Chapter 1
Epidemiology of Stroke

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Key Points

- Stroke is the fourth leading cause of death in the USA, and it is the *second* leading cause of death worldwide.
- Although there has been a decline in stroke incidence and mortality in the USA, this trend is not expected to last. With the aging of the population, the incidence and deaths from stroke are likely to skyrocket, and epidemiologists have warned of a stroke epidemic in the next 25 years.
- Stroke incidence and mortality will increase more quickly in low-income and middle-income countries because of the increases in the prevalence of risk factors for cardiovascular disease, including urbanization and Western-style dietary changes.

Keywords Epidemiology • Stroke • Mortality • Incidence • Intracerebral hemorrhage

Abbreviations

AF	Atrial Fibrillation
DALYs	Disability Adjusted Life Years
ICH	Intracerebral Hemorrhagic Stroke
SAH	Subarachnoid Hemorrhage
TIA	Transient Ischemic Attack

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Overview of Stroke in the USA

Stroke is a major public health concern. The prevalence of stroke in the USA is roughly 3 % of the adult population. Each year, approximately 795,000 people experience a new or recurrent stroke. Most of these (610,000) are first-ever strokes. This translates to someone in the USA having a stroke every 40 s, on average [1]. Although stroke can occur at any age, the incidence increases with age: there is a doubling for each decade after age 55 [1].

Of all strokes, 87 % are ischemic, 10 % are intracerebral hemorrhagic strokes (ICH), and 3 % are subarachnoid hemorrhage strokes (SAH) [1]. Mexican Americans, Latin Americans, African Americans, Native Americans, Japanese people, and Chinese people have higher incidences of hemorrhagic stroke than do white Americans.

African Americans have a risk of first-ever stroke that is almost twice that of whites. The increased incidence is most prominent for young and middle-aged African Americans, who have a substantially higher risk of SAH and ICH than whites of the same age [2]. In 27,744 participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study, which were followed over 4.4 years (2003–2010), the overall age and sex-adjusted black/white incidence rate ratio was 1.51, but it was lower for the very old and very young. For ages 45–54 years, it was 4.02, and for those ≥85 years of age, it was 0.86 [3].

Stroke ranks fourth among all causes of death, behind diseases of the heart, cancer, and chronic lower respiratory disease. In 2008, stroke accounted for ~1 of every 18 deaths in the USA. In comparison, coronary heart disease caused ~1 of every 6 deaths that year. On average, someone dies of a stroke every 4 min [4].

Several studies have shown a decrease in the age-adjusted annual incidence of first stroke among both men and women. One of the larger analyses is from the Framingham Heart Study. The age-adjusted incidence of first stroke per 1,000 person-years in this analysis declined in men from 7.7 during years 1950–1977, 6.2 during years 1978–1989, and down to 5.3 during 1990–2004. The decline in women was 6.2, 5.8, and 5.1 per 1,000 person-years, respectively. Although the incidence declined over time, the lifetime risk did not decline to the same degree, likely due to improved life expectancy.

In addition to the decline in incidence, there has been some decline in stroke mortality. From 1998 to 2008, the stroke death rate in the USA fell 34.8 %, and the actual number of stroke deaths declined 19.4 % [1]. This decline also occurred in heart disease; over the same time period, the rate of death from cardiovascular disease declined 30.6 %. The decline in mortality has been attributed to both a decreasing case fatality and a decrease in stroke incidence [1].

Although the incidence and mortality of overall stroke has decreased in the USA, a review of published studies and data from clinical trials found that hospital admissions for intracerebral hemorrhage have increased by 18 % in the past 10 years. This is likely due to an increase in age of population and the increasing use of anticoagulants, thrombolytics, and antiplatelet agents. In the Greater Cincinnati/Northern Kentucky Stroke Study, the annual incidence of anticoagulant-associated intracerebral hemorrhage per 100,000 people increased over time, from 0.8 (95 % CI 0.3–1.3) in

1988 to 1.9 (95 % CI 1.1–2.7) in 1993/1994 and 4.4 (95 % CI 3.2–5.5) in 1999 ($P<0.001$ for trend). Among people ≥80 years of age, the rate of anticoagulant-associated intracerebral hemorrhage increased from 2.5 (95 % CI 0–7.4) in 1988 to 45.9 (95 % CI 25.6–66.2) in 1999 ($P<0.001$ for trend). Over this period of time, incidence rates of cardioembolic ischemic stroke were similar, but warfarin use in the USA increased fourfold, suggesting a difference in preventive management strategies [1].

