Current and future concepts in stroke prevention

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Abstract

STROKE IS A MAJOR CAUSE OF MORBIDITY and mortality in an aging population. The current understanding of the pathophysiology of atherosclerotic diseases, the most common cause of stroke, and the evidence for existing therapeutic interventions for the prevention of stroke are presented. Specifically, we review the evidence for antiplatelet agents, anticoagulants, antihypertensive medications, lipid-lowering agents and carotid endarterectomy for stroke prevention.

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Each year in Canada stroke occurs in 50 000 people and accounts for 7% of all deaths. Canada's population of stroke survivors numbers almost 300 000, of whom 30% remain permanently disabled.[1–3] Care for stroke patients accounts for 2.1% of Canadian health care expenditures.[4] Primary prevention of a first stroke and secondary prevention of recurrent events require rapid identification of risk factors and implementation of appropriate preventive measures.

The risk of stroke following an initial cerebrovascular event is high. Of patients presenting to an emergency department with a transient ischemic attack (TIA), 10.5% will have a stroke (half of these occurring in the first 2 days) and 2.6% will die within 90 days.[5] Overall, 8.8% of stroke survivors will have a recurrent stroke within the first 6 months, and 15% within 5 years.[6] In most cases (about 50%) the stroke is atherothrombotic in origin, with a further 25% attributable to small-vessel lacunar disease and 20% to cardioembolism. Data from a stroke registry reveal that patients who have an atherothrombotic stroke have the highest rates of recurrence within 30 days (18.5%), as compared with those who have a lacunar (1.4%) or cardioembolic (5.3%) stroke.[7]

In this review we present the current understanding of the pathophysiology of atherosclerotic disease, the most common cause of stroke. We also provide an overview of the available evidence for common therapeutic interventions used for stroke prevention: antiplatelet agents, anticoagulants, antihypertensive medications, lipid-lowering agents and carotid endarterectomy.

Atherogenesis

Atherosclerotic plaques begin to appear in the second and third decade of life. It is now widely agreed that inflammation at an endothelial level is the trigger for atherosclerosis.[8] Leukocytes (predominantly monocytes and T-lymphocytes) localize in the earliest atherosclerotic lesions. They bind to vascular cell adhesion molecules (VCAM-1) on the vascular endothelium and migrate into the intima.[9,10] This initiates and perpetuates a local inflammatory response. The monocytes mature into lipid-scavenging macrophages and subsequently foam cells. T-lymphocytes express inflammatory cytokines, which continue to stimulate macrophages and endothelial cells and further proliferation of smooth muscle cells[11] (Fig. 1).

Sites that experience disturbed blood flow and increased wall stresses, such as arterial branch points, seem to be at highest risk of atherosclerosis and demonstrate impaired atheroprotective mechanisms.[12] Nitric oxide production, which inhibits platelet aggregation, proliferation of arterial smooth muscle cells and expression of VCAM-1, may be reduced in these sites.[13] Furthermore, smooth muscle cells at these sites produce increased proteoglycans that promote inflammation by facilitating the oxidation of lipoproteins.[14]

Acute rupture of atherosclerotic plaques, rather than gradual encroachment of the plaque causing luminal narrowing, is the main cause of vascular morbidity and mortality. Both immunologic and mechanical forces are thought to be responsible for plaque rupture, which then precipitates thrombosis. Macrophages produce proteolytic enzymes that degrade the collagen of the plaque's fibrous cap, which makes it susceptible to rupture,[15] and produce procoagulant tissue factor, which triggers plaque thrombosis.[16]

An elevated C-reactive protein level, a marker of inflammation, inhibits nitric oxide release and thus promotes monocyte activation and adhesion to endothelium and increases low-density lipoprotein (LDL) uptake into existing plaques.[17–19] It is associated with an increased risk of coronary and cerebrovascular events, independent of other known risk factors for vascular disease.[20] Stroke risk in the highest quartile of C-reactive protein levels is almost double among men and threefold among women as compared with the lowest quartile.[21] Therefore, it is hoped that interventions that reduce C-reactive protein levels may also reduce endothelial inflammation and vascular risk. ASA, for example, appears to offer its greatest protective effect in patients in the highest quartile of C-reactive protein levels, reducing the risk of myocardial infarction in this group of men by 55.7% compared with a nonsignificant 13.9% in the lowest quartile of C-reactive protein levels.[22]

Antiplatelet agents

ASA irreversibly blocks platelet cyclooxygenase and thus prevents the formation of thromboxane A_2 (Fig. 2). As a

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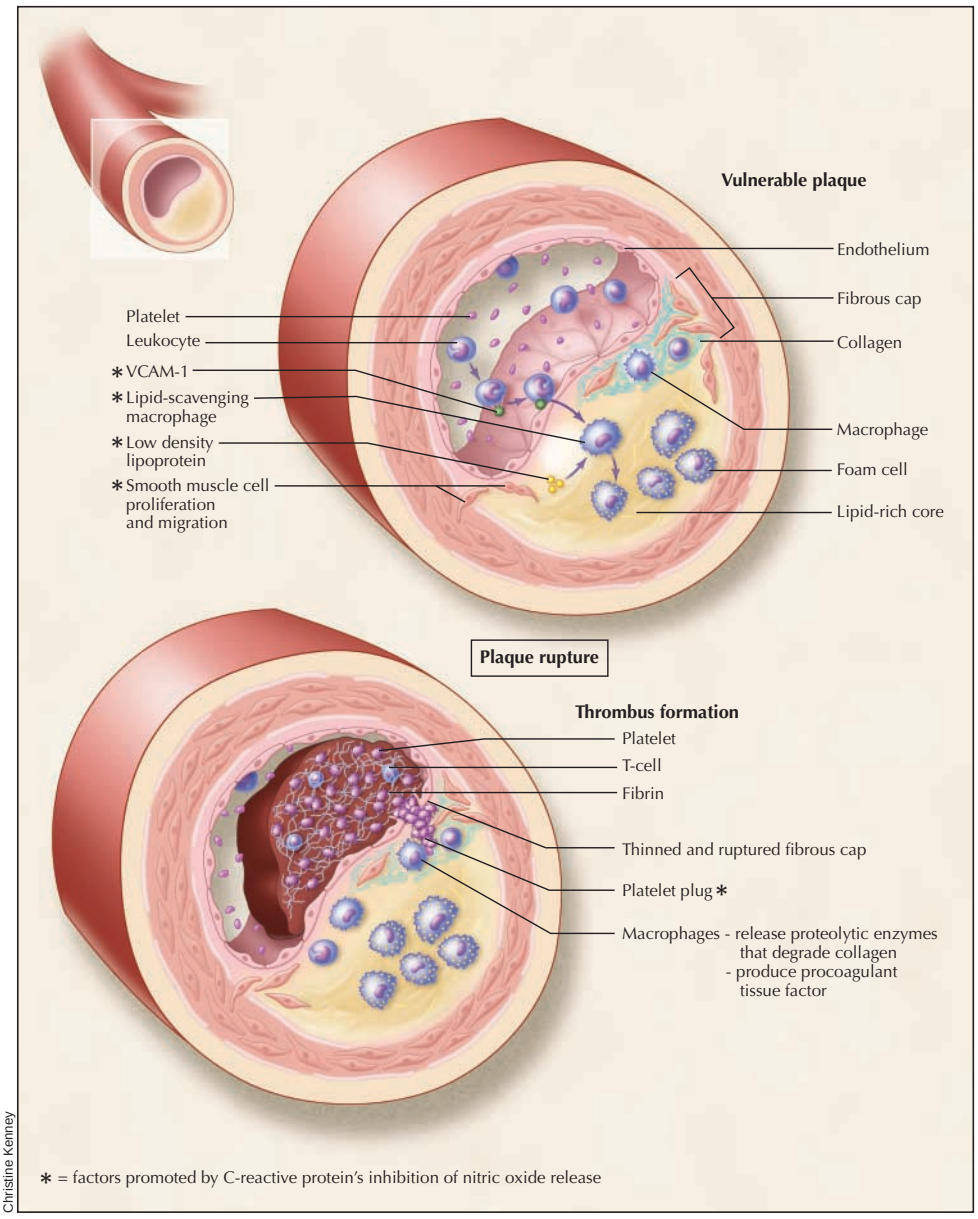
primary preventive measure, antiplatelet agents do not reduce the risk of ischemic stroke among patients without vascular disease. They are associated with an increased risk of intracranial hemorrhage (odds ratio [OR] 1.35, 95% confidence interval [CI] 0.88–2.10)[23] and major noncerebral hemorrhage (OR 1.73, 95% CI 1.14–2.63).[24]

The benefits of ASA in the secondary prevention of stroke have been well documented in the period immediately after a stroke[25] (Table 1). Long-term antiplatelet treatment after stroke shows an even more impressive reduction of 25 nonfatal strokes and 36 serious vascular events per 1000 treated over a 29-month follow-up period.[25] There appears to be no difference in efficacy between low (50 mg) and higher doses (up to 1500 mg) of ASA.[29,30]



Christine Kenney

Fig. 1: The role of inflammatory processes in thrombus formation and plaque rupture. Leukocytes localize in the earliest atherosclerotic lesions, binding to vascular cell adhesion molecules (VCAM-1) on the vascular endothelium and migrating into the intima. This initiates and perpetuates a local inflammatory response. Monocytes mature into lipid-scavenging macrophages and subsequently foam cells. T-lymphocytes express inflammatory cytokines, which continue to stimulate macrophages and endothelial cells and further proliferation of smooth muscle cells. Later, macrophages produce proteolytic enzymes that degrade the collagen of the plaque's fibrous cap, making it susceptible to rupture, and produce procoagulant tissue factor, which triggers plaque thrombosis.

The combination of dipyridamole and ASA has been shown to reduce the relative risk of recurrent stroke compared with ASA alone[26] (Table 1). Dipyridamole inhibits platelet aggregation by increasing levels of cyclic adenosine monophosphate and cyclic guanosine monophosphate. The limiting factor in the use of the ASA–dipyridamole combination is the latter's potential effects on coronary perfusion. Dipyridamole can cause coronary vasodilation, which results in increased blood flow to nonstenosed coronary arteries. The result is that myocardial ischemia may be provoked during exercise. As such, the current American College of Cardiology/American Heart Association guidelines recommend that dipyridamole not be used in patients with chronic stable angina.[31] However, this recommendation was based on short-acting dipyridamole, which also *reduced* myocardial ischemia in a similar number of patients in the study quoted by these guidelines.[32] With the use of sustained-release dipyridamole, no increase in cardiac events was observed in subjects with prior coronary artery disease.[33]

Thienopyridines block adenosine-diphosphate–mediated platelet aggregation. Ticlopidine was the first of this class of drug to be studied for stroke prevention. One clinical trial demonstrated that patients treated with ticlopidine had similar rates of stroke as those treated with ASA[28] (Table 1). However, serious granulocytopenia associated with ticlo-

pidine has limited its use. Clopidogrel is a second-generation thienopyridine that has also shown similar efficacy to ASA in stroke prevention[27] (Table 1), without any increased risk of major hemorrhage or granulocytopenia. Among patients with acute coronary syndromes, vascular events occurred in 9.3% of those given clopido-

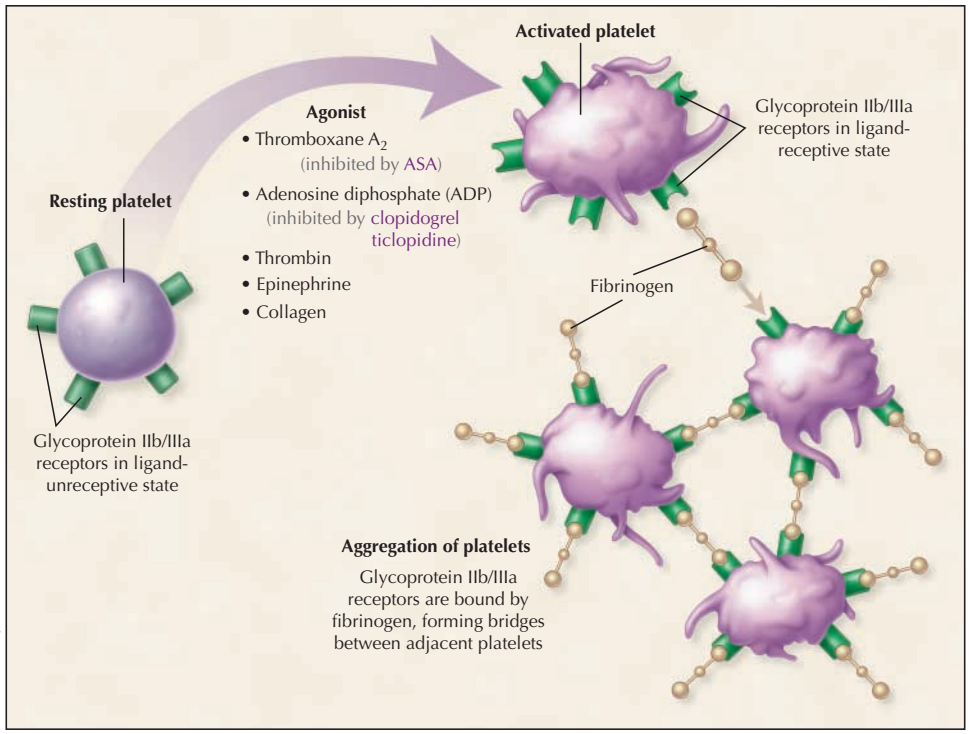


Fig. 2: Platelet aggregation and subsequent thrombosis may be prevented by several mechanisms and agents. ASA blocks platelet cyclooxygenase and the formation of thromboxane A_2, while the thienopyridines block adenosine-diphosphate–mediated aggregation.

Table 1: Major trials of antiplatelet agents

Trial	Patients	Follow-up	Intervention	Absolute risk, %	OR (95% CI)	Superior	Comments
IST/CAST Combined analysis[25] *n = 40 000*	Acute stroke in previous 48 h	CAST 28 d; IST 14 d	ASA v. placebo	Recurrent IS 1.6 2.3 Death 6.1 6.5	0.70 (0.61–0.80) 0.92 (0.85–1.00)	ASA	NNT 7/1000 (CAST); NNT 4/1000
ESPS-2[26] *n = 6602*	Stroke or TIA in previous 3 mo	2 yr	ASA v. DP v. ASA + DP v. placebo	Stroke risk 12.9 13.2 9.9 15.8	v. placebo 0.79 (0.65–0.97) 0.81 (0.67–0.99) 0.59 (0.48–0.73) –	ASA + DP	Avoid DP in patients with chronic stable angina
CAPRIE[27] *n = 19 185*	Prior MI, stroke or peripheral arterial disease	1.91 yr	Clopidogrel v. ASA	Composite of IS, MI, vascular death 5.3 5.8	0.91 (0.83–0.96)	Clopidogrel	No difference in efficacy for stroke prevention; no major safety differences
TASS[28] *n = 927*	Minor stroke in previous 3 mo	2–6 yr	Ticlopidine v. ASA	All strokes 14.2 16.0 Nonfatal stroke or death 20.8 24.8	0.88 (0.61–1.26) 0.79 (0.58–1.08)	No difference	Ticlopidine rarely used because of safety concerns (2.6% rate of neutropenia in study)

Note: When not provided in the study, unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. ASA = acetylsalicylic acid, IS = ischemic stroke, NNT = number needed to treat, TIA = transient ischemic attack, DP = dipyridamole, MI = myocardial infarction.

grel and ASA, as compared with 11.4% of those given placebo and ASA.[34] Although there were significantly more patients with major hemorrhage in the clopidogrel group than in the placebo group (3.7% v. 2.7%), there were not significantly more patients with life-threatening or intracranial hemorrhage. To date, there are no published studies specifically examining the ASA–clopidogrel combination in stroke prevention, although several are ongoing.

