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REVIEW

Treatment of Risk Factors to Prevent Stroke

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Abstract Much of the decline in stroke incidence and mortality for the past several decades in Western countries has been attributed to better treatment of risk factors. Many epidemiological studies and clinical trials confirmed the importance of managing hypertension. Comparative trials of anti-hypertensive drugs or drug classes have not yielded clear results, but blood pressure variability may play an important role beyond the absolute value of blood pressure. Diabetes therapy remains a conundrum. Although diabetes is clearly a risk factor for ischemic stroke, treatment trials targeting different glycemic goals have not indicated that glucose lowering results in stroke prevention. Trials focused on insulin resistance are ongoing and they may be able to help establish the management of diabetes/impaired glucose tolerance. Evidence for treatment of dyslipidemia has contrasted science to diabetes mellitus. Dyslipidemia has not been strongly or consistently linked to ischemic stroke but the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed the impact of statin treatment in stroke prevention. The results of clinical trials investigating dabigatran and rivaroxaban clearly indicate alternative strategies to vitamin K antagonists in stroke prevention for persons with atrial fibrillation. Evidence for stroke prevention by life style modification, treating metabolic syndrome, sleep disordered breathing, lipoprotein (a), hyperhomocysteinemia, and coagulation disorders are also discussed.

Keywords Stroke prevention · Risk factors · Treatment · Blood pressure · Cerebrovascular disease

Introduction

When we examine persons with stroke, we often find risk factors. Although one may look for "the cause," or the direct mechanism of stroke, such as atherosclerotic plaque or embolic source, common risk factors contribute a significant extent to the underlying processes that lead to strokes. Treatment of risk factors is essential to prevent the first and subsequent stroke of all types, including ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage [1, 2]. The reduction in stroke incidence in Western countries for the past several decades has been attributed to better treatment of risk factors [3, 4]. The Framingham study was the first major epidemiological study that identified specific risk factors associated with cardiovascular disease. Specifically, the study demonstrated a correlation between cigarette smoking, hypertension, impaired glucose intolerance, atrial fibrillation, obesity, and the development of cardiovascular disease. Subsequent epidemiological studies, such as the Honolulu Heart study and Northern Manhattan Stroke Study corroborated these findings and added new data regarding alcohol and inflammation. First, we will discuss the new scientific data regarding the traditional established risk factors of hypertension, diabetes mellitus, dyslipidemia, and atrial fibrillation. Next, life-style related risk factors are discussed, namely smoking, alcohol-consumption, better diet, exer-

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cise, and obesity. Finally, we will discuss ongoing research and controversy regarding less established risk factors of metabolic syndrome, sleep disordered breathing, lipoprotein (a), hyperhomocysteinemia, and coagulation disorders.

Established Risk Factors

Hypertension

The goal of antihypertensive treatments is to reduce the incidence of stroke, as well as coronary heart disease (CHD) and renal failure. Meta-analyses of treatment trials have confirmed the impact of blood pressure (BP) observed in previously in epidemiological studies. Lowering of systolic BP by 10 mm Hg reduces the risk of stroke by 30 to 40% [5, 6]. Most treatment recommendations have focused on reducing the average or usual blood pressure of repeated measurements over multiple visits over time. Studies during the past decade, however, indicate blood pressure variability as an additional risk factor beyond the absolute value of mean or usual BP. These include measurement-to-measurement variation at the same clinic encounter, visit-to-visit variation, as well as abnormal circadian patterns of BP [7]. The BP level follows circadian rhythm and typically decreases approximately 10 to 20% during sleep [8]. A study of ambulatory BP monitoring showed that an abnormal diurnal BP of decline of average BP by ≥20% during sleep ("extreme dipping") or rise in nocturnal BP ("reverse dipper") are associated with new occurrence of silent and clinical cerebral ischemia [9]. Orthostatic hypotension is also associated with higher stroke risk [10]. Secondary analyses of a comparative trial of BP regimen suggests that the differences in visit-to-visit variability among the drug regimen accounts for the differences in cardiovascular events better than mean BP differences alone [11]. Therefore, it is inferred that reduction in BP variation might improve the prognosis of hypertensive patients and among those who exhibit episodic hypertension. How to intervene on these observed patterns remains a challenge.

The absolute value of goal BP and its importance remains uncertain. On 1 hand, the current American Heart Association and the American Stroke Association (AHA/ASA) guidelines for primary stroke prevention recommended BP reduction based on the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) [1, 12]. On the other hand, the AHA/ASA secondary stroke prevention guideline stated that the absolute target BP level and reduction are uncertain, and should be individualized [2]. In general, the JNC-7 stated the traditional goal has been to avoid hypertension with the usual systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure <90 mmHg. In patients with diabetes or chronic kidney disease the BP goal is <130/80 mmHg. However, this aggressive BP control recommendation is not confirmed by trial evidences. Reappraisal of the European Society of Hypertension guideline states that although this recommendation may be wise, it remains controversial [13]. Although additional benefits are suggested by observational studies, the role of more intensive BP lowering has also not been established. In a recent large-scale clinical trial of persons with type 2 diabetes mellitus, the group with SBP target <120 mm Hg, indeed, had lower stroke occurrence by 40% compared to the group with SBP target <140, but this was counterbalanced by higher incidence of hypotension, syncope, bradycardia, and hyperkalemia without any impact on death, myocardial infarction, or need for hemodialysis.

In secondary prevention of stroke, blood pressure lowering is clearly effective and important, and appears to confirm that stroke is reduced by ~40% by reduction of SBP by 10 mmHg [14]. However, are anti-hypertensives given to persons with stroke who have normal BP helpful in preventing strokes? The normotensive subgroup in the Post-Stroke Antihypertensive Treatment Study seems to suggest this to be as a result [14], and a recent meta-analysis suggest that anti-hypertensives given to normotensive individuals with prior cardiovascular disease or its risk equivalent (i.e., stroke, CHD, congestive heart failure (CHF), or diabetes mellitus) reduced risk of stroke by 23% [15]. However, the results should be interpreted with caution because the meta-analysis found heterogeneity among studies, and two other secondary stroke prevention studies after stroke, namely the Perindopril Protection against Recurrent Stroke Study (PROGRESS) and the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study, did not find significant stroke reduction among normotensive persons [16, 17].

The algorithm for treatment of hypertension initiates with lifestyle modifications. Body weight loss, better diet, limited alcohol intake, exercise, and a combination of these decrease BP not only in patients with hypertension but also in those with pre-hypertension (SBP 120–139 mmHg or diastolic blood pressure 80–89 mmHg) [18]. Better diet includes sodium reduction and the Dietary Approaches to Stop Hypertension (DASH) diet plan, which is a diet rich in fruits, vegetables, and low fat dairy products with a reduced content of dietary cholesterol, as well as saturated and total fat. Pharmacological treatment should be considered in the next step. In JNC-7, thiazide-type diuretics are recommended as the first choice. Diuretics have been used as a basis in many antihypertensive trials and are less expensively available than other agents. While lowering blood pressure appears to be the most important factor, it is less clear whether a particular drug or drug class is advantageous in lowering stroke risk. JNC-7 recommends choosing a drug that is tailored toward individual needs, such as comorbidities of coronary arteries and diabetes mellitus. Trials

comparing different drugs have not yielded clear consistent results, partly due to differences in BP achieved. Recent analyses in BP variability suggest nonloop diuretics and calcium channel blockers have lower BP variability and may explain the apparent prior conflicting data regarding differential drug class effect on cardiovascular outcomes [7, 19]. The meta-regression analyses results suggested superiority of a calcium channel blocker in comparison with beta-blockers [6]. Another meta-analysis comparing diuretics to renin-angiotensin inhibitors in secondary stroke prevention concluded greater effect seen in diuretics than renin-angiotensin inhibitors [14]. However, before focusing on the idea that 1 drug class is superior to another, it is important to note that more 50% of persons with hypertension need more than 1 antihypertensive drug in clinical practice [20]. We should pay attention to reduction of BP itself before focusing on specific drug choice.

Diabetes Mellitus

Approximately 33% of persons with ischemic strokes have diabetes mellitus, an established risk factor for stroke [21]. Among persons without diabetes, insulin resistance has also been associated with the first stroke and is prevalent in approximately 50% of persons with transient ischemic attack (TIA) or ischemic stroke [22, 23]. Yet, it remains uncertain whether treatment of hyperglycemia or a particular glycated hemoglobin target is associated with reduction in ischemic stroke or cardiac events. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial compared 10,251 persons with diabetes randomized to intensive treatment group with target A1C level <6.0% and a standard group with target A1C level of 7.0 to 7.9%. The study was halted early, because all-cause mortality was higher in the intensive therapy group without any difference in stroke or cardiovascular outcomes [24]. Similarly, the United Kingdom Prospective Diabetes Study (UKPDS), the Action in Diabetes and Vascular Disease (ADVANCE), and the Veterans Affairs Diabetes trial failed to show the benefit of intensive therapy for stroke prevention [25–27]. The American Diabetes Association states that the general glycated hemoglobin goal of <7.0% appears reasonable to prevent macrovascular disease in diabetes patients [28].

