Stroke: Prevention and Treatment

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Disclosures: none

1 in 6 people have a stroke in their lifetime
No 2 cause of death worldwide
No 1 cause of disability in adults

Infections, 19%
Cancer, 15%
Injuries, 10%
Other, 32%
Ischemic stroke, 5.4%
Intracerebral hemorrhage, 5.8%
Ischemic heart disease, 13%


Projected trends for stroke deaths:
Less in developed world
More in developing world…

Major stroke types

- Ischemic stroke (cerebral infarction)
- Intracerebral hemorrhage (ICH)
- Subarachnoid hemorrhage (SAH)
- Cerebral venous sinus thrombosis (CVST)

Risk factors for stroke

Can’t control:
- Age
- Sex
- Family history

Can control (either through lifestyle modification or medication):
- High blood pressure
- Atrial fibrillation
- Smoking
- High cholesterol
- Diabetes
- Obesity/overweight
- Poor diet
- Lack of exercise
Blood pressure lowering

- moved away from “hypertension” to absolute risk
- nonetheless difficult to manage without targets
- for secondary prevention most patients should be taking an antihypertensive
- ACEI, A2RA, Calcium antagonist etc,
  Beta-blockers not first-line unless IHD
- available RCT data suggest systolic 120-140mmHg
  reasonable target
  – benefit of BP lowering regardless of baseline BP
  unless symptomatic hypotension

Antithrombotics & Statins

- in the absence of AF use antiplatelets:
  – aspirin
  – aspirin+dipyridamole
  – clopidogrel
- clopidogrel ≅ aspirin+dipyridamole and slightly better than aspirin
- short term (~1 month) A+C useful in high risk group
- long term A+C: bleeding risk outweighs stroke benefit
- high potency statins reduce stroke

AF - anticoagulation key messages

- Anticoagulants are grossly underutilised in Australia (and worldwide)
  → unnecessary strokes & disability
- Act of omission vs act of commission discrepancy in prescriber thinking regarding risk-benefit
- Age discrimination, lack of creativity and effort to circumvent relative contraindications
- Myths about DOACs versus warfarin

Atrial fibrillation – CHA2DS2-VASc score

<table>
<thead>
<tr>
<th>Q1</th>
<th>Patient aged ≥ 75?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>GAC</td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q2</th>
<th>Does the patient have a history of TIA, stroke or embolism?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>GAC</td>
</tr>
<tr>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q3</th>
<th>Patient gender?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>GAC and two or more risk factors below are present</td>
</tr>
<tr>
<td>Female</td>
<td>GAC if any of the risk factors below are present</td>
</tr>
</tbody>
</table>

Age 65-74,
Hypertension
Valvular disease
*Myocardial infarction, peripheral artery disease or aortic plaque
Diabetes
Dyslipidaemia
Gender

NB Paroxysmal AF and permanent AF have similar stroke risk

Warfarin or NOAC/DOAC?

Figures obtained by the ABC reveal Pradaxa has been associated with 280 deaths in Australia and 1,400 adverse drug reactions in the past five years, including abdominal hemorrhages, strokes and heart attacks.

Dabigatran, bleeding, and... 
Bmj 2014: 349: d5647

Analysis

Dabigatran, bleeding, and... 
Bmj 2014: 349: d5647

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Hemorrhages, strokes and heart attacks.

By comparison, the older blood-thinning drug Warfarin has been linked to 30 deaths and 270 reactions over the same period – Sophie Scott, ABC News Medical Reporter.
### Warfarin or DOAC?

- **valvular AF still needs warfarin**
  - mechanical prosthetic valve, rheumatic mitral disease
- **DOACs require CrCl >30ml/min**
  (or >25ml/min for apixaban)
- **DOACs similar/slightly less ischemic stroke,**
  important reduction in ICH, convenience advantage
- **Reversal agent now available for dabigatran,** in trials for Xa (and warfarin “reversal” is slow and doesn’t improve prognosis after ICH)

### Does lower CrCl alter risk-benefit?

**APIXABAN vs WARFARIN**

**Stroke or Systemic embolism**

<table>
<thead>
<tr>
<th>CrCl (ml/min)</th>
<th>Warfarin 95% CI</th>
<th>Apixaban 95% CI</th>
<th>p-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>0.88 (0.65, 1.19)</td>
<td>0.90</td>
<td>0.57</td>
</tr>
<tr>
<td>50–80</td>
<td>0.85 (0.67, 1.08)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>0.94 (0.67, 1.31)</td>
<td>0.92</td>
<td></td>
</tr>
</tbody>
</table>

Hohnloser et al Eur Heart J 2012

**Major Bleeding**

### Aspirin for AF? – NO!

- **Meta-analysis:** 19% reduction in stroke (non-significant)
- **AVERROES trial** – apixaban 5mg BD same risk of ICH (0.4%pa) and much more effective (dabigatran rate of ICH similar)
- **NICE (UK) 2014 recommendations:**
  “Do not offer aspirin monotherapy solely for stroke prevention to people with atrial fibrillation.”
Use the correct dose: don’t compromise efficacy

- Calculate Renal function = CrCl (Cockcroft-Gault, not just eGFR!)

