TIA & Secondary Stroke Prevention

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Telestroke Fellow
Burden of Stroke

- 1 in 6 people will have a stroke in their lifetime
- No 2 cause of death worldwide
- No 1 cause of disability in adults
- Two-thirds of stroke survivors will be permanently disabled and require some assistance with ADLs

Top 10 global causes of deaths, 2016

- Ischaemic heart disease
- Stroke
- Chronic obstructive pulmonary disease
- Lower respiratory infections
- Alzheimer disease and other dementias
- Trachea, bronchus, lung cancers
- Diabetes mellitus
- Road injury
- Diarrhoeal diseases
- Tuberculosis

TIA: The last chance to prevent a stroke…

- A patient who has suffered a TIA has:
  - A ~10% risk of major stroke within first 10 days
  - A 25% risk of a vascular event or death within 90 days (Most of which occur within 48 hours)
  - Up to 80% of this risk is preventable with urgent assessment and treatment

Coutts SB. Diagnosis and Management of Transient Ischemic Attack. Continuum (Minneap Minn). 2017 Feb;23(1, Cerebrovascular Disease):82-92
New definitions of TIA

- Historical time-based definition: acute neurological deficit, vascular origin, < 24 hours in duration
  - Up to 50% of these patients demonstrated infarction on MRI

- Current tissue-based definition: Sudden onset, focal, transient neurological deficit caused by brain/ cord / retinal ischaemia without acute infarction

- Brief episodes < 24 hours but with brain injury = Stroke, not TIA
• 68yo male: 2 episodes of expressive dysphasia, 5 minutes each
• Now entirely normal
Diagnostic assessment:

- **History:** Abrupt onset, maximal at onset, and focal: Referable to a single site in the CNS

- **Examination:** If ongoing neurological deficits while you are examining → Hyperacute stroke pathway
  - Most TIAs last ~ 10 minutes

- **Consider TIA/ Stroke mimics:** Can make up to 60% of patients initially suspected of having TIA

Final diagnosis of suspected TIA (n=512) by GPs in the community

<table>
<thead>
<tr>
<th></th>
<th>195</th>
<th>38%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TIA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non TIA</strong></td>
<td>317</td>
<td>62%</td>
</tr>
<tr>
<td>• Migraine aura</td>
<td>52</td>
<td>10%</td>
</tr>
<tr>
<td>• Syncope</td>
<td>48</td>
<td>9%</td>
</tr>
<tr>
<td>• Vestibular neuritis/ BPPV</td>
<td>32</td>
<td>6%</td>
</tr>
<tr>
<td>• Epilepsy/ partial Sz</td>
<td>29</td>
<td>6%</td>
</tr>
<tr>
<td>• Transient Global Amnesia</td>
<td>17</td>
<td>3%</td>
</tr>
<tr>
<td>• Isolated diplopia</td>
<td>4</td>
<td>1%</td>
</tr>
<tr>
<td>• Drop attack</td>
<td>3</td>
<td>0.6%</td>
</tr>
<tr>
<td>• Menigioma/ AVM</td>
<td>2</td>
<td>0.4%</td>
</tr>
<tr>
<td>• Metabolic</td>
<td>1</td>
<td>0.2%</td>
</tr>
<tr>
<td>• Hyperventilation/ anxiety</td>
<td>1</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Ddx: Migraine with aura

- Gradual onset with spread/ ‘migrainous march’ over minutes
- Gradual resolution of Sx
- Positive symptoms
- Personal or family history of migraine
- Unilateral, throbbing headache, Nausea/ vomiting, photophobia

*Scintillating scotoma: Build up over 20 minutes*
Ddx: Focal seizure

- Can have abrupt onset or gradual onset over a few seconds/minutes
- Positive phenomena – psychic/ sensory aura is common
- Automatisms (brief unconscious behaviours e.g chewing), jerking movements
- Symptoms may spread
- Consciousness may or may not be impaired

Transient Global Amnesia

- Sudden onset
- Anterograde and retrograde memory loss
- Repetitive questioning
- Recognises familiar faces and places: No loss of personal identity
- Complete recovery within a few hours leaving a dense amnesia gap
- Headache can be associated
- Witness history is key for diagnosis
<table>
<thead>
<tr>
<th></th>
<th>TIA</th>
<th>Migraine</th>
<th>Seizure</th>
<th>Syncope</th>
<th>Functional/ anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td>Older age&lt;br&gt;Vascular risk factors&lt;br&gt;More common in men</td>
<td>Younger age&lt;br&gt;More common in women</td>
<td>Any age</td>
<td>Any age, often younger&lt;br&gt;More common in women</td>
<td>Younger&lt;br&gt;More common in women</td>
</tr>
<tr>
<td><strong>Neurological symptoms</strong></td>
<td>Negative symptoms, usually maximal at onset: for example, numbness, weakness, visual loss. Transient diplopia and monocular visual loss are often due to TIA&lt;br&gt;Does not spread into other sensory modalities. Alteration or loss of consciousness almost never occur</td>
<td>Positive, spreading symptoms at onset. Visual the most common. May be followed by negative symptoms in the same domain&lt;br&gt;Symptoms may evolve into another modality (e.g., visual followed by somatosensory)&lt;br&gt;True alteration or loss of consciousness almost never occur, though there may be ‘confusion’ or muddled thinking</td>
<td>Positive symptoms including painful sensory disturbance, limb jerking, head turning, dystonic posturing, lip smacking. Loss of awareness and amnesia for event unless simple partial seizures&lt;br&gt;Postictal negative symptoms (e.g., Todd’s paresis) may persist for days</td>
<td>Faint or light headed (presyncopal). Vision may darken, or hearing becomes muffled. Loss of awareness</td>
<td>Isolated sensory symptoms common</td>
</tr>
<tr>
<td><strong>Timing</strong></td>
<td>Abrupt onset, gradual offset (minutes). Usually total duration minutes, nearly always &lt;1 h&lt;br&gt;Recur over days or weeks, usually not months or years.</td>
<td>Usually last 20–30 min, but may be much longer&lt;br&gt;Can recur over years</td>
<td>Usually less than 2 min. Can recur over years</td>
<td>Seconds to less than a minute. Can recur over years</td>
<td>Tend to be recurrent and stereotyped</td>
</tr>
<tr>
<td><strong>Associated symptoms</strong></td>
<td>Headaches may occur, usually during the attacks</td>
<td>Headache usually afterwards with migrainous features (nausea, vomiting, photophobia, phonophobia, mechanosensitivity)</td>
<td>Tongue biting (especially lateral), incontinence, muscle pains, exhaustion or disorientation, headache follow</td>
<td>Sweating, pallor, nausea, rapid recovery to full alertness</td>
<td>May be preceded by emotional or psychosocial stressors&lt;br&gt;Anxiety</td>
</tr>
</tbody>
</table>
Probable TIA: Consider aetiology
Important for secondary prevention

Cardioembolic 20%
Large artery 25%
Cryptogenic 25%
Small vessel 25%
Other (e.g. dissection, arteritis) 5%
Investigations:

- ECG immediately

- CT/CTA within 24 hours. If contraindication to CTA or unavailable then carotid doppler (only shows short segment of cervical carotid).
  - For posterior circulation symptoms CTA/ MRA required

- Fasting lipids, glucose

- MRI / interval CT scan: Diagnostic confirmation

- TTE and 24 hour holter within 2 weeks
  - Atrial fibrillation
  - Akinetic LV segment
  - Endocarditis/vegetation
  - PFO – TTE with bubble study if age<60 and no other cause

- Consider additional workup in selected patients with no other cause found:
  - Thrombophilia (antiphospholipid)/ vasculitis screen
  - Prolonged cardiac monitoring and TOE
  - Fabry’s dx
Risk stratification: To admit or not to admit

- Has now gone out of favour as its predictive performance in distinguishing between low and high risk TIAs as well as between TIA and mimics was very poor.
- ABCD2 + I is probably the best predictor (I = brain infarction on DWI scan)

<table>
<thead>
<tr>
<th>ABCD²</th>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥ 60 years</td>
<td>1</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥140/80</td>
<td>1</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Unilateral weakness</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Speech impairment without weakness</td>
<td>1</td>
</tr>
<tr>
<td>Duration of Sx</td>
<td>&gt;60 minutes</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>10-59 minutes</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>2day-risk for stroke</th>
<th>Recurrence within 90days</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>Low</td>
<td>1.0%</td>
</tr>
<tr>
<td>4-5</td>
<td>Moderate</td>
<td>4.1%</td>
</tr>
<tr>
<td>6-7</td>
<td>High</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

Risk factors for recurrent stroke:

<table>
<thead>
<tr>
<th>Feature</th>
<th>High Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing</td>
<td>Hours ago</td>
<td>Weeks ago</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&gt;60</td>
<td>&lt;45</td>
</tr>
<tr>
<td>Blood pressure at presentation (mm Hg)</td>
<td>&gt;140/90</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Speech, weakness</td>
<td>Dizziness, numbness</td>
</tr>
<tr>
<td>Duration (minutes)</td>
<td>&gt;60</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Frequency of events</td>
<td>One or few</td>
<td>Many</td>
</tr>
<tr>
<td>Degree of clinical improvement</td>
<td>Vanishing severe deficit</td>
<td>Improving mild deficit</td>
</tr>
<tr>
<td>Intracranial stenosis</td>
<td>Severe</td>
<td>None</td>
</tr>
<tr>
<td>Extracranial stenosis</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Intracranial occlusion</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Diffusion-weighted imaging lesion</td>
<td>Multiple greater than single</td>
<td>None</td>
</tr>
<tr>
<td>Transcranial Doppler emboli detection</td>
<td>&gt;50</td>
<td>None</td>
</tr>
</tbody>
</table>

Crescendo TIA

- > 2/ week often increasing in frequency and duration
- High risk of impending stroke
- Consider admission for these patients
Management of TIA

Early secondary prevention reduces risk of disabling stroke by 80% which is greatest within the first 24 hours.

1. Commence antiplatelet as soon as the CT Head confirms there is no bleed (unless AF) and commence high dose statin regardless of baseline lipids – do this before the patient leaves your sight

2. Antihypertensive

3. Consider revascularization as early as possible in patients with symptomatic carotid stenosis

4. Anticoagulation for those with atrial fibrillation and TIA can be commenced day 1

5. Lifestyle modification including diet, smoking cessation and physical exercise
Carotid stenosis:

- Accounts for 10% of all stroke however causes 50% of all early recurrences

- Revascularization is most effective when performed within 2 weeks of the ischaemic event

- In stable patients should be performed ASAP. Patients should be kept on a single antiplatelet agent before and during surgery.
Carotid revascularisation

- **Symptomatic (4-6mo) stenosis 70-99%**:  
  - strong evidence of benefit (NASCET, ECST) not if already severely disabled  
  - CEA has the greatest benefit within the first 3-14 days of the TIA/Stroke if able  
  - **Grade 1A recommendation**

- **Symptomatic stenosis 50-70%**  
  - Benefit in men if low surgical morbidity and good life expectancy: **Grade 2A recommendation**  
  - Benefit uncertain in women; Medical management preferable

- **Carotid occlusion/trickle flow**  
  - low risk of recurrent stroke, generally not suitable for surgery

- **Asymptomatic carotid stenosis**  
  - surgery rarely indicated – risk of stroke on optimal medical therapy (antiplatelet, statin, antihypertensives) estimated ~0.5%pa

- **Carotid stenting**  
  - risk of stroke/death higher with CAS than CEA  
  - (possible role in patients aged <70?): CREST 1 trial showed that patients below age 70 did better with CAS, and above 70 did better with CEA  
  - Other patients with unfavourable anatomy, previous radiotherapy can be considered for stenting
Atrial Fibrillation: anticoagulation is underutilized

1. Determine if non-valvular or valvular AF
   • Valvular AF: mechanical valve or mod-severe mitral stenosis – warfarin

2. Other indications for warfarin:
   • If creatinine clearance < 25ml/min
   • LV thrombus
   • Other causes of VTE e.g. malignancy
   • Stable long term control
   • Drug interactions: phenytoin, carbamazepine, HAART, azole antifungals

