Recent Advances in Stroke Management

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**Stroke**

- rapidly evolving episode of focal/global loss of cerebral function
  - symptoms lasting > 24 hrs or leading to death

- not a single syndrome
  - disruption of CBF
  - secondary focal ischaemia

- types of stroke
  - ischaemic (80%)
  - intracerebral haemorrhage (20%)
    - 25 % - subarachnoid haemorrhage
    - 75% - primary intracerebral haemorrhage
Ischaemic stroke

- incidence
  - 1 - 2 per 1000 population in UK
    • 55 to 65 yrs: 2.2 - 3.5 per 1000
    • 75 to 84 yrs: 9.6 – 24.2 per 1000

- high mortality
  - 25% after first stroke
  - 41% after recurrent stroke

Hardie et al, Stroke 2004;35:731-5
Stroke risk factors

- traditional risk factors
  - fixed
    - age
    - male sex
  - modifiable
- previous ‘silent’ infarcts
- stroke triggers
  - inflammatory triggers
  - ‘stroke prone state’
### Established Modifiable Stroke Risk Factors

<table>
<thead>
<tr>
<th>Risk of new stroke</th>
<th>Prior TIA or stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5% at 90 days after TIA</td>
<td>Hypertension</td>
</tr>
<tr>
<td>12% at 1 year after previous stroke/TIA</td>
<td>Cardiac disease</td>
</tr>
<tr>
<td>5% p.a. thereafter</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>Hyperlipidaemia</td>
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<tr>
<td></td>
<td>Carotid stenosis</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
</tr>
<tr>
<td></td>
<td>Cigarette smoking</td>
</tr>
<tr>
<td></td>
<td>Physical inactivity</td>
</tr>
<tr>
<td></td>
<td>Heavy alcohol use</td>
</tr>
</tbody>
</table>

_Sanossian & Ovbiagele, Neurologist 2006;12:14-31_
Stroke prevention

- greatest potential for reducing stroke burden

*Number needed to treat for various stroke prevention measures*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Relative risk reduction</th>
<th>Number needed to treat (1 stroke/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive agents</td>
<td>28%</td>
<td>51</td>
</tr>
<tr>
<td>Statins</td>
<td>25%</td>
<td>57</td>
</tr>
<tr>
<td>Aspirin</td>
<td>28%</td>
<td>77</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>33%</td>
<td>43</td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>44%</td>
<td>26</td>
</tr>
</tbody>
</table>

Sanossian & Ovbiagele, Neurologist 2006;12:14-31
• ICA stenosis accounts for 10-20% all cases of TIA and acute ischaemic stroke

• large RCTs show clear advantage for carotid endarterectomy in high-grade symptomatic stenosis

Kaplan-Meier survival curves - survival free of major stroke in surgery and control patients with 80–99% stenosis of symptomatic ICA
Carotid endarterectomy

- indications
  - symptomatic patients with > 70% stenosis
    
  
  - asymptomatic patients with > 60% stenosis, low surgical risk and 5 year life expectancy
    
    ACAS, JAMA 1995;273:1421-8
Endovascular techniques

- carotid artery angioplasty
  - risk of distal thromboembolism & re-stenosis

- carotid artery stenting
  - with or without angioplasty

- distal protection devices
Meta-analysis of randomised comparisons of safety of endovascular treatment versus carotid endarterectomy

Plot shows outcome of death or stroke within 30 days after treatment

Acute treatment of stroke

- airway, adequate ventilation & cardiovascular resuscitation
- close monitoring & management in a dedicated stroke unit
- attention to management of medical aspects of care
- careful selection of patients for thrombolysis
Irreversible injury occurs immediately in some areas.

Ischaemic penumbra - blood supply only marginally sufficient to keep neurones alive.

Time-related neuronal death occurs if blood supply is not restored.

Thrombolytic agents represent a treatment option for reperfusion of the ischaemic penumbra.

i.v. rt-PA approved for treatment in 1996 – NNT 7 within three hours and 11 within six hours.
Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials

- chance of good outcome increased by
  - 2.8 (95% CI 1.8-4.5) if treatment started < 90 mins
  - 1.6 (95% CI 1.1-1.9) at 91-180 mins
  - 1.2 (95% CI 0.9-1.5) at 181-360 mins

- symptomatic ICH occurred in 5.9% rt-PA treated patients vs. 1.1% for placebo (p<0.0001)
Thrombolysis

New therapeutic options

• intra-arterial thrombolysis
  – effective clot lysis
  – extends treatