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Therapeutic Options

FOCUS ON PRIMARY PREVENTION OF STROKE

Despite advances in modern medicine, stroke remains a major healthcare problem associated with an enormous human and economic toll.[1] Over 50,000 strokes occur in Canada each year, resulting in nearly 14,000 deaths (six per cent of all deaths).[2] Of stroke survivors, only 10 per cent recover completely; 25 per cent of survivors are left with minor impairment, 40 per cent are left with moderate to severe impairment, and 10 per cent have such severe disability they require long-term care.[2] In addition, stroke survivors have a 20 per cent chance of suffering another stroke within two years.[2] Overall, stroke costs the Canadian economy $3.6 billion annually in physician services, hospital costs, lost wages, and decreased productivity.[2]

Since greater than 77 per cent of strokes are first events, effective primary prevention strategies are the best means of reducing the significant burden of stroke and its consequences.[1] To that end, this article provides an overview of primary prevention recommendations from recently published American Heart Association/American Stroke Association (AHA/ASA) guidelines[1] and other relevant Canadian guidelines, with a focus on pharmacotherapy. Those interested in further detail and background information are referred to the complete online versions of the guidelines (see References, below, for URLs).

RISK FACTORS

The AHA/ASA guidelines categorize stroke risk factors according to potential for modification and strength of evidence (see Box 1).

RISK FACTOR MANAGEMENT

Rigorous treatment of the well-documented and modifiable risk factors listed below has the potential to substantially reduce an individual's risk for first stroke. Given the high prevalence of several of these risk factors in the general population, significant opportunities exist to improve primary prevention strategies.

A discussion of the management of less well-documented or potentially modifiable risk factors (See Box 1) is beyond the scope of this review; however, detailed recommendations are available in the complete online version of the AHA/ASA guidelines[1] (see References, below, for URL).

Hypertension

Hypertension is considered the most important modifiable risk factor for stroke, contributing significantly to the risk of ischemic stroke and intracerebral hemorrhage.[1,3,4] Within the range of usual blood pressure (BP) values (including the nonhypertensive range), there is a progressive increase in stroke risk with increasing BP.[1]

A large body of clinical trial evidence demonstrates that treatment of hypertension is one of the most effective strategies for preventing both ischemic and hemorrhagic stroke.[1,4] In a meta-analysis of 147 randomized trials, a BP reduction of 10 mmHg systolic or 5 mmHg diastolic was associated with a 41 per cent (95% confidence interval 33% to 48%) reduction in stroke.[5]

Consistent with the AHA/ASA guidelines, current Canadian hypertension guidelines recommend a BP treatment goal of less than 140/90 mmHg for most individuals, and a target of less than 130/80 mmHg for patients with diabetes or chronic kidney disease.[6] It is unclear whether lowering BP beyond these targets confers additional stroke risk reduction.[1]

To achieve BP goals, both pharmacotherapy and lifestyle interventions should be

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Box 1 – Stroke risk factors[1]

Nonmodifiable risk factors*
- Age†
- Male gender
- Low birth weight
- Race/ethnicity
- Genetic predisposition

Well-documented and modifiable risk factors‡
- Hypertension
- Dyslipidemia
- Atrial fibrillation and other cardiac conditions
- Carotid artery stenosis
- Diabetes
- Cigarette smoking
- Poor diet
- Physical inactivity
- Obesity and unfavourable body fat distribution
- Postmenopausal hormone therapy
- Oral contraceptives
- Sickle cell disease

Less well-documented or potentially modifiable risk factors§
- Migraine
- Metabolic syndrome
- Excessive alcohol consumption
- Drug abuse
- Sleep-disordered breathing
- Hyperhomocysteinemia
- Elevated lipoprotein(a)
- Hypercoagulability
- Inflammation
- Infection

* While generally not modifiable, these risk factors identify individuals at increased risk who may benefit from rigorous prevention/treatment of modifiable risk factors.[1]

† After age 55, the risk of stroke doubles every 10 years.[2]

‡ For these risk factors, there is clear and supportive epidemiological evidence in addition to evidence of risk reduction from randomized trials.[1]

§ For these risk factors, epidemiological evidence is less clear or evidence of risk reduction from randomized trials is lacking.[1]

instituted.[1,6] At present, there is no convincing evidence that any specific class of antihypertensive agent confers special protection against stroke beyond its BP-lowering effects.[1]

Dyslipidemia

The majority of epidemiological studies suggest that higher total cholesterol levels increase the risk of ischemic stroke, whereas lower total cholesterol levels appear to increase the risk of hemorrhagic stroke.[1] As well, most epidemiological studies show an inverse relationship between high-density lipoprotein (HDL) cholesterol and ischemic stroke, whereas the relationship between triglycerides and ischemic stroke has been inconsistent.[1]

Compelling clinical trial evidence demonstrates that pharmacological therapy to lower low-density lipoprotein (LDL) and total cholesterol levels in coronary heart disease (CHD) patients markedly reduces risk for first stroke.[7] To date, this benefit has only been clearly demonstrated with statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitors), and only in individuals at high risk of stroke (i.e., those with CHD or other risk factors for atherosclerosis).[1,3] Reducing LDL cholesterol by 1.5 mmol/L reduces risk of ischemic stroke by about 33 per cent (~15% reduction in stroke risk for each 10% reduction in LDL cholesterol).[1,3]

Based on available evidence, statins (in addition to lifestyle interventions) are recommended for primary prevention of ischemic stroke in patients with CHD or other high-risk conditions such as diabetes, peripheral vascular disease, or symptomatic carotid artery disease.[1] According to current dyslipidemia guidelines from the Canadian Cardiovascular Society (CCS), the LDL cholesterol target for such high-risk individuals is less than 2 mmol/L (or a decrease of ≥50% from baseline).[8] The primary goal in U.S. guidelines is an LDL cholesterol less than 2.6 mmol/L, with an optional goal of less than 1.8 mmol/L.[1]

Other agents, including fibric acid derivatives, niacin, bile acid sequestrants, and ezetimibe, have not been proven to prevent ischemic stroke.[1] Nonetheless, these agents may be used to help attain dyslipidemia treatment goals.[1,8]

Atrial fibrillation

The risk of stroke in patients with atrial fibrillation (AF) varies from less than one per cent to over 20 per cent per year based on the presence or absence of additional risk factors, which can be assessed using the $CHADS_2$ index.[9] $CHADS_2$ stratifies patients into risk categories by assigning one point each for congestive heart failure, hypertension, age greater than 75 years, and diabetes mellitus, and two points for a history of stroke or transient ischemic attack (TIA).[9]

Recent AF guidelines from the CCS recommend that all patients with AF (or atrial flutter) be stratified for risk of stroke and risk of bleeding, and that most should receive antithrombotic therapy.[9] Specifically, they recommend that:
- patients at very low risk of stroke ($CHADS_2 = 0$) should receive aspirin (75–325 mg/day*);
- patients at low risk of stroke ($CHADS_2 = 1$) should receive oral anticoagulant (OAC) therapy with either warfarin, adjusted to achieve an international normalized ratio (INR) of 2 to 3, or dabigatran; and
- patients at moderate risk of stroke ($CHADS_2 \geq 2$) should receive OAC therapy with either warfarin (INR 2–3) or dabigatran.[9]

Of note, the CCS guidelines suggest that aspirin may be a reasonable alternative to OAC therapy for some low-risk patients based on individual risk-benefit considerations, and that dabigatran (150 mg twice daily†) is generally preferred to warfarin when OAC therapy is indicated.[9] The AHA/ASA guidelines make similar recommendations for antithrombotic therapy, with the exception that dabigatran is not included in their management strategy (i.e., warfarin is the only OAC recommended).[1] The

* Recent literature suggests that the minimum daily dose of aspirin required for primary prevention of stroke in patients with AF is 325 mg daily.[10,11]

† When given at a dosage of 150 mg twice daily, dabigatran is superior to warfarin for stroke prevention without any increase in major bleeding or need for INR monitoring; a dose of 110 mg twice daily (which is as effective as warfarin with a lower risk of major bleeding) is appropriate for patients with low body weight, decreased renal function, or increased risk of major bleeding.[7,9]

AHA/ASA guidelines also note that for high-risk patients deemed unsuitable for OAC therapy, dual antiplatelet therapy with clopidogrel and aspirin reduces stroke risk more than aspirin alone, but also increases the risk of major bleeding.[1]

For antithrombotic recommendations specific to AF patients with CHD, acute coronary syndrome, or percutaneous coronary intervention, the complete online version of the CCS guidelines[9] (see References, below, for URL) should be consulted.

Other cardiac conditions

For stroke prevention in patients with valvular heart disease, unstable angina, chronic stable angina, and acute myocardial infarction (MI) the AHA/ASA guidelines defer to other guidelines from the American College of Cardiology/American Heart Association.[1] For post-ST-segment elevation MI patients with left ventricular mural thrombi or an akinetic left ventricular segment, they note that warfarin therapy is a reasonable stroke prevention strategy.[1]

Aysmptomatic carotid stenosis

In patients with aysmptomatic carotid stenosis for whom carotid endarterectomy is deemed appropriate, treatment with aspirin is recommended.[1] Doses ranging from 81 to 325 mg daily appear to be appropriate.[10]