Worldwide Perspective

Although stroke is the fourth leading cause of death in the USA, it is the *second* leading cause of death worldwide. It is estimated that 87 % of stroke deaths occur in low- and middle-income countries. Stroke is also the fourth leading cause of lost productivity [5] and in disability-adjusted life years (DALYs) worldwide, behind only HIV/AIDS, unipolar depression and heart disease [6]. Disease burden is typically quantified in DALYs where 1 DALY is 1 year of "healthy" life lost. The burden of disease is defined as the gap between the current health of a population and an ideal situation in which everyone in the population lives to old age in full health [6]. Although incidence of stroke is higher in the elderly, because of the increased longevity of younger stroke survivors, two-thirds of the burden of stroke in the world occurs in people under age 70 years.

Worldwide estimates indicate that primary hemorrhages constitute a higher percentage of all strokes than in the USA, ranging from 10 to 25 %. Individuals of Asian, African, and Latin American origin tend to have a higher frequency of primary hemorrhage than persons of European origin [1].

Future Trends

Although there has been a decline in stroke incidence and mortality in the USA, this trend is not expected to last. With the aging of the population, the incidence and deaths from stroke are likely to skyrocket, and epidemiologists have warned of a stroke epidemic in the next 25 years [7–9]. Projections show that by 2030, an additional four million people in the USA will have had a stroke, a 24.9 % increase in prevalence from 2010 [10].

Using data from the National Center of Health Statistics and population projections from the US Census Bureau, Elkins and Johnston calculated an expected number of deaths in the USA from ischemic stroke in 30 years. They projected a 98 % increase over the 30-year period from 2002 to 2032. The total US population was projected to increase by only 27 % in the same period and much of this estimated increase in death was due to aging of the population and changes in the racial and ethnic composition of the USA [11].

It is possible that, although improvement in primary prevention efforts for stroke and heart disease will help, it may paradoxically complicate the problem to

some extent. Patients treated with antithrombotics for stroke prevention may suffer a more severe hemorrhagic stroke, and patients who avoid cardiac death may survive and be at risk for the development of stroke, since the stroke risk increases with age [12].

The situation is even more dire when looking at projections worldwide. Stroke incidence and mortality will increase more quickly in low-income and middle-income countries because of the increases in the prevalence of risk factors for cardiovascular disease, including urbanization and Western-style dietary changes [6]. Without additional population-wide interventions, figures are predicted to increase to a 23 million first-ever strokes, 77 million stroke survivors, and 7.8 million deaths by 2030. This suggests that for any management strategies to have impact on world mortality, they must be implemented within low- and middle-income countries [6].

Risk Factors

Prevention is the most effective method of reducing the burden of stroke on society [6, 7]. The 2009 standardized case–control INTERSTROKE study provides important information on risk factors for stroke across the globe [13]. The study was the first large standardized case–control study of risk factors for stroke in which countries of low and middle income were included. The study evaluated attributable risk of stroke in 3,000 cases and 3,000 controls in 22 countries (Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Croatia, Denmark, Ecuador, Germany, India, Iran, Malaysia, Mozambique, Nigeria, Peru, Philippines, Poland, South Africa, Sudan, and Uganda) and found the same risk factors in low- and middle-income countries as in high-income countries [13]. The study also found that five risk factors accounted for more than 80 % of the global risk of all stroke: hypertension, current smoking, abdominal obesity, diet, and physical activity [13]. An additional five risk factors increase the populational attributable risk of stroke to 90 %: excessive alcohol consumption, dyslipidemia (measured by ratio of apolipoproteins B to A1), cardiac causes (atrial fibrillation or flutter, previous myocardial infarction, rheumatic valvular heart disease, and prosthetic heart valve), and psychosocial stress/depression (see Table 1.1). Importantly, many of these risk factors are actionable. Some of the most significant ones are discussed below.

Hypertension

In INTERSTROKE, hypertension was associated with the highest estimated population-attributable fraction of 52 %, as has been seen in the past in prior epidemiology studies. Participants in INTERSTROKE with self-reported hypertension or blood pressure (BP) >160/90 mmHg were 2.8 times more likely to have a stroke than those without hypertension. Control of blood pressure is associated with a significant reduction in risk of stroke. A large meta-analysis of clinical trials found a 41 %

Table 1.1
Risk of stroke associated with risk factors in the INTERSTROKE study (multivariate analyses)

