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Epidemiology and prevention of stroke: a worldwide perspective

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Abstract

This paper reviews how epidemiological studies during the last 5 years have advanced our knowledge in addressing the global stroke epidemic. The specific objectives were to review the current evidence supporting management of ten major modifiable risk factors for prevention of stroke: hypertension, current smoking, diabetes, obesity, poor diet, physical inactivity, atrial fibrillation, excessive alcohol consumption, abnormal lipid profile and psychosocial stress/depression.

Keywords

anticoagulation therapy; antihypertensive therapy; antiplatelet therapy; risk factors; statins; stroke

According to estimates by the WHO, stroke accounted for 5.7 million deaths and 16 million first-time events in 2005 and these numbers may reach 7.8 million and 23 million by 2030, respectively [1]. Stroke is the second leading cause of preventable death worldwide and the fourth leading cause of lost productivity [2], as measured by disability-adjusted life years. Evidence obtained from large epidemiological studies has revealed that the risk factors for stroke and their associations with stroke were similar in different parts of the world [3].

Several risk factors for stroke have been documented, mostly by studies conducted in high-income countries [4]. Nonetheless, the 2009 standardized case–control INTERSTROKE study in 22 countries worldwide (Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Croatia, Denmark, Ecuador, Germany, India, Iran, Malaysia, Mozambique, Nigeria, Peru, Philippines, Poland, South Africa, Sudan and Uganda) confirmed the significance of the same risk factors in low- and middle-income countries [3]. Results from this study found that hypertension, current smoking, diabetes, abdominal obesity, poor diet and physical inactivity accounted for more than 80% of the global risk of all types of stroke (ischemic and hemorrhagic); other risk factors included excessive alcohol consumption, dyslipidemia (measured by ratio of apolipoproteins B to A1), cardiac causes (atrial

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fibrillation or flutter, previous myocardial infarction, rheumatic valvular heart disease and prosthetic heart valve) and psychosocial stress/depression [3].

The overall objectives of this article were to review how epidemiological studies during the last 5 years have advanced our knowledge in addressing the global stroke epidemic. The specific objectives were to review the current evidence supporting management of ten major modifiable risk factors for stroke.

Methods: search strategy & selection criteria

In the current article we have reviewed risk factors for stroke that were identified as leading risk factors in the INTERSTROKE study [3] and/or the recently issued Guidelines for the Primary Prevention of Stroke for Healthcare Professionals from the American Heart Association (AHA)/American Stroke Association (ASA) [4]: hypertension, current smoking, diabetes, atrial fibrillation, dyslipidemia, obesity, poor diet, physical inactivity, excessive alcohol consumption and psychosocial stress/depression. Excessive alcohol consumption and psychosocial stress/depression were considered by the AHA/ASA as less well-documented risk factors for stroke [4] but we have included them in this review since they emerged as major risk factors for stroke in the INTERSTROKE study [3].

Eligibility criteria were as follows: only papers published in English in journals that were indexed in PubMed during the last 5 years were reviewed. We searched PubMed from January 2006 to 30 November, 2011, with the words “stroke”, “isch(a) emic stroke”, “intracerebral”, “intraparenchymal”, “subarachnoid”, “h(a)emorrhage” and “epidemiology”, “epidemiological”, “hypertension”, “high blood pressure”, “smoking”, “obesity”, “body mass index”, “waist circumference”, “waist-to-hip ratio”, “diet”, “fat”, “sodium”, “vitamin”, “physical inactivity”, “physical activity”, “exercise”, “diabetes”, “alcohol consumption”, “psychosocial stress”, “depression”, “apolipoproteins”, “lipoproteins”, “cholesterol”, “atrial fibrillation”, “meta-analysis” and “review”.

Hypertension

High blood pressure (BP) is the major risk factor for all stroke types with an estimated population-attributable fraction (PAF) ranging from 35 to 52%, depending on the definition of hypertension and stroke subtypes [3]. However, evidence suggests that the prevalence of risk factors and stroke types varies by region, gender and race ethnicity, thus resulting in differences in the estimated PAF. In the 2009 INTERSTROKE study, compared with participants without hypertension, participants with hypertension (self-reported hypertension or BP >160/90 mmHg) were 2.8 times more likely to have a stroke [3]. Stronger associations between stroke and hypertension were found in individuals younger than 45 years than in those aged 45 years or older (odds ratios 8.5 vs 3.9, respectively). Current evidence indicates substantial benefits of reducing BP for the prevention of stroke. The results from the 2009 meta-analysis of clinical trials from 1966 to 2007 demonstrated a 41% reduction in stroke for a BP reduction of 10 mmHg systolic or 5 mmHg diastolic regardless of BP before treatment (down to 110 mmHg systolic and 70 mmHg diastolic), similar to 36% reductions expected for the same difference in BP from the cohort study meta-analysis [5]. The

percentage reductions in coronary heart disease (CHD) events and stroke also were similar in people with and without cardiovascular disease (CVD) [5].

