Three Stories of Ischemic Stroke: Aging Dependence, Carotid Procedures, and Asymptomatic Carotid Disease

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THESIS

Submitted as partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Public Health Sciences (Epidemiology)
in the Graduate College of the
University of Illinois at Chicago, 2013

Chicago, Illinois

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To Jacob Brody,

for the years of friendship and contagious intellectual curiosity

ACKNOWLEDGMENTS

Frank LeFevre, MD for assistance reviewing and critiquing publications including in Chapter 4.

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LIST OF ABBREVIATIONS

ACAS	Asymptomatic Carotid Atherosclerosis Study
ACST	Asymptomatic Carotid Surgery Trial
CAS	Carotid Angioplasty and Stenting
CEA	Carotid Endarterectomy
CREST	Carotid Revascularization Endarterectomy vs. Stenting Trial
CI	Confidence Interval
CrI	Credible Interval
NASCET	North American Carotid Endarterectomy Surgery Trial
NHDS	National Hospital Discharge Survey
QALY	quality adjusted life year
TIA	transient ischemic attack

SUMMARY

Ischemic Stroke—An Aging-Dependent Disease?

Aging-dependent diseases are largely a consequence of the underlying chronic degenerative accompaniments of aging. The incidence of aging-dependent diseases are expected to increase exponentially with age. Ischemic stroke should be aging-dependent because most of the underlying pathology is a consequence of aging. To examine this hypothesis, data from 4,487,873 discharges over 40 years (1970 to 2009) of the National Hospital Discharge Survey (NHDS) were analyzed to define secular trends in sex- and age-specific ischemic stroke incidence. Incidence rates were higher in men than women—a difference diminishing at older ages. Sex-specific distributions for quinquinquennia of age and year demonstrated exponentially increasing ischemic stroke incidence in men and women without secular changes in the exponential form. The results support the hypothesis os ischemic stroke as an aging-dependent disease. Recent secular declines in ischemic stroke incidence are unlikely attributable to changes in some underlying aging process—the aging-dependent form of age-specific disease incidence appears constant over time.

Risings and Fallings of Carotid Artery Procedures

When extracranial carotid artery stenosis is identified, the potential benefit in stroke risk reduction from carotid endarterectomy (CEA) or angioplasty and stenting (CAS) must be weighed against periprocedural (in the 30 days following the procedure) risk of stroke and death. Few interventions have been as highly scrutinized in randomized controlled trials as CEA, likely due to the fine line between benefit and harm. We examined rates of carotid endarterectomies performed

in the United States from 1970 through 2010, and CAS beginning in 2005, using NHDS data. Over four decades, there have been two substantial rises in CEA rates followed by subsequent falls. Adoption of CAS appears limited. Juxtaposing the risings and fallings of carotid artery procedures against highly cited studies and trials suggests that underlying the variation were increases driven by enthusiasm tempered first by results of observational studies in the 1980s, and later by clinical trial results in asymptomatic patients in the late 1990s.

Medical Treatment for Asymptomatic Carotid Stenosis

Ischemic stroke rates have declined over recent decades concurrent with improving medical care. Lower stroke rates result in less potential absolute benefit from CEA or CAS. There is controversy over magnitude of decline in strokes attributable to asymptomatic carotid artery disease among patients considered candidates for CEA or CAS. Many argue that with contemporary best medical care the rate is 0.5% annually. We identified, critically appraised, and pooled estimates from nine studies reporting ipsilateral stroke rates in patients with asymptomatic carotid disease—all following the 2004 publication of the Asymptomatic Carotid Surgery Trial (ACST). Seven studies were judged to have included patients who were not likely candidates for CAS or CAS (selection bias). Potential performance, detection, and attrition biases were prominent in all but one study. The pooled annual ipsilateral stroke rate from the nine studies was 0.98% (95% CrI: 0.54 to 1.57); excluding the three most biased studies 1.36% (95% Credible Interval [CrI]: 0.88 to 1.83). The pooled rates are consistent with the relative risk reduction observed in landmark trials and ipsilateral stroke incidence among asymptomatic patients in the recent Carotid Revascularization Endarterectomy vs. Stenting Trial. After considering study biases as well as consistency with

the relative risk reduction from CEA, the best estimate of ipsilateral stroke incidence with current medical care is somewhat greater than 1%.

Comparing Endarterectomy with Medical Therapy for Asymptomatic Carotid Artery Disease

The most recent trial comparing CEA with medical care in asymptomatic patients (ACST) found benefit modestly outweighed harm. But the trial was completed a decade ago during a period of improving medical therapies. In the United States approximately 50,000 CEAs are performed annually in patients with asymptomatic carotid artery disease. Whether these patients benefit from CEA is controversial and a randomized controlled trial is not on the horizon. Using a Monte Carlo approach, we synthesized evidence and combined it with a decision model comparing CEA with contemporary medical care. Estimates from Bayesian meta-analyses of ipsilateral stroke rates and relative risk reduction of stroke following CEA were incorporated in a Markov cohort model to examine outcomes over a five-year time horizon. Given contemporary stroke rates, to gain expected quality adjusted life years (QALYs), during the periprocedural period following CEA death rates must approach 0% and stroke rates must be under 1.5%—50% lower than typically recommended.

CHAPTER 1

INTRODUCTION

Apoplexy — "A malady, very sudden in its attack, which arrests more or less completely the powers of sense and motion,"... Oxford English Dictionary

Through most of recorded history stroke was known as apoplexy. It occurs commonly. Approximately seven million American adults aged 20 years or older have experienced a stroke—3% or one of every 33 adults [1]. By 2030 the prevalence of stroke is expected to reach four million [2]. Incident stroke occurs in almost 800,000 individuals in the United States annually of which 610,000 are the first experienced [1].

Cerebrovascular diseases include those conditions affecting circulation supplying the brain. When they result in stroke the consequences can debilitate, impairing both physical and cognitive function or even death. Those consequences impact the public's health and are of concern to patients, health care practitioners, and public health policy makers. This thesis addresses three aspects of stroke and underlying cerebrovascular causes: 1) stroke as an aging-dependent disease; 2) secular trends in the use of procedural interventions intended to decrease stroke risk from atherosclerotic carotid artery disease; and 3) bridging epidemiological evidence and decisions to intervene procedurally in asymptomatic carotid artery disease (a prevalent condition in the elderly).

Although the incidence of many diseases increases with age, patterns of increase have been infrequently scrutinized. Yet those patterns may hold potential insights into understanding not

only disease epidemiology but also the role of underlying aging pathologies [3] with implications for prevention or postponing disease onset [4]. In 1986 Brody and Schneider suggested that stroke is a condition one might scrutinize from the perspective of its relationship to aging, [5] but to date it remains unexamined in this regard. As populations age, gaining insight into diseases of aging is increasingly important—many are accompanied by substantial morbidity. Examining the hypothesis that the most common cause of stroke (non-embolic ischemia) is aging-dependent, or related to underlying aging, is the first story. In recent decades, stroke incidence and mortality have decreased owing to improving medical care. The analyses in Chapter 2 provide a glimpse into aging and cerebrovascular disease and emphasize that absent some ability to alter the aging process, in an aging population the burden of stroke will likely continue to grow.

The prevalence of atherosclerotic carotid artery disease increases with age and not uncommonly causes stroke. Some have concluded that as many as 12.5% of men and 6.9% of women over age 70 years have moderate carotid artery stenosis (greater than 50%) [6]. Patients with significant atherosclerotic carotid artery disease can be treated medically, surgically (carotid endarterectomy [CEA]), or non-invasively (carotid angioplasty and stenting [CAS])—CAS being used for less than a decade. While the rationales underlying these interventions have been argued by enthusiasts and skeptics alike, owing to uncertain evidence for a net benefit, CEA rates have undergone large changes over time. Possibly the most detailed analysis included data from California, New York and Ontario, “The Fall and Rise of Carotid Endarterectomy in the United States and Canada,” and examined procedure use through 1995 [7] preceding the introduction of CAS. Since then, uncertainty has increased that CEA provides any benefit to asymptomatic patients; evidence supporting

benefit to asymptomatic patients from CAS is effectively non-existent. In Chapter 3 we examine the risings and fallings in CEAs between 1970 and 2010, and the contribution of CAS to trends. It is a story suggesting periods of enthusiasm tempered by results of observational studies and clinical trials.

For many diseases causal associations are incompletely defined as are the comparative benefits and harms of interventions. Despite these uncertainties, health policy and treatment decisions must be made. As noted by Davis et al. "[t]he importance of moving epidemiologic evidence into policy and practice is no longer a debate, but the question remains as to how to effectively impact policy change aligned with the knowledge we generate" [8]. These notions motivate Chapters 4 and 5 concluding the CEA story. Although CEA is performed in approximately 50,000 asymptomatic patients in the United States each year, it is unclear that benefit is provided. Whether results from clinical trials completed one or two decades ago can be applied to the current milieu is questionable. Yet there is little prospect of evidence from a randomized controlled trial in the near future. The story is one of informing decisions with evidence but the desired evidence (a clinical trial) is lacking.

CHAPTER 2

ISCHEMIC STROKE—AN AGING-DEPENDENT DISEASE?

2.1 Introduction

Notions of aging-dependent and age-dependent diseases [4, 5] emerge from contemplating both disease epidemiology and etiology. Aging-dependent diseases are largely a consequence of the underlying chronic degenerative accompaniments of aging. The incidence of aging-dependent diseases is anticipated to increase in an exponential manner with age following the pattern of overall mortality. Age-dependent diseases, such as multiple sclerosis, tend to occur during a particular susceptible period of life—presumably accompanied by exposure to a necessary risk factor. A reason to consider these distinct perspectives of age-associated diseases are implications for prevention and postponing disease onset. For an age-dependent disease, the focus of prevention is passing through the period of susceptibility unaffected; for aging-dependent diseases, it is postponing onset either by avoiding risk factors or delaying the responsible aging process.

A primary focus when examining the occurrence of aging-dependent diseases are patterns of age-specific incidence and how those patterns might change over time. Any secular changes in the age-specific pattern could yield insights into whether interventions have postponed disease onset to older ages and altered underlying aging processes. From a broader perspective, the question is whether with increasing life expectancy, does disease incidence data imply that the underlying aging process has been altered? Or conversely, are individuals simply living longer with theses

disease following occurrence in the absence of a fundamental change in the underlying pathologic processes.

The incidence of ischemic stroke increases with age and is accompanied by significant morbidity and mortality. It is expected to be aging-dependent because much of the underlying pathology is a consequence of aging. [9, 10] Risk factors for atherosclerosis and ischemic stroke such as blood pressure and lipid levels increase with age while diabetes becomes more prevalent. At the same time, all are modifiable to some extent and their control (along with smoking) has resulted in decreased age-adjusted stroke incidence and mortality over the latter decades of the 20th century. [11] This interplay of aging-dependence and risk factor control offers an opportunity to examine whether described secular changes in risk factor control at the population level has impacted aging-dependence. Finally, important to note is that age-adjusted incidence does not allow examining aging -dependence—to do so requires scrutinizing patterns of age-specific disease incidence.

In this context, the chapter has two purposes. The first is to examine ischemic stroke from the standpoint of an aging-dependent disease; to explore whether the age-specific incidence pattern fits the exponential pattern hypothesized. The second is to analyze secular changes in patterns which would have occurred coincident with improved risk factor control—an unchanging pattern considered consistent with the hypothesis that the underlying aging process has not been altered.

2.2 Methods

The National Center for Health Statistics conducts the annual National Hospital Discharge Survey (NHDS)—a nationwide probability sample of patients discharged from non-institutional

short-stay hospitals in the 50 states, excluding all federal, military, and Veterans Administration institutions. The survey has operated continuously since inception in 1965, undergoing operational revisions in 1988. [12] Prior to 1988 approximately 400 hospitals were surveyed; between 1988 and 2007, 500 hospitals; in 2008 the number of hospitals was reduced to 239. The survey's complex sample design allows calculating national estimates for diagnoses, procedures, and mortality. Up to seven diagnostic and four procedure codes were recorded for each discharge beginning in 1979 and prior to then five diagnoses and three procedures. In 1979 disease classification also changed from ICD-8 to ICD-9. Diagnoses are listed in the order in which they appeared on abstract forms, except in cases of acute myocardial infarction which is always considered the primary diagnosis. These analyses include NHDS data from 1970 through 2009 or 40 years.

The sudden focal neurologic deficits accompanying a stroke are invariably clinically significant. Because the event uncommonly causes sudden death, patients are hospitalized for evaluation and treatment. On this basis, ischemic stroke incidence should be estimable from hospital claims.

Discharge codes likely to represent incident ischemic stroke were selected based on claims algorithms evaluated in comparison to medical records (i.e., those most sensitive and specific). [13] While these algorithms were evaluated using ICD-9, a similar scheme was applied to the ICD-8 codes used prior to 1979. There is, however, there is incomplete consensus in which codes most accurately identify stroke.[1] Although some inaccuracy is therefore likely present, it should apply

[1] http://www.queri.research.va.gov/tools/stroke-quality/ICD9.doc

consistently over time—the primary purpose is examining age- and sex-specific secular trends as opposed to incidence at a specific point in time.

The hypothesis posed concerns ischemic stroke from the perspective of an aging-dependent disease; ischemic stroke that is a consequence of atherosclerotic or atheroembolic pathology as opposed to thromboembolism related to atrial fibrillation. Accordingly, ischemic stroke diagnoses without comorbid atrial fibrillation were ascertained [14] as any discharge diagnosis of non-embolic ischemic stroke (ICD-9 434.XX, 435.XX; ICD-8 432, 433, 434 without any atrial fibrillation diagnosis [ICD-9 427.31, ICD-8 427.9]). [15] Sensitivity analyses were also performed with similar results to those shown using: 1) a primary discharge diagnosis ischemic stroke without comorbid atrial fibrillation, and 2) a more sensitive but less specific algorithm with ICD-9 and ICD-8 436 (acute, but ill-defined, cerebrovascular disease) included in both of these approaches as any diagnosis or as primary diagnosis only.

Given the infrequent occurrence of ischemic stroke in younger individuals, analyses were restricted to patients aged 50 years or older. Incidence rates were calculated using mid-year census estimates as denominators. Because census data for some years is reported as 85 years or older, this was the oldest age category used. Age-adjusted incidence rates were estimated standardize to the year 2000 populations. Secular trends according to age in 10-year increments were first explored over the 40 survey years. To examine age-specific incidence patterns, non-embolic ischemic stroke rates were then calculated by quinquinquennia of age and year. [16]

Underreporting of race is documented in NHDS data affecting both whites and blacks. [17] For this reason, the main analyses are presented for all races combined. However, owing to racial

differences in stroke risk, we repeated all analyses separately for those reporting white and black race (shown in Appendix A).

All analyses were weighted to account for the sampling scheme and performed in R. [18, 19] Population-level estimates are reported to the nearest thousand consistent with accompanying survey error. Numbers of survey discharge calculations are reported to single digits as they represent individual observations. Figures display rates on a logarithmic scale to examine the hypothesis of an exponential pattern of increasing incidence with age being characteristic of an aging-dependent disease. Cubic splines were applied to smooth curves.

2.3 Results

There were 4,487,873 discharges in the NHDS sample over the 40 years among patients aged 50 years or older. This represented almost 660 million hospitalizations in the general population and 9.8 million discharges with a non-embolic ischemic stroke (Table I). Approximately two thirds of the patients discharged were aged 65 or older with more women than men. The number of discharges increased steadily over the 40 years from 1.1 million in 1970 to almost 2.2 million in 2009. A decline was observed from 1981 through 1989 (Figure 1)—previously described and attributed to changes in provision of medical care. [20] There was no decline in non-embolic ischemic stroke discharges over the same period. The small decrease in 1978 is likely attributable to adoption of ICD-9. Table II shows discharges for non-ischemic stroke by age, sex, and time in five-year intervals (Tables XI and XII, Appendix A for reported white and black race).

Sex- and age-specific rates for non-embolic ischemic stroke discharges are displayed in Figures 2 and 3. Four features of the figures are notable: sex-differences, age-adjusted rates, age-

specific rates, and secular trends. Over the 40 survey years, rates were higher among men compared with women (also shown in Table II). The sex difference in age-specific rates appeared to diminish with increasing age. In contrast, age-adjusted rates were rather similar among men and women over the 40 survey years. As a weighted mean, this can be attributed to the larger proportion of older women than men. The figures reveal an increase in incidence appearing to peak in the late 1990s followed by a decline, but not evident in those under age 60. Rates were higher for those reporting black race with greater sampling variability compared with whites (Figures 15 through 18, Appendix A). In blacks there was also a more pronounced secular increase in rates between 1970 and 1995. Finally, a perspective of the age-specific and age-adjusted rates to consider is that at each year (cross-sectionally) an incidence distribution is defined analogous to a probability distribution not normalized to sum to unity. This distribution, and its constancy over time, is of interest with respect to aging-dependent diseases.

Sex-specific-age-incidence distributions are shown for quinquinquennia in Figures 4 and 5. These figures display five-year cross-sections of Figures 2 and 3 with age categorized in five-year increments (the mean of each age group was used for plotting evident as a slight jitter in the abscissa). The patterns appeared similar among women and men, although the distributions shifted higher in men. The secular trends previously noted are less apparent, but evident by following the curves according to five-year periods. Among both women and men, discharge rates increased slightly from 1970 and 1984 peaking sometime between 1995 and 1999. The increases with age follow an exponential pattern that flattens at older ages for both women and men. Furthermore,

absent are any apparent changes in the form with secular changes in rates. Results for black and whites were similar (Figures 19 through 22, Appendix A).

TABLE I: RELEVANT CHARACTERISTICS OF THE NHDS SAMPLE FROM 1970 THROUGH 2009.

	Total (N)	**%**
Years		
1970–1974	60,193,000	9.1
1975–1979	74,337,000	11.3
1980–1984	87,144,000	13.2
1985–1989	79,256,000	12.0
1990–1994	78,314,000	11.9
1995–1999	85,019,000	12.9
2000–2004	92,878,000	14.1
2005–2009	101,400,000	15.4
Sex		
Male	297,490,000	45.2
Female	361,060,000	54.8
Age		
50–64	232,470,000	35.3
65–74	186,810,000	28.4
75–84	165,160,000	25.1
85+	74,096,000	11.3
Race		
White	485,160,000	73.7
Black	55,204,000	8.4
Other/NR	118,180,000	17.9
Diagnoses		
Stroke	9,754,300	1.5
TIA	8,465,000	1.3

TIA: Transient Ischemic Attack; NR: Not Reported

TABLE II: HOSPITAL DISCHARGES FOR NON-EMBOLIC ISCHEMIC STROKE FROM THE NHDS SAMPLE—1970 THROUGH 2009.

	Men		**Women**		**Total**	
	N	(%)	N	(%)	N	(%)
Age						
50–64	2,175,000	(27.2)	1,628,000	(25.8)	3,802,000	(13.2)
65–74	2,818,000	(35.2)	2,512,000	(33.5)	5,330,000	(17.2)
75–84	2,369,000	(29.6)	2,902,000	(28.1)	5,271,000	(14.4)
85+	646,600	(8.1)	1,380,000	(7.7)	2,026,000	(3.9)
Year						
1970–1974	532,200	(6.6)	550,400	(6.3)	1,083,000	(3.2)
1975–1979	668,400	(8.3)	654,300	(7.9)	1,323,000	(4.1)
1980–1984	694,900	(8.7)	684,000	(8.3)	1,379,000	(4.2)
1985–1989	967,700	(12.1)	1,068,000	(11.5)	2,036,000	(5.9)
1990–1994	1,123,000	(14.0)	1,211,000	(13.3)	2,334,000	(6.8)
1995–1999	1,348,000	(16.8)	1,421,000	(16)	2,770,000	(8.2)
2000–2004	1,261,000	(15.7)	1,312,000	(15)	2,573,000	(7.7)
2005–2009	1,413,000	(17.6)	1,520,000	(16.8)	2,933,000	(8.6)
Race						
White	5,854,000	(73.1)	6,102,000	(69.5)	11,960,000	(35.6)
Black	630,900	(7.9)	804,100	(7.5)	1,435,000	(3.8)
Other/NR	1,524,000	(19.0)	1,515,000	(18.1)	3,039,000	(9.3)

NR: Not Reported

TABLE III: HOSPITAL DISCHARGES FOR ISCHEMIC STROKE (PER/1000 POPULATION) BY SEX, YEAR, AND AGE (NON-ATRIAL FIBRILLATION RELATED); AGE-ADJUSTED RATES TO 2000 POPULATION STANDARD.

	Age								**Adjusted**	
	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+	Yes	No
Men										
1970–1974	1.4	2.3	3.7	5.8	8.2	10.1	11.8	12.6	4.9	4.6
1975–1979	1.6	2.8	4.6	6.7	9.0	11.9	11.6	14.0	5.6	5.3
1980–1984	1.4	2.8	3.7	6.7	8.8	11.1	12.7	12.7	5.4	5.2
1985–1989	1.7	3.2	4.9	8.7	12.0	14.5	16.6	17.3	7.0	7.1
1990–1994	1.7	3.5	5.3	8.7	12.4	16.5	17.9	20.2	7.5	7.8
1995–1999	1.7	3.7	6.2	9.8	13.4	18.4	21.6	18.3	8.2	8.5
2000–2004	1.6	3.5	5.3	7.9	11.4	15.3	16.8	17.1	6.9	6.8
2005–2009	1.9	2.8	4.9	8.3	11.2	14.2	18.7	18.5	6.9	6.7
Women										
1970–1974	0.8	1.5	2.4	3.9	5.7	8.4	10.9	13.7	4.5	3.9
1975–1979	0.9	1.7	2.8	4.6	6.2	7.7	10.9	12.3	4.6	4.2
1980–1984	0.8	1.6	2.8	4.3	6.0	7.7	9.3	10.2	4.2	4.1
1985–1989	1.1	1.9	3.4	5.3	8.9	11.9	15.2	15.3	6.1	6.1
1990–1994	1.0	2.0	3.9	6.5	8.5	11.5	16.2	16.4	6.4	6.6
1995–1999	1.3	2.6	4.4	7.1	10.1	12.4	16.9	16.7	7.1	7.2
2000–2004	1.4	2.3	3.5	5.6	8.3	10.7	14.0	15.6	6.0	5.9
2005–2009	1.4	2.3	3.4	6.0	8.7	12.3	13.9	18.4	6.5	6.1

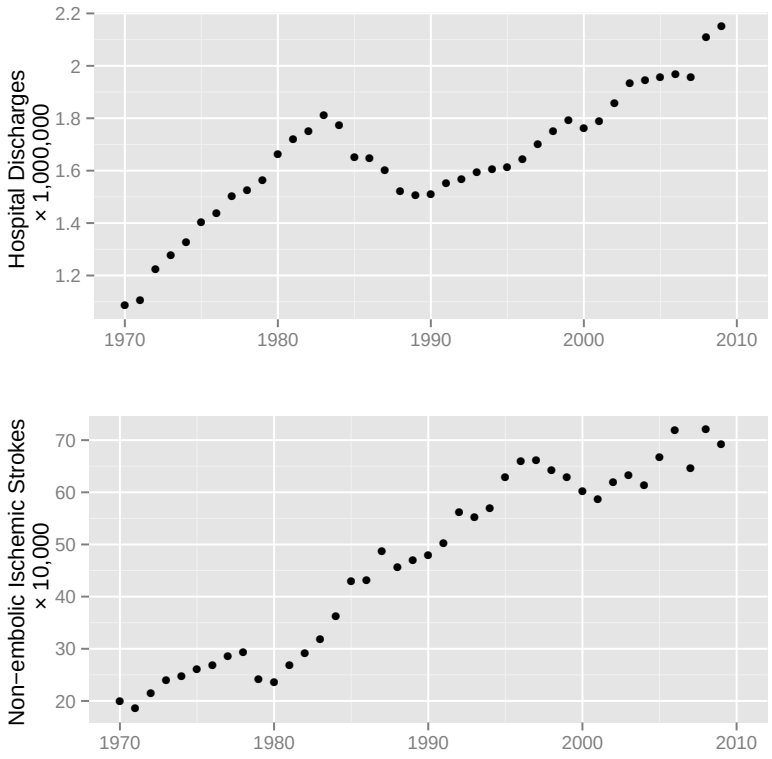

Figure 1: Forty-year trends in the number of hospital discharges and non-embolic ischemic stroke.

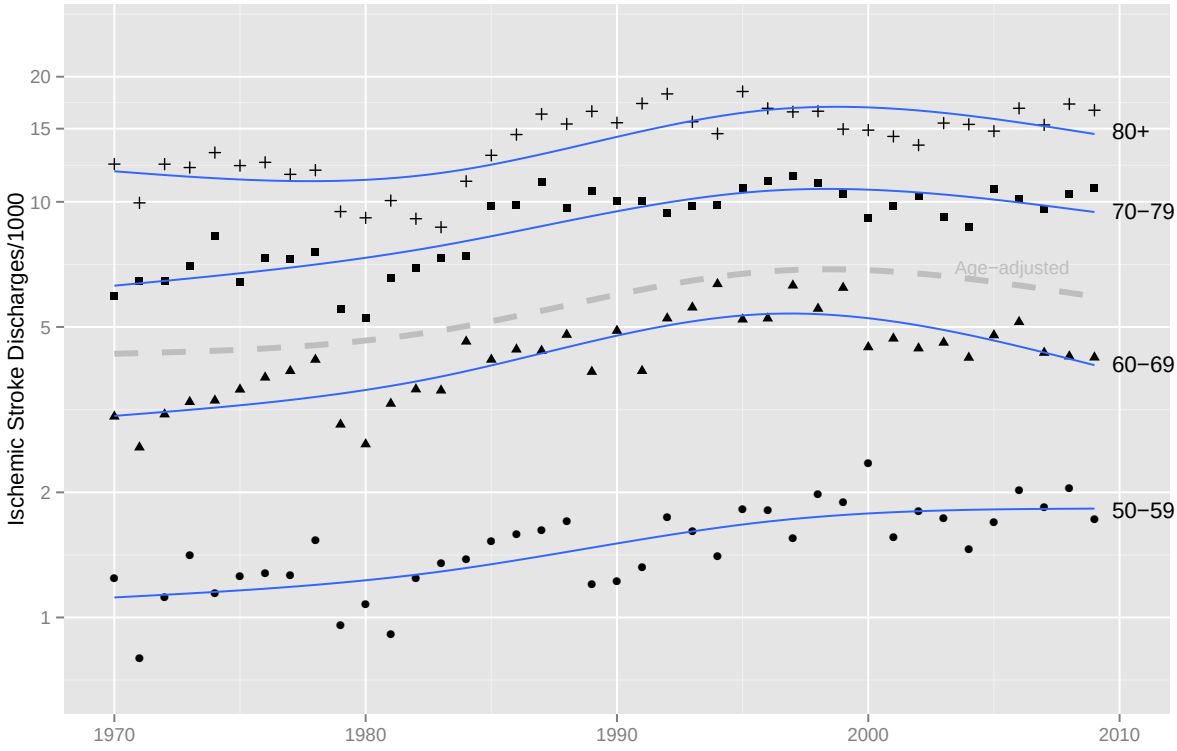

Figure 2: Estimated discharge rates for non-embolic ischemic stroke from 1970 through 2009 in the US population among women.

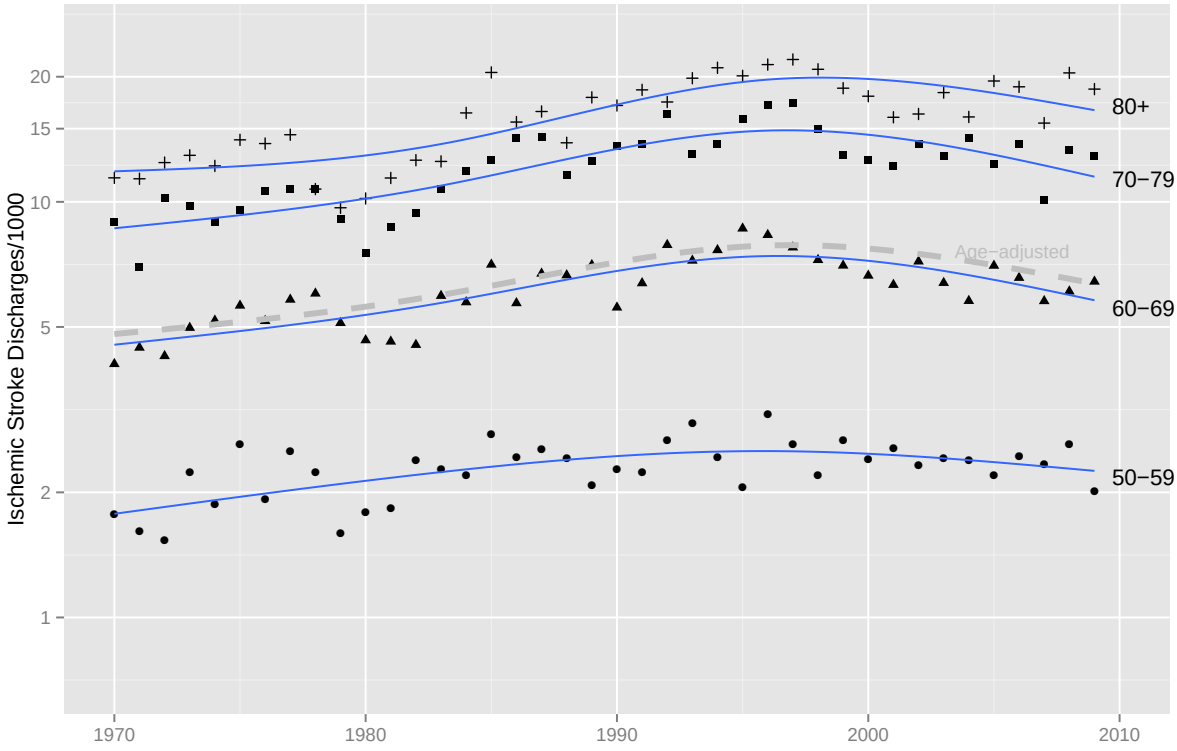

Figure 3: Estimated discharge rates for non-embolic ischemic stroke from 1970 through 2009 in the US population among men.

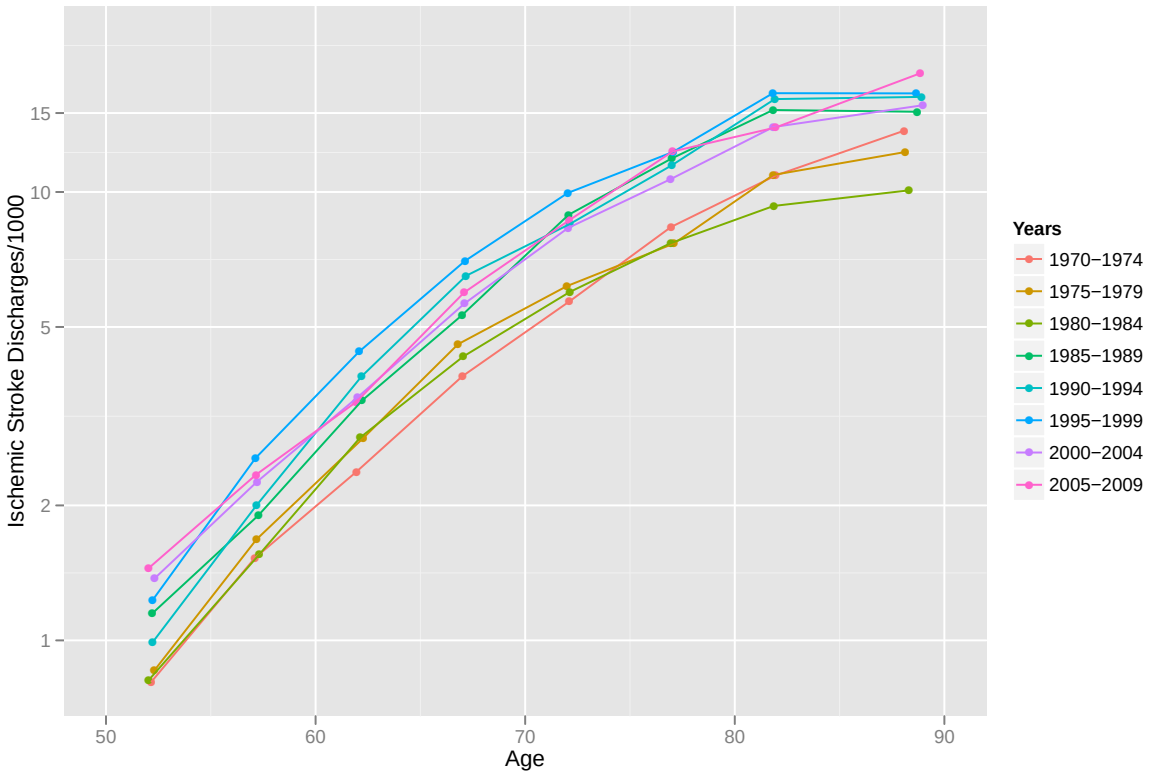

Figure 4: Pattern of discharge rates for non-embolic ischemic stroke with increasing age among women over 40 years of the NHDS.

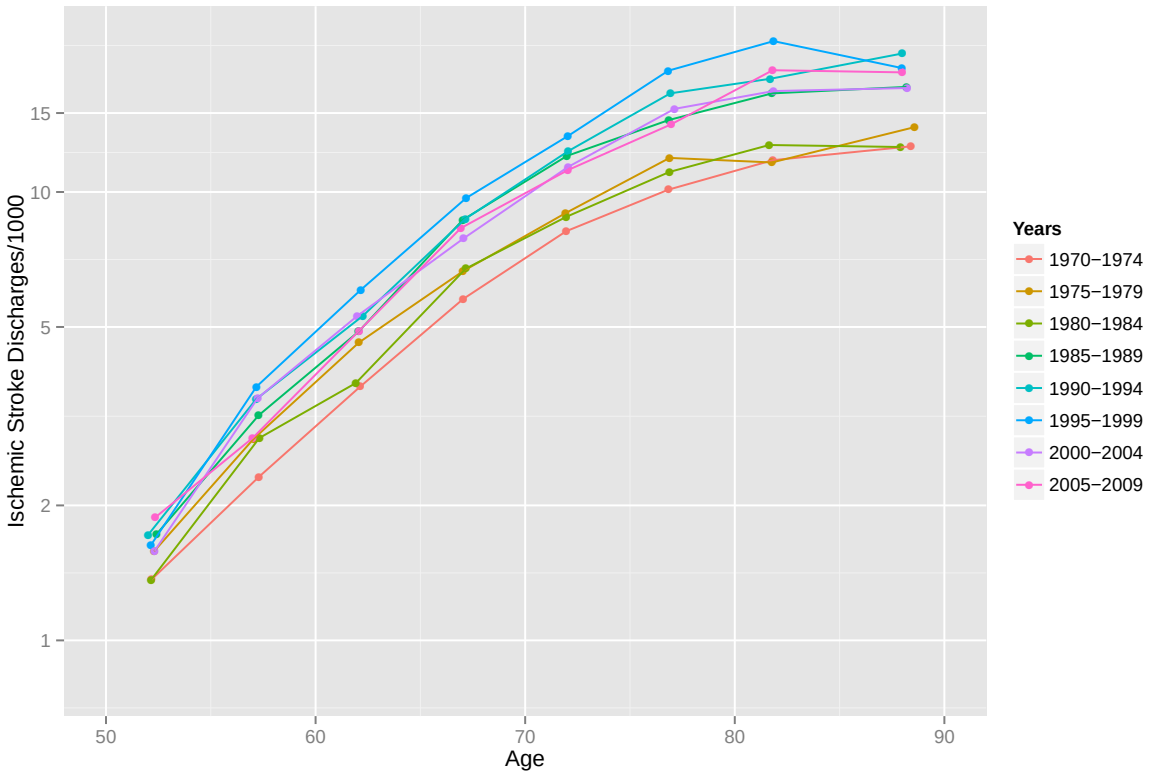

Figure 5: Pattern of discharge rates for non-embolic ischemic stroke with increasing age among men over 40 years of the NHDS.

2.4 Discussion

Incidence data supporting hypotheses that specific diseases are aging-dependent have not been extensively examined. Yet a number of diseases are in theory aging-dependent. Ischemic stroke, one of these, has significant physical and cognitive consequences, and contributes substantially to overall mortality. Studies have found declining stroke incidence over recent decades, attributing the decline to better risk factor control. [11,21] Given that evidence, considering whether changes in underlying aging processes have altered incidence is of interest from two perspectives. First, interventions altering aging processes could potentially increase life span by decreasing mortality and also diminish the morbidity from stroke. Second, there may be different limits to benefits obtained from interventions that do, and do not, alter aging-dependent processes underlying ischemic stroke. These perspectives, even if not mutually exclusive, offer potential insights and ways to think about aging, disease prevention and postponement.

Non-embolic ischemic stroke has the hallmarks of an aging-dependent disease—underlying aging-dependent pathologies have been described and disease incidence increases with age. Examining ischemic stroke from the vantage of an aging-dependent disease is best accomplished with representative incidence data collected over time. Because stroke almost invariably leads to hospitalization, incidence can be ascertained with substantially good accuracy from administrative data. [13] Data from the NHDS, collected in a standardized manner over many decades, are well-suited to this purpose.

Although hospital discharges for ischemic stroke were uniformly higher in men than women over the 40 years examined, the sex-specific secular trends were similar. Consistent with an aging-

dependent disease, incidence rates increased in an exponential pattern with age. The trend in rates then flattened at the oldest ages—more so among men than women. Notably, the sex- and age-specific pattern of increasing incidence was similar over the 40 years analyzed despite the secular decreases in overall rates.

How can these dimensions of disease incidence be interpreted? The sex difference is consistent with increased stroke risk and higher prevalence of risk factors in men. The flattening of the exponential increase at the oldest ages is undoubtedly attributable to competing cardiovascular causes of death—e.g., depletion of individuals at risk and disproportionately among men. Notably, the exponential pattern of increase with age was maintained in similar form over the 40 survey years, although altered some in location (e.g., mean rate) corresponding to secular trends. This can be interpreted as consistent with no changes in the underlying aging phenomenon; changes would have altered the pattern of increase. The shift in position or location of the age-specific patterns is consistent with altered risk factor control affecting all ages proportionately according to their underlying risk (on a multiplicative scale).

Although the results may be intriguing and it is tempting to conjecture about underlying aging-associated phenomenon, these data and analyses have important limitations to consider. First, even if incident disease could be observed without error, it is a result of many contributory causes of which aging is but one, albeit critically important, component cause. This limitation might be circumvented somewhat if a cardiovascular aging biomarker could be measured, but one does not exist. Next are limitations inherent in diagnostic accuracy and the method or algorithm used to identify likely incident disease. Although the approach adopted here has a clinical rationale

(non-embolic ischemic stroke) and studies have defined the accuracy of administrative data to identify ischemic stroke, other approaches could be employed. Yet adopting other approaches, such as ischemic stroke including possible embolism, or only a primary diagnosis led to similar patterns although with obviously different incidence estimates—an informal sensitivity analyses. Additionally, atrial fibrillation is undoubtedly under-ascertained, as it can be silent in many cases of stroke. [22] Accordingly, interpretations should be considered mainly consistent with some underlying explanation. Second, the NHDS despite being large, representative, and uniformly conducted over many years has limitations other than accuracy of diagnosis. Individuals are not followed longitudinally, so some may contribute more than a single hospital episode to the survey. How often individuals appear more than once is unclear, but given the sampling scheme it is likely to be infrequent. Being able to ascertain incident initial stroke would be desirable to supplement the results. Next, it is not possible to define a mean age at onset of first stroke or ascertain first incident ischemic stroke. In addition, these data do not account for secular trends in decreasing mortality following a stroke. [21] The shift from ICD-8 to ICD-9 cannot be completely accounted for, but smoothing estimates and performing calculations over five-year periods diminishes the small discontinuity. Finally, although the sample is large, due to underreporting of race [17] examining ethnic or racial subgroups can be problematic due to the necessary sex-, age-, and time-period stratification. Still, although rates were higher among blacks than whites patterns were similar.

The promise of longer and healthier lives has been pursued for much of recorded history, but only recently for those reaching the oldest ages. The incidence of some age-associated diseases such as ischemic stroke have seen apparent substantial declines; any decline in the incidence of

others such as Alzheimer's disease appear only slight. [23] Both disease can be considered aging-dependent. For ischemic stroke there are well-characterized risk factors amenable to intervention; for Alzheimer's disease defined risk factors have not been translated into effective interventions. Endeavoring to understand the interplay between disease and underlying aging phenomenon offers a glimpse into complex causal webs and insight into interventions as well as their limits. While preventing disease occurrence is always sought, in the case of aging-dependent diseases the inexorable advance of aging makes postponement the more attainable goal. Although these results cannot discern whether there has been postponement in the onset of ischemic stroke, they do suggest that the aging-dependent nature of the disease has not likely been altered. While further progress in risk factor control is possible and even likely, the limits of interventions in ischemic stroke may well be the process of aging itself.

CHAPTER 3

RISINGS AND FALLINGS OF CAROTID ARTERY PROCEDURES PERFORMED IN THE UNITED STATES

3.1 Introduction

In 1937, angiography provided the first visual images of atherosclerotic plaque in the carotid artery. [24] Almost two decades later Eastcott reported performing carotid endarterectomy (CEA) successfully in a patient experiencing transient ischemic attacks (TIA). [25] In 1970, results were published from the Joint Study of Extracranial Arterial Occlusion—a trial randomizing 316 patients with carotid atherosclerosis and TIAs to CEA or "nonsurgical" therapy. [26] Although patients randomized to CEA experienced a substantial surgical risk (11.4% stroke or death), the investigators concluded benefit conferred. Over the next 20 years, CEA became widely performed in both symptomatic (those with TIAs) and asymptomatic patients.

Tu et al. [7] described a fall followed by a rise in CEAs performed between 1983 and 1995 in California, New York, and Ontario. The fall was attributed to increasing uncertainty surrounding the potential benefits in the face of procedure-related harms—namely stroke and death. The subsequent rise was tied to results from North American Carotid Endarterectomy Surgery Trial (NASCET) published in 1991. [27]

Few surgical interventions have witnessed the waxing and waning enthusiasm and skepticism that have surrounded CEA. Controversy has only increased following introduction of a non-invasive

alternative—carotid angioplasty and stenting (CAS). The many influences underlying shifting enthusiasm and skepticism have been the focus of poignant and sometimes colorful debate—from Barnett's 1984 commentary "Carotid Endarterectomy—An Expression of Concern" [28] to Naylor and colleague's "Who Benefits Most from Intervention for Asymptomatic Carotid Stenosis: Patients or Professionals?" [29] From this perspective, decades since the widespread adoption of CEA, the use of procedures to treat atherosclerotic carotid artery disease is a longer story of enthusiasm and skepticism, observational studies and trials. The purpose here is to examine secular procedure trends alongside evidence defining benefits and harms—exploring the interplay between surrogates for enthusiasm (increases in procedure use) and evidence (observational study and trial results).

3.2 Methods

3.2.1 Data

The National Hospital Discharge Survey (NHDS) is a nationwide probability sample of patients discharged from non-institutional short-stay hospitals in the 50 states, excluding all federal, military, and Veterans Administration institutions. The survey has operated continuously since inception in 1965, undergoing operational revisions in 1988. [12] In these analyses, NHDS data collected from 1970 through 2010 were analyzed. Prior to 1988 approximately 400 hospitals were surveyed; between 1988 and 2007, 500 hospitals; while in 2008 was reduced to 239. The survey's complex sample design allows the calculation of national estimates for diagnoses, procedures, and mortality. Before 1979 up to five diagnoses and three procedures were recorded for each discharge, from 1979 through 2009 up to seven diagnostic and four procedures, and in 2010 up to 15 diagnoses and eight procedures. Diagnoses are listed in the order in which they appeared on ab-

stract forms, except in cases of acute myocardial infarction, which is always considered the primary diagnosis. Patients undergoing CEA were identified by ICD-8-CM (prior to 1979) and ICD-9-CM procedure codes 261 and 38.12 or CAS by ICD-9-CM 00.63, yielding 25,142 sample discharges (unweighted).

3.2.2 Person

Analyses were restricted to patients aged 50 years or older given the lower prevalence of carotid disease and stroke in younger individuals. Age was categorized as 50 to 64, 65 to 74, 75 to 84, or 85 years or older in these analyses. Population level rates were calculated using mid-year census estimates as denominators. Other ascertained diagnoses of interest included: ischemic stroke (ICD-8/9 434); TIA (ICD-8 435, ICD-9 435.9); diabetes (ICD-8/9 250); myocardial infarction (ICD-8/9 410, 412); and atrial fibrillation (ICD-8 427.3, ICD-9 427.9). Claims do not allow precisely distinguishing patients experiencing symptoms before procedural intervention because comorbid diagnoses might have occurred during, or prior to, the index hospitalization. Accordingly, diagnoses cannot be used to determine whether symptoms were the indication for a procedure.

3.2.3 Place

Region is reported in the NHDS corresponding to Census Bureau classifications (Northeast, South, West, and Midwest). [12] To calculate procedure rates by region, census estimates for each region were obtained by querying the Integrated Public Use Microdata Series (IPUMS). [30] Between 1970 and 1979 the 4.5% of the population not assigned to a locale and was distributed proportionately to other regions.

3.2.4 Time

We examined secular trends in procedure rates. Sex-specific rates were estimated owing to differences in stroke risk. Secular changes in mean age were also analyzed. Finally, highly publicized observational studies possibly influencing procedure use and all published randomized controlled trials were identified and juxtaposed against the main secular trends. We identified years during which substantial changes in rates were most probable in a Bayesian change point analysis. [31,32] When the probability exceeded 0.5 we considered a change likely. Analyses were performed separately for men and women.

All analyses were weighted to account for the sampling scheme and performed in R. [18]

3.3 Results

3.3.1 Person

Between 1970 and 2010, an estimated 3,290,500 CEAs were performed in the United States in patients aged 50 years or older (Table IV). Carotid angioplasty and stenting procedures were first ascertained in 2005 following US Food and Drug Administration approval during the previous year; through 2010, approximately 80,600 were performed (Table V). Three quarters of procedures (CEA or CAS) were performed in patients aged 65 years or older, but few in those 85 years or older (3.8%). Almost 80% of patients were white; race was recorded as black in fewer than 3% of discharges. Procedures were also more common in men. Beginning in 1980 when CEA became widely adopted, men were between 1.3 and 2.1 times more likely to be discharged following a procedure than women. Ischemic stroke was listed as a diagnosis in more than 90% of discharges while transient ischemic attacks (TIA) listed in fewer than 10%. Other cardiovascular diagnoses

were recorded in a minority of discharges and diabetes in about 20%. Finally, between 1970 and 2010 the mean age of patients undergoing the procedure increased by more than five years in both men (from 65.0 to 70.7 years) and women (from 66.2 to 71.5 years).

3.3.2 Place

Over the 41-year period procedure rates were lowest in the Northeast (101.5/100,000) and highest in the Midwest (135.8/100,000) (Table VI). There were marked regional differences in the initial rise in CEAs between 1970 and 1985 (Figure 6) ranging from a gradual increase in the northeast to a rapid rise in the West. After 1990, secular trends in all regions appeared similar but reaching a lower level in the west.

3.3.3 Time

Between 1970 and 1985, discharges reporting a CEA being performed rose sharply (Figure 7)—among men from 31.0 to 213.8 per 100,000 and among women from 14.1 to 135.1 per 100,000. These rises were followed by sharp declines reaching nadirs by approximately 1990 for both men and women. Preceding the declines were highly publicized studies showing high rates of stroke or death following CEA [33–36] (Table VII). From 1991 through the late 1990s procedure rates again rose—among men to 245.6 per 100,000 and among women to 157.2 per 100,000. At the start of this increase in 1991 three trial results were published indicating benefit in symptomatic patients with severe stenosis. [27, 37, 38] The second rise persisted until 1997. Endarterectomy rates subsequently fell steadily in both men and women. This period of decline coincided with dissemination of results from a series of seminal trials conducted in symptomatic patients with moderate stenoses and trials enrolling asymptomatic patients (Figure 6 and Table VII). [39–42]

With the introduction of CAS, the rate any carotid artery procedure (CEA or CAS) may have increased, but only slightly. Results from trials comparing CAS to CEA, reported beginning in 2004 (Table VII) have favored CEA. [43–47]

The changepoint analyses of CEA rates were consistent with the graphical depiction (Figures 23 and 24, Appendix B) showing greater than 0.50 probability of changing rates among men or women in 1981, 1986–1987, 1992–1993, and 2004–2005. The first 1981 changepoint corresponds to the sharp early increase. The second over 1986-1987 was coincident with the fall following publication of observational results suggesting harms. In 1992–1993 there was a second rise, and in 2004–2005 evidence for a final fall.

TABLE IV: NUMBER OF DISCHARGES IDENTIFIED DURING WHICH A CAROTID ENDARTERECTOMY WAS PERFORMED ACCORDING TO AGE, COMORBID DIAGNOSES, RACE, AND YEAR (ROUNDED TO CONVEY SAMPLING UNCERTAINTY).

	Men		**Women**		**Total**	
	N	(%)	N	(%)	N	(%)
Age						
50–64	517,300	(27.4)	348,100	(24.8)	865,400	(26.3)
65–74	787,400	(41.7)	551,500	(39.3)	1,338,900	(40.7)
75–84	519,200	(27.5)	443,200	(31.6)	962,400	(29.2)
85+	62,300	(3.3)	61,400	(4.4)	123,700	(3.8)
Diagnoses						
Stroke	1,750,800	(92.8)	1,306,100	(93.0)	3,056,900	(92.9)
TIA	146,200	(7.7)	121,500	(8.7)	267,600	(8.1)
MI	140,500	(7.4)	78,400	(5.6)	218,900	(6.7)
CHF	81,300	(4.3)	58,600	(4.2)	139,900	(4.3)
Atrial Fibrillation	106,800	(5.7)	61,300	(4.4)	168,100	(5.1)
DM	355,100	(18.8)	289,400	(20.6)	644,500	(19.6)
Race						
White	1,496,600	(79.3)	1,111,600	(79.2)	2,608,100	(79.3)
Black	43,700	(2.3)	47,700	(3.4)	91,400	(2.8)
Other/NR	346,000	(18.3)	244,900	(17.4)	590,900	(18.0)
Year						
1970–1974	50,500	(2.7)	32,300	(2.3)	82,900	(2.5)
1975–1979	118,000	(6.3)	76,500	(5.4)	194,500	(5.9)
1980–1984	215,200	(11.4)	167,200	(11.9)	382,400	(11.6)
1985–1989	221,600	(11.7)	174,100	(12.4)	395,600	(12.0)
1990–1994	238,600	(12.6)	172,900	(12.3)	411,400	(12.5)
1995–1999	359,700	(19.1)	281,800	(20.1)	641,400	(19.5)
2000–2004	343,600	(18.2)	244,300	(17.4)	587,900	(17.9)
2005–2009	284,200	(15.1)	213,000	(15.2)	497,100	(15.1)
2010	54,800	(2.9)	42,300	(3.0)	97,200	(3.0)
Total	1,886,200	(100.0)	1,404,200	(100.0)	3,290,500	(100.0)

TIA: Transient Ischemic Attack; MI: Myocardial Infarction; CHF: Congestive Heart Failure; DM: Diabetes Mellitus; NR: Not Reported

TABLE V: NUMBER OF DISCHARGES IDENTIFIED DURING WHICH A CAROTID ANGIOPLASTY AND STENTING WAS PERFORMED ACCORDING TO AGE, COMORBID DIAGNOSES, RACE, AND YEAR (ROUNDED TO THE NEAREST 100 TO CONVEY SAMPLING UNCERTAINTY).

	Men		**Women**		**Total**	
	N	(%)	N	(%)	N	(%)
Age						
50–64	13,900	(27.5)	5,100	(16.9)	19,000	(23.5)
65–74	22,600	(44.8)	14,100	(47.1)	36,800	(45.6)
75–84	11,500	(22.7)	8,300	(27.7)	19,800	(24.5)
85+	2,600	(5.1)	2,500	(8.4)	5,100	(6.3)
Diagnoses						
Stroke	47,100	(93.1)	29,200	(97.4)	76,300	(94.7)
TIA	1,800	(3.6)	1,300	(4.3)	3,100	(3.9)
MI	2,200	(4.4)	700	(2.2)	2,900	(3.6)
CHF	3,900	(7.8)	3,500	(11.5)	7,400	(9.2)
Atrial Fibrillation	5,400	(10.7)	1,600	(5.4)	7,000	(8.7)
DM	12,900	(25.5)	8,700	(29.0)	21,600	(26.8)
Race						
White	36,300	(71.8)	21,100	(70.2)	57,400	(71.2)
Black	2,000	(4.0)	2,200	(7.3)	4,200	(5.2)
Other/NR	12,200	(24.2)	6,800	(22.5)	19,000	(23.6)
Year						
1970–1974	0	(0.0)	0	(0.0)	0	(0.0)
1975–1979	0	(0.0)	0	(0.0)	0	(0.0)
1980–1984	0	(0.0)	0	(0.0)	0	(0.0)
1985–1989	0	(0.0)	0	(0.0)	0	(0.0)
1990–1994	0	(0.0)	0	(0.0)	0	(0.0)
1995–1999	0	(0.0)	0	(0.0)	0	(0.0)
2000–2004	0	(0.0)	0	(0.0)	0	(0.0)
2005–2009	45,000	(89.0)	25,700	(85.6)	70,700	(87.7)
2010	5,600	(11.0)	4,300	(14.4)	9,900	(12.3)
Total	50,600	(100.0)	30,000	(100.0)	80,600	(100.0)

TIA: Transient Ischemic Attack; MI: Myocardial Infarction; CHF: Congestive Heart Failure; DM: Diabetes Mellitus; NR: Not Reported

TABLE VI: PROCEDURE RATE PER 100,000 POPULATION BY GEOGRAPHIC REGION AND MEAN AGE OVER TIME.