Variable	Odds ratio (99 % CI)	Population-attributable risk
Hypertension (self-reported history of hypertension or BP >160/90 mmHg)	3.89 (3.33–4.54)	51.8 % (47.7–55.8)
Current smoker	2.09 (1.75–2.51)	18.9 % (15.3–23.1)
Waist-to-hip ratio		
Tertile 2 vs. tertile 1	1.42 (1.18–1.71)	26.5 % (18.8–36.0)[a]
Tertile 3 vs. tertile 1	1.65 (1.36–1.99)	
Diet risk score		
Tertile 2 vs. tertile 1	1.35 (1.12–1.61)	18.8 % (11.2–29.7)[a]
Tertile 3 vs. tertile 1	1.35 (1.11–1.64)	
Regular physical activity	0.69 (0.53–0.90)	28.5 % (14.5–48.5)
Diabetes mellitus	1.36 (1.10–1.68)	5.0 % (2.6–9.5)
Alcohol intake		
1–30 drinks per month	0.90 (0.72–1.11)	3.8 % (0.9–14.4)[a]
>30 drinks per month or binge drinker	1.51 (1.18–1.92)	
Psychosocial factors		
Psychosocial stress	1.30 (1.06–1.60)	4.6 % (2.1–9.6)
Depression	1.35 (1.10–1.66)	5.2 % (2.7–9.8)
Cardiac causes (atrial fibrillation or flutter, previous myocardial infarction, rheumatic valve disease, or prosthetic heart valve)	2.38 (1.77–3.20)	6.7 % (4.8–9.1)
Ratio of ApoB to ApoA1		
T2 vs. T1	1.13 (0.90–1.42)	24.9 % (15.7–37.1)[a]
T3 vs. T1	1.89 (1.49–2.40)	

T tertile, *Apo* apolipoprotein, *BP* blood pressure
[a]For variables expressed in tertiles, population-attributable risk was calculated from T2 plus T3 vs. T1. Population-attributable risk of alcohol calculated from any vs. none
Adapted from The Lancet, 360, O'Donnell MJ, Xavier D, Liu L, et al., "Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the interstroke study): A case-control study," 1903–1913, Copyright 2010, with permission from Elsevier

reduction in stroke for a BP reduction of 10 mmHg systolic or 5 mmHg diastolic regardless of BP before treatment [14]. The risk of stroke has a continuous association with blood pressure down to 115/75 mmHg [15]. Subjects with BP <120/80 mmHg have approximately half the lifetime risk of stroke of subjects with hypertension. Current guidelines for primary prevention of stroke recommend treatment of BP to a goal of 140/90 mmHg, and for patients with diabetes or renal disease, the BP goal is <130/80 mmHg [2].

Diabetes Mellitus

In 2008, approximately 8 % of the adult population in the USA, which comprise 18,300,000 people, had diagnosis of diabetes mellitus. An additional 3.1 % (7,100,000) had undiagnosed diabetes [1]. The prevalence of diabetes mellitus has

been dramatically increasing over time, along with the increases in prevalence of overweight and obesity. Intensive glucose-lowering therapy (a glycolated hemoglobin [HbA_{1c}] level <7.0 %) has been shown to decrease the risk of microvascular complications and may or may not be beneficial for long-term reduction in the risk of cardiovascular disease [16]. Stroke risk can be reduced in patients with diabetes who receive risk factor modification in multiple areas. In the Steno-2 Study, 160 patients with type 2 diabetes and persistent microalbuminuria were assigned to receive either intensive therapy, including behavioral risk factor modification and a statin, antihypertensives, and an antiplatelet, or conventional therapy with a mean treatment period of 7.8 years. Patients were followed up for an average of 5.5 years. The risk of cardiovascular events was reduced by 60 % (HR, 0.41; 95 % CI, 0.25–0.67; $P<0.001$) with intensive treatment vs. conventional therapy, and the number of strokes was reduced from 30 to 6 [17].

Obesity

The estimated prevalence of being overweight (having a body mass index (BMI) of 25–29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) in US adults ≥20 years of age is 67.3 % in 2008, representing 149,300,000 people. One-third of US adults are obese. Men and women of all race/ethnic groups in the population are affected by the epidemic of overweight and obesity [1] The relative risk of death from stroke is 1.39 (95 % CI 1.31–1.48) per increase of 5 kg/m^2 in BMI [18]. Although no clinical trials have evaluated the effects of weight loss on stroke risk, several trials have demonstrated a reduction in BP with weight reduction [2].

Cigarette Smoking

There is strong and pervasive evidence of the deleterious effects of smoking on stroke, cardiovascular disease in addition to cancer. In 2010, among Americans 18 years of age or older, 21.2 % of men and 17.5 % of women were cigarette smokers. Perhaps more disheartening, the rate is similar in adolescents: in 2009, 19.5 % of students in grades 9 through 12 reported current cigarette use [1]. The risk of stroke among smokers tends to peak at middle age and declines with advancing age [19].