There is some evidence for advantage or disadvantage of 1 diabetes therapy in comparison to another in preventing stroke or cardiovascular complications. Rosiglitazone garnered attention when meta-analyses of randomized clinical trials noted an increase in risk in myocardial infarction [29, 30]. Data regarding stroke is more limited. A restrospective cohort study comparing two types of thiazolidinediones using United States (U.S.) Medicare prescription data showed that prescription of rosiglitazone compared to pioglitazone resulted in significant 1.3-fold increase in stroke, as well as myocardial infarction [31]. In 1 meta-analysis of randomized controlled studies, piogliazone appears to have a favorable cardiovascular results, with lower overall 0.82-fold lower combined endpoint of death, myocardial infarction, or stroke [32]. The individual stroke and myocardial infarction had similar trends without statistical significance. The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) adds to the evidence for pioglitazone therapy. In this randomized clinical trial among persons with diabetes and evidence of macrovascular complications, adding pioglitazone or placebo to diabetes regimen showed that pioglitazone reduced both overall cardiovascular events as a secondary endpoint in the study and stroke among those with history of stroke [33].

The combination of diabetes with hypertension doubles the stroke risk and triples the risk of coronary heart disease [34, 35]. Thus, intensive BP reduction toward <130/80 mmHg is described in several existing guidelines. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial compared the risk of cardiovascular events between the intensive therapy (<120 mmHg) group and the standard therapy (<140 mmHg) group. Cardiovascular events was not different between the two groups. Stroke was assessed as a pre-specified secondary endpoint. Although the total stroke number was small, the intensive therapy group had lower stroke occurrence than the standard therapy group [36]. In contrast, a secondary analysis of the International Verapamil SR-Trandolapril (INVEST) study of patients with diabetes and coronary artery disease did not show any association of tight BP control (average SBP during study <130 mmHg) with improved overall cardiovascular outcome or specifically stroke occurrence compared to usual BP control (average SBP during study 130 mmHg to <140 mmHg) [37]. At this point the benefit of the aggressive BP control below 130 mm Hg remains uncertain.

Dyslipidemia

High serum levels of total cholesterol or low-density lipoprotein (LDL) cholesterol have not been related to stroke risk overall in multiple observational epidemiological studies [38, 39]. It seems that cholesterol has the opposite relationship to ischemic stroke (positive relation) and hemorrhagic stroke (inverse relation) [40]. Yet, lipid lowering using 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins") in clinical trials have reduced overall stroke risk in both at-risk populations and after ischemic stroke [41–43]. Meta-regression analysis of data from more than 160,000 participants in 24 randomized trials showed that statin treatment decreases 21% of the nonfatal first ischemic stroke per 1.0 mmol/L (39 mg/dL) reduction in LDL cholesterol.

For those without known ischemic stroke or TIA, an approach to treat dyslipidemia should be based on the

guideline of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol on Adults (NCEP ATP III) [44]. The primary target of dyslipidemia treatment is LDL cholesterol. Based on the presence of CHD risk factors (including cigarette smoking, hypertension, high-density lipoprotein (HDL) cholesterol <40 mg/dL, CHD in a male first-degree relative <55 years or in a female first-degree relative <65 years, or age >45 years for men or >65 years for women), the 10-year risk calculation and CHD risk equivalents (diabetes or other forms of atherosclerotic disease, such as peripheral arterial disease, abdominal aortic aneurysm, or symptomatic carotid artery disease) and the goal of LDL levels are defined. The 10-year risk calculation is available at www.nhlbi.nih.gov/guidelines/cholesterol/index.htm. The goal of persons with 0 to 1 risk factor is <160 mg/dL and those with 2 risk factors is <130 mg/dL when the 10-year risk is <20%. High-risk patients with CHD, a CHD risk equivalent, or 2 risk factors with 10-year risk of >20% are recommend to control LDL levels to <100 mg/dL.

An alternative risk stratification for primary prevention has arisen from the results of the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) [45, 46]. The study selected apparently low-risk individuals with LDL cholesterol <130, but elevated risks were identified by elevated highly sensitive C-reactive protein (hsCRP) >2 mg/L. In this trial, LDL reduction by 50% and hsCRP reduction by 37% through rosuvastatin of 20 mg daily was associated with overall cardiovascular event reduction and 48% reduction in stroke. The absolute risk reduction, however, was 0.59% per year for combined cardiovascular endpoint and 0.16% per year for stroke, which would translate to the number needed to treat of 34 for a 5-year time span to prevent 1 MI, stroke, arterial revascularization, unstable angina, or death, or number needed to treat of 125 during the 5 years to prevent 1 stroke.