Summary

ASA remains a first-line therapy in the secondary prevention of atherothrombotic stroke after a first episode, although combination therapy with ASA and dipyridamole is also justified in the absence of coronary artery disease. Clopidogrel is recommended if the patient is ASA-intolerant. Patients with recurrent TIA or stroke while taking ASA should be re-evaluated to exclude other pathogeneses. If none is found, ASA–dipyridamole combination therapy should be given if not already prescribed. Further events, intolerance to dipyridamole or the presence of coexisting coronary or peripheral vascular disease should merit consideration of an ASA–clopidogrel combination therapy.

Anticoagulants

Anticoagulation is achieved primarily with heparin and warfarin. Unfractionated heparin binds with antithrombin III and thus accelerates its neutralizing effects on thrombin and inactivates clotting factors. Warfarin, a vitamin K antagonist, prevents the vitamin K-dependent activation of clotting factors II, VII, IX and X.

There is no evidence supporting anticoagulation in the treatment of acute stroke. Although heparin decreases the incidence of recurrent ischemic stroke in the short term, the benefits are offset by increases in the rates of hemorrhagic stroke[35–37] (Table 2). The remainder of this section examines the role of warfarin in modifying various clinical risk factors for the long-term prevention of stroke.

Atrial fibrillation

As previously mentioned, ischemic stroke is due to cardioembolism in about 20% of cases. Of these, the majority occur because of a mural thrombus in patients with atrial fibrillation. The annual rate of stroke with atrial fibrillation is about 4.5%. The risk of stroke is increased among patients who have hypertension, diabetes mellitus, left ventricular dysfunction, prior TIA or stroke and are older than 65. Anticoagulation reduces the annual risk to 1.4%. Patients younger than 65 with atrial fibrillation and no other risk factors had only a 1% rate of stroke, even without treatment.[42] Long-term treatment with warfarin to achieve an international normalized ratio (INR) above 2.0 decreases not only the risk of stroke, but also its clinical severity and the risk of death.[43] ASA has also been shown to be more effective than placebo in this group of patients but less effective than warfarin[38] (Table 2).

The risk of hemorrhagic complications is often a concern when considering long-term anticoagulation for atrial fibrillation. However, one study[39] demonstrated that the annual risk of ischemic stroke or systemic embolism was greater among patients assigned to low-intensity anticoagulation combined with ASA than among those given full anticoagulation (7.9% v. 1.9%), with no difference in major bleeding (Table 2).

Until recently, conversion of atrial fibrillation to sinus rhythm with the use of electrical or pharmacological methods was felt to be beneficial in reducing long-term embolic complications. However, 2 studies have challenged this concept, showing no significant difference in mortality or stroke reduction between a strategy of restoring and maintaining sinus rhythm and another aimed at rate control of chronic atrial fibrillation. Most strokes occurred only when anticoagulation was stopped or was subtherapeutic.[44,45]

Other causes of cardioembolic stroke

Patients with mechanical prosthetic heart valves are at high risk of stroke from thromboembolism and require anticoagulation at a level determined by the type of valve. If systemic embolism occurs despite adequate anticoagulation with a target INR of 3.0, 80–100 mg of ASA should be added. Patients with bioprosthetic valves require anticoagulation only for the first 3 months after valve insertion. Thereafter, ASA alone is sufficient prophylaxis.[46]

Despite treatment with thrombolytic agents, left ventricular thrombus may occur in 28% of patients who have an acute anterior myocardial infarction, with even higher rates in the presence of apical hypokinesis.[47,48] The high risk of subsequent embolic events (OR 5.45, 95% CI 3.02–9.83) may be significantly reduced with anticoagulation (OR 0.14, 95% CI 0.04–0.52)[49] and has been suggested for 1–3 months after anterior myocardial infarction[50] especially when complicated by severe left ventricle dysfunction or previous emboli.

The presence of aortic atheroma of 4 mm or more in thickness causes a 3- to 9-fold increased risk of stroke.[51–53] This risk is further increased if the atheroma is mobile[53,54] or noncalcified.[52] The limited evidence available[53,54] suggests that anticoagulation is superior to antiplatelet treatment in preventing a combined end-point of embolic events and death for atheroma that are 4 mm or more in thickness or are mobile.

The presence of patent foramen ovale (PFO) may increase the risk of ischemic stroke via paradoxical embolism through right-to-left shunting. PFO is found at autopsy in 26% of the general population and 46% of patients with cryptogenic stroke under the age of 55.[55] A meta-analysis of treatments showed that anticoagulation was superior to antiplatelet therapy for secondary stroke

prevention in the presence of PFO (OR 0.37, 95% CI 0.23–0.60) and that surgical PFO closure was comparable to anticoagulation (OR 1.19, 95% CI 0.62–2.27).[56] Definitive percutaneous transcatheter closure of PFO has been shown to be successful in preventing neurologic events in previously symptomatic patients, in addition to being safe and minimally invasive.[57] However, a recent study found no difference in 2-year recurrent event rates (stroke or TIA, death) between those with or without PFO and atrial septal aneurysm,[58] which raises the question of