Physical Activity

A meta-analysis of studies found that moderately or highly active individuals had lower risk of stroke incidence or mortality than did low-active individuals [20]. Overall, moderately active individuals had a 20 % lower risk (RR = 0.80; 95 % CI, 0.74–0.86; $P<0.001$), and highly active individuals had a 27 % lower risk of stroke

incidence or mortality (RR = 0.73; 95 % CI, 0.67–0.79; $P < 0.001$) than low-active individuals. The 2008 Physical Activity Guidelines for Americans recommends that adults should engage in at least 150 min (2 h and 30 min) per week of moderate intensity or 75 min (1 h and 15 min) per week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity [21].

Lipids

Most but not all epidemiological studies have found an association between higher cholesterol levels and an increased risk of ischemic stroke, and they have demonstrated a benefit of lowering LDL in lowering stroke risk. One meta-analysis, for example, found that a reduction in LDL-C by 1 mmol/l (39 mg/dl) results in a decreased incidence of ischemic stroke by 16–17 % regardless of age, blood pressure, and pretrial blood lipid profile. Primary prevention guidelines for stroke recommend following the NCEP guidelines, which tailor goals and implementation of cholesterol-lowering agents based upon risk of cardiovascular event [2].

Atrial Fibrillation

Atrial fibrillation (AF) is a powerful risk factor for stroke that increases risk fivefold through all age groups. The prevalence of AF increases with age, from 1 % in the population aged under 50 years to approximately 10 % of those above 80 years. Because of the increasing prevalence with age, the percentage of strokes attributable to AF increases in older age groups, from 1.5 % at 50–59 years of age to 23.5 % at 80–89 years of age [1]. Because AF can be clinically undiagnosed, the stroke risk attributed to AF may be substantially underestimated [22]. The current American Heart Association/American Stroke Association guidelines recommend anticoagulation with either adjusted-dose warfarin (target international normalized ratio, 2.0–3.0) dabigatran, apixaban, or rivaroxaban for all high-risk patients at with nonvalvular atrial fibrillation [23]. Antiplatelet therapy is recommended for patients considered low risk for stroke.

Depression

Psychosocial stressors and depression have received less attention than other risk factors in stroke prevention efforts. There is growing evidence that these factors pose an increased risk factors for stroke. In a 2007 meta-analysis, for example, the pooled estimate for total stroke was 1.43 (95 % CI 1.17–1.75) [24]. There has been

some thought that the use of antidepressant medications could be contributing to this increased risk. Results from the Women's Health Initiative prospective cohort study among postmenopausal women demonstrated that antidepressant use, specifically selective serotonin reuptake inhibitors, increased the risk of stroke by almost 45 % [25]. The findings of an association between antidepressant use and stroke have been variable, however [26].

Transient Ischemic Attacks

Approximately 15 % of all strokes are heralded by a transient ischemic attack (TIA), and they provide an important opportunity for intervention to prevent a stroke. Estimates of the prevalence of TIAs in the USA have varied widely, ranging from 1.1 to 6.3 %, depending on the specific population studied, definition of TIA, and study design [27].

There is a significant short-term risk of stroke in patients who have experienced a TIA. One of the seminal studies evaluating this involved 1,707 TIA patients seen in the emergency departments of Kaiser Permanente, Northern California. Ten percent (108 patients) had a stroke within 90 days and 5 % (91 patients) had a stroke within 2 days [28]. Other cohorts of patients with TIA have confirmed the high short-term risk of stroke after TIA, which has been shown to be as high as 10 % at 2 days and as high as 17 % at 90 days [29]. Predictors of stroke in TIA patients in the Kaiser study and another cohort study of patients from Oxford UK [30] were jointly evaluated to develop the ACBD2 scale that determines the short-term risk of stroke based on specific symptoms [31] Items on the scale include age >60, blood pressure >140/90, clinical features (unilateral weakness, 2 points, or speech impairment without weakness, 1 point), duration (>60 min, 2 points, or 10–59 min,1 point), and diabetes.

Variability in the use of brain imaging and the type of diagnostic imaging used can markedly affect estimates of the incidence and prevalence of TIAs. With increasing use of imaging in the evaluation of TIAs, especially magnetic resonance imaging (MRI), there is realization that as many as 50 % of patients with transient deficits lasting <24 h have evidence of a stroke [32].