3. Otherwise, select a NOAC. But which one?
<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Direct thrombin inhibitor</td>
<td>Factor Xa inhibitor</td>
<td>Factor Xa inhibitor</td>
</tr>
<tr>
<td><strong>Peak plasma levels</strong></td>
<td>1-2hrs</td>
<td>2-4hrs</td>
<td>3-4hrs</td>
</tr>
<tr>
<td><strong>Stroke incidence: Warfarin vs NOAC %/year</strong></td>
<td>RE-LY trial N=18,113 Warfarin: 1.69% Dab 110mg: 1.53% Dab 150mg: 1.11%</td>
<td>ROCKET - AF trial N=14,264 Warfarin: 2.2% Rivaroxaban: 1.7%</td>
<td>ARISTOTLE trial N=18,201 Warfarin: 1.6% Apixaban: 1.27%</td>
</tr>
<tr>
<td><strong>Safety: Major bleeding warfarin vs NOAC %/year</strong></td>
<td>Warfarin: 3.36% Dab 110mg: 2.71% Dab 150mg: 3.11%</td>
<td>Warfarin: 3.4% Rivaroxaban: 3.6%</td>
<td>Warfarin: 3.09% Apixaban: 2.13%</td>
</tr>
<tr>
<td><strong>GI bleeding %/year</strong></td>
<td>Warfarin: 1.02% Dab 110mg: 1.12% Dab 150mg: 1.51%</td>
<td>Warfarin: 2.2% Rivaroxaban: 3.2%</td>
<td>Warfarin: 0.86% Apixaban: 0.76%</td>
</tr>
<tr>
<td><strong>ICH %/year</strong></td>
<td>Warfarin: 0.38% Dab 110mg: 0.12% Dab 150mg: 0.10%</td>
<td>Warfarin: 0.7% Rivaroxaban: 0.5%</td>
<td>Warfarin: 0.80% Apixaban: 0.33%</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>P-gp inhibitors/ inducers</td>
<td>P-gp/CYP 3A4 inhibitors/ inducers</td>
<td>P-gp/CYP 3A4 inhibitors/ inducers</td>
</tr>
<tr>
<td><strong>Reversal agents</strong></td>
<td>Idaricizumab, haemodialysis removes ~65% of active drug</td>
<td>Andexanet in trials (recombinant modified human factor Xa decoy protein)</td>
<td>Andexanet in trials (recombinant modified human factor Xa decoy protein)</td>
</tr>
<tr>
<td><strong>Renal clearance</strong></td>
<td>80%</td>
<td>36%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>Half life with normal renal function</strong></td>
<td>12-18 hrs</td>
<td>5-13 hrs</td>
<td>12-15 hrs</td>
</tr>
</tbody>
</table>
Selecting a NOAC based on patient characteristics:

- Recurrent ischaemic events, low bleeding risk: Dabigatran 150mg BD
- Mod – severe renal impairment: Rivaroxaban or apixaban (2.5mg BD) (or warfarin)
- High risk of bleeding (HAS BLED score 3 or higher): Apixaban, Dabigatran 110mg BD
- High risk of GI bleeding: Apixaban or dabigatran 110mg BD
- Compliance: Rivaroxaban (or warfarin)
- Apixaban Dose reduction: Age 80 years or older, Weight 60kg or less, Serum creatinine 133 mmol/L

Hypertension

- Hypertension promotes the formation of atherosclerotic lesions and is the single most important treatable risk factor for stroke

- Antihypertensive therapy (including pre-existing antihypertensives) should be deferred in the acute period after ischaemic stroke (48-72 hours); or longer if there is large vessel occlusion

- Long term blood pressure management:
  - All stroke and TIA patients with BP >140/90mmHg should have initiation of antihypertensive therapy long term
  - Acceptable first line agents include ACEi, ARB, CCBs or thiazide diuretics. Beta blockers should not be used as first line agents unless the patient has ischaemic heart disease.