- **Apixaban**: 5mg BD unless two of:
  - age > 80
  - Cr > 133μmol/L, wt < 60kg → 2.5mg BD
  - Do not use if CrCl < 25ml/min (27% renal clearance)

- **Dabigatran**: 150mg BD unless:
  - CrCl 30-50ml/min or age > 75 → 110mg BD
  - Do not use if CrCl < 30ml/min (80% renal clearance)

- **Rivaroxaban**: 20mg daily unless:
  - CrCl 30-50ml/min → 15mg daily
  - Do not use if CrCl < 30ml/min (35% renal clearance)

Using direct oral anticoagulants

- peri-operative management
  - first ask if it is necessary to stop at all
  - very different to warfarin, read the PI
    - do NOT stop 1 week pre-op, no “bridging”
  - 24 hours is appropriate for low risk and 48 hours for high risk unless impaired kidney function
  - in an emergency dabigatran can be instantly reversed with idarucizumab with no prothrombotic effect (in contrast to warfarin)

Maximising safety

- Control blood pressure
- Avoid concurrent antiplatelets
- Monitor CrCl, especially if intercurrent illness
- True contraindications?
  - active bleeding (if can’t address cause)
  - very frequent falls if can’t address cause?

Take home messages

- For NVAF patients new to anticoagulation with CrCl > 25ml/min why would you use warfarin?
- For patients “stable” on warfarin consider TTR and weigh the risk of ICH
- “reversibility” of warfarin after ICH is an illusion
- Poor renal function with CrCl > 25ml/min – apixaban may be safer than warfarin
- Maintain tight BP control and avoid concurrent antiplatelets
- Don’t use aspirin for AF

TIA is an emergency

- High risk of stroke in next few days - preventable
- What are the key investigations?
  - **CT brain** (low yield but occasional tumour, small bleed etc)
  - **Carotid imaging** (Doppler US or CT Angiogram, if >50% symptomatic stenosis consider carotid endarterectomy)
  - **12-lead ECG** (?atrial fibrillation)
- What are the key management steps?
  - Commence an **antiplatelet** (unless AF → anticoagulate (DOAC/warfarin)
  - Commence a **statin** and oral **antihypertensives**
- Before the patient leaves your sight!
  - This approach can reduce stroke by 80%

* Subject to local resources - in some circumstances rapid outpatient investigation is necessary but start the medications!

- **68yo M**: 2 episodes dysphasia, each ~5mins
- **Now examination entirely normal**

- **CT brain – normal**
- **Diffusion MRI = stroke**
**Carotid Endarterectomy (CEA)**

- Symptomatic stenosis 70-99% - strong evidence of benefit (NASCET, ECST) NB not if already severely disabled
- Symptomatic stenosis 50-70% - benefit if low surgical morbidity and good life expectancy
- 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 ~0.3%/pa
- Carotid stenting currently has a higher risk of stroke than endarterectomy (possible role in patients aged <70?)

**Is stroke different in women?**

- In general no – more women have stroke than men due to living longer (but age-adjusted men are at higher risk)
- outcomes tend to be worse – reasons unclear
  - women tend to be older and more often living alone (widowed) pre-stroke – less likely to discharge home
  - less likely to receive thrombolysis (delayed presentation?)
  - less benefit from endarterectomy
  - but none of this should change management
- some causes of stroke are increased in women:
  - cerebral venous sinus thrombosis
  - hormonal effects? migraine OCP smoking \(\rightarrow\) stroke risk

**CVST**

- **Risks:**
  - Inherited thrombophilia
  - Acquired thrombophilia (malignancy, APLS, Behcets, IBD, OCP, pregnancy, severe dehydration, nephrotic, polycythemia)
  - Local sepsis – sinusitis/mastoiditis

