

EPIDEMIOLOGY AND NATURAL HISTORY

CHAPTER 1

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REDUCING THE GLOBAL BURDEN OF STROKE

Stroke is the second leading cause of both death and disability-adjusted life years worldwide.^{1, 2} Around 15 million people suffer a stroke every year. Of these, 5 million are fatal and another 5 million leave people with permanent disability.³ Around 85% of strokes are ischemic in origin, resulting from an arterial occlusion of the cerebral circulation. Fifteen percent of ischemic strokes are caused by carotid artery stenosis, an athero-occlusive disease of the internal carotid artery.⁴⁻⁶ Compared to other stroke subtypes, carotid strokes tend to be unheralded, more disabling, and more likely to be fatal than strokes arising from intracranial atherosclerosis.⁷

Over the last half century age-standardized stroke incidence has declined markedly in developed countries, mainly due to effective primary prevention strategies (Figure 1). However in many developing countries, the transition from communicable disease burden to non-communicable disease burden has led to a large increase in the overall incidence of stroke. Evidence-based stroke care, such as thrombolysis and rehabilitation, are often not available in low-income settings, leading to particularly devastating outcomes for patients in these regions.^{8, 9} The most effective and practicable method for reducing the global burden of stroke is therefore through population and targeted prevention. Identification and widespread implementation of effective primary and secondary prevention strategies are key to reducing the enormous loss-of-life and disability that is currently caused by stroke.

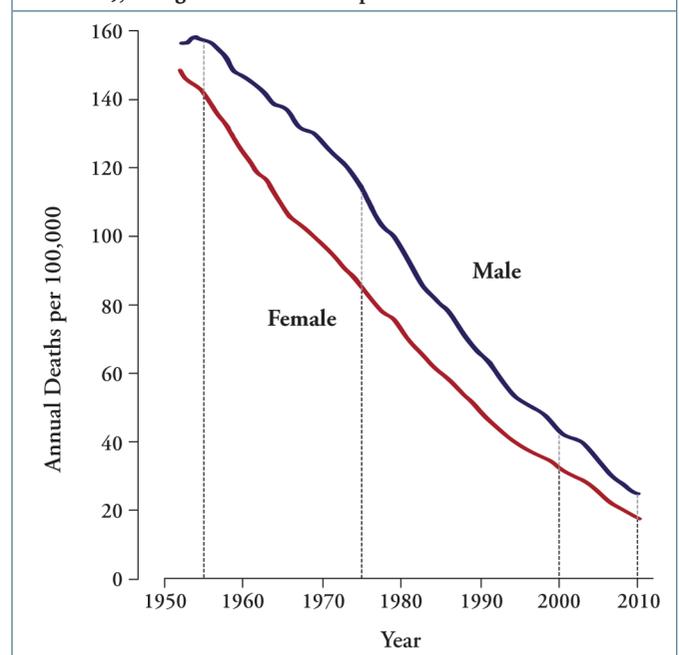
Primary stroke prevention involves lifestyle changes and medical treatments aimed at preventing the early development of vascular disease. Tobacco control, blood pressure-lowering and cholesterol-lowering treatments have been highly effective

in reducing cardiovascular mortality and morbidity in developed countries. Smoking is one of the strongest risk factors for cardiovascular disease, and is associated with about a three-fold increased risk of stroke mortality.¹⁰ Over half of all persistent tobacco smokers are killed by their habit.¹¹ However much of this excess risk can be avoided through early smoking cessation. For example, stopping smoking before the age of 40 avoids >90% of this excess mortality, and stopping before

Figure 1.1

Trends in UK age-standardized stroke mortality rates among people aged 35-69 years from 1950-2010.

