COMMONWEALTH OF AUSTRALIA

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Stroke and TIA

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Department of Neurology, Royal Melbourne Hospital
University of Melbourne
Global burden of stroke

• 20 million strokes each year
• 2\textsuperscript{nd} leading cause of death worldwide
• >50 million stroke/TIA survivors alive
• 20\% have further stroke <5 years
• Recent trials BP lowering therapy, statins, antiplatelet therapy, atrial fibrillation strategies, stents are changing practice
Case vignette

63 year old Mrs Faul with a past history of smoking and BP always elevated at medicals, thought to be “white coat” hypertension and untreated.

Whilst attending national sales conference in Melbourne, giving a presentation, sudden onset of speech difficulties and right sided weakness, seems “confused”

What should bystanders do?
If you recognise the signs of **STROKE** act

**FAST**

- **Facial weakness**
  - Can the person smile? Has their mouth or eye drooped?

- **Arm weakness**
  - Can the person raise both arms?

- **Speech difficulty**
  - Can the person speak clearly and understand what you say?

- **Time to act fast**
  - If you recognise the signs of stroke, seek immediate medical attention.

**The signs of Stroke are:**

- Weakness, numbness or paralysis of the face, arm or leg
- Difficulty speaking or understanding
- Dizziness and loss of balance
- Loss of vision
- Headache, usually severe and abrupt
- Difficulty swallowing

**Act FAST – seek immediate medical attention.**

For more information call 1800 787 653 or visit www.strokefoundation.com.au.
Cincinnati Prehospital Stroke Scale

Facial Droop: Have Patient Smile
Arm Drift: Close Eyes & Hold Out Both Arms
New definitions stroke and transient ischemic attack (TIA)

• Old definition 1960’s acute neurological deficit, vascular origin, >24 hour deficits

• New definitions
  • Strokes can be silent
  • Brief episodes < 24 hours but with brain injury = stroke, not TIA
  • Brief neurological episodes (usually < 24 hours) without damage on imaging = TIA
Time is brain
Rapid transport to a stroke centre

• Rapid ambulance transport
• Paramedical diagnostic stroke tools
  • FAST, Cincinatti, LAPS
• Potential in future for ambulance-based therapy
Assessment in ED

O/E (90 mins after onset of symptoms)

- alert, BP 170/100, irregular pulse
- expressive dysphasia, moderate right hemiparesis
- Appears frustrated

What should be done next?
Emergency Department – Code Stroke

1. Urgent triage and high priority for stroke patient
2. Mobilise the stroke team
3. IV - glucose, routine biochemistry, FBE
4. ECG
5. Accurate clinical diagnosis – exclude mimics
6. Urgent CT
## Conditions that mimic stroke

Hand et al. Stroke 2006

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total Number (%)†</th>
<th>Within 6 hrs‡</th>
<th>After 6 hrs‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>23 (21.1%)</td>
<td>18 (29.0%)</td>
<td>5 (10.6%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>14 (12.8%)</td>
<td>6 (9.7%)</td>
<td>8 (17.0%)</td>
</tr>
<tr>
<td>Toxic / metabolic</td>
<td>12 (11.0%)</td>
<td>6 (9.7%)</td>
<td>6 (12.8%)</td>
</tr>
<tr>
<td>Space occupying lesion§</td>
<td>10 (9.2%)</td>
<td>3 (4.8%)</td>
<td>7 (14.9%)</td>
</tr>
<tr>
<td>Syncope / presyncope</td>
<td>10 (9.2%)</td>
<td>9 (14.5%)</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Acute confusional state</td>
<td>7 (6.4%)</td>
<td>3 (4.8%)</td>
<td>4 (8.5%)</td>
</tr>
<tr>
<td>Vestibular dysfunction</td>
<td>7 (6.4%)</td>
<td>3 (4.8%)</td>
<td>4 (8.5%)</td>
</tr>
<tr>
<td>Acute mononeuropathy</td>
<td>6 (5.5%)</td>
<td>4 (6.5%)</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>Functional/medically unexplained symptoms</td>
<td>6 (5.5%)</td>
<td>4 (6.5%)</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>Dementia</td>
<td>4 (3.7%)</td>
<td>2 (3.2%)</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>Migraine</td>
<td>3 (2.8%)</td>
<td>2 (3.2%)</td>
<td>2 (4.3%)</td>
</tr>
<tr>
<td>Spinal cord lesion¶</td>
<td>3 (2.8%)</td>
<td>- (0%)</td>
<td>3 (6.4%)</td>
</tr>
<tr>
<td>Other?</td>
<td>3 (3.7%)</td>
<td>2 (3.2%)</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>109 (100%)</strong></td>
<td><strong>62 (100%)</strong></td>
<td><strong>47 (100%)</strong></td>
</tr>
</tbody>
</table>
Clinical features that distinguish between stroke & mimic

