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Chapter 9

Stroke

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INTRODUCTION

According to the World Health Organization's Global Health Estimates, stroke was the second-leading cause of death and the third-leading cause of disability-adjusted life years (DALYs) lost globally in 2012. In certain low- and middle-income countries (LMICs), such as China, the disease burden of stroke increased significantly over the past two decades, accounting for the most years of life lost in 2010. This chapter—the first on stroke in the history of the *Disease Control Priorities* publications—presents evidence on the disease burden of stroke, describing the epidemiology, disability, and socioeconomic burdens, then discusses modifiable and other risk factors for stroke. The chapter describes primary prevention, treatment, and management of stroke during the acute phase as well as secondary prevention of, and rehabilitation after, stroke, with a focus on cost-effective strategies in LMICs, where such evidence exists. The chapter concludes with recommendations for policy makers and future research directions.

There are two main types of stroke—ischemic, including transient ischemic attack, and hemorrhagic, including intracerebral and subarachnoid. The term *stroke* refers to all subtypes. The two main subtypes are distinguished from one another when appropriate because the etiology and management of these subtypes can be very different. Within the hemorrhagic subtype, we focus mainly on

intracerebral hemorrhage, given that subarachnoid hemorrhage occurs spontaneously, usually from a ruptured cerebral aneurysm, or results from a head injury.

DISEASE BURDEN

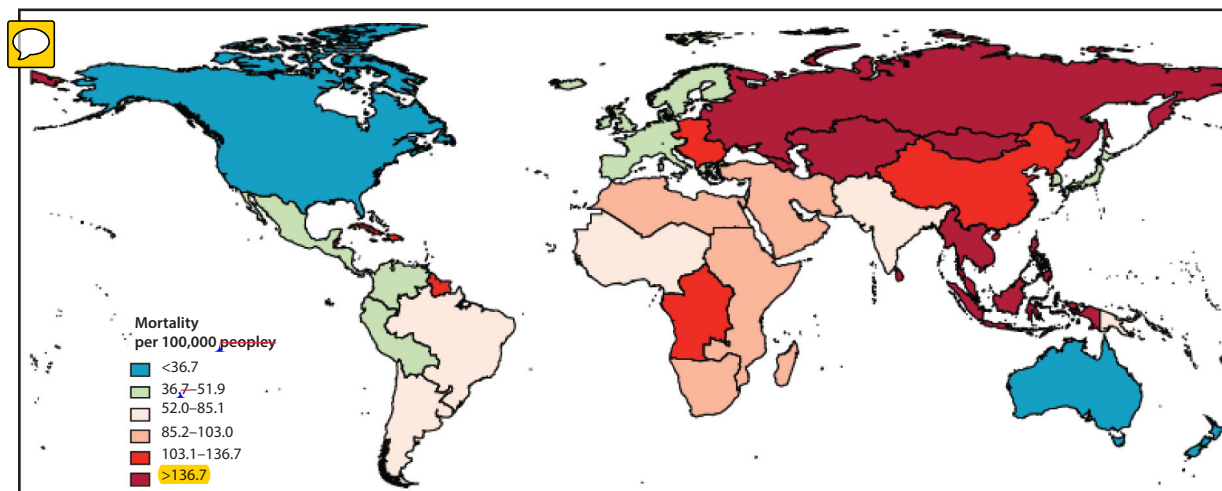
Existing Evidence

In 2010, there were 16.9 million cases of incident stroke; an additional 33 million stroke survivors were alive worldwide, more than half of them in LMICs (Feigin and others 2014). A systematic review of 12 population-based studies from 10 LMICs and 44 studies from 18 high-income countries (HICs) found significant disparities in stroke incidence trends between HICs and LMICs. Over the past four decades, stroke incidence decreased 42 percent in HICs but increased more than 100 percent in LMICs. From 2000 to 2008, estimated stroke incidence rates in LMICs surpassed those in HICs by approximately 20 percent (Feigin and others 2009).

Stroke mortality was highest in Central, Southeast, and East Asia; Central and Eastern Europe; and central Sub-Saharan Africa; it was lowest in HICs, Latin America, western Sub-Saharan Africa, and South Asia (map 9.1) (Feigin and others 2014). However, estimated mortality may be unreliable because few LMICs have the necessary funding and resources either to establish surveillance networks or to register data on stroke mortality.

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Map 9.1 Age-Standardized Stroke Mortality per 100,000 People, 2010



Source: Feigin and others 2014.

Projections indicate that stroke incidence, mortality, and DALYs will continue to rise in LMICs and that by 2030 there will be almost 12 million stroke deaths, 70 million stroke survivors, and more than 200 million DALYs lost globally each year. The heavy and increasing global burden of stroke reflects a pressing need for well-designed and comparable surveillance systems to track current trends and for prevention, treatment, and management programs to curb and treat strokes worldwide, especially in LMICs.

Impact on Disability

Disability often persists for a long time, sometimes permanently, after a stroke. According to an international survey of 11 sites in seven LMICs, stroke is the fourth-largest contributor to disability among people older than age 65 years (Sousa and others 2009). Yet the impact of stroke on disability could be underestimated because the impact of limb paralysis or weakness is not accounted for and the extent of cognitive impairment is not always fully assessed.

SOCIAL AND ECONOMIC BURDEN

Stroke results in substantial social and economic burdens around the world. The burden on caregivers is increasingly recognized as a significant health problem. Caregiving has been linked to higher rates of depression, anxiety, cardiovascular disease (CVD), general ill health, and mortality.

The economic burden of stroke is also significant. An international comparison of cost studies showed

that national health systems spent, on average, 0.27 percent of gross domestic product on stroke and that stroke care accounted for about 3 percent of total health care expenditures (Evers and others 2004). In the United States in 2008, the total direct and indirect costs of stroke were estimated to be US\$65.5 billion (Rosamond and others 2008). In the 27 European Union countries, the total annual costs of stroke were estimated to be US\$35.8 billion: US\$24.6 billion (68.5 percent) for direct and US\$11.3 billion (31.5 percent) for indirect costs (Allender, Scarborough, and Peto 2008). In China, the average cost for a stroke admission in 2004 was twice the annual income of rural residents, and the cost of stroke care for government-funded hospitals increased 117 percent annually between 2003 and 2007. The current literature provides no comprehensive analysis of the economic burden of stroke in LMICs, but it is reasonable to assume that it will continue to rise if current trends in stroke incidence and mortality persist and if prevention and control efforts are not intensified.