Table 2: Major trials of anticoagulants

Trial	Patients	Follow-up	Intervention	Absolute risk	OR (95% CI)	Superior	Comments
IST[35] *n = 19 435*	Acute stroke in previous 48 h	14 d	Heparin v. no heparin	IS, % 2.9 3.8 Death or nonfatal stroke, % 11.7 12.0	0.76 (0.65–0.89) 0.97 (0.89–1.05)	No heparin	Decrease in recurrent IS in heparin group offset by increased risk of HS (OR 2.95, 95% CI 2.07–4.21)
IST subgroup[36] *n = 3169*	Acute stroke in previous 48 h + AF	14 d (no effect on death/ dependency at 6 mo follow-up	High-dose heparin v. low-dose heparin v. no heparin (half of patients in each group received ASA 300 mg)	IS, % 2.3 3.4 4.9 Death or nonfatal stroke, % 18.8 19.4 20.7	Heparin v. none 0.56 (0.39–0.82) 0.91 (0.76–1.08)	No heparin	Decrease in recurrent IS in heparin group offset by increased risk of HS (OR 4.81, 95% CI 2.12–10.9)
TAIST[37] *n = 1486*	Acute stroke in previous 48 h	10 d (no difference in 6 mo independence between groups)	High-dose tinzaparin v. low-dose tinzaparin v. ASA	Stroke, % 3.3 4.7 3.1 Death, % 3.5 5.5 3.5	High- and low-dose tinzaparin v. ASA 1.08 (0.53–2.21) 1.58 (0.82–3.04) 1.07 (0.55–2.11) 1.63 (0.88–3.02)	No difference in main outcome measures	Large increase in early SICH with tinzaparin treatment (OR for high-dose tinzaparin 7.15, 95% CI 1.10–163)
EAFT[38] *n = 1007*	AF + recent TIA or stroke	2.3 yr	AC v. ASA v. placebo	Stroke risk, % 4 10 12 Major and fatal bleeding, % 2.8 0.9 0.7	AC v. ASA 0.38 (0.23–0.64)	AC	Clear benefit of AC over ASA in preventing recurrent stroke secondary to AF; significant increase in bleeding events for AC compared to ASA (HR 2.8, CI 1.7–4.8) and placebo (HR 3.4, CI 1.9–6.0)
SPAF-III[39] *n = 1044*	AF + 1 thrombo-embolic risk factor	1.1 yr (stopped early)	AC (INR 2–3) v. AC (INR 1.2–1.5) + ASA	Stroke or systemic embolism per yr 1.9 7.9 Disabling stroke per yr 1.7 5.6	 0.23 (0.11–0.46) 0.30 (0.14–0.63)	AC (INR 2–3)	Rates of major bleeding similar in both groups (2.4% and 2.1%)
SPIRIT[40] *n = 1316*	TIA or IS of noncardiac origin in previous 6 mo	14 mo	AC (INR 3.0–4.5) v. ASA 30 mg	Composite of death, stroke, MI, major bleeding, % 12.4 5.4	 HR 2.3 (1.6–3.5)	ASA	No benefit for high-intensity AC over ASA in noncardioembolic stroke
WARSS[41] *n = 2206*	IS of noncardiac origin in previous 30 d	2 yr	AC (INR 1.4–2.8) v. ASA 325 mg	IS or death, % 17.8 16.0 Major bleeding per 100 patient-yr 2.2 1.5	1.13 (0.92–1.38) 1.48 (0.93–2.44)	No difference	No benefit for low- to mid-intensity AC over ASA in noncardioembolic stroke

Note: When not provided in the study, unadjusted ORs and 95% CIs were calculated. HS = hemorrhagic stroke, AF = atrial fibrillation, SICH = symptomatic intracranial hemorrhage, AC = anticoagulation, INR = international normalized ratio, HR = hazard ratio, DM = diabetes mellitus, LVH = left ventricular hypertrophy.

whether aggressive anticoagulation or surgical treatment is truly warranted.

Recurrent stroke of noncardioembolic origin

Anticoagulation may seem an attractive option for patients with recurrent cerebrovascular ischemia without an identifiable cardiac source in whom antiplatelet options have been exhausted. However, one study demonstrated no difference between ASA and warfarin (target INR 1.4–2.8) in reducing the risk of recurrent noncardioembolic stroke[41] (Table 2). A similar study also found that anticoagulation (target INR 3.0–4.5) was associated with an increased risk of overall bleeding compared with ASA (OR 1.43, 95% CI 0.96–2.13 for each 0.5 unit increase in INR) largely attributable to an increase in intracranial hemorrhage[40] (Table 2).

The presence of antiphospholipid antibody is an independent risk factor for first ischemic stroke, occurring in 9.7% of stroke patients versus 4.3% of control subjects in one study (adjusted OR 2.31).[59] Although ASA is sufficient prophylaxis as primary prevention,[60] for patients who have had a previous thrombotic event, anticoagulation greatly reduces the risk of recurrent events, both venous and arterial (hazard ratio [HR] 0.32, 95% CI 0.15–0.7 for INR < 3) as compared with ASA (HR 0.93, 95% CI 0.51–1.68).[61]

Summary

Heparin should be avoided in the treatment of acute stroke. Treatment with warfarin for patients with atrial fibrillation without prior TIA or stroke is outlined in Table 3. Warfarin is also indicated as primary stroke prevention for patients with prosthetic heart valves and for recent acute myocardial infarction (< 3 months) with apical hypokinesis or thrombus and as secondary prevention in the presence of antiphospholipid antibody. It may also be indicated for recurrent cryptogenic stroke with PFO.