Adapted from <http://www.mortality-trends.org> (Gary Whitlock), using WHO and UN Population Division data.



age 30 avoids >97% excess mortality.¹⁰ In terms of medical therapy, every 10 mmHg reduction in systolic blood pressure from antihypertensive medication reduces the risk of stroke by a quarter (relative risk [RR] 0.73, 95% confidence interval [CI] 0.68-0.77).¹² A 1 mmol/L reduction in low density lipoprotein cholesterol (LDL-C) from statin therapy also reduces stroke risk by one quarter.¹³ More contemporary statin regimens can produce about a 2 mmol/L reduction in LDL-C, reducing stroke risk by up to 45%.¹⁴ Individual patient-data meta-analysis of all available randomized statin trials suggest a probable, but small excess of hemorrhagic stroke ($\leq 0.1\%$ absolute risk increase over 5 years); however this is outweighed by the much larger reductions in ischemic stroke, myocardial infarction and death.¹⁵ In the primary prevention setting, antiplatelet therapy has no net effect on stroke, as reductions in ischemic stroke are offset by increased risk of hemorrhagic stroke.¹⁶ Current guidelines therefore do not recommend aspirin for primary stroke or cardiovascular prevention.¹⁷

The absolute risk of stroke in people with pre-existing vascular disease is considerably higher than in the primary prevention setting. Therefore, while the proportional benefits of effective medical therapy are similar to those seen in primary prevention studies, the absolute benefits (in terms of number of strokes avoided) are large in the secondary prevention setting. In addition to blood pressure-lowering and LDL-C-lowering medication, antiplatelet therapy produces a net reduction in stroke and other vascular events in this population.¹⁶ Taken together, effective triple medical therapy (*i.e.*, aspirin, antihypertensive and statin) may proportionally reduce the risk of stroke by more than 50%.

In addition to population prevention measures, targeted interventions aimed at removing key causes of arterial embolization, including carotid stenosis and atrial fibrillation, can substantially reduce the risk of stroke. Interventions, such as carotid revascularization and long-term anticoagulation, carry inherent risks but may produce large reductions in stroke risk for selected people with carotid stenosis and atrial fibrillation, respectively. As will be discussed in depth, successful carotid revascularization reduces the long-term risk of stroke by about a half in selected patients with carotid stenosis $\geq 60\%$. Whilst the benefits of revascularization are clear in both asymptomatic and symptomatic patients, the absolute benefits are greater in symptomatic patients who have a higher absolute stroke risk. Understanding the patient's absolute stroke risk, as determined by their demographic background, clinical history, and imaging features is therefore of particular importance in guiding the decision for carotid surgery in asymptomatic patients. Together, widespread implementation of tobacco control, effective medical therapy and targeted interventions in people with carotid stenosis and atrial fibrillation may reduce the global burden of stroke substantially. The following chapters explore specifically the burden of stroke caused by carotid stenosis, including epidemiology and natu-

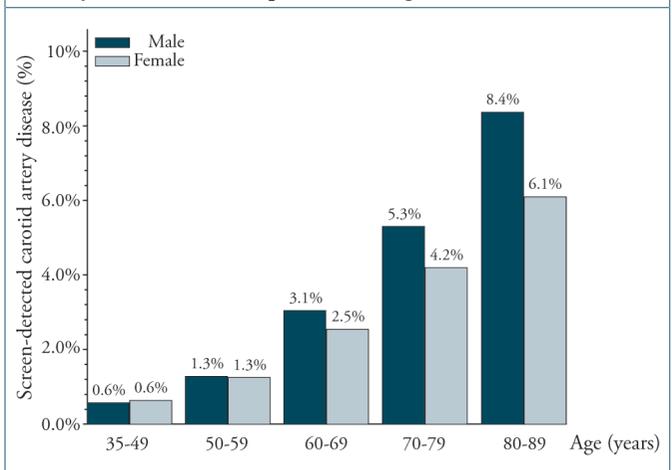
ral history, diagnostic imaging modalities, effective treatment as determined by randomized clinical trials, and issues specific to carotid revascularization.

