Advances in Primary Stroke Prevention

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Because ~75% of strokes are first-ever strokes, it is likely that effective prevention in persons with established risk factors who have not had a stroke (ie, primary prevention) can have as great or a greater impact on reducing the burden of the disease as effective prevention of recurrent stroke. The cost associated with inadequate primary prevention is at least as great as that resulting from inadequate secondary prevention. There were several important studies published over the last year providing new data addressing primary stroke prevention.

Blood Pressure–Lowering

Lowering systolic blood pressure by 10 mm Hg is associated with a reduction in the risk of stroke by about one third, irrespective of baseline blood pressure (BP) levels. It remains uncertain whether long-acting dihydropyridine calcium-channel blockers (CCBs), angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers (ARBs) are more effective than other classes of antihypertensive drugs, and whether the very elderly benefit from treatment.

The Anglo-Scandinavian Cardiac Outcomes Trial–Blood pressure Lowering Arm (ASCOT-BPLA) randomly allocated 19,257 individuals aged 40 to 79 years with hypertension and at least 3 other cardiovascular risk factors to an amlopipine-based (amlodipine 5 to 10 mg adding perindopril 4 to 8 mg as required) as compared with an atenolol-based drug regimen (atenolol 50 to 100 mg adding bendroflumethiazide 1.25 to 2.5 mg and potassium as required). After 5.5 years median follow-up, the amlopipine-based regimen was associated with lower rates of stroke (hazard ratio [HR]=0.77, 95% CI: 0.66 to 0.89), coronary events (HR=0.86, 95% CI: 0.77 to 0.96) and new-onset diabetes (HR=0.70, 95% CI: 0.63 to 0.78). The CCB-angiotensin-converting enzyme inhibitor regimen may be associated with a greater reduction in pulse pressure and better patient compliance (ie, fewer adverse effects), but stroke reduction was at least partially attributable to lower BPs among patients randomized to the amlopipine-based regimen (mean difference: 2.7/1.9 mm Hg). Although not a primary prevention study, the MOrbidity and mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention (MOSES) trial randomly assigned 1,405 patients to treatment with an ARB (eprosartan) or a CCB (nitrendipine). There was a reduction in cerebrovascular events (incidence density ratio: 0.75; 95% CI: 0.58 to 0.97) among those treated with the ARB during 2.5 years (mean) follow-up with no significant difference in BP between the 2 groups. Caveats of the MOSES trial are that it was a pilot study, treatment allocation was not masked, 53 patients were excluded from the analyses because they withdrew consent after randomization, and the analysis was based on the number of outcome events, which could include double counting of patients, rather than an actuarial analysis of time to first event (with censoring).

The benefits of lowering BP in the very elderly are supported by the results of the Study on Cognition and Prognosis in the Elderly (SCOPE) that randomly assigned 4,964 patients aged 70 to 89 years with mild to moderate hypertension to double-blind treatment with candesartan 8 to 16 mg daily or placebo. Open-label antihypertensive therapy (mostly thiazide diuretics) was added as needed to control the BP. Assignment to candesartan was associated with a 27.8% (95% CI: 1.3% to 47.2%) relative risk reduction of nonfatal strokes, and a nonsignificant reduction of all strokes (relative risk reduction=23.6%, 95% CI: −0.7% to 42.1%) as compared with placebo. This was achieved with a lower mean BP (mean difference: 3.2/1.6 mm Hg) in the active treatment group. The results were consistent among different subgroups with the exception of those with isolated systolic hypertension and a previous stroke, for whom the benefit appeared greater.

Taken together, these studies suggest that there may be marginal cerebrovascular benefits for regimens that include an ARB and CCB, but the available data are not definitive. Hypertension should be treated in the very elderly to reduce their risk of nonfatal stroke.