Although there is an agreement that BP >140/90 mmHg should be treated, the ideal BP target has not been established [6–8], and the definitive evidence confirming that any class of antihypertensive agents offers special protection against stroke is lacking [4,5]. In addition, the results of several recent studies showed that lower BP levels may not always result in better outcomes in patients with diabetes or clinically manifest vascular disease. The data from the ACCORD BP trial showed that achieving a systolic BP below 120 mmHg compared with standard therapy of targeting below 140 mmHg among subjects with diabetes mellitus or those with impaired fasting glucose/glucose tolerance reduced the risk of stroke but not composite cardiovascular events [9]. The author of a meta-analysis of 13 clinical trials published in 2011 concluded that in patients with Type 2 diabetes mellitus/ impaired fasting glucose/impaired glucose tolerance, a systolic BP treatment goal of 130 to 135 mmHg remains acceptable [10]. The continued risk reduction for stroke to a systolic BP of <120 mmHg was reported among these patients, however, there was a 40% increase in serious adverse events with no benefit for other outcomes at levels <130 mmHg (macrovascular or microvascular [cardiac, renal and retinal events]).

Several recent studies also investigated the association between achieving systolic BP <140 mmHg and risk of CVD events or total mortality among patients with pre-existing CVD. In a multicenter prospective study of patients with recent noncardioembolic ischemic stroke, the very low–normal (systolic BP <120 mmHg) compared with the high–normal (systolic BP 130–139 mmHg) BP was associated with increased risk of stroke (hazard ratio [HR]: 1.29; 95% CI: 1.07–1.56) [11]. In another observational *post hoc* analysis of patients with coronary artery disease and Type 2 diabetes mellitus from the INVEST study, no nonfatal or stroke-risk reduction was observed among patients with a systolic BP below 130 mmHg compared with patients with a systolic BP from 130 to 140 mmHg [12]. In the ONTARGET trial, which included patients at high CVD risk, an increased frequency of BP control to <140/90 or <130/80 mmHg was associated with a progressive reduction in the risk of stroke, new onset of microalbuminuria or macroalbuminuria, and the return to normoalbuminuria in albuminuric patients [13]. However, no consistent effect on the adjusted risk of myocardial infarction and heart failure were observed in this study and achieving the <130/80 mmHg target had little effect on the adjusted risk of overall cardiovascular events or cardiovascular mortality [13]. The results of a meta-analysis that included 25 clinical trials showed that antihypertensive treatment was associated with a 23% decreased risk of stroke among patients with a clinical history of CVD but without hypertension [14]. However, only a few studies included in this meta-analysis reported baseline BP levels and, thus, the associations between BP levels and risk of first occurrence or recurrence of CVD events can not be evaluated [14]. As the authors noted, the observed benefit associated with use of antihypertensive treatment may have been attributable to BP lowering as well as to other tissue or neurohormonal mechanisms [14]. Finally, although 35% reduced risk of stroke was observed in a meta-analysis of randomized controlled trials among hypertensive patients 80 years of age and older with or without pre-existing CVD, an inverse relationship between total mortality and higher intensity of antihypertensive treatment was reported [15].

Concerns also have been raised that lowering diastolic BP below optimal (80 mmHg) may increase the risk for coronary events by impairing coronary perfusion, especially in elderly patients, patients with left ventricular hypertrophy and/or coronary heart disease and with a wide pulse pressure [16]. By contrast, findings from a recent review did not find enough evidence to support a J-shaped curve relationship of low diastolic BP with stroke, pointing out that cerebral blood flow may not be substantially affected by low diastolic BP [17].

Dyslipidemia

While the relationship between lipids and CHD is well established, results from observational studies examining the associations between lipid profile and stroke are less conclusive. In a meta-analysis of long-term prospective studies, mostly in Europe and North America, low-density lipoprotein cholesterol (LDL-C) was only modestly related to ischemic stroke and unrelated to hemorrhagic stroke [18]. Similar results were found in a binational study in Northern Ireland and France [19]. The relationship between serum LDL-C and ischemic stroke varies by type of ischemic stroke. Although a significant and positive association was found for atherothrombotic infarctions, a negative significant association was observed for cardioembolic infarction [20].