PREVALENCE AND DETERMINANTS OF CAROTID ARTERY STENOSIS

Carotid stenosis is a relatively common disease in Western countries. Published screening studies report the prevalence of moderate carotid stenosis to be around 3-4% in older adults. An individual patient data meta-analysis, comprising 23,706 participants from four population screening studies, showed that the prevalence of moderate carotid stenosis was very low below the age of 50 years, but increased approximately linearly with every decade of age thereafter. For men, the prevalence increased to almost 8% in those over 80 years old: 0.2% (<50 years), 0.7% (50-59 years), 2.3% (60-69 years), 6.0% (70-79 years) and 7.5% (≥ 80 years); whereas in women the prevalence increased to 5% in those over 80 years old: 0.0% (<50 years), 0.5% (50-59 years), 2.0% (60-69 years), 3.6% (70-79 years), 5.0% (≥ 80 years). In the large Life Line Screening study, which included 2.5 million people who attended commercial vascular screening in the USA and UK, the prevalence of moderate carotid stenosis was also about 3%, and was higher in men than women (Figure 2). Interestingly, given that the Life Line Screening population reflects a self-selected population who may be from a higher socio-economic background and therefore healthier, the prevalence estimates in this study may well underestimate the true population prevalence of carotid artery stenosis. Data from Life Line Screening suggests possible ethnic differences in the prevalence of carotid stenosis.¹⁸ Native American and Caucasian individuals had the highest

Figure 1.2

Age- and sex-specific prevalence of carotid artery stenosis among Life Line Screening attendees. Carotid artery stenosis generally defined as a peak systolic velocity ≥ 110 cm/s on duplex screening.



prevalence of carotid stenosis overall, whereas the prevalence was low among people with African-American, Asian and Hispanic backgrounds. These findings differ from other population studies that report higher stroke rates among people with African-American and Asian backgrounds.¹⁹

Several modifiable risk factors have been identified for cardiovascular disease through large prospective observational studies. As carotid stenosis shares the same underlying pathology as coronary artery disease, many of the risk factors are similar. The major modifiable risk factors for carotid stenosis include smoking, blood pressure, adiposity, blood cholesterol and diabetes.

Smoking

Tobacco smoking is a strong risk factor for vascular disease, including carotid stenosis, and remains an important public health problem. Over the first half of the twentieth century, tobacco consumption increased greatly while the harms of smoking were largely unsuspected. This resulted in a rapid increase in lung cancer, leading to several case-control studies reporting in the 1950s that smoking was “a cause, and an important cause” of lung cancer.²⁰ However it was not until larger prospective studies were conducted, such as the British Doctors study, that the hazards of smoking were fully appreciated.¹¹ Large epidemiological studies of over one million people demonstrate that smoking is associated with a four-fold higher risk of ischemic heart disease mortality, and a three-fold higher risk of stroke mortality.¹⁰ Data from Life Line Screening suggests that smokers have more than a three-fold risk of developing carotid stenosis compared to people who have never smoked, and previous smokers have about half this risk.²¹

Blood pressure

High blood pressure is a leading cause of preventable death worldwide, with rates of hypertension increasing substantially over the last 25 years.²² The largest analysis of the association between blood pressure and cardiovascular events is the Prospective Studies Collaboration which included over one million people from 61 different studies. This pooled analysis reported that each 20 mmHg higher systolic blood pressure and 10 mmHg higher diastolic blood pressure was associated with a doubling in vascular risk. Importantly, the PSC accounted for measurement error and regression-dilution bias that had previously led to systematic underestimation of the magnitude of association between blood pressure and vascular events. Large randomized clinical trials confirm that the association between blood pressure and vascular disease is causal and that the risk is reversible.²³ In the Life Line Screening study, the association between systolic blood pressure and carotid stenosis was slightly more moderate.²¹

Every 20 mmHg higher systolic blood pressure was associated with about a 60% higher risk of carotid stenosis. Screening attendees with a systolic blood pressure of over 160 mmHg had more than double the risk of carotid stenosis compared to people with a systolic blood pressure of 120 mmHg.²¹ There was no apparent hazardous effect of low systolic blood pressure on carotid stenosis risk. Traditionally, the target of 140 mmHg has been used to guide the decision to treat blood pressure, however recent randomized evidence suggest systolic blood pressure targets as low as 120 mmHg may prevent many more cardiovascular events in the secondary prevention setting.^{24, 25}