Alcohol

- **Current recommendations:** < 2 standard drinks per day for men and <1 drink per day in women
- Recent study shows that alcohol > 100g per week (5-6 standard UK glasses of wine or pints of beer) increases risk of stroke

- 599912 current drinkers followed for 5.4 million person years in 83 prospective studies
- The main finding of this analysis was that the threshold for lowest risk for all-cause mortality was ~ 100g/week

Smoking one cigarette per day: Risk of stroke and CHD much greater than expected: half of that of people smoking 20 cigarettes per day.

No safe level of smoking exists for cardiovascular disease. Smokers should aim to quit instead of cutting down to significantly reduce their risk of these two common major disorders.
Diet & Exercise

- Australian Dietary Guidelines
  - Plenty of vegetables and legumes, fruits, wholegrain/high fibre options, lean meats and reduced fat dairy products, with limited intake of foods containing saturated fat, added salt and added sugars

- Mediterranean diet improves outcomes in patients with established cardiovascular disease

- Regular aerobic physical exercise & weight control
  - Indirectly reduces stroke risk by improving other parameters e.g. BP, BGLs and serum lipid levels
Driving after TIA or Stroke

- **TIA**: 2 weeks (private) or 4 weeks (commercial)

- **Stroke**:
  - Minimum of 4 weeks then doctors clearance
  - If ongoing deficits – on road driving assessment
  - Visual field defects: Formal ophthalmology review for VF assessment
    - Horizontal VF of 110 degrees (normally 160-200)
Take home messages:

- TIA is a high risk presentation
- Requires urgent assessment and treatment
  - ECG
  - Carotid Imaging
  - Antiplatelet
  - Antihypertensive
  - Statin
- Best available evidence suggests that this approach reduces the relative risk of stroke by 80%
5 Transient ischaemic attack

**Strong recommendation**

- All patients with suspected transient ischaemic attack (TIA), i.e. focal neurological symptoms due to focal ischaemia that have fully resolved, should have urgent clinical assessment. (Lavallée et al. 2007 [25]. Rothwell et al. 2007 [26]) (Refer to the 'Practical Information' section for further useful information)

- Patients with symptoms that are present or fluctuating at time of initial assessment should be treated as having a stroke and be immediately referred for emergency department and stroke specialist assessment, investigation and reperfusion therapy where appropriate. (Lavallée et al. 2007 [25]. Rothwell et al. 2007 [26])

- In pre-hospital settings, high risk indicators (e.g. crescendo TIA, current or suspected AF, current use of anticoagulants, carotid stenosis or high ABCD² score) can be used to identify patients for urgent specialist assessment. (Lavallée et al. 2007 [25]. Rothwell et al. 2007 [26])

When TIA patients present to primary care, the use of TIA electronic decision support, when available, is recommended to improve diagnostic and triage decisions. (Ranta et al. 2015 [15])
Questions
## Applying classification of recommendations and level of evidence

<table>
<thead>
<tr>
<th>Class I</th>
<th>Class IIA</th>
<th>Class IIB</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit &gt;&gt;&gt; Risk</td>
<td>Benefit &gt;&gt; Risk</td>
<td>Benefit ≥ Risk</td>
<td>Risk ≥ Benefit</td>
</tr>
<tr>
<td>Additional studies with focused objectives needed</td>
<td>Additional studies with broad objectives needed; Additional registry data would be helpful</td>
<td>Procedure/Treatment MAY BE CONSIDERED</td>
<td>Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL</td>
</tr>
<tr>
<td>Procedure/Treatment SHOULD be performed/administered</td>
<td>IT IS REASONABLE to perform procedure/administer treatment</td>
<td></td>
<td></td>
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</tbody>
</table>

### Size of treatment effect

#### Level of Evidence:

<table>
<thead>
<tr>
<th>Level A:</th>
<th>Level B:</th>
<th>Level C:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
<td>Data derived from a single randomized trial or nonrandomized studies</td>
<td>Only consensus of experts opinion, case studies, or standard of care</td>
</tr>
<tr>
<td>Multiple populations evaluated</td>
<td>Limited populations evaluated</td>
<td>Very limited populations evaluated</td>
</tr>
</tbody>
</table>