	Procedures/100,000				**Age (Mean)**	
	Northeast	South	Midwest	West	Men	Women
Years						
1970–1974	24.2	36.0	35.0	41.6	65.0	66.2
1975–1979	36.5	74.3	84.2	89.4	66.0	66.9
1980–1984	83.8	114.7	135.1	200.6	68.2	69.8
1985–1989	75.4	131.7	139.4	171.2	68.4	69.7
1990–1994	122.5	144.0	131.2	81.6	69.6	70.9
1995–1999	167.2	196.3	186.4	138.7	70.9	71.4
2000–2004	160.8	175.6	144.0	98.1	71.4	71.6
2005–2010	111.2	140.6	129.0	90.8	70.7	71.5
Overall	101.5	126.0	135.8	112.2	69.7	70.6

TABLE VII: HIGHLY CITED (INFLUENTIAL) CEA AND CAS TRIALS, OBSERVATIONAL STUDIES, AND REVIEWS (CORRESPONDING TO FIGURE 6).

Study	**Intervention**	**Design**	**N**	**Conclusion**
Fields 1970 [26]	OMT/CEA	RCT	316	Over an average 42 month follow-up 46.6% randomized to surgery, 28.2% randomized to medical therapy remained symptom free; 11.4% periprocedural stroke and death rate.
Winslow 1984 [34]	CEA	Review	1302	35% CEAs “appropriate”; 32% “equivocal”; 32% “inappropriate”; “We conclude that carotid endarterectomy was substantially overused in the three geographic areas we studied. Furthermore, in situations in which the complication rate is equal to or above the study’s aggregate rate, carotid endarterectomy would not be warranted, even in cases with an appropriate indication, because the risks would almost certainly outweigh the benefits.”
Warlow 1984 [33]	OMT/CEA	Review	1442 Case Series 316 Trial	Review of 13 case series & Joint Study of Extracranial Arterial Occlusion. “Having reviewed the evidence, the conclusion is drawn that there is not sufficient data available to allow a rational decision as to whether carotid endarterectomy does or does not increase the duration of survival free of stroke after TIA have developed in the carotid artery territory.”
Muuronen 1984 [36]	CEA	Case Series	227	“The results emphasize that patients with TIA or ischemic brain infarction should be carefully evaluated before recommending surgical treatment for prevention of threatened stroke. Patients with severe risk factors may fare better on medical treatment than with surgical intervention.”
Brott 1984 [35]	CEA	Case Series	431	Perioperative stroke and death rate 9.5%.
NASCET 1991 [27]	OMT/CEA	RCT	659 severe stenosis	“Carotid endarterectomy is highly beneficial to patients with recent hemispheric and retinal transient ischemic attacks or nondisabling strokes and ipsilateral high-grade stenosis (70 to 99%) of the internal carotid artery.”

TABLE VII (continued)

Study	Intervention	Design	N	Conclusion
ECST 1991 [37]	OMT/CEA	RCT	374 mild stenosis 778 severe stenosis	"For 374 patients with only mild' (0-29%) stenosis there was little 3-year risk of ipsilateral ischaemic stroke, even in the absence of surgery, so any 3-year benefits of surgery were small, and were outweighed by its early risks. For 778 patients with severe; (70-99%) stenosis, however, the risks of surgery were significantly outweighed by the later benefits:"
VA 309 1991 [38]	OMT/CEA	RCT	189 mod/severe stenosis	"For a selected cohort of men with symptoms of cerebral or retinal ischemia in the distribution of a high-grade internal carotid artery stenosis, carotid endarterectomy can effectively reduce the risk of subsequent ipsilateral cerebral ischemia."
VA Study 1993 [48]	OMT/CEA	RCT	444	"Carotid endarterectomy reduced the overall incidence of ipsilateral neurologic events in a selected group of male patients with asymptomatic carotid stenosis. We did not find a significant influence of carotid endarterectomy on the combined incidence of stroke and death, but because of the size of our sample, a modest effect could not be excluded."
ACAS 1995 [39]	OMT/CEA	RCT	1662	"Initially, transient ischemic attack or cerebral infarction occurring in the distribution of the study artery and any transient ischemic attack, stroke, or death occurring in the perioperative period. In March 1993, the primary outcome measures were changed to cerebral infarction occurring in the distribution of the study artery or any stroke or death occurring in the perioperative period."
ECST 1996 [40]	OMT/CEA	RCT	1599	"Previous interim results from this study showed that surgery is beneficial in patients with severe stenosis but harmful in those with mild stenosis. With more randomised patients and longer follow-up, the study now shows that endarterectomy is not indicated for most, possibly all, patients with moderate symptomatic carotid stenosis."

TABLE VII (continued)

Study	Intervention	Design	N	Conclusion
NASCET 1998 [41]	OMT/CEA	RCT	2226	"Endarterectomy in patients with symptomatic moderate carotid stenosis of 50 to 69 percent yielded only a moderate reduction in the risk of stroke. Decisions about treatment for patients in this category must take into account recognized risk factors, and exceptional surgical skill is obligatory if carotid endarterectomy is to be performed. Patients with stenosis of less than 50 percent did not benefit from surgery. Patients with severe stenosis (»70 percent) had a durable benefit from endarterectomy at eight years of follow-up."
ACST 2004 [42]	OMT/CEA	RCT	3120	"In asymptomatic patients younger than 75 years of age with carotid diameter reduction about 70% or more on ultrasound (many of whom were on aspirin,antihypertensive, and, in recent years, statin therapy), immediate CEA halved the net 5-year stroke risk from about 12% to about 6% (including the 3% perioperative hazard). Half this 5-year benefit involved disabling or fatal strokes. But, outside trials, inappropriate selection of patients or poor surgery could obviate such benefits.antihypertensive, and, in recent years, statin therapy), immediate CEA halved the net 5-year stroke risk from about 12% to about 6% (including the 3% perioperative hazard). Half this 5-year benefit involved disabling or fatal strokes. But, outside trials, inappropriate selection of patients or poor surgery could obviate such benefits."
SAPPHIRE 2004 [43]	CEA/CAS	RCT	334	"Among patients with severe carotid-artery stenosis and coexisting conditions, carotid stenting with the use of an emboli-protection device is not inferior to carotid endarterectomy."
SPACE 2006 [45]	CEA/CAS	RCT	1200	"SPACE failed to prove non-inferiority of carotid-artery stenting compared with carotid endarterectomy for the periprocedural complication rate. The results of this trial do not justify the widespread use in the short-term of carotid-artery stenting for treatment of carotid-artery stenoses. Results at 6–24 months are awaited."

TABLE VII (continued)

Study	Intervention	Design	N	Conclusion
EVA 3S 2006 [44]	CEA/CAS	RCT	527	"In this study of patients with symptomatic carotid stenosis of 60% or more, the rates of death and stroke at 1 and 6 months were lower with endarterectomy than with stenting."
CREST 2010 [47]	CEA/CAS	RCT	2502	"Among patients with symptomatic or asymptomatic carotid stenosis, the risk of the composite primary outcome of stroke, myocardial infarction, or death did not differ significantly in the group undergoing carotid-artery stenting and the group undergoing carotid endarterectomy. During the periprocedural period, there was a higher risk of stroke with stenting and a higher risk of myocardial infarction with endarterectomy."
ICSS 2010 [46]	CEA/CAS	RCT	1713	"Completion of long-term follow-up is needed to establish the efficacy of carotid artery stenting compared with endarterectomy. In the meantime, carotid endarterectomy should remain the treatment of choice for patients suitable for surgery."

RCT: Randomized Controlled Trial; CEA: Carotid Endarterectomy; CAS: Carotid Angioplasty and Stenting; OMT: Optimal Medical Therapy

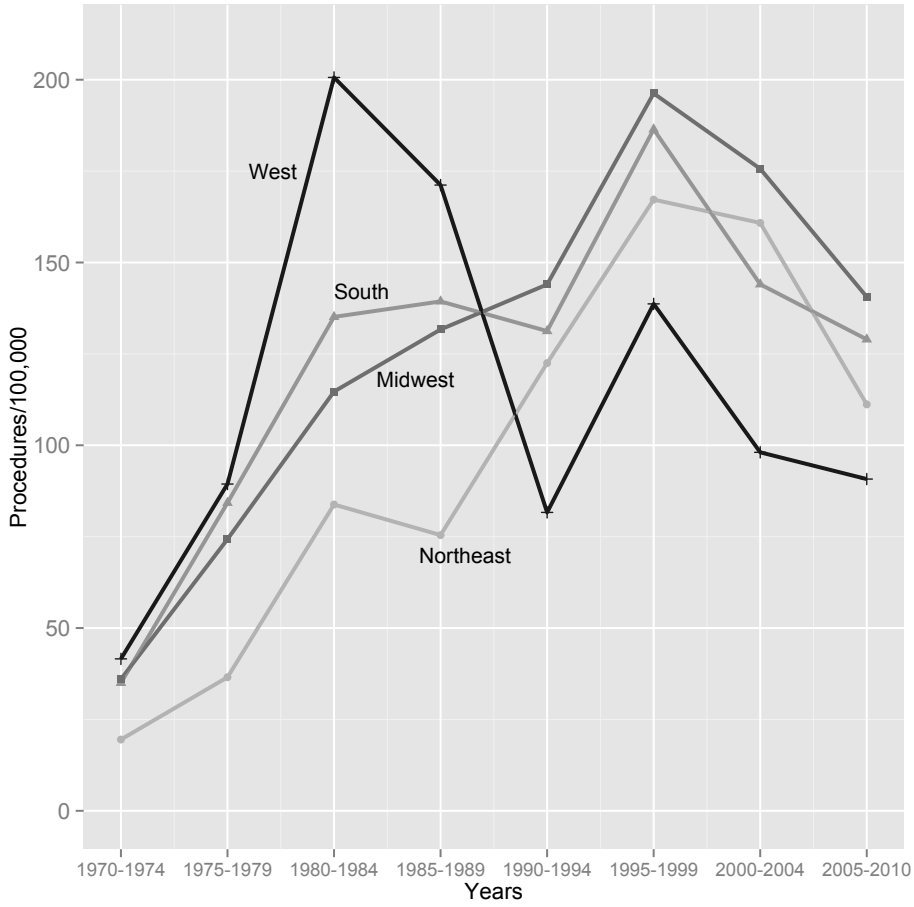

Figure 6: CEA and CAS discharge rates by region in patients aged 50 years or older per 100,000 population over time.

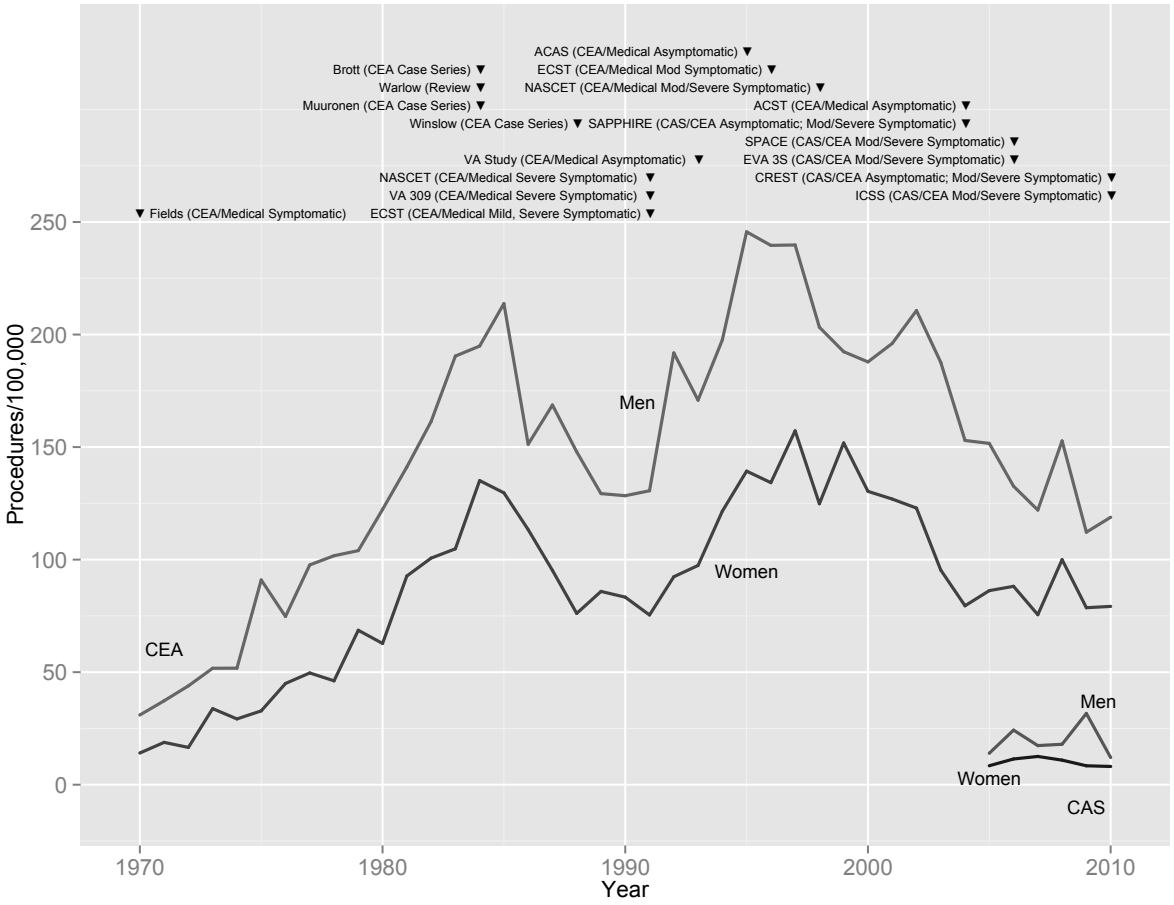

Figure 7: CEA and CAS discharge rates in men and women aged 50 years or older per 100,000 population over time. Pivotal trials and highly publicized CEA case series and reviews shown according to publication dates indicated by triangles.

3.4 Discussion

Medical technologies are frequently adopted in the face of uncertain evidence. Over time, benefits and harms are defined determining ineffective or harmful interventions that should be abandoned or use modified. What is unusual in the case of CEA were two large shifts in use since its introduction—poignant because of the stark tradeoffs involved (stroke and death for potential stroke-free survival) and the fine line between benefit and harm. What course CAS use will follow is unclear, but data the person, place, and time of CEA use may provide some clues.

The characteristics of patients undergoing CEA or CAS were not surprising. Procedures were more often performed in men than women consistent with men being at higher risk for atherosclerotic vascular diseases. [1] Women undergoing procedures were slightly older, likely due to later onset of cardiovascular disease. [1] The mean patient age increased over the 40 years by more than five years—possibly an accompaniment of both population aging and surgeon expertise intervening in the elderly. The profile of discharge diagnoses was consistent with patients at risk for cardiovascular disease. A stroke diagnosis was recorded in almost all discharges. This may be at odds with recent large registries indicating that roughly half of CEA and CAS procedures are performed in asymptomatic patients (i.e., no prior stroke or TIA). [49] The distribution of reported race is somewhat perplexing given such a small proportion of blacks. However, this may be attributable to underreporting. [17]

What underlies regional differences in rates is unclear. Over the 41 years, there was a 34% relative difference comparing the region with the highest (Midwest) with the lowest (Northeast). More notable were the regional differences in secular changes prior to 1990 with a substantial

increase and then decline in the West. Although not so pronounced as in these data, a generally similar difference in trends was noted between California and New York from 1983 through 1990. [7] Although we can only hypothesize underlying reasons, the absence of robust randomized controlled trial results before 1991 was likely consequential. Prior to their completion, clinical decision making was influenced by other factors. Subsequently, secular changes were remarkably similar, albeit with a lower absolute rate in the West. Although the level of geographic detail does not allow further scrutinizing patterns, the results highlight the sometimes fickle nature of the factors influencing use of medical interventions.

The inconstant secular trends over more than 40 survey years are striking. However, detailed patient, provider, and facility data are not available in the NHDS to examine possible associations with trends. Using California, New York, and Ontario discharge data, Tu et al. noted the first decline evident here in the late 1980s. [7] The fall was attributed to a series of publications highlighting both poor outcomes [33–36] and the absence of data from randomized controlled trials enrolling patients similar to those undergoing CEA. [28] The subsequent nadir coincided with early results from three clinical trials showing benefit but only in patients with most severe stenosis accompanied by neurologic symptoms. [27, 37, 38] Despite being limited to a small patient subgroup, those results appeared to revive enthusiasm, which was later dampened with reporting of results for symptomatic patients with moderate stenosis [40, 41] along with asymptomatic patients. [39] It then was apparent that potential benefit was confined to well-defined patient subgroups. Symptomatic patients with low-grade stenosis were harmed. In asymptomatic patients the net clinical benefit was modest and required accepting a risk of procedural stroke and death. Currently, the

decline that began in the late 1990s persists, reaching rates close to those observed some 30 years ago. Although the introduction of CAS was met with considerable enthusiasm following publication of SAPPHIRE, [43] it appeared short-lived when three [44–46] of four [44–47] subsequent trials comparing CAS to CEA failed to show similar outcomes.

Although the NHDS allows examining the use of CEA and CAS over many years, its limitations are important to note. First, it is a probability sample and provides only estimates for the number of procedures performed. Sampling variability becomes more apparent when discharges in any subgroup are few in number. Yet here, the interest being primarily descriptive and examining trends over time, sampling variability should not affect conclusions. Second, it is not possible to evaluate secular trends in mortality because in-hospital deaths were too few to provide reliable estimates. Third, discharge diagnoses imprecisely portray clinical conditions and are accompanied by no indication of severity. The most serious limitation in this regard is being unable to discern which patients were symptomatic prior to CEA or CAS being performed. Fourth, potential racial disparities cannot be examined due to underreporting of race. [17] Finally, it is impossible to identify patients undergoing multiple procedures, but that number is likely very small. Still, these data are robust in many respects and suited to the purposes here; they provide a sample representative of the US population obtained over many years using standardized data collection procedures.

In summary, few if any medical interventions have witnessed such wide swings in use. This portrayal of carotid artery procedures performed over 40 years is likely to be seen as intriguing by some but sobering by others. The large regional differences prior to robust generalizable randomized controlled trial results suggests CEA use influenced by factors other than convincing evidence.

In the end, if there is some “appropriate” rate, it is best informed by the many clinical trials. Implied in Figure 6 is that over the past 4 decades many individuals did not experience benefit, while others likely harmed.

CHAPTER 4

MEDICAL TREATMENT FOR ASYMPTOMATIC CAROTID STENOSIS—RE-EXAMINING THE EVIDENCE

4.1 Introduction

Improved medical therapies have decreased the risk of ischemic stroke. [50, 51] For patients with asymptomatic carotid artery disease, the magnitude of decrease is of considerable interest because alternatives to medical care—carotid endarterectomy (CEA) [39, 42] or angioplasty and stenting (CAS) [43, 47]—are accompanied by procedural risks of stroke and death. The landmark trials [39, 42, 48] comparing CEA with medical therapy were completed during a period of improving medical therapies and no trials have compared CAS with medical care. Some have concluded that among patients with asymptomatic carotid artery disease, the benefit from medical therapy now surpasses CEA. [29, 52–54] This perspective is reflected in guidelines that express uncertainty concerning the benefit of CEA (or CAS) in asymptomatic patients. [55]

Lacking contemporary trial data, comparing the benefits and harms of CEA with current medical therapy relies on two indirect arguments. The first is that population-based studies show decreasing stroke incidence over recent decades. [51] Although a small minority of strokes is attributed to asymptomatic carotid artery disease (2% to 7%), [51] it is reasonable to believe that declines have occurred for all stroke etiologies. The second argument relies on comparing ipsilat-

eral stroke incidence in patients with asymptomatic carotid artery disease in recent cohort studies with the medically treated arms from older CEA trials.

Evidence for declining ipsilateral stroke incidence has been highlighted in systematic reviews, [52, 56] as well as less systematic discussions. [29, 57] Still, the most widely cited review [52] (approximately seven monthly citations since publication) included no appraisal of possible biases in observational studies reporting ipsilateral stroke incidence. A more recent publication did assess potential biases, but applied a tool [58] most applicable to randomized controlled trials—other approaches are arguably better suited to studies of incidence. [59]

The risk of ipsilateral stroke with medical therapy is a critical factor determining whether CEA or CAS offer benefit. Absent a direct comparison of either procedure with contemporary medical care in a randomized trial, an unbiased and generalizable estimate of ipsilateral stroke incidence in medically treated patients is required to perform an indirect comparison. There are accordingly two purposes here: 1) to systematically appraise potential internal and external biases among studies reporting ipsilateral stroke incidence published following landmark trials comparing CEA with medical therapy, and 2) pool estimates from all studies and those least biased. The goal was to obtain an estimate for a subsequent indirect comparison of CEA outcomes with contemporary medical care in asymptomatic patients (Chapter 5).

4.2 Methods

4.2.1 Identifying and Selecting Studies

Potential studies were identified by searching the Medline® database, bibliographies of reviews, and other publications. [29, 52, 56, 57] Selective searches of Science Citation Index Ex-

panded® were also performed to identify any reports more recent than those included in prior reviews. The focus was on the impact of medical care following completion of CEA trials. We included studies reporting ipsilateral stroke incidence in patients with an asymptomatic stenosis exceeding 50% published after 2004 or following ACST, the most recent randomized trial. [42] If more than one published result was identified from a specific cohort, data from the most recent were included.

4.2.2 Data Abstraction

Relevant data from selected studies were abstracted into REDCap [60] and subsequently verified. If information was not reported in a publication, any prior or contemporary reports from the same study were sought. Annual ipsilateral stroke rates were abstracted if reported, or calculated according to parameters reported in the following order of preference: 1) using reported person-years, 2) person-years calculated from Kaplan-Meier figures, 3) person-years calculated as the product of mean or median follow-up and number of subjects, or 4) from Kaplan-Meier or equivalent (e.g., life-table) analysis. When Kaplan-Meier estimates were used without an estimate of person-years, annual rates were approximated using the relationship between cumulative and person-time incidences. For comparison, we calculated ipsilateral stroke rates from the Asymptomatic Carotid Atherosclerosis Study (ACAS) [39] and ACST [42] during the post-procedural periods of the medically treated and CEA arms. Post-procedural ipsilateral stroke rates in asymptomatic patients undergoing CEA and CAS in CREST were similarly calculated. [47]

4.2.3 Bias Assessment

The bias assessment approach outlined by Thompson et al. [61] was adapted for use. First, we outlined the characteristics of an observational study that would validly assess stroke rates (minimal internal bias) and be generalizable (minimal external bias). Those characteristics were used to identify potential internal and external biases as a guide for evaluating included studies. The target population was defined as individuals with asymptomatic carotid stenosis greater than 60% that could be considered candidates for CEA or CAS (an inclusion criteria in clinical trials). Criteria used to assess similarity of the sample and target population included: (1) degree of stenosis of enrolled patients, (2) exclusions because a surgeon or physician was unwilling to manage medically, and (3) other characteristics that would make the population dissimilar. Internal biases assessed included: (1) performance bias (antiplatelet and cholesterol lowering agents prescribed (less than 70% of patients at any reported point was used as a cutoff and derived from use in CREST); dates of enrollment specified; consecutive patients enrolled, (2) attrition bias (losses to follow-up reported and minimal, i.e., less than 10%; if unreported we assumed a small potential risk for bias), (3) detection bias (ideal was regularly scheduled visits with study investigators skilled at neurological evaluation), and (4) other biases (included analytic issues such as potential influence of competing risks [62] and overall mortality rate). Potential external and internal biases were rated on a 1 to 4 scale corresponding to negligible, small, medium, and large [61] by consensus of two reviewers. We did not elicit potential magnitude of biases, [61] but used the appraisal to facilitate interpretation of patterns and likely impact on estimated ipsilateral stroke rates.

Although selective reporting for incidence studies would not be anticipated—i.e., issues of significance or even effect sizes would play little role is selective publication—there was no suggestion in the funnel plot or by Egger test (p=0.62).

4.2.4 Pooled Stroke Rates

Ipsilateral stroke rates from identified studies were combined in a random-effects meta-analytic model for binomial data. Study results were also pooled in a Bayesian model using non-informative priors for the mean and between study variance. The Gelman-Rubin statistic, Brooks-Gelman-Rubin plot, together with autocorrelation and history plots were examined to assess convergence. Three chains and 50,000 iterations were used discarding the initial 10,000 samples to obtain estimates. Posterior densities were examined to obtain rates to assess certainty from individual studies. Finally, a cumulative analysis was performed to assess the potential impact of assessed biases, adding studies in order of increasing combined internal and external biases. Models were fitted using R [18, 63] and JAGS. [64, 65]

4.3 Results

Nine studies published after 2004 were identified that reported ipsilateral stroke rates in patients with asymptomatic carotid stenosis (Figure 8). [57, 66–73] The final year of study enrollment ranged from 2002 through 2011. Sample sizes varied from 62 to 1121 and person-years of follow-up from 301 to 4484. Although ACAS, ACST, and CREST enrolled asymptomatic patients with 60% to 99% stenosis, only one [66] of the nine identified studies included patients with a similar range of stenosis. Six studies included patients with 50% to 59% stenosis [57, 68–71] and two [72, 73] only patients with greater than 70%. Use of lipid lowering agents was reported in seven studies—

taken by 60% to 85% of patients. For comparison, in CREST lipid lower agents were used in just over 75% of participants (Figure 8). [74]

There was incomplete reporting of whether patients were excluded because a surgeon or physician was unwilling to manage medically. An exclusion was noted in three publications, [67, 72,73] but not mentioned in the remainder. Some samples clearly differed from the landmark trials in other patient characteristics. One enrolled only patients with manifestations of cerebrovascular disease (TIA or stroke), [57] and another excluded patients with cerebrovascular disease. [67] Mean patient ages ranged from 65.2 to 75.2 years (median 71.1); mean ages of patients in ACAS, ACST, and asymptomatic patients in CREST were 67, 68, and 69.2 years respectively.

Outcomes were ascertained from scheduled visits in most studies [57, 66, 68, 70–73] while two utilized follow-up of patient-completed questionnaires. [67, 69] Losses to follow-up, when reported or inferred from results, appeared low in six studies, [57, 66, 68–71] but were not clearly stated in four. [57, 67, 69, 73]

Other potential biases considered important included correlated events, competing risks, study results inconsistent with prior data, and extremely low or high overall mortality. Abbott et al. included two diseased arteries in 14.4% of patients without noting how any correlated events were taken into account. [66] Marquardt et al. [57] reported the lowest ipsilateral stroke rate, but the impact of competing risks [62] from high mortality (greater than 2-fold that of any trial) and contralateral stroke (exceeding 8% annually) was not considered. In a prior publication from the ACRS cohort, [75] investigators described more severe stenosis accompanied by greater stroke

risk, a finding generally contrary to accepted wisdom. Lastly, the overall mortality rate in Ballotta et al. [71] was approximately half that in the post-procedural period of any trial.

Next, we pooled event rates, overall and cumulatively adding studies in order of overall combined external and internal biases, keeping in mind that a single study enrolled patients with a range of stenoses similar to trials (Figure 9 and Figure 10). In the Bayesian analysis, the pooled annual rate from all studies was 0.98% (95% CrI: 0.54 to 1.57); excluding the three most biased studies [57, 67, 69] 1.36% (95% CrI: 0.88 to 1.83).