In patients with a history of non-cardioembolic stroke or TIA without known CHD, the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed that atorvastatin (80 mg) compared with a placebo lowers overall stroke recurrence by 16%, regardless of the ischemic stroke subtype at entry [42, 47]. The absolute risk reduction during a 5-year time span was 2.2%, with a number needed to treat of 45 during the 5 years. A greater relative benefit seems to be derived for those with atherosclerosis. Post-hoc analysis showed that ≥50% LDL cholesterol reductions had 31% reduction in stroke risk and LDL cholesterol level <70 mg/dl was significantly associated with a 28% reduction in risk of stroke [48]. In an apparent paradox, in a meta-analysis the group of secondary prevention of stroke derived a lower relative benefit than primary prevention of stroke [43]. The SPARCL trial had reduced LDL cholesterol by an average of 1.4 mmol/L, which resulted in just 16% relative reduction. This apparent paradox is explained by the observations that the primary stroke population in meta-analyses derives mostly from patients at risk for atherosclerotic coronary events and when subset of patients in SPARCL is limited to atherosclerotic stroke or those with carotid stenosis, the risk reduction approximates observed in meta-analyses [43, 47]. Although elevation of liver enzymes levels, renal dysfunction, myalgia, and myositis are known side effects of statins, their favorable risk-benefit profile has been shown in clinical trials and observational studies [41, 49]. These findings led to the current AHA/ASA guideline recommendation for patients with "atherosclerotic" ischemic stroke or TIA, and without known CHD, it is reasonable to target a reduction of at least 50% in LDL cholesterol or a target LDL cholesterol level of <70 mg/dL to obtain maximum benefit [50].

Most epidemiological studies suggested the association between lower levels of total and LDL cholesterol and higher risk of hemorrhagic stroke [51, 52]. In the SPARCL trial, statin increased the incidence of hemorrhagic stroke, but overall stroke risk was reduced. The subgroup that appeared not to benefit from atorvastatin was those with hemorrhagic stroke at entry [47]. No relation between risk of hemorrhage and baseline or recent LDL cholesterol level was observed in patients treated with statin, and only those with hemorrhagic stroke at entry appeared not to benefit from statin treatment [53]. In addition, meta-analyses have not yielded increased risk of hemorrhagic stroke with statins, although the data relies mostly on patients without prior stroke [41, 43]. Caution for statin use is advised for those who has suffered cerebral hemorrhage without known CHD. Statin use for those who have coronary artery disease and spontaneous cerebral hemorrhage remains less certain.

It is not clear whether lipid-lowering drugs other than statins reduce stroke risk. Ezetimibe reduces LDL cholesterol, and a large-scale trial to study its effects on clinical outcome is ongoing, but to date, it has failed to show any effect on measured atherosclerosis biomarkers [54, 55]. Niacin (also known as nicotinic acid, vitamin B_3) increases HDL cholesterol and reduces LDL cholesterol, but has not been studied in well-designed trials with clinical outcomes. In a recent study comparing ezetimibe to niacin given in conjunction with a statin demonstrated reduction by niacin in atherosclerosis (measured by intima-media thickness) and cardiovascular events (stroke was not reported and was probably too infrequent to generate interpretable results) [55]. Although triglycerides are not consistently associated with stroke in epidemiologic studies, it has been a target in clinical trials of cardiovascular prevention using fibrates, such as gemfibrozil and fenofibrate. These drugs reduce both LDL cholesterol and triglycerides and raise HDL slightly. Gemfibrozil reduced myocardial infarction and

stroke among men with coronary artery disease with low HDL and LDL in the Veterans Affairs HDL Intervention Trial (VA-HIT), but recent meta-analysis of fibrates suggested that it has effects on coronary events, but no effect on stroke [56, 57].

