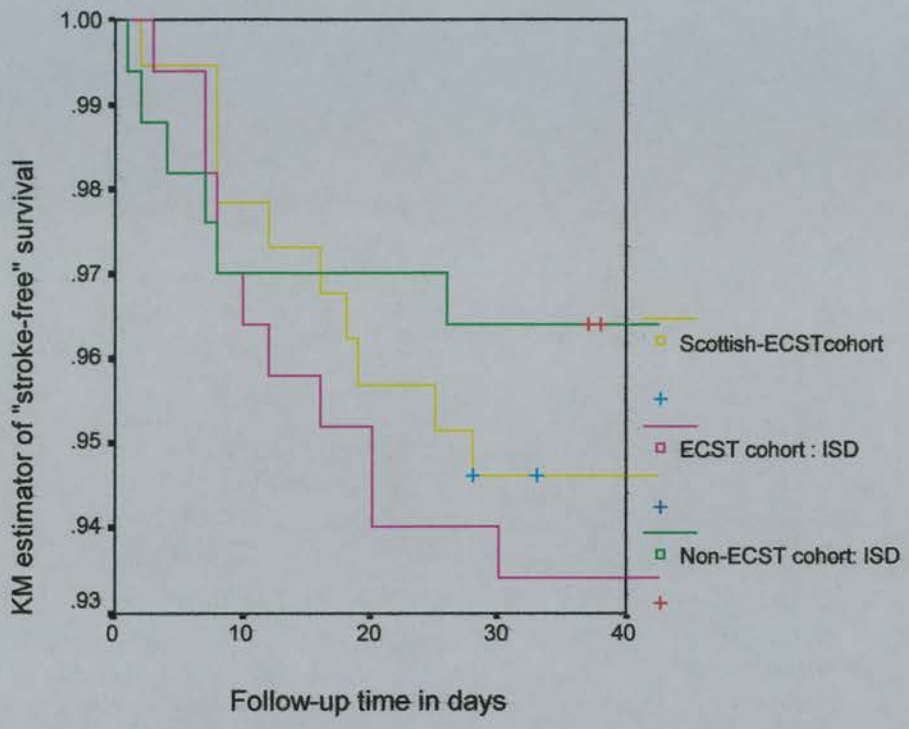


Figure 5.6: Kaplan-Meier estimates of death from any cause (curtailed at five years) after CEA for the Scottish ECST cohort (trial data set); Scottish-ECST cohort (ISD-CEA data set) and Scottish non-ECST matched control cohort (ISD-CEA data set).

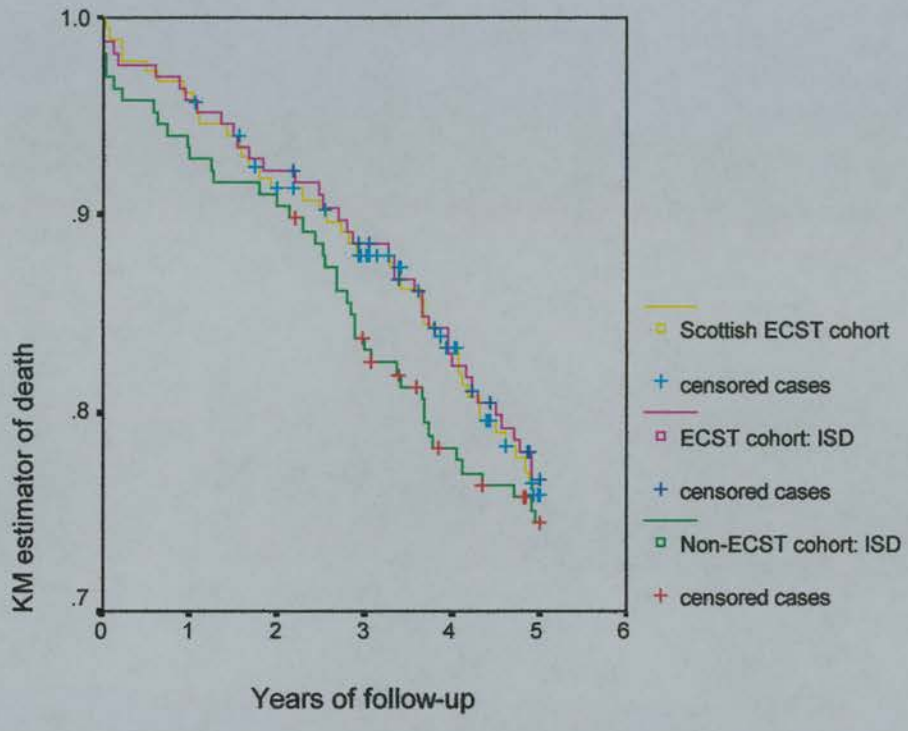


Figure 5.7: The mean total cost (£) distribution for a period of five years from randomisation for the Scottish-ECST surgery and medical cohort based on CEA cost description study results. (Mean = £13 008; n =293)

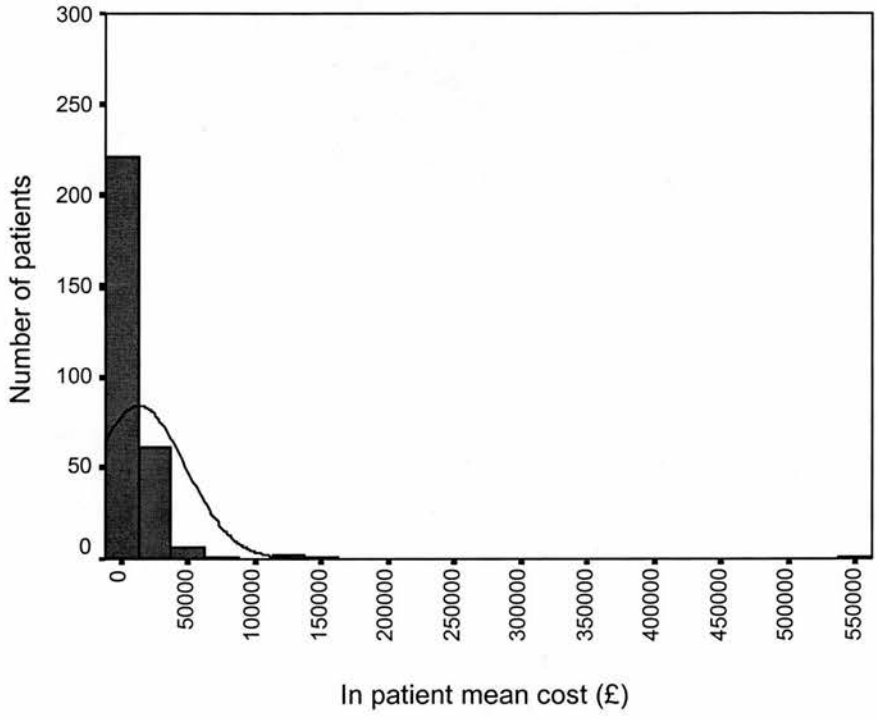


Figure 5.8: The mean total cost (£) distribution for a period of five years from randomisation for the Scottish-ECST surgery group based on CEA cost description study results. (Mean = £14 751; n =172)

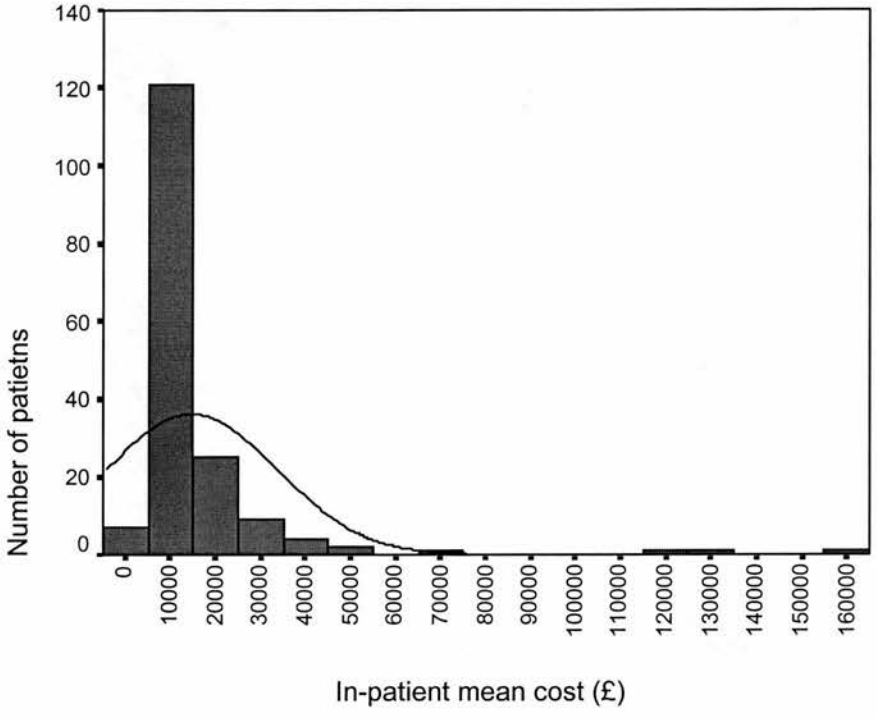


Figure 5.9: Resource use (£) over five years for the Scottish-ECST surgical and medical cohorts from date of randomisation (CEA cost description study results).

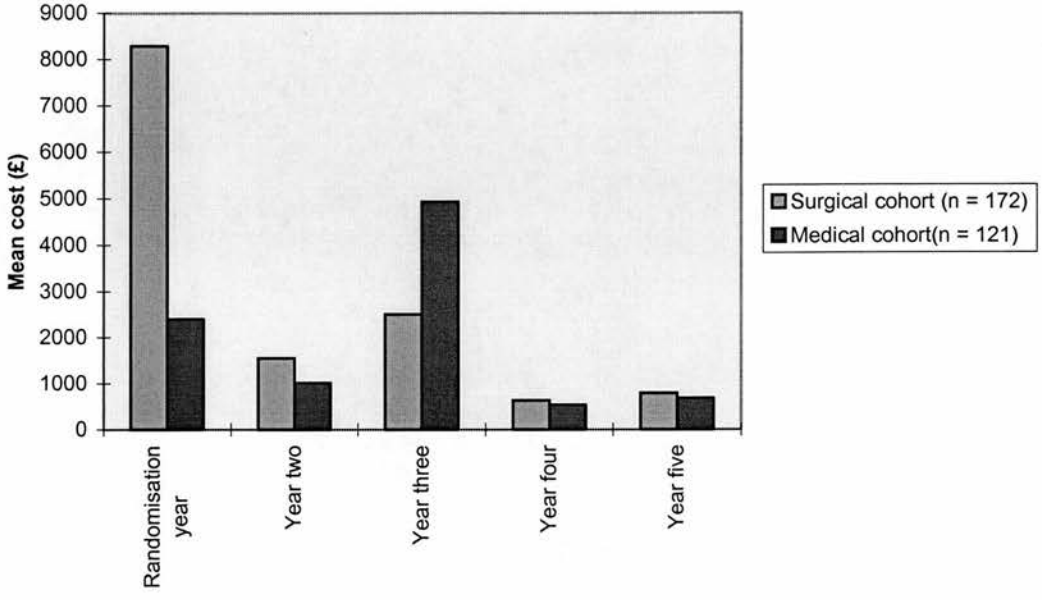


Figure 5.10: Resource use (£) over five years for the Scottish-ECST surgical and medical cohorts from date of randomisation (HRG reference costs).

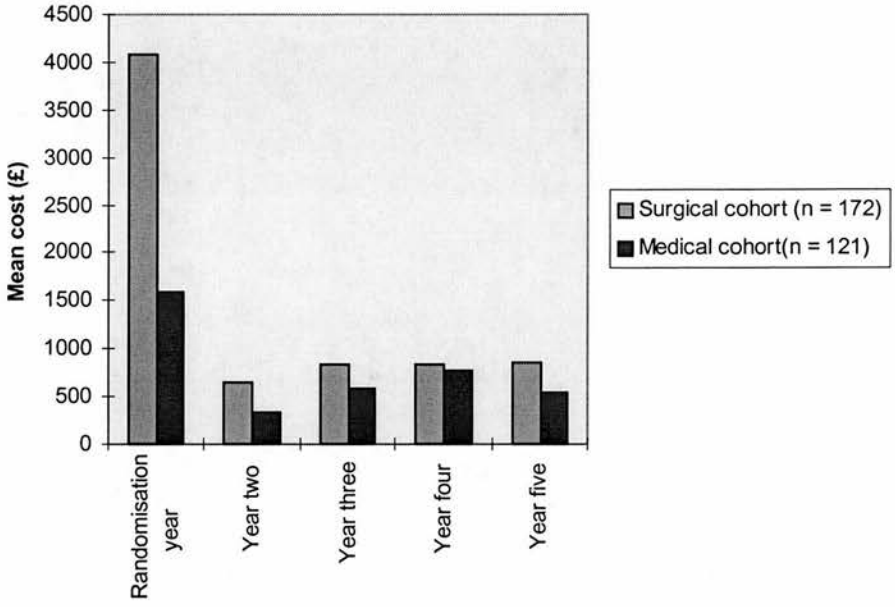


Figure 5.11: The mean total cost (£) distribution for five years from randomisation for the Scottish-ECST surgery and medical care cohorts based on HRG costs. (Mean = £7832;n = 172 (surgical) n = 121 (medical))

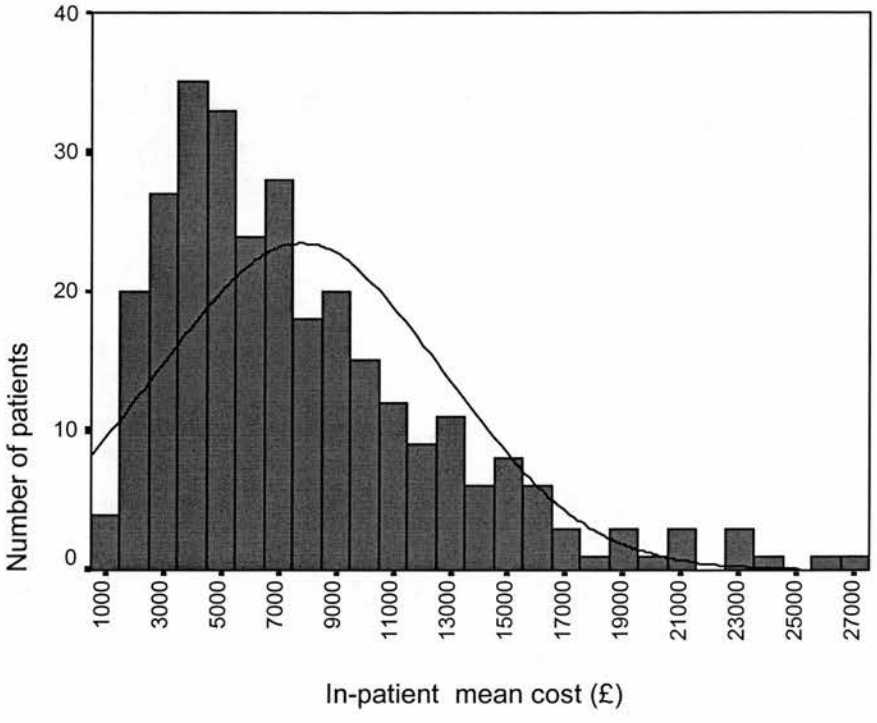
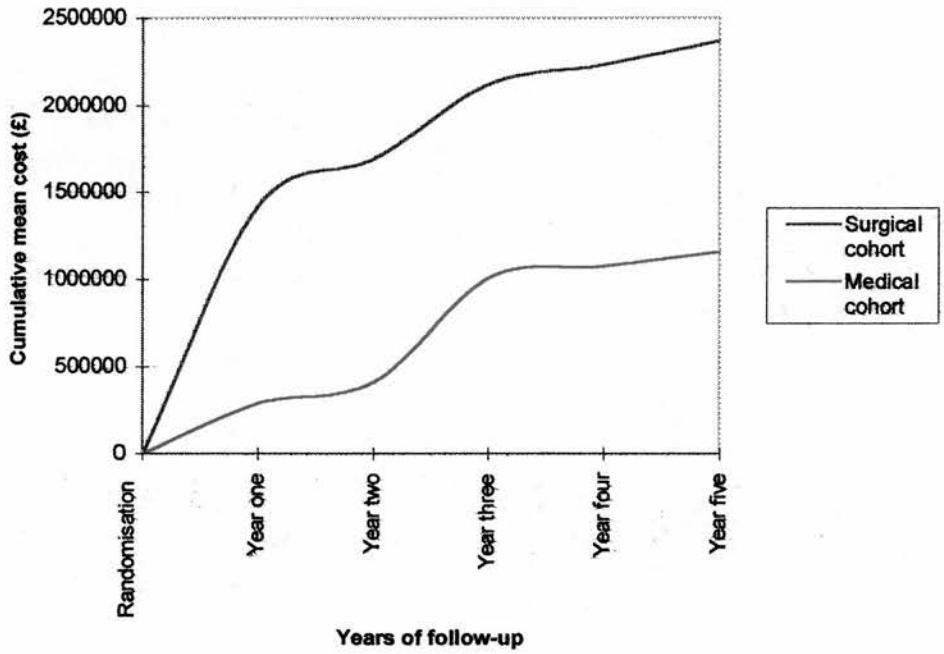


Figure 5.12: Cumulative mean cost (£) for Scottish-ECST surgical and medical cohort (CEA cost description data) over five years of follow-up.



CHAPTER SIX: CONCLUSIONS.

6.1 Concluding remarks

Carotid endarterectomy is a cost-effective strategy to prevent stroke in carefully selected patients provided that the cost of the procedure is within the lower cost limits (£3330) of this study and provided stroke-free life expectancy of 12 months or more are gained. Carotid endarterectomy as a universal recommendation for all patients with severe carotid stenosis (70 - 99%) is not cost-effective.

The systematic review of the literature reporting on the cost and cost-effectiveness of carotid endarterectomy and the pre-operative investigations has highlighted the need for more rigorously designed and conducted economic research. Economic assessment of interventions should form an integral part of clinical research and should not be attached as an afterthought to already completed clinical research.

The cost of carotid endarterectomy estimated in the prospective study suggested that the actual procedure is relatively inexpensive (£3700), and comparable with similar vascular procedures. The cost of "working-up" a cohort of patients who might benefit from carotid endarterectomy accounted for most (68%) of the "total" carotid endarterectomy programme cost. Although the total programme cost of carotid endarterectomy, (i.e. the work-up cost and procedure cost) was estimated, it might be considered inappropriate to include the work-up cost of all patients who might be

potential carotid endarterectomy candidates in the total cost of carotid endarterectomy, since this is a cost to the basic health care delivery service anyway.

Unacceptable time delays in this study from the most recently recorded transient ischaemic symptoms to carotid endarterectomy which, diminish the benefit derived from carotid endarterectomy, were found in about 25% of patients from assessment at a neurovascular clinic to carotid surgery. If the first recorded transient ischaemic attack symptom were used, instead of the most recent symptom, it is more than likely that these time delays described in this study would have been greater, thereby reducing the benefit derived form carotid endarterectomy even further. Achieving cost-effective carotid endarterectomy will require a concerted effort by all health care providers to ensure that the management of patients who have the most to gain is expedited. Maximising the cost-effectiveness of carotid endarterectomy will also demand a certain amount of knowledge and understanding by the general population to recognise transient ischaemic events and to report them timeously to health care providers.

This study assessing a cohort for potential carotid endarterectomy, provided original information in determining a patient ratio from initial assessment at a neurovascular clinic, to duplex, to angiogram to carotid endarterectomy which might be invaluable in the planning and development of neurovascular clinic services such as "one-stop" clinics.

Although it was considered that cost estimates based on National Reference Costs to assess the resource use in a cohort of patients who presented with similar symptoms, but who were treated either surgically or medically, presented an underestimation of

actual resource use, using a bottom-up approach might again lead to an overestimation of costs. The use of inaccurate information to allocate resources might have serious implications for health care planners, purchasers and providers.

Assessing carotid endarterectomy over a period of almost twenty years in Scotland, an increased frequency was found over time, which could be linked to the publication of the results form the two large carotid endarterectomy randomised controlled trials. Routinely collected data were used as the primary data source in this investigation, and demonstrated again the importance of previous concerns regarding the accuracy of these data sources. I acknowledge that the routinely collected data source, the Scottish medical record linkage database, is exceptional because of its size, comprehensiveness and "proven" quality of records. However, the high degrees of accuracy previously quoted (90 - 99%) were not easily achieved. Although data on the number of admissions, by diagnostic code (ICD 9-code), operation code (OPCS 3 and 4) and by speciality, as well as length of hospital stay are available, these data are poor proxies for the more directly relevant information such as clinical variables (for example the degree of carotid stenosis where relevant, blood pressure, body mass index, serum cholesterol, etceteras).

This study found that the majority of hospitals in Scotland performing carotid endarterectomies after the publication of the randomised controlled trials are so-called low-volume hospitals performing one to twelve operations per year. Most of the carotid endarterectomies performed were in a small number of high-volume hospitals. This is in sharp contrast to the minimum numbers of operations of 50 per

year per centre as suggested in the Scottish Intercollegiate Guidelines Network on the Management of Carotid Stenosis and Carotid Endarterectomy. The findings in this study suggest that these recommendations might not be appropriate for Scotland with a relatively small and geographically dispersed population.

In assessing the transferability of results from randomised controlled trials into general everyday practice settings, it is suggested that routinely collected data sets should be extended to capture more clinically relevant information, thus increasing the potential for definitive comparisons.

The cost-effectiveness of carotid endarterectomy as a stroke prevention strategy can only be assiduously assessed once the life-time cost of a stroke is known and once the cost of the alternative treatment modalities are carefully considered. We have at best only approximations of the total lifetime cost of a disease, which is considered the third leading cause of death and disability in the developed world. The cost of the alternative treatments to carotid endarterectomy, medical as well as surgical, has not yet formally been assessed. The cost of medical care, as was also the case in this study, is usually crudely defined. Although it is recognised that the cost of one year treatment of aspirin might be negligible, and thus not have a pronounced influence on the cost-effectiveness measure obtained in this study, this might not be the case with the newer more costly antiplatelet treatments which might result in an economic outcome more in favour of carotid endarterectomy. The cost of managing the adverse effects experienced by some patients, such as gastrointestinal haemorrhage which is a major complication of chronic aspirin use, should be accounted for in any rigorous economic evaluation of costs and benefits.

6.2 Future related research and recommendations.

Several further areas of research arise from this thesis and I summarise some of them with suggested recommendations below:

6.2.1 Administrative routinely collected data sets

- Although not directly derived from the results of this study, it was clear throughout the investigation that the absence of clinical variables in the data sources investigated limited the potential of the study. Therefore, consideration should be given to incorporating clinically relevant variables in routinely collected data sets.
- Wider consultation should be encouraged between researchers, academic institutions and national institutions in order to decide on data to be collected in national data sets that are relevant to national health objectives.
- Again not directly derived from the results, but evident during investigation that coding errors could be minimised if clinicians and health care professionals responsible for submitting records to national organisations should be made aware of the importance of these returns in terms of quality, accuracy and application of routinely collected data.
- A sense of "ownership of data" should be aimed at in order to improve the quality and validity of data.
- The development of a National Reference Cost for the Healthcare Resources Groups in the NHS, Scotland should be pursued since the current study had to rely on the National Reference cost for the UK with discrepancies in HRGs between

what is published for the UK and HRGs used in Scotland. E.g. Invalid primary diagnosis used as HRG in Scotland but not in the National Reference cost on the UK.

6.2.2 Health Service Delivery.

- Since most of the cost in the work-up of a cohort who might be considered for potential CEA is associated with the consultation at the neurovascular clinics, it seems prudent to allow primary health care physicians autonomy to refer patients with symptoms suggestive of transient ischaemic attacks directly for carotid duplex ultrasound prior to referring these patients for a specialist consultation.
- One-stop transient ischaemic attack clinics should be implemented as an extension of the existing neurovascular clinics to avoid delays in the work-up of patients who might benefit from carotid endarterectomy and to maximise the cost-effectiveness of this procedure.

6.2.3 Cost aspects

- A study estimating the lifetime cost of stroke in the United Kingdom is long overdue. Closely associated with such a study should be measures to assess quality of life preferences in stroke patients.
- A well-designed study measuring the direct cost of medical interventions is needed before the cost effectiveness of carotid endarterectomy can be unambiguously be assessed.

6.3 Summary.

In this thesis, I have demonstrated that carotid endarterectomy is relatively inexpensive, and that an increase in the numbers of carotid endarterectomy is evident since the publication of the randomised controlled clinical trials. I have further demonstrated that the results from randomised controlled trials might not be transferable to settings outside trials conditions, though this finding was influenced by the data source investigated. I have also illustrated that carotid endarterectomy might be cost-effective in carefully selected patients, provided maximum benefit in terms of stroke-free life expectancy, is conferred by surgery. The important finding from this study is that we need a more precise estimate of the life-time cost of stroke as well as more reliable cost estimates for the alternative treatments to carotid endarterectomy. It will not be possible to give a definitive answer to the question of the cost-effectiveness of carotid endarterectomy as a stroke prevention strategy until reliable estimates of these costs are available.

GLOSSARY:

For the purpose of this investigation the following definitions and terms applied except where otherwise defined in the text.

All cause mortality is defined as a death from any cause including a fatal stroke and reflects *overall survival.*

Stroke was defined as a clinical syndrome characterised by "rapidly developing symptoms and/or signs of focal and at times global loss of cerebral function, lasting longer than 24 hours or leading to death, with no apparent cause other than that of vascular origin" (Aho et al., 1980).

"Stroke-free" survival was defined as surviving for a total period of five years after successful carotid surgery, without experiencing any *hospitalised* stroke event.

Any stroke event included a major stroke as defined with symptoms lasting longer than seven days; disabling stroke was a stroke that after six months was associated with disability as recorded on the modified Rankin Scale of 3, 4 or 5. A fatal stroke was considered to have caused the death of the patient. (ECST Trialists' Collaborative Group, 1998)

*A **minor stroke*** was an acute disturbance of focal neurological function with symptoms lasting more than 24 hours and less than seven days. A minor stroke was by definition not disabling after one week of onset.

A ***transient ischaemic attack*** was an acute disturbance of focal neurological or mononuclear function with symptoms lasting less than 24 hours and (after adequate investigation) assumed to be due to vascular disease of an embolic or thrombotic kind. (UK-TIA study group, 1991)

All stroke events included any stroke event and transient ischaemic attacks.

"Stroke-free" survival was defined as surviving for a total period of 5 years after successful carotid surgery, without experiencing any *hospitalised* stroke event.

ECST refers to the European Carotid Surgery Trial.

NASCET refers to the North American Symptomatic Carotid endarterectomy Trial.

ACAS refers to the Asymptomatic Carotid Atherosclerotic Study.

Programme cost of CEA includes the work-up cost of a cohort of patients for CEA and the procedure cost of CEA of the patients who received surgery.

CEA Cost description study refers to the prospective cost description study performed at the Royal Infirmary Edinburgh and the Southern General Glasgow.

ISD database refers to the Scottish National database of the Information and Statistics Division of the National Health Service in Scotland.

***CEA ISD-CEA data* set** refers to all the patients who had a CEA between 1981 and 1996 and were extracted from the ISD database using CEA as identifying event.

Scottish-ECST cohort *refers* to all Scottish participants (both medical and surgical) in the ECST.

Scottish-ECST surgical cohort refers to all Scottish participants who were randomised to surgery and best medical care in the ECST.

Scottish-ECST medical cohort refers to all Scottish participants who were randomised to medical in the ECST.

Real life populations refer to patients encountered in everyday clinical and practice situations.

Pre-operative refers to the assessment and work-up period before surgery usually as an outpatient with the exception of the angiogram for which the patient requires admission.

Perioperative refers to the period in hospital prior to the carotid surgery.

CEA refers to carotid endarterectomy.

RCT refers to randomised controlled trial.

LSR refers to the Lothian Stroke Register

NVCs refer to the neurovascular clinics at the Western General Hospital, the Southern General Hospital and the vascular clinics at the Royal Infirmary Edinburgh.

QALYs refer to quality adjusted life-years.

APPENDICES

Appendix 1: MEDLINE and EMBASE search strategies.

MEDLINE search strategy (Databases: 1966 – 1998)

1. exp economics/
2. expl health care resources
3. exp length of stay.
4. exp technology assessment, biomedical
5. cost$.tw
6. charge$.tw
7. economic$.tw
8. fianan$.tw
9. (length adj10 stay),tw,
10. 1 or 2 or 3 or 4 or 5 or6 or 7 or 8 or 9
11. exp endarterectomy/
12. exp carotid arteries/
13. exp carotid artery disease/
14. carotid$.tw
15. 11 or 12 or 13 or 14
16. 10 and 15
17. human/
18. animals/
19. 17 and 18
20. 18 not 19
21. 16 not 20

Appendix 1 *(Continue): EMBASE* search strategy (Databases 1974 – 1998)

1. exp economic aspect/
2. exp audit/
3. exp health care cost/
4. exp hospital running cost/
5. exp biomedical technology assessment/
6. exp medical audit/
7. length of stay/
8. cost$.tw.
9. charge$.tw.
10. finan$.tw.
11. (length adj10 sray).tw.
12. (hospital adj10 stay).tw.
13. economic$.tw.
14. economic evaluation/
15. "0139"tg.
16. Exp health economics/
17. or/1 –16
18. exp carotid artery/
19. exp carotid artery disease/
20. exp carotid artery surgery
21. endarterectomy/
22. carotid$.tw.
23. 18 or 19 or 20 or 21 or 22
24. human ti, ab,hw, tn, mf. or "888".tg
25. animal ti, ab,hw, tn, mf. or "777".tg
26. 24 and 25
27. 25 not 26
28. 17 and 23
29. 28 not 27

Appendix 2: Checklist for the economic evaluation.

Referees' checklist (also to be used, implicitly by authors)

Item	Yes	No	Not Clear	Not appropriate
Study design				
1.The research question is stated	☐	☐	☐	
2.The economic importance of the research question is stated	☐	☐	☐	
3. The viewpoint(s) of the analysis are clearly stated	☐	☐	☐	
4. The rationale for choosing the alternative programmes or interventions compared is stated.	☐	☐	☐	
5. The alternatives being compared are described.	☐	☐	☐	
6. The form of economic evaluation used is stated.	☐	☐	☐	
7. The choice of form of the economic evaluation is justified in relation to the question addressed.	☐	☐	☐	
Data collection				
8. The source(s) of effectiveness estimates used are stated.	☐	☐	☐	
9. Details of the design and results of effectiveness study are given (if based only on a single study)	☐	☐	☐	☐
10. Details of the methods of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	☐	☐	☐	☐
11.The primary measure(s) for the economic evaluation are clearly stated.	☐	☐	☐	
12. Methods to evaluate health states and other benefits are stated	☐	☐	☐	☐
13. Details of the subjects from whom valuations were obtained are given.	☐	☐	☐	☐
14. Productivity changes (if included) are reported separately	☐	☐	☐	☐

Referees' checklist ***(Continue)***

15. The relevance of productivity chances to the study question is discussed.	☐	☐	☐	☐
16. Quantities of resources are reported separately from their unit costs	☐	☐	☐	
17. Methods for the estimation of quantities and unit costs re described.	☐	☐	☐	
18. Currency and price data are recorded	☐	☐	☐	
19. Details of currency of price adjustments for inflation or currency conversion are given	☐	☐	☐	
20. Details of any model used are given.	☐	☐	☐	☐
21. The choice of model used and the key parameters on which it is based are justified.	☐	☐	☐	☐
22.Analysis and interpretation of results.				
23. Time horizon of costs and benefits is stated.	☐	☐	☐	
24. The discount rate(s) is stated.	☐	☐	☐	☐
25. The choice of rate(s) is justified.	☐	☐	☐	☐
26. An explanation is given if costs or benefits are not discounted.	☐	☐	☐	☐
27. Details of statistical tests and confidence intervals are given for stochastic data	☐	☐	☐	☐
28.The choice of variables for sensitivity analysis is justified.	☐	☐	☐	☐
29. The ranges over which the variables are varied are stated.	☐	☐	☐	☐
30. Relevant alternatives are compared	☐	☐	☐	
31. Incremental analysis is reported	☐	☐	☐	☐
32. Major outcomes are presented in a disaggregated as well as aggregated form	☐	☐	☐	
33. The answer to the study question is given.	☐	☐	☐	
34. Conclusions follow form the data reported.	☐	☐	☐	
35. Conclusions are accompanied by the appropriate caveats.	☐	☐	☐	

Appendix 3: Lothian Stroke Register Protocol

1 *Aims*

The Register aims to collect information on Stroke, Transient Ischaemic Attack (TIA) and Retinal Artery Occlusion (RAO) (qualifying 'events') victims presenting at the Western General Hospital, whether admitted or not. This information will be available for individual patient care. The primary purpose for collecting this information will be for long term research.

2 *Notification*

Any patient showing symptoms consistent with one or more of the qualifying events may be notified for entry into the database. Notification requires that the patient is examined by a registering neurologist who completes a notification form. Where a patient is subsequently shown not to meet required criteria, the information need NOT be removed from the database, but the patient will not be 'registered'. Once registered, a patient may be considered for continued observation - 'Follow up'. Criteria for Registration and Follow up are shown below:

	Register	**Follow up**
No base date (a)	NO	NO
Other diagnosis (b)	NO	NO
Strokes not seen within 6 months (c)	YES	NO
TIAs not seen within 12 months (d)	YES	NO
Otherwise	YES	YES

Note **a)** base date is date of first symptoms for stroke, examination for TIA or RAO;

b) ie not stroke nor TIA nor RAO;

c) from date of first symptoms;

d) from date of *last* event (updated 29/11/95).

A patient may be notified repeatedly if they fall victim to repeated qualifying events. A patient may only be followed up on one qualifying event at any one time.

3 *Data restrictions*

Many investigations may be carried out on patients at any time, but are only of relevance to our study if conducted within defined time intervals from their event. Ranges permitted in days from base date are -30 to +30 for blood tests, ECG or CXR, 0 to +99 for CT or Doppler, or -30 to +99 where the diagnosis is NOT stroke, -30 to +99 for trans-thoracic and trans-oesophageal echo-cardiograms.

Appendix 4: Lothian Stroke Register Notification form.

LOTHIAN STOKE REGISTER

Personal details

Study No. | | | | | | |

*Please PRINT all details in **BLACK** ink*
Use reverse for details or narrative

WGH Hospital No. WG0

DCN X-ray no. | | | | | | | | |

Surname _____ Title _____

Forenames _____

Address _____

_____

_____

Postcode _____ Tel. No. _____

Date of birth / / Sex **M** / **F** *(circle)*

Next of kin / Contact person

Address _____

_____

Postcode _____ Tel. No. _____

General Practitioner

Address _____

_____

_____

Postcode _____ Tel. No. _____

Patient of interest ? *(circle)* **Y** / **N**

Reasons : *(continue overleaf)*

Notes on completion are available on page 3

Admission details

Name _____ LSR No.. _____

Inpatient : **Y** / **N** *(circle)*

Time is by 24 hour clock, dates are dd/mm/yy

Time ____:____ Date ____/____/____ of admission
(if known) Date ____/____/____ of discharge

Consultant's department *(circle)* **G**eneral medicine / **N**eurology / **S**troke / **N**euro**S**urgery / **O**ncology / **U**rology / **S**urgery / other :

Time ____:____ Date ____/____/____ of examination

Examined by *(circle)* CPW / MSD / PAGS / other :

Summary of this event due to : **C**erebrovascular disease at any time
Other
Abnormal neurological signs on examination **N**o residual signs

Final diagnosis

		Code
Stroke (> 24 h)		*1 = possible (not permitted for RAO)*
Transient Ischaemic Attack (< 24 h)		*2 = probable (not permitted for RAO)*
Retinal Artery Occlusion *(RAO)*		*3 = definite*
Other *(specify):*		*9 = not applicable*

Include events within the last 6 months only. You may code multiple cerebrovascular diagnoses. Leave no blanks.

Patient history

Code boxes 1 = Yes, 2 = No, 9 = unassessable, Blank = may be completed later.

Patient able to give adequate history			
Previous Myocardial Infarction		Year *(if known)*	
Previous stroke with residual disability		Year *(if known)*	
Previous stroke without residual disability		Year *(if known)*	
Previous TIA of the brain		Amaurosis Fugax	ROA

Code TIA/ROA: L = left, M = Mid, R = right, B= both, 1 = Yes but side n/k, 2= No 9 = not known – specify territories

Previous carotid endarterectomy		Year *(if known)*	
(Code side of CEA 1 = R, 2 = L, 3 = both, 9 = not known)		Side *(if known)*	
Hypertension *(history or treatment at any time)*		Non-caucasian *(specify):*	
Angina pectoris known before stroke		Alcohol > 2 units daily	
Atrial fibrillation known before stroke		Smoker (incl. Given up < 12 months)	
Breathless walking on an incline		Ex-smoker > 12 months	
Cardiac surgery (e.g angioplasty)*(Specify):*		Employed until this event	
Intermittent claudication		Car driver in past 3 months	
Peripheral vascular surgery		Lives alone	
Diabetes mellitus known before stroke		Known prior malignancy	
Epilepsy known before stroke			
History of migraine with aura			
Oxford Handicap Scale before stroke			

(Modified Rankin Scale)

Oxford Handicap Scale
0 = no symptoms
1 = minor symptoms which do not interfere with life style
2= some restriction to lifestyle but look after themselves
3= significant restriction to lifestyle, preventing total independence
4 = severe handicap preventing independent existence but not requiring constant attention
5 = severe handicap, totally dependent, requiring constant attention day and night.

Treatment *Code boxes 1 = Yes, 2 = No, 9 = unassessable, Blank = may be completed later.*

	At time of event	Started since event
Antiplatelet		
Anticoagulant		
Antihypertensive *(if history of hypertension)*		
Anticonvulsants *(if history of epilepsy)*		
Antifailure		

General Examination

List all drugs in use at examination (in narrative):

Blood pressure
(admission) _____ / _____
(examination) _____ / _____

Cervical Bruits *(specify)* R L

Clinical heart failure *(i.e. signs of LVF / RVF, not just on Rx, specify)*

Clinical valvular heart disease *(not simple flow murmur < 2/6, specify)*

Peripheral vascular disease *(both foot pulses absent or femoral bruits)*

Irregular pulse

Right handed

Left handed

Notes :

Sections **1-6** (above) must be completed for *all* patients.

? Stroke - If a patient has exhibited *Brain Symptoms for more than 24 hours* (i.e. a Stroke), section **7** must be completed. Before finalising the Stroke Diagnosis part of this section, you may find it useful to complete section 9 - Persistent neurological signs. Code duration of symptoms *only* when symptoms are resolved at examination. If not, code '**U**'.

? TIA / RAO - If a patient exhibited episodes with *Brain Symptoms resolved within 24 hours*, or with *Eye Symptoms* (i.e. Transient Ischaemic Attack - TIA, or Retinal Artery Occlusion - RAO), section **8** must be completed. Note that a patient may have a *definite* TIA, but distribution may be *probable* or *definite* etc.

? multiple events - You may record more than one type of event on this form. You may record a series of TIAs in each distribution and a series of RAOs and a stroke on one form. However, you may only record one stroke on this form. You must record all relevant cerebrovascular diagnoses in section 3. If any cerebrovascular diagnosis is made, ignore *Other* diagnoses.

If a patient shows any *Abnormal neurological signs on examination*, regardless of diagnosis section **9** must be completed. This applies even if none of the features specifically mentioned are abnormal. Please record residual neurological signs from previous events and / or other diagnoses. If present, specify in narrative.

Sections **10-11** must be completed for all patients.

Brain Symptoms > 24 hours *Complete for patients exhibiting brain symptoms longer than 24h i.e. STROKES*

History of ictus

Time is by 24 hour clock, dates are dd/mm/yy

Time : Date / / symptoms first noticed

Time : Date / / of maximum deficit

Symptoms present on waking

Headache within 2 hours of onset

Vomited since symptom onset

Loss of consciousness at onset

Drowsiness since symptom onset

Seizure(s) since symptom onset

- date / /
- confirmed of first
- type
- number

1 = Generalised
2 = Partial
9 = Uncertain

Mental Test Score *(Hodkinson, tick below, score 0-10)*

Age
Time
42 West St.
Name of Hospital
Year
Recognise 2 people (e.g.*Dr. & Sr)*
Date of birth
Dates of World War I or II
Present Monarch **Total**

(Code '88' if clinically unassessable)

Duration of symptoms, if resolved at examination *(number of days / Unresolved)*

Stroke diagnosis

Side of brain lesion *(one only)*

1 = right
2 = left
3 = brainstem/ cerebellum
4 = uncertain
5 = bilateral

Clinical classification *(one only)*

1 = TACS
2 = PACS
3 = LACS
4 = POCS
5 = uncertain

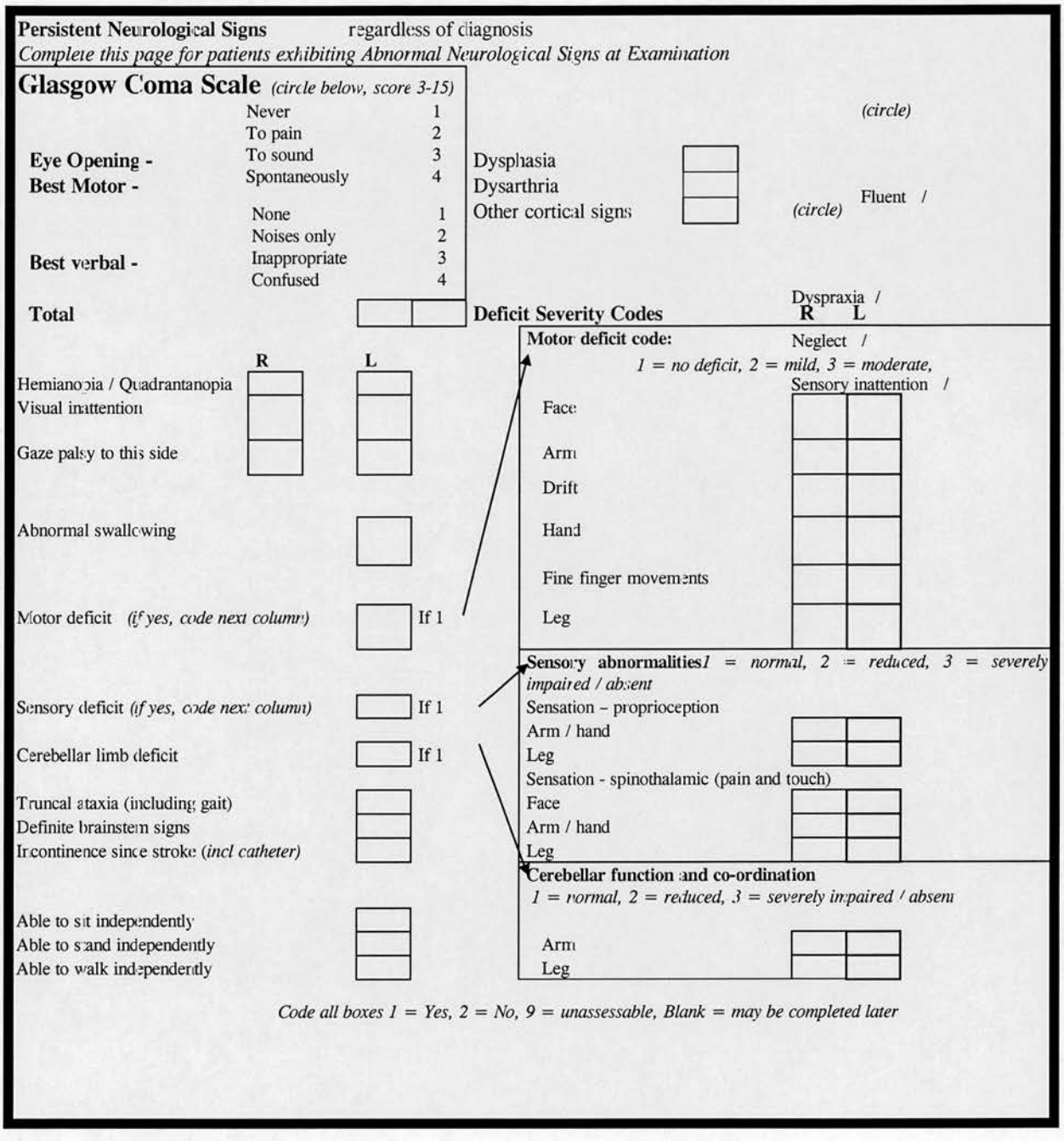
Clinical prediction of outcome at 1 year

(0-6 on Oxford Handicap Scale - see p2, 6 = dead)

Brain Symptoms lasting < 24h or any Eye Symptoms

Complete this section for patients exhibiting Brain Symptoms lasting less than 24 hours or Eye Symptoms i.e. TIAs or RAOs
Code distribution : 2 = Probable, 3 = Definite, 9 = none. Probable is NOT accepted for RAO

Type	Distribution		Date of first	Date of last	Duration of Longest	Total (n)
RAO	**R**				N/a	n/a
	L				N/a	n/a
A Fx	**R**				Hh:mm	
	L				:	
Cortical	**R**				:	
	L				:	
LACS	**R**				:	
	L				:	
POCS	**R**				:	
	L				:	
	M				:	



Persistent Neurological Signs regardless of diagnosis

Complete this page for patients exhibiting Abnormal Neurological Signs at Examination

Glasgow Coma Scale *(circle below, score 3-15)*

Eye Opening -	Never	1
	To pain	2
	To sound	3
	Spontaneously	4
Best Motor -		
	None	1
	Noises only	2
Best verbal -	Inappropriate	3
	Confused	4
Total		

(circle)

Dysphasia
Dysarthria
Other cortical signs

(circle) Fluent / Dyspraxia /

Deficit Severity Codes **R** **L**

Motor deficit code: Neglect /

1 = no deficit, 2 = mild, 3 = moderate, Sensory inattention /

	R	L
Hemianopia / Quadrantanopia		
Visual inattention		
Gaze palsy to this side		
Abnormal swallowing		
Motor deficit *(if yes, code next column)*		If 1
Sensory deficit *(if yes, code next column)*		If 1
Cerebellar limb deficit		If 1
Truncal ataxia (including gait)		
Definite brainstem signs		
Incontinence since stroke *(incl catheter)*		
Able to sit independently		
Able to stand independently		
Able to walk independently		

	R	L
Face		
Arm		
Drift		
Hand		
Fine finger movements		
Leg		

Sensory abnormalities *1 = normal, 2 = reduced, 3 = severely impaired / absent*

	R	L
Sensation – proprioception		
Arm / hand		
Leg		
Sensation - spinothalamic (pain and touch)		
Face		
Arm / hand		
Leg		

Cerebellar function and co-ordination

1 = normal, 2 = reduced, 3 = severely impaired / absent

	R	L
Arm		
Leg		

Code all boxes 1 = Yes, 2 = No, 9 = unassessable, Blank = may be completed later

Registration *Code boxes 1 = Yes, 2 = No, Blank = may be completed later.*

Trials **Enter patient into Register** ☐ Months of follow-up required ☐☐

Studies

	Eligible	Randomised
Food	☐	☐

MRS ☐
ULTRASOUND ☐

Investigations

Test	Ordered	Date done	Results	
Haemoglobin	☐	___/___/__	☐☐•☐	g/dl
Haematocrit	☐	___/___/__	☐☐•☐	%
Platelets	☐	___/___/__	☐☐☐☐	x 109/l
ESR	☐	___/___/__	☐☐☐☐	mm/hr
Urea	☐	___/___/__	☐☐•☐	mmol/l
Glucose	☐	___/___/__	☐☐•☐	mmol/l
Cholesterol	☐	___/___/__	☐☐•☐	mmol/l
ECG	☐	___/___/__	If 1 →	
Doppler *(but not in study)*	☐	___/___/__		
Trans-thoracic echocardiogram	☐	___/___/__		
Trans-oesophageal echocardiogram	☐	___/___/__		
CT	☐	___/___/__		
MRI		___/___/__		

Atrial fib / flutter	☐
LBBB, RBBB, LAD[1]	☐
ST / T wave change	☐
LVH	☐
Acute MI	☐
Old MI	☐
Other abnormality	☐
Normal	

[1] Left Bundle Branch Block, Right Bundle Branch Block, Left Axis Deviation

Appendix 5: Breakdown of the cost associated with having a carotid duplex examination at the Western General Hospital.

		Per annum (£)	**Per duplex(£) n = 1200**
Capital	Room	1019	0.85
	Ultrasound machine	23 500	19.58
Human resources	Radiographer (full-time) Radiologist (30%)	46 405	38.67
Consumables and Maintenance	Gel, colour and black and white printer paper, paper towels, report forms	7 400	6.17
Overheads	Electricity, heating, administration etc.	5 820	5.17
Total			**£70.44**

Appendix 6: Carotid endarterectomy cost description study data collection forms.

Patient registration

Section I: PATIENT REGISTRATION

Admission date | d | d | m | m | y | y |

Study number

Family name _____

First name _____

Address _____

Postcode | | | | | | | | |

Telephone | | | | | | | | |

Code | | | | |

Sex: Male ☐ Female ☐

Date of Birth | d | d | m | m | y | y |

Age | | |

Referred from:

- General practitioner ☐
- Physician ☐
- Neurologist ☐
- Neurosurgeon ☐
- Neurovascular clinic ☐
- Other ☐

Address of referral source:

_____

_____

Presenting symptom:

- TIA ☐
- Minor stroke ☐
- AF ☐

Date of first symptom: | | | | | | | |

Date of most recent symptom: | | | | | | | |

Affected side:

	R	L
90% +		
80-89%		
70-79%		
60-69%		
50-59%		

- Elective surgery ☐
- Emergency surgery ☐

Patient name		Operation date	*d* *d* *m* *m* *y* *y*	Study no	

Section 2: ADMISSION AND DISCHARGE DETAILS

Was the patient admitted for an initial assessment of carotid stenosis	Yes		No		
If yes, for how many days			Days		
Date admitted for angiogram					
Date discharged after angiogram					
Date admitted for CEA					
Date discharged (or died)					
Date of surgery					
Date admitted to ITU					
Date discharged from ITU					
Date admitted to HDU					
Date discharged from HDU					
Date admitted to surgery ward					
Date discharged from surgery ward					
Any serious complications on returning to the main ward?	Yes		No		

Give details: _____

_____

_____

_____

Status on discharge: Alive ☐ Dead ☐

Patient discharged to:

- Own home ☐
- Acute hospital ☐
- Convalescent hospital ☐
- Nursing home ☐
- Other:(specify) ☐

Patient name		Operation date	*d* *d* *m* *m* *y* *y*	Study no	

Section 3: MEDICATION

On admission

Drug name	Dose/unit	Frequency

During hospitalisation

Drug name	Dose/unit	Route	Doses given

On Discharge (only changes from admission drugs)

Drug name	Dose/unit	Frequency

Investigations

Patient name		Operation date	*d* *d* *m* *m* *y* *Y*	Study no	

Section 4: INVESTIGATIONS

DUPLEX ULTRASOUND — Number: Right ☐ Left ☐ — Date: ☐☐☐☐☐☐

CAROTID ANGIOGRAPHY — Right ☐ Left ☐ — Date ☐☐☐☐☐☐

CT SCAN ☐ — Date ☐☐☐☐☐☐

X-RAY: Chest: ☐ Other: ☐ Specify:

ECG ☐

OTHER TESTS:(SPECIFY) _____

_____

_____

HEAMATOLOGY:

Full blood count	☐
ESR	☐
Urea and electrolytes	☐
Blood glucose	☐
Serum cholesterol	☐
LFT	☐
Coagulation studies	☐
Other	☐
	☐
	☐

Nursing 1

Patient name		Operation date	*d* *d* *m* *m* *Y* *Y*	Study no	

Section 5: OPERATION TIME:
(to be completed by theatre staff nurse please)

	Hours	Minutes
Time of arrival in anaesthetic room		:
Time of start of anaesthetic procedures		:
Time of departure from theatre		:
Time of departure from recovery room		:

Section 6: HUMAN RESOURCES:

SURGEONS:

Consultant	
Registrar	
Senior House Officer	
House Officer	

ANAESTHETIST:

Consultant	
Senior registrar	
Registrar	
Senior House Officer	

NURSING STAFF:

Grade A		Grade B	
Grade C		Grade D	
Grade E		Grade F	
Grade G			

TECHNICIANS:

ODA/ODP	

Nursing 2

Patient name		Operation date	*d* *d* *m* *m* *Y* *y*	Study no	

Section 7: SURGICAL MATERIALS:
(to be completed by theatre staff nurse please)

SUTURES:	***Number***
Prolene 6/0	
Vicryl 3/0 9717	
Vicryl 2/0 9150	
Vicryl 2/0 tie 9044	

INSTRUMENTS:	
Mr Murie Needle holder	
Shunt	
Javid Clamp	
Lectrocath	

PATCH:	
Dacron	
Vein	

TRAYS:	
Medium Basic Trays	
Arterial Limbaneck	
Diathermy thongs	
Diathermy pad	
Diathermy pad cleaner	
Vessel retractor x 1	

SWABS AND GOWNS:	
Gowns (disp) x 1	
Gowns (disp) x 3	
Gowns (linen) x 1	
Gowns (linen) x 3	
Swabs x 5	
Gauze tissue pad	
Mepore dressings	
Pledgelets x 5	

MISCELLANEOUS:	***Number***
Suction tubing	
Suction catheters	
Opsite	
Medinorm drain	
Irrigation jet	
Discard-a-pad	

	Number
Scalpel blades	
Needles	
50 ml syringes	
20 ml syringes	
10ml,5ml,2 ml syringes	
Masks	
Caps	
Sterile gloves	

ADDITIONAL INFORMATION / EQUIPMENT

Anaesthetics 1

Patient name		Operation date	*d* *d* *m* *m* *y* *y*	Study no	

Section 8: MEDICATIONS IN THEATRE:
(to be completed by anaesthetist please)

REGIONAL CERVICAL BLOCK:

Drug name	**Dose / % per ampoule**	**No of amps used**
Bupivacaine	0.25%/10ml	
	0.50%/10ml	
	0.75%/10ml	

ANAESTHETIC DRUGS:

Drug name	**Dose / % per ampoule**	**No of amps used**
Propofol	200mg	
Propofol pre-filled syringes	500mg	
Thiopentone	250 – 500mg	
Fentanyl	100 μg	
Remifentanil	1mg	
Vecuronium	10 mg	
Atracurium	50mg	
Methoxamine	20 mg	
Ephedrine	30mg	
Heparin	5000units	
Ondansetron	4mg	
Esmolol	100mg	
Neostigmine	2.5mg	
Glycopyrrolate	600μg	
Atropine	0.6mg	
Saline	10 ml	

OTHER DRUGS:

Temazepam (pre-med)	10 mg	
Cefuroxime	750 mg	
Other		

MAINTENANCE ANAESTHETIC:

Isoflurane	
Sevoflurane	
O_2	
N_2O	
Propofol	
Other	

INTRAVENOUS FLUIDS:

TYPE	VOLUME OF UNITS	NUMBER GIVEN
Hartmanns Solution	500 ml	
Normal Saline	500 ml	
Gelofusine	500ml	
PPS	400 ml	
Dextran 70	500 ml	

EQUIPMENT AND DISPOSABLES USED BY ANAESTHETIST:

ITEM	Number
IV giving sets	
IV cannula: Venflon	
Arterial cannula:	
Vygon Ledercath	
Arrow	
Vasocan	
Quickcath	
Arterial pressure kit	
Tegaderm dressing	
Lectrocath	
Cerebral Oximeter Sensor	
Regional Block pack	
Regional block needle	
Stimuplex needle	
3-way tap	
Endotracheal tube	
Guedel airway	
Post-op oxygen mask	
Nasal cannulae	
Eye pads	
Syringes: 50 ml ; 20 ml	
10ml; 5ml; 2ml	
Needles	
ECG electrodes	
Sterile gloves	

Other: _____

_____

_____

_____

Appendix 7: League table of costs and quality-adjusted-life-years (QALYs) for selected health care interventions.

	Cost /QALY (£ Aug 1990)
Cholesterol testing and diet therapy only (all adults, aged 40 – 69)	220
Neurosurgical intervention for head injury	240
GP advice to stop smoking	270
Neurosurgical intervention for subarachnoid haemorrhage	490
Anti-hypertensive therapy to prevent stroke	940
Pacemaker implantation	1100
Hip replacement	1180
Valve replacement for aortic stenosis	1140
Cholesterol testing and treatment	1480
CABG[1] (left main vessel disease, severe angina)	2090
Kidney transplant	4710
Breast cancer screening	5780
Heart transplantation	7840
Cholesterol testing and treatment (incrementally) of all adults aged, 25 –39 years	14 150
Home haemodialysis	17 260
CABG[1] (one vessel disease, moderate angina)	18 830
CAPB[2]	19 870
Hospital haemodialysis	21 970
Erythropoietin treatment for anaemia in dialysis patients (assuming a 10% reduction in mortality)	54 380
Neurosurgical intervention for malignant intracranial tumours	107 780
Erythropoietin treatment for anaemia in dialysis patients (assuming no reduction in survival)	126 290

Appendix 8: My contribution to this thesis.

This work was carried out at the Departments of Public Health Sciences and Clinical Neurosciences at the University of Edinburgh.

I designed the study under the supervision of Dr John Forbes and Prof. Charles Warlow. I performed a situation analysis of carotid endarterectomy in Scotland. This constitutes the largest historical cohort analysed to date over the longest time period and in excess of 12 500 patient-years of observation. The systematic review was entirely my own work. This is the first systematic review on the literature assessing the costs and benefits of carotid endarterectomy and not only the cost of the procedure. This is also the first economic review that has been conducted using a standard evaluation protocol recommended to authors, referees and editors for the review of economic submissions to journals.

I performed the first prospective study in Scotland and the United Kingdom estimating the cost of carotid endarterectomy. I designed the data collection forms, collated and analysed the data. Data were collected by the personnel in the Vascular surgery theatres under the supervision of Sr. Grace Ross at the Royal Infirmary Edinburgh and Dr George Welsh at the Southern General Glasgow. I performed a sensitivity analysis to address the uncertainty associated with cost analysis of this nature.

Alan Finlayson compiled the data set of all patients who had a CEA over the last sixteen years in Scotland form the national database at ISD. Chris Povey and Brian Reid, also from ISD, attached the cost data for these patients to the data set. The data so obtained allowed me to describe CEA over 16 years in Scotland and to assess the transferability of the efficacy results of the European Carotid Surgery Trial in a "real" patient population over the same study period. I performed all the analysis including the survival analysis for this data set.

I extracted all the Scottish patients who were randomised into the ECST from the ECST data set, linked these patients to the ISD database and performed the analysis to test various hypotheses.

I analysed the cost data from ISD and described the use of resources of the Scottish surgical and medical cohorts in the ECST using generic cost measures as well as Healthcare Resource Groups. These cost estimates in conjunction with the cost estimates form the carotid endarterectomy cost description study allowed cost effectiveness analysis.

It is hoped for that the findings of this thesis might provide more definitive answers to the uncertainty associated with the cost-effectiveness of CEA as reported by previous modelling studies addressing this issue.

Appendix 9: Publications so far.

Benade MM, Warlow CP, Forbes JF. Carotid endarterectomy: What does it really cost? Poster presentation 8th European Stroke conference, Venice April 1999)

Benade MM, Warlow CP, Forbes JF. Carotid endarterectomy: Survival in a Scottish cohort and randomised controlled trials

Poster presentation 8th European Stroke conference, Venice April 1999

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