Finally, we examined consistency of ipsilateral stroke rates with landmark trial data. Compared with medical care, the relative risk of ipsilateral stroke in the post-procedural period after CEA was 0.28 in ACAS and 0.26 in ACST. Of note the relative risks are effectively identical despite the almost 40% lower annual ipsilateral stroke rate in the medical arm of ACST attributed to improved medical care (2.2% versus 1.4%). The similar relative risks are consistent with a causal effect of CEA [76, 77] invariant to underlying risk (ipsilateral stroke rate). Although CREST did not include a medically treated arm, the relative risk reduction in ACAS and ACST would project an annual ipsilateral stroke rate of approximately 1.4% or remarkably consistent with the 1.36% pooled ipsilateral stroke rate obtained excluding the most biased studies.

				Sample Characteristics								
		Bar data range		*50%–99%*			*0–100%*					
							Lipid Lowering					
Name	Year	Author	Centers	Stenosis 50% 99%	Enrollment		Start	End	Sample Size	Mean Age	Mean or Median FU	Person Years
Cohorts												
ASED	2005	Abbott	2		05/1996	04/2002		74.8	202	74	2.8	566
ACRS	2010	Nicolaides	78		01/1998	12/2002	24.8	85	1121	70	4.0	4484
ACES	2010	Markus	26		07/1999	08/2007	65.8	72.1	482	71.5	1.8	852
—	2009	Zhang	1		NR	NR			62	65.5	1.0	56
—	2005	Dick	1		01/1997	12/2002	61.5		525	73.5	3.2	1762
—	2007	Ballotta	1		01/1995	12/2004			98	71	4.1	496
PRIMARI	2006	Takaya	3		NR	NR	64		154	71.1	3.2	490
OXVASC	2010	Marquardt	—		04/2002	03/2009	85.9	81	101	75.2	3	301
SMART	2013	den Hartog	1		09/1996	01/2011	59.4	60	293	65.2	6.3	1846
Trials												
ACAS/Medical	1995				12/1987	12/1993			834	67	2.7	2259
ACST/Medical	2004				04/1993	07/2003	17	58	1560	68	3.4	5110
ACAS/CEA	1995				12/1987	12/1993			825	67	2.7	2259
ACST/CEA	2004				04/1993	07/2003	17	58	1560	68	3.4	5068
CREST/CEA	2010				12/2000	07/2008	75.2		587	69.2	2.5	1366
CREST/CAS	2010				12/2000	07/2008	75.1		594	68.9	2.5	1394

Figure 8: Characteristics of included studies.

										Ipsilateral Stroke Rates			Validity							
		Bar data range	*50%-99%*	*0%–12%*						*0%–2.5%*							Large 4; Medium 3; Small 2; Negligible 1				
Name	Author Year		Stenosis 50% 99%	Any Stroke	CVD Mort	All-cause	CEA	Ipsilateral TIA		Ipsilateral Strokes and Rate/100		Pooled Cumulative (95% CI)	Selection/External	Performance	Attrition	Detection	Other	Selection	Perform	Attrition	Detect	Other
Cohorts																						
ASED	Abbott 2005			2.3		6.6	1.8			6	1.06	1.06 (0.38-2.07)						1	1	1	1	2
ACRS	Nicolaides 2010				3.5	4.77	2.8			59	1.32	1.29 (0.99-1.61)						3	2	1	1	1
ACES	Markus 2010			2.12	2.2		4.0	2.59		10	1.17	1.27 (1.00-1.57)						3	2	1	1	1
—	Zhang 2009				3.6			5.36		1	1.79	1.27 (1.00-1.57)						4	3	1	1	1
—	Dick 2005			2.5	6.4	7.9	5			35	1.99	1.43 (1.13-1.77)						4	2	2	1	1
—	Ballotta 2007					1.5		3.02		3	0.60	1.32 (0.97-1.73)						4	3	1	1	1
PRIMARI	Takaya 2006									6	1.22	1.33 (1.02-1.67)						4	2	2	2	1
OXVASC	Marquardt 2010			8.66	7.7	9.7	0.33	1.78		1	0.34	1.21 (0.88-1.60)						4	1	2	1	3
SMART	den Hartog 2013			0.43		6.4	2.1			5	0.27	0.98 (0.57-1.49)						4	2	2	2	1
Trials																						
ACAS/Medical				3.7	2.7	3.7	2.0			49	2.2											
ACST/Medical				2.3	3.3	4.1	3.9			72	1.4											
ACAS/CEA				1.8	2.0	3.7	—			14	0.62											
ACST/CEA				1.9	3.1	4.9	—			19	0.37											
CREST/CEA						3.1	—			5	0.37											
CREST/CAS						3.1	—			9	0.65											

Figure 9: Study outcomes, assessed potential biases, and meta-analytic results.

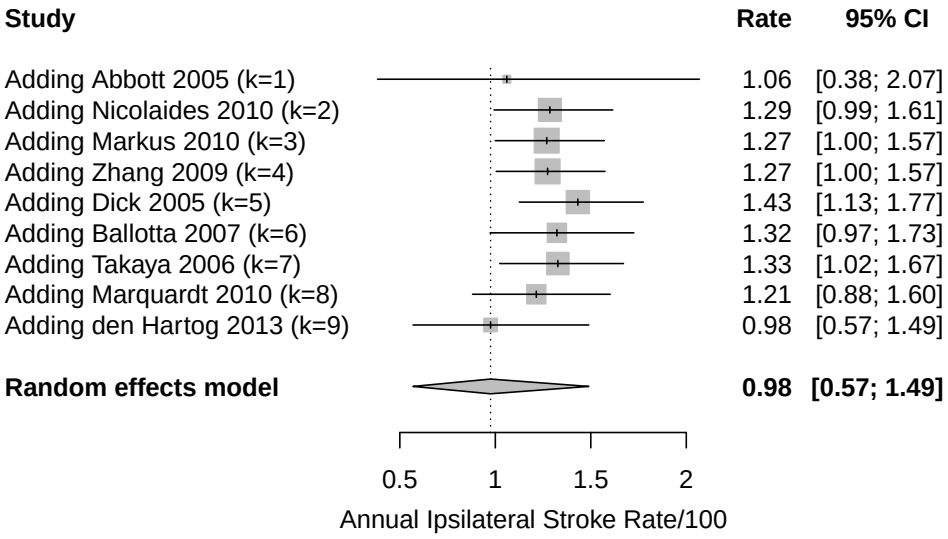

Figure 10: Forest plot of cumulative meta-analysis with studies adding according to increasing potential bias. Overall pooled rate from the Bayesian model was 0.98% (95% CrI: 0.54–1.57).

4.4 Discussion

The estimated prevalence of asymptomatic carotid stenosis that might be appropriate for CEA varies. De Weerd et al. concluded that approximately 12.5% of men and 6.9% of women over age 70 years have moderate carotid stenosis (greater than 50%). [6] Others have suggested a prevalence considerably lower—e.g., stenosis greater than 60% affecting approximately 1% of individuals aged 65 years or older. [78] Regardless of the true prevalence, many asymptomatic individuals are potential candidates for CEA or CAS. Yet since completion of trials establishing that benefit can be conferred following CEA in asymptomatic patients, medical therapy has improved and stroke rates have declined. How much stroke rates have declined in patients with asymptomatic carotid stenosis is a critical factor influencing decisions by patients and providers. Some have concluded the magnitude of decline so substantial—to annual ipsilateral stroke rates of 0.5%—that neither CEA nor CAS are appropriate. [54] We found ipsilateral stroke rates have declined since completion of landmark trials, but that for patients who might be considered for CEA or CAS, the least biased evidence is consistent with ipsilateral stroke rates somewhat greater than 1%.

A systematic review of evidence requires assessing potential internal and external study biases. While assessing bias in observational studies can be difficult, Thompson et al. [61] provide a method that is arguably coherent and fit for purpose here. Adopting that approach, we identified relevant internal and external biases then evaluated their likely presence in included studies. The assessed magnitude of external bias was large in all but two studies and important internal biases were present in all but one study. Accordingly, the validity of estimated ipsilateral stroke rates and

applicability to patients who could be considered for CEA or CAS must be carefully considered. Moreover, rates were generally higher in less biased studies.

At the same time, there are limitations here to consider. The review of evidence and potential biases does not allow determining some precise bounds for an unbiased ipsilateral stroke rate; we did not attempt to quantify and apply a bias correction to the pooled estimate. Arguably the direction of the bias in all studies was to rates lower than some true value. Next, while other reviews have examined secular trends using study-level data we avoided doing so for specific reasons. Foremost, is the view that potential bias must be considered first when interpreting results. Performing a meta-regression in a small sample taking into account time and bias would be problematic at best. Equally important is that event rates were low and patient-level data concerning medical therapies and dates of event occurrences were lacking. Using a mean or median of study enrollment (or even follow-up) for analysis is problematic owing to measurement error in the independent variable (time). More importantly, a large decline in ipsilateral stroke incidence exceeding 60% (e.g., from 1.4% to 0.5% annually) since the completion of ACST is not highly plausible; secular declines in overall stroke rates have not approached that magnitude. [52, 54, 79]

Regardless of these limitations (and conclusions of others), an ipsilateral stroke rate somewhat greater than 1% is consistent with the post-procedure relative risk reduction seen in ACST, [42] ACAS, [39] and even the earlier Veterans Affairs Cooperative Study Group trial [48]—trials also documenting secular declines in ipsilateral stroke rates in medically treated patients. It is difficult to posit that between ACST and CREST somehow the relative risk reduction accompanying CEA

has changed so dramatically to account for an ipsilateral stroke rate in medically treated patients less than 1%.

In conclusion, secular declines in stroke incidence have been well documented. Similarly, the medically treated arms of landmark CEA trials enrolling patients with asymptomatic carotid artery disease show declining ipsilateral stroke incidence. How much further ipsilateral stroke rates have declined since completion of ACST in patients who might be CEA candidates requires examining observational data. Observational data are informative, but interpretation requires assessing and considering potential internal and external biases. While uncertainty remains, after considering those biases as well as consistency with the effect of CEA on reduction in ipsilateral stroke occurrence, the best estimate of ipsilateral stroke incidence with current medical care is somewhat greater than 1%.

CHAPTER 5

A SYNTHESIS OF EVIDENCE COMPARING ENDARTERECTOMY WITH MEDICAL THERAPY FOR ASYMPTOMATIC CAROTID ARTERY DISEASE

5.1 Introduction

Asymptomatic carotid stenosis affects 2% to 8% of the US population. Whether the benefit provided from carotid endarterectomy (CEA)[1] preventing stroke outweighs procedural risk of stroke and death in asymptomatic individuals is controversial. [54, 57, 80, 81] The randomized controlled trials comparing CEA with medical therapy completed patient enrollment over a decade ago. [39,42,48] Even while trials were in progress, medical therapy to prevent stroke was improving. [51,52] How CEA would compare with contemporary medical therapy if a trial were performed today is uncertain. Additionally, periprocedural complication rates (stroke and death) accompanying CEA reported in trials have decreased over time. For example, in the Asymptomatic Carotid Atherosclerosis Study (ACAS) [39] completed in 1993, 2.3% of patients died or had a stroke in the 30 days following the procedure. In CREST, [47] completed in 2008, 1.4% of asymptomatic CEA patients experienced a stroke in those 30 days with no deaths.[2] Earlier trial results may not apply to decisions in contemporary practice.

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[1]The same can be said for CAS but there are no randomized trials of CAS versus medical therapy.

[2]A similar trend has also accompanied CAS (W. Gray, in press).

The rationale for performing CEA or CAS is based on trading a risk of periprocedural stroke or death for subsequent stroke prevention. Many factors influence the tradeoff including rates of periprocedural stroke and death, stroke incidence with medical therapy, reduction in stroke risk from the procedure, and life expectancy or competing causes of death. Decisions by patients, providers, and policy makers require a less than straightforward risk-benefit calculus. Ideally, a randomized controlled trial would inform decisions, but it has neither been conducted nor is on the horizon.

Absent a randomized controlled trial, two approaches to the risk-benefit calculus can be considered. The first would be to formulate a simple conceptual or minimal model for the decision [82]—a model sufficiently intuitive and straightforward to be performed with mental arithmetic or minimal calculations. Shortcomings of the approach are evident in the face of the tradeoff complexity. The circumstances here argue that a conceptual model may fall short. Alternatively, a model for decisions can be made explicit. The purpose here is to perform the latter—synthesize evidence and combine it with a model for decisions—with a goal of examining the tradeoff if a trial had been performed comparing CEA with medical therapy in a contemporary setting.

5.2 Methods

Analyses combined a Markov cohort model and Bayesian meta-analyses for the uncertain key parameters—ipsilateral stroke rate with contemporary medical care and relative risk reduction of stroke following CEA. Meta-analytic results were incorporated into the decision model using a Monte Carlo approach (detailed further below) to capture and propagate uncertainty through the

decision model estimates. [83] Life years, QALYs, and strokes were estimated from the model for a cohort of 1000 patients over a five-year time horizon.

5.2.1 Decision Model (Markov Cohort)

Two Markov decision models were developed—one for CEA (surgical) and a second for medical care—each including five relevant states and transitions between them: asymptomatic, experiencing a TIA, minor stroke, major stroke, and death (Figure 11). Estimates were obtained from the models using one-month cycles over a five-year time horizon. All patients began in the asymptomatic state (e.g., specified as the vector [1000,0,0,0,0]). In the medical care model, outcomes were estimated through iterative multiplication with the five-by-five transition matrix. In the CEA model, a separate initial transition was included to account for periprocedural stroke and death followed by a similar iterative procedure. Results with CEA and medical care were then compared.

Uncertainty in the most important parameters, ipsilateral stroke rate with medical care and relative risk reduction with CEA, were incorporated directly into the respective transition matrices with posterior estimates obtained in the meta-analyses—both for the CEA model, and ipsilateral stroke rates in the medical care model. Outcomes from the Markov models were calculated for each posterior estimate. This provided 50,000 values from each Markov model that were used to compare outcomes following CEA with medical care. Additionally, a set a analyses were performed excluding the three most biased studies from the meta-analysis of ipsilateral stroke incidence with medical care.

The analyses were then repeated but allowing for uncertainty in other transition matrix parameters (Table VIII). Parametric distributions for these parameters were specified based on pub-

lished values. [57, 66, 72, 74, 84] Results from these analyses incorporate plausible uncertainty in all transition parameters into the Markov model estimates.

In lieu of examining convergence of the estimates from the Markov models, batch means and standard errors were calculated (samples of 263 or $\sqrt{50,000}$). [85] All errors were small. In the medical care base models yielding the following estimates and standard errors: QALYs (4568.730 [0.084]), life-years (4673.200 [0.013]), strokes (89.791 [0.062]), deaths (129.184 [0.007]); for the surgical model QALYs (4595.906 [0.060]), life-years (4683.500 [0.010]), strokes (59.211 [0.030]), and deaths (125.9101 [0.005]).

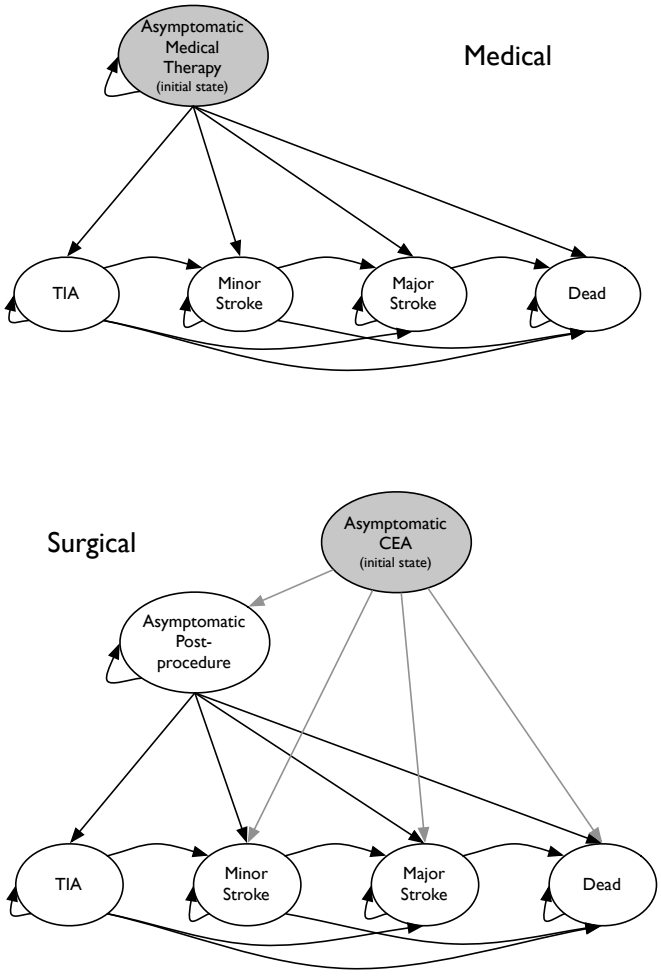

Figure 11: States and transitions included in Markov models. Five states were specified in both surgical (CEA) and medical care models, with an initial transition in the surgical model to include the occurrence of periprocedural stroke and death.

Rates (transitions) from asymptomatic to non-ipsilateral stroke and TIA, and major stroke following a minor one were obtained or estimated from studies of patients with asymptomatic carotid stenosis (Table VIII). [57, 66, 72, 74, 84] In the periprocedural period 80% of strokes were presumed minor as reported in CREST. [74] In the base case we included no periprocedural deaths

as reported in CREST. But as the upper bound of an exact confidence interval for 0 events in 587 individuals (the number in CREST) is 6/1000, we examined periprocedural mortality as high as 1.0%. After the periprocedural period, 80% of strokes were also assumed to be minor. Annual mortality following a stroke was obtained from Hill et al. [74] and for a major stroke mortality double that of a minor stroke. Utilities were assigned for minor (0.65, Rankin score ≈2) and major (0.27, Rankin score 4 to 5) stroke. [86] Because a large majority of patients remain asymptomatic, the model was simplified by applying non-stroke related causes of death only to the asymptomatic state. Following a stroke, an individual remained in that state (e.g., transitions from minor stroke to asymptomatic state were not included). Further, although the risk of stroke following a TIA is higher in the first weeks after onset, [87] any initially increased risk was not incorporated because transitions were modeled at one-month intervals. No discounting was applied for utilities given the relatively short time horizon.

To verify model specification, results were evaluated using parameters for periprocedural stroke and death as well as ipsilateral stroke rates from the most recent CEA trial (ACST). [42] With medical care the model predicted 67 ipsilateral strokes compared with 72 observed; for CEA including periprocedural death and stroke 58.7 predicted versus 59 observed.

Outcomes were examined for an average patient enrolled in CREST [47] experiencing an annual all-cause mortality of approximately 3.0% over the five-year time horizon (mean age approximately 69).

TABLE VIII: DECISION MODEL TRANSITION PARAMETER VALUES (ANNUAL), DISTRIBUTIONS, AND SOURCES.

Parameter (annual incidence)	Value	Distribution [SD]	Reference
Non-ipsilateral stroke	0.010	β [0.003]	[66, 72]
TIA	0.026	β [0.007]	[72]
Non-stroke mortality	0.025[a]	β [0.0025]	[47]
Stroke following TIA	0.021	β [0.005]	[84]
Major stroke following minor stroke	0.040	β [0.01]	estimated [57]
Mortality following minor stroke	0.058	β [0.01]	[74]
Mortality following major stroke	0.116		2×minor
Periprocedural stroke rate	0.014	*Unif*(0.01, 0.02)	[47]
Periprocedural death rate	0.0	—	[47]
Annual ipsilateral stroke rate	current review		
Post-procedure ipsilateral relative risk	current review		

[a] to yield a 3% overall mortality

5.2.2 Meta-analyses

Meta-analytic models were used to estimate ipsilateral stroke rate given contemporary medical care and relative risk reduction with CEA. For ipsilateral stroke, rates per 100 person-years were abstracted (Chapter 4) from nine identified studies and pooled as binomial outcomes. Because some studies included patients not likely eligible for CEA (i.e., exchangeable with a trial population), the impact of excluding the three studies judged most biased [57, 67, 69] was also examined. A pooled estimate of the relative risk for ipsilateral stroke following procedural intervention was obtained in a meta-analysis of three trials—Veterans Affairs Cooperative Study Group, [48] ACAS, [39] and ACST. [42] Although enrolling patients from 1983 [48] through 2003, [42] during a period of declining ipsilateral stroke rates, [66] the relative risk reductions in the trials were

remarkably similar and consistent with a causal effect. [77] Because event rates were low (4% or lower annually) odds ratios were used as they are effectively identical to relative risks and more tractably estimated. [88]

Meta-analyses were performed using a Bayesian approach incorporating uncertainty directly into decision model estimates from the two key parameters—ipsilateral stroke rate and relative risk reduction of stroke following CEA. Hierarchical random effects models were specified using binomial likelihoods with non-informative priors for the mean and between study variance. With a specified likelihood and prior distribution, a Bayesian model is fitted by iteratively sampling from the posterior distributions after supplying initial starting values (two or more sets of starting values are specified each defining a distinct chain that iterated). Sampling for each chain is repeated until convergence of the posterior estimates is obtained. Samples before convergence are discarded ("burn in") and the model is then allowed to iterate obtaining posterior values then used for estimation. Adequacy of convergence for the specified chains is evaluated with graphical and statistical approaches. Here, model convergence was assessed by the Gelman-Rubin statistic, Brooks-Gelman-Rubin plot, autocorrelation plots, mixing in trace plots, and equality of means. [89,90] Three chains and 70,000 iterations were used discarding a burn-in of 20,000 samples. Models were fitted using JAGS [64] using R2Jags. [65]

Annotated syntax for the two meta-analytic models (BUGS language) is shown below:

```
################################## Stroke Rates ###################################
# Likelihood
for( i in 1 : k ) {                    # k studies
rc[i] ~ dbin(pc[i], nc[i])             # binomial likelihood
logit(pc[i]) <- mu[i]                  # logit transformation to obtain rates
mu[i] ~ dt(d, tau, 10)                 # random effect as a 10 df t-distribution
rate[i] <- exp(mu[i])}                 # rates for each study, shruken

# Priors
d ~ dnorm(0.0,1.0E-6)                  # random effect
tau ~ dgamma(0.001,0.001)              # between study precision (1/variance)

# Estimates
sigma <- 1 / sqrt(tau)                 # between study variance; BUGS uses precision parameterization
mu[k+1] <- d                           # pooled log rate
rate[k+1] <- exp(mu[k+1])              # pooled rate

################################### Trials ########################################
# Likelihood
for( i in 1 : trk ) {                  # trk trials
trrc[i] ~ dbin(trpc[i], trnc[i])       # control
trrt[i] ~ dbin(trpt[i], trnt[i])       # treatment
logit(trpc[i]) <- trmu[i]
logit(trpt[i]) <- trmu[i] + delta[i]   # delta is log(odds) treatment effect
trmu[i] ~ dnorm(0.0,1.0E-6)            # non-informative prior
delta[i] ~ dt(trd, trtau, 10)          # random effect as a 10 df t-distribution
delta.or[i] <- exp(delta[i])}          # odds ratio for each trial, shruken

# Priors
trd ~ dnorm(0.0,1.0E-6)                # random effect
trtau ~ dgamma(0.001,0.001)            # between study precision (1/variance)

# Estimates
sigmatr <- 1 / sqrt(trtau)             # between study variance; BUGS uses precision parameterization
or <- exp(trd)                         # odds ratio
```

5.2.3 Incorporating Meta-Analytic Results into the Markov Model

The general approach for evidence synthesis adopted was first outlined by Eddy [91] and elaborated by Ades et al. [83] using contemporary Bayesian methods. Posterior samples from the meta-analyses were incorporated into the Markov model using a Monte Carlo approach. The Markov model was evaluated for each posterior value (n=50,000) that were then used to obtain medians and quantiles (2.5%, 97.5%) for life-years, strokes, QALYs, and mortality. The probability CEA differed from medical therapy in expected QALYs was estimated as the proportion of samples

favoring CEA. The approach is outlined graphically for medically treated patients in Figure 12. Finally, model results were obtained allowing only for uncertainty in meta-analytic results and the incorporating the parametric distributions for other parameters in Table VIII. Analyses were performed using R [18] and complete code shown in Appendix C.

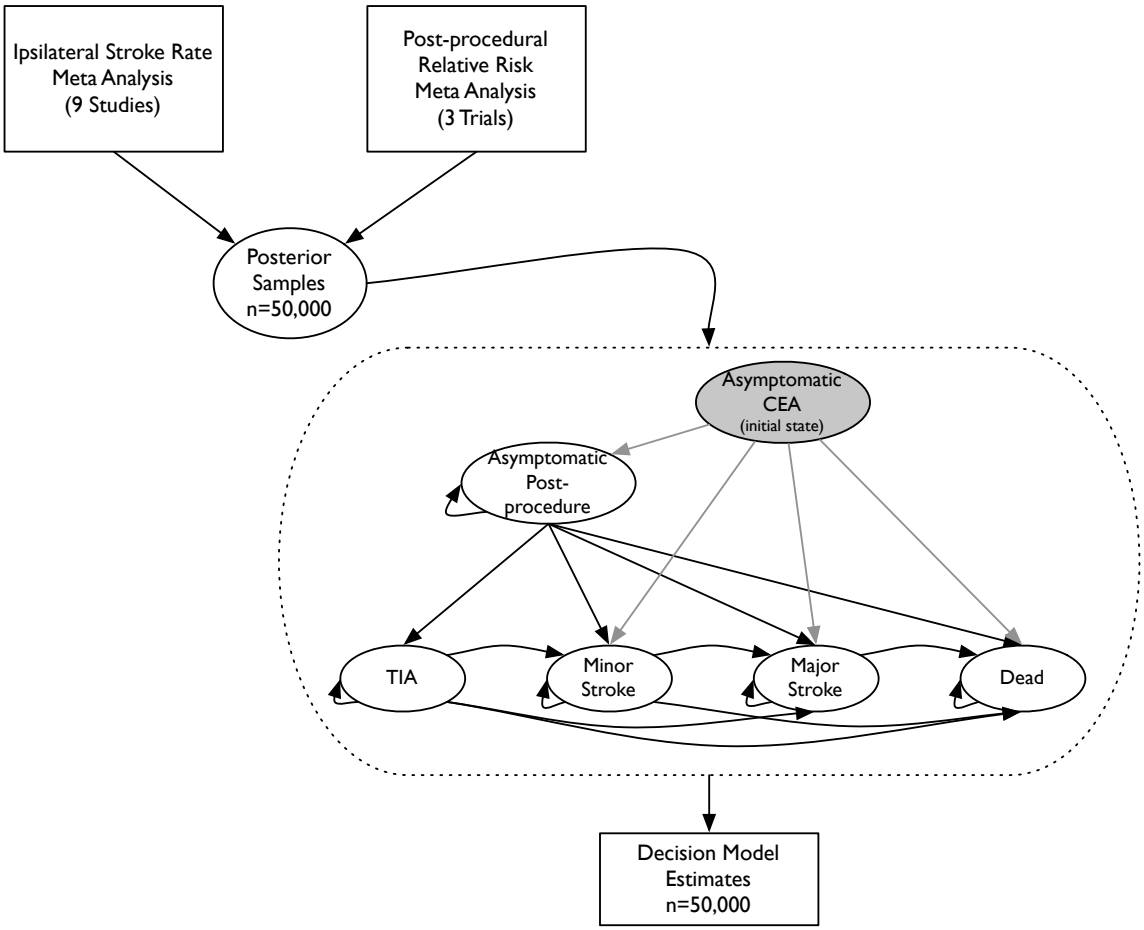

Figure 12: Graphical depiction of combining meta-analyses and Markov Cohort Models (CEA model shown). Posterior estimates for ipsilateral stroke rate with medical care and relative risk reduction were obtained from the meta-analyses. The decision model was then run using posterior estimates (50,000 times) and distributions obtained for mortality, life-years, QALYs, and strokes.

