eNeurologicalSci 2 (2016) 21–30

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: http://ees.elsevier.com/ensci/

Review article

Prevention, management, and rehabilitation of stroke in low- and middle-income countries

Lijing L. Yan [a,b,c,*], Chaoyun Li [a], Jie Chen [d], J. Jaime Miranda [e,f], Rong Luo [c], Janet Bettger [g,h], Yishan Zhu [c], Valery Feigin [i], Martin O'Donnell [j], Dong Zhao [k], Yangfeng Wu [c,l,**]

[a] Global Health Research Center, Duke Kunshan University, Kunshan, China
[b] Duke Global Health Institute, Duke University, Durham, USA
[c] The George Institute for Global Health at Peking University Health Science Center, Beijing, China
[d] Institute for Medical Humanities, Peking University Health Science Center, Beijing, China
[e] CRONICAS Center of Excellence for Chronic Diseases, Universidad Peruana Cayetano Heredia, Lima, Peru
[f] Department of Medicine, School of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru
[g] Duke School of Nursing, Duke University, Durham, USA
[h] Duke Clinical Research Institute, Duke University, Durham, USA
[i] National Institute for Stroke and Applied Neuroscience, Auckland University of Technology, Auckland, New Zealand
[j] National University of Ireland Galway, Galway, Ireland
[k] Department of Epidemiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China
[l] Department of Epidemiology and Biostatistics, Peking University School of Public Health and Clinical Research Institute, Beijing, China

ARTICLE INFO

Article history:
Received 21 October 2015
Received in revised form 26 February 2016
Accepted 29 February 2016
Available online 2 March 2016

Keywords:
Stroke
Prevention
Treatment
Rehabilitation
Low- and middle-income countries

ABSTRACT

Although stroke incidence in high-income countries (HICs) decreased over the past four decades, it increased dramatically in low- and middle-income countries (LMICs). In this review, we describe the current status of primary prevention, treatment, and management of acute stroke and secondary prevention of and rehabilitation after stroke in LMICs. Although surveillance, screening, and accurate diagnosis are important for stroke prevention, LMICs face challenges in these areas due to lack of resources, awareness, and technical capacity. Maintaining a healthy lifestyle, such as no tobacco use, healthful diet, and physical activity are important strategies for both primary and secondary prevention of stroke. Controlling high blood pressure is also critically important in the general population and in the acute stage of hemorrhagic stroke. Additional primary prevention strategies include community-based education programs, polypill, prevention and management of atrial fibrillation, and digital health technology. For treatment of stroke during the acute stage, specific surgical procedures and medications are recommended, and inpatient stroke care units have been proven to provide high quality care. Patients with a chronic condition like stroke may require lifelong pharmaceutical treatment, lifestyle maintenance and self-management skills, and caregiver and family support, in order to achieve optimal health outcomes. Rehabilitation improves physical, speech, and cognitive functioning of disabled stroke patients. It is expected that home- or community-based services and tele-rehabilitation may hold special promise for stroke patients in LMICs.

Contents

* Correspondence to: L.L. Yan, Duke Global Health Institute and Global Health Research Center, Duke Kunshan University, No. 8 Duke Avenue, Kunshan 215316, China.
** Correspondence to: Y. Wu, The George Institute for Global Health at Peking University Health Science Center, Level 18, Tower B, Horizon Tower, No. 6 Zhichun Road, Beijing 100088, China.
E-mail addresses: lijing.yan@duke.edu (L.L. Yan), ywu@george.org.cn (Y. Wu).

http://dx.doi.org/10.1016/j.ensci.2016.02.011

1. Introduction

According to World Health Organization (WHO) Global Health Estimates in 2012, stroke was the second leading cause of death and the third leading cause of disability-adjusted life years (DALYs) lost globally [1]. A systematic review that synthesized 12 population-based studies from 10 low- and middle-income countries (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% in HICs, but increased more than 100% in LMICs. From 2000 to 2008, estimated stroke incidence rates in LMICs surpassed those in HICs by about 20% [2].

Stroke has created heavy social and economic burdens in LMICs. In China in 2004, the average cost for a stroke admission was two times the annual income of rural residents, and the cost of stroke care for the government-funded hospitals increased 117% annually between 2003 and 2007 [3]. The global burden of stroke reflects a pressing need for well-designed strategies to help track current trends as well as to curb the projected spread of stroke worldwide, especially in LMICs.

In this review, we present evidence of modifiable and other risk factors for stroke and then discuss current trends in 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. However, our review of current literature has revealed that evidence on comparative cost-effectiveness of stroke prevention and management strategies in LMICs is far from adequate. Finally, the review concludes with recommendations for policy-makers and future research directions.

2. Risk factors for stroke

Increased stroke incidence is largely associated with aging and urbanization and propelled by the increasing prevalence of key risk factors, especially in LMICs. 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 [4]. Non-modifiable risk factors related to hereditary or natural processes include age, sex/gender, and race/ethnicity. Relative risks, odds ratios, and hazard ratios associated with risk factors for stroke are summarized in Table 1.

3. Surveillance, screening and diagnosis

3.1. 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 WHO 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 heath facilities (step 1), number of fatal stroke events in the community (step 2), and estimated number of non-fatal 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 [25].

3.2. Screening for populations at high risk for stroke

Screening for stroke risk factors provides an excellent opportunity to identify and educate those 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 step-wise 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 may be more cost-effective for stroke screening.

Table 1
Relative risks, odds ratios or hazard ratios of risk factors for stroke.

Risk factor	Type of study	Results	Reference
High blood pressure	Review	A close, progressive, and approximately linear relationship exists between BP levels and primary incidence of stroke	[5]
	Review of 45 observational cohorts involving 13,397 participants	A fivefold difference in stroke risk exists between the highest BP categories (usual DBP 102 mm Hg) and the lowest ones (usual DBP 75 mm Hg)	[6]
	Meta-analysis of 61 prospective observational studies	At ages 40–69, each difference of 20 mm Hg in usual SBP is associated with more than a twofold difference in the stroke death rate.	[7]
	Cohort studies involving 124,774 participants from 13 cohorts in China and Japan	Each 5 mm Hg lower usual DBP is associated with lower risk of both non-hemorrhagic (odds ratio 0.61, 95% CI 0.57–0.66) and hemorrhagic stroke (0.54, 0.50–0.58).	[8]
	National Health Survey of Pakistan	The relative risk comparing the hypertension group with the normal group is approximately 4.	[9]
Tobacco use	Cohort studies in US	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).	[10]
	Cohort study involving 202,248 participants in US	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 (1.0–2.8) for men.	[11]
	Review	Current smokers have at least a two- to four-fold increased risk of stroke than lifelong nonsmokers or individuals who have not smoked for more than 10 years.	[12]
Diabetes mellitus	Review	People with diabetes have more than double the risk of ischemic stroke, relative to individuals without diabetes.	[13]
	Cohort study involving 3298 stroke-free participants in US	Compared to nondiabetic participants, those with diabetes for 0–5 years (adjusted HR, 1.7; 95% CI, 1.1–2.7), 5–10 years (1.8; 1.1–3.0), and more than 10 years (3.2; 2.4–4.5) are at increased risk of ischemic stroke.	[14]
Diet and Nutrition	Cohort study involving 174,888 participants in US	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, 0.84; 95% CI, 0.68–1.04).	[15]
	Cohort study involving 14,407 participants in US	Among overweight persons, a 100 mmol higher sodium intake is associated with a 32% increase (relative risk, 1.32; 95% CI, 1.07–1.64; $P = 0.01$) in stroke incidence, 89% increase (1.89; 1.31–2.74; $P < 0.001$) in stroke mortality.	[16]
	Cohort study involving 29,079 participants in Japan	Associations between sodium intake and death from ischemic stroke are significantly positive (hazard ratio, 3.22; 95% CI, 1.22 to 8.53).	[17]
Overweight and obesity	Cohort study involving 17,643 participants in US	Body mass index increases the risk of stroke not only through its impacts on other risk factors but also independently.	[18]
Physical activity	Meta-analysis of 18 cohort and 5 case–control studies	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. Moderately active individuals compared with inactive persons (relative risks were 0.83 for cohort, 0.52 for case–control, and 0.80 for both combined).	[19]
Age	Cohort study involving 5201 participants in US	Risk of stroke approximately doubles for each successive decade of life after age 65.	[20]
Gender	Review	Women have more stroke events due to 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.	[21]
	Systematic review of 98 articles	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.	[22]
	Systematic review of 31 articles in Arab countries	Stroke is more common in males than females (range for males 55.9–75%).	[23]
Atrial fibrillation	Cohort study involving 5070 participants in US	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, the attributable risk of stroke from atrial fibrillation is 23.5%.	[24]

Congleton and others reported that Eastern North Carolina in the United States, where previous stroke mortality had been 12% higher than the rest of the state, saw a decrease in stroke prevalence and mortality after approximately 4900 community outreach risk factor screenings were conducted between 2007 and 2011 [26]. 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 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 screening benefits.

3.3. Diagnosis

The American Heart Association/American Stroke Association introduced best practice guidelines for stroke diagnosis that include patient history, physical examination, neurological examination and stroke scales, and diagnostic tests. Neurological examinations should be performed if patient history and physical examination are suggestive of a stroke, and National Institute of Health Stroke Scale (NIHSS) or other standardized stroke scales can assist in estimating the severity of stroke. Brain imaging can distinguish ischemic stroke from intracranial hemorrhage, identify the subtype of stroke, and often the cause of stroke; vascular imaging may identify the site and cause of arterial obstruction as well as patients at high risk of stroke recurrence. Computed Tomography (CT) scanning, Magnetic Resonance Imaging (MRI), Doppler ultrasound, CT angiography, magnetic resonance angiography are also 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 healthcare facilities and the cost of individual use of CT scanning for patients are still high for low-resource countries and areas. For example, plain CT scanning in India costs US$90, which is a significant burden in the context of average monthly middle-class income of US$500 and lack of universal health insurance. Moreover, CT scanning is not sensitive for old hemorrhage, a condition that requires the use of other technologies such as MRI 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.

4. Primary prevention

The main primary preventive approaches for stroke are the promotion and maintenance of healthy lifestyle and blood pressure control. A healthy lifestyle includes not smoking (and smoking cessation for smokers), no binge drinking, being physically active, and a healthy diet characterized by adequate fruit and vegetable intake, reduced dietary trans fat intake, and reduced sodium intake. Prevention strategies for cardiovascular disease (CVD) may target those at high-risk or populations. Although a high-risk target strategy is recommended by clinical guidelines as the primary strategy, it has been argued that most CVD events occur in individuals who are at low to moderate absolute risk of CVD [27]; therefore, prevention strategies based on the high-risk approach might have a limited population impact on stroke risk reduction. It remains debatable which strategy is more cost-effective, and a more effective approach may be a combination of the two.

4.1. Tobacco control

Tobacco control was ranked number one among the top five priority interventions for non-communicable diseases (NCDs), according to a group of experts [28]. According to a micro-simulation model based on Indian data, smoke-free legislation and tobacco taxation in combination could avert 25% (95% CI: 17%–34%) of myocardial infarctions and strokes if the effects of the interventions are additive [29]. They were likely to be more effective than brief cessation advice by healthcare providers, mass media campaigns, and an advertising ban. Cessation advice was expected to be the least effective strategy at the population level.

4.2. 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 blood pressure reduction and stroke among Asian populations, a 10 mm Hg reduction in systolic blood pressure was associated with a 30% reduction in risk of stroke, regardless of the anti-hypertensive agents used (renin–angiotensin blockers, calcium-channel blockers, or diuretics) [30].

All clinical guidelines and expert consensus statements on prevention of stroke place great emphasis on high blood pressure prevention and control. Both a healthcare provider-centered high-risk approach as well as population-based measures for prevention of hypertension in the general population are needed. Many LMICs, such as China, Thailand, Brazil, and Mexico, have initiated nation-wide programs for high blood pressure prevention and management through a combination of public health, clinical, and health system approaches [31–33]. It is necessary to monitor and evaluate the long-term cost-effectiveness of these programs, and to develop and refine evidence-based, feasible, sustainable, and specific measures to guide their implementation.

4.3. Sodium reduction

Reduction of sodium intake has been ranked as the second most cost-effective intervention, after tobacco control, for addressing the NCD crisis [28]. Achievement of actual and sustained reduction in sodium intake remains a challenge for both researchers and policymakers, due to the notorious difficulty of changing lifelong dietary habits. More emphasis is needed on programs that discourage younger generations from establishing a high-sodium dietary pattern earlier in life.

The use of low-sodium high-potassium salt substitutes, a safe product commercially available for many years, remains a useful strategy to circumvent the need to change dietary habits. In developed countries, over 70% of sodium intake comes from processed pre-packaged food; thus, HIC residents would not be expected to benefit from the use of salt substitutes as much as LMICs, where the majority of sodium intake comes from salt added during cooking. Salt substitutes have been shown in a meta-analysis of six clinical trials to reduce systolic blood pressure by an average of 4.9 mm Hg and diastolic by 1.5 mm Hg in adults, compared to usual salt [34]. These trials on salt substitutes – to be substantiated in the future by larger trials on hard outcomes (e.g. mortality or morbidity), such as a trial of 21,000 patients currently underway in rural China (ClinicalTrials.gov No. NCT02092090) – suggest that a policy of subsidizing and promoting salt substitutes may have potential as a useful tool in reducing sodium intake, blood pressure, and stroke incidence in LMICs [35].

4.4. Pharmaceutical treatments

In addition to lifestyle modifications, another mainstay strategy for primary prevention of stroke is through pharmaceutical means to address hypertension, dyslipidemia, and atrial fibrillation. The most compelling evidence – from Class I Level A from multiple randomized clinical trials or meta-analyses – recommends treating hypertensive patients primarily with thiazide-type diuretics, as well as angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), beta-blockers (BB), calcium channel blocker (CCB), or combination, with the aim of achieving blood pressure goals that are reflected in the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8) [36]. In patients with coronary heart disease or diabetes, the recommended treatment is a 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitor (statin) medication, with the aim of achieving LDL-cholesterol goals that are reflected in the National Cholesterol Education Program (NCEP) guidelines. By contrast, intensive glucose therapy in patients with type 2 diabetes did not yield significant reduction in the incidence of stroke or other macrovascular events in the ACCORD or ADVANCE trials [37].

The awareness, treatment, and control rates of hypertension and statin use in LMICs were universally lower than that in HICs [38–41]. To close the guideline-practice gaps, LMICs need to find innovative and effective strategies to overcome many health system and socio-economical barriers, such as their 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.

4.5. Polypill

Polypill was originally proposed by Yusuf [42] and Wald and Law [43] in the early 2000s and is estimated to have reduced ischemic heart disease events and stroke by over 70% as, respectively, either a secondary prevention drug among those with vascular disease or as a primary prevention measure. This 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. Already completed and published trials (TIPS, UMPIRE and IMPACT) were mostly completed in India and New Zealand and focused on risk factor improvements [44, 45]. 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, though the differences are not statistically significant.

Controversies regarding polypill are likely to continue, given its multi-faceted appeal for overcoming the problems of polypharmacy, low cost, and large anticipated effect. At the same time, unresolved inherent issues with polypill remain: defining the optimal components of the polypill and evaluating the pharmacodynamics and pharmacokinetics of a multiple-component formulation. Ongoing and future trials on polypill and hard outcomes are needed to establish its safety and

effectiveness. Cost-effectiveness of such a strategy in LMICs also needs to be established. Meanwhile, a balanced view regarding its role in primary prevention of stroke is called for. Polypill use should not lead to abandonment or reduced emphasis on the healthy lifestyle measures, which should remain the mainstay of stroke prevention.

4.6. Atrial fibrillation

Prevention of recurrent atrial fibrillation is one of the best protections against stroke caused by this condition. Antiplatelet compounds such as aspirin are indicated for atrial fibrillation patients with a low to moderate risk of thrombosis (CHA2DS2-VASc scores 0–1) and can reduce the risk of stroke from atrial fibrillation by 20%–25%. Anticoagulation with 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 prevention of embolic events in patients with atrial fibrillation and a moderate to high risk of thrombosis, reducing the risk of stroke by up to 62% [46]. However, warfarin does have significant limitations including bleeding, need for continued follow-up blood tests, and drug–drug interactions. Although newer anticoagulants such as apixaban, rivaroxaban and dabigatran have been developed, they still have the potential side effect of causing significant bleeding. Nevertheless, in a modeling study in Slovakia, rivaroxaban was cost-effective compared to warfarin with an Incremental Cost-Effectiveness Ratio of 17.4 [47]. A large international trial involving 14,264 patients with AF reported that rivaroxaban was non-inferior to dose-adjusted warfarin in regard to all-cause stroke [48]. Other studies found that use of dabigatran and apixaban were cost-effective compared to warfarin to prevent stroke among atrial fibrillation patients [49,50,51].

Due to their limitations, effective use of warfarin or other anticoagulants has faced barriers, especially in LMICs. In health resource-limited settings such as China, new oral anticoagulants were not found to be cost-effective because of high prices of the drugs [52]. The left atrial appendage has been shown to be 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, the safety and effectiveness of which have yet to be fully established [53].

4.7. Community-based education program

Community education encompasses all approaches that are concerned with screening, raising awareness, 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 of the educational programs were judged successful using the evaluation criteria. They included two large-scale programs and five narrowly targeted programs [54]. 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. Through 10 years of intervention, incident risk of strokes decreased by 11.4%, 13.2%, and 7.2%, respectively, in the three interventions compared with control communities [55].

4.8. Digital health prevention strategies

Digital health is emerging as a promising field that involves the use of new information and communication technology to improve healthcare management for both healthcare providers and patients. So far, no clear consensus about the terminology or the definition concerning digital health has been made. Other terminology includes "eHealth," "telemedicine," and "m-Health" (for mobile Health). In this chapter, we use digital health to encompass all the related terms.

Digital health is often associated with improved clinical decision-making and increased efficiency for healthcare 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 about a patient [56].

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 App, offer an opportunity to address these issues [2,57]. Digital health makes it possible to individualize interventions for physical activity and dietary behavior change. For stroke prevention, some applications have already been developed based on the Framingham Heart Study stroke prediction algorithm plus additional major risk factors for stroke. Users can identify personal stroke risk factors and find out their absolute risk of stroke development, as well as their relative risk compared to those of the same age and gender; knowledge of one's relative risk may be more motivating for behavior change than that of absolute risk. Digital health programs in LMICs have the potential to expand access to necessary prevention and treatment services using ubiquitous and low-cost communication infrastructure. However, more research on its effectiveness and best strategies for implementation to harness its potential for stroke prevention and control is needed.

Cost-effectiveness studies that compare multiple prevention strategies in LMICs are few. A review including nine studies and evaluating 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. The authors commented that, "The available economic evidence to guide resource allocation for CVD in Argentina seems to be scarce and limited" [58].

5. Treatment of stroke during the acute stage

5.1. Ischemic stroke

Intravenous thrombolysis has been approved for the treatment of acute ischemic stroke in most countries for more than 10 years and is therefore recommended as evidence-based treatment in stroke guidelines [59]. Intravenous tissue plasminogen activator (tPA), administered within 4.5 h of symptom onset, is the only therapeutic agent approved for achieving arterial recanalization and tissue reperfusion in acute ischemic stroke. Current major guidelines recommend the use of a standard dose (0.9 mg/kg bodyweight; maximum 90 mg) of tPA. However, the recommended dosage of tPA in Asian populations varies, partly influenced by treatment costs of this expensive medicine in developing countries [60]. In Japan, the only approved dosage of tPA is 0.6 mg/kg bodyweight, one of the reasons to utilize such a lower dosage is racial differences in treatment response. Consensus regarding the optimal dosage of tPA should be reached, and ongoing trials should begin to illuminate whether low-dose tPA could be effective or not, and for which populations. Although a possibility for stroke management in HICs, tPA may not be an option in certain areas in LMICs due to delayed presentation and cost [61]. Thrombolysis is used in <1% of strokes in China because patients cannot afford it, a situation paralleled in India [62].