The inverse associations of blood total cholesterol as well as LDL-C concentrations with hemorrhagic stroke found in some studies have raised concern that intensive therapy with lipid-lowering medication that result in low LDL-C levels may increase risk of hemorrhagic stroke [21]. However, evidence indicates that low LDL-C levels achieved during intensive statin treatment, are not significantly associated with an increased risk for hemorrhagic stroke, except in patients with a history of intracerebral hemorrhagic stroke [22,23]. Furthermore, findings from both the 2006 [22] and 2010 meta-analyses [23] of patients using statin therapy, show that reduction in LDL-C by 1 mmol/l (39 mg/dl) results in a decreased incidence of ischemic stroke by 16–17% regardless of age, BP and pretrial blood lipid profile. In the second 2010 meta-analysis, the risk of total stroke was decreased significantly by treatment of statins, with each 1% reduction of total cholesterol predicting a 0.8% relative risk [RR] reduction of total stroke [24]. Moreover, in nonsystematic review, pretreatment with statins in patients with ischemic stroke was associated with lower stroke severity with a better protective effect observed in atherothrombotic and lacunar infarctions. However, discontinuation of statin treatment during acute stroke is associated with loss of the protective effect and with higher mortality at 1 year of follow-up [25].

Fibrates have been shown to be effective in raising high-density lipoprotein cholesterol (HDL-C) and lowering triglyceride concentrations, and could potentially reduce LDL-C and chylomicron remnants [26]. However, a recent meta-analysis of 18 randomized clinical trials did not find a significant association between the use of fibrates and the decreased risk of stroke [27]. According to the results of a pooled meta-analysis of six randomized placebo-controlled clinical trials among patients with Type 2 diabetes mellitus, fibrates did not decrease the risk of stroke [28]. Finally, the results of a meta-analysis of the five large trials assessing the impact of fibrates on cardiovascular end points demon strated a larger risk reduction (by 28%; 95% CI: 15–39%; or 30%; 95% CI: 19–40%, in patients with high triglyceride levels (>200 mg/dl) or atherogenic dyslipidemia (HDL-C <35 and tri glycerides

>200 mg/dl) respectively, compared with nonatherogenic dyslipidemia patients (by 6%; 95% CI: 2–13%) [29].

In the 2009 systematic review of five studies, two studies showed a significant inverse relationship between HDL-C and stroke mortality in all subpopulations studied, while in three studies the association in any subpopulations studied were nonsignificant. The associations between HDL-C and subsequent stroke events were also inconsistent: six studies showed a significant inverse relationship in all subpopulations studied, one study found a significant inverse association in some subpopulations, whereas four studies did not find any statistically significant association [30].

Diabetes mellitus

Diabetes is another risk factor for stroke. Findings from the 2010 meta-analysis of 102 prospective studies showed that diabetes is associated with an approximately twofold increased risk for all types of stroke [31]. Furthermore, a review of clinical trials show that early aggressive insulin management among younger individuals with Type 1 diabetes reduces stroke incidence, but not among older patients with long-term Type 2 diabetes [32]. The intensive glucose-lowering therapy (a glycated hemoglobin [HbA_{1c}] level <7.0%) has been shown to decrease the risk of microvascular complications and may or may not be beneficial for long-term reduction in the risk of CVD [33].

The results of recent clinical trials support treatment of diabetic patients with hypertension with an renin–angiotensin system blocking agent (angiotensin-converting enzyme inhibitors and angiotensin II receptor blocker) combined with a calcium channel blockers or a thiazide-type diuretic [34]. The growing number of clinical trials favors renin–angiotensin system blocking agent/calcium channel blockers combinations in risk reduction of major fatal and nonfatal cardiovascular events as compared with diuretic-based combinations in these patients [34].

Atrial fibrillation

Atrial fibrillation (AF) is a common, well-established and strong cardiac risk factor for ischemic stroke [35]. AF has been shown to independently increase the risk of stroke by two- to ten-times among all age groups [35,36]. Since the prevalence of AF increases with age from 1% in the population aged under 50 years to approximately 10% of those above 80 years, AF accounts for 10–15% of all ischemic strokes and nearly a quarter of strokes in patients aged 80 and over in the UK [35]. The risk of stroke among patients with paroxysmal (self-terminating) and persistent (lasting more than 7 days or requiring intervention to terminate) AF is similar to that for patients with permanent AF (permanent AF is AF that either does not respond to cardioversion, surgery or medication, or a decision has been made to leave a patient in AF) [35]. Furthermore, compared with stroke patients without AF, patients with AF have higher mortality and morbidity, greater disability and longer hospitalization [35].