RISK FACTORS

Increased stroke incidence is associated with aging and urbanization and propelled by the increasing prevalence of key modifiable risk factors, especially in LMICs.

Modifiable Risk Factors

The INTERSTROKE Study, a large international case-control study of risk factors for incidence of stroke in 22 countries, including LMICs, found evidence of

10 significant modifiable risk factors, including history of hypertension, current smoking, diabetes mellitus, waist-to-hip ratio, diet risk score, physical inactivity, alcohol intake, psychosocial stress and depression, cardiac causes, and ratio of apolipoproteins B to A1 (O'Donnell and others 2010). All 10 risk factors were significant predictors of ischemic stroke; hypertension, smoking, waist-to-hip ratio, diet, and alcohol intake were significant predictors of hemorrhagic stroke. Table 9.1 summarizes evidence-based

estimates of relative risks, odds ratios, and hazard ratios associated with risk factors for stroke.

High Blood Pressure

High blood pressure is the leading risk factor for stroke, accounting for an estimated 52 percent of all stroke deaths (O'Donnell and others 2010). Lower blood pressure is associated not only with a lower risk of stroke, but also with a lower risk of reoccurrence among stroke survivors.

Table 9.1 Relative Risks, Odds Ratios, or Hazard Ratios of Risk Factors for Stroke

Risk factor	Reference	Type of study	Results
High blood pressure	Di Legge and others 2012	Review	A close, progressive, and approximately linear relationship exists between blood pressure levels and primary incidence of stroke.
	Prospective Studies Collaboration 1995	Review	A fivefold difference in stroke risk exists between the highest blood pressure categories (usual diastolic blood pressure of 102 mmHg) and the lowest ones (usual diastolic blood pressure of 75 mmHg).
	Lewington and others 2002	Meta-analysis	At ages 40–69 years, each difference of 20 mmHg in usual systolic blood pressure is associated with a more than twofold difference in the stroke death rate.
	Asia Pacific Cohort Studies Collaboration 1998	Cohort studies	Each 5 mmHg lower increment of usual diastolic blood pressure is associated with lower risk of both nonhemorrhagic (odds ratio of 0.61; 95% CI, 0.57–0.66) and hemorrhagic stroke (odds ratio of 0.54; 95% CI, 0.50–0.58).
Tobacco use	Thun and others 2013	Cohort studies	In contemporary cohorts, male and female current smokers have similar relative risks for death from stroke (1.92 for men and 2.10 for women).
	Jha and others 2013	Cohort study	Adjusted hazard ratios for death from stroke among current smokers compared with persons who never smoked is 3.2 (99% CI, 2.2–4.7) for women and 1.7 (99% CI, 1.0–2.8) for men.
	Shah and Cole 2010	Review	Current smokers have at least a two- to fourfold higher risk of stroke than lifelong nonsmokers or individuals who have not smoked for more than 10 years.
Diabetes mellitus	Luitse and others 2012	Review	People with diabetes have more than double the risk of ischemic stroke relative to individuals without diabetes.
	Banerjee and others 2012	Cohort study	Compared with nondiabetic participants, those with diabetes for 0–5 years (adjusted hazard ratio of 1.7), 5–10 years (1.8), and more than 10 years (3.2) are at increased risk of ischemic stroke.
Diet and nutrition	Sharma and others 2013	Cohort study	High consumption of fruits and vegetables is associated with lower risk of stroke; adherence to the U.S. Department of Agriculture dietary recommendations for vegetable intake among women is associated with a reduced risk of fatal stroke, although this result is not statistically significant (relative risk of 0.84; 95% CI, 0.68–1.04).
	He and others 1999	Cohort study	Among overweight persons, a 100 mmol higher sodium intake is associated with a 32% increase (relative risk of 1.32; 95% CI, 1.07–1.64) in stroke incidence and 89% increase (relative risk of 1.89; 95% CI, 1.31–2.74) in stroke mortality.
	Nagata and others 2004	Cohort study	Associations between sodium intake and death from ischemic stroke are significantly positive (hazard ratio of 3.22; 95% CI, 1.22–8.53).

table continues next page

Table 9.1 Relative Risks, Odds Ratios, or Hazard Ratios of Risk Factors for Stroke (continued)

Risk factor	Reference	Type of study	Results
Overweight and obesity	Yan and others 2006	Cohort study	Overweight and obesity increases the risk of stroke not only through its impacts on other risk factors but also independently.
Physical activity	Lee, Folsom, and Blair 2003	Meta-analysis	Highly active individuals have a 27% lower risk of stroke incidence or mortality (relative risk of 0.73; 95% CI, 0.67–0.79) than less-active individuals, with moderately active individuals compared with inactive persons (relative risks were 0.83 [95% CI, 0.76–0.89] for cohort, 0.52 [95% CI, 0.40–0.69] for case control, and 0.80 [95% CI, 0.74–0.86] for the two combined).
Age	Manolio and others 1996	Cohort study	Risk of stroke approximately doubles for each successive decade of life after age 65.
Gender	Reeves and others 2008	Review	Women have more stroke events because of their longer life expectancy and older age at the time of stroke onset; stroke-related outcomes, including disability and quality of life, are poorer in women than in men.
	Appelros, Stegmayr, and Terent 2009	Systematic review	Stroke is more common among men, but women become more severely ill; incidence and prevalence rates of men are 33% and 41% higher, respectively, than those of women; stroke is more severe in women, with a case fatality at one month of 24.7% compared with 19.7% for men.
Atrial fibrillation	Wolf, Abbott, and Kannel 1991	Cohort study (Framingham Study)	In persons with coronary heart disease or cardiac failure, atrial fibrillation doubles the stroke risk in men and trebles the risk in women; in older patients ages 80–89 years, the attributable risk of stroke from atrial fibrillation is 23.5%.

