Update on Secondary Ischemic Stroke Prevention

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Stroke is the third leading cause of death in HK and results in significant morbidity and disability among the survivors. Every year about 17,000 patients are hospitalized with first-ever stroke of which 70% is ischemic in nature, mostly due to atherothrombotic occlusion and cardiogenic embolism. Elucidation of the stroke aetiology and mechanism dictates the preventive strategy, which should be implemented as soon as possible. Recently, promising data from stroke prevention trials have equipped us with a wide range of armamentarium to tackle this fatal and disabling disorder.

The preventive strategies for ischemic stroke can be summarized as follows:

1. Modification of risk factors and improving the cardiovascular risk profile

(a) Lifestyle modification:
General recommendations include weight reduction (achieving body mass index < 25 kg/m²), regular exercise (daily for > ½ hour), stress management, abstinence from smoking and heavy alcohol consumption (e.g. > 5 glasses of wine); aggressive lifestyle modification is especially indicated in those with metabolic syndrome (prediabetic) or obstructive sleep apnoea.

(b) Control of hypertension and target BP < 140/90 mmHg
A lower BP (< 130/80 mmHg) is indicated for secondary stroke prevention and the optimal BP is in the range of 115/75 mmHg; combination of antihypertensive is often required e.g. ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB) + β-blocker or diuretic or calcium channel antagonist. Compliance is always a problem with long-term drug treatment and care should be taken to reduce the side-effects associated with treatment.

(c) Control DM and target HbA1c < 7%
Although solid evidence is not available to show that good glycemic control can prevent stroke, current data on prevention of microvascular complications (e.g. retinopathy, nephropathy, neuropathy) provide compelling evidence that tight control is beneficial.

(d) Statins for normal or hypercholesteronemia
The target for LDL is < 2.6 mmol/L and HDL > 1.1 mmol/L. Apart from direct lowering of LDL, statin is beneficial by increasing tissue plasminogen level, decreasing inflammatory response and promoting plaque stabilization. A meta-analysis of twelve major randomized trials (n=85,039) including the recent HPS protective effect is apparent within 2 years of starting treatment, irrespective of the baseline cholesterol level.

(e) Improve endothelial dysfunction with ACEI/ARB
The PROGRESS trial showed that addition of a diuretic +/- ACEI prevent recurrent stroke (both ischemic and hemorrhagic) irrespective of the baseline BP level. Other trials using ACEI (e.g. HOPE) or ARB (e.g. LIFE) also showed similar results, suggesting a protective effect via correction of endothelial dysfunction.

(f) Possibly lowering homocysteine level by vitamin B6/B12/folate
Both homocysteine and C-reactive protein (CRP) are new markers for determining cardiovascular and stroke risk. However, the protective effect of lowering homocysteine or CRP remains to be shown by clinical trials.

2. Antithrombotics: Antiplatelets vs Anticoagulants vs Combinations

(a) Aspirin confers a 15-25% ischemic stroke risk reduction, which should be given within 48 hours after an ischemic event.

(b) Clopidogrel offers 10% more risk reduction compared to Aspirin alone. It is indicated for those with Aspirin failure or intolerance, and its effect is amplified in high risk patients.

(c) Dipyridamole + Aspirin: the relative risk reduction (RRR) of this combination doubles the effect of Aspirin or Dipyridamole alone (37% vs 18% and 16% respectively) according to the ESPS II study. Systematic reviews suggest that the extra benefit may be modest and further confirmatory trials (e.g. Espirit, Profess) are required.

(d) Dipyridamole suppresses platelet-endothelial wall interaction and platelet phosphodiesterase inhibitor. The sustained release formulation is an alternative to aspirin in those without coronary heart disease. Instant release dipyridamole is not effective due to its irregular absorption and short half-life.

(e) Aspirin + Clopidogrel: Supportive data from the CURE trial suggest that this combination is
3. Surgical revascularization for major vascular stenosis

(a) Carotid endarterectomy (CEA) vs Carotid angioplasty and stenting (CAS): CEA is effective in symptomatic patients with > 70% carotid stenosis provided that the procedural stroke/death rate is < 6%. However, only a minority will benefit from surgery as extracranial disease is relatively rare among Chinese. CAS appears to be a promising alternative following the use of clopidogrel and distal protection device. Although there are less minor complications (e.g. cranial neuropathy, neck hematoma), CAS is associated with a higher re-stenosis rate according to the CAVATAS study (18% vs 5% after 1 year).