The optimal treatment control strategy – rate versus rhythm – remains controversial since both strategies result in reducing mortality or stroke [37]. The results of a recent study

showed that rate control is less costly and more effective than rhythm control among patients with coexisting heart failure [38]. The efficacy of anticoagulation therapy among patients with AF for prevention of stroke and thromboembolism is also well established. The current clinical guidelines recommend an individualized anticoagulation therapy for patients based on age, comorbidities, contraindications and personal stroke risk [35,39–42]. The recently issued guidelines for the primary prevention of stroke by the AHA/ASA guidelines recommend the adjusted-dose warfarin (target international normalized ratio: 2.0–3.0) for all high-risk patients at with nonvalvular atrial fibrillation [4]. Antiplatelet therapy with aspirin is recommended for low-risk patients. The choice of therapy for moderate-risk patients between anticoagulation and antiplatelet therapy is based on patient preference, estimated bleeding risk if anticoagulated and access to high-quality anticoagulation monitoring [4]. For high-risk patients with atrial fibrillation who were deemed unsuitable for anticoagulation therapy, dual antiplatelet therapy with clopidogrel and aspirin is suggested [4]. Finally, since the use of vitamin K antagonists including warfarin is complicated by numerous food and drug interactions and the need for regular coagulation monitoring, novel anticoagulants targeting factors IIa (dabigatran) and Xa (rivaroxaban, apixaban, edoxaban) in the coagulation cascade have been developed [43]. These novel anticoagulants have been shown to be as effective as warfarin with similar or even enhanced safety [43].

Cigarette smoking

Smoking, an established and modifiable risk factor for stroke [44], accounts for 15–50% of stroke, depending on age, gender, stroke subtypes and study population [45,46]. Cigarette smoking increases the RR approximately twofold and threefold for ischemic stroke and subarachnoid hemorrhage, respectively [45]. The strongest association between smoking and stroke was observed among female smokers, especially among those who take oral contraceptives and have migraine with aura [45]. Moreover, the risk of stroke grows with the number of cigarettes smoked (odds ratio [OR] increasing from 2.2 to 2.5, 4.3 and 9.1 for consumption of 1–10, for 11–20, for 21–39, and for 40 or more cigarettes smoked per day, respectively) [47], but may disappear within the first 5 years after cessation of cigarette smoking [48]. The risk of stroke among smokers tends to peak at middle age and declines with advancing age; the largest benefits of smoking cessation have been observed among individuals before the age of 30 years, because they can potentially have a life expectancy similar to nonsmokers [49]. Finally, evidence is accumulating that second-hand (passive) smoking increases risk of stroke: pooled estimates of 16 studies showed that passive smoking increases risk of stroke by 25% and this risk may reach up to 52% with increased exposure [50].

Obesity

In the 2010 systematic review and meta-analysis of 25 prospective studies, the crude unadjusted RR of ischemic stroke compared with normal weight was 1.22 (95% CI: 1.05–1.41) for overweight and 1.64 (95% CI: 1.36–1.99) for obese individuals, whereas crude unadjusted RR for hemorrhagic stroke was smaller in magnitude and was borderline significant only for the obese (RR: 1.01; 95% CI: 0.88–1.17 for overweight and RR: 1.24; 95% CI: 0.99–1.54 for obese individuals) [51]. The authors stated that unadjusted estimates

