PRESCRIPTION FOR
RECURRENT STROKE PREVENTION

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THE SCOPE OF THE PROBLEM

- 795,000 people in the United States have a stroke each year
  - One every 40 seconds
- 150,000 people in the United States die from a stroke each year
  - One every 4 minutes
  - Third leading cause of death
- Big issue
- Stroke is the “cinderella” in medicine

www.strokeassociation.org
Acute Stroke Registry Malaysia, 2010-2014: Results from the National Neurology Registry

Zariah A. Aziz, MBBS, Yvonne Y.L. Lee, MPH, Bahari Awang Ngah, MBBS, Norsima Nafizah Sidek, BPPharm, Irene Looi, MBBS, Md. Rafia Hanip, MBBS, and Hamidon B. Basri, MD


Table 3. Age-adjusted incidence and prevalence rates by year for ischemic stroke

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence rate (100,000)</th>
<th>Prevalence rate (100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude</td>
<td>ASR Malaysia</td>
</tr>
<tr>
<td>2010</td>
<td>30.99</td>
<td>34.21</td>
</tr>
<tr>
<td>2011</td>
<td>33.73</td>
<td>37.3</td>
</tr>
<tr>
<td>2012</td>
<td>49.28</td>
<td>54.34</td>
</tr>
<tr>
<td>2013</td>
<td>56.27</td>
<td>62.09</td>
</tr>
<tr>
<td>2014</td>
<td>87.03</td>
<td>96.21</td>
</tr>
</tbody>
</table>

Abbreviations: ASR, age-adjusted rate; WHO, World Health Organization. Crude rate is age adjusted in the Terengganu state population census.
STROKE RECURRENCE

RECURRENT STROKE IS OFTEN ..... 

..... MORE SEVERE 

....MORE DISABLING (OFTEN IS)

25 – 30 % OF ALL STROKES

(RECURRENT STROKES REPRESENT UNSUCCESSFUL SECONDARY PREVENTION)

SUSTAINED IMPLEMENTATION OF EFFECTIVE AND APPROPRIATE SECONDARY PREVENTION STRATEGIES IS PRIORITY
SECONDARY PREVENTION OF STROKE

A - Antithrombotics (aspirin, clopidogrel, extended-release dipyridamole, ticlopidine) and anticoagulants (warfarin)

B - Blood pressure-lowering medications

C - Cessation of cigarette smoking, cholesterol-lowering medications, carotid revascularization, control of other vascular risk factors.

D - Diet

E – Exercise
Risk of recurrent stroke is highest early after an IS or TIA
A medical emergency requiring urgent evaluation and management
About 15% of strokes are preceded by a TIA
The risk of a stroke after a TIA is very high, and most of the risk is very early
- 9.9% at 2 days
- 13.4% at 30 days
- 17.3% at 90 days
TIA are heterogenous, still one can predict who is headed for big trouble …

*Stroke* 2006;37:320-22
*Arch Intern Med* 2007;167(22)2417-22
The ABCD² score is a risk assessment tool designed to improve the prediction of short-term stroke risk after a transient ischemic attack (TIA). The score is optimized to predict the risk of stroke within 2 days after a TIA, but also predicts stroke risk within 90 days. The ABCD² score is calculated by summing up points for five independent factors.

### ABCD² Score

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP ≥ 140 mm Hg OR Diastolic BP &gt; 90 mm Hg</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Clinical features of TIA (choose one)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral weakness with or without speech impairment OR</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Speech impairment without unilateral weakness</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA duration ≥ 60 minutes</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>TIA duration 10-59 minutes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Total ABCD² score</strong></td>
<td>0-7</td>
<td></td>
</tr>
</tbody>
</table>

7-day risk of CVA
- 6 = 31.4%
- 5 = 12.1%
- 4 or less = 0.4%

All patients with a stroke within one week had scores ≥ 4

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ABCD3 and ABCD3-I Scores Are Superior to ABCD2 Score in the Prediction of Short- and Long-Term Risks of Stroke After Transient Ischemic Attack