  **Mx:**
  - IV heparin even if hemorrhagic infarction!
  - Then warfarin for ~6months

**OCP, migraine & stroke**

- **migraine with aura** increases stroke risk
- OCP + migraine with aura + smoking is a bad combination also increased risk if age >35, high BP
  (NB over age 50 traditional risks make migraine no longer a significant factor)
- For women of child-bearing age who have had a stroke, non-hormonal methods of contraception should be considered.
- If systemic hormonal contraception is required, a non-oestrogen containing medication is preferred

**HRT & stroke**

- Inconsistent effects of hormone replacement therapy (HRT)
- Meta-analysis of secondary prevention trials (participants with existing cardiovascular disease) did not show an increased risk for stroke (Boardman et al 2015).
- In primary prevention trials in healthy postmenopausal women, HRT increased stroke risk by ~25% and did not have any overall cardiovascular disease benefit.

**ISCHEMIC STROKE**

Pathophysiology and Treatment
Stroke diagnosis - CT Brain

Anterior Cerebral Artery collaterals
Ischemic Core
Ischemic Penumbra
Posterior Cerebral Artery collaterals

CT perfusion imaging

DwI MRI
TTP
Delayed TTP = collateral territory

Area = CBV
Low CBV = likely irreversibly damaged

CT Perfusion imaging

Area = CBV
TTP concentration
CBV concentration

Advanced imaging: Perfusion CT & MRI
Positive diagnosis of ischemic stroke + "dead vs salvageable"

CT perfusion
CT relCBF /
Diffusion MRI
RAPID ischemic core segmentation
Tmax
RAPID Tmax+Volume segmentation

MRI

Acute Stroke interventions: evidence base

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke types and severities Stroke Unit care Cochrane 2007</td>
<td>Death/Dependency</td>
<td>3.6</td>
<td>28</td>
</tr>
<tr>
<td>Ischemic Stroke tPA &lt;4.5hr Emberson et al, 2014</td>
<td>mRS 0-1</td>
<td>6.8</td>
<td>15</td>
</tr>
<tr>
<td>Thrombectomy &lt;6hr MR-CLEAN, EXTEND-IA, ESCAPE, SWIFT-PRIME, RESUSCAT 2015</td>
<td>Death/Dependency</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Aspirin IST, CAST 1997</td>
<td>Recurrent stroke/Death</td>
<td>0.9</td>
<td>111</td>
</tr>
<tr>
<td>Hemicraniectomy Vahedi K et al, 2007</td>
<td>Death</td>
<td>49</td>
<td>2</td>
</tr>
<tr>
<td>Intracerebral hemorrhage BP lowering in ICH Anderson et al, 2013</td>
<td>Death/Dependency</td>
<td>3.6</td>
<td>28</td>
</tr>
</tbody>
</table>
Excellent outcome (mRS 0-1) n=6756

Number Needed to Treat

4.5          9                  14.1

Our aim: shift patients up the curve!

Emberson Lancet 2014

Number Needed to Treat (NNT)

1.3 2.5 2.9 3.4 4.2 5.5 8.6

Endovascular – time still critical

Endovascular Therapy for Stroke — It’s about Time

Anthony J. Furlan, M.D.

New Eng J Med 2015:

- 5 Positive randomized trials
- 2 Editorials

Endovascular Therapy for Ischemic Stroke with Penumbra Imaging Selection

Thrombectomy within 8 hours after symptom onset in ischemic stroke

Saver JAMA 2016

Solitaire stent retriever

tPA indication/contra-indications

- Potentially disabling deficit <4.5 hr from onset and no blood/established infarct on CT brain

Exclusions:

- PHx intracranial bleeding
- surgery/trauma 2/52
- GI/GU bleeding 3/52
- BP >185/105 (fix first)
- Symptomatic hypoglycaemia (fix first)
- Warfarin with INR>1.7, other coagulopathy/low platelets
- Aortic dissection
Who benefits from endovascular thrombectomy?

- Any age
- Any clinical severity
- Proven large vessel occlusion
- Start procedure within 6 hours after stroke onset

- Future?
  - smaller vessels
  - later time window in patients with favourable imaging

At a glance

- 185 hospitals
- 4,087 patients

Melbourne metropolitan area

- 11 tPA centres
- 120min drive time to tPA centers (95% coverage)
- 180min drive time to endovascular center (88% coverage)
- Thrombolysis center (rural via telestroke)
Conclusions

- Many strokes are preventable and treatable
- Blood pressure & AF are particularly strong risk factors for stroke + usual vascular risk factors
- AF is under-treated leading to unnecessary strokes
- Early recognition of stroke and treatment are time-critical – time is brain

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BMH Comprehensive Stroke Center