Mechanical thrombectomy using a new generation of endovascular tools, stent retrievers, is found to improve functional outcome in combination with pharmacological thrombolysis when indicated. Successful recanalization was achieved in the clinical settings in most patients with the Solitaire device and TREVO device [63,64]. Based on a consensus group discussion at the ESO-Karolinska Stroke Update conference in Stockholm in November 2014, and its final statement in February 2015, several European professional organizations, including the European Stroke Organization (ESO), the European Society of Minimally Invasive

Neurological Therapy (ESMINT) and the European Society of Neuroradiology (ESNR), issued new recommendations on mechanical thrombectomy, including that: 'Mechanical thrombectomy, in addition to intravenous thrombolysis within 4.5 h, when eligible, is recommended to treat acute stroke patients with large artery occlusions in the anterior circulation up to 6 h after symptom onset' [65].

5.2. Hemorrhagic stroke

Results of data analysis from 404 hemorrhagic stroke patients in the INTERACT study showed that early (within 6 h of onset) intensive BP-lowering treatment (target systolic blood pressure 140 mm Hg) attenuated hematoma growth over 72 h in hemorrhage. There were no appreciable effects on peri-hematomal edema [66]. A larger trial based on 2794 hemorrhagic stroke patients in the INTERACT2 study did not find intensive lowering of blood pressure within 1 h to reduce the primary outcome of death or severe disability. Additional analyses indicated improved functional outcomes with intensive lowering of blood pressure [67].

5.3. Stroke unit

Organized inpatient stroke unit care is provided by multidisciplinary teams that exclusively manage stroke patients in a dedicated ward (stroke ward), with a mobile team (stroke team) or within a generic disability service (a mixed rehabilitation ward). Stroke unit has long been shown to be an effective model of care delivery that improves clinical outcomes for stroke patients. The Stroke Unit Trialists' Collaboration published a series of Cochrane reviews on stroke unit. The systematic review of randomized trials in 1997 indicated that stroke patients who were managed in an organized (stroke unit) setting were less likely to die, remain physically dependent, or require long-term institutional care, compared to those in conventional care. Further analyses showed that organized inpatient stroke unit care probably benefitted a wide range of stroke patients in a variety of different ways, e.g., reducing death from secondary complications of stroke and reducing the need for institutional care through a reduction in disability. The review published in 2002 and updated in 2007 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 a discrete ward. No systematic increase was observed in the length of inpatient stay. Several studies from five continents (China, India and South Asia, South America, Africa, and East Europe/Middle East) noted lower death rates in the stroke unit group compared with the control group, indicating that stroke units should also be effective in LMICs [68]. However, establishing such units in LMICs is a challenge in itself, particularly where there is a lack of specialists, capacity, and other system-level barriers. More translational studies are needed to assess whether and how stroke unit can be implemented in resource-limited settings.

6. Secondary prevention of stroke

Secondary prevention of stroke is of particular importance due to high risk of recurrent stroke, which occurs in approximately one third of stroke survivors in 5 years. Evidence-based guidelines for secondary prevention stress the benefits of healthy lifestyle, such as healthful diet, appropriate physical activity, and non-smoking, similar to those described for primary prevention. Additional measures are discussed below.

6.1. 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 protect against stroke recurrence [69]. 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, compared to HICs [70], because of the higher prevalence of stroke, more limited access to high-quality healthcare, and lower affordability of medicine in these countries, especially in rural areas.

6.2. Antiplatelet and lipid-lowering therapy

Antiplatelet and lipid-lowering therapies are considered to be effective treatments for secondary prevention of ischemic stroke. Aspirin as the most common antiplatelet therapy and statin as lipid-lowering therapy are recommended by major clinical guidelines for secondary prevention of stroke. However, uptake of aspirin has been low and even lower for statin [70]. A study of 4782 ischemic stroke inpatients in urban China in 2006 showed that in-hospital initiation of antiplatelet therapy was acceptable (81%), but its use decreased to 66% by 12 months after stroke. While for lipid-lowering therapy, in-hospital initiation was only 31% and it decreased to 17% by 12 months. Unlike the controversy surrounding use of polypill for primary prevention, polypill has special appeal for secondary prevention in LMICs because of its relative ease of use, effectiveness, and low cost. How to overcome barriers to its production, distribution, and sustained use by patients are key issues to be addressed in order to reap population-wide benefits.

6.3. Homocysteine-lowering therapy

Elevated circulating homocysteine level has been postulated as a risk factor for CVD [71]. However, an updated Cochrane review published in 2013 that included a total of 12 trials (four new trials since the last review in 2009) did not find support for homocysteine-lowering therapy in the form of supplements of vitamins B6, B9, or B12, either alone or in combination, for preventing cardiovascular events [72]. The review included 47,429 participants either with or without existing CVD, suggesting that the finding of non-effectiveness may apply to both primary and secondary prevention of 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.

6.4. Surgery for carotid stenosis

Surgical interventions for symptomatic or asymptomatic carotid stenosis may be one option for certain patients for secondary prevention. The less invasive carotid artery stenting was not inferior to traditional carotid endarterectomy [73]. However, the cost of stenting is much higher than endarterectomy [74]. More evidence is needed to determine whether and under which circumstances surgical interventions for carotid stenosis are useful.

6.5. Self-management and family support

Community-based self-management intervention is a promising strategy to address public health problems of chronic conditions worldwide by emphasizing patient responsibility and acting in concert with community healthcare providers. Self-management in stroke involves conscious effort 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 provision, support, and education about behavior change, tailored to the beliefs, attitudes, and cognitions of those who have had a stroke, their social circle, and healthcare providers. It was reported that 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 have positive impacts on healthcare resource utilization, which is of great significance for resource-scarce settings. However, the benefits of self-management remain inconclusive. The latest systematic review reported that only six of the nine randomized controlled studies and three of the six non-randomized trials found benefits associated with post-stroke self-management [75]. None of the trials were conducted in LMICs; thus, further studies are needed in those resource-poor settings.

Between 25% and 74% of stroke survivors require help with daily living activities from informal caregivers, often family members. Results from the London Stroke Carers Training Course (LSCTC) – a systematic structured training program delivered in a stroke unit for caregivers – showed a reduction in caregiver burden, anxiety, and depression and improved psychological outcomes for patients' post-LSCTC, compared with usual care. However, the Training Programme for Caregivers of Inpatients after Stroke (TRACS) – a larger scale, robust trial – showed no significant difference between LSCTC trainees and controls in any of the assessed outcomes above [76]. Recently, the ATTEND [77] trial and RECOVER trial have been implemented in India and China, respectively, aiming to determine whether home-based stroke recovery supported by a trained family member is an effective, affordable strategy for those with disabling stroke. The results of these two trials should yield strong evidence on the effects of caregiver training program in LMICs.

7. Stroke 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 recreation therapies. The availability of and access to rehabilitation services and care for patients transitioning from their acute hospitalization varies dramatically around the globe, especially in LMICs. Factors contributing to the limited availability and accessibility include: poor physician knowledge of the role of rehabilitation; lack of rehabilitation component in the standard of care; the long interval from stroke onset to admission to rehabilitation; the infrequent, unskilled, and short-lived provision of rehabilitation care; and inadequate public insurance or financial support for rehabilitation care [78]. Below, we discuss stroke rehabilitation by both models of care delivery and discipline-specific interventions (Table 2).

7.1. Physical, occupational or movement therapy

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 Mexico (physiotherapy plus caregiver education in rehabilitation) [87], Iran (physical therapy on balance, exaggerated muscle tonicity and quality of life) [88], and China (Problem-Oriented Willed-Movement, Therapy and Neurodevelopmental Treatment) [89] showed that patients improved significantly over time in outcomes including Barthel index (BI), Mini-Mental State Examination (MMSE) and Stroke Rehabilitation Assessment of Movement (STREAM). The research to-date demonstrates interest in examining efficacy and effectiveness of physical rehabilitation and medicine; however, study quality is often low as study limitations are significant [87–89].

7.2. Speech therapy or cognitive rehabilitation

No individual studies were identified for "rehabilitation of speech and language disorders," and completed systematic reviews have not

Table 2
Models of care delivery for stroke rehabilitation.

Model of care delivery	Description	General evidence		Evidence in LMICs		Evidence gap
		Type of study	Evidence	Type of study	Evidence	
Stroke unit	Provided in hospitals by nurses, doctors, and therapists specializing in care for stroke patients	Meta-analysis of 28 RCTs involving 5855 patients	Improved likelihood of survival, return home, and independence after a stroke [79]	None	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 prior to patients returning home	Prospective pre-post intervention study involving 83 patients from a rehabilitation center in Turkey	Functional improvements from admission to discharge were negatively associated with number of days from stroke onset to admission to rehabilitation [80]	Prospective pre-post intervention study involving 327 patients from Thai tertiary hospitals RCT involving 1209 patients from 20 hospitals in China	Stroke survivors improved in activities of daily living, psychological status and quality of life [81] Neurologic function significantly improved [82]	The effectiveness of task-shifting and cross-training health care providers to provided rehabilitation therapies
Early Supported Discharge	Supports patients to return home from the hospital earlier than usual to then continue care and rehabilitation from teams of therapists, nurses and doctors in the home	Meta-analysis of 14 RCTs involving 1957 patients	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 [83]	RCTs from communities in India and China	Results from pilot studies including ATTEND trial [75] and RECOVER trial to be seen	Implementation and evaluation in LMIC needed
Home- and Community-based rehabilitation	Therapy and treatment provided for community-dwelling stroke survivors in or outside of the home	Meta-analysis of 14 RCTs involving 1617 patients	Improved and maintained independence in activities of daily living in the year following a stroke [84]	RCT involving 80 patients from a Iran hospital	Treatment group had better basic and instrumental activities of daily living performance than controls [85]	Therapeutic benefit or harm is unclear for rehabilitation provided to stroke survivors living at home a year or longer after the stroke
Tele-rehabilitation	Information technologies used for communications with patients and caregivers in a remote location	Meta-analysis of 10 RCTs involving 933 patients	No sufficient evidence to draw conclusions on the effectiveness of tele-rehabilitation on mobility, health-related quality of life or participant satisfaction with the intervention [86]	None	May be especially relevant for LMIC where expertise or resources do not reach the country's borders	Requires further assessment of feasibility and effectiveness globally

identified any studies from LMICs that meet inclusion criteria for specific questions related to speech and language or cognition. Given that an estimated 67% of stroke patients experience cognitive challenges (e.g., decreased attention, poor recall) post-stroke, this gap in the evidence requires attention from researchers.

7.3. 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 sub-acute phase, with differences by disability level [90]. Compared to conventional hospital care, home-based rehabilitation for ischemic stroke patients resulted in a greater number of patients avoiding disability at a lower cost.

In spite of large gaps in stroke rehabilitation research, there has been dramatic growth over the past years as 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.

8. Conclusions and recommendations

Over the last two decades, the incidence, prevalence, and mortality rates of stroke decreased in most developed countries, while the opposite was true in LMICs, but the absolute number of people annually affected by stroke, living with stroke (prevalence) and dying from stroke (deaths) is increasing worldwide. Globally, stroke is the second leading cause of death and the third leading cause of DALYs lost in 2010 [91]. 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 strategies, evidence shows that:

- Surveillance to obtain current epidemiological data, screening for stroke risk factors, and accurate diagnoses of stroke are important for preventing and controlling stroke. However, LMICs face challenges in all three activities, due to 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. However, there is clearly a pressing need to develop and distribute accessible (e.g. mobile), inexpensive, and reliable diagnostic equipment and technologies in LMICs.
- Maintaining a healthy lifestyle, such as no tobacco use, healthful diet, physical activity, and weight control, are important strategies for both primary and secondary prevention of stroke in LMICs.
- Population-based strategies, such as tobacco tax, universal sodium reduction, and subsidizing healthful dietary choices such as fruits and vegetables, appear to be cost-effective options for LMICs because these strategies do not rely on screening for high-risk individuals and can shift population distribution of risk factors downward for substantial reduction in disease risk. However, no trial evidence or rigorous cost-effectiveness analyses are available to support these claims yet.
- 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 its impact on severe disability and death were not significant [92]. Nevertheless, controlling high blood pressure is critically important for preventing and controlling stroke in LMICs.
- 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 maintaining healthy lifestyle and pharmaceutical means such as anticoagulants. Physicians, family caregivers, and patients in LMICs need to be trained and made aware of stroke risk factor reduction and importance of timely referral and evidence-based primary and secondary prevention of stroke
- Digital health technology, such as tablet-based risk assessment tools, mobile-phone apps for physicians, and text messaging interventions, represents a new approach for stroke prevention and control. Many studies on digital health, including some in LMICs, are ongoing and are expected to provide evidence on how best to utilize these technological means for NCD prevention and control.
- Though stroke unit care delivered by trained multidisciplinary teams may be too costly for wide implementation in LMICs, it has repeatedly been shown to provide high quality care that leads to better patient outcomes.
- Evidence to support the use of polypill for secondary prevention of stroke (along with other CVDs) in LMICs is emerging because of its relative ease of use, effectiveness, and low cost, even as its use for primary prevention remains controversial.
- Chronic conditions like stroke often require lifelong pharmaceutical treatment, maintenance of lifestyle changes, improved self-management skills, and caregiver and family support skills in order to achieve optimal health outcomes. Evidence in LMICs is lacking, but LMICs may face special challenges in this regard because health literacy and self-efficacy of patients are typically low.
- Rehabilitation improves physical, speech, and cognitive functioning of disabled stroke patients. It is not clear which mode of delivery is better for LMICs, but it is expected that home- or community-based services and tele-rehabilitation may hold special promise.
- System-based solutions should address health system barriers in efficiency and lack of capacity and human resources not only for stroke prevention and control but also to address other public health problems. Such solutions are needed to underpin any specific approach. For example, shifting and sharing tasks among specialists and community healthcare workers has received considerable attention as a system-based solution in resource-limited regions.
- Evidence on the cost-effectiveness of various strategies in LMICs is limited. Nevertheless, prompt attention to and action on what is known – the importance of tobacco control, sodium reduction, blood pressure control, and promotion of healthful diet and physical activity – will contribute to curbing the rising epidemic of stroke in the coming years.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