Antihypertensive medications

Observational studies demonstrate the strong positive association of stroke risk with rising blood pressure in patients with or without previous cerebrovascular events.[63] Each 7.5-mm Hg rise in diastolic blood pressure doubles the risk of stroke,[64] while isolated systolic hypertension confers an even greater risk, especially among middle-aged men, who have an almost 5-fold risk of stroke.[65] A meta-analysis of some of the largest primary prevention trials of thiazides and β-blockers, totalling nearly 50 000 patients, demonstrated a 38% relative risk reduction in the rates of primary stroke with a difference of 5–6 mm Hg in diastolic blood pressure over 5 years.[66] Numerous guidelines have been developed for the treatment of hypertension[67–70] that emphasize a target blood pressure of less than 140/90 mm Hg and less than 130/85 mm Hg for patients who have had a previous cerebrovascular event and have diabetes or other vascular disease.

The question of which antihypertensive medication should be the first choice remains controversial. Thiazide diuretics, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blockers and β-blockers have all been studied (Table 4). Although thiazides and ACE inhibitors are both widely accepted as first-line therapy, choosing one over the other remains a contentious issue. While some studies have favoured thiazides[71] and others ACE inhibitors,[73,74] others have found no difference[72] (Table 4). Practically, many patients require more than 1 antihypertensive to achieve normal blood pressure, which makes the need to choose one over the other irrelevant. Indeed, in one study the combination of ACE inhibitors and the diuretic indapamide was shown to be more effective than monotherapy for secondary stroke prevention.[77] The LIFE study[75] (Table 4) suggests a role for angiotensin-receptor blockers (ARBs) in primary stroke prevention, demonstrating a 25% reduction in stroke for losartan when compared with atenolol. A substudy[76] of patients with left ventricular hypertrophy and isolated systolic hypertension demonstrated an even more impressive 40% stroke reduction.

Although restoration of normal blood pressure remains central to preventing strokes, studies of ACE inhibitors or angiotensin-receptor blockers have demonstrated reductions in rates of stroke with very modest reductions in blood pressure.[74,78] Angiotensin-II is known to increase VCAM-1 expression and the production of inflammatory cytokines that promote atherogenesis[79,80] (Fig. 1). Therefore, inhibition of angiotensin-II may have protective effects beyond blood pressure control.

Summary

Treatment of hypertension significantly reduces the risk of stroke. Both thiazides and ACE inhibitors have been shown to reduce this risk. Although there is controversy in the choice of the first-line medication, many patients require a combination of 2 or more antihypertensive drugs to

Table 3: Treatment of atrial fibrillation in primary stroke prevention*

Age	Treatment
< 65 yr	
No risk factors	ASA
1 or more risk factors†	Warfarin (INR 2–3)
65–75 yr	
No risk factors	ASA or warfarin (INR 2–3)
1 or more risk factors†	Warfarin (INR 2–3)
> 75 yr	Warfarin (INR 2–3)

*Adapted, with permission, from Laupacis et al.[62]
†Risk factors include prior transient ischemic attack, systemic embolus or stroke, hypertension, left ventricular dysfunction, diabetes mellitus and coronary artery disease.

normalize blood pressure.[70] Therefore, thiazides, ACE inhibitors or a combination of both should all be considered as first-line therapy. Additional therapies should depend on the clinical circumstances. Patients intolerant of ACE inhibitors should be treated with an angiotensin-receptor blocker, particularly in the presence of diabetes or left-ventricular hypertrophy for renal protective effects and cardiac afterload reduction respectively. β-Blockers may be preferred in the presence of diabetes, coronary artery disease or congestive heart failure.[67]

Lipid-lowering agents

LDL plays an important role in the formation of atherosclerotic plaques and the endothelial inflammatory pathway. Traditionally, the rationale of treating hyperlipidemia was to reduce the amount of substrate available for plaque formation. However, there is increasing evidence that agents used to treat hyperlipidemia, in particular the HMG–CoA reductase inhibitors (statins), also have anti-inflammatory and endothelial protective effects that are independent of lipid lowering and confer protection against vascular events. For example, statins have been shown to reduce levels of C-reactive protein, which results in a decreased risk of coronary events independent of lipid lowering.[81,82]

Unlike coronary artery disease, there is surprisingly little evidence to support a correlation between elevated serum cholesterol levels and overall cerebrovascular events. Prospective observational cohorts, with 450 000 patients, demonstrated no correlation except among patients under the age of 45.[83] This may be in part because a positive association with nonhemorrhagic stroke is offset by an observed inverse relation with intracranial hemorrhage.[84,85]