of the association minimized the risk of overadjustment for related factors, such as age, hypertension, diabetes, dyslipidemia, sedentary lifestyle and abuse of alcohol that are components of the pathway between overweight and stroke. However, the results of the multivariate estimates were qualitatively similar but the strength of the association with risk of ischemic stroke was attenuated for both overweight (RR: 1.18; 95% CI: 1.08–1.28) and obese individuals (RR: 1.50; 95% CI: 1.34–1.67), whereas the associations with hemorrhagic stroke were statistically nonsignificant (RR: 1.14; 95% CI: 0.96–1.37, for overweight) or borderline significant (RR: 1.34; 95% CI: 1.01–1.79, for obesity). Participants with high waist-to-hip ratio (WHR; >0.96 cm in men and >0.93 cm in women), compared with participants with low WHR (<0.91 cm in men and <0.86 cm in women) had an increased risk of 65% (OR: 1.65; 95% CI: 1.36–1.99) and approximately 25% of stroke (PAF: 26.5%; 95% CI: 18.8–36.0) was attributable to abdominal obesity in the in the INTERSTROKE study [3]. The ARIC Study, among participants in the USA aged 45–65 years with a median follow-up of 16.9 years were not included in the 2010 meta-analysis [51] owing to timing of publication [52]. Results indicated that obesity, regardless of the measure (BMI, waist circumference and WHR) was a risk factor for ischemic stroke [52]. There was no statistically significant difference in the association between obesity and the risk of stroke by race or sex [52]. Adjustment for diabetes and hypertension significantly attenuated these associations, suggesting that these factors may account for the majority of the risk of stroke that is associated with obesity. Furthermore, subsequent analysis of these data by subtypes of ischemic stroke demonstrated that the incidence of lacunar, nonlacunar and cardio embolic stroke were all significantly positively associated with the degree of obesity, regardless of the measure used to assess obesity (BMI, waist circumference and WHR) [53].

A recent prospective observational study showed that obese (HR: 0.71; 95% CI: 0.59–0.86) and overweight (HR: 0.82; 95% CI: 0.71–0.94) stroke patients had significantly better 10-year survival rates compared with those with a normal BMI [54]. Data from clinical trials evaluating the impact of purposeful weight reduction on outcome after stroke are not available and assessment of markers of body fat distribution and changes in bodyweight during follow-up may provide further insight into this paradox.

Diet

Several studies have reported that foods rich in vitamins B, C and E may be beneficial in reducing the risk of stroke and improving the post-stroke-associated functional declines. However, current available evidence from both observational and intervention studies is insufficient to recommend supplementation of these for the prevention of stroke [55]. The 2010 meta-analysis of nine randomized controlled trials investigating the effect of vitamin E on incident stroke concluded that vitamin E supplementation increased the risk for hemorrhagic stroke by 22% and reduced the risk of ischemic stroke by 10%. The authors cautioned against widespread use of vitamin E supplementation [56].

The relationship between saturated fat intake and stroke remains controversial. In a recent systematic review, dietary intake of saturated fat did not appear to increase the risk of stroke, and a protective effect was demonstrated in some studies [57]. Similar results were found in

a meta-analysis of eight prospective studies, where the pooled estimate for associations between dietary saturated fat intake (high vs low quantiles) and an increased risk of stroke (RR: 0.81; 95% CI: 0.62–1.05) did not reach significance [58]. On the other hand, a large community-based prospective cohort study in Japan, found that compared with low dietary intake of saturated fat (9.2 g/day), high intake (20.3 g/day) was inversely associated with mortality from total stroke (RR: 0.69; 95% CI: 0.53–0.89), intraparenchymal hemorrhage (RR: 0.48; 95% CI: 0.27–0.85), and ischemic stroke (RR: 0.58; 95% CI: 0.37–0.90), but not for subarachnoid hemorrhage (RR: 0.91; 95% CI: 0.46–1.80) [59]. Sodium is another nutrient potentially associated with stroke. Strong evidence shows that higher sodium intake results in higher BP levels, but not necessarily stroke or mortality [60]. Nevertheless, the pooled estimates obtained from the 2009 meta-analysis of 19 independent cohort samples from 13 studies showed that higher sodium intake was indeed associated with a greater risk of stroke (RR: 1.23; 95% CI: 1.06–1.43), and a higher magnitude observed in studies with a larger range of sodium intake and a longer follow-up period [61].

Compared to single nutrients, the quality and variety of the entire diet may be a stronger predictor of cardiovascular mortality and morbidity. In the 2009 INTERSTROKE study, dietary patterns measured by diet risk score using a simple 19-item qualitative food group frequency questionnaire was consistently associated with ischemic, intracerebral hemorrhagic, all stroke (increased risk 29, 53, 35% for highest vs lowest tertile, respectively) and accounted almost for 20% of all stroke [3]. The results of this study also indicate that increased consumption of fruits and fish was associated with reduced stroke risk, whereas red meat, organ meats, eggs, fried foods, pizza, salty snacks and cooking with lard was associated with an increased risk of stroke [3]. Adherence to four *a priori*-defined dietary patterns: Healthy Eating Index 2005 (HEI-2005), Dietary Approaches to Stop Hypertension (DASH), Greek Mediterranean Index and Italian Mediterranean Index, was significantly inversely associated with risk of all types of stroke (except for HEI) and risk of ischemic stroke (except the Greek Index) in a large longitudinal study (more than 40,000 participants) from Italy [62]. In addition, according to a recent nonsystematic review, tea drinking and consumption of soy foods and dairy products decreases risk of stroke while consumption of rice-based foods increase the risk of stroke [63]. Finally, participants with the highest levels of chocolate consumption had a 29% reduction in stroke compared with participants with the lowest levels in a meta-analysis of seven observational studies [64].