Antithrombotic Therapy for Atrial Fibrillation

Patients with atrial fibrillation (AF) and coronary heart disease (CHD) are commonly prescribed both an anticoagulant (to reduce the risk of cardiogenic ischemic stroke) and antiplatelet therapy (to reduce the risk of atherothrombotic ischemic coronary events or stroke). The National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) trial randomly assigned 714 intermediate risk AF patients to receive antiplatelet therapy (triflusal 600 mg/day; n=242),...
anticoagulation (acenocumarol, international normalized ratio [INR] range 2 to 3; n=237) or combination therapy (triflusal 600 mg/d + acenocumarol, INR 1.25 to 2.00; n=235). After 2.7 years (median) follow-up, the primary outcome of stroke, systemic embolism or vascular death was lower among patients assigned combination therapy (0.92%) as compared with triflusal (3.8%) or anticoagulation (2.7%) alone (HR = 0.33, 95% CI: 0.12 to 0.91; P = 0.02). There was no excess of severe bleeding with combination therapy (0.92% versus 1.80% with anticoagulation and 0.35% with antiplatelet therapy alone). The primary outcome plus severe bleeding was lower with combination therapy (1.48% versus 3.78% with anticoagulation and 3.82% with antiplatelet therapy; P < 0.05). The study suggests that intermediate risk patients with AF who are also at risk for atherothrombotic events benefit from combined therapy.

Based on the promising results of the open-label Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) III trial, the double-blind SPORTIF V trial randomly assigned 3922 patients with nonvalvular AF to ximelagatran (36 mg twice daily) or dose-adjusted warfarin (INR 2.0 to 3.0). As compared with warfarin, ximelagatran treatment was associated with a similar annual rate of stroke and systemic embolic events (1.2% warfarin versus 1.6% ximelagatran, absolute rate ratio [RR] = 0.45, 95% CI: −0.13% to 1.03%), fewer major and minor bleeding events (47% versus 37% per year, 95% CI: −14% to −6%), but a greater proportion of patients with abnormalities of liver function tests (defined as serum alanine aminotransferase levels increased to >3 times the upper limit of normal; 0.8% versus 6.0%; P < 0.001). Abnormal liver function tests typically occurred within 6 months and declined, whether or not ximelagatran was continued, but 1 patient had fatal liver disease and another suggestive case occurred. Despite the similar efficacy of ximelagatran as compared with warfarin for patients with atrial fibrillation, concerns remain about potential long-term risks of hepatic toxicity and difficulty identifying which patients may be at risk.

Lipid-Lowering Therapy
Supporting an earlier meta-analysis (primarily in those with CHD or major CHD risk) that demonstrated a reduction in stroke with statin treatment (odds ratio [OR] = 0.79, 95% CI: 0.73 to 0.85 with reductions of low-density lipoprotein cholesterol (LDL-C) explaining 33% to 80% of the benefit), a new meta-analysis revealed a 12% proportional reduction in all-cause mortality per mmol/L reduction in LDL-C (RR = 0.88, 95% CI: 0.84 to 0.91; P < 0.0001). There was a 21% reduction in the rate of major vascular events (RR = 0.79, 95% CI: 0.77 to 0.81; P < 0.0001) including a 17% reduction in fatal and nonfatal stroke (RR = 0.83, 95% CI: 0.78 to 0.88; P < 0.0001).

The Treating to New Targets (TNT) trial prospectively randomized 10 001 patients with stable CHD and an LDL-C <130 mg/dL (3.4 mmol/L) to double-blind treatment with either 10 mg or 80 mg of atorvastatin daily to assess the efficacy and safety of lowering LDL-C to <100 mg/dL (2.6 mmol/L). Subjects were followed for a median of 4.9 years for a primary end point of the occurrence of a first major cardiovascular event (CHD death, nonfatal nonprocedure-related MI, resuscitated cardiac arrest, or fatal or nonfatal stroke). High-dose atorvastatin lowered LDL-C to a mean of 77 mg/dL (2.0 mmol/L) versus 101 mg/dL (2.6 mmol/L) with low-dose atorvastatin. High-dose treatment was associated with a reduction in the primary event rate from 10.9% to 8.7% (HR = 0.78, 95% CI: 0.69 to 0.89; P < 0.001). This included reductions in cerebrovascular events (HR = 0.77, 95% CI: 0.64 to 0.93; P = 0.007), major coronary events (HR = 0.80, 95% CI: 0.69 to 0.92; P = 0.002), any coronary event (HR = 0.79, 95% CI: 0.73 to 0.86; P < 0.001), and any cardiovascular event (HR = 0.81, 95% CI: 0.75 to 0.87; P = 0.001), but no reduction in mortality (HR = 1.01, 95% CI: 0.85 to 1.19; P = 0.92). Persistent elevations in liver aminotransferase levels were more frequent in the high-dose group (1.2% versus 0.2%; P < 0.001). Consistent with the meta-analyses, the TNT study shows greater reductions in stroke and cardiovascular events in patients with stable CHD treated to a target LDL-C below 100 mg/dL (2.6 mmol/L), but with a greater risk of hepatic toxicity.