Atrial Fibrillation

Anticoagulation is available for stroke prevention in patients with atrial fibrillation. As primary stroke prevention, anticoagulation is recommended to all patients with atrial fibrillation at high or moderate risk for stroke who can receive it safely [1]. For patients with ischemic stroke or TIA with atrial fibrillation, anticoagulation is recommended as an established prevention strategy [2]. Warfarin adjusted to international normalized ratio between 2 and 3 reduces stroke incidence by 64% compared to a placebo [58]. Warfarin compared to aspirin provides further reduction of stroke by 39% [59]. The expected baseline stroke risk and the risk of bleeding should help in the decision to choose warfarin or aspirin. The CHADS2 scoring system has been developed to select moderate-to-high-risk persons with atrial fibrillation that would benefit from anticoagulation therapy. The "C" indicates the presence of congestive heart failure; the "H" indicates hypertension; the "A" stands for age ≥75; the "D" is for diabetes with a score of 1 point; the "S" represents a history of stroke or TIA with a score of 2 points. Patients with atrial fibrillation and a CHADS2 score of ≥2 are defined as high risk of stroke (1.9% to 7.6% annually) and are recommended to receive warfarin [60]. To select more candidates among patients with CHADS2 score ranging from 0 to 1, the European Society of Cardiology suggested the use of CHA2DS2-VASc scoring system [61].

Direct thrombin inhibitors that do not require dose adjustment or monitoring are being developed. Dabigatran does not require dose adjustment and has been shown to be a good alternative to warfarin in preventing stroke in an open-label randomized clinical trial [62]. The U.S. Food and Drug Administration approved dabigatran for the indication of stroke prevention in atrial fibrillation in October 2010. The dose of 150 mg twice daily appears to prevent stroke better than warfarin without higher hemorrhagic complications rates, except in gastrointestinal bleeding. A direct factor Xa inhibitor rivaroxaban is also expected to be an alternative to oral anticoagulant and does not need routine blood coagulation analysis. In a recently completed comparative trial, rivaroxaban taken once daily has been demonstrated not to be inferior to adjusted warfarin in prevention of stroke and other embolism with similar rates of hemorrhagic complications and lower rates of intracranial hemorrhage [63].

For those who cannot use anticoagulation, use of antiplatelet therapy for patients with atrial fibrillation has been studied. Aspirin alone reduces strokes in atrial fibrillation by ~22% [58]. The Atrial Fibrillation Clopidogrel Trial with Irberartan for Prevention of Vascular Events (ACTIVE)-A & W studies failed to show the clinical benefit of combined antithrombotic therapy of aspirin and clopidogrel [64, 65]. In these trials, an adverse effect of hemorrhage was significantly higher in aspirin–clopidogrel combination therapy compared to aspirin or warfarin. When patients with atrial fibrillation need temporary interruption of oral anticoagulation, a low-molecular-weight heparin bridge is reasonable [50].

Nonpharmacologic approaches in preventing stroke in atrial fibrillation include attempts to stop the rhythm of atrial fibrillation and to occlude the left atrial appendage, in which most thrombus in atrial fibrillation is believed to arise. In selected patients, the Cox maze procedures achieve >80% freedom from atrial fibrillation at 1-year follow-up [66]. Catheter-based ablation of atrial fibrillation is less invasive and seems to reduce recurrence of atrial fibrillation in selected patients by ~70% [67, 68]. However, these attempts to eliminate the rhythm still have significant atrial fibrillation recurrence at approximately 25% in controlled trials and should not be an approach to avoid anticoagulation. Devices to occlude left atrial appendage have demonstrated relative safety and might reduce stroke risk without anticoagulation. However, the clinical trial with Percutaneous Left Atrial Appendage Transcatheter Occlusion (PLAATO) device was an uncontrolled trial and only compared to the expected rate of stroke occurrence [69]. The randomized trial that compared the WATCHMAN device (Atritech, Incorporated, Plymouth, Minnesota) with warfarin recruited persons who had atrial fibrillation with relative low stroke risk, resulting in low event rates [70]. The study protocol required 45 days of warfarin after device implantation, limiting applicability to those who cannot tolerate anticoagulation even in the short-term. In addition, significant procedure–related complication was reported especially early in the trial. These procedures may overcome limitations of medical treatment and warrant proper scientific investigation.