Blood cholesterol

Blood cholesterol, in particular LDL-C, is causally associated with cardiovascular disease. The main determinants of circulating cholesterol concentrations appear to be dietary intake, genetic polymorphisms, and other factors.²⁶ Pooled analysis of prospective observational studies demonstrate continuous positive associations between LDL-C, triglycerides with cardiovascular disease, and inverse associations between high density lipoprotein cholesterol (HDL-C) and cardiovascular disease.^{27, 28} In the Life Line Screening study, the risk of carotid stenosis increased by over 40% per 1 mmol/L higher usual LDL-C, and by three quarters per doubling in usual triglyceride concentration.²¹ Conversely, each 1 mmol/L higher usual HDL-C, was associated with about a 40% lower risk of carotid stenosis. After adjusting the lipid fractions mutually for each other, LDL-C remained strongly associated with carotid stenosis whereas the associations for the other lipid fractions were considerably attenuated.²¹ These findings coincide with evidence from large randomized trials, which demonstrate important vascular benefits from LDL-C lowering drugs such as statins, mild benefit from triglyceride-lowering therapy and no benefit from HDL-C raising drugs.^{15, 29-33}

Adiposity

Like hypertension, the prevalence of overweight and obesity are increasing worldwide.³⁴ The association between adiposity and cardiovascular disease is more moderate, but still highly relevant. Small changes in population body mass index (BMI) could potentially produce large absolute changes in the prevalence of cardiovascular disease. The Global BMI Mortality Collaboration reported that each 5-unit increase in BMI above 25 kg/m² was associated with a 50% higher risk of cardiovascular death.³⁵ However people with a BMI less than 20 kg/m² had a higher risk of cardiovascular death than those with a BMI between 22.5 and 25. Importantly, this study was restricted to people who had never smoked and did not have cardiovascular disease at baseline to avoid reverse causation of these effects on body weight. Similar analyses of Life Line

Screening data suggest a 20% higher risk of carotid stenosis with every 5 unit increase in BMI above 25 kg/m².²¹ Few of the Life Line Screening attendees were underweight so it was not possible to assess the association of very low BMI with carotid stenosis.

Diabetes

Diabetes now affects over a third of older adults in the USA and the prevalence is increasing considerably in developing countries.³⁶ Large-scale meta-analysis of published prospective studies show that having diabetes is associated with double the risk of vascular mortality.³⁷ Similarly, in the Life Line Screening study, people with a history of diabetes had double the risk of having carotid stenosis. Interestingly, higher blood glucose levels across the normal reference range were also associated with increased risk of carotid stenosis.²¹ These findings suggest that blood glucose-lowering interventions, such as lifestyle modifications or pharmacotherapy, may potentially also reduce the risk of carotid stenosis and cardiovascular disease in people without diabetes.

Many major risk factors for carotid stenosis have been established, and large randomized clinical trials have demonstrated that modification of these risk factors reduces the risk of stroke. While worldwide tobacco consumption is decreasing in many countries, the trends for increasing rates of hypertension, obesity, and diabetes are concerning. Increasing efforts to tackle these important risk factors are needed, particularly in developing countries, to reduce the early development of vascular disease such as carotid stenosis.

NATURAL HISTORY OF CAROTID ARTERY STENOSIS

Observational studies on the natural history of carotid stenosis, among people who do not receive a carotid intervention, provide important information on the long-term harm caused by this disease. Such information can be used together with randomized evidence to guide the decision for carotid intervention. The risk of stroke is highly dependent on the symptomatic status of the patient, so these two populations should be considered separately. Asymptomatic patients tend to have more stable disease and a lower risk of stroke. Symptomatic patients, who have had a recent ipsilateral stroke or TIA, have a high risk of having a stroke within weeks of their symptoms onset. Other major determinants of stroke risk in people with carotid stenosis include the use of effective cardiovascular medical therapy (such as aspirin, blood pressure lowering, and a statin) and, in symptomatic patients, the degree of their carotid artery narrowing.

Analysis of observational studies conducted in people with asymptomatic disease demonstrate reductions in the rates of

ipsilateral stroke over the last 30 years, but reports which seek to compare event rates between very heterogeneous study populations have statistical and methodological flaws and should be read with caution.³⁸ Early studies recruiting before 1985 reported ipsilateral stroke rates of about 2-4% *per annum*. The ipsilateral stroke rates have steadily declined to around 1% per annum in 2010, suggesting at least a halving in stroke risk consistent with effective medical therapy. Interestingly, the same downward trends have not been observed for any-territory stroke. Early reports of the rates of any-territory stroke were highly heterogeneous, and few studies have been published after the year 2000 when statin use increased dramatically. Rates of contralateral strokes may be declining in this population, although there is limited observational evidence available on this. Some features that have been shown to be associated with a higher risk of stroke in asymptomatic people include chronic kidney disease, high grade ipsilateral stenosis, prior contralateral symptoms, cerebral infarction on imaging and adverse plaque morphological features.³⁹⁻⁴¹