Takuya Kiyohara, Masahiro Kamouchi, Yasuhiro Kumai, Toshiharu Ninomiya, Jun Hata, Sohei Yoshimura, Tetsuro Ago, Yasushi Okada, Takanari Kitaono, Takao Ishitsuka, Shigeru Fujimoto, Setsuro Ibayashi, Kenji Kusuda, Shuji Arakawa, Kinya Tamaki, Seizo Sadoshima, Katsumi Irie, Kenichiro Fujii, Yasushi Okada, Masahiro Yasaka, Tetsuhiko Nagao, Hiroaki Ooboshi, Tsuyoshi Omae, Kazunori Toyoda, Hiroshi Nakane, Hiroshi Sugimori, Kenji Fukuda, Ryu Matsuo, Junya Kuroda and Yoshihisa Fukushima and for the FSR investigators

Conclusions—The present study demonstrates that ABCD3 and ABCD3-I scores are superior to the ABCD2 score for the prediction of subsequent stroke in patients with TIA. Addition of neuroimaging in the ABCD3 score may enable prediction of long-term stroke risk after TIA.
FIRST THINGS FIRST

Do the best you can to determine the mechanism of the ischemic event

Proper classification of the causative mechanism of stroke is important for optimizing stroke treatment and assessing prognosis
MECHANISMS OF TIA/STROKE

- Large artery atherosclerotic
- Cardioembolic
- Small-vessel disease
- Hemorrhagic
- Undetermined cause
- Other:
  - Dissections
  - Hypercoagulable states
RECURRENT STROKE

Consider specific circumstances

- Aortic Arch Atherosclerosis
- Arterial Dissection
- Patent Foramen Ovale
- Hyperhomocysteinemia
- Hypercoagulable States
- Antiphospholipid Antibody Syndrome
- Sickle Cell Disease
- Cerebral Venous Sinus Thrombosis
<table>
<thead>
<tr>
<th>Early recurrent stroke</th>
<th>Outcome</th>
<th>Stroke rate</th>
<th>RRR (95% CI)</th>
<th>ARR</th>
<th>NNT and time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (vs no aspirin)</td>
<td>Stroke at 2-4 weeks</td>
<td>3.9%</td>
<td>3.4%</td>
<td>12% (3 to 21)</td>
<td>0.5%</td>
</tr>
<tr>
<td>Clopidogrel plus aspirin (vs aspirin)</td>
<td>Stroke at roughly 3 months</td>
<td>11.1%</td>
<td>7.8%</td>
<td>20% (18 to 41)</td>
<td>3.3%</td>
</tr>
<tr>
<td>Aspirin plus dipyridamole (vs aspirin)</td>
<td>Stroke at 3-28 months</td>
<td>7.9%</td>
<td>5.3%</td>
<td>35% (-10 to 63)</td>
<td>2.6%</td>
</tr>
<tr>
<td>Aspirin plus dipyridamole (vs clopidogrel)</td>
<td>Stroke at 3 months</td>
<td>2.9%</td>
<td>1.6%</td>
<td>44% (-17 to 73)</td>
<td>1.8%</td>
</tr>
<tr>
<td>Clopidogrel plus aspirin (vs clopidogrel)</td>
<td>Stroke at 18 months</td>
<td>4.7%</td>
<td>3.9%</td>
<td>17% (-93 to 64)</td>
<td>0.8%</td>
</tr>
<tr>
<td>Carotid endarterectomy or stent (vs no carotid revascularisation)</td>
<td>Stroke at 5 years</td>
<td>33%</td>
<td>17%</td>
<td>48% (38 to 60)</td>
<td>16%</td>
</tr>
<tr>
<td>70-99% stenosis, symptomatic</td>
<td>Stroke at 5 years</td>
<td>27%</td>
<td>19%</td>
<td>28% (14 to 42)</td>
<td>8%</td>
</tr>
<tr>
<td>50-69% stenosis, symptomatic</td>
<td>Stroke at 5 years</td>
<td>27%</td>
<td>19%</td>
<td>28% (14 to 42)</td>
<td>8%</td>
</tr>
<tr>
<td>Acute specialty units (vs outpatient clinics)</td>
<td>Stroke at 90 days</td>
<td>10.3%</td>
<td>2.1%</td>
<td>80% (51 to 92)</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Longer-term recurrent stroke</th>
<th>Outcome</th>
<th>Stroke, MI, or YD, per year</th>
<th>RRR (95% CI)</th>
<th>ARR</th>
<th>NNT and time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (vs no aspirin)</td>
<td>Recurrent stroke, per 2-6 years (mean)</td>
<td>11.3%</td>
<td>9.0%</td>
<td>22% (10 to 32)</td>
<td>2.3%</td>
</tr>
<tr>
<td>Clopidogrel (vs aspirin)</td>
<td>Stroke, MI, or YD, per year</td>
<td>5.8%</td>
<td>5.3%</td>
<td>9% (0.3 to 16)</td>
<td>0.5%</td>
</tr>
<tr>
<td>All high vascular risk patients</td>
<td>Stroke, MI, or YD, per year</td>
<td>7.7%</td>
<td>7.1%</td>
<td>7% (-5 to 19)</td>
<td>0.5%</td>
</tr>
<tr>
<td>Ischaemic stroke patients</td>
<td>Stroke, MI, or YD, per year</td>
<td>7.7%</td>
<td>7.1%</td>
<td>7% (-5 to 19)</td>
<td>0.5%</td>
</tr>
<tr>
<td>Aspirin and extended-release dipyridamole (vs aspirin)</td>
<td>Stroke, MI, or YD, per 2-6 years (mean)</td>
<td>15.2%</td>
<td>12.5%</td>
<td>18% (8 to 28)</td>
<td>2.7%</td>
</tr>
<tr>
<td>Clopidogrel and aspirin (vs aspirin)</td>
<td>Stroke, MI, or YD, per 2-6 years (mean)</td>
<td>13.1%</td>
<td>13.1%</td>
<td>1% (-7 to 8)</td>
<td>0% (NS)</td>
</tr>
<tr>
<td>Aspirin and extended-release dipyridamole (vs clopidogrel)</td>
<td>Stroke, MI, or YD, per week</td>
<td>8.8%</td>
<td>6.3%</td>
<td>28% (11 to 43)</td>
<td>2.5%</td>
</tr>
<tr>
<td>Cilostazol (vs aspirin)</td>
<td>Stroke, MI, or YD, per 1-25 years (mean)</td>
<td>8.8%</td>
<td>6.3%</td>
<td>28% (11 to 43)</td>
<td>2.5%</td>
</tr>
<tr>
<td>Warfarin for atrial fibrillation (vs no warfarin)</td>
<td>Recurrent stroke, per year</td>
<td>12%</td>
<td>4%</td>
<td>61% (37 to 75)</td>
<td>8%</td>
</tr>
<tr>
<td>New direct oral anticoagulants for atrial fibrillation (vs warfarin)</td>
<td>Stroke and systemic embolism, per 1-9 years</td>
<td>5.3%</td>
<td>4.5%</td>
<td>14% (0 to 26)</td>
<td>0.8%</td>
</tr>
<tr>
<td>Lowering of blood pressure (vs no lowering of blood pressure)</td>
<td>Recurrent stroke, per 3 years (roughly)</td>
<td>9.9%</td>
<td>8.6%</td>
<td>22% (10 to 32)</td>
<td>1.3%</td>
</tr>
<tr>
<td>Statins to reduce low-density lipoprotein cholesterol (vs no statin)</td>
<td>Recurrent stroke, per 5 years</td>
<td>11.9%</td>
<td>10.5%</td>
<td>12% (1 to 22)</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