LL Yan and C Li are supported by the National Natural Sciences Foundation of China grants (71233001 and 71490732).

References

[1] R. Lozano, M. Naghavi, K. Foreman, et al., Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010, Lancet 380 (9859) (2012) 2095–2128.
[2] V.L. Feigin, B. Norrving, A new paradigm for primary prevention strategy in people with elevated risk of stroke, Int. J. Stroke 9 (5) (2014) 624–626.
[3] L. Liu, D. Wang, K.L. Wong, et al., Stroke and stroke care in China huge burden, significant workload, and a national priority, Stroke 42 (12) (2011) 3651–3654.
[4] M.J. O'Donnell, D. Xavier, L. Liu, et al., Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case–control study, Lancet 376 (9735) (2010) 112–123.
[5] S. Di Legge, G. Koch, M. Diomedi, et al., Stroke prevention: managing modifiable risk factors, Stroke Res. Treat. 2012 (2012) 391538.
[6] Prospective Studies Collaboration, Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. Prospective studies collaboration, Lancet 346 (8991–8992) (1995) 1647–1653.
[7] S. Lewington, R. Clarke, N. Qizilbash, et al., Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies, Lancet 360 (9349) (2002) 1903–1913.

[8] Asia Pacific Cohort Studies Collaboration, Blood pressure, cholesterol, and stroke in eastern Asia. Eastern Stroke and Coronary Heart Disease Collaborative Research Group, Lancet 352 (9143) (1998) 1801–1807.
[9] M.U. Farooq, A. Majid, M.J. Reeves, et al., The epidemiology of stroke in Pakistan: past, present, and future, Int. J. Stroke 4 (5) (2009) 381–389.
[10] M.J. Thun, B.D. Carter, D. Feskanich, et al., 50-year trends in smoking-related mortality in the United States, N. Engl. J. Med. 368 (4) (2013) 351–364.
[11] P. Jha, C. Ramasundarahettige, V. Landsman, et al., 21st-century hazards of smoking and benefits of cessation in the United States, N. Engl. J. Med. 368 (4) (2013) 341–350.
[12] R.S. Shah, J.W. Cole, Smoking and stroke: the more you smoke the more you stroke, Expert. Rev. Cardiovasc. Ther. 8 (7) (2010) 917–932.
[13] M.J. Luitse, G.J. Biessels, G.E. Rutten, et al., Diabetes, hyperglycaemia, and acute ischaemic stroke, Lancet Neurol. 11 (3) (2012) 261–271.
[14] C. Banerjee, Y.P. Moon, M.C. Paik, et al., Duration of diabetes and risk of ischemic stroke: the Northern Manhattan Study, Stroke 43 (5) (2012) 1212–1217.
[15] S. Sharma, M. Pakserescht, K. Cruickshank, et al., Adherence to the USDA dietary recommendations for fruit and vegetable intake and risk of fatal stroke among ethnic groups: a prospective cohort study, BMC Neurol. 13 (2013) 120.
[16] J. He, L.G. Ogden, S. Vupputuri, et al., Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults, JAMA 282 (21) (1999) 2027–2034.
[17] C. Nagata, N. Takatsuka, N. Shimizu, et al., Sodium intake and risk of death from stroke in Japanese men and women, Stroke 35 (7) (2004) 1543–1547.
[18] L.L. Yan, M.L. Daviglus, K. Liu, et al., Midlife body mass index and hospitalization and mortality in older age, JAMA 295 (2) (2006) 190–198.
[19] C.D. Lee, A.R. Folsom, S.N. Blair, Physical activity and stroke risk: a meta-analysis, Stroke 34 (10) (2003) 2475–2481.
[20] T.A. Manolio, R.A. Kronmal, G.L. Burke, et al., Short-term predictors of incident stroke in older adults, Cardiovasc. Health Stud. Stroke 27 (9) (1996) 1479–1486.
[21] M.J. Reeves, C.D. Bushnell, G. Howard, et al., Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes, Lancet Neurol. 7 (10) (2008) 915–926.
[22] P. Appelros, B. Stegmayr, A. Terent, Sex differences in stroke epidemiology: a systematic review, Stroke 40 (4) (2009) 1082–1090.
[23] H.T. Benamer, D. Grosset, Stroke in Arab countries: a systematic literature review, J. Neurol. Sci. 284 (1–2) (2009) 18–23.
[24] P.A. Wolf, R.D. Abbott, W.B. Kannel, Atrial fibrillation as an independent risk factor for stroke: the Framingham Study, Stroke 22 (8) (1991) 983–988.
[25] T. Truelsen, P.U. Heuschmann, R. Bonita, et al., Standard method for developing stroke registers in low-income and middle-income countries: experiences from a feasibility study of a stepwise approach to stroke surveillance (STEPS Stroke), Lancet Neurol. 6 (2) (2007) 134–139.
[26] T.M. Congleton, C.W. Small, S.D. Freeman, Stroke risk factors screening and education: a regional strategy to address stroke prevalence and mortality in eastern North Carolina, Stroke 44 (2) (2013) (MeetingAbstracts:AWP345).
[27] P. Brindle, J. Emberson, F. Lampe, et al., Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study, BMJ 327 (7426) (2003) 1267.
[28] R. Beaglehole, R. Bonita, R. Horton, et al., Priority actions for the non-communicable disease crisis, Lancet 377 (9775) (2011) 1438–1447.
[29] S. Basu, S. Glantz, A. Bitton, et al., The effect of tobacco control measures during a period of rising cardiovascular disease risk in India: a mathematical model of myocardial infarction and stroke, PLoS Med. 10 (7) (2013), e1001480.
[30] Y. Yano, A. Briasoulis, G.L. Bakris, et al., Effects of antihypertensive treatment in Asian populations: a meta-analysis of prospective randomized controlled studies (CARdiovascular protectioN group in Asia: CARNA), J. Am. Soc. Hypertens. (2013).
[31] L.S. Liu, 2010 Chinese guidelines for the management of hypertension, Zhonghua Xin Xue Guan Bing Za Zhi 39 (7) (2011) 579–615.
[32] M. Rosas, G. Pastelin, G. Vargas-Alarcon, et al., Clinical guidelines for detection, prevention, diagnosis and treatment of systemic arterial hypertension in Mexico (2008), Arch. Cardiol. Mex. 78 (Suppl. 2) (2008), S2-5-57.
[33] Sociedade Brasileira de C, Sociedade Brasileira de H, Sociedade Brasileira de N, VI Brazilian guidelines on hypertension, Arq. Bras. Cardiol. 95 (1 Suppl) (2010) 1–51.
[34] Y.G. Peng, W. Li, X.X. Wen, et al., Effects of salt substitutes on blood pressure: a meta-analysis of randomized controlled trials, Am. J. Clin. Nutr. 100 (6) (2014) 1448–1454.
[35] H. Mara, China tries to kick its salt habit, Science 345 (6202) (2014) 1268–1269.
[36] P.A. James, S. Oparil, B.L. Carter, et al., 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8), JAMA 311 (5) (2014) 507–520.
[37] Advance Collaborative Group, A. Patel, S. MacMahon, et al., Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes, N. Engl. J. Med. 358 (24) (2008) 2560–2572.