Note: CI = confidence interval; mmHG = millimeters of mercury, a measure of pressure; mmol = millimoles.

Tobacco Use

Smoking is an independent and important risk factor for both ischemic and hemorrhagic stroke in all regions, with a stronger association with incident ischemic stroke. Smokers have stroke risk two times higher than non-smokers. Cigarette smoking accounts for 12 percent to 14 percent of all stroke deaths. In addition to smoking, exposure to environmental tobacco smoke—secondhand or passive smoking—is also a substantial risk factor for stroke.

Diabetes Mellitus

Diabetes is a well-recognized independent risk factor for stroke and also a strong predictor of worse long-term outcomes of stroke. Diabetes increases the risk of ischemic stroke more than hemorrhagic stroke, resulting in a higher ratio of ischemic to hemorrhagic stroke in people with diabetes compared with the general population. The duration of diabetes is also an important factor contributing to the risk of stroke. In addition, a prediabetic state is associated with increased stroke risk.

Diet and Nutrition

Adequate consumption of fruits and vegetables—at least five servings a day—is associated with lower risk of stroke, a relationship consistent across ethnic groups. Minerals

such as sodium and potassium also affect the risk of stroke. Excess sodium intake is considered the greatest factor leading to high blood pressure. Despite ongoing controversies regarding whether low salt intake (less than 3 grams per day) is a health risk (O'Donnell and others 2014) and the lack of direct trial data on sodium and hard outcomes (for example, mortality or morbidity), studies have shown that higher levels of sodium intake are associated with a higher risk of stroke, and higher levels of potassium intake are associated with a lower risk of stroke (He and others 1999; Nagata and others 2004). Other dietary factors, such as moderation of alcohol intake and vegetarian diets, may affect the risk of stroke, but the evidence is insufficient to make specific recommendations.

Overweight and Obesity

Overweight and obesity are risk factors for many chronic conditions, including stroke. Higher body mass index, a common measure of overweight and obesity, has been shown to increase the risk of stroke independently as well as through its impact on other risk factors such as blood pressure and lipids (Yan and others 2006).

Physical Activity

Physical inactivity is associated with numerous adverse health effects, including stroke. A large and generally

consistent body of evidence from prospective observational studies indicates that routine physical activity can prevent stroke (Lee, Folsom, and Blair 2003). The benefits can be obtained from a variety of activities, including leisure time physical activity, occupational activity, and walking. Overall, the relationship between activity and stroke is not influenced by gender or age.

OTHER RISK FACTORS

In addition to modifiable risk factors, factors such as age, gender, and race or ethnicity are related to hereditary or natural processes and cannot be modified. The cumulative effects of aging on the cardiovascular system and the progressive nature of stroke risk factors over a prolonged period substantially increase the risks of both ischemic and hemorrhagic stroke. Men and women have significantly different risks for the incidence, mortality, severity, and recovery from stroke. Worldwide, stroke is more common in men than in women, but the difference tends to decrease with age. Some systematic reviews have reported that stroke-related outcomes, including disability and quality of life, are consistently poorer in women than in men and that case fatality at one month is higher among women (Appelros, Stegmayr, and Terent 2009).

Atrial fibrillation is the most common cardiac rhythm abnormality among adults and accounts for 20 percent of all ischemic strokes. One of the complications of atrial fibrillation is the development of thromboembolism leading to stroke. A pooled analysis of atrial fibrillation studies suggests that paroxysmal atrial fibrillation carries risk of stroke similar to the risk from sustained atrial fibrillation (Laupacis and others 1994).

Many studies have investigated novel factors for stroke, including hyperhomocysteinemia, obstructive sleep apnea, air pollution, psychosocial factors such as depression and stress, and genetic factors. These factors are not discussed further in this chapter because of lack of conclusive evidence.

PREVENTION AND TREATMENT OF STROKE

Stroke prevention and control involve surveillance, screening, diagnosis, primary and secondary prevention, management in the acute phase, and poststroke rehabilitation. Innovative system-based solutions beyond these approaches, such as task-shifting and task-sharing, are needed to achieve better prevention and control. These solutions are discussed in detail in chapters _ and _ of this volume.

Surveillance, Screening, and Diagnosis

Surveillance

Few LMICs have the necessary funding and resources either to establish surveillance networks or to register data for detecting health trends in the population. The World Health Organization recommends a stepwise stroke surveillance approach (STEPS Stroke) for collecting data and monitoring trends. STEPS Stroke recommends collecting three types of data: information on stroke patients admitted to health facilities (step 1), number of fatal stroke events in the community (step 2), and estimated number of nonfatal stroke events in the community (step 3). A study synthesizing STEPS Stroke surveillance in nine sites in India, the Islamic Republic of Iran, Mozambique, Nigeria, and the Russian Federation showed that STEPS Stroke surveillance is possible and feasible in low-resource settings (Truelsen and others 2007).

Screening

Screening for stroke risk factors provides an excellent opportunity to identify and educate persons at high risk. It usually includes surveys of demographic and lifestyle information; blood pressure measurement; carotid bruit detection; cholesterol measurement; blood glucose tests; and education on warning signs or symptoms, such as transient ischemic attack, and heart-related symptoms, such as atrial fibrillation.

Similar to surveillance initiatives, a stepwise approach is suggested for screening. At a most basic level, screening for risk factors may include collection of information on demographics and lifestyle, such as diet, physical activity, and smoking or alcohol use. A second tier of screening might include data obtained from physical examination, including height, weight, girth, and blood pressure measurements. A final tier might include laboratory measures, such as blood glucose and cholesterol levels. In resource-poor settings, where clinical tests may be inaccessible and unaffordable, patient history and physical examinations are more cost-effective than laboratory measures (Olson and Roth 2007).