Lifestyle Changes

Smoking

Cigarette smoking or passive smoking is one of the modifiable risk factors [71]. Cigarette smoking causes endothelial dysfunction, hypercoagulability, and inflammation, resulting in progression of atherosclerosis. Although the risk of smokeless tobacco is relatively low, smokeless tobacco is also associated with an increased risk of fatal stroke [72]. Current smokers have a 2-fold risk of ischemic stroke and subarachnoid hemorrhage. A dose-response relationship exists between cigarette smoking and stroke risk. Smoking is a modifiable risk factor and cessation of

smoking reduces the risk of stroke and other outcomes after several years of quitting [73]. In a cohort study of women, the stroke and cardiovascular mortality reached a comparable risk to never smokers after 20 years of cessation [74]. Combination of pharmacotherapy interventions and behavioral counseling are available to stop smoking. The U.S. Food and Drug Administration has approved 7 types of smoking cessation agents. Five are nicotine replacement products (gum, inhaler, lozenge, patch, and nasal spray) and 2 are non-nicotine pharmacologic agents (bupropion sustained-release and varenicline). Clonidine and nortriptyline should only be used in patients who do not tolerate the approved agents due to potential adverse effects. The role of smokeless tobacco as an alternative method of smoking cessation remains uncertain and controversial, because it still may confer health risk and is not consistently associated with smoking cessation.

Alcohol Consumption

Avoidance of heavy consumption of alcohol is important to reduce stroke occurrence. On one hand, a dose-response relationship has been observed between hemorrhagic stroke (intracerebral hemorrhage and subarachnoid hemorrhage) and the amount of alcohol consumed. On the other hand, a "J"-shaped association between ischemic stroke and alcohol consumption has been reported [75]. Mild alcohol intake decreases fasting insulin, improves insulin sensitivity and lipid profile, and increases the adiponection plasma level, but the true mechanism of detrimental and beneficial effects of alcohol remains unknown [76]. Recent meta-analysis showed that in male alcohol consumption of less than 35 g/day, or less than 3 drinks per day based on U.S. conversions, was significantly associated with a decreased relative risk for ischemic stroke, and the risk curve had a global minimum for 12 g of pure alcohol or 1 drink per day. For women, the lowest risk of mortality of ischemic stroke was among those consuming less than 12 g/day, or about 1 drink/day [77]. The ASA/AHA guideline stated that continuation of light-to-moderate alcohol consumption may be reasonable [2]. Yet, it is important to note that these epidemiological observational studies cannot completely overcome the possibilities of confounding (i.e., healthy cohort effect) and there are other negative health consequences of alcohol (e.g., trauma, liver disease). Current AHA guidelines ended with the following sentences: "nondrinkers should not be counseled to start drinking" [2].

Dietary Habits

Weight control, reduced intake of sodium, and increased dietary potassium prevent and treat hypertension [78]. In epidemiological studies, vegetarians are more likely to have lower blood pressures than nonvegetarians [79]. One of the reasons may be that they consume more, potassium, and magnesium. The effect of blood pressure lowering has also been shown by sodium reduction and the Dietary Approaches to Stop Hypertension (DASH) diet, which is low in saturated and total fats, but rich in fruits, vegetables, and low-fat dairy products [80]. In addition, the DASH diet likely reduces the components of metabolic syndrome. The DASH diet also provides a favorable effect on blood lipid profile and other components of the metabolic syndrome, with lower total, LDL, and higher HDL cholesterol concentrations and improved insulin sensitivity. Observational data indicated that increased fruit and vegetable intake in the range commonly consumed and dietary habits conforming to the DASH diet are associated with a reduced risk of stroke [81, 82].

The Mediterranean diet has also gained attention. It also seems to have beneficial effects in reducing myocardial infarction, but the effects on stroke is less clear [83, 84]. Among older adults, modest consumption of fish (not fried fish) was associated with lower prevalence of subclinical infarcts and white matter abnormalities on magnetic resonance images [85]. These data support the benefit of lifestyle modification.

Physical Inactivity

In epidemiological studies comparing highly active to sedentary individuals, physical activity are observed to reduce the risk of both ischemic and hemorrhagic strokes [86, 87]. The 2008 Physical Activity Guidelines for Americans concur in recommending regular physical activity to reduce adverse health outcomes [88]. In this guideline, most health benefits occur with at least 150 minutes a week of moderate intensity, or 75 minutes a week of vigorous intensity of aerobic physical activity. When adults with disabilities are not able to meet these guidelines, they should engage in regular physical activity according to their abilities, and they should avoid inactivity. Exercise reduces blood pressure, decreases body weight, and improves other risk factors, including metabolic syndrome [89]. The role of the health provider is important and the physician's advice regarding physical activity to patients can significantly modify exercise and diet style, including those with a prior stroke [90]. One recent observation of note is associated with the onset of stroke with physical activity [91]. There might be an increased risk of stroke occurrence within 1 hour of moderate or vigorous physical activity.