5.3 Results

Nine cohort studies [57, 66–73] published subsequent to ACST, including a total of 10,583 person years of follow-up, reported ipsilateral stroke rates (Chapter 4). There was a range of sample similarity with a population of patients that could be considered eligible for CEA. The studies also varied in assessed potential bias for reported stroke rates with the most recently published [57, 67] judged most biased (Chapter 4). The pooled ipsilateral annual stroke rate from the nine studies was 0.98% (95% CrI 0.54 to 1.57) and excluding the three most biased studies, 1.36% (95% CrI 0.88 to 1.83). The pooled relative risk of stroke following CEA compared with medical therapy (excluding the periprocedural period) was 0.26 (95% CrI 0.15 to 0.43).

In a cohort of 1000 patients over five years, incorporating meta-analytic results into the decision model under contemporary medical care and surgical expertise in CREST, CEA was accompanied by 25.8 (95% CI: 12.2 to 43.3) fewer strokes 20.9 (95% CI: 2.3 to 44.7) more QALYs (Table IX). Although fewer deaths were expected following CEA, in the base case there were no periprocedural deaths as in CREST. Allowing for plausible distributions for all parameters (Table VIII) increased the uncertainty—most notably for QALYs (Table X). Endarterectomy was still expected to be accompanied by fewer strokes and more QALYs (probability = 0.65). Finally, when the three most biased studies of ipsilateral stroke rates were excluded from the analyses, results were somewhat more favorable following CEA—0.76 probability of more quality adjusted years (Table IX and Table X).

Periprocedural stroke and death rates for surgeons in CREST were the lowest reported in any CEA trial. For example in ACST periprocedural mortality was 1%. [42] For this reason, we evaluated model results over a range of higher periprocedural mortality and stroke rates that might

be observed in real world (non-trial) settings. Results are shown in Figure 11 and Figure 12. With small increases in periprocedural mortality and stroke the balance of expected quality adjusted life-years changes rapidly—the impact of mortality effectively twice that of stroke. When the periprocedural death rate was 0.2% there was no gain in expected quality adjusted life-years with a 1.8% ipsilateral stroke rate. For the balance of life-years, when the periprocedural mortality exceeded 0.2% medical therapy resulted in longer life expectancy with periprocedural stroke rates having only a modest impact. In contrast, owing to the substantial protective effect of CEA on stroke, periprocedural mortality and strokes had modest impact on the expected difference in strokes between CEA and medical therapy.

TABLE IX: EXPECTED MEDIAN STROKES, QALYS, LIFE YEARS, AND DEATHS FOR 1000 PATIENTS OVER FIVE YEARS. BASE CASE AND EXCLUDING THE 3 MOST BIASED STUDIES OF IPSILATERAL STROKE RATES.

	Medical (95% CI)	Surgical (95% CI)	Difference (95% CI)
Stroke			
Base Case	83.3 (66.7, 105.0)	57.0 (51.8, 66.6)	-25.8 (-43.3, -12.2)
Least Biased Studies	97.3 (79.5, 114.5)	60.5 (54.0, 70.7)	-36.3 (-51.2, -21.0)
QALY			
Base Case	4577.6 (4548.0, 4600.0)	4599.2 (4584.4, 4607.3)	20.9 (2.3, 44.7)
Least Biased Studies	4558.6 (4535.0, 4582.8)	4594.2 (4578.2, 4604.1)	34.8 (13.5, 55.6)
Life Years			
Base Case	4674.6 (4669.9, 4678.2)	4684.0 (4681.9, 4685.1)	9.3 (6.4, 13.0)
Least Biased Studies	4671.6 (4667.8, 4675.4)	4683.2 (4680.9, 4684.6)	11.5 (8.2, 14.8)
Deaths			
Base Case	128.4 (126.4, 131.0)	125.6 (125.0, 126.8)	-2.7 (-4.8, -1.1)
Least Biased Studies	130.1 (128.0, 132.1)	126.1 (125.3, 127.4)	-3.9 (-5.7, -2.1)

TABLE X: EXPECTED MEDIAN STROKES, QALYS, LIFE YEARS, AND DEATHS FOR FOR 1000 PATIENTS OVER FIVE YEARS. BASE CASE AND EXCLUDING THE 3 MOST BIASED STUDIES OF IPSILATERAL STROKE RATES. INCORPORATES UNCERTAINTY IN ALL PARAMETERS.

	Medical (95% CI)	Surgical (95% CI)	Difference (95% CI)
Stroke			
Base Case	82.9 (57.2, 116.0)	57.3 (38.4, 83.9)	-25.5 (-61.1, 9.1)
Least Biased Studies	96.5 (70.9, 127.4)	60.6 (41.2, 87.8)	-35.7 (-70.3, -1.3)
QALY			
Base Case	4578.3 (4506.1, 4643.3)	4596.9 (4528.1, 4657.5)	18.7 (-73.8, 111.6)
Least Biased Studies	4559.7 (4489.9, 4623.9)	4592.3 (4523.2, 4653.4)	32.3 (-60.3, 123.8)
Life Years			
Base Case	4675.6 (4614.9, 4729.9)	4683.9 (4625.0, 4736.5)	8.5 (-71.9, 89.0)
Least Biased Studies	4672.7 (4612.2, 4726.7)	4683.6 (4624.6, 4735.9)	10.9 (-69.5, 90.6)
Deaths			
Base Case	128.1 (107.5, 150.8)	125.6 (105.4, 148.1)	-2.4 (-33.0, 28.1)
Least Biased Studies	129.7 (109.2, 152.3)	125.9 (105.7, 148.5)	-3.6 (-34.0, 27.0)

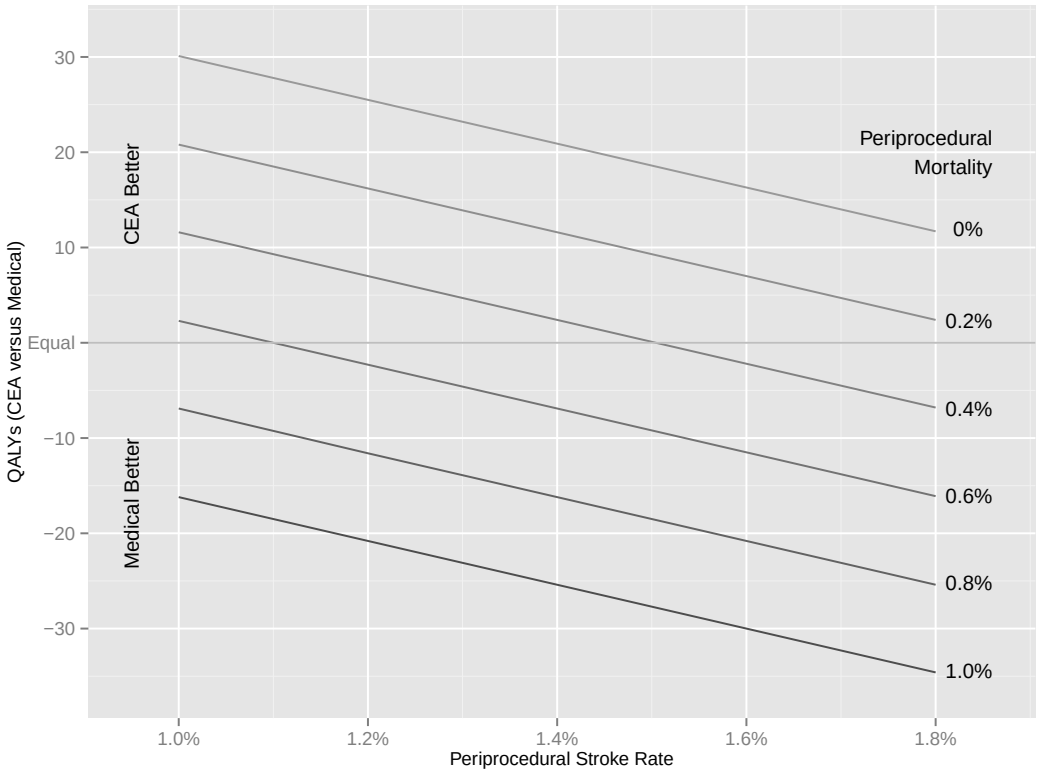

Figure 13: For 1000 patients over five years, difference in expected QALYs comparing CEA with medical care, by periprocedural death and stroke rates. With contemporary medical care, to obtain any benefit from CEA requires effectively no periprocedural deaths and exceedingly low stroke rates.

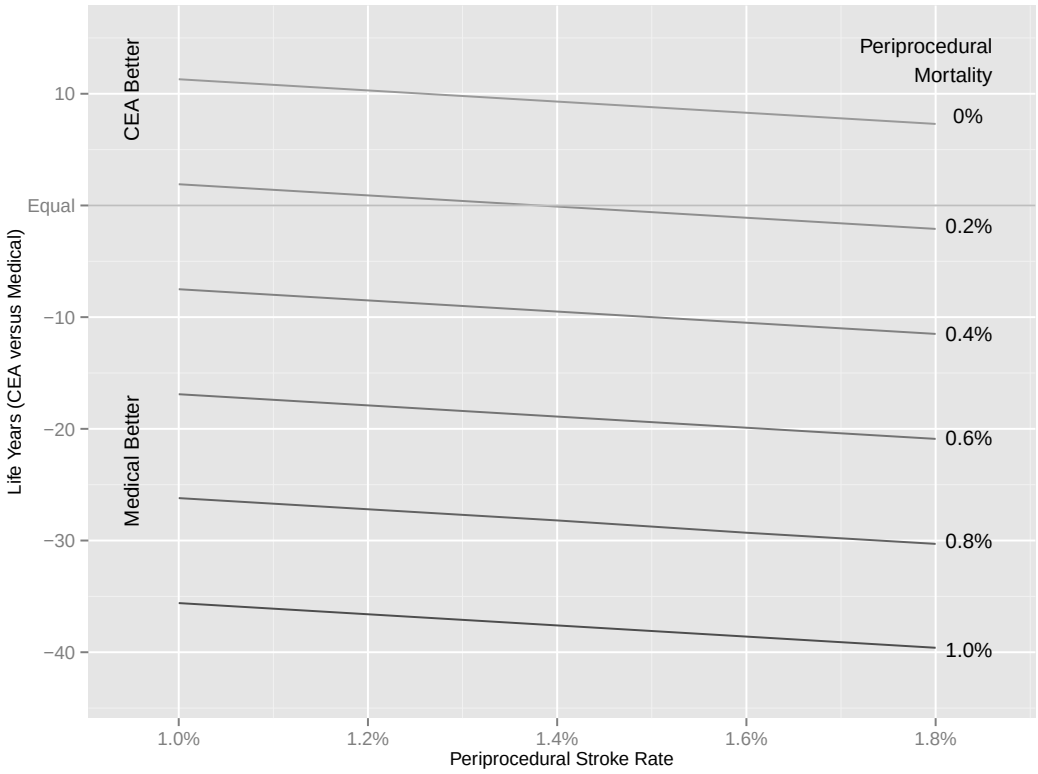

Figure 14: For 1000 patients over five years, difference in expected life years comparing CEA with medical care, by periprocedural death and stroke rates. With contemporary medical care, to obtain any mortality benefit from CEA requires no periprocedural deaths.

5.3.1 Discussion

The role of CEA in asymptomatic carotid artery disease has been surrounded by uncertainty and controversy. A fine line between benefit and harm is well recognized. These analyses indicate that with contemporary medical care that line has become even finer. Despite this, over half of patients undergoing CEA are asymptomatic [92] and the number of individuals who could be considered candidates in the populations is large.

If surgeons achieve the expertise seen in CREST with no, or almost no mortality, these results indicate that over five years CEA for asymptomatic carotid disease is accompanied by fewer strokes and more QALYs. The differences are not large but favor CEA. When periprocedural mortality increases even slightly, any expected benefit appears lost. Depending on periprocedural stroke rates, with periprocedural mortality exceeded 0.4% to 0.5% (approaching ACST or 1%), fewer quality adjusted years are expected with CEA. At the same time, under all circumstances examined there were fewer expected strokes.

Allowing for variability in model parameters other than ipsilateral stroke and stroke risk reduction increased uncertainty, but not to a degree that would alter this conclusion. What is most important is that uncertainty in ipsilateral stroke rates and relative risk reduction reflects current evidence. As anticipated, excluding the most biased studies of ipsilateral stroke rates resulted in a balance favoring CEA somewhat more, assuming low periprocedural mortality.

What emerge are intuitive conclusions from an arguably complex evidence synthesis. Although a reduction in ipsilateral stroke rates has occurred over recent decades, because CEA is highly effective reducing stroke risk, stroke occurrence will be diminished albeit less in absolute

terms. If procedural risk is at a minimum with effectively no mortality and low stroke occurrence, expected benefit exceeds harms over a five-year time horizon. An intervention for an asymptomatic condition without a severe prognosis (i.e., approximately 1% annual stroke rates) must be nearly risk free. Under those circumstances, a decision to undergo CEA could be considered reasonable or rational. [93]

At the same time these conclusions are accompanied by limitations. The first is that as noted there are no contemporary randomized controlled trial data to support or refute these results. Some simplifying assumptions for disease history and treatment were made, but the model calibrated reasonably well with ACST (favoring medical treatment slightly). Additionally, the synthesis allows uncertainty in ipsilateral stroke rates and relative risks to propagate from meta-analysis through the Markov model results. For other parameters plausible parametric distributions were included as ascertained from published results. However, these parameters concerned transitions after stroke occurrence and because stroke rates are low, error in their specifications have little impact. Additionally, these analyses were limited to an average patient enrolled in CREST and did not attempt to project some result to those with higher mortality or at higher risk for periprocedural complications. [43] Finally, we examined only a five year time horizon because it is the time frame over which most guidelines are framed and mortality in patients with vascular disease accumulates. Over longer periods in low mortality populations, results would likely appear more favorable for CEA. A recent analysis [94] supports this perspective.

We do not suggest any conclusions concerning applicability of these results to CAS for a number of reasons. First, there are no data concerning the post-procedural relative risk reduction of

stroke in comparison with medical therapy. For symptomatic carotid disease, two trials have found CEA and CAS similar in preventing stroke. [95, 96] For asymptomatic patients, in CREST there were more post-procedural ipsilateral strokes following CAS (n=9) compared with CEA (n=5). Although the number of strokes was not large, the lack of more comparative evidence argues for caution drawing any conclusions concerning CAS.

In summary, many contend—arguably persuasively and eloquently, but indirectly based on declining stroke rates—that CEA (and CAS) provide no expected benefit to asymptomatic patients. Yet an estimated 50,000 procedures for asymptomatic carotid disease are performed in the United States annually. These results suggest a somewhat more subtle risk-benefit calculus. With little or no periprocedural mortality and exceedingly low periprocedural stroke risk, a decision to undergo CEA could be considered reasonable. However, periprocedural mortality and stroke rates over bare minima would be expected accompanied by a net harm. These results provide guidance as to how minimal rates should be.

CHAPTER 6

CONCLUSIONS

Stroke is a vexing disease. It is estimated that one in six middle aged individuals in the United States will experience a stroke during their lifetime. [97] A secular decline in stroke incidence over recent decades has been a major public health success. It has been well appreciated that better risk factor control is responsible for the decline. These data support a perspective that ischemic stroke is aging-dependent and that the dependence has remained constant over time. Although further declines achieved by controlling risk factors are possible, the limits of interventions may well be the process of aging itself.

While there is no argument that controlling stroke risk factors has had a major public health impact, the same cannot be said for procedures intended to prevent stroke from carotid artery disease. Substantial variability in procedure use over time appears attributable to tensions between enthusiasm and evidence. Few would argue that symptomatic patients with significant carotid artery disease accrue benefit from CEA; many would argue that asymptomatic patients are harmed. If the many are correct, results here indicate that the potential for harm is real and the number of individuals harmed may not be small. Whether surgeons can achieve the periprocedural stroke and death rates required to obtain a net clinical benefit from CEA in asymptomatic patients is unclear. Given that surgeons in CREST were among and possibly the most skilled ever assembled, it is natural to be skeptical that in the real world patients accrue benefit.

In the end, theses stories of ischemic stroke provide insights not just into the disease and its determinants, but the benefits and potential limits of prevention in the context of aging. The stories take evidence at hand to inform decisions about procedural interventions that cannot wait for results from future clinical trials.

APPENDICES

Appendix A

DISCHARGES FOR NON-EMBOLIC ISCHEMIC STROKES IN WHITES AND BLACKS

TABLE XI: HOSPITAL DISCHARGES FOR ISCHEMIC STROKE (PER/1000 POPULATION) BY SEX, YEAR, AND AGE (NON-ATRIAL FIBRILLATION-RELATED, WHITES).

	Age								**Adjusted**	
	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+	Yes	No
Men										
1970–1974	1.2	2.0	3.2	5.1	7.5	9.0	11.0	11.3	4.4	4.1
1975–1979	1.3	2.5	4.1	6.0	7.8	10.7	10.3	12.4	5.0	4.7
1980–1984	1.3	2.6	3.5	6.3	8.2	10.6	12.4	12.2	5.1	5.0
1985–1989	1.6	2.8	4.4	7.7	10.9	12.9	15.4	16.2	6.3	6.4
1990–1994	1.4	2.7	4.3	6.9	10.3	13.7	14.2	16.8	6.1	6.4
1995–1999	1.2	2.9	4.7	8.1	10.8	15.0	17.1	13.8	6.5	6.8
2000–2004	1.2	2.5	3.8	5.6	8.6	12.1	13.5	11.2	5.2	5.2
2005–2009	1.3	2.0	3.6	6.3	7.9	10.8	15.0	13.7	5.1	5.0
Women										
1970–1974	0.7	1.3	2.0	3.2	5.0	7.4	9.9	11.5	3.9	3.4
1975–1979	0.8	1.5	2.6	4.1	5.2	6.7	9.1	11.2	4.0	3.7
1980–1984	0.7	1.5	2.6	4.0	5.4	7.0	8.6	9.7	3.9	3.8
1985–1989	1.0	1.7	2.9	4.8	8.1	11.0	14.4	13.8	5.6	5.7
1990–1994	0.8	1.6	3.4	5.1	6.9	9.6	13.6	13.0	5.2	5.5
1995–1999	1.0	2.0	3.2	5.5	8.1	9.8	12.5	13.5	5.5	5.7
2000–2004	0.9	1.8	2.4	4.1	6.5	8.2	10.5	11.7	4.5	4.5
2005–2009	0.8	1.6	2.5	4.4	6.3	9.6	10.6	13.9	4.8	4.6

Appendix A (continued)

TABLE XII: HOSPITAL DISCHARGES FOR ISCHEMIC STROKE (PER/1000 POPULATION) BY SEX, YEAR, AND AGE (NON-ATRIAL FIBRILLATION-RELATED, BLACKS).

	Age								Adjusted	
	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Yes	No
Men										
1970–1974	1.3	1.8	3.8	4.1	5.2	8.0	5.9	10.2	3.7	3.4
1975–1979	2.0	2.0	2.6	4.5	6.7	6.3	6.7	7.0	3.7	3.5
1980–1984	1.1	2.8	3.6	3.9	5.4	6.7	5.7	6.4	3.6	3.5
1985–1989	2.1	3.9	4.3	7.4	10.3	14.6	12.5	12.7	6.4	6.2
1990–1994	2.6	5.1	6.0	10.6	12.7	13.2	14.5	17.5	7.9	7.7
1995–1999	2.7	4.5	8.3	8.7	11.2	14.6	21.1	16.4	8.1	7.8
2000–2004	2.0	4.9	7.1	9.0	9.5	13.2	9.3	18.6	6.9	6.4
2005–2009	3.1	4.3	7.1	10.1	11.7	14.7	18.2	17.5	8.1	7.1
Women										
1970–1974	0.4	1.7	2.2	4.1	4.7	6.0	7.1	14.5	3.8	3.1
1975–1979	0.6	1.6	2.6	3.2	7.5	5.6	8.1	7.8	3.8	3.2
1980–1984	0.8	1.3	3.1	3.3	5.0	6.5	10.9	7.4	3.8	3.3
1985–1989	1.8	2.1	4.1	5.9	9.1	10.0	15.5	14.7	6.3	5.7
1990–1994	1.4	2.8	4.1	8.1	12.2	9.7	16.7	20.9	7.5	6.9
1995–1999	1.6	3.6	6.7	7.3	11.4	11.3	24.7	21.2	8.6	7.9
2000–2004	1.9	2.7	5.2	6.2	8.2	10.7	14.4	15.1	6.5	5.8
2005–2009	3.4	4.2	4.9	8.2	11.3	13.3	15.5	15.9	8.0	7.0

Appendix A (continued)

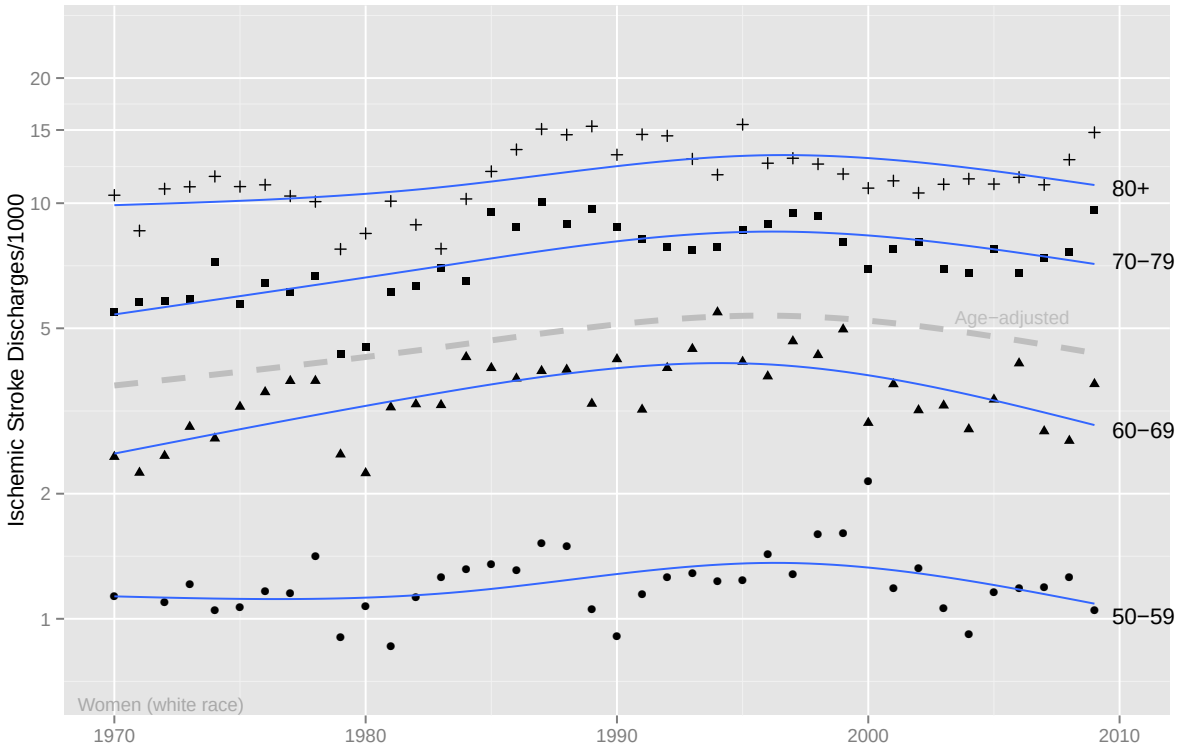

Figure 15: Estimated discharge rates for non-embolic ischemic stroke from 1970 through 2009 in the US population among white women.

Appendix A (continued)

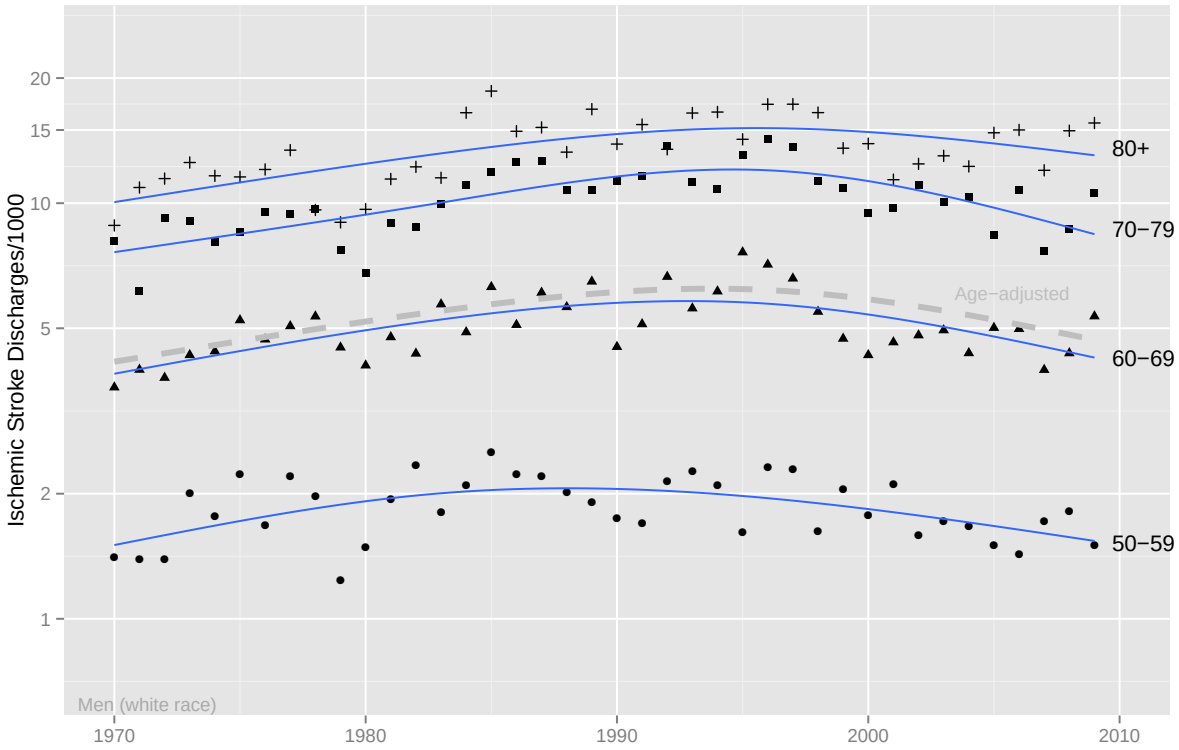

Figure 16: Estimated discharge rates for non-embolic ischemic stroke from 1970 through 2009 in the US population among white men.