Congleton, Small, and Freeman (2013) report that in eastern North Carolina, where previous stroke mortality had been 12 percent higher than in the rest of the state, stroke prevalence and mortality declined after approximately 4,900 community outreach risk factor screenings were conducted between 2007 and 2011. The cost-effectiveness of national stroke screening has not been analyzed comprehensively in LMICs, but it is reasonable to assume that targeted or opportunistic screening would decrease the stroke burden in LMICs. China launched the Stroke Screening, Prevention, and Treatment Project in 2009 to establish a nationwide stroke screening network

[[AU: Provide lead authors' names and chapter numbers for cross-references]]

consisting of nearly 140 stroke screening centers in selected hospitals, aiming to standardize evidence-based stroke care throughout China and explore the need to establish an electronic national stroke registry. However, many LMICs have no stroke screening projects, which is likely attributable to limited resources and lack of awareness of the benefits of screening.

Diagnosis

The American Heart Association and the American Stroke Association introduced best-practice guidelines for stroke diagnosis that include patient history, physical examination, neurological examination and use of stroke scales, and diagnostic tests. Neurological examinations should be performed if patient history and physical examination are suggestive of a stroke, and the National Institutes of Health Stroke Scale or other standardized stroke scales can assist in estimating the severity of stroke. Brain imaging can distinguish ischemic stroke from intracranial hemorrhage and identify the subtype of stroke and often its cause; vascular imaging may identify the site and cause of arterial obstruction and also identify patients at high risk of stroke recurrence. Computed tomography (CT) scanning, magnetic resonance imaging, Doppler ultrasound, CT angiography, and magnetic resonance angiography are widely used in HICs to determine the subtypes and causes of stroke.

The most widely used strategy for stroke diagnosis is immediate CT scanning. However, the expense of CT equipment for health care facilities and the cost of individual use of CT scanning for patients are still high for low-resource countries and areas. Moreover, CT scanning is not sensitive for old hemorrhage, a condition that requires the use of other technologies such as magnetic resonance imaging and digital subtraction angiography, which may not be available in resource-poor countries. The need to develop and distribute accessible, inexpensive, and reliable diagnostic equipment and technologies continues to present a growing challenge to LMICs.

Primary Prevention

The main primary preventive approaches for stroke are the promotion and maintenance of a healthy lifestyle and blood pressure control. A healthy lifestyle includes not smoking (and stopping smoking for smokers); not engaging in binge drinking; being physically active; and eating a healthy diet characterized by adequate intake of fruits and vegetables, reduced intake of dietary trans fat, and reduced intake of sodium. Prevention strategies for CVD may target persons at high risk or whole populations. Although clinical guidelines recommend

targeting persons at high risk as the primary strategy, most CVD events occur in individuals who are at low to moderate absolute risk of CVD; therefore, prevention strategies based on the high-risk approach might have a limited impact on reducing stroke risk in populations. Which strategy is more cost-effective remains debatable, and a more sensible approach may be a combination of the two.

Tobacco Control

Tobacco control is ranked as the most important of five priority interventions for preventing noncommunicable diseases (Beaglehole and others 2011). According to a microsimulation model based on Indian data, smoke-free legislation and tobacco taxation in combination could avert 25 percent of myocardial infarction and stroke if the effects of the interventions were additive (Basu and others 2013). These approaches are likely to be more effective than brief cessation advice provided by health care providers, mass media campaigns, and advertising bans. Cessation advice is considered the least-effective strategy at the population level.

High Blood Pressure Prevention and Control

Reducing blood pressure has been demonstrated to reduce the risk of stroke effectively. In a meta-analysis of 11 clinical trials on reducing blood pressure and stroke among Asian populations, a 10 millimeters of mercury (mmHg) reduction in systolic blood pressure was associated with a 30 percent reduction in risk of stroke, regardless of the antihypertensive agent used (renin-angiotensin blockers, calcium-channel blockers, or diuretics) (Yano and others 2013). Another meta-analysis involving 19 trials indicated that a 7 mmHg and 5 mmHg reduction in systolic and diastolic blood pressure, respectively, reduced the relative risk of stroke by 22 percent (Xie and others 2015).

All clinical guidelines and expert consensus statements on prevention of stroke place great emphasis on preventing and controlling high blood pressure. Both a health care provider-centered high-risk approach as well as population-based measures for preventing hypertension in the general population are needed. Many LMICs, such as Brazil, China, Mexico, and Thailand, have initiated nationwide programs for preventing and managing high blood pressure through a combination of public health, clinical, and health system approaches. Both monitoring and evaluation of the long-term cost-effectiveness of these programs are necessary, as are developing and refining evidence-based, feasible, sustainable, and specific measures to guide their implementation.

Sodium Reduction

A particularly cost-effective strategy for reducing blood pressure is to reduce sodium intake. Achievement of actual and sustained reduction in sodium intake remains a challenge for both researchers and policy makers because of the well-established difficulty of changing lifelong dietary habits. More emphasis is needed on programs that discourage younger generations from establishing high-sodium dietary patterns earlier in life.

The use of low-sodium high-potassium salt substitutes, a safe product commercially available for many years, remains useful for circumventing the need to change dietary habits. In HICs, more than 70 percent of sodium intake comes from processed prepackaged food; persons in HICs probably would not benefit from the use of salt substitutes as much as persons in LMICs, where the majority of sodium intake comes from salt added during cooking. A meta-analysis of six clinical trials found that salt substitutes reduce systolic blood pressure by an average of 4.9 mmHg and diastolic blood pressure by 1.5 mmHg in adults, compared with salt (Peng and others 2014). These trials on salt substitutes—to be substantiated in the future by larger trials on hard outcomes, such as a trial of 21,000 patients currently under way in rural China—suggest that a policy of subsidizing and promoting salt substitutes may be useful for reducing sodium intake, blood pressure, and stroke incidence in LMICs.