Obesity

Obesity is commonly defined using body mass index (BMI), a measurement of body weight; body weight (kg) divided by the square of his or her height (m^2). BMI between 18.5 and 24.9 (kg/m^2) is categorized as normal, BMI between 25.0 and

30 (kg/m^2) is categorized as overweight, and BMI greater than 30 (kg/m^2) is obese. Epidemiological data indicate that the risk of stroke-related mortality increases linearly when greater than a BMI of 25 kg/m^2 (i.e., greater than normal range [92]). This finding is likely due to increased stroke incidence with increasing weight and not increased mortality after stroke [93], because paradoxically, obesity may be associated with reduced long-term mortality after stroke. Some studies have demonstrated a protective effect of increasing BMI or obesity category in both the ischemic stroke and intracerebral hemorrhage [94, 95]. The phenomenon may be limited to the elderly individuals [96]. Although there is no randomized trial that investigated the benefit of weight reduction for the purpose of reducing stroke incidence, many studies show control of weight is associated with BP and insulin sensitivity, and thereby may reduce the risk of stroke [97].

Putative Risk Factors under Investigation

Metabolic Syndrome

The metabolic syndrome is a constellation of physical and metabolic characteristics that are associated with higher cardiovascular risk, including abdominal obesity, insulin resistance, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, and hypertension. The National Cholesterol Education Program criteria for the metabolic syndrome are to have 3 of the 5 risk factors. Many trials have reported the increased risk of total and ischemic strokes independently of other known factors, such as alcohol consumption, LDL cholesterol, and smoking [98]. However, in assessing and treating cardiovascular risk, it is not clear whether the concept and definition of the metabolic syndrome adds beyond the individual risk factors that compose the metabolic syndrome. For patients and physicians, the concept of the syndrome might be a useful tool in recognizing the frequent combination of the risk factors. The management of metabolic syndrome is not clearly established and individual components should be treated, including lifestyle modification with diet and exercise to decrease the abdominal obesity.

Sleep Disordered Breathing

Sleep disordered breathing (SDB) is observed in the majority of stroke patients [99]. Obstructive sleep apnea syndrome (OSA) is the most common form of SDB affecting 5 to 15% of the general population. Cheyne-Stokes respiration and central sleep apnea are other types of SDB. The main treatment for OSA syndrome is the use continuous positive airway pressure (CPAP), which can provide mild reductions in blood pressure, an effect that might decrease stroke risk [100]. Oxygen, mechanical ventilation, and tracheostomy are available options in patients with central sleep apnea, central hypoventilation, and Cheyne-Stroke respiration. Although CPAP compliance was 70% in the rehabilitation setting, in the acute phase the rate remains at approximately 25% [101]. In another study, stroke patients with SDB who did not tolerate CPAP had higher 5-year mortality than those who tolerated CPAP [102]. Beyond hypertension and obesity, the link between SDB and stroke may include intermittent hypoxemia of OSA and pulmonary vasoconstriction, increased pulmonary artery, pressure, diastolic cardiac dysfunction, and atrial fibrillation. Patients with untreated OSA have a higher recurrence of AF after cardioversion and treating OSA may reduce the risk of arrhythmia [103]. In this theory, patients with OSA may benefit from screening for AF, because both OSA and AF predispose to stroke.

Lipoprotein(a)

Lipoprotein(a) is similar to low-density lipoprotein and is associated with atherogenesis and coronary heart disease [104]. Independent relationship of lipoprotein(a) with stroke and carotid atherosclerosis are also reported [105, 106]. When LDL goals are achieved, lowering lipoprotein(a) level or raising HDL level can be considered as targets of intervention. However, the benefit of reduction in lipoprotein(a) is not established. Niacin lowers lipoprotein(a), but it also lowers LDL cholesterol and triglycerides and raises HDL cholesterol levels [107, 108]. With these favorable changes in multiple lipid measures, niacin supplementation seems to reduce atherosclerosis and have a protective effect against stroke in a meta-analysis [55, 109]. However, more trial evidence is needed to determine whether lowering lipoprotein(a) actually works in the previously mentioned theory and reduces vascular events, especially stroke occurrence.