(Hand et al 2006)

• **Stroke predicted by**
  - exact time of onset
  - patient could recall exactly what they were doing at symptom onset
  - well in the last week
  - definite focal symptoms or signs, worse NIHSS

• **Mimic predicted if**
  - known cognitive impairment
  - lost consciousness or seizure at onset
  - patient could still walk
  - no lateralising symptoms
  - confusion, non-vascular or no neurological signs
L MCA Infarct – DWI lightbulb
R MCA Infarct 4.5 hours
early ischemic changes on CT
Deep putaminal ICH
Major stroke types

- Ischemic stroke (cerebral infarction)
- Intracerebral hemorrhage (ICH)
- Subarachnoid hemorrhage (SAH)
Major stroke types

• **Ischemic stroke**
  1. Large artery thromboembolism
  2. Cardiogenic embolism
  3. Small vessel (lacunar) infarction
  4. Rarer causes
  5. Unclassified or cryptogenic

• **Intracerebral hemorrhage (ICH)**
  1. Deep hypertensive location
  2. Lobar

• **Subarachnoid hemorrhage (SAH)**
  1. Aneurysm
  2. Arteriovenous malformation
  3. Other
Ischemic Stroke Classification 1

- **Large artery thromboembolism**
  - Cortical infarction, >50% relevant large artery stenosis, absence of cardiac source

- **Cardiogenic embolism**
  - Cortical infarction, cardiac source (most often Afib), absence of large artery disease

- **Lacunar Infarction**
  - Subcortical infarction, absence of large artery or cardiac source, clinical syndromes
Ischemic Stroke Classification 2

• Rare causes
  – For example, arterial dissection, drugs, vasculitis, rarer arteriopathies such as Moyamoya disease

• Dual Pathology
  – For example, cardiac + large artery source

• Unclassified
  – Despite adequate investigation
  – Inadequate investigation
Intracerebral Hemorrhage

• 15% stroke in NZ, 30% in Asia
• The most lethal stroke subtype
• Higher mortality (30-40%), worse functional outcome
• Stroke Unit Care effective
• BUT to date surgery and other therapies have shown NOT shown benefit in randomized clinical trials
Classification ICH

• Deep
  • Putamen, thalamus, brainstem, cerebellum
  • Usually due to hypertension and rupture of deep penetrating arteries

• Lobar
  • Superficial
  • Often secondary to amyloid angiopathy, tumour, arteriovenous malformation, aneurysm
Assessment in ED

Mrs Faul has had an ischaemic stroke.

What should be done next?
Why are early recognition and diagnosis time-critical?

• Both ischemic stroke and hemorrhagic stroke are dynamic, evolving conditions
• Stroke evolution results in increased lesion volume = worse outcome
• Therapies for both ischemic stroke and ICH are aimed at limiting stroke growth
Rescuing the penumbra: the aim of acute ischemic stroke treatment
Anterior Cerebral Artery collaterals

Infarct Core

Ischemic Penumbra

Posterior Cerebral Artery collaterals
Time is brain – Quantified

Saver J. Stroke 2006;37:263-266

**Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acute Ischemic Stroke**

<table>
<thead>
<tr>
<th></th>
<th>Neurons Lost</th>
<th>Synapses Lost</th>
<th>Myelinated Fibers Lost</th>
<th>Accelerated Aging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Stroke</td>
<td>1.2 billion</td>
<td>8.3 trillion</td>
<td>7140 km/4470 miles</td>
<td>36 y</td>
</tr>
<tr>
<td>Per Hour</td>
<td>120 million</td>
<td>830 billion</td>
<td>714 km/447 miles</td>
<td>3.6 y</td>
</tr>
<tr>
<td>Per Minute</td>
<td>1.9 million</td>
<td>14 billion</td>
<td>12 km/7.5 miles</td>
<td>3.1 wk</td>
</tr>
<tr>
<td>Per Second</td>
<td>32,000</td>
<td>230 million</td>
<td>200 meters/218 yards</td>
<td>8.7 h</td>
</tr>
</tbody>
</table>

**Every minute counts!**
Thrombolysis
Salvaging the Ischemic Penumbra

How should she be treated?