Pharmaceutical Treatments

In addition to lifestyle modifications, another mainstay strategy for primary prevention of stroke is the use of pharmaceutical means to address hypertension, dyslipidemia (high cholesterol), and atrial fibrillation. The most compelling evidence—from multiple randomized clinical trials or meta-analyses—recommends treating hypertensive patients primarily with thiazide-type diuretics, as well as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, calcium channel blockers, or a combination, with the aim of achieving blood pressure goals set in the eighth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (James and others 2014). In patients with coronary heart disease or diabetes, the recommended treatment is a 3-hydroxy-3-methyl-glutaryl coenzyme-A reductase inhibitor (statin) medication, with the aim of reaching low-density lipoprotein-cholesterol goals set in the National Cholesterol Education Program guidelines (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001). In contrast, intensive glucose therapy in patients with type 2 diabetes

did not significantly reduce the incidence of stroke or other macrovascular events, according to the ACCORD or ADVANCE trials (ADVANCE Collaborative Group and others 2008).

The awareness, treatment, and control rates of hypertension and statin use in LMICs are universally lower than in HICs. To close the gap between guidelines and practice, LMICs need to find innovative and effective strategies for overcoming many health system and socioeconomic barriers, such as the prevalence of curative, acute care-oriented systems with limited resources and capacity, to improve identification of those at risk and to develop more comprehensive medication formularies on public and private health and pharmacy insurance plans.

Polypill Use

Polypill was originally proposed in the early 2000s and is estimated to have reduced ischemic heart disease events and stroke by more than 70 percent each as, respectively, either a secondary prevention drug among persons with vascular disease (Yusuf 2002) or as a primary prevention measure (Wald and Law 2003). The concept of a fixed-dose combination drug has been controversial since its inception and sparked many debates and several clinical trials intended to test the efficacy of polypill in similar but slightly different formations. Trials (TIPS, UMPIRE, and IMPACT) conducted in India, New Zealand, and three European countries (Ireland, the Netherlands, and the United Kingdom) focused on improving risk factors (Mohan 2009; Selak and others 2011; Thom and others 2013). Their results showed smaller-than-theorized improvements in blood pressure and lipid levels, but the relative and absolute benefits of polypill on clinical outcomes are likely to be larger in high-risk than in low-risk subgroups. However, the differences are not statistically significant.

Although these initial results are not as promising as expected, controversies regarding polypill are likely to continue given its multifaceted appeal for overcoming the problems of polypharmacy, low cost, and large anticipated effects. At the same time, unresolved issues with polypill include the need to define its optimal components and to evaluate the pharmacodynamics and pharmacokinetics of a multiple-component formulation. Ongoing and future trials and hard outcomes are needed to establish safety and effectiveness. The cost-effectiveness of such a strategy in LMICs also needs to be established. Meanwhile, a balanced view regarding its role in the primary prevention of stroke is warranted. Polypill use should not lead to reduced emphasis on healthy lifestyle measures because these are the mainstays of stroke prevention.

Atrial Fibrillation Control

Prevention is one of the best protections against stroke caused by recurrent atrial fibrillation. Antiplatelet compounds such as aspirin are indicated for atrial fibrillation patients with a low to moderate risk of thrombosis and can reduce the risk of stroke from atrial fibrillation by 20 percent to 25 percent. Anticoagulation using vitamin K antagonists (most commonly warfarin in the United States and some other countries and acenocoumarol and phenprocoumon in Europe) has been the treatment of choice for preventing embolic events in patients with atrial fibrillation and a moderate to high risk of thrombosis, reducing the risk of stroke by up to 62 percent (Finsterer and Stollberger 2008). However, warfarin has significant limitations, including bleeding, need for continued follow-up blood tests, and drug-drug interactions. Although newer anticoagulants such as rivaroxaban and dabigatran have been developed, they potentially cause significant bleeding.

Because of their limitations, effective use of warfarin or other anticoagulants has faced many barriers, especially in LMICs. In health resource-limited settings such as China, new oral anticoagulants were not found to be cost-effective because of their high price. The left atrial appendage is the site of thrombus formation in the majority of strokes associated with atrial fibrillation. Closure or exclusion of the left atrial appendage has emerged as an alternative therapeutic approach to medical therapy, but its safety and effectiveness are yet to be fully established.

Community-Based Education

Community education encompasses all approaches that are concerned with screening, awareness raising, health education on risk factors, ways to reduce disease risks, and other health-promotion activities conducted in communities. A systematic review of peer-reviewed articles published between 1999 and 2006 on the topic of public education for stroke prevention included 32 studies on educational programs. Seven educational programs were judged successful using the evaluation criteria. They included two large-scale programs and five narrowly targeted programs (Wilson and others 2007). A community-based intervention trial was conducted in two communities (one intervention, one control) in three cities in China. Regular health education and health-promotion activities were conducted between 1991 and 2000 in the intervention communities, but no special action was taken in the control communities. Over the 10 years of the intervention, incident risk of strokes decreased by 11.4 percent, 13.2 percent, and 7.2 percent, respectively, in the three

intervention communities compared with controls (Wang and Shuaib 2007).

Digital Health Strategies

Digital health is a promising field that involves the use of new information and communication technologies to improve health care management for both providers and patients. So far, no clear consensus has emerged regarding its terminology or definition. Other terminology includes e-Health, telemedicine, and **m-Health**. In this chapter, digital health is used to encompass all related terms.

Digital health is often associated with improved clinical decision making and increased efficiency for health care providers. For example, electronic health records, which are replacing traditional paper-based health records, integrate and organize patient health information so that every health provider involved in a patient's care can have the same accurate and up-to-date information.

The growing global burden of stroke requires innovative, effective, and widely available strategies for stroke prevention. Mobile technologies, such as the recently introduced Stroke Riskometer application (app), offer an opportunity to address these issues (Feigin and Norrving 2014; Parmar and others 2015). Digital health makes it possible to individualize interventions for physical activity and dietary behavior change. Some digital health apps have already been developed to address stroke prevention, based on the Framingham Heart Study stroke prediction algorithm; these apps have been enhanced by data on major risk factors for stroke. Users can identify their personal risk factors, their absolute risk of stroke, and their relative risk compared with persons of the same age and gender; knowledge of one's relative risk may be more motivating for behavior change than knowledge of absolute risk. Digital health programs in LMICs have the potential to expand access to prevention and treatment services by using ubiquitous and low-cost communication infrastructure. However, more research on the effectiveness of digital health and best strategies for implementation is needed to harness its potential for stroke prevention and control.