Hyperhomocysteinemia

Higher levels of homocysteine (a metabolite of methionine) have been associated with venous thrombosis, atherogenesis, myocardial infarction, and stroke [110, 111]. Homocysteine levels is influenced by diet, B vitamins, and folic acid, renal function, and genetic composition, including allele variants of β-cystathione synthase and methylene-tetra-hydro-folate reductase. The mechanism by which homocysteine increases stroke risks is unclear. Homocysteine increases thrombotic risk, as evidenced by its association with venous thromboembolism [111, 112]. It has been less consistently linked with markers of atherosclerosis [113]. Hyperhomocysteinemia can be treated by B vitamin supplementation. Folate and vitamin B12 combination can decrease homocysteine levels than folate alone [114]. However, it is uncertain whether reduction of

homocysteine level is accompanied by reduction of stroke. Whereas individual trials of folic acid or combination B vitamin supplementation have failed to demonstrate reduction in cardiovascular endpoints, meta-analyses have reported modest, if any, lowering of stroke risk. This finding in meta-analysis is greater with combination supplementation after therapy duration of several years and in populations without folic acid fortification of grain [115]. In addition, because the large scale clinical trials of folic acid and vitamin supplementation did not screen for hyperhomocysteinemia for the trial enrollment, it remains even more unclear whether homocysteine testing is worthwhile.

Thrombophilia

Most coagulation disorders are associated with venous thrombosis and are weakly, if any, associated with arterial ischemic stroke. The role of hereditary thrombophilia, such as factor V Leiden, prothrombin 20210 mutation, proteins C and S, and anti-thrombin deficiency, as risk factors of arterial ischemic stroke is not clear. Multiple large case-control studies have not convincingly shown the association of the inherited thrombophilias with ischemic stroke, even in young patients >18 years old or patients with patent foramen ovale [116]. These venous thrombotic factors may still be relevant as a factor in stroke-selected patients within the young [117]. In addition, greater relevance for secondary prevention is the question whether there is a higher risk of stroke recurrence in this population. Limited data of small studies do not indicate greatly increased risk [118]. Among children, a meta-analysis indicates that thrombophilia has a stronger role in pediatric arterial ischemic stroke and cerebral venous thrombosis [119]. Due to this uncertain association, a person with arterial ischemic stroke with venous thrombophilia does not require anticoagulation, but it can be considered.

The presence of anti-phospholipid antibodies, including anti-cardiolipin antibodies (immunoglobulin M and immunoglobulin G types), lupus anticoagulant, or anti-β_2 glycoprotein-I antibody (β_2 GPI) are all considered acquired autoimmune thrombophilia. The consensus criteria for anti-phospholipid syndrome require thrombotic event and persistent elevated levels of anti-phospholipids [120]. Stroke patients can easily qualify if laboratory abnormalities are persistent. Data from various populations (population-based study or hospital based study; all ischemic strokes, selected by age or selected for lack of causative stroke mechanism) and study design (cohort *vs* case control) are conflicting in regard to the importance of the laboratory markers. A case control study has reported elevation of anti-cardiolipin among 9.7% of ischemic stroke patients compared to 4.3% among control subjects, indicating greater than 2-fold odds of anti-cardiolipin antibody elevation among ischemic stroke persons [121]. Larger case-cohort studies have not consistently indicated higher prevalence of anti-cardiolipin antibodies among stroke compared to controls [122, 123]. In another study, anti-cardiolipin antibodies were detectable in 11% of 1020 elderly controls without any clinical consequences [124]. Higher titers of anti-cardiolipin antibodies might not be associated with higher stroke recurrence risk [125]. The Antiphospholipid Antibody and Stroke Study (a substudy of a randomized clinical trial) demonstrated no association of the presence of anti-cardiolipin antibodies with either subsequent vascular occlusive events or a differential response to aspirin or warfarin therapy among general ischemic stroke patients [126]. Compared to less specific anti-cardiolipin antibodies, lupus anticoagulant may pose a stronger risk, particular among young women [127]. Thus, anti-platelet therapy can be considered for primary stroke prevention in persons with anti-phospholipid antibodies alone, particularly of lupus anticoagulant and data casts doubt on anticoagulation. Although some advocate warfarin anticoagulation at high intensity with international normalized rate target >3 for those meeting the criteria for anti-phospholipid syndrome, the studies on stroke have not established anticoagulation at any intensity with any certainty [128]. Oral anticoagulation may be helpful in selected population.

Conclusion

Management of risk factors is critical to prevent stroke. Not only pharmacological treatment, but also life-style modification including diet and exercise are recommended. Evidence-based recommendations found in treatment guidelines are useful, especially for hypertension, dyslipidemia, and atrial fibrillation in which the clinical trial evidence is rich. Yet there are many established and less-established risk factors lacking scientific evidence for screening and treatment. Although science seeks independent contribution of each risk factor to disease, management to one can bring additional improvement of other factors in practice and the accumulation of each improvement will finally decrease the stroke risk. Further investigations are much needed to establish the best management of important and common risk factors.

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