Diabetes

Diabetes is an independent risk factor for ischemic stroke, and persons with diabetes have an increased prevalence of other major stroke risk factors, including hypertension and dyslipidemia.[1] Accordingly, appropriate management of high blood pressure and abnormal lipid levels is recommended (see Hypertension and Dyslipidemia, above). For hypertension, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are useful and confer additional renal benefits.[1,8] Statin therapy is also recommended to lower stroke risk in diabetic patients, particularly when additional risk factors are present.[1]

Evidence supporting fibrate monotherapy to lower stroke risk in those with diabetes is not as strong as for statins, but the AHA/ASA guidelines state that such therapy "might be considered".[1] The guidelines also note that the addition of a fibrate to a statin is not useful for decreasing stroke risk.[1]

As for fibrate therapy, data supporting routine use of aspirin for primary prevention of stroke in persons with diabetes are not available.[1,12] Still, current CCS antiplatelet guidelines suggest that low-dose therapy (75–162 mg daily) may be considered for diabetic patients with other cardiovascular risk factors known to be positively affected by aspirin.[12]

While there are no data suggesting that tight glycemic control improves stroke risk in patients with type 1 or type 2 diabetes,[1] adequate glycemic control (i.e., glycated hemoglobin [A1C] ≤7.0% for most individuals) is still a major therapeutic goal.[13]

Lifestyle factors

Several lifestyle factors, including cigarette smoking, poor diet, physical inactivity, and obesity/unfavourable body fat distribution have been linked to increased stroke risk and/or potentiation of stroke risk factors such as hypertension.[1] Thus, lifestyle interventions are a critical component of primary prevention strategies to reduce stroke risk. In fact, those who practice a healthy lifestyle decrease their risk of a first stroke by 80% compared with those who do not.[1]

Key lifestyle recommendations for reduction of risk of stroke and overall cardiovascular disease are summarized in Box 2.

Postmenopausal hormone therapy

Studies are conflicting regarding the effects of traditional postmenopausal hormone therapy (HT; estrogen therapy or combined estrogen-progestogen therapy) on risk of stroke.[16] Some data indicate a timing effect, with risk not significantly increased in younger women (50–59 years) or in those who initiate HT within five years of menopause.[16] Nonetheless, the totality of evidence suggests that HT cannot be recommended for the prevention of stroke, and that it may increase the rate of first stroke (particularly in women initiating treatment over age 60).[16]

Selective estrogen receptor modulators (e.g., raloxifene, tamoxifen, tibolone) should also not be used for primary prevention of stroke.[1] In fact, tibolone is associated with an increased risk of stroke, and raloxifene may increase the risk of fatal stroke.[1]

Oral contraceptives

Data are conflicting as to whether there is an increased risk of stroke associated with modern low-dose oral contraceptives (OCs)

Box 2 – Lifestyle management recommendations[1,6,8,14,15]

Stop smoking

- Quit/abstain from smoking and avoid environmental tobacco smoke

Eat a healthy diet; reduce sodium intake and increase potassium intake

- DASH-like diet:* (1) emphasize fresh fruits and vegetables, low-fat dairy products, dietary and soluble fibre, whole grains, and protein from plant sources; and (2) minimize saturated fat and cholesterol
- Daily sodium intake: 1,500 mg (65 mmol) for adults ≤50 years; 1,300 mg (57 mmol) for adults 51–70 years; and 1,200 mg (52 mmol) for adults >70 years
- Daily potassium intake: at least 120 mmol/day

Engage in regular physical activity

- 30–60 minutes (cumulative) of moderate intensity dynamic exercise (e.g., walking, jogging, cycling, swimming) 4–7 days per week (in addition to routine activities of daily living)

Attain and maintain an ideal body weight/waist circumference

- Body mass index (BMI) 18.5–24.9 kg/m^2
- Waist circumference <94 cm for men† and <80 cm for women

* Refer to page 31 of reference #6 for details (see References, below, for URL).

† Waist circumference should be <90 cm for men of South Asian, Japanese, and Chinese descent.

in otherwise healthy women.[1,17] If there is a true increase in risk, the absolute increase appears to be very small (e.g., from approximately 1 in 10,000 [baseline risk in young women] to 2 in 10,000).[1,17] However, OCs may be more harmful in women with additional risk factors (e.g., advanced age, cigarette smoking, hypertension, diabetes, obesity, hypercholesterolemia, history of thromboembolism).[1]

ASPIRIN FOR PRIMARY STROKE PREVENTION

In addition to the specific scenarios discussed above, the AHA/ASA guidelines make the following recommendations regarding the use of aspirin for primary stroke prevention:[1]

- "The use of aspirin for cardiovascular (including but not specific to stroke) prophylaxis is recommended for persons whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (a 10-year risk of cardiovascular events of 6% to 10%)";
- "Aspirin (81 mg daily or 100 mg every other day) can be useful for prevention of a first stroke among women whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment"; and
- "Aspirin is not useful for preventing a first stroke in persons at low risk".

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