See appendix pp 1–3 for explanations of statistical terms. RRR=relative risk reduction (risk ratio). ARR=absolute risk reduction. NNT=number needed to treat. NS=not significant. MI=myocardial infarction. YD=vascular death. NA=not applicable.

**Table 1:** Summary of effective strategies to prevent recurrent stroke
ANTIPLATELET THERAPY

Aspirin (50 – 325mg/d) monotherapy (class 1 level evidence A) or combination of ASA 25mg and ER dipyridamole 200mg bd (class 1 level evidence B) indicated as initial therapy after TIA or IS for prevention of future stroke. Clopidogrel 75mg monotherapy a reasonable option for secondary prevention of stroke (class Iia, level evidence B)

In dysphagic patients, aspirin can be given by enteral tube or by rectal suppository.

In Chinese patients with acute (<24 h) TIA or minor ischaemic stroke should be given a bolus loading dose of at least 160 mg of aspirin and 300 mg of clopidogrel immediately, followed by clopidogrel 75 mg plus aspirin 75 mg for 21 days, and then clopidogrel alone for a total of 90 days before continuing on long-term clopidogrel, aspirin, or the combination of aspirin and extended-release dipyridamole (evidence level B)

Lancet Neurol vol 13 Feb 2014
Conclusions — For patients with acute noncardioembolic ischemic stroke or TIA, dual therapy was more effective than monotherapy in reducing risks of early recurrent stroke. The results of the CHANCE study are consistent with previous studies done in other parts of the world.