- Mrs Faul was given IV tPA and admitted to the Stroke Unit. She had a good response to thrombolysis.
- An ECG confirms atrial fibrillation
- CTA (on admission) shows tight left ICA stenosis

How should she be treated to prevent recurrent stroke?
# Acute interventions based on level I evidence

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>INITIAL OR IMPORTANT</th>
<th>STUDY, YEAR</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke unit</td>
<td>Langhorne et al, 1993</td>
<td>6.5</td>
<td>3.8</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>tPA</td>
<td>NINDS 1995;ECASS 3 2008</td>
<td>9.8</td>
<td>5.5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>IST, CAST 1997</td>
<td>2.6</td>
<td>1.2</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Hemicraniectomy</td>
<td>Vahedi K et al, 2007</td>
<td>48.8</td>
<td>23.0</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

GA Donnan, M Fisher, M Macleod SM Davis
All trials strongly positive

Table 1: summary of recent endovascular trial results

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age (years)</th>
<th>Baseline severity (NIHSS)</th>
<th>IV rtPA Treatment Rate</th>
<th>Artery opened</th>
<th>Time to open artery</th>
<th>Independent (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR CLEAN</td>
<td>65</td>
<td>18</td>
<td>89%</td>
<td>59%</td>
<td>332 min</td>
<td>33% vs. 19%</td>
<td>21% vs 22%</td>
</tr>
<tr>
<td>EXTEND-IA</td>
<td>71.5</td>
<td>15</td>
<td>100%</td>
<td>86%</td>
<td>248 min</td>
<td>71% vs 40%</td>
<td>9% vs 20%</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>71</td>
<td>16</td>
<td>76%</td>
<td>72%</td>
<td>241 min</td>
<td>53% vs 29%</td>
<td>10% vs 19%</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>66</td>
<td>17</td>
<td>100%</td>
<td>88%</td>
<td>257 min</td>
<td>60% vs 36%</td>
<td>9% vs 12%</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>65</td>
<td>17</td>
<td>68%</td>
<td>66%</td>
<td>355 min</td>
<td>44% vs 28%</td>
<td>18% vs 16%</td>
</tr>
</tbody>
</table>

Around double the rate of independent outcome
Mortality reduction up to 50%
TIAs and ischemic strokes are high-risk patients

- 5-10% stroke at 1 week
- 10-20% stroke at 3 months
- Even higher recurrence rate if DWI performed
- Probably similar for ischemic stroke
- Patients with CVD are at high risk CHD and vascular death
Primary Prevention

What are the risk factors?
How can we reduce the risk?
# Primary prevention - Risk factors for ischemic stroke

<table>
<thead>
<tr>
<th>Non-modifiable risk factors</th>
<th>Established</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>HT</td>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Gender</td>
<td>Diabetes</td>
<td>Obesity</td>
</tr>
<tr>
<td>Family history</td>
<td>Smoking</td>
<td>Dietary factors</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>AF/heart disease</td>
<td>Oral</td>
</tr>
<tr>
<td>contraceptive use</td>
<td>↑ cholesterol</td>
<td>Lack of HRT</td>
</tr>
<tr>
<td></td>
<td>Alcohol consumption</td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>Prothrombotic factors</td>
<td>Stress</td>
</tr>
<tr>
<td></td>
<td>Prior TIA</td>
<td>Sleep apnea</td>
</tr>
<tr>
<td></td>
<td>Prior stroke</td>
<td>Socio economic</td>
</tr>
</tbody>
</table>
Primary Prevention

• Main modifiable risk factors are smoking, hypertension, diabetes and obesity
• Encourage smoking cessation, weight loss, increased physical activity and a healthy diet
• Antihypertensive drugs reduce the risk of primary stroke by up to 40%
• There is no clear indication for antiplatelet treatment in low risk, or intermediate risk (uncomplicated diabetes, hypertension or hypercholestrolaemia) of stroke
• In high risk of cardiovascular disease consider aspirin
What rhythm is this and why are we asking?
Atrial fibrillation (AF)

• AF is the most common heart rhythm disturbance\(^1\)