Meta-analyses have shown that statins reduce the risk of

Table 4: Major trials of antihypertensive drugs

Trial	Patients	Follow-up	Intervention	Absolute risk	OR (95% CI)	Superior	Comments
ALLHAT[71] *n = 33 357*	HTN + 1 other CAD risk factor	4.9 yr	Chlorthalidone v. amlodipine v. lisinopril	Stroke, % 5.6 5.4 6.3	AM v. CT 0.93 (0.82–1.06) LS v. CT 1.15 (1.02–1.30)	None	15% greater risk of stroke in LS group and 40% in black population, but mean BP also higher
STOP-2[72] *n = 6614*	Age 70–84 yr; SBP ≥ 180 mm Hg or DBP ≥ 105 mm Hg or both	5 yr	Conventional v. ACE inhibitors v. CCB	Stroke per 1000 patient-yr 22.2 20.2 19.5	ACE inhibitors v. conventional 0.90 (0.74–1.08) CCB v. conventional 0.88 (0.73–1.06)	None	BP lowering similar in all groups (35/16–17 mm Hg). Conventional treatment included β-blocker or thiazides, or both
Second Australian National Blood Pressure Study Group[73] *n = 6083*	Age 65–84 yr; SBP ≥ 160 mm Hg or DBP ≥ 90 mm Hg	4.1 yr	ACE inhibitors v. thiazide	Nonfatal stroke per 1000 patient-yr 7.5 7.8 Fatal stroke per 1000 patient-yr 2.3 1.2	HR 0.93 (0.70–1.26) HR 1.91 (1.04–3.50)	Possibly ACE inhibitors	BP lowering 26/12 mm Hg in both groups. Reduced number of cardiovascular events in ACE inhibitor group, but increase in fatal strokes
HOPE[74] *n = 9297*	Vascular disease or DM + additional vascular risk factor	4.5 yr	ACE inhibitors v. placebo	Total stroke, % 3.4 4.9	0.68 (0.56–0.84)	ACE inhibitors	BP lowering 3.8/2.8 mm Hg in ACE inhibitor group and 0.7/1.1 mm Hg in placebo group
LIFE[75] *n = 9193*	Age 55–80 yr; SBP 160–200 mm Hg + DBP 95–115 mm Hg + LVH	4.8 yr	Losartan v. atenolol	Total stroke per 1000 patient-yr 10.8 14.5	0.75 (0.63–0.89)	Losartan	BP lowering similar in both groups: losartan 30/17 mm Hg atenolol 29/17 mm Hg
LIFE substudy[76] *n = 1326*	As above except DBP < 90 mm Hg	4.7 yr	Losartan v. atenolol	Total stroke per 1000 patient-yr 10.6 18.9	0.60 (0.38–0.92)	Losartan	BP lowering 28/9 mm Hg in both groups
PROGRESS[77] *n = 6105*	Stroke or TIA in previous 5 yr	3.9 yr	ACE inhibitors v. placebo	Total stroke, % 12.3 12.9	0.95 (0.77–1.19)	ACE inhibitors + diuretic	BP lowering 5/3 mm Hg in ACE inhibitor group and 12/5 mm Hg in ACE inhibitor + diuretic group
			ACE inhibitors + diuretic v. double placebo	8.5 14.4	0.57 (0.46–0.70)		

Note: When not provided in the study, unadjusted ORs and 95% CIs were calculated. HTN = hypertension, CAD = coronary artery disease, AM = amlodipine, CT = chlorthalidone, LS = lisinopril, BP = blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, ACE = angiotensin-converting enzyme, CCB = calcium-channel blocker.

stroke.[86–88] For primary prevention, an earlier study of pravastatin did not demonstrate a reduced risk of stroke among hyperlipidemic subjects.[89] However, atorvastatin was recently shown to decrease the risk of stroke among patients not traditionally deemed hyperlipidemic (total cholesterol < 6.5 mmol/L) but who had multiple vascular risk factors.[90] Among patients who have had previous coronary artery disease, both simvastatin and pravastatin have been shown to decrease the risk of stroke without any increase in the risk of hemorrhagic stroke[91,92] (Table 5). The Heart Protection Study (HPS)[93] (Table 5) has now lowered the lipid treatment threshold even further in high-risk groups, demonstrating marked reductions in all vascular events with baseline LDL as low as 2.5 mmol/L, irrespective of age, sex and other treatments.

Patients with low or normal LDL (< 3.6 mmol/L), low high-density lipoprotein (HDL) levels (< 0.81 mmol/L) and coronary artery disease may also benefit from gemfibrozil, a fibrate drug, which has been shown to reduce the risk of stroke by 31%[94] (Table 5). However, the safety and efficacy of gemfibrozil in combination with statins are unclear.

A meta-analysis of nonstatin interventions showed that a treatment strategy to reduce total cholesterol below 6 mmol/L with fibrate drugs, niacin and diet reduced the risk of stroke.[88]

Summary

All patients with prior TIA, ischemic stroke or with high risk factors for vascular disease as defined by HPS criteria should be treated with a statin irrespective of their serum cholesterol level. Fibrate drugs may also reduce the risk of stroke; however, the safety and efficacy of the combination of the fibrate and statin drugs are not clear.

Carotid endarterectomy

Carotid endarterectomy of a symptomatic severe stenosis of an internal carotid artery remains one of the most effective methods of preventing recurrent stroke, reducing the risk by up to two thirds[95,96] (Table 6). The number-needed-to-treat (NNT) to prevent 1 stroke at 2 years is 8 for high grade stenosis (≥ 70%) and 20 for moderate stenosis (50%–69%).[99]

Endarterectomy for asymptomatic stenosis of the internal carotid artery remains controversial. Although one study demonstrated a 53% relative risk reduction in ipsilateral stroke and death over 5 years, the number of events was small, with a higher NNT and men appeared to benefit considerably more than women.[97,99] Long-term benefits may also be outweighed by the early risks of excess perioperative stroke or death (relative risk [RR] 6.52, 95% CI 2.66–15.96) and are influenced by the complication rates of individual surgeons.[100] Guidelines suggest that surgery should be considered only for asymptomatic carotid disease if the complication rate is less than 3% and the stenosis is greater than 60%.[101] The age and health of the patient, plaque stability and presence of coexisting cerebral artery disease should also be considered.