Few cost-effectiveness studies compare multiple prevention strategies in LMICs. A review of nine studies that evaluated 14 comparative strategies for CVD (both heart disease and stroke) in Argentina concluded that salt reduction in breads, antihypertensive treatment, mass educational campaigns, and polypill strategies could be considered cost-effective. However, the authors cautioned that the economic evidence available to guide CVD resource allocation in Argentina seems to be limited (Colantonio, Marti, and Rubinstein 2010).

Treatment during the Acute Stage

Ischemic Stroke

The evidence regarding treatment in the acute stage of stroke is limited and based on a few small randomized trials, extrapolation of results from larger trials, and two well-conducted nonrandomized studies (Rothwell, Algra, and Amarenco 2011). A combination of preventive treatments (antiplatelet agents, antihypertensive treatment and statins, and anticoagulation and carotid endarterectomy, as appropriate) started quickly in specialist units appears to be effective.

Carotid endarterectomy has been shown in randomized trials to be highly effective when done within two weeks after a nondisabling stroke, although there is uncertainty about the safety of the intervention in the first 48 hours. Additionally, two trials with a total of 40,000 randomized patients showed that oral aspirin within 48 hours of onset of major ischemic stroke reduced 14-day morbidity and mortality, mostly by reducing the risk of a recurrent stroke. However, intensive lowering of blood pressure during the acute phase of ischemic stroke was not found to reduce the risk of recurrent stroke or death.

Intravenous tissue plasminogen activator (tPA), administered within 4.5 hours of symptom onset, is the only therapeutic agent approved for achieving arterial recanalization in acute ischemic stroke. Current major guidelines recommend the use of a standard dose (0.9 milligram per kilogram of body weight; maximum of 90 milligrams) of tPA. However, the recommended dosage of tPA in Asian populations varies, partly influenced by the treatment costs of this expensive medicine and the perceived racial differences in treatment response. In Japan, the only approved dosage of tPA is 0.6 milligram per kilogram of body weight; one of the reasons for using such a low dosage is treatment response. Consensus regarding the optimal dosage of tPA is wanting, and ongoing trials should begin to demonstrate whether low-dose tPA could be effective and for which populations. Based on reported use, tPA for acute ischemic stroke is available to some patients in approximately one-third of countries globally.

Hemorrhagic Stroke

Results of data from 404 hemorrhagic stroke patients showed that early (within six hours of onset) intensive blood pressure-lowering treatment (target systolic blood pressure of 140 mmHg) attenuated hematoma growth for 72 hours. There were no appreciable effects on perihematomal edema (Anderson and others 2010). A larger trial based on 2,794 hemorrhagic stroke patients did not find that intensive lowering of blood pressure within one hour reduced the primary outcome of

death or severe disability. Additional analyses indicated improved functional outcomes with intensive lowering of blood pressure (Anderson and others 2010).

Stroke Units

Organized inpatient stroke unit care is provided by multidisciplinary teams that exclusively manage stroke patients in a dedicated ward, with a mobile team, or within a generic disability service (a mixed rehabilitation ward). Stroke units have long been shown to be an effective care-delivery model that improves clinical outcomes for stroke patients. The Stroke Unit Trialists' Collaboration published a series of Cochrane reviews on stroke units. This systematic review of randomized trials in 1997 indicated that stroke patients who were managed in an organized setting (stroke unit) were less likely to die, remain physically dependent, or require long-term institutional care, compared with patients managed in a conventional care setting (Stroke Unit Trialists' Collaboration 1997). Further analyses showed that organized inpatient stroke unit care probably benefited a wide range of stroke patients in a variety of ways—for example, reducing death from secondary complications and reducing the need for institutional care through a reduction in disability. The review, published in 2002 and updated in 2007 and in 2013 (Stroke Unit Trialists' Collaboration 2002, 2007, 2013), concluded that stroke patients who received organized inpatient care in a stroke unit were more likely to be alive, independent, and living at home one year after the stroke. The benefits were most apparent in units based in discrete wards. No systematic increase in the length of inpatient stay was observed. Evidence of care in stroke units is limited in LMICs, where establishing such units is a challenge in itself, possibly due to lack of specialists, capacity, and other system-level barriers. More translational studies are needed to assess whether and how stroke units can be implemented in resource-limited settings.

Secondary Prevention

Secondary prevention of stroke is of particular importance because of the high risk of recurrent stroke, which occurs in approximately a third of stroke survivors in five years. Evidence-based guidelines for secondary prevention stress the benefits of a healthy lifestyle, including a healthy diet, appropriate physical activity, and no smoking, similar to the guidelines described for primary prevention.

Blood Pressure Control

Control of high blood pressure remains the most important strategy for secondary prevention of stroke.

Existing evidence shows that lowering blood pressure with lifestyle changes and antihypertensive medicines protects against stroke recurrence. No comprehensive data are available on how well blood pressure treatment has been achieved among stroke patients in LMICs; however, it is intuitively logical that the situation is worse in LMICs than in HICs, because of the higher prevalence of stroke, more limited access to high-quality health care, and lower affordability of medicine, especially in rural areas.

Antiplatelet and Lipid-Lowering Therapies

Antiplatelet and lipid-lowering therapies are effective treatments for secondary prevention of ischemic stroke. Major clinical guidelines for secondary prevention of stroke recommend aspirin as the mainline antiplatelet therapy and statins as lipid-lowering therapy. However, uptake has been low for aspirin and even lower for statins, especially in LMICs. A study of 4,782 ischemic stroke inpatients in urban China in 2006 showed that use of antiplatelet therapy and lipid-lowering therapy declined substantially after discharge, from 81 percent and 31 percent, respectively, in hospital to 66 percent and 17 percent, respectively, a year later. Unlike the controversy surrounding use of polypill for primary prevention, polypill for secondary prevention has special appeal in LMICs because of its relative ease of use, effectiveness, and low cost. How to overcome barriers in its production, distribution, and sustained use by patients is a key issue that needs to be addressed to reap its population-wide benefits.