• It is estimated 1 in 4 individuals aged 40 years will develop AF\(^1\)

• In 2007, 6.3 million people in the US, Japan, Germany, Italy, Spain, France and UK were living with diagnosed AF\(^2\)

• Due to the aging population, this number is expected to double within 30 years\(^3\)

Stroke Risk in Atrial Fibrillation

Control Groups in Randomized Trials

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Stroke Rate (% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>1</td>
</tr>
<tr>
<td>65-75</td>
<td>5</td>
</tr>
<tr>
<td>&gt;75</td>
<td>9</td>
</tr>
</tbody>
</table>

Stroke severity in patients with AF

Effect of first ischemic stroke in patients with AF (n=597)¹

<table>
<thead>
<tr>
<th>Severity</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disabling</td>
<td>60%</td>
</tr>
<tr>
<td>Fatal</td>
<td>40%</td>
</tr>
</tbody>
</table>

Warfarin in Atrial Fibrillation
Stroke risk reduction

New Oral Anticoagulants (NOAC)

• Direct Thrombin Inhibitor
  — Dabigatran (RE-LY study)
• Factor Xa Inhibitors
  — Rivaroxaban (ROCKET-AF study)
  — Apixaban (ARISTOTLE study)
• Essentially, at least as effective and safe as warfarin in stroke prevention
• Registered and PBS subsidised for prevention of stroke (or systemic embolism) in non-valvular AF in a patient with one or more risk factors for developing stroke (see CHADS2)

Assessing stroke risk in non-valvular AF

• There needs to be consideration of benefit to risk. Oral anticoagulation carries a risk of haemorrhage at least 1-1.5% per annum, greater in over 80 years old.

• There are a number of published models for calculating risk and maybe used as an aid to balancing the risks

• Most widely used is the CHADS2 score
The CHADS2 scoring system (score 1 for each risk factor of heart failure, hypertension age >75, and diabetes, score 2 for previous stroke of TIA).

- If score zero, can undertake a more comprehensive risk assessment e.g. CHADSVASc
- CHADS2 score ≥ 1 recommends an oral anticoagulant
- Oral anticoagulants reduce the risk of stroke by about 60% in people with AF (aspirin RRR ~25%)
Secondary Prevention

- Tailored to stroke pathogenesis in individual
- Recurrent stroke risk is 4% per annum
- Secondary prevention should start in hospital
Stroke Begets Stroke

Stroke patients are most at risk of having another stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>% of Patients With Events</th>
<th>Stroke</th>
<th>MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATS</td>
<td>13.5%</td>
<td>2.5%</td>
<td></td>
</tr>
<tr>
<td>TASS</td>
<td>12.5%</td>
<td>6.5%</td>
<td></td>
</tr>
<tr>
<td>CAPRIE*</td>
<td>10.0%</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>ESPS 2</td>
<td>12.5%</td>
<td>2.5%</td>
<td></td>
</tr>
</tbody>
</table>

*Stroke patient subgroup only (n = 6,431)
ABCD$^2$ Score

Generated from 2 derivation cohorts (California, Oxford, 1916 pts) and validated in 4 independent cohorts (2893 patients)

Age $\geq 60$ 1
BP SBP$\geq 140$ or DBP $\geq 90$ 1
Clinical Focal weakness 2
Speech imp w/o focal weakness 1
Duration $\geq 60$min 2
10-59min 1

Diabetes 1

TOTAL _ / 7

## Prevalence of stroke

<table>
<thead>
<tr>
<th>Risk group (ABCD2 score)</th>
<th>Prevalence DAY 2</th>
<th>Prevalence DAY 7</th>
<th>Prevalence DAY 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0-3)</td>
<td>1.0%</td>
<td>1.2%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Moderate (4-5)</td>
<td>4.1%</td>
<td>5.9%</td>
<td>9.8%</td>
</tr>
<tr>
<td>High (6-7)</td>
<td>8.1%</td>
<td>12%</td>
<td>18%</td>
</tr>
</tbody>
</table>
Overview of secondary prevention

• Blood pressure lowering
• Cholesterol and statins
• Antiplatelet therapy – which strategy?
• Atrial fibrillation and anticoagulation
• Carotid revascularization
  endarterectomy and stenting
BP and recurrent stroke