(b) Intracranial angioplasty +/- stenting: This becomes technically feasible with advances in catheter design. However, the peri-procedural complication rate can be high, especially performed in the setting of acute ischemic stroke and following use of t-PA. It should be reserved in stroke centres specialized in vascular intervention.

(c) Extracranial-intracranial bypass surgery: This was generally abandoned following a large randomized trial report in 1985. Clinical trials are now looking into its efficacy in symptomatic patients selected with hemodynamic criteria (e.g. Moya-moya syndrome).

Timing of intervention

The Oxford vascular study group recently reported the incidence of stroke one week following a TIA is 8% and 11.5% after a minor stroke. The recurrent stroke rate is about 15% in the next 3 months, much higher than previously thought. This 3-month period is now considered the prime window for intervention so that a major stroke can be prevented. Patients should be promptly evaluated and aggressively treated, ideally within 48 hours after the first ischemic event. A stroke/TIA clinic providing rapid access to neuroimaging (e.g. MRI brain, MRA of neck and brain, carotid ultrasound) and multidisciplinary service with input from neurologist, cardiologist, neurosurgeon, and neuroradiologist is essential to achieve this purpose. For patients at high risk of recurrent stroke, a combination of the above preventive strategies is often required (Table 1).

<table>
<thead>
<tr>
<th>Table 1 Useful tips for secondary ischemic stroke prevention</th>
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<tbody>
<tr>
<td>1. Evaluate stroke cause as soon as possible after TIA/stroke</td>
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<tr>
<td>2. Identify and control risk factors aggressively</td>
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<td>3. Administer appropriate anti-thrombotic(s)</td>
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<td>4. For high risk cases, consider:</td>
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<td>(1) Combination of antiplatelet agents</td>
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<td>(2) Identify vascular stenosis amenable to revascularization</td>
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<td>(3) Statin for those with normal cholesterol</td>
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<td>(4) ACEI/ARB for normotensive subjects</td>
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<td>(5) Lowering homocysteine with B6/B12/folate</td>
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Conclusion:

Stroke is now becoming a much more preventable disease. A significant drop in the incidence of stroke in the future should not be far away. Expedite diagnosis and early implementation of preventive measures would help to translate the observed benefit from trials to clinical practice. The role of the general practitioner in stroke
prevention and treatment is summarized in Table 2 and a comparison of the cost-effectiveness of various stroke preventive strategies is given in Table 3.

### Table 2: Role of the General Practitioner in Stroke Prevention

1. Recognize and tightly control hypertension, DM and hypercholesterolemia
2. Educate and insist on lifestyle changes (smoking cessation, drug consumption, obesity and physical inactivity)
3. Introduce and assure effective anticoagulation in most atrial fibrillation patients and certain cardiac diseases
4. Recognize and promptly investigate possible TIAs, minor strokes and carotid bruises +/- referral to neurology specialist
5. Refer acute stroke patients urgently to the Emergency Department or stroke centre
6. Control/supervise secondary prevention after TIA/strokes

Ref: Stroke prevention by the practitioner; Cerebrovascular diseases, vol 15, suppl 2, April 2003

### Table 3: A comparison of the cost-effectiveness of various stroke preventive strategies

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<th>Intervention</th>
<th>Cost</th>
<th>NNT (efficacy)</th>
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<tbody>
<tr>
<td>Aspirin for 2° prevention</td>
<td>$100</td>
<td>100</td>
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<tr>
<td>Thiazide for HT</td>
<td>$45</td>
<td></td>
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<tr>
<td>Quit smoking, GP advice</td>
<td>$43</td>
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<tr>
<td>Combination therapy for HT</td>
<td>$35</td>
<td></td>
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<tr>
<td>Anticoagulation for AF</td>
<td>$35</td>
<td></td>
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<tr>
<td>Aspirin + Dipyridamole or Clopidogrel</td>
<td>$53</td>
<td></td>
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<tr>
<td>Cholesterol lowering by statin</td>
<td>$35</td>
<td></td>
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<tr>
<td>Carotid endarterectomy</td>
<td>$8-80</td>
<td></td>
</tr>
</tbody>
</table>

*NNT = numbers of patients needed to treat to prevent one stroke in 1 year

### References

2) Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20,536 people with cerebrovascular disease or other high-risk conditions. Lancet 2004;363:757-67
3) PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regime among 6,105 patients with previous stroke or transient ischemic attack. Lancet 2001;358:1033-1041