Although no significant association was found with vegetable intake in the INTERSTROKE study, the 2006 meta-analysis of eight observational studies found a significant protective effect against stroke of fruit and vegetables intake [65]. This effect had a dose–response realtionship: compared with individuals who had less than three servings of fruit and vegetables per day, those with three to five and those with more than five servings per day had an 11 and 26% lower RR of stroke, respectively [65]. Furthermore, subgroup analyses showed that fruit and vegetables had a significant protective effect on both ischemic and hemorrhagic stroke [65]. The models-based study showed that achieving the recommended consumption of five portions of fruits and vegetables of a day in the UK is likely to offer the most benefit for stroke mortality compared with achieving dietary targets for sodium and saturated fat [66]. Finally, it should be noted that the results of all stroke-related nutritional

studies should be interpreted with caution owing to the inherent limitations of dietary assessment and variability of stroke end points that were included in these studies [67].

Alcohol intake

The role of alcohol intake as a risk factor for stroke has been widely studied. Current epidemiological data shows that associations between alcohol intake and stroke vary depending on the amount of alcohol consumed and type of stroke [68]. Light-to-moderate drinking in observational studies decreased the risk of CHD, ischemic stroke and diabetes mellitus. Moderate consumption of wine has been shown to be more protective against CHD than moderate consumption of liquor or beer [68]. This may be due to the nonalcohol beneficial components in wine (especially red wine), but also may be due to a different pattern of drinking or more favorable risk profiles among wine drinkers.

Regular heavy alcohol intake seems to increase the risk of hemorrhagic stroke while light-to-moderate drinking may have a protective effect for ischemic stroke [68,69]. Binge drinking was found to increase the risk of any type of stroke. The results of a recent Korean study showed that the relationship between stroke and binge drinking may be modified by hypertensive status with markedly increased associations (a 12-fold risk of cardiovascular mortality) observed in the hypertensive group vs the normotensive group [70]. In addition, according to the results of the 2010 systematic reviews of ten studies, the risk of ischemic stroke increased by two- to threefold after alcohol intake within 24 h (>40–60 g = three to five drinks) or 1 week (>150 g = 11 drinks), and the strength of the association increases with the amount of alcohol [71]. Finally, in the 2011 review of 84 studies of alcohol consumption and CVD, alcohol consumption >60 g/day increased the risk of incident stroke by 62% compared with abstaining from alcohol [72].

Physical activity

In the 2009 INTERSTROKE study, regular physical activity (PA) was associated with approximately 30% of reduced risk of stroke and could prevent approximately 30% of stroke regardless of stroke type [3]. According to the results of the 2010 meta-analysis of 13 studies from 1986 to 2005, increased PA level appears beneficial in reduction of stroke risk [73]. Since measurements of the level of PA (mostly self-reported) varied among the studies, the authors of the 2010 meta-analysis characterized PA level as low, moderate or high as it was reported in the articles or reported in a manner for reclassification. Compared with low PA, high PA resulted in a 19% (95% CI: 16–23) and 24% (95% CI: 11–36) reduction in risk of stroke among the men and women, respectively [73]. Among the men, results showed a 12% reduction in risk associated with moderate PA (95% CI: 6–18) but no significant risk reduction associated with a moderate PA level in women [73].

Clearly a dose–response relationship between PA and stroke was found in a review study [74]. While higher levels (intensity, duration and frequency) of both occupational and leisurely PA, have been shown to be significantly protective against stroke, even a moderate increase in one’s activity level can have significant benefit in reducing the risk of stroke [74]. Finally, although no studies show that increased PA after stroke reduces risk of

recurrent stroke, evidence shows that a higher level of PA results in lesser stroke severity and a better long-term outcome following stroke [75].

Depression

Although numerous studies have documented a high prevalence of depression (33%) after stroke [76], there is growing evidence that depression and depressive symptoms are indeed, risk factors for stroke [77]. The 2007 meta-analysis reported that the pooled estimate for total stroke was 1.43 (95% CI: 1.17–1.75) [77]. However, these results should be interpreted with caution owing to the heterogeneity of the studies. The results of the meta-analysis that was published in 2011 were in line with the 2007 meta-analysis [78]. The pooled adjusted HRs were 1.45 (95% CI: 1.29–1.63), 1.55 (95% CI: 1.25–1.93) and 1.25 (95% CI: 1.11–1.40) for total stroke, fatal stroke and ischemic stroke, respectively.