(Circulation. 2013;128:1656-1666.)

CHANCE (Clopidogrel in High risk patients with Acute Non disabling Cerebrovascular event)

dual therapy was more effective in reducing stroke risk (hazard ratio [HR], 0.68; 95% CI, 0.57–0.81; P<0.001) without increasing risks of severe or moderate bleeding (P=0.73) at 3 months
A Stroke of Genius
Introduction

Atrial fibrillation (AF) has been widely studied in the Western countries [1-3]. However, there are few published studies about AF in developing countries particularly in South East Asia. AF posed a major public health issue in these developing countries as they transition from communicable to non-communicable diseases [4]. Economic burden of AF was substantial. Rizzo and colleagues estimated annual AF direct health care cost in selected developing countries range from USD 24 million in India to USD 84 million in Turkey; USD 178 million in Russia and USD 397 million in China [5].

Clinical implications of AF were stroke and cognitive dysfunction [6,7]. Framingham longitudinal cohort study suggested that age is

Results: 4762 first-ever ischemic stroke patients were available for analysis from July 29, 2009 to June 1, 2015. 311 (6.5%) had AF and they were 5.6 years older than patients without AF ($p<0.001$). Patients with AF had severe stroke, poorer functional outcome, increased stroke complications and mortality. Stroke recurrence was not an independent AF risk factor. Increasing age, (OR: 1.07, 95% CI: 1.04-1.10), smoking (OR: 2.60, 95% CI: 1.35-5.06) and stroke recurrence (OR: 4.76, 95% CI: 2.14-10.59) were associated with increased 30-day mortality risk after controlling for confounders. While female gender (OR: 2.31, 95% CI: 1.01-5.27), severe stroke (OR: 1.09, 95% CI: 1.02-1.17) and increased hospitalizations days (OR: 1.21, 95% CI: 1.07-1.38) were related to poorer functional outcome among AF patients.

Conclusions: Our hospital-based registry indicates that first-ever ischemic patients with AF have markedly reduced functional outcome, increased stroke severity and 30-day mortality compared to patients without AF.

Keywords

Atrial fibrillation; Clinical; Outcomes; Registry; Ischemic; Malaysia
Patients with TIA and IS who have AF should be treated with anticoagulation, not antiplatelet.

The optimum timing of oral anticoagulation after acute cardioembolic ischaemic stroke is unclear; it is common practice to wait 2–14 days and repeat brain imaging (CT or MRI) to rule out asymptomatic intracranial bleed before starting oral anticoagulation (evidence level C).

Patients with atrial fibrillation and acute transient ischaemic attack can begin oral anticoagulation (warfarin, dabigatran, rivaroxaban, or apixaban) immediately because the risk of intracranial haemorrhage is probably low (ie, there is no fresh brain infarction to become haemorrhagic).

AHA 2014
Concomitant antiplatelet and anticoagulant is not recommended unless there is a specific indication e.g. mechanical heart valve, ACS or stenting.
After you determine the mechanism,

THEN ...
TARGET THE “BIGGIES”

HYPERTENSION

DIABETES MELLITUS

HYPERLIPIDAEMIA
B IS FOR ....
Global burden of stroke and risk factors in 188 countries, during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013

Prof Valery L Feigin, MD, Gregory A Roth, MD, Prof Mohsen Naghavi, MD, Priya Parmar, PhD, Rita Krishnamurthi, PhD, Sumeet Chugh, MD, George A Mensah, MD, Prof Bo Norrving, MD, Ivy Shiue, PhD, Marie Ng, PhD, Kara Estep, BA, Kelly Cercy, BA, Prof Christopher J L Murray, MD, Prof Mohammad H Forouzanfar, PhD for the Global Burden of Diseases, Injuries and Risk Factors Study 2013 and Stroke Experts Writing Group†
**Figure 2:** Top risk factors ranked by number of DALYs attributable to stroke for both sexes combined in 21 regions in 2013