Homocysteine-Lowering Therapy

Elevated circulating homocysteine level has been postulated as a risk factor for CVD. However, an updated Cochrane review published in 2013 that included 12 trials (4 new trials since the last review in 2009) found no support for homocysteine-lowering therapy in the form of vitamin B6, B9, or B12 supplements, either alone or in combination, for preventing cardiovascular events (Martí-Carvajal and others 2013). The review included 47,429 participants either with or without CVD, suggesting that the finding of lack of effectiveness may apply to both primary and secondary intervention to prevent myocardial infarction and stroke. New trials are underway in China to evaluate the combined effect of folic acid and B vitamins for secondary prevention of stroke.

Surgery for Carotid Stenosis

Surgical interventions for symptomatic or asymptomatic carotid stenosis may be one option for certain patients. The less-invasive carotid artery stenting was not inferior to traditional carotid endarterectomy. However, the cost

is much higher for stenting than for endarterectomy. More evidence is needed to determine whether and under what circumstances surgical interventions for carotid stenosis are useful.

Self-Management and Family Support

Community-based self-management intervention—a promising strategy for addressing chronic conditions across the world—emphasizes patient responsibility and action in concert with community health care providers. Self-management in stroke involves conscious efforts by patients themselves to deal with stroke-induced impairments, threat of stroke recurrence, and challenges of long-term recovery. Patients require a combination of information, support, and education about behavior change, tailored to the beliefs, attitudes, and cognitions of those who have had a stroke, their social circles, and health care providers. Three key dimensions affect stroke self-management equally: individual capacity, support for self-management, and self-management environment. Each component has the potential to facilitate or hinder successful self-management.

Self-management interventions have been demonstrated to reduce the risk of stroke recurrence and to have a positive impact on the use of health care resources, which is of great significance for resource-scarce settings. However, the benefits of self-management are inconclusive. The latest systematic review reported that only six of nine randomized controlled studies and three of six nonrandomized trials found that benefits were associated with poststroke self-management (Lennon, McKenna, and Jones 2013). None of the trials was conducted in LMICs, further limiting conclusions for resource-poor settings.

Between 25 percent and 74 percent of stroke survivors require help with daily living activities from informal caregivers, often family members. Results from the London Stroke Carers Training Course (LSCTC), which is a systematic, structured, training program delivered in a stroke unit for caregivers, showed a reduction in caregiver burden, anxiety, and depression and an improvement in psychological outcomes for patients, when compared with usual care. However, the Training Programme for Caregivers of Inpatients after Stroke, a large-scale, robust trial, showed no significant differences between the LSCTC and usual care on any of the assessed outcomes. Currently, the RECOVER (clinicaltrials.gov registration number NCT02247921) and ATTEND (Trial Registration Number: ACTRN12613000078752) trials are being implemented in China and India to determine whether stroke recovery care at home given by a trained family member is an effective, affordable strategy for persons who have suffered a disabling stroke. The results of these

two trials will provide strong evidence on the effects of caregiver training programs in LMICs.

Rehabilitation

Although stroke is experienced as an acute event, stroke survivors live with long-term consequences and often manage their resulting limitations and health status as a chronic condition. As the population of elderly stroke survivors increases, and the number of survivors with disability and chronic care needs grows, rehabilitation care and therapy will play an increasingly important role. Stroke rehabilitation can be provided in inpatient, home, and community-based programs and may include physical, occupational, speech, and recreational therapies. The availability of and access to rehabilitation services and care for patients making the transition from acute care hospitalization varies dramatically around the globe, especially in LMICs. Factors contributing to the limited availability and accessibility of rehabilitation services include poor physician knowledge of the role of rehabilitation; lack of a rehabilitation component in the

standard of care; long interval from stroke onset to admission to rehabilitation; infrequent, unskilled, and short-lived provision of rehabilitation care; and inadequate public insurance or financial support for rehabilitation care. This section discusses both care delivery and discipline-specific rehabilitation interventions. Table 9.2 summarizes various models of care delivery currently in practice.

Physical, Occupational, or Movement Therapy

Several interventions to improve physical function in the upper or lower limbs and activities of daily living have been studied in LMICs. Studies examining physical therapy in LMICs showed that patient outcomes improved significantly over time, including as measured by the Barthel index, Mini-Mental State Examination, and Stroke Rehabilitation Assessment of Movement. The research to date demonstrates interest in examining the efficacy and effectiveness of physical rehabilitation and medicine; however, studies are often hampered by low quality and significant limitations.

Table 9.2 Models of Care Delivery for Stroke Rehabilitation

Model of care delivery	Description	General evidence	LMIC relevance and evidence	Evidence gap
Stroke unit	Provided in hospitals by nurses, doctors, and therapists specializing in care for stroke patients	Improved likelihood of survival, return home, and independence after a stroke (Stroke Unit Trialists' Collaboration 1997)	None	The extent to which organized stroke unit care is or can be provided globally
Multidisciplinary inpatient rehabilitation services	Therapy and treatment provided primarily to address mobility, self-care, cognition, communication, and mental health before patients return home	Functional improvements from admission to discharge negatively associated with number of days from stroke onset to admission to rehabilitation (Gökkaya and others 2006)	In Thailand, stroke survivors improved in activities of daily living, psychological status, and quality of life (Kuptniratsaikul and others 2009); in China, neurologic function significantly improved (Research Group of the Standardized Tertiary Rehabilitation Program in Cerebral Diseases' Patients 2006).	The effectiveness of task-shifting task and cross-training of health care providers to provide rehabilitation therapies
Early supported discharge	Supports patients who return home from the hospital earlier than usual with continued care and rehabilitation from teams of therapists, nurses, and doctors in the home	Long-term dependence, admission to institutional care, and length of hospital stay could be reduced with a structured and coordinated model of early supported discharge, especially for stroke patients with mild to moderate disability (Fearon and Langhorne 2012)	Results from pilot studies, including RECOVER and ATTEND trials in China and India, are to be reported.	Implementation and evaluation needed in LMICs

table continues next page

Table 9.2 Models of Care Delivery for Stroke Rehabilitation (continued)