[38] Y. Bi, R. Gao, A. Patel, et al., Evidence-based medication use among Chinese patients with acute coronary syndromes at the time of hospital discharge and 1 year after hospitalization: results from the Clinical Pathways for Acute Coronary Syndromes in China (CPACS) study, Am. Heart J. 157 (3) (2009) 509–516, e1.
[39] CRUSADE Executive Committee, CRUSADE 4th quarter results, 2005.
[40] L. Mandelzweig, A. Battler, V. Boyko, et al., The second Euro Heart Survey on acute coronary syndromes: characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004, Eur. Heart J. 27 (19) (2006) 2285–2293.
[41] F. Van de Werf, Dual antiplatelet therapy in high-risk patients, Eur. Heart J. Suppl. 9 (2007) D3–D9 (suppl D).
[42] S. Yusuf, Two decades of progress in preventing vascular disease, Lancet 360 (9326) (2002) 2–3.
[43] N.J. Wald, M.R. Law, A strategy to reduce cardiovascular disease by more than 80%, BMJ 326 (7404) (2003) 1419.
[44] V. Mohan, Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial, Lancet 373 (9672) (2009) 1341–1351.
[45] V. Selak, C.R. Elley, S. Crengle, et al., IMProving Adherence using Combination Therapy (IMPACT): design and protocol of a randomised controlled trial in primary care, Contemp. Clin. Trials 32 (6) (2011) 909–915.
[46] J. Finsterer, C. Stollberger, Strategies for primary and secondary stroke prevention in atrial fibrillation, Neth. J. Med. 66 (8) (2008) 327–333.
[47] Psenkova M, Lukac M, Mackovicova S, Stachova M, Bielik J, Pietsch GA, et al. Prevention of stroke in patients with atrial fibrillation: Costutility analysis of rivaroxaban versus warfarin in Slovakia. Value in health. 2012; Conference: ISPOR 15th Annual European Congress Berlin Germany. Conference Start: 20121103 Conference End: 20121107. Conference Publication: (var.pagings). 15 (7):A375.
[48] M.R. Patel, K.W. Mahaffey, J. Garg, et al., Rivaroxaban versus warfarin in nonvalvular atrial fibrillation, N. Engl. J. Med. 365 (10) (2011) 883–891.
[49] L. Silva Miguel, E. Rocha, J. Ferreira, Economic evaluation of dabigatran for stroke prevention in patients with non-valvular atrial fibrillation, Rev. Port. Cardiol. 32 (7–8) (2013) 557–565.
[50] A. Clemens, S. Peng, S. Brand, et al., Efficacy and cost-effectiveness of dabigatran etexilate versus warfarin in atrial fibrillation in different age subgroups, Am. J. Cardiol. 114 (6) (2014) 849–855.
[51] Z. Ademi, K. Pasupathi, D. Liew, Cost-effectiveness of apixaban compared to warfarin in the management of atrial fibrillation in Australia, Eur. J. Prev. Cardiol. 22 (3) (2015) 344–353.
[52] B. Wu, L. Kun, X. Liu, et al., Cost-effectiveness of different strategies for stroke prevention in patients with atrial fibrillation in a health resource-limited setting, Cardiovascular Drugs and Therapy/Sponsored by the International Society of Cardiovascular Pharmacotherapy, 28 2014, pp. 87–98 (1).
[53] O. Alli, D.R. Holmes Jr., Left atrial appendage occlusion for stroke prevention, Curr. Probl. Cardiol. 37 (10) (2012) 405–441.
[54] D.L. Wilson, R.J. Beyth, P. Linn, et al., Systematic review of public education and policy for stroke prevention, Curr. Drug Targets 8 (7) (2007) 874–879.
[55] C.X. Wang, A. Shuaib, Neuroprotective effects of free radical scavengers in stroke, Drugs Aging 24 (7) (2007) 537–546.
[56] B. Bell, K. Thornton, From promise to reality: achieving the value of an EHR, Healthcare Financial Management : Journal of the Healthcare Financial Management Association 65 (2011) 50–56 (2).
[57] P. Parmar, R. Krishnamurthi, M.A. Ikram, et al., The Stroke Riskometer(TM) App: validation of a data collection tool and stroke risk predictor, Int. J. Stroke 10 (2) (2015) 231–244.
[58] L.D. Colantonio, S.G. Marti, A.L. Rubinstein, Economic evaluations on cardiovascular preventive interventions in Argentina, Expert. Rev. 10 (4) (2010) 465–473.
[59] E.C. Jauch, J.L. Saver, H.P. Adams Jr., et al., Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 44 (3) (2013) 870–947.
[60] S.S. Ramaiah, B. Yan, Low-dose tissue plasminogen activator and standard-dose tissue plasminogen activator in acute ischemic stroke in Asian populations: a review, Cerebrovasc. Dis. 36 (3) (2013) 161–166.
[61] G.J. Hankey, C.P. Warlow, Treatment and secondary prevention of stroke: evidence, costs, and effects on individuals and populations, Lancet 354 (9188) (1999) 1457–1463.
[62] J. Joubert, L.F. Prentice, T. Moulin, et al., Stroke in rural areas and small communities, Stroke 39 (6) (2008) 1920–1928.
[63] J.S. Koh, S.J. Lee, C.W. Ryu, et al., Safety and efficacy of mechanical thrombectomy with solitaire stent retrieval for acute ischemic stroke: a systematic review, Neurointervention 7 (1) (2012) 1–9.
[64] L. San Roman, V. Obach, J. Blasco, et al., Single-center experience of cerebral artery thrombectomy using the TREVO device in 60 patients with acute ischemic stroke, Stroke 43 (6) (2012) 1657–1659.
[65] Consensus Statement on Mechanical Thrombectomy in Acute Ischemic Stroke – ESO-Karolinska Stroke Update 2014 in collaboration with ESMINT and ESNR. (2016) (Available from): http://2014.strokeupdate.org/consensus-statement-mechanical-thrombectomy-acute-ischemic-stroke.
[66] P.M. Rothwell, A. Algra, P. Amarenco, Medical treatment in acute and long-term secondary prevention after transient ischaemic attack and ischaemic stroke, Lancet 377 (9778) (2011) 1681–1692.
[67] C.S. Anderson, Y. Huang, H. Arima, et al., Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT), Stroke 41 (2) (2010) 307–312.
[68] P. Langhorne, L. de Villiers, J.D. Pandian, Applicability of stroke-unit care to low-income and middle-income countries, Lancet Neurol. 11 (4) (2012) 341–348.
[69] P. Armario, A. de la Sierra, Blood pressure as a therapeutic target in stroke, Curr. Top. Med. Chem. 9 (14) (2009) 1278–1284.
[70] S. Yusuf, S. Islam, C.K. Chow, et al., Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey, Lancet 378 (9798) (2011) 1231–1243.
[71] S.M. Grundy, R. Pasternak, P. Greenland, et al., Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology, Circulation 100 (13) (1999) 1481–1492.
[72] J. Martí-Carvajal Arturo, I. Solà, D. Lathyris, et al., Homocysteine-lowering interventions for preventing cardiovascular events, Cochrane Database of Systematic