Appendix A (continued)

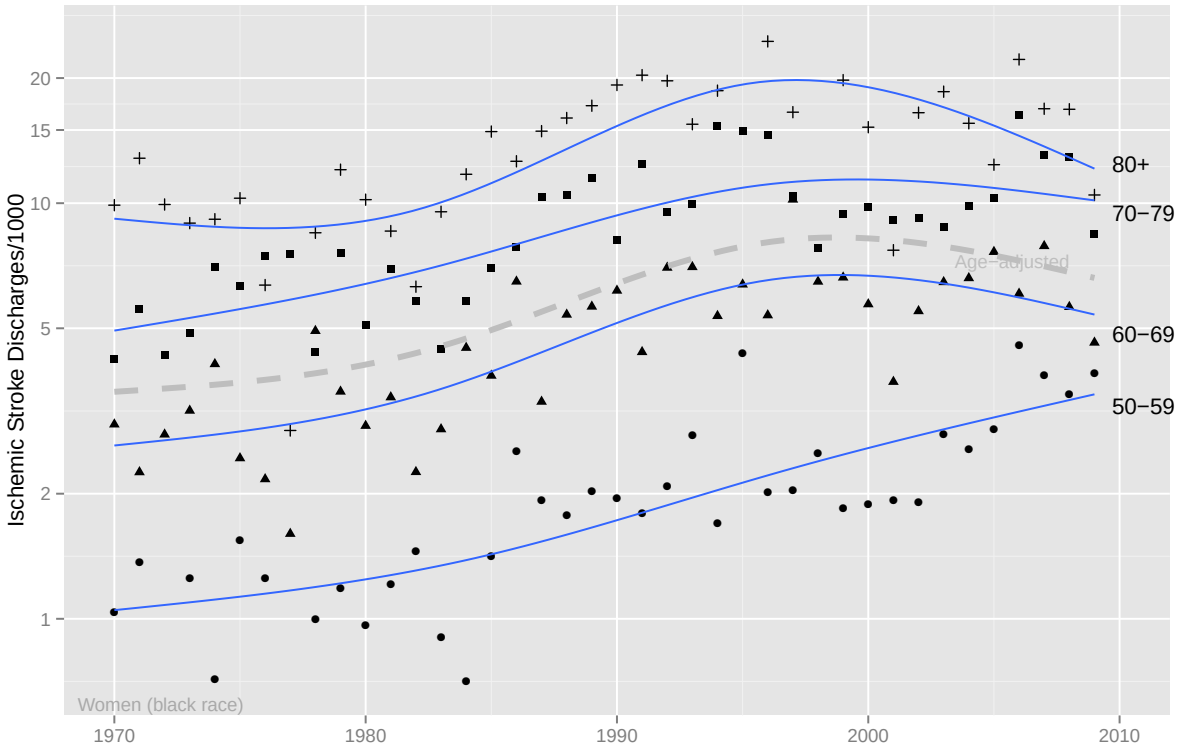

Figure 17: Estimated discharge rates for non-embolic ischemic stroke from 1970 through 2009 in the US population among black women.

Appendix A (continued)

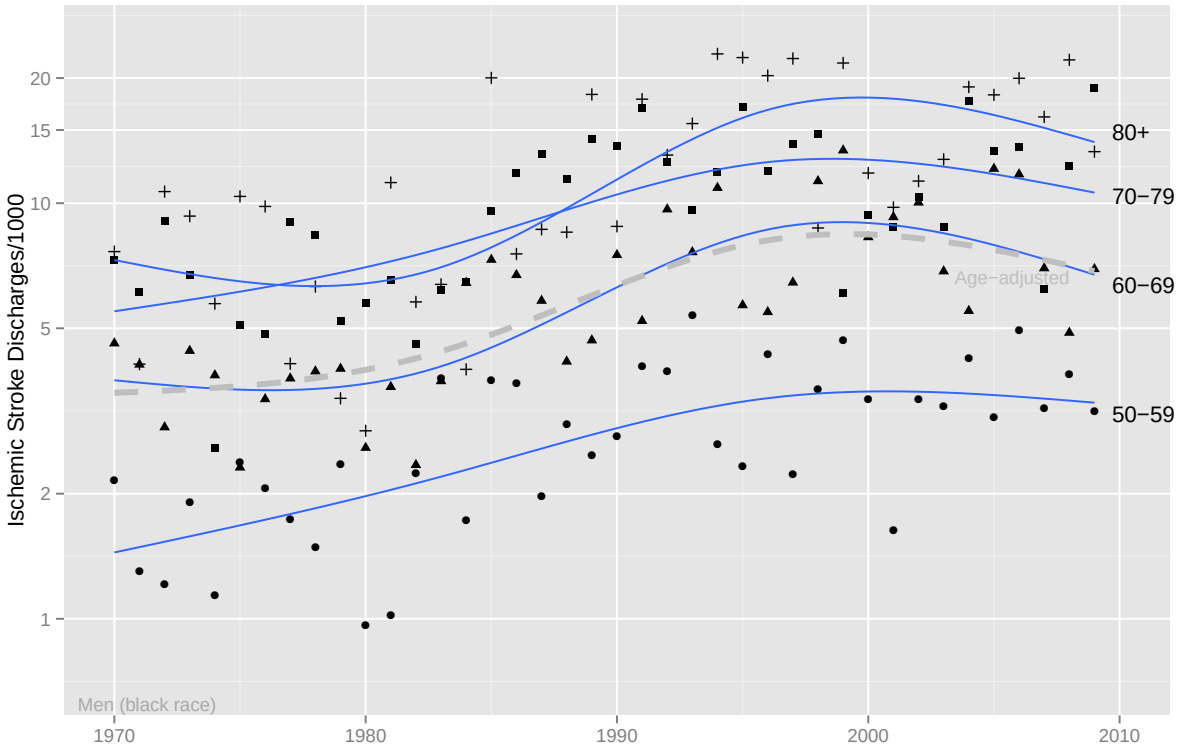

Figure 18: Estimated discharge rates for non-embolic ischemic stroke from 1970 through 2009 in the US population among black men.

Appendix A (continued)

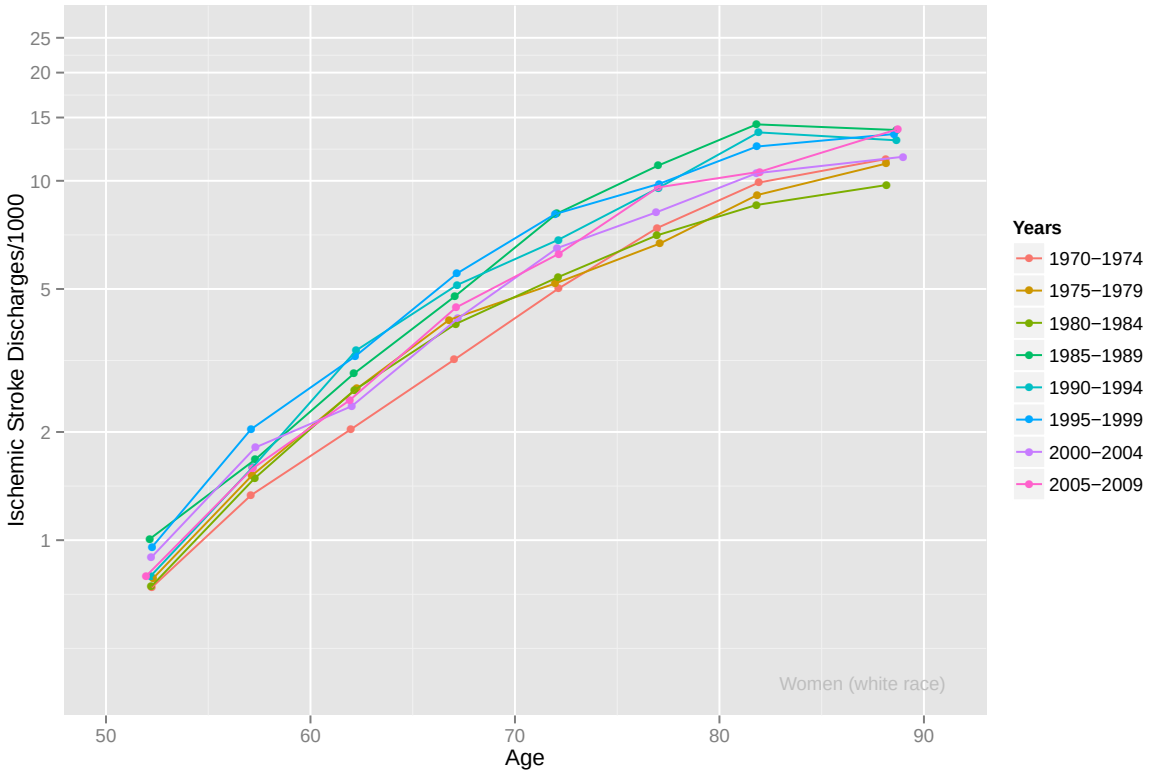

Figure 19: Pattern of discharge rates for non-embolic ischemic stroke with increasing age among white women over 40 years of the NHDS.

Appendix A (continued)

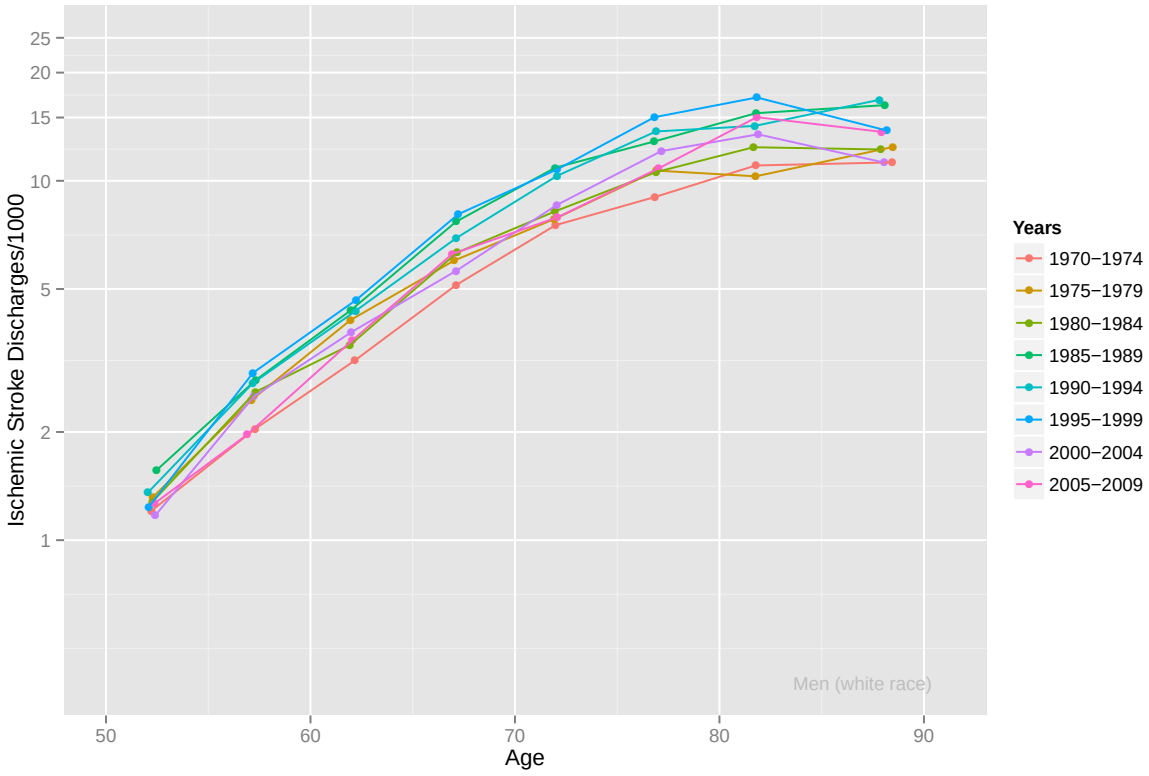

Figure 20: Pattern of discharge rates for non-embolic ischemic stroke with increasing age among white men over 40 years of the NHDS.

Appendix A (continued)

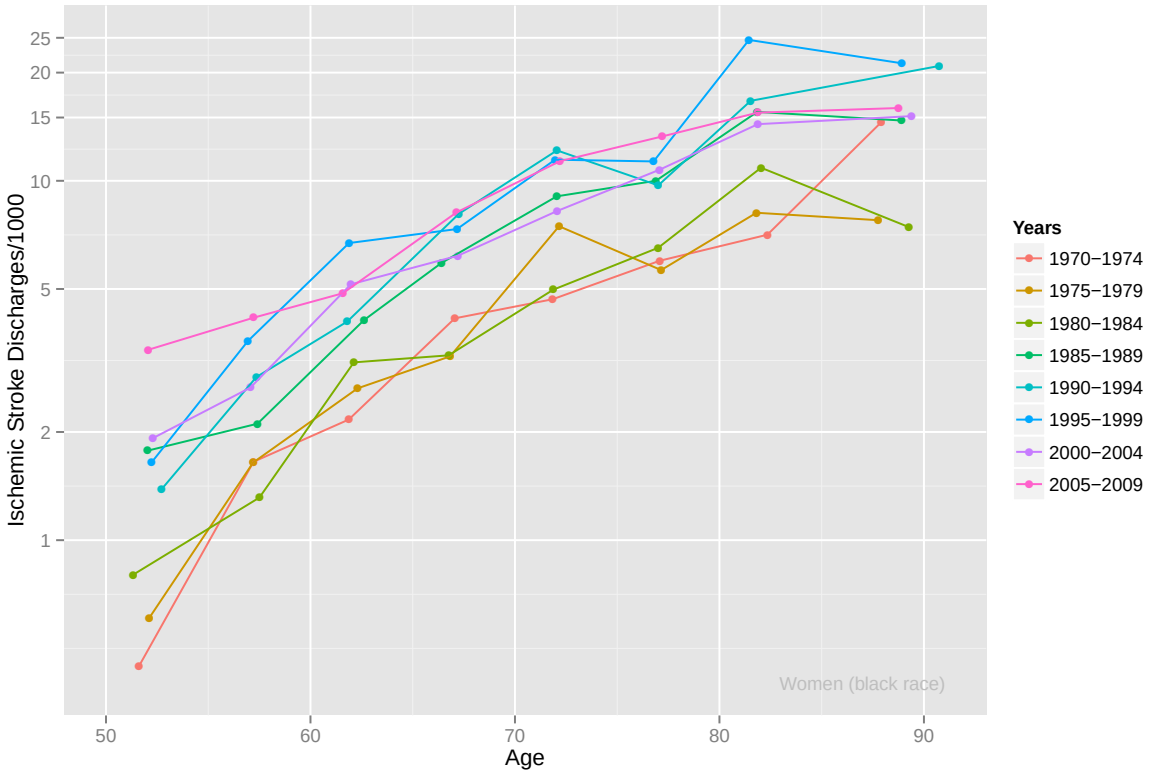

Figure 21: Pattern of discharge rates for non-embolic ischemic stroke with increasing age among black women over 40 years of the NHDS.

Appendix A (continued)

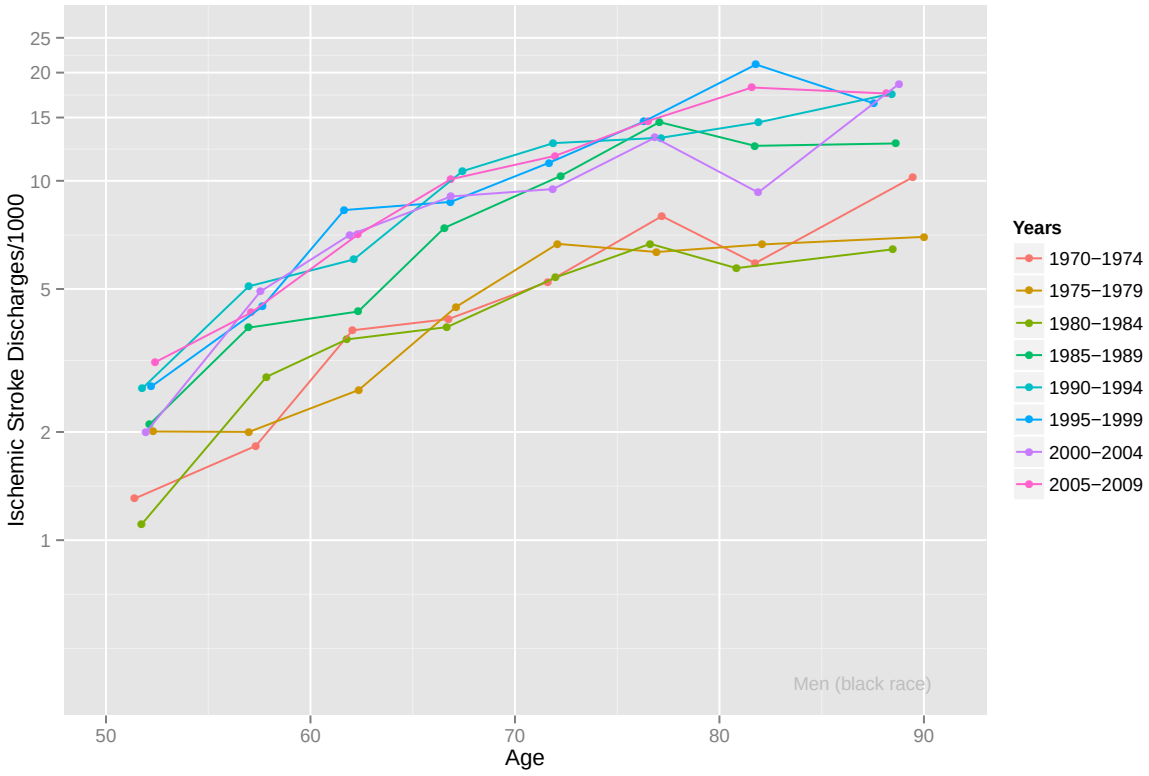

Figure 22: Pattern of discharge rates for non-embolic ischemic stroke with increasing age among black men over 40 years of the NHDS.

Appendix B

CHANGE POINT ANALYSES OF CEA RATES FROM 1970 TO 2010

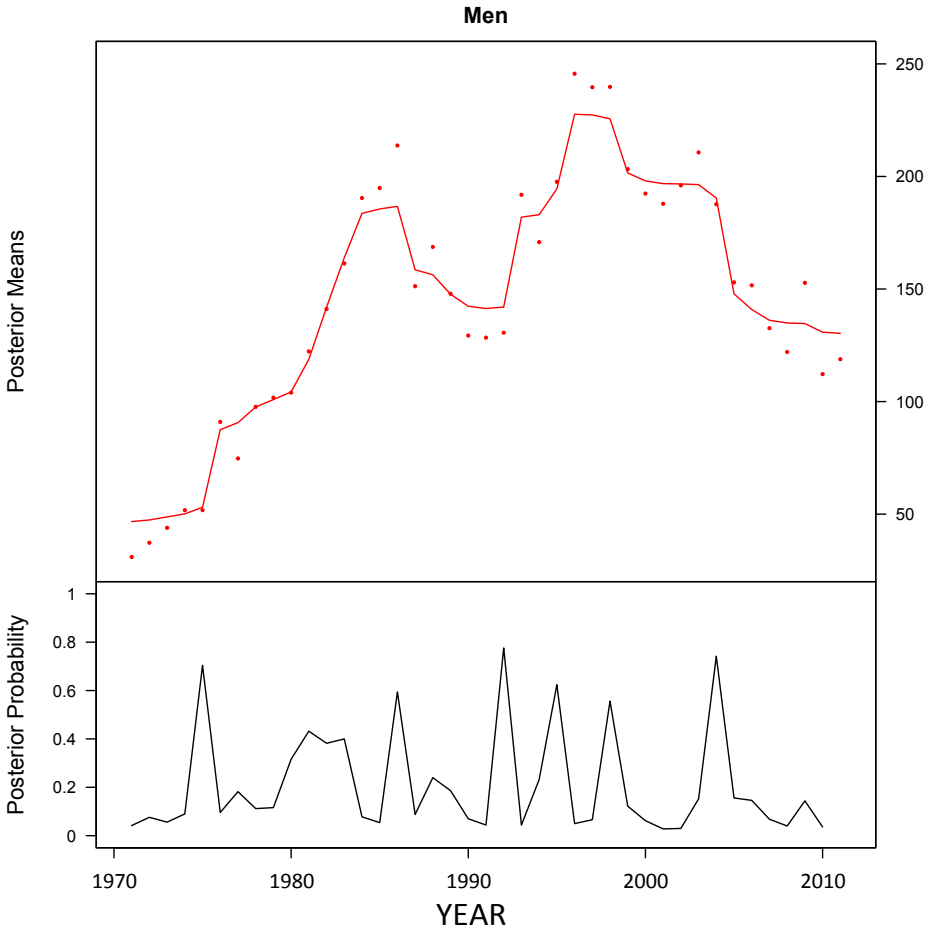

Figure 23: Posterior probability of changes in CEA rates among men between 1970 and 2010 in the NHDS.

Appendix B (continued)

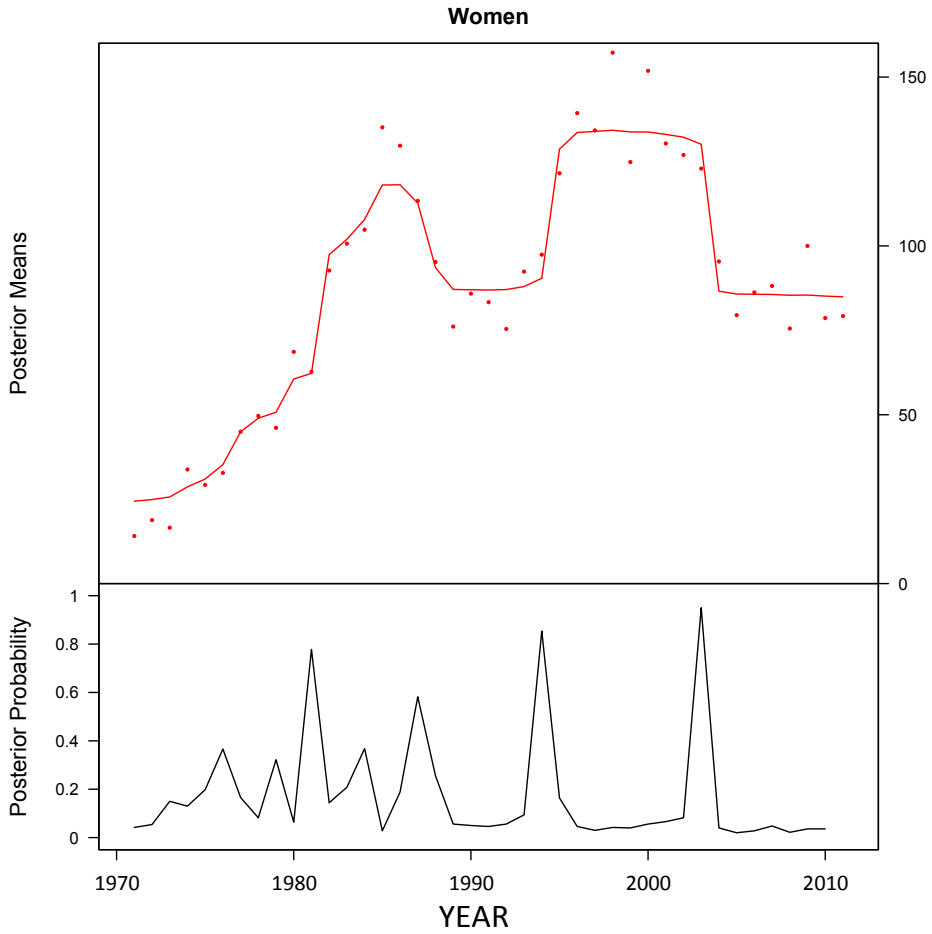

Figure 24: Posterior probability of changes in CEA rates among women between 1970 and 2010 in the NHDS.

