Secondary Prevention of Recurrent Stroke

Graeme J. Hankey, MD, FRCP, FRACP

Recurrence stroke constitutes about one quarter of all strokes and arguably represents failed secondary prevention. In 2004, evidence emerged to refine the estimates of the early risk of recurrent stroke and optimize the secondary prevention of recurrent stroke by carotid revascularization, vascular risk factor control, and antiplatelet therapy.

Risk of Recurrent Stroke

The risk of stroke after a transient ischemic attack (TIA) or mild ischemic stroke was $\approx 10\%$ within 1 week and $18\%$ within the first 3 months in Oxfordshire, UK, in 2002 to 2003. This substantial early risk is 3-fold higher if the TIA or ischemic stroke is caused by large artery disease and 5-fold lower if the cause is small artery disease. The prevalence and level of other causal vascular risk factors also influence risk of recurrence.

Carotid Revascularization to Prevent Recurrent Stroke

Carotid Endarterectomy

Carotid endarterectomy reduces the risk of stroke in patients with recently symptomatic stenosis, and the benefit is greater in patients with greater degrees of stenosis (until the artery distal to the stenosis begins to collapse). An analysis of pooled data from 5893 patients randomized in the European Carotid Surgery Trial (ECST) and North American Symptomatic Carotid Endarterectomy Trial (NASCET) and followed up for 33 000 patient-years, revealed that the benefit from surgery was also greater in men, patients aged $\geq 75$ years, and those randomized and operated upon within 2 weeks after their last ischemic event (and fell rapidly with increasing delay). Carotid endarterectomy should be targeted to these patients who are most likely to benefit.

Carotid Stent

Carotid artery stenting is less invasive than carotid endarterectomy but has only been compared with endarterectomy in a few small randomized controlled trials with inconclusive results. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial aimed to determine whether stenting was not inferior to endarterectomy for patients with severe carotid stenosis and coexisting conditions that would have excluded them from previous trials of endarterectomy. The SAPPHIRE trial enrolled 334 patients with neurologically symptomatic carotid stenosis of $\geq 50\%$ or asymptomatic stenosis of $\geq 80\%$ and at least 1 coexisting condition that potentially increased the risk posed by endarterectomy. Patients (n=167) were randomly assigned to stenting with an emboli-protection device or to endarterectomy (n=167). After 3 years, the cumulative incidence of death, stroke, or myocardial infarction within 30 days after the procedure, or death or ipsilateral stroke between 31 days and 1 year, occurred in 20 patients assigned stenting (cumulative incidence 12.2\%) and 32 patients assigned endarterectomy (cumulative incidence 20.1\%). The absolute difference of 7.9\% (95\% CI, $-0.7\%$ to $16.4\%$) confirmed noninferiority ($P=0.004$) but not superiority ($P=0.053$). If these results can be generalized to other patients and operators, they suggest that carotid stenting with a protection device is a reasonable alternative to carotid endarterectomy in patients at high risk of perioperative complications of carotid endarterectomy.

Vascular Risk Factor Control to Prevent Recurrent Stroke

Lowering Blood Cholesterol Concentration With Statins

The Heart Protection Study (HPS) showed that among 3289 people with a history of symptomatic ischemic cerebrovascular disease several years (mean 4.3; SE 0.1) previously, random assignment to simvastatin 40 mg daily for 4.8 years (mean) was associated with a significant reduction in major vascular events (24.7\% simvastatin versus 29.8\% placebo; relative risk reduction [RRR] 20\%; 95\% CI, 8\% to 29\%; $P=0.001$). The proportional reduction in risk (one fifth) was consistent, irrespective of the individual’s age, sex, and baseline blood cholesterol when simvastatin treatment was initiated. The benefit of simvastatin emerged in the second year after randomization and increased with time.

These results cannot be generalized, however, to patients with acute ischemic stroke when the risk of recurrent ischemic stroke and hemorrhagic transformation of the brain infarct is higher. Statins may be more effective in preventing early recurrent ischemic stroke and more hazardous in causing or exacerbating hemorrhagic stroke. Indeed, a retrospec-
tive subgroup analysis of HPS data indicated that among patients with previous cerebrovascular disease, simvastatin produced no reduction in recurrent stroke (10.3% simvastatin, 10.4% placebo; risk ratio [RR] 0.98; 95% CI, 0.79 to 1.22) in contrast to other high-risk patients in whom simvastatin produced a highly significant reduction in stroke (3.2% simvastatin, 4.8% placebo; heterogeneity $P=0.002$). Although the investigators attributed this inconsistent finding to chance, the chance is only 1 in 500 that they are not heterogeneous. Other explanations must be considered, such as the possibility that some hemorrhagic stroke outcome events may have been (mis)coded as nonclassified or ischemic strokes, because the recurrent stroke patients failed to undergo early computed tomography brain imaging (within 1 to 2 weeks) or necropsy. Patients with a history of cerebrovascular disease who were assigned simvastatin experienced a nonsignificant reduction in ischemic stroke (6.1% simvastatin, 7.5% placebo; RRR 19%; SE 12; $P=0.1$) and a nonsignificant near doubling in hemorrhagic stroke (0.7% placebo, 1.3% simvastatin; RR 1.91; 95% CI, 0.92 to 3.96). The nonsignificantly higher risk of subsequent hemorrhagic stroke among ischemic stroke and TIA patients assigned statins contrasts significantly with the nonsignificantly lower risk of hemorrhagic stroke in other high vascular risk patients (heterogeneity $P=0.03$). Because these subgroup analyses were not prespecified, they should be interpreted cautiously and considered only hypothesis generating. However, the hypothesis that lowering cholesterol may increase the risk of hemorrhagic stroke existed before HPS was analyzed. Several nonrandomized observational studies and 1 underpowered randomized trial had earlier reported that lower blood cholesterol concentrations might be associated with higher risks of hemorrhagic stroke.9–12 Current trials and a prospectively planned meta-analysis of all trials will provide further information about the overall effect of statins on risk of recurrent stroke and the specific effect of statins on risk of hemorrhagic stroke.13,14 In the meantime, these uncertainties should not discourage the widespread use of statins after atherothrombotic ischemic stroke. Even if statins are associated with an excess of hemorrhagic strokes in patients with previous ischemic stroke and no reduction in stroke recurrence, any small absolute increase in hemorrhagic stroke ($\approx 2$ to 6 per 1000 patients treated for 5 years) is likely to be offset substantially by a larger absolute reduction in major ischemic vascular events ($\approx 51$ per 1000 patients treated for 5 years). A similar situation exists with antiplatelet therapy for secondary stroke prevention, where a small excess risk of hemorrhagic adverse events is offset by a greater absolute reduction in major ischemic events. The benefit of statins in reducing the risk of major ischemic vascular events has also been established in patients with type 2 diabetes, “normal” low-density lipoprotein concentrations (ie, $\leq 4.14$ mmol/L), and no previous occlusive vascular disease.15,16 The Collaborative Atorvastatin Diabetes Study (CARDS) randomized 2838 patients with type 2 diabetes, but without high concentrations of low-density lipoprotein cholesterol (ie, $\geq 4.14$ mmol/L) or a history of cardiovascular disease, to atorvastatin 10 mg daily or placebo for a median of 3.9 years.16 Assignment to atorvastatin was associated with a significant reduction in the rate of the composite primary outcome event (stroke, coronary event, or coronary revascularization) from 2.46 per 100 person-years (placebo) to 1.54 per 100 person-years (atorvastatin; RRR, 37%; 95% CI, 17 to 52; $P=0.001$).16 Assessed separately, atorvastatin reduced the rate of stroke by 48% (11% to 69%), acute coronary events by 36% (9% to 55%), and death by 27% (1% to 48%). No excess of adverse events was recorded in the atorvastatin group.

### Lowering Plasma Homocysteine Concentration With B-Vitamins

An elevated plasma concentration of total homocysteine (tHcy) is associated with laboratory evidence of atherogenesis and thrombosis and epidemiological evidence of an increased risk of ischemic stroke, independent of other vascular risk factors. This association is strong, dose-related, and biologically plausible. However, it remains to be established whether tHcy causes stroke. This is important to determine because tHcy can be lowered effectively, safely, and affordably by B-vitamins (folic acid, vitamin B$_{12}$, and vitamin B$_{6}$).17