Table 5: Major trials of lipid-lowering agents

Trial	Patients	Follow-up	Intervention	Absolute risks	OR (95% CI)	Superior	Comments
WOSCOPS[89] *n = 6595*	Men aged 45–64 yr, TC ≥ 6.5 mmol/L, no history of MI	4.9 yr	Pravastatin v. placebo	Stroke, % 1.4 1.5	–	None	In pravastatin group, TC decreased 20%, LDL decreased 26%
ASCOT-LLA[90] *n =10 305*	HTN + ≥ 3 other vascular risk factors, TC ≤ 6.5 mmol/L	3.3 yr	Atorvastatin v. placebo	Total stroke per 1000 patient-yr 5.4 7.4	HR 0.73 (0.56–0.96)	Atorvastatin	In atorvastatin group, TC decreased 19%, LDL decreased 29%
4-S[91] *n = 4444*	CAD + TC 5.5–8.0 mmol/L	5.4 yr	Simvastatin v. placebo	Stroke rate, % 2.7 4.3	0.63 (0.46–0.88)	Simvastatin	In simvastatin group, TC decreased 25%, LDL decreased 35%
PPP CARE + LIPID trials combined[92] *n = 6593*	CAD + "average" lipid levels; mean TC: CARE 5.4 mmol/L LIPID 5.7 mmol/L	CARE 4.8 yr LIPID 6.1 yr	Pravastatin v. placebo	Strokes per 1000 patient-yr 6.2 7.9	HR 0.78 (0.65–0.93)	Pravastatin	–
HPS[93] *n = 20 536*	History of vascular disease or DM	5 yr	Simvastatin v. placebo	All stroke, % 4.3 5.7	0.75 (0.66–0.85)	Simvastatin	Benefits irrespective of initial cholesterol levels
VA-HIT[94] *n = 2531*	CAD HDL < 1.03 mmol/L LDL < 3.6 mmol/L Trig < 3.39 mmol/L	5.1 yr	Gemfibrozil v. placebo	Total stroke, % 4.6 6.0	Unadjusted OR 0.76 (0.53–1.07) Adjusted RRR 31% (2%–52%)	Gemfibrozil	In gemfibrozil group, HDL increased 6%, TC decreased 4%, Trig decreased 31%

Note: When not provided in the study, unadjusted ORs and 95% CIs were calculated. TC = total cholesterol, LDL = low-density lipoprotein, HTN = hypertension, HDL = high-density lipoprotein, Trig = triglycerides, RRR = relative risk reduction.

Summary

Carotid endarterectomy remains the definitive treatment in patients with symptomatic stenosis of the internal carotid artery of 70% or higher and in selected patients with a stenosis of 50%–69%. We do not currently recommend surgery for asymptomatic disease, preferring to treat proven vascular risk factors aggressively with immediate follow-up in the event of any stroke symptoms.

Conclusion

We have presented the current understanding of the pathophysiology of atherosclerosis, the most important cause of stroke and the evidence available for the medical and surgical interventions for the prevention of stroke. Based on the evidence, it is clear that the use of an antiplatelet agent or warfarin and the correction of hypertension and hyperlipidemia all reduce the risk of stroke. In patients with symptomatic and severe internal carotid stenosis, it is also clear that carotid endarterectomy is the treatment of choice for stroke prevention.

The research in stroke prevention is ongoing with the evaluation of new drugs, refinement of knowledge of current medications and the tailoring of treatments for appropriate patient groups. Although beyond the scope of this review, the modification of lifestyle factors such as smoking and obesity remain crucial components to the prevention of stroke. Stroke risk may be reduced by almost 50% with regular exercise alone.[102]

The management of risk factors after stroke in general is not optimal[103] and requires an increase in both the awareness of these risk factors and the appropriate, evidence-based use of existing therapeutic interventions. We have attempted to present the findings of important clinical trials to ascertain these risks and potential benefits, and we believe there is a need for more aggressive monitoring and treatment by both primary care physicians and specialists alike.

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Table 6: Major trials of carotid endarterectomy

Trial	Patients	Follow-up	Intervention	Absolute risk, %	OR (95% CI)	Superior	Comments
NASCET[95] *n = 649*	70%–99% symptomatic carotid stenosis	18 mo	CEA v. medical care	Stroke or death 15.8 32.3	0.50 (0.33–0.77)	CEA	Clear early benefits for CEA in severe symptomatic carotid disease
NASCET[95] *n = 858*	50%–69% symptomatic carotid stenosis	5 yr	CEA v. medical care	Stroke or death 33.2 43.3	0.67 (0.51–0.90)	CEA	Benefits obtained largely in first 2–3 yr after CEA; no benefits from CEA with stenosis < 50%
ECST[96] *n = 3024*	TIA or nondisabling stroke in previous 6 mo related to carotid stenosis	CEA 3 yr; Medical care 3.2 yr	CEA v. medical care	Stroke or death at 3 yr for ≥ 80% ICA stenosis 14.9 26.5	HR 0.78 (CI not provided) $p = 0.01$	CEA	80% stenosis on ECST criteria is equal to 70% stenosis on NASCET criteria
ACAS[97] *n = 1662*	Asymptomatic carotid stenosis ≥ 60%	2.7 yr	CEA v. medical care	Ipsilateral stroke and perioperative stroke or death 5.1 11.0	0.63 (0.40–0.98)	CEA	CEA for asymptomatic carotid disease remains controversial
CAVATAS[98] *n = 504*	Carotid stenosis suitable for CEA or endovascular treatment	CEA 1.98 yr; Endovascular 1.95 yr	Endovascular treatment v. CEA	Death or disabling stroke 14.3 14.2	1.03 (0.64–1.64)	None	Higher rates of procedural stroke than those reported in other major trials for CEA

Note: When not provided in the study, unadjusted ORs and 95% CIs were calculated. CEA = carotid endarterectomy, ICA = internal carotid artery.

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