The relationship between stroke and depression may be modified by age. Salaycik *et al.* did not find a significant relationship between depressive symptoms and stroke among adults ≥65 years [79], two recent studies suggest that depression increases the risk of stroke among the elderly [80,81]. In a Swedish study of 494, 85-year-old adults, depression at baseline increased the risk of first stroke twofold during a 3-year follow-up (HR: 2.7; 95% CI: 1.5–4.7), and this relationship remained even after accounting for dementia [80]. Additionally, the results from the Cardiovascular Health Study of 5525 men and women aged 65 years and older, demonstrated a higher risk between baseline depressive symptoms and ischemic stroke (32%) after adjusting for sociodemographic and traditional stroke risk factors; no significant risk was found to be associated with hemorrhagic stroke [81]. Findings from recent studies suggest a higher risk of morality due to stroke among depressed individuals [82,83].

There is some concern as to whether these results are due to depression itself or a result of the use of antidepressant medication. Some studies have found that use of antidepressant medication did not alter the relationship between depressive symptoms and the increased risk of stroke/transient ischemic attack among men and women [79,80]. On the other hand, the results from the Women’s Health Initiative prospective cohort study among postmenopausal women, demonstrated that antidepressant use, specifically selective serotonin reuptake inhibitors, increases the risk of stroke by almost 45% [84].

Psychological distress

Psychological distress encompasses a wide range of emotions that generally impairs daily cognitive and social functions; it includes: anxiety, stress, nervousness, frustration and general negative moods (excluding depression) [85]. Although only a few studies have examined the relationship between psychological distress and incidence of stroke, evidence indicates that psychological distress is a significant risk factor for stroke [86–89]. Among 20,627 participants aged 41–80 years in the UK EPIC-Norfolk study, the risk for stroke for a one standard deviation decrease of the Mental Health Inventory (MHI-5 scale) score (representing higher emotional distress) assessed at baseline, was 11%; and conformed to a dose–response relationship [87]. This association remained the same for men and women, however it was more pronounced for fatal stroke (22%). In addition, using the general health

questionnaire to measure psychological distress, researchers found that middle-aged men (45–59 years) enrolled in the Caerphilly study, had a higher risk of fatal ischemic stroke (45%), but not nonfatal stroke or transient ischemic attack [90].

Furthermore, evidence indicates that self-perceived psychological stress was associated with higher risk of stroke (3.49; 95% CI: 2.06–5.93) [89]. One study even found that occupational stress associated with job strain increased the risk of stroke by twofold [86]. In a systematic review of 26 studies published between January 1980 and June 2010 from MEDLINE and Embase, anger (OR: 14; 95% CI: 2.8–253.6), negative (OR: 14; 95% CI: 4.4–89.7) or positive emotions (OR 4.0; 95% CI: 1.0–26.5), sudden posture change in response to a startling event (OR: 24; 95% CI: 5.1–428.9), birthdays (OR: 1.3; 95% CI: 1.1–1.5) and psychological distress (OR: 3.9; 95% CI: 1.8–8.4) were among significant triggers of ischemic stroke [71].

Expert commentary & five-year view

Although there is considerable variation in stroke incidence and mortality across countries, approximately 90% of stroke deaths occur in low- and middle-income countries (including much of Eastern Europe, Russia, China, India, Nigeria and Tanzania) and are expected to increase in low-income countries owing to increases in the prevalence of risk factors for CVD, including urbanization and Western-style dietary changes [1]. In China alone, there were 7 million strokes in 2005 [91] and predictions estimate a more than 50% increase in CVD events (including stroke) in China between 2010 and 2030 [92]. Stroke is the leading cause of cardiovascular mortality among adults 40 years and older in China, claiming 277 lives per 100,000 person-years, compared with CHD at 85 per 100,000 person-years [93]. In 2005, stroke-related deaths in China accounted for approximately a fourth of total deaths from stroke in the world [94].