The Vitamins in Stroke Prevention (VISP) trial was the first large randomized controlled trial to evaluate the effect of lowering Hcy by B-vitamin supplementation on “hard” clinical outcomes, such as recurrent stroke.18 It compared high-dose vitamins (folic acid 2.5 mg, vitamin B$_{12}$ 0.4 mg, and vitamin B$_{6}$ 25 mg) with low-dose vitamins (folic acid 0.02 mg, vitamin B$_{12}$ 0.006 mg, and vitamin B$_{6}$ 0.2 mg). Both treatment groups received the same daily dose of 9 other vitamins, according to the recommendation of the Food and Drug Administration. An absolute difference in mean tHcy of 2 $\mu$mol/L was achieved; 13 $\mu$mol/L in the low-dose group versus 11 $\mu$mol/L in the high-dose group. After 2 years of follow-up, the cumulative incidence of recurrent cerebral infarction was 8.4% among 1814 patients allocated high-dose vitamins compared with 8.1% among 1835 patients allocated low-dose vitamins (RR 1.0; 95% CI, 0.8 to 1.3; $P=0.80$).18 The cumulative incidence of death was 5.4% in the high-dose group versus 6.3% in the low-dose group (RR 0.9; 95% CI, 0.7 to 1.1).

Although the VISP trial did not identify a significant benefit of high-dose compared with low-dose therapy, it did not reliably exclude a modest but important reduction in the relative risk of stroke of $\approx 20\%$ and perhaps an even greater reduction with greater reductions in tHcy. The unexpectedly small difference in tHcy between the high- and low-dose groups may reflect the fortification of grains and staple foods with folate and widespread use of vitamin supplements in North America. These factors have reduced the mean concentrations of tHcy in the population and the number of people with severe folate deficiency.19 It may also reflect that, in the presence of folate repletion, blood concentrations of tHcy are highly dependent on vitamin B$_{12}$.20 In the VISP trial (a) the low-dose group received the recommended daily intake of vitamin B$_{12}$ (raising their tHcy); (b) the high-dose group received a dose of vitamin B$_{12}$ that may have been too low for adequate absorption in elderly patients (and therefore too low to reduce their tHcy);21 and (c) in both treatment...
groups, patients who had low blood concentrations of vitamin B12 (<150 pmol/L) were treated with B12 injections (thus reducing statistical power). The lower-than-anticipated rates of recurrent strokes in both treatment groups and the short duration of follow-up (2 years) also limited the statistical power of the VISP trial to reliably identify or exclude a modest but important benefit of B-vitamin therapy.

More data are needed to refine the estimates of effectiveness of B-vitamins and to provide placebo-controlled estimates of their effectiveness in other populations with different prevalences of genetic and environmental factors that influence tHcy. The VITamins TO Prevent Stroke (VITATOPS) trial has randomized >4400 patients with recent ischemic stroke from 19 countries on 4 continents to placebo or B-vitamins (folic acid, 2 mg; vitamin B12, 0.5 mg; and vitamin B6, 25 mg) and aims to randomize and follow up 8000 patients before the end of 2006 (http://vitatops.highway1.com.au).22

While awaiting the results of the ongoing clinical trials of B-vitamin therapy in stroke and other patient groups,23 insufficient evidence exists to recommend routine screening and treatment of high tHcy with B-vitamins to prevent atherothrombotic vascular disease.

**Antiplatelet Therapy**

For patients with TIA or ischemic stroke, the most widely used effective antiplatelet regimens include aspirin, clopidogrel, and the combination of aspirin and dipyridamole.24 However, after the impressive results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, which showed that adding clopidogrel to aspirin in patients with non-ST-segment elevation acute coronary syndrome (ACS) reduced the RR of serious vascular events by ≈20% (95% CI, 10% to 28%) compared with aspirin,25 stroke clinicians wondered if these results could be generalized to patients with recent ischemic stroke.