-10 mmHg:
RR 28% SE 8

Rodgers et al. BMJ 1996
SPARCL: Study design

- Stroke or TIA in ≤6 months, no known CHD, LDL-C 100–190 mg/dL
  - N = 4731

- Randomized
  - Double blind

- Atorvastatin 80 mg daily
  - n = 2365

- Placebo
  - n = 2366

Primary end point: Fatal/nonfatal stroke
Secondary end points: Major coronary or CV events
Follow-up: ~5 years (until >540 primary end points)

SPARCL: Statin treatment reduces fatal/nonfatal stroke

Primary outcome

Time since randomization (years)

Fatal/nonfatal stroke (%)

Placebo

16% RRR*
HR 0.84 (0.71–0.99)
P = 0.03

NNT = 46 patients for 5 years

Atorvastatin

*Adjusted

Paradigm shift in BP, cholesterol

• Lowering blood pressure and cholesterol at any level equally effective in secondary stroke prevention
• SPARCL results (atorvastatin post stroke) in 2005
• Move away from concepts of normal vs high BP and cholesterol
• The “polypill” to reduce CVD by > 80%
  (Wald, Law BMJ 2003)

  – Statin
  – 3 BP drugs eg thiazide, beta blocker, ACE inhibitor
  – Aspirin
  – Folic acid
Antiplatelet Therapy

• Aspirin reduces the risk of subsequent stroke by approx. 13% and all vascular events by 20%\textsuperscript{1}
• Dipyridamole plus aspirin was marginally more effective than aspirin alone. Preferred if patient at moderate to severe absolute risk, or recurrent stroke. Side effect of headache common. \textsuperscript{2}
• Clopidogrel is modestly more effective than aspirin in the prevention of serious high risk vascular events. \textsuperscript{3}
• A+C may have a role in first 90 days after stroke, TIA

1. Algra, van Gijn JNNP 1996
3. CAPRIE Lancet 1996
Comparison of Best Medical Therapy vs. Carotid Endarterectomy in Patients with Advanced Symptomatic Carotid Artery Disease

Ipsilateral stroke and perioperative death (%)

- ECST 3 yr: 39%
- NASCET 2 yr: 65%
- VA 1 yr: 60%

Advanced (>70%) symptomatic stenoses
Absolute Benefits of Carotid Endarterectomy (CEA)

CEA showed only marginal benefits on annual rates of ipsilateral stroke for patients with asymptomatic or moderate lesions. Dramatic benefit was seen for high-grade symptomatic stenoses.

Benefits of Endarterectomy are time-linked to last symptomatic event

P M Rothwell, M Eliasziw, S A Gutnikov, C P Warlow, H J M Barnett, for the Carotid Endarterectomy Trialists Collaboration

Figure 5: Absolute reduction with surgery in the 5-year cumulative risk of ipsilateral carotid ischaemic stroke and any stroke or death within 30 days after trial surgery in patients with 50–69% stenosis and ≥70% stenosis without near-occlusion stratified by the time from last symptomatic event to randomisation

Lancet 2004; 363: 915–24
# CEA Complications

<table>
<thead>
<tr>
<th></th>
<th>NASCET</th>
<th>ECST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or stroke</td>
<td>5.8% (6.7%)</td>
<td>7.1%</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>7.6%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Wound complications</td>
<td>8.9%</td>
<td>3.3%</td>
</tr>
<tr>
<td>CVS complications</td>
<td>3.9%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Other</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td><strong>Total complications</strong></td>
<td>26.2%</td>
<td>19.3%</td>
</tr>
</tbody>
</table>
How should Mrs Faul be treated?

• Lifestyle issues
  • stop smoking
  • Regular exercise
  • Ideal weight

• Reduce BP to <120/80

• Statin

• Carotid endarterectomy or stenting

• long-term anticoagulation with dabigatran or other new OAC
Conclusions

• Important to understand basic definition and classification of stroke
• This is vital because of the link to both acute treatment and secondary prevention
• Strokes evolve, providing an opportunity for treatments aimed at attenuation of growth of infarct and ICH
• Stroke is now regarded as a preventable and treatable disease
Secondary prevention summary

- High-risk patients benefit from BP, cholesterol lowering regardless of baseline
- Antiplatelet therapy routine if patient not anticoagulated
- Warfarin may be replaced for atrial fibrillation by new OAC
- Carotid endarterectomy proven therapy for carotid artery stenosis
- Carotid stenting may be equivalent for patients < 70 years