Model of care delivery	Description	General evidence	LMIC relevance and evidence	Evidence gap
Home- and community-based rehabilitation	Therapy and treatment provided for community-dwelling stroke survivors in or outside the home	Improved and maintained independence in activities of daily living in the year following a stroke (Outpatient Service Trialists 2003)	In the Islamic Republic of Iran, treatment group had better basic and instrumental activities-of-daily-living performance than controls (Sahebalzamani, Aliloo, and Shakibi 2009).	Understanding needed of therapeutic benefit or harm of rehabilitation provided to stroke survivors living at home a year or longer after the stroke
Telerehabilitation	Information technologies used for communications between patients and caregivers in remote locations	No sufficient evidence to draw conclusions on the effectiveness of telerehabilitation on mobility, health-related quality of life, or participant satisfaction with the intervention (Laver and others 2013)	May be especially relevant for LMICs where expertise or resources do not reach the country's borders.	Globally, further assessment needed of feasibility and effectiveness

Speech Therapy or Cognitive Rehabilitation

No individual studies were identified for “rehabilitation of speech and language disorders,” and systematic reviews have not identified any studies from LMICs that meet inclusion criteria for specific questions related to speech and language or cognition. Given that an estimated 67 percent of stroke patients experience cognitive challenges, such as decreased attention and poor recall, this gap in the evidence requires attention from researchers.

Cost-Effectiveness

Cost-effectiveness studies of rehabilitation services in LMICs are also lacking. Investigators from Thailand reported that the cost of the acute phase of care was higher than that of the subacute phase, with differences by disability level (Khiaocharoen, Pannarunothai, and Zungsontiporn 2012). Compared with conventional hospital care, home-based rehabilitation for ischemic stroke patients resulted in a greater number of patients avoiding disability at a lower cost. Despite large gaps in stroke rehabilitation research, studies have increasingly included rehabilitation outcomes or evaluations of rehabilitation and therapy services. There is also tremendous opportunity in stroke rehabilitation research, and the intersection of disciplines and policy agendas provides the ideal platform for continued growth and success.

CONCLUSIONS AND RECOMMENDATIONS

Over the past two decades, the incidence, prevalence, and mortality rates of stroke declined in most HICs, but rose in LMICs. The absolute number of people

annually affected by stroke, living with stroke, and dying from stroke is increasing worldwide. Globally, stroke was the second-leading cause of death and the third-leading cause of DALYs lost in 2010. Major modifiable risk factors for stroke include high blood pressure, tobacco use, diet (high salt intake, in particular), physical inactivity, overweight and obesity, diabetes, and atrial fibrillation.

For stroke prevention and control, evidence shows the following:

- Surveillance to obtain current epidemiological data, screening for risk factors, and accurate diagnoses are important for preventing and controlling stroke. LMICs face challenges in all three activities because of lack of resources, awareness, and technical capacity. Screening is most successful in high-risk groups; its value to risk reduction in the general population is debatable. The development and distribution of accessible (mobile), inexpensive, and reliable diagnostic equipment and technologies is clearly a pressing need in LMICs. Maintaining a healthy lifestyle, such as no tobacco use, a healthy diet, physical activity, and weight control, are important strategies for both primary and secondary prevention of stroke.
- Population-based strategies, such as a tobacco tax, universal sodium reduction, and subsidies for healthy dietary choices such as fruits and vegetables, appear to be cost-effective options for LMICs. These strategies do not rely on screening for high-risk individuals, shift the distribution of risk factors in the population downward, and substantially reduce

disease risk. However, no trial evidence or rigorous cost-effectiveness analyses are yet available to support these claims.

- Recent trials of intensive blood pressure control in the acute stage of hemorrhagic stroke found improvements in functional outcomes and health-related quality of life, although the impact on severe disability and death was not significant (Anderson and others 2013). Nevertheless, controlling high blood pressure is critically important for preventing and controlling stroke in general.
- Besides lifestyle modification and blood pressure control, additional primary prevention strategies for stroke include community-based education programs and prevention and management of atrial fibrillation through maintenance of a healthy lifestyle and use of pharmaceuticals, such as anticoagulants.
- Digital health technology, such as tablet-based risk-assessment tools, mobile phone apps for physicians, and text messaging interventions, is a new approach to stroke prevention and control. Many studies on digital health, including some in LMICs, are ongoing; these studies are expected to provide best evidence on how to use these technological tools for prevention and control of noncommunicable diseases.
- In addition to specific surgical procedures and medications for stroke, organized inpatient stroke care units have repeatedly been found to provide higher-quality care that leads to better patient outcomes.
- Evidence to support the use of the polypill for secondary prevention of stroke (as well as other CVDs) is emerging, although its use for primary prevention remains controversial.
- Patients with chronic conditions like stroke may require lifelong pharmaceutical treatment, lifestyle maintenance and self-management skills, and caregiver and family support skills to achieve optimal health outcomes. Evidence in LMICs is lacking, but it is anticipated that LMICs will face special challenges in this regard because the health literacy and self-efficacy of patients are typically lower.
- Rehabilitation improves physical, speech, and cognitive functioning of patients disabled by stroke. It is not clear which mode of delivery is best for LMICs, but home- or community-based services and telerehabilitation may hold particular promise.
- System-based solutions need to address health system barriers to efficiency and lack of capacity and human resources to prevent and control stroke, as well as address other public health problems. Such solutions are needed to underpin any specific approach. For example, the shifting and sharing

of tasks among specialists and community health care workers have received considerable attention as system-based solutions.

Evidence on the cost-effectiveness of specific strategies in LMICs is limited. Nevertheless, prompt attention to and action on what is known—the importance of controlling tobacco use, reducing sodium intake, controlling blood pressure, and promoting a healthy diet and physical activity—will contribute to curbing the rising epidemic of stroke in the coming years.

NOTE

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US\$1,045 or less
- Middle-income countries (MICs) are subdivided:
 - a) lower-middle-income = US\$1,046 to US\$4,125
 - b) upper-middle-income (UMICs) = US\$4,126 to US\$12,745
- High-income countries (HICs) = US\$12,746 or more.

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