The Management of ATherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attack or Ischemic Stroke (MATCH) trial26 was a double-blind controlled trial that aimed to determine whether adding aspirin 75 mg per day to clopidogrel 75 mg per day was safe and more effective than clopidogrel 75 mg per day in 7599 patients with recent TIA (21%) or ischemic stroke (79%), who were at high risk of recurrent vascular events (history of diabetes 68%, ischemic stroke 26%, TIA 19%, myocardial infarct 5%, angina 12%, or symptomatic peripheral arterial disease 10%).26

The rationale for testing the combination of clopidogrel and aspirin against clopidogrel, instead of aspirin (the most widely used antiplatelet drug), was that clopidogrel had been shown to be marginally but statistically significantly more effective than aspirin in all high vascular risk patients in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Stroke (CAPRIE) trial.27 Although it seemed more relevant clinically to test whether adding clopidogrel to aspirin would be more effective than aspirin alone (because clinicians were using aspirin more commonly than clopidogrel), it was considered by the investigators more relevant scientifically and ethically to test whether adding aspirin to clopidogrel was more effective than clopidogrel alone (because clopidogrel was more effective than aspirin).27

The patients were randomized a median of 15 days (range, 0 to 119 days) after TIA or ischemic stroke and treated for 18 months.26 The MATCH trial was designed to have 80% power to reliably identify a 14% reduction in the RR of ischemic stroke, myocardial infarction, vascular death, and rehospitalization for acute ischemic events (the primary outcome measure) from 13.3% with clopidogrel alone to 11.4% with clopidogrel plus aspirin.26

**Efficacy**

After 18 months, intention to treat analysis revealed that compared with clopidogrel, the addition of aspirin to clopidogrel was associated with no statistically significant reduction in the RR of the primary outcome measure of efficacy (RRR, 6.4%; 95% CI, −4.6% to 16.3%; P=0.244; from 16.7% [clopidogrel] to 15.7% [aspirin + clopidogrel] at 18 months; absolute RR 1.0%).26 The results were consistent among all subgroups examined, including etiological subtypes of stroke and different vascular risk factors, although there was a nonsignificant trend toward a greater benefit of combination antiplatelet therapy in patients randomized within the first week, rather than later after the qualifying event.

**Safety**

Intention to treat analysis also revealed that compared with clopidogrel alone, the addition of aspirin to clopidogrel was associated with a statistically significant increase in life-threatening hemorrhage (the primary outcome measure of safety) from 1.3% (clopidogrel) to 2.6% (aspirin + clopidogrel), which is a 2-fold increase in RR and an increase in absolute risk of 1.26% (95% CI, 0.64% to 1.88%) over 18 months (P<0.001).26 Life-threatening hemorrhage was intracranial (0.7% clopidogrel, 1.1% clopidogrel + aspirin) and gastrointestinal (GI; 0.6% clopidogrel, 1.4% clopidogrel + aspirin). The risk of bleeding was cumulative over time. The Kaplan–Meier survival curves for survival free of primary intracerebral hemorrhage for each treatment group did not separate until at 3 to 4 months after randomization, suggesting that the benefit, risk ratio of clopidogrel + aspirin versus clopidogrel, may be greatest in the first few months after stroke.

The MATCH trial reported a benefit of 10 (95% CI, −7 to +27) fewer recurrent ischemic events per 1000 patients treated for 18 months, which was offset by an excess of 13 (95% CI, 6 to 19) life threatening hemorrhages into the GI tract (8 per 1000) or brain (4 per 1000). The results are consistent with the known effects of aspirin in TIA and ischemic stroke patients28 and the combination of aspirin and clopidogrel compared with aspirin in acute coronary syndrome patients.29 This is because the MATCH trial compared aspirin and clopidogrel with clopidogrel rather than aspirin (as in CURE27). Statistical power for efficacy and safety were compromised by choosing clopidogrel as the comparator instead of aspirin, because clopidogrel is more effective than aspirin (by 9% in relative terms) and probably safer with respect to GI hemorrhage.27 Furthermore, patients in the
MATCH trial were not treated until 15 days (median) after their stroke, during which time at least 10% would have experienced a recurrent stroke; 2 half the patients had symptomatic small vessel disease, which is associated with a low risk of early recurrent ischemic stroke and a higher risk of intracranial hemorrhage, only one third of patients had symptomatic large artery atherothrombosis, which is associated with a high risk of early recurrent stroke; and a loading dose of clopidogrel was not used.

Future trials are needed to evaluate the potential additional benefit and safety of the combination of aspirin and clopidogrel when administered immediately after TIA and ischemic stroke (ie, within 12 to 24 hours rather than 15 days) with a loading dose of clopidogrel (300 mg or 600 mg) in patients with symptomatic large artery atherothrombosis (who are at high risk in early recurrent ischemic stroke), and for a short period of ~3 months (when the benefits are likely to be greatest and the cumulative risks of bleeding avoided).

References