Appendix C

EVIDENCE SYNTHESIS R CODE

```
R Code for synthesis and model
# ********************************************************************************************* #
#                              Preliminaries                                                    #
library(XLConnect)
library(car)
library(R2jags)
setwd('/Users/mgrant/Documents/_projects/phd/_r/_bugsjags')
# function to obtain shape and scale for beta from mean and sd
betaPar <- function(m,s){
    a <- m*((m*(1-m)/s^2)-1)
    b <- (1-m)*((m*(1-m)/s^2)-1)
    list(a=a,b=b)
}
# obtain monthly transition from annual exponential relationship
parYr <- function(prob){
    rate <- -(log(1-prob))/12
    times <- seq(1,12,1)
    transitions <- 1 - exp(-rate*times)
    return(transitions[1])
}
set.seed(123456789)
#                                                                                              #
# ********************************************************************************************* #


###                            Meta Analyses                                                 ###
# ********************************************************************************************* #
#                              Synthesis Meta Analysis                                          #
# Ipsilateral Stroke Rates
fname <- '/Users/mgrant/Documents/_projects/phd/_excel/asymptStudyTable_030313.xlsx'
asymptDat <- readWorksheet(loadWorkbook(fname, create=FALSE), sheet='data', startRow=0, endRow=10, startCol=0, endCol=9)
# exclude marquardt den hartog takaya
# asymptDat <- asymptDat[-c(7:9),]
rc <- asymptDat[,'events']
nc <- asymptDat[,'pyr']
k <- length(asymptDat[,'id'])

# Read Trial Data
fname <- '/Users/mgrant/Documents/_projects/phd/_excel/asymptStudyTable_030313.xlsx'
asymptDatTrial <- readWorksheet(loadWorkbook(fname, create=FALSE), sheet='data', startRow=35, endRow=38, startCol=0, endCol=5)
trrc <- asymptDatTrial[,'trrc']
trnc <- asymptDatTrial[,'trnc']
trrt <- asymptDatTrial[,'trrt']
trnt <- asymptDatTrial[,'trnt']
trk <- length(asymptDatTrial[,'id'])

# Dataset for JAGS
data <- list(trrc=trrc,trnc=trnc,trrt=trrt,trnt=trnt,trk=trk,rc=rc,nc=nc,k=k)

# Meta Analysis Models
combModel <- function(){
```

Appendix C (continued)

```
        # submodel stroke rates
        for( i in 1 : k ) {
        rc[i] ~ dbin(pc[i], nc[i])
        logit(pc[i]) <- mu[i]
        mu[i] ~ dt(d, tau, 10)
        rate[i] <- exp(mu[i])
        }

        # submodel trials
        for( i in 1 : trk ) {
        trrc[i] ~ dbin(trpc[i], trnc[i])
        trrt[i] ~ dbin(trpt[i], trnt[i])
        logit(trpc[i]) <- trmu[i]
        logit(trpt[i]) <- trmu[i] + delta[i]
        trmu[i] ~ dnorm(0.0,1.0E-6)
        delta[i] ~ dt(trd, trtau, 10)
        delta.or[i] <- exp(delta[i])
        }

        # parameters stroke rates
        d ~ dnorm(0.0,1.0E-6)
        tau ~ dgamma(0.001,0.001)
        sigma <- 1 / sqrt(tau)
        mu[k+1] <- d
        rate[k+1] <- exp(mu[k+1])

        # parameters trials
        trd ~ dnorm(0.0,1.0E-6)
        trtau ~ dgamma(0.001,0.001)
        delta.new ~ dt(trd, trtau, 10)
        sigmatr <- 1 / sqrt(trtau)
        sigmasqtr <- 1 / trtau
        prob <- step(delta)
        prob.new <- step(delta.new)
        or <- exp(trd)
        or.new <- exp(delta.new)
        }

fn <- 'combModel.bug'
write.model(combModel, fn)
params <- c('or','delta.or','rate')
thin <- 30
n.simu <- 70000*thin
n.burnin <- 20000*thin
combEvid.fit <- jags(data=data, n.chains=3, parameters.to.save=params, n.iter = n.simu, n.thin=thin,
    n.burnin = n.burnin,
model.file = 'combModel.bug')
print(combEvid.fit, digits=5)

# select rate and or for use in decision model
temp.mcmc <- as.mcmc(combEvid.fit)
rate <- temp.mcmc[[1]][,15]
# for exclude 3
rate <- temp.mcmc[[1]][,12]
or <- temp.mcmc[[1]][,5]
#                                                                                          #
# ******************************************************************************************* #
```

Appendix C (continued)

```
###                            Synthesis Markov Model                                    ###
# ************************************************************************************** #
#                              Markov Model Parameters                                   #
# outputs; length(rate) is number of samples/iterations of models here 50,000
temp            <- c(rep(NA, length(rate)))
# total qualys
qualyTot        <- temp
qualyPerThou    <- temp
# person-years
lifeYr          <- temp
# final state
final           <- temp
tiaT            <- temp
minT            <- temp
majT            <- temp
totT            <- temp
deadT           <- temp
strokeSubtract  <- temp

for (j in 1:length(rate)){
# annual base rates
ipsi        <-  rate[j]                         # ipsilateral stroke rate with medical care
# ipsi        <-  0.014                         # ACST

# flag for probablistic
prob <- 0
if(prob==0){
mort        <-  0.000                           # peri procedural death rate
peri        <-  0.014                           # periprocedural stroke rate
rrmed       <-  1.0000                          # not used; parameter to improve medical care outcomes
rrsurg      <-  or[j]                           # relative risk ipsilateral stroke post-procedure
backa       <-  0.0100                          # non-ipsilateral stroke rate
atiaa       <-  0.0260                          # tia rate
amorta      <-  0.0250                          # to achieve a 3% overall mortality rate
tmina       <-  0.0168                          # minor stroke following tia
tmaja       <-  0.021-tmina                     # major stroke following tia
tmorta      <-  amorta                          # mortality after tial; SMR = 1.0 per clark
minmaja     <-  0.0400                          # major stroke following a minor one
minmorta    <-  0.0580                          # mortality following minor stroke
}

if(prob==1){
peri        <-  runif(1, 0.010, 0.02)                                  # uniform 1.3 to 2.0
mort        <-  0.0000                                                 # periprocedural death rate
rrmed       <-  1.0000                                                 # to improve medical care outcomes
rrsurg      <-  or[j]                                                  # rr ipsilateral stroke post-procedure
backa       <-  rbeta(1, betaPar(.010, .003)$a, betaPar(.010, .003)$b)   # non-ipsilateral stroke rate
atiaa       <-  rbeta(1, betaPar(.026, .007)$a, betaPar(.026, .007)$b)   # asymptomatic to tia rate
amorta      <-  rbeta(1, betaPar(.025, .0025)$a, betaPar(.025, .0025)$b) # non-stroke mortality rate
tmina       <-  rbeta(1, betaPar(.017, .005)$a, betaPar(.017, .005)$b)   # minor stroke following tia
tmaja       <-  0.021-tmina                                            # major stroke following tia
tmorta      <-  amorta                                                 # mortality after tia
minmaja     <-  rbeta(1, betaPar(.04, .01)$a,   betaPar(.04, .01)$b)     # major stroke following a minor one
minmorta    <-  rbeta(1, betaPar(.058, .01)$a,  betaPar(.058, .01)$b)    # mortality following minor stroke
}

majmorta    <-  minmorta*2                      # mortality following major stroke
amina       <-  ipsi*0.8                        # ipsilateral minor stroke rate
amaja       <-  ipsi-amina                      # ipsilateral major stroke rate
```

Appendix C (continued)

```
asympta     <-  1-atiaa-amina-amaja-amorta        # asymptomatic state

# medical
backm       <-  parYr(backa)                      # nonipsilateral stroke rate medical
atiam       <-  parYr(atiaa)*rrmed                # ipsilateral tia rate medical
aminm       <-  parYr(amina)*rrmed+backm*0.8      # minor ispsilateral and contralateral stroke rate
amajm       <-  parYr(amaja)*rrmed+backm*0.2      # major ispsilateral and contralateral stroke rate
amortm      <-  parYr(amorta)                     # non-stroke mortality medical (same surgical)
tminm       <-  parYr(tmina)*rrmed                # minor stroke following tia
tmajm       <-  parYr(tmaja)*rrmed                # major stroke following tia
tmortm      <-  parYr(tmorta)                     # mortality after tia medical arm (same surgical)
minmajm     <-  parYr(minmaja)*rrmed              # major stroke following minor stroke
minmortm    <-  parYr(minmorta)                   # mortality after minor stroke (same surgical)
majmortm    <-  parYr(majmorta)                   # mortality after major stroke (same surgical)
tiam        <-  1-tminm-tmajm-tmortm              # tia state
minm        <-  1-minmajm-minmortm                # minor stroke state
majm        <-  1-majmortm                        # major stroke state
asymptm     <-  1-atiam-aminm-amajm-amortm        # asymptomatic state

# surgical
cal         <-  1                                 # calibration to ACST; preserves RR
back        <-  parYr(backa)                      # nonipsilateral stroke rate (same medical)
atia        <-  parYr(atiaa)*rrsurg*1.5           # ipsilateral tia rate surgical
amin        <-  parYr(amina)*rrsurg*cal+back*0.8  # minor ispsilateral and contralateral stroke rate surgical
amaj        <-  parYr(amaja)*rrsurg*cal+back*0.2  # major ispsilateral and contralateral stroke rate surgical
amort       <-  parYr(amorta)                     # non-stroke mortality surgical (same medical)
tmin        <-  parYr(tmina)                      # minor stroke following tia surgical
tmaj        <-  parYr(tmaja)                      # major stroke following tia
tmort       <-  parYr(tmorta)                     # mortality following tia
minmaj      <-  parYr(minmaja)                    # major stroke following minor stroke
minmort     <-  parYr(minmorta)                   # mortality following minor stroke
majmort     <-  parYr(majmorta)                   # mortality following major stroke
tia         <-  1-tmin-tmaj-tmort                 # tia state note change from tiaa
min         <-  1-minmaj-minmort                  # minor stroke state
maj         <-  1-majmort                         # major stroke state
asympt      <-  1-atia-amin-amaj-amort            # asymptomatic state

# utilties for various states/month
uasympt <- 1
utia    <- 0.98
umin    <- 0.65
umaj    <- 0.27
udead   <- 0
util <- c(uasympt, utia, umin, umaj, udead)

# create transition matrix
tranMed <- matrix(c(asymptm,atiam,aminm,amajm,amort,0,tiam,tminm,tmajm,tmortm,0,0,minm,minmajm,minmortm,
0,0,0,majm,majmortm,0,0,0,0,1), nrow=5, ncol=5, byrow=TRUE)
# transition matrix from excel spreadsheet (commented out); 2013-03-27 medical identical to surgical
tranSurg <- matrix(c(asympt,atia,amin,amaj,amort,0,tia,tmin,tmaj,tmortm,0,0,min,minmaj,minmort,0,0,0,maj,majmort,
0,0,0,0,1), nrow=5, ncol=5, byrow=TRUE)
#                                                                                              #
# ******************************************************************************************** #


# ******************************************************************************************** #
#                              Markov Model Medical                                            #
# markov model
cycles <- 60
```

Appendix C (continued)

```
index <- cycles + 1                                 # Starts at 0; will later delete state
state <- array(rep(0,5*index), c(index,5))          # Create empty array indexed 0 to 61 for values
start <- c(1,0,0,0,0)                               # Individuals start in asymptomatic state
state[1,] <- start
state[1,] <- start %*% tranMed

lifeYears   <- numeric(index)
quals       <- numeric(index)
tiaTot      <- numeric(index)
minStroke   <- numeric(index)
majStroke   <- numeric(index)
anyStroke   <- numeric(index)
dead        <- numeric(index)
minDead     <- numeric(index)
majDead     <- numeric(index)
minMaj      <- numeric(index)

for (i in 1:cycles) {
    state[i+1,]     <- state[i,] %*% tranMed        # Transition to next monthly state
    lifeYears[i]    <- sum(state[i,1:4])            # Alive individuals
    tiaTot[i]       <- state[i,2]                   # Tias
    minStroke[i]    <- state[i,3]                   # Minor Stroke
    majStroke[i]    <- state[i,4]                   # Major Stroke
    anyStroke[i]    <- sum(state[i,3:4])            # Any Stroke
    dead[i]         <- state[i,5]                   # Dead
    quals[i+1]      <- sum(state[i,] * util)
    minDead[i]      <- state[i,3]*minmortm
    majDead[i]      <- state[i,4]*majmortm
    minMaj[i]       <- state[i,3]*minmajm
    }
# total qualys
qualyTot[j]         <- sum(quals)/12
qualyPerThou[j]     <- sum(quals)/12*1000
lifeYr[j]           <- sum(lifeYears)/12*1000
# person-years
tiaT[j]             <- tiaTot[60]       *1000
minT[j]             <- minStroke[60]    *1000
majT[j]             <- majStroke[60]    *1000
totT[j]             <- anyStroke[60]    *1000
deadT[j]            <- dead[60]         *1000
# stroke accounting
strokeSubtract[j]  <- (sum(minDead) + sum(majDead) - sum(minMaj))*1000
}
#                                                                                                 #
# ******************************************************************************************** #


# ******************************************************************************************** #
#                               Results                                                           #
# stats
# resultsMed <- data.frame(cbind(qualyPerThou, lifeYr, minT, majT, totT, totT + strokeSubtract, deadT))
resultsMed <- data.frame(cbind(qualyPerThou, lifeYr, totT + strokeSubtract, deadT))
names(resultsMed) <- c('qalyPerThou', 'lifeYr', 'strokes', 'dead')
resultsMed.sum <- data.frame(apply(resultsMed, 2, function(x) quantile(x, probs=c(0.025, .5, .975))))
names(resultsMed.sum) <- c('qalyPerThou', 'lifeYr', 'strokes', 'dead')
print(resultsMed.sum, digits=5)
# ******************************************************************************************** #
```

Appendix C (continued)

```
# ************************************************************************************************ #
# Run Markov Model Parameters first
# ************************************************************************************************ #
#                              Markov Model Surgical                                               #
cycles <- 60
index <- cycles + 1                                  # Starts at 0; will later delete state
state <- array(rep(0,5*index), c(index,5))           # Create empty array indexed 0 to 61 for values
start <- c(1,0,0,0,0)                                # Individuals start in asymptomatic state
# state[1,] <- start
state[1,] <- start - c(peri+mort, 0, -peri*.8, -peri*.2, -mort)
# state[1,] <- c(1560-40, 0, 9, 16, 15)/1560         # ACST
lifeYears   <- numeric(index)
quals       <- numeric(index)
tiaTot      <- numeric(index)
minStroke   <- numeric(index)
majStroke   <- numeric(index)
anyStroke   <- numeric(index)
dead        <- numeric(index)
minDead     <- numeric(index)
majDead     <- numeric(index)
minMaj      <- numeric(index)
for (i in 1:cycles) {
    state[i+1,]     <- state[i,] %*% tranSurg        # Transition to next monthly state
    lifeYears[i]    <- sum(state[i,1:4])             # Alive individuals
    tiaTot[i]       <- state[i,2]                    # Tias
    minStroke[i]    <- state[i,3]                    # Minor Stroke
    majStroke[i]    <- state[i,4]                    # Major Stroke
    anyStroke[i]    <- sum(state[i,3:4])             # Any Stroke
    dead[i]         <- state[i,5]                    # Dead
    quals[i+1]      <- sum(state[i,] * util)
    minDead         <- numeric(index)
    majDead         <- numeric(index)
    minMaj          <- numeric(index)
    }
# total qulys
qualyTot[j]         <- sum(quals)/12
qualyPerThou[j]     <- sum(quals)/12*1000
lifeYr[j]           <- sum(lifeYears)/12*1000
# person-years
tiaT[j]             <- tiaTot[60]       *1000
minT[j]             <- minStroke[60]    *1000
majT[j]             <- majStroke[60]    *1000
totT[j]             <- anyStroke[60]    *1000
deadT[j]            <- dead[60]         *1000
# stroke accounting
strokeSubtract[j]  <- (sum(minDead) + sum(majDead) + sum(minMaj))*1000
}
# ************************************************************************************************ #
#                              Results                                                             #
# stats
resultsSurg <- data.frame(cbind(qualyPerThou, lifeYr, totT + strokeSubtract, deadT))
names(resultsSurg) <- c('qalyPerThou', 'lifeYr', 'strokes', 'dead')
resultsSurg.sum <- data.frame(apply(resultsSurg, 2, function(x) quantile(x, probs=c(0.025, .5, .975))))
names(resultsSurg.sum) <- c('qalyPerThou', 'lifeYr', 'strokes', 'dead')
print(resultsSurg.sum, digits=5)
print(resultsMed.sum, digits=5)
#                                                                                                  #
# ************************************************************************************************ #
```

Appendix C (continued)

```
# ********************************************************************************************* #
#                               Compare Med to Surg Table                                       #
resultsCompare.sum <- apply(resultsSurg - resultsMed, 2, function(x) quantile(x, probs=c(0.025, .5, .975)))
# make table
tabN <- function(x){formatC(x, digits=1, format='f')}
surR <- data.frame(resultsSurg.sum)
medR <- data.frame(resultsMed.sum)
comR <- data.frame(resultsCompare.sum)

a <- data.frame(diag(6))[-c(5:6),]
names(a) <- c('outcome','parms','prob','Medical (95% CI)', 'Surgical (95% CI)', 'Difference (95% CI)')
a[,1] <- c('Stroke','Qaly','Life Years','Deaths')

# a$parms <- 'base'
a$parms <- 'exclude'
# a$parms <- 'acst'
a$prob <- prob

# Formatted table to save
a[1,4] <- with(medR, paste(tabN(strokes[2]), ' (',  tabN(strokes[1]), ', ', tabN(strokes[3]), ')', sep='' ))
a[2,4] <- with(medR, paste(tabN(qalyPerThou[2]), ' (',  tabN(qalyPerThou[1]), ', ', tabN(qalyPerThou[3]), ')',
       sep='' ))
a[3,4] <- with(medR, paste(tabN(lifeYr[2]), ' (',  tabN(lifeYr[1]), ', ', tabN(lifeYr[3]), ')',
       sep='' ))
a[4,4] <- with(medR, paste(tabN(dead[2]), ' (',  tabN(dead[1]), ', ', tabN(dead[3]), ')', sep='' ))
a[1,5] <- with(surR, paste(tabN(strokes[2]), ' (',  tabN(strokes[1]), ', ', tabN(strokes[3]), ')', sep='' ))
a[2,5] <- with(surR, paste(tabN(qalyPerThou[2]), ' (',  tabN(qalyPerThou[1]), ', ', tabN(qalyPerThou[3]), ')',
       sep='' ))
a[3,5] <- with(surR, paste(tabN(lifeYr[2]), ' (',  tabN(lifeYr[1]), ', ', tabN(lifeYr[3]), ')', sep='' ))
a[4,5] <- with(surR, paste(tabN(dead[2]), ' (',  tabN(dead[1]), ', ', tabN(dead[3]), ')', sep='' ))
a[1,6] <- with(comR, paste(tabN(strokes[2]), ' (',  tabN(strokes[1]), ', ', tabN(strokes[3]), ')', sep='' ))
a[2,6] <- with(comR, paste(tabN(qalyPerThou[2]), ' (',  tabN(qalyPerThou[1]), ', ', tabN(qalyPerThou[3]), ')',
       sep='' ))
a[3,6] <- with(comR, paste(tabN(lifeYr[2]), ' (',  tabN(lifeYr[1]), ', ', tabN(lifeYr[3]), ')', sep='' ))
a[4,6] <- with(comR, paste(tabN(dead[2]), ' (',  tabN(dead[1]), ', ', tabN(dead[3]), ')', sep='' ))

# check no errors in estimtes should be 0
61 - round(sum(apply(state, 1, sum)), 12)
# probability qaly surg > med
sum((resultsSurg$qalyPerThou - resultsMed$qalyPerThou)>0)/50000
mort
peri
a
fname <- '/Users/mgrant/Documents/_projects/phd/_r/_decision/mpesResult.xlsx'
wb <- loadWorkbook(fname, create = FALSE)
writeWorksheet(wb, a, sheet = "save", startRow = 1, startCol = 1)
saveWorkbook(wb)
rm(wb, fname)
# ********************************************************************************************* #
#                     Read Output and Write Tables to Latex File                                  #
# Ipsilateral Stroke Rates
fname <- '/Users/mgrant/Documents/_projects/phd/_r/_decision/mpesResult.xlsx'
mpesTab <- readWorksheet(loadWorkbook(fname, create=FALSE), sheet='result', startRow=0, endRow=157,
       startCol=0, endCol=8)
rm(fname)
back <- mpesTab

# table 1
```

Appendix C (continued)

```
mpesTab <- mpesTab[mpesTab$peri==0.014 & mpesTab$perimort==0 & mpesTab$prob==0,]
mpesTab$outcome <- factor(mpesTab$outcome, levels=c('Stroke', 'Qaly', 'Life Years', 'Deaths'))
mpesTab[order(mpesTab$outcome, mpesTab$prob, mpesTab$parms),]

require(Hmisc)
latex(mpesTab[order(mpesTab$outcome, mpesTab$prob, mpesTab$parms),4:6], rowlabel='', caption='',
    file='tableMpes1r.tex',
   rgroup=c('Stroke', 'Qaly', 'Life Years', 'Deaths'), n.rgroup=c(2,2,2,2))

mpesTab <- back
# table 2
mpesTab <- mpesTab[mpesTab$prob==1,]
mpesTab$outcome <- factor(mpesTab$outcome, levels=c('Stroke', 'Qaly', 'Life Years', 'Deaths'))
mpesTab[order(mpesTab$outcome, mpesTab$prob, mpesTab$parms),]

require(Hmisc)
latex(mpesTab[order(mpesTab$outcome, mpesTab$prob, mpesTab$parms),4:6], rowlabel='', caption='',
    file='tableMpes2r.tex',
   rgroup=c('Stroke', 'Qaly', 'Life Years', 'Deaths'), n.rgroup=c(2,2,2,2))
#                                                                                                 #
# ******************************************************************************************** #
```

CITED LITERATURE

1. Roger, V. L., Go, A. S., Lloyd-Jones, D. M., Benjamin, E. J., Berry, J. D., Borden, W. B., Bravata, D. M., Dai, S., Ford, E. S., Fox, C. S., Fullerton, H. J., Gillespie, C., Hailpern, S. M., Heit, J. A., Howard, V. J., Kissela, B. M., Kittner, S. J., Lackland, D. T., Lichtman, J. H., Lisabeth, L. D., Makuc, D. M., Marcus, G. M., Marelli, A., Matchar, D. B., Moy, C. S., Mozaffarian, D., Mussolino, M. E., Nichol, G., Paynter, N. P., Soliman, E. Z., Sorlie, P. D., Sotoodehnia, N., Turan, T. N., Virani, S. S., Wong, N. D., Woo, D., Turner, M. B., and American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics–2012 update: A report from the American Heart Association. *Circulation*, 125(1):e2–e220, Jan 2012.

2. Heidenreich, P. A., Trogdon, J. G., Khavjou, O. A., Butler, J., Dracup, K., Ezekowitz, M. D., Finkelstein, E. A., Hong, Y., Johnston, S. C., Khera, A., Lloyd-Jones, D. M., Nelson, S. A., Nichol, G., Orenstein, D., Wilson, P. W. F., Woo, Y. J., American Heart Association Advocacy Coordinating Committee, Stroke Council, Council on Cardiovascular Radiology and Intervention, Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Arteriosclerosis, Thrombosis and Vascular Biology, Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Cardiovascular Nursing, Council on the Kidney in Cardiovascular Disease, and Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research: Forecasting the future of cardiovascular disease in the united states: A policy statement from the American Heart Association. *Circulation*, 123(8):933–44, Mar 2011.

3. Farmer, M. E., White, L. R., Brody, J. A., and Bailey, K. R.: Race and sex differences in hip fracture incidence. *Am J Public Health*, 74(12):1374–80, Dec 1984.

4. Brody, J. A. and Grant, M. D.: Age-associated diseases and conditions: Implications for decreasing late life morbidity. *Aging (Milano)*, 13(2):64–7, Apr 2001.

5. Brody, J. A. and Schneider, E. L.: Diseases and disorders of aging: An hypothesis. *J Chronic Dis*, 39(11):871–6, 1986.

6. de Weerd, M., Greving, J. P., de Jong, A. W. F., Buskens, E., and Bots, M. L.: Prevalence of asymptomatic carotid artery stenosis according to age and sex: Systematic review and metaregression analysis. *Stroke*, 40(4):1105–1113, Apr 2009.

CITED LITERATURE (continued)

7. Tu, J. V., Hannan, E. L., Anderson, G. M., Iron, K., Wu, K., Vranizan, K., Popp, A. J., and Grumbach, K.: The fall and rise of carotid endarterectomy in the United States and Canada. *N Engl J Med*, 339(20):1441–7, Nov 1998.

8. Davis, F. G., Peterson, C. E., Bandiera, F., Carter-Pokras, O., and Brownson, R. C.: How do we more effectively move epidemiology into policy action? *Ann Epidemiol*, 22(6):413–6, Jun 2012.

9. Najjar, S. S., Scuteri, A., and Lakatta, E. G.: Arterial aging: Is it an immutable cardiovascular risk factor? *Hypertension*, 46(3):454–62, Sept 2005.

10. Higashi, Y., Sukhanov, S., Anwar, A., and Shai, S.-Y.: Aging, atherosclerosis, and IGF-1. *J Gerontol A Biol Sci Med Sci*, 2012.

11. Carandang, R., Seshadri, S., Beiser, A., Kelly-Hayes, M., Kase, C. S., Kannel, W. B., and Wolf, P. A.: Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. *JAMA*, 296(24):2939–46, Dec 2006.

12. Dennison, C. and Pokras, R.: Design and operation of the National Hospital Discharge Survey: 1988 redesign. *Vital Health Stat 1*, (39):1–42, Dec 2000.

13. Andrade, S. E., Harrold, L. R., Tjia, J., Cutrona, S. L., Saczynski, J. S., Dodd, K. S., Goldberg, R. J., and Gurwitz, J. H.: A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiol Drug Saf*, 21 Suppl 1:100–28, Jan 2012.

14. Jensen, P. N., Johnson, K., Floyd, J., Heckbert, S. R., Carnahan, R., and Dublin, S.: A systematic review of validated methods for identifying atrial fibrillation using administrative data. *Pharmacoepidemiol Drug Saf*, 21 Suppl 1:141–7, Jan 2012.

15. Leppälä, J. M., Virtamo, J., and Heinonen, O. P.: Validation of stroke diagnosis in the national hospital discharge register and the register of causes of death in Finland. *Eur J Epidemiol*, 15(2):155–60, Feb 1999.

16. Breslow, N. E. and Day, N. E.: *Statistical Methods in Cancer Research. Volume II – The Design and Analysis of Cohort Studies*, volume no. 382 of *IARC Scientific Publications*. Lyon, International Agency for Research on Cancer, 1987.

17. Kozak, L. J.: Underreporting of race in the National Hospital Discharge Survey. *Adv Data*, 265(265):1–12, Jul 1995.

CITED LITERATURE (continued)

18. R Development Core Team: *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria, 2013. ISBN 3-900051-07-0.

19. Wickham, H.: *ggplot2: Elegant Graphics for Data Analysis*. Springer New York, 2009.

20. Pokras, R., Kozak, L. J., McCarthy, E., and Graves, E. J.: Trends in hospital utilization, 1965–86. *Am J Public Health*, 80(4):488–90, Apr 1990.

21. Lee, L. K., Bateman, B. T., Wang, S., Schumacher, H. C., Pile-Spellman, J., and Saposnik, G.: Trends in the hospitalization of ischemic stroke in the United States, 1998–2007. *Int J Stroke*, 7(3):195–201, Apr 2012.

22. Healey, J. S., Connolly, S. J., Gold, M. R., Israel, C. W., Van Gelder, I. C., Capucci, A., Lau, C. P., Fain, E., Yang, S., Bailleul, C., Morillo, C. A., Carlson, M., Themeles, E., Kaufman, E. S., Hohnloser, S. H., and ASSERT Investigators: Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*, 366(2):120–9, Jan 2012.

23. Matthews, F. E., Arthur, A., Barnes, L. E., Bond, J., Jagger, C., Robinson, L., Brayne, C., and on behalf of the Medical Research Council Cognitive Function and Ageing Collaboration: A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: Results of the Cognitive Function and Ageing Study I and II. *Lancet*, Jul 2013.

24. Moniz, E., Lima, A., and de l'Acerda, R.: Hemiplegies par thrombose de la carotide interne. *Press Med*, 1:977–80, 1937.

25. Eastcott, H. H. G., Pickering, G. W., and Rob, C. G.: Reconstruction of the internal carotid artery in a patient with intermittent attacks of hemiplegia. *Lancet*, 2:994–6, 1954.

26. Fields, W. S., Maslenikov, V., Meyer, J. S., Hass, W. K., Remington, R. D., and Macdonald, M.: Joint study of extracranial arterial occlusion. V. progress report of prognosis following surgery or nonsurgical treatment for transient cerebral ischemic attacks and cervical carotid artery lesions. *JAMA*, 211(12):1993–2003, Mar 1970.

27. NASCET Trial Collaborators: Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*, 325(7):445–53, 1991.

28. Barnett, H. J., Plum, F., and Walton, J. N.: Carotid endarterectomy—an expression of concern. *Stroke*, 15(6):941–3, 1984.

CITED LITERATURE (continued)

29. Naylor, A. R., Gaines, P. A., and Rothwell, P. M.: Who benefits most from intervention for asymptomatic carotid stenosis: Patients or professionals? *Eur J Vasc Endovasc Surg*, 37(6):625–32, Jun 2009.

30. Ruggles, S. J., Alexander, T., Genadek, K., Goeken, R., Schroeder, M. B., and M, S.: *Integrated Public Use Microdata Series: Version 5.0 [Machine-readable database]*. Minneapolis, MN: Minnesota Population Center [producer and distributor], 2010.

31. Barry, D. and Hartigan, J. A.: A Bayesian analysis for change point problems. *JASA*, 88(421):309–319, March 1993.

32. Chandra, E. and Emerson, J. W.: bcp: An R package for performing a Bayesian analysis of change point problems. *Journal of Statistical Software*, 23(3):1–13, 2007.