For the list of countries included within these regions, please see the appendix (pp 1–2). DALY = disability-adjusted life-year.
Table 2. **Overall risk factors by stroke type and stroke event, 2010-2014**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Ischemic</th>
<th></th>
<th>Hemorrhagic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Recurrent</td>
<td>First</td>
<td>Recurrent</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>None</td>
<td>426</td>
<td>9.1</td>
<td>34</td>
<td>2.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3224</td>
<td>68.8</td>
<td>1078</td>
<td>84</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2116</td>
<td>45.2</td>
<td>684</td>
<td>53.3</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1452</td>
<td>31</td>
<td>469</td>
<td>36.6</td>
</tr>
<tr>
<td>Smoker</td>
<td>2671</td>
<td>57</td>
<td>776</td>
<td>60.5</td>
</tr>
<tr>
<td>Alcohol</td>
<td>61</td>
<td>1.3</td>
<td>17</td>
<td>1.3</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>592</td>
<td>12.6</td>
<td>226</td>
<td>17.6</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>141</td>
<td>3</td>
<td>49</td>
<td>3.8</td>
</tr>
<tr>
<td>Family history stroke</td>
<td>326</td>
<td>7</td>
<td>91</td>
<td>7.1</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>0</td>
<td>.2</td>
<td>2</td>
<td>.2</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>187</td>
<td>4</td>
<td>71</td>
<td>5.5</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 25)</td>
<td>302</td>
<td>6.5</td>
<td>74</td>
<td>5.8</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>7</td>
<td>.2</td>
<td>0</td>
<td>.0</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>69</td>
<td>1.5</td>
<td>25</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index.
- Which patients should be treated?

- **When should therapy be initiated?**

- Which antihypertensive drugs should be used?

- What is the target blood pressure?
Which patients should be treated?

Initiation of antihypertensive therapy for previously untreated patients with any type of ischemic stroke or TIA who have an established blood pressure of ≥140 mmHg systolic or ≥90 mmHg diastolic (level evidence B)

Initiation of antihypertensive therapy for patients with BP of systolic of < 140 mmHg and diastolic of < 90 mmHg is of uncertain benefit

When should therapy be initiated?

Ideal time to start lowering of BP after stroke is uncertain, but it should be started before discharge from hospital. (level B)
Which antihypertensive drugs should be used?

Choice of specific drugs and targets should be individualized, data indicates thiazide plus ACE-I post stroke is beneficial. Combi of ACE-I plus diuretics (PROGRESS), combi of ACE-I plus Ca channel blocker (ACCOMPLISH)

Caution with beta blockers
What is the goal blood pressure?

The target blood pressure level and degree of reduction are uncertain, and treatment should be individualized, but it is reasonable to achieve a systolic pressure of <140 mmHg and a diastolic pressure of <90 mmHg. For patients with a recent lacunar stroke, it might be reasonable to target a systolic blood pressure of <130 mmHg.

Target below 140/90 and lower with SBP < 130 in lacunar stroke (level evidence B)

AHA 2014
Statin therapy should be started during hospitalization for patients with TIA/stroke, regardless of baseline LDL.

Class I, LOE A if known atherosclerotic disease or elevated cholesterol levels.
Class IIa, LOE B if no evidence of atherosclerosis and normal cholesterol levels.

Stroke. 2002;35:1023
Stroke. 2006;37:577-617
C IS FOR THE CAROTID REVASCULARISATION
Patients with recently symptomatic carotid territory transient ischaemic attack or non-disabling ischaemic stroke and ipsilateral 50–99% internal carotid artery stenosis (measured by two concordant non-invasive imaging modalities) who are fit and willing for surgery should be offered carotid endarterectomy as soon as possible, ideally within the first few days and up to 1 week after the ischaemic event and when the patient is clinically stable (evidence level A).

Carotid endarterectomy should be done by a surgeon with an audited perioperative morbidity and mortality of less than 5% (evidence level A).
CEA VS CS

> 70 yrs old & fit for surgery

Short term higher risk of stroke

Long term issues restenosis
ISSUES

- Human Resource
  - Patients factor
  - Clinicians factor
  
- Infrastructure

- Service
PREVENTION OF FIRST EVER STROKE
Public awareness
Public health
Media
MOH MOE

Rapid diagnosis & treatment of TIA/stroke
Prompt identification of stroke etiology

Appropriate ABC including control of vascular risk factors

Continuity of care at community level strengthened our current NCD team, NGO

Stroke centers
Stroke unit
Dedicated stroke team

Step down care
Comprehensive rehab centre
TERENGGANU STROKE UPDATE