Poor management of hypertension may be one of the major factors contributing to the disparity in stroke incidence and mortality between low- or middle- and high-income regions. Hypertension control rate among hypertensive patients was reported as low as 2–4% in population-based studies of Chinese adults [95,96]. The limited availability of healthcare providers, budgetary constraints for the majority of population, and the problem that drugs are not in stock are among additional factors contributing to poor control of hypertension in middle- and low-income countries [97]. Although smoking among males has declined by more than 10% since the mid-1980s, approximately 60% of Chinese men continue to smoke, and at least 50% of nonsmokers (predominantly women) are exposed to self-reported passive smoking [92]. Moreover, it has been estimated that this rate of decline in smoking will not be sufficient to counteract approximately 26 million CVD events and 9 million cardiovascular deaths added by deleterious trends in high BP, high cholesterol, diabetes and obesity [92]. The estimated number of cardiovascular events (CHD and stroke) in adults aged 35–84 years is projected to double by 2030, given the aging, growing population and increase in stroke risk factors [92]. The changes in CVD risk profile at the population level may not only contribute to increasing trends in stroke, especially among young adults but also to changes in the predominance of hemorrhagic stroke to ischemic stroke [98]. Similar concerns apply to many other low- and middle-income countries.

International examples of successful population-level efforts across the world to address risk factors for stroke such as hypertension (including sodium consumption), tobacco use, excessive alcohol consumption, lack of healthy dietary options exist. Further work is required to reduce these significant but modifiable contributors to the global burden of stroke, especially where the burden of stroke is greatest – low- to middle-income countries. In addition to to public health challenges in prevention [46], challenges in monitoring, studying and treating stroke, including the lack of available imaging such as CT scans, and use of advanced care techniques, substantially slow down the progress in reducing stroke-related mortality and morbidity in low- and middle-income countries.

The described ten traditional risk factors in this review are major contributing factors for stroke for most populations [3,4]. However, none of these risk factors have been studied in some populations, especially young children and young adults aged <45 years. Several longitudinal studies showed that CVD risk factors presenting during childhood may persist into adulthood and adoption of healthy lifestyle behaviors appears to be promising as a counteractive force [99,100]. Consistent with these findings, the results from the US national population-based cohort demonstrated that adolescence or early adulthood exposure may be a stronger predictor of lifetime development of hypertension than exposures at other times [101].

Finally, several other modifiable risk factors may be less important for population-level interventions owing to a relatively low prevalence or moderate associations with stroke but may be of great importance for the individual patient. In the Guidelines for the Primary Prevention of Stroke for Healthcare Professionals from the AHA/ASA, they were classified as well-documented and less well-documented [4]. The well-documented factors included certain cardiac conditions, carotid artery stenosis, sickle cell disease and postmenopausal hormone therapy. Drug abuse, use of oral contraceptives, sleep-disordered breathing, migraine, hyperhomocysteinemia, hypercoagulability, inflammation and infection were listed as the less well-documented risk factors. Future studies focusing on these risk factors and their role in the pathogenesis of stroke, as well as assessing concurrently several risk factors, are needed to develop effective interventions and programs for prevention of stroke at population level.

The current evidence supports addressing the ten major modifiable risk factors for stroke. The international scientific and public health community recognized that a population-level intervention focused on tobacco control and ultimate elimination, reduction of sodium intake, promotion of a healthy diet low in saturated fats and sugar, reduction in the consumption of alcohol, and increased PA would be the most cost-effective way to address the fast-growing epidemic of noncommunicable diseases including CVD [102].

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•• of considerable interest

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Key issues

- Hypertension, diabetes, current smoking, atrial fibrillation, abdominal obesity, poor diet, physical inactivity, heavy alcohol consumption, abnormal lipid profile and psychosocial stress/depression are recognized as major population-level risk factors for stroke. Although there is an agreement that blood pressure (BP) >140/90 mmHg should be treated, the ideal BP target has not been established and the definitive evidence confirming that any class of antihypertensive agents offers special protection against stroke is lacking.
- The results of several recent studies showed that lower BP levels may not always result in better outcomes in patients with diabetes or clinically manifest vascular disease.
- Current evidence supports treatment of diabetic patients with hypertension with a calcium-channel blocker combined with blockers, angiotensin converting enzyme inhibitors or angiotensin II receptor, as compared with diuretic-based combinations in risk reduction of major fatal and nonfatal cardiovascular events.
- The adjusted-dose warfarin for all high-risk patients with nonvalvular atrial fibrillation is recommended. Antiplatelet therapy with aspirin is recommended for low-risk patients. Novel anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban) that do not require regular coagulation monitoring have been shown to be as effective as warfarin with similar or even enhanced safety.
- Reduction in low-density lipoprotein cholesterol by 1 mmol/l (39 mg/dl) using statin therapy results in a decreased incidence of ischemic stroke by 16–17%.