Symptomatic patients with tight carotid stenosis have a higher absolute stroke risk and are generally recommended to undergo a carotid procedure to prevent stroke.⁴²⁻⁴⁵ Therefore there is limited data on the natural history of symptomatic carotid artery stenosis in the 21st century. The risk of stroke in symptomatic patients who are treated medically increases by about 20% with every 10% greater stenosis until near occlusion.⁴⁶ Symptomatic patients with complete occlusion who are medically treated have half the risk of stroke than people without occlusion. Importantly, the risk of stroke increases with symptoms. Those with ocular symptoms have the lowest risk of stroke. This risk increases across people who have had a single TIA (40% higher risk), multiple TIAs (doubling in risk), minor stroke (doubling in risk) and major stroke (2.5 x risk).⁴⁶ As with asymptomatic patients, symptomatic patients with adverse plaque morphological features, such as ulceration, have about twice the risk of stroke.⁴⁶ These risk factors can be used to identify patients who may derive greatest benefit from a carotid intervention. For example, the use of a simple symptomatic risk model incorporating patient's age, sex, percent stenosis, symptoms, time since last event and plaque morphological features, can help stratify patients with a 5-year absolute stroke risk ranging from <10% to >50%.⁴⁶ Individuals with the highest absolute stroke risk derived the greatest absolute reductions from carotid surgery, whereas lower risk individuals may derive more moderate benefits.

THE NEED FOR LARGE-SCALE RANDOMIZED EVIDENCE

Most of the available evidence for the management of carotid stenosis comes from clinical trials and observational studies. Observational studies have had an important role in the

identification of medical treatments with very large benefits or adverse effects, but are prone to systematic biases that may distort the assessment of moderate treatment effects.⁴⁷ In the 20th century, many highly effective medical treatments were detected through observational studies, such as the benefits of penicillin on survival for patients with sepsis, and the effect of introducing oral rehydration therapy in a cholera endemic.^{48, 49} In these examples, the magnitude of the effect size far outweighed that of any possible confounders, leading to definitive conclusions about the efficacy of the treatment. However most chronic diseases, such as carotid stenosis, have complex multi-factorial pathologies, so the most plausible expectation of benefit is that a treatment produces moderate, yet clinically worthwhile effects on serious outcomes, particularly if that condition (like stroke) is common. In general, if uncertainty still exists regarding a commonly used treatment, such as carotid endarterectomy or stenting, then any effects on mortality or major morbidity are likely to be at best moderate in magnitude.⁵⁰ In many cases, moderate treatment effects may still be regarded as worthwhile by patients and doctors, provided the risks are small. If moderate treatment effects are to be detected or refuted reliably, then any errors in their measurement must be much smaller than the effect of the treatment. This

implies that assessment of potentially effective treatments requires both strict control of confounding bias, through proper randomization, and minimization of random error with a sufficiently large sample size.⁵¹ There are many areas in the management of carotid stenosis where there is clinical uncertainty, such as the decision for intervention in asymptomatic patients, the choice of carotid endarterectomy *vs.* carotid stenting, and the timing of carotid interventions. Large randomized clinical trials, and meta-analyses of such trials, are required to provide reliable evidence on the management of carotid stenosis for the decades to come.⁵² If current trials comparing carotid procedure *vs.* no carotid procedure in the era of good medical therapy with statins, anti-thrombotics, and anti-hypertensives, confirm the finding of additional benefit from a carotid procedure in asymptomatic patients, then throughout the 2020s and beyond, the key question will be which procedure to recommend. The Asymptomatic Carotid Surgery Trial-2 (ACST-2) and an individual patient data meta-analysis including over 6000 patients (from ACST-2, Carotid Revascularization Endarterectomy *versus* Stenting Trial-1 [CREST-1], Stent Protected Angioplasty *versus* Carotid Endarterectomy-2 [SPACE-2], Asymptomatic Carotid Trial I [ACT I]) will provide uniquely reliable results in the 2020s.⁵³⁻⁵⁶

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