Reviews [Internet], 2013 (1 Available from) http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006612.pub3/abstract.
[73] J.S. Yadav, M.H. Wholey, R.E. Kuntz, et al., Protected carotid-artery stenting versus endarterectomy in high-risk patients, N. Engl. J. Med. 351 (15) (2004) 1493–1501.
[74] E.M. Mahoney, D. Greenberg, T.A. Lavelle, et al., Costs and cost-effectiveness of carotid stenting versus endarterectomy for patients at increased surgical risk: results from the SAPPHIRE trial, Catheter. Cardiovasc. Interv. 77 (4) (2011) 463–472.
[75] S. Lennon, S. McKenna, F. Jones, Self-management programmes for people post stroke: a systematic review, Clin. Rehabil. 27 (10) (2013) 867–878.
[76] A. Forster, J. Young, J. Nixon, et al., A cluster randomized controlled trial of a structured training programme for caregivers of inpatients after stroke (TRACS), Int. J. Stroke 7 (1) (2012) 94–99.
[77] J.D. Pandian, C. Felix, P. Kaur, et al., FAmily-Led RehabiliTaTion aftEr Stroke in INDia: the ATTEND pilot study, Int. J. Stroke 10 (4) (2015) 609–614.
[78] S. Mendis, Prevention and care of stroke in low- and middle-income countries; the need for a public health perspective, Int. J. Stroke 5 (2) (2010) 86–91.
[79] Trialists' Collaboration Stroke Unit, Organised inpatient (stroke unit) care for stroke, Cochrane Database Syst Rev 4 (4) (2007).
[80] N. Gökkaya, M. Aras, D. Cardenas, et al., Stroke rehabilitation outcome: the Turkish experience, Int. J. Rehabil. Res. 29 (2) (2006) 105–111.
[81] V. Kuptniratsaikul, A. Kovindha, P. Dajpratham, et al., Main outcomes of stroke rehabilitation: a multi-centre study in Thailand, J. Rehabil. Med. 41 (1) (2009) 54–58.
[82] Research Group of the Standardized Tertiary Rehabilitation Program in Cerebral Diseases' Patients, Effects study of standardized tertiary rehabilitation on promoting of the neurological functions in stroke patients with hemiplegia, Zhonghua yi xue za zhi 86 (37) (2006) 2621.
[83] P. Fearon, P. Langhorne, Early Supported Discharge Trialists, Services for reducing duration of hospital care for acute stroke patients, Cochrane Database Syst. Rev. (2012) 9.
[84] Outpatient Service Trialists, Therapy-based rehabilitation services for stroke patients at home, Cochrane Database Syst. Rev. (1) (2003), CD002925.
[85] M. Sahebalzamani, L. Aliloo, A. Shakibi, The efficacy of self-care education on rehabilitation of stroke patients, Saudi Med. J. 30 (4) (2009) 550–554.
[86] K.E. Laver, D. Schoene, M. Crotty, et al., Telerehabilitation Services for StrokeStatus and date: new, published in 2013 12.
[87] LdP Torres-Arreola, S.F. Hernandez, L.E. Torres-Valdez, et al., Effectiveness of two rehabilitation strategies provided by nurses for stroke patients in Mexico, J. Clin. Nurs. 18 (21) (2009) 2993–3002.
[88] M.R. Hoseinabadi, H.R. Taheri, F. Keavanloo, et al., The effects of physical therapy on exaggerated muscle tonicity, balance and quality of life on hemiparetic patients due to stroke, JPMA J. Pak. Med. Assoc. 63 (6) (2013) 735–738.
[89] Q.P. Tang, Q.D. Yang, Y.H. Wu, et al., Effects of problem-oriented willed-movement therapy on motor abilities for people with poststroke cognitive deficits, Phys. Ther. 85 (10) (2005) 1020–1033.
[90] O. Khiaocharoen, S. Pannarunothai, C. Zungsontiporn, Cost of acute and sub-acute care for stroke patients, J. Med. Assoc. Thail. 95 (10) (2012) 1266–1277 (Chotmaihet Thangphaet).
[91] V.L. Feigin, M.H. Forouzanfar, R. Krishnamurthi, et al., Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010, Lancet 383 (9913) (2014) 245–254.
[92] C.S. Anderson, E. Heeley, Y. Huang, et al., Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage, N. Engl. J. Med. 368 (25) (2013) 2355–2365.