Aspirin for Primary Stroke Prevention in Women
The Women’s Health Study (WHS) randomized 39 876 initially asymptomatic women ≥45 years of age to receive 100 mg of aspirin on alternate days or placebo. The women were followed for 10 years for the occurrence of a first major vascular event (nonfatal MI, nonfatal stroke or cardiovascular death). The study was negative for the primary end point (RR = 0.91, 95% CI: 0.80 to 1.03; P = 0.13). However, treatment was associated with an overall reduction in stroke (RR = 0.83, 95% CI: 0.69 to 0.99; P = 0.04) including a 24% reduction in ischemic stroke (RR = 0.76, 95% CI: 0.63 to 0.93; P = 0.009), and a nonsignificant increase in hemorrhagic stroke (RR = 1.24, 95% CI: 0.82 to 1.87; P = 0.31). The stroke rates were 0.11% per year in aspirin-treated and 0.13% per year in placebo-treated women (absolute RR = 0.02% per year, number needed to treat = 5000). Even this low dose of aspirin was associated with an increased risk of gastrointestinal hemorrhage requiring transfusion (RR = 1.40, 95% CI: 1.07 to 1.83; P = 0.02). The risk of major cardiovascular events was reduced among women ≥65 years of age at study entry (RR = 0.74, 95% CI: 0.59 to 0.92; P = 0.008), but without a reduction in the overall risk of stroke (RR = 0.71, 95% CI: 0.57 to 1.08; P = 0.13). Other subgroup analyses showed a reduction in stroke for those women with a history of hypertension (RR = 0.76, 95% CI: 0.59 to 0.98; P = 0.04), hyperlipidemia (RR = 0.62, 95% CI: 0.47 to 0.83; P = 0.001), diabetes (RR = 0.46, 95% CI: 0.25 to 0.85; P = 0.01), or having a 10-year cardiovascular risk ≥10% (RR = 0.54, 95% CI: 0.30 to 0.98; P = 0.04). The study supports the use of aspirin in women over age 65 and those who are at increased risk of atherothrombotic events.

Hormone Replacement Therapy
Observational studies suggested a protective effect of estrogens on cardiovascular risk among women receiving postmenopausal hormone replacement therapy. A meta-analysis identified 28 relevant randomized trials with 39 769 subjects.
addressing this question.\textsuperscript{21} Hormone replacement therapy—use was associated with increases in total stroke (OR = 1.29, 95% CI: 1.13 to 1.47), nonfatal stroke (OR = 1.23, 95% CI: 1.06 to 1.44), fatal or disabling stroke (OR = 1.56, 95% CI: 1.11 to 2.20), ischemic stroke (OR = 1.29, 95% CI: 1.06 to 1.56), with a trend toward more fatal strokes (OR = 1.28, 95% CI: 0.87 to 1.88) and no increase in hemorrhagic stroke (OR = 1.07, 95% CI: 0.65 to 1.75). Hormone replacement therapy cannot be recommended for the primary stroke prevention and likely increases risk.

Acknowledgements

This work was supported by the National Institutes of Health, Veterans Administration (L.B.G.) and by the National Health and Medical Research Council, Australia (G.J.H.), and the National Heart Foundation, Australia (G.J.H). The authors have activities that could be perceived as conflicts of interest: L.B.G is a consultant for Heart Foundation, Australia (G.J.H). The authors have activities that could be perceived as conflicts of interest: Pfizer-Parke-Davis, Bayer, Johnson & Johnson, Astra Zeneca, Sanofi-Aventis, Bristol-Myer Squibb, Pfizer, Steering Committee, AMADEUS trial; a member of the outcome adjudication committee: ACTIVE trial; as well as a speaker for Bayer, Boehringer-Ingelheim, Sanofi-Aventis, Bristol-Myer Squibb, Pfizer.

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