The traditional definition of a TIA is "a sudden, focal neurological deficit of presumed vascular origin lasting <24 h" [32]. The arbitrary 24-h time window used to differentiate TIA from stroke arose in the mid-1960s when less was known about pathophysiology of cerebral ischemia. There has been a move over the last few years for a formal change in the definition of TIA that would remove the time-based portion in the traditional definition. The new proposed definition is "transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction" [32]. One analysis estimated that the potential epidemiologic impact of adopting a tissue-based definition of TIA in the USA would lower annual incidence rates of TIA by 33 % and would increase the number of cases labeled as stroke by 7 % [33]. Regardless of official change in definition of TIA, the increased identification of permanent tissue injury on imaging in patients with transient deficits has already impacted current estimates of incidence and mortality.

Silent Strokes

With the increasing use of brain imaging, there is an increased recognition of "silent" strokes, which are not associated with focal clinical symptoms. Silent strokes are actually more common than clinical strokes, with prevalence estimates ranging from 6 to 28 % compared to a 3 % prevalence of clinical strokes. There is a higher prevalence of silent infarcts with increasing age [1]. These "silent infarcts" may cause memory symptoms. One cardiovascular health study evaluated 1,433 patients >65 years over a 5-year period with MRI scans. New infarctions not associated with focal neurological deficits were seen in 15.7 % subjects. The authors classified them as "covert" infarcts rather than silent because they showed decreased scores on the Modified Mini-Mental State Examination and Digit Symbol Substitution Test [34]. Similar findings were seen in the Rotterdam Scan Study, where1,015 patients underwent a neuropsychological and MRI twice an average of 3.6 years apart. Having a silent brain infarct at baseline doubled the risk of subsequent dementia (HR 2.26; 95 % CI, 1.09–4.70) and was associated with a steeper decline in global cognitive function [35].

Women

Women have lower age-adjusted stroke incidence than men; although each year, about 55,000 more women than men have a stroke. This is because of the larger numbers of elderly women compared to men. More women than men also die of stroke each year; in 2008 women accounted for 60.1 % of US stroke deaths [4] This differential mortality is due in part to the larger number of elderly women compared to men, but may also be partly due to a higher frequency of subarachnoid hemorrhage and a greater severity of ischemic stroke in women [36]. In addition, women are older at stroke onset on average than men (~75 years compared with 71 years) and may have poorer compensatory ability because of their older age at the time of stroke [37].

On top of the higher death rate from stroke, there are currently more women stroke survivors (2.1 million) than men (1.9 million). Most of these stroke survivors live with some disability, and it has been estimated that women spend approximately twice as many years disabled prior to death as their male counterparts [38]. Studies have also suggested worse functional outcomes after compared with men [36, 39] although it is likely that the older age at initial stroke in women largely accounts for this difference [39].

Finally, stroke also has a significant *indirect* impact on women. They significantly outnumber men as caregivers to stroke survivors. In the USA, 72 % of the caregivers are women. With the aging of the population, the global burden of stroke will increase and the mortality from stroke is expected to double in the next 25 years [9]. Because life expectancy is projected to increase more in women than men, the burden of stroke will continue to be heavier in women [40].

Outcomes

Stroke is a leading cause of major disability in adults. Living with severe disability from stroke has been considered by some to be worse than death [41]. Over 50 % of stroke survivors are functionally disabled. According to the Framingham Heart Study, among ischemic stroke survivors at 6 months who were >=65 years of age [42], 50 % had hemiparesis, 30 % were unable to walk without some assistance, 26 % were dependent in activities of daily living, 19 % had aphasia, 35 % had depressive symptoms, and 26 % were institutionalized in a nursing home. In addition to the physical and emotional toll, the cost of stroke is immense. Recent estimate of the mean lifetime cost of ischemic stroke in the USA is $140,048. This includes inpatient care, rehabilitation, and follow-up care necessary for lasting deficits (1999 dollars). This direct medical cost is estimated to increase by 238 % between 2010 and 2030, which is the largest relative increase of all cardiovascular diseases [10].

Conclusion

The prevalence of stroke in the USA is high and its cost will increase as the population ages. In addition, stroke incidence and mortality will increase in less developed countries due to changing lifestyles and population characteristics. The health burden from stroke will be tremendous and will further tax healthcare resources here in the USA and across the world. However, improvement in control of vascular risk factors could help offset the ominous stroke projections. One analysis, using the Archimedes model, estimated that if everyone received 11 recommended prevention activities, such as aspirin if their 10-year MI risk ≥10 %, lowering BP to 140/90 in nondiabetic people, lowering HgbA1C to <7.0 in diabetics, or reducing weight to body mass index <30 kg/m^2, and they achieved feasible improvements in their vascular risk factor status, strokes would be reduced 20 % in the next 30 years [37, 43]. For stroke that does occur, optimizing management will be critical to reduce disability and maximize functional outcomes.

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