33. Warlow, C.: Carotid endarterectomy: Does it work? *Stroke*, 15(6):1068–76, 1984.

34. Winslow, C. M., Solomon, D. H., Chassin, M. R., Kosecoff, J., Merrick, N. J., and Brook, R. H.: The appropriateness of carotid endarterectomy. *N Engl J Med*, 318(12):721–7, 1988.

35. Brott, T. and Thalinger, K.: The practice of carotid endarterectomy in a large metropolitan area. *Stroke*, 15(6):950–5, 1984.

36. Muuronen, A.: Outcome of surgical treatment of 110 patients with transient ischemic attack. *Stroke*, 15(6):959–64, 1984.

37. ECST Collaborative Group: MRC European Carotid Surgery Trial: Interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. *Lancet*, 337(8752):1235–43, 1991.

38. Mayberg, M. R., Wilson, S. E., Yatsu, F., Weiss, D. G., Messina, L., Hershey, L. A., Colling, C., Eskridge, J., Deykin, D., and Winn, H. R.: Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. *JAMA*, 266(23):3289–94, Dec 1991.

39. ACAS Executive Committee: Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA*, 273(18):1421–8, 1995.

CITED LITERATURE (continued)

40. ECST Collaborative Group: Endarterectomy for moderate symptomatic carotid stenosis: Interim results from the MRC European Carotid Surgery Trial. *Lancet*, 347(9015):1591–3, 1996.

41. Barnett, H. J., Taylor, D. W., Eliasziw, M., Fox, A. J., Ferguson, G. G., Haynes, R. B., Rankin, R. N., Clagett, G. P., Hachinski, V. C., Sackett, D. L., Thorpe, K. E., Meldrum, H. E., and Spence, J. D.: Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med*, 339(20):1415–25, 1998.

42. Halliday, A., Mansfield, A., Marro, J., Peto, C., Peto, R., Potter, J., Thomas, D., and MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group: Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: Randomised controlled trial. *Lancet*, 363(9420):1491–502, May 2004.

43. Yadav, J. S., Wholey, M. H., Kuntz, R. E., Fayad, P., Katzen, B. T., Mishkel, G. J., Bajwa, T. K., Whitlow, P., Strickman, N. E., Jaff, M. R., Popma, J. J., Snead, D. B., Cutlip, D. E., Firth, B. G., Ouriel, K., and Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators: Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*, 351(15):1493–501, Oct 2004.

44. Mas, J.-L., Chatellier, G., Beyssen, B., Branchereau, A., Moulin, T., Becquemin, J.-P., Larrue, V., Lièvre, M., Leys, D., Bonneville, J.-F., Watelet, J., Pruvo, J.-P., Albucher, J.-F., Viguier, A., Piquet, P., Garnier, P., Viader, F., Touzé, E., Giroud, M., Hosseini, H., Pillet, J.-C., Favrole, P., Neau, J.-P., Ducrocq, X., and EVA-3S Investigators: Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med*, 355(16):1660–71, Oct 2006.

45. SPACE Collaborative Group, Ringleb, P. A., Allenberg, J., Brückmann, H., Eckstein, H.-H., Fraedrich, G., Hartmann, M., Hennerici, M., Jansen, O., Klein, G., Kunze, A., Marx, P., Niederkorn, K., Schmiedt, W., Solymosi, L., Stingele, R., Zeumer, H., and Hacke, W.: 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: A randomised non-inferiority trial. *Lancet*, 368(9543):1239–47, Oct 2006.

46. ICSS Investigators: Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): An interim analysis of a randomised controlled trial. *Lancet*, 375(9719):985–97, Mar 2010.

CITED LITERATURE (continued)

47. Brott, T. G., Hobson, II, R. W., Howard, G., Roubin, G. S., Clark, W. M., Brooks, W., Mackey, A., Hill, M. D., Leimgruber, P. P., Sheffet, A. J., Howard, V. J., Moore, W. S., Voeks, J. H., Hopkins, L. N., Cutlip, D. E., Cohen, D. J., Popma, J. J., Ferguson, R. D., Cohen, S. N., Blackshear, J. L., Silver, F. L., Mohr, J. P., Lal, B. K., Meschia, J. F., and CREST Investigators: Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*, 363(1):11–23, Jul 2010.

48. Hobson, 2nd, R. W., Weiss, D. G., Fields, W. S., Goldstone, J., Moore, W. S., Towne, J. B., and Wright, C. B.: Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. *N Engl J Med*, 328(4):221–7, Jan 1993.

49. Longmore, R. B., Yeh, R. W., Kennedy, K. F., Anderson, H. V., White, C. J., Longmore, L. S., Rosenfield, K., Ho, K. K. L., and Spertus, J. A.: Clinical referral patterns for carotid artery stenting versus carotid endarterectomy: Results from the carotid artery revascularization and endarterectomy registry. *Circ Cardiovasc Interv*, 4(1):88–94, Feb 2011.

50. Amarenco, P., Bogousslavsky, J., Callahan, III, A., Goldstein, L. B., Hennerici, M., Rudolph, A. E., Sillesen, H., Simunovic, L., Szarek, M., Welch, K. M. A., Zivin, J. A., and Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators: High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*, 355(6):549–59, Aug 2006.

51. Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Borden, W. B., Bravata, D. M., Dai, S., Ford, E. S., Fox, C. S., Franco, S., Fullerton, H. J., Gillespie, C., Hailpern, S. M., Heit, J. A., Howard, V. J., Huffman, M. D., Kissela, B. M., Kittner, S. J., Lackland, D. T., Lichtman, J. H., Lisabeth, L. D., Magid, D., Marcus, G. M., Marelli, A., Matchar, D. B., McGuire, D. K., Mohler, E. R., Moy, C. S., Mussolino, M. E., Nichol, G., Paynter, N. P., Schreiner, P. J., Sorlie, P. D., Stein, J., Turan, T. N., Virani, S. S., Wong, N. D., Woo, D., Turner, M. B., and American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics–2013 update: A report from the American Heart Association. *Circulation*, 127(1):e6–e245, Jan 2013.

52. Abbott, A. L., Bladin, C. F., Levi, C. R., and Chambers, B. R.: What should we do with asymptomatic carotid stenosis? *Int J Stroke*, 2(1):27–39, Feb 2007.

53. Abbott, A. L.: Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: Results of a systematic review and analysis. *Stroke*, 40(10):e573–83, Oct 2009.

CITED LITERATURE (continued)

54. Abbott, A. L., Adelman, M. A., Alexandrov, A. V., Barnett, H. J. M., Beard, J., Bell, P., Björck, M., Blacker, D., Buckley, C. J., Cambria, R. P., Comerota, A. J., Connolly, Jr, E. S., Davies, A. H., Eckstein, H.-H., Faruqi, R., Fraedrich, G., Gloviczki, P., Hankey, G. J., Harbaugh, R. E., Heldenberg, E., Kittner, S. J., Kleinig, T. J., Mikhailidis, D. P., Moore, W. S., Naylor, R., Nicolaides, A., Paraskevas, K. I., Pelz, D. M., Prichard, J. W., Purdie, G., Ricco, J.-B., Riles, T., Rothwell, P., Sandercock, P., Sillesen, H., Spence, J. D., Spinelli, F., Tan, A., Thapar, A., Veith, F. J., and Zhou, W.: Why the US Center for Medicare and Medicaid Services should not extend reimbursement indications for carotid artery angioplasty/stenting. *Angiology*, 63(8):639–44, Nov 2012.

55. Writing Committee Members, Brott, T. G., Halperin, J. L., Abbara, S., Bacharach, J. M., Barr, J. D., Bush, R. L., Cates, C. U., Creager, M. A., Fowler, S. B., Friday, G., Hertzberg, V. S., McIff, E. B., Moore, W. S., Panagos, P. D., Riles, T. S., Rosenwasser, R. H., Taylor, A. J., Jacobs, A. K., and Smith, Jr, S. C.: 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease. *Stroke*, 42(8):e464–540, Aug 2011.

56. Raman, G., Kitsios, G. D., Moorthy, D., Hadar, N., Dahabreh, I. J., O'Donnell, T. F., Thaler, D. E., Feldmann, E., and Lau, J.: Management of asymptomatic carotid stenosis. *Technology Assessment Report, Agency for Healthcare Research and Quality (AHRQ), Rockville, MD*, 2012.

57. Marquardt, L., Geraghty, O. C., Mehta, Z., and Rothwell, P. M.: Low risk of ipsilateral stroke in patients with asymptomatic carotid stenosis on best medical treatment: A prospective, population-based study. *Stroke*, 41(1):e11–7, 2010.

58. Harris, R. P., Helfand, M., Woolf, S. H., Lohr, K. N., Mulrow, C. D., Teutsch, S. M., Atkins, D., and Methods Work Group, Third US Preventive Services Task Force: Current methods of the US Preventive Services Task Force: A review of the process. *Am J Prev Med*, 20(3 Suppl):21–35, Apr 2001.

59. Shamliyan, T. A., Kane, R. L., Ansari, M. T., Raman, G., Berkman, N. D., Grant, M., Janes, G., Maglione, M., Moher, D., Nasser, M., Robinson, K. A., Segal, J. B., and Tsouros, S.: Development quality criteria to evaluate nontherapeutic studies of incidence, prevalence, or risk factors of chronic diseases: Pilot study of new checklists. *J Clin Epidemiol*, 64(6):637–57, Jun 2011.

60. Institute for Health Research and Policy grant support (Center for Clinical and Translational Science (CCTS) UL1RR029879).

CITED LITERATURE (continued)

61. Thompson, S., Ekelund, U., Jebb, S., Lindroos, A. K., Mander, A., Sharp, S., Turner, R., and Wilks, D.: A proposed method of bias adjustment for meta-analyses of published observational studies. *Int J Epidemiol*, 40(3):765–77, Jun 2011.

62. Koller, M. T., Raatz, H., Steyerberg, E. W., and Wolbers, M.: Competing risks and the clinical community: Irrelevance or ignorance? *Stat Med*, 31(11-12):1089–97, May 2012.

63. Schwarzer, G.: *meta: Meta-Analysis with R*, 2013. R package version 2.4-0.

64. Plummer, M.: JAGS: A Program for Analysis of Bayesian Graphical Models Using Gibbs Sampling. In *Proceedings of the 3rd International Workshop on Distributed Statistical Computing (DSC 2003), March 20–22, Vienna, Austria. ISSN 1609-395X*, 2003.

65. Su, Y.-S. and Yajima, M.: *R2jags: A Package for Running JAGS from R*, 2012. R package version 0.03-08.

66. Abbott, A. L., Chambers, B. R., Stork, J. L., Levi, C. R., Bladin, C. F., and Donnan, G. A.: Embolic signals and prediction of ipsilateral stroke or transient ischemic attack in asymptomatic carotid stenosis: A multicenter prospective cohort study. *Stroke*, 36(6):1128–33, Jun 2005.

67. den Hartog, A. G., Achterberg, S., Moll, F. L., Kappelle, L. J., Visseren, F. L. J., van der Graaf, Y., Algra, A., de Borst, G. J., and on behalf of the SMART Study Group: Asymptomatic carotid artery stenosis and the risk of ischemic stroke according to subtype in patients with clinical manifest arterial disease. *Stroke*, Feb 2013.

68. Nicolaides, A. N., Kakkos, S. K., Kyriacou, E., Griffin, M., Sabetai, M., Thomas, D. J., Tegos, T., Geroulakos, G., Labropoulos, N., Doré, C. J., Morris, T. P., Naylor, R., Abbott, A. L., and Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group: Asymptomatic internal carotid artery stenosis and cerebrovascular risk stratification. *J Vasc Surg*, 52(6):1486–1496.e1–5, Dec 2010.

69. Takaya, N., Yuan, C., Chu, B., Saam, T., Underhill, H., Cai, J., Tran, N., Polissar, N. L., Isaac, C., Ferguson, M. S., Garden, G. A., Cramer, S. C., Maravilla, K. R., Hashimoto, B., and Hatsukami, T. S.: Association between carotid plaque characteristics and subsequent ischemic cerebrovascular events: A prospective assessment with mri–initial results. *Stroke*, 37(3):818–23, Mar 2006.

CITED LITERATURE (continued)

70. Zhang, C., Qu, S., Zhang, C., Qu, S., Li, H., Li, G., Chen, G., Wang, J., and Wu, C.: Microembolic signals and carotid plaque characteristics in patients with asymptomatic carotid stenosis. *Scand Cardiovasc J*, 43(5):345–51, 2009.

71. Ballotta, E., Da Giau, G., Meneghetti, G., Barbon, B., Militello, C., and Baracchini, C.: Progression of atherosclerosis in asymptomatic carotid arteries after contralateral endarterectomy: A 10-year prospective study. *J Vasc Surg*, 45(3):516–22, Mar 2007.

72. Markus, H. S., King, A., Shipley, M., Topakian, R., Cullinane, M., Reihill, S., Bornstein, N. M., and Schaafsma, A.: Asymptomatic embolisation for prediction of stroke in the Asymptomatic Carotid Emboli Study (ACES): A prospective observational study. *Lancet Neurol*, 9(7):663–71, Jul 2010.

73. Dick, P., Sherif, C., Sabeti, S., Amighi, J., Minar, E., and Schillinger, M.: Gender differences in outcome of conservatively treated patients with asymptomatic high grade carotid stenosis. *Stroke*, 36(6):1178–83, Jun 2005.

74. Hill, M. D., Brooks, W., Mackey, A., Clark, W. M., Meschia, J. F., Morrish, W. F., Mohr, J. P., Rhodes, J. D., Popma, J. J., Lal, B. K., Longbottom, M. E., Voeks, J. H., Howard, G., Brott, T. G., and CREST Investigators: Stroke after carotid stenting and endarterectomy in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST). *Circulation*, 126(25):3054–61, Dec 2012.

75. Nicolaides, A. N., Kakkos, S. K., Griffin, M., Sabetai, M., Dhanjil, S., Tegos, T., Thomas, D. J., Giannoukas, A., Geroulakos, G., Georgiou, N., Francis, S., Ioannidou, E., Doré, C. J., and Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) Study Group: Severity of asymptomatic carotid stenosis and risk of ipsilateral hemispheric ischaemic events: Results from the ACRS study. *Eur J Vasc Endovasc Surg*, 30(3):275–84, Sep 2005.

76. Greenhouse, S. W.: Jerome Cornfield's contributions to epidemiology. *Biometrics*, 38 Suppl:33–45, Mar 1982.

77. Cornfield, J., Haenszel, W., Hammond, E. C., Lilienfeld, a. M., Shimkin, M. B., and Wynder, E. L.: Smoking and lung cancer: Recent evidence and a discussion of some questions. *J Natl Cancer Inst*, 22(1):173–203, Jan 1959.

78. U. S. Preventive Services Task, F.: Screening for carotid artery stenosis: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*, 147(12):854–859, Dec 2007.

CITED LITERATURE (continued)

79. Naylor, A. R.: What is the current status of invasive treatment of extracranial carotid artery disease? *Stroke*, 42(7):2080–5, Jul 2011.

80. Naylor, A. R. and Bell, P. R. F.: Treatment of asymptomatic carotid disease with stenting: Con. *Semin Vasc Surg*, 21(2):100–7, 2008.

81. Halm, E. A.: The good, the bad, and the about-to-get ugly: National trends in carotid revascularization: Comment on "Geographic variation in carotid revascularization among Medicare beneficiaries, 2003-2006". *Arch Intern Med*, 170(14):1225–7, 2010.

82. Hoomans, T., Seidenfeld, J., Basu, A., and Meltzer, D.: Systematizing the use of value of information analysis in prioritizing systematic reviews. *Med Dec Making*, in press, 2011.

83. Ades, A. E. and Sutton, A. J.: Multiparameter evidence synthesis in epidemiology and medical decision-making: Current approaches. *Journal of the Royal Statistical Society. Series A (Statistics in Society)*, 169(1):pp. 5–35, 2006.

84. Clark, T. G., Murphy, M. F. G., and Rothwell, P. M.: Long term risks of stroke, myocardial infarction, and vascular death in "low risk" patients with a non-recent transient ischaemic attack. *J Neurol Neurosurg Psychiatry*, 74(5):577–80, May 2003.

85. Haran, M. and Hughes, J.: *batchmeans: Consistent Batch Means Estimation of Monte Carlo Standard Errors*. Minneapolis, MN, 2012. R package version 1.0-1.

86. Samsa, G. P., Reutter, R. A., Parmigiani, G., Ancukiewicz, M., Abrahamse, P., Lipscomb, J., and Matchar, D. B.: Performing cost-effectiveness analysis by integrating randomized trial data with a comprehensive decision model: Application to treatment of acute ischemic stroke. *J Clin Epidemiol*, 52(3):259–71, Mar 1999.

87. Giles, M. F. and Rothwell, P. M.: Risk of stroke early after transient ischaemic attack: A systematic review and meta-analysis. *Lancet Neurol*, 6(12):1063–72, Dec 2007.

88. Warn, D. E., Thompson, S. G., and Spiegelhalter, D. J.: Bayesian random effects meta-analysis of trials with binary outcomes: Methods for the absolute risk difference and relative risk scales. *Stat Med*, 21(11):1601–23, Jun 2002.

89. Gelman, A., Carlin, J., Stern, H., and Rubin, D. B.: *Bayesian data analysis*. Boca Raton, Fla., Chapman & Hall/CRC, 2nd ed edition, 2004.

CITED LITERATURE (continued)

90. Geweke, J.: *In Bayesian statistics 4: Proceedings of the Fourth Valencia International Meeting, April 15-20, 1991 (Oxford science publications)*. Oxford University Press, USA, 1991.

91. Eddy, D. M., Hasselblad, V., and Shachter, R. D.: *Meta-analysis by the confidence profile method: The statistical synthesis of evidence*. Boston, Academic Press, 1992.

92. Schermerhorn, M. L., Fokkema, M., Goodney, P., Dillavou, E. D., Jim, J., Kenwood, C. T., Siami, F. S., White, R. A., and SVS Outcomes Committee: The impact of Centers for Medicare and Medicaid Services high-risk criteria on outcome after carotid endarterectomy and carotid artery stenting in the SVS vascular registry. *J Vasc Surg*, 57(5):1318–24, May 2013.

93. Hastie, R. and Dawes, R. M.: *Rational choice in an uncertain world: The psychology of judgment and decision making*. Los Angeles, SAGE, 2nd edition, 2010.

94. Thapar, A., Garcia Mochon, L., Epstein, D., Shalhoub, J., and Davies, A. H.: Modelling the cost-effectiveness of carotid endarterectomy for asymptomatic stenosis. *Br J Surg*, 100(2):231–9, Jan 2013.

95. Mas, J.-L., Trinquart, L., Leys, D., Albucher, J.-F., Rousseau, H., Viguier, A., Bossavy, J.-P., Denis, B., Piquet, P., Garnier, P., Viader, F., Touzé, E., Julia, P., Giroud, M., Krause, D., Hosseini, H., Becquemin, J.-P., Hinzelin, G., Houdart, E., Hénon, H., Neau, J.-P., Bracard, S., Onnient, Y., Padovani, R., Chatellier, G., and EVA-3S investigators: Endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S) trial: Results up to 4 years from a randomised, multicentre trial. *Lancet Neurol*, 7(10):885–92, Oct 2008.

96. Eckstein, H.-H., Ringleb, P., Allenberg, J.-R., Berger, J., Fraedrich, G., Hacke, W., Hennerici, M., Stingele, R., Fiehler, J., Zeumer, H., and Jansen, O.: Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: A multinational, prospective, randomised trial. *Lancet Neurol*, 7(10):893–902, Oct 2008.

97. Seshadri, S., Beiser, A., Kelly-Hayes, M., Kase, C. S., Au, R., Kannel, W. B., and Wolf, P. A.: The lifetime risk of stroke: Estimates from the Framingham Study. *Stroke*, 37(2):345–50, Feb 2006.

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Persky, V. W., Chatterton, R. T., Van Horn, L. V., Grant, M. D., Langenberg, P., and Marvin, J.: Hormone levels in vegetarian and nonvegetarian teenage girls: potential implications for breast cancer risk. *Cancer Res*, 52(3):578–83, Feb 1992.

Furner, S., Grant, M., and Brody, J. A.: Geriatric Urology, chapter, *The Aging Population*. Boston, Little, Brown, 1st edition, 1994.

Grant, M. D., Piotrowski, Z. H., and Chappell, R.: Self-reported health and survival in the Longitudinal Study of Aging, 1984-1986. *J Clin Epidemiol*, 48(3):375–87, Mar 1995.

Hunter-Smith, D. G., Kessel, K., Grant, M., and Piotrowski, Z. H.: Association between elevated body-mass index and impaired sense of smell in older people. *J Am Geriatr Soc*, 44(1):100–1, Jan 1996.

Grant, M. D., Piotrowski, Z. H., and Miles, T. P.: Declining cholesterol and mortality in a sample of older nursing home residents. *J Am Geriatr Soc*, 44(1):31–6, Jan 1996.

Grant, M. D.: Gastrostomies in older patients: The 1990 National Hospital Discharge Survey. *J Am Board Fam Pract*, 11(3):187–92, 1998.

Brody, J. A., Grant, M. D., Frateschi, L. J., Miller, S. C., and Zhang, H.: Epidemiology and aging: Maximum reproductive age unaffected by increased life expectancy in the twentieth century. *Aging (Milano)*, 10(2):170–1, Apr 1998.

Grant, M. D., Rudberg, M. A., and Brody, J. A.: Gastrostomy placement and mortality among hospitalized Medicare beneficiaries. *JAMA*, 279(24):1973–6, Jun 1998.

Brody, J. A., Grant, M. D., Frateschi, L. J., Miller, S. C., and Zhang, H.: Reproductive longevity and increased life expectancy. *Age Ageing*, 29(1):75–8, Jan 2000.

Rudberg, M. A., Egleston, B. L., Grant, M. D., and Brody, J. A.: Effectiveness of feeding tubes in nursing home residents with swallowing disorders. *JPEN J Parenter Enteral Nutr*, 24(2):97–102, 2000.

Brody, J. A. and Grant, M. D.: Age-associated diseases and conditions: Implications for decreasing late life morbidity. *Aging (Milano)*, 13(2):64–7, Apr 2001.

Grant, M. D. and Lauderdale, D. S.: Cohort effects in a genetically determined trait: Eye colour among US whites. *Ann Hum Biol*, 29(6):657–66, 2002.

Grant, M. D.: This is the first study. *Lancet*, 364(9440):1126, 2004.

Grant, M. D. and Brody, J. A.: Musical experience and dementia. Hypothesis. *Aging Clin Exp Res*, 16(5):403–5, Oct 2004.

Grant, M. D. and Herman, S.: Ethnic and geographic variation in gastrostomy placement among hospitalized older patients. *J Natl Med Assoc*, 96(10):1346–9, Oct 2004.

Sears, B. W., Luchette, F. A., Esposito, T. J., Dickson, E. L., Grant, M., Santaniello, J. M., Jod- lowski, C. R., Davis, K. A., Poulakidas, S. J., and Gamelli, R. L.: Old fashion clinical judgment in the era of protocols: is mandatory chest x-ray necessary in injured pa- tients? *J Trauma*, 59(2):324–30; discussion 330–2, Aug 2005.

Olshansky, S. J., Grant, M., Brody, J., and Carnes, B. A.: Biodemographic perspectives for epidemiologists. *Emerg Themes Epidemiol*, 2:10, Sep 2005.

Grant, M.: Special report: Current and evolving strategies in the treatment of age-related macular degeneration. *Technol Eval Cent Assess Program Exec Summ*, 20(11):1–2, Dec 2005.

Samson, D. and Grant, M.: Special Report: Measuring and reporting pain outcomes in randomized controlled trials. *Technol Eval Cent Assess Program Exec Summ*, 21(11):1–2, Oct 2006.

Flamm, C. R. and Grant, M. D.: Microvolt T-wave alternans testing to risk stratify patients being considered for icd therapy for primary prevention of sudden death. *Technol Eval Cent Assess Program Exec Summ*, 21(14):1–3, May 2007.

Grant, M. D.: Angioplasty and stenting of the cervical carotid artery with embolic protection of the cerebral circulation. *Technol Eval Cent Assess Program Exec Summ*, 22(1):1–4, Jun 2007.

Samson, D. J., Grant, M. D., Ratko, T. A., Bonnell, C. J., Ziegler, K. M., and Aronson, N.: Treatment of primary and secondary osteoarthritis of the knee. *Evid Rep Technol Assess (Full Rep)*, (157):1–157, Sep 2007.

Grant, M. D.: Artificial intervertebral disc arthroplasty for treatment of degenerative disc disease of the cervical spine. *Technol Eval Cent Assess Program Exec Summ*, 24(3):1–4, Aug 2009.

Grant, M. D.: Angioplasty and stenting of the cervical carotid artery with embolic protection of the cerebral circulation. *Technol Eval Cent Assess Program Exec Summ*, 24(12):1–3, Aug 2010.

Shamliyan, T. A., Kane, R. L., Ansari, M. T., Raman, G., Berkman, N. D., Grant, M., Janes, G., Maglione, M., Moher, D., Nasser, M., Robinson, K. A., Segal, J. B., and Tsouros, S.: Development quality criteria to evaluate nontherapeutic studies of incidence, prevalence, or risk factors of chronic diseases: pilot study of new checklists. *J Clin Epidemiol*, 64(6):637–57, Jun 2011.

Grant, M. D.: Fractional flow reserve and coronary artery revascularization. *Technol Eval Cent Assess Program Exec Summ*, 26(2):1–2, Jul 2011.

Grant, M.: Coronary computed tomographic angiography in the evaluation of patients with acute chest pain. *Technol Eval Cent Assess Program Exec Summ*, 26(9):1–3, Nov 2011.

Shamliyan, T., Ansari, M. T., Raman, G., Berkman, N., Grant, M., Janes, G., Maglione, M., Moher, D., Nasser, M., Robinson, K., Segal, J., and Tsouros, S.: Development and implementation of the standards for evaluating and reporting epidemiologic studies on chronic disease incidence or prevalence. *Am J Pub Health Res*, 7:183–90, 2013.

Mauger, B., Benloucif, S., and Grant, M.: Beta amyloid imaging with positron emission tomography (PET) for evaluation of suspected Alzheimer's disease or other causes of cognitive decline. *Technol Eval Cent Assess Program Exec Summ*, 27(5):1–4, Feb 2013.

Grant, M. D., Piper, M., Bohlius, J., Tonia, T., Robert, N., Vats, V., Bonnell, C., Ziegler, K. M., and Aronson, N.: Epoetin and darbepoetin for managing anemia in patients undergoing cancer treatment: Comparative effectiveness update. *AHRQ Comparative Effectiveness Reviews*, Apr 2013.

Gutman, S. I., Piper, M., Grant, M. D., Basch, E., Oliansky, D. M., and Aronson, N.: Progression-free survival: What does it mean for psychological well-being or quality of life? AHRQ Methods for Effective Health Care, Apr 2013.

Piper, M. and Grant, M.: Sequencing-based tests to determine fetal Down syndrome (Trisomy 21) from maternal plasma DNA. *Technol Eval Cent Assess Program Exec Summ*, 27(10):1–6, Apr 2013.

Piper, M. and Grant, M.: Special Report: Exome sequencing for clinical diagnosis of patients with suspected genetic disorders. *Technol Eval Cent Assess Program Exec Summ*, 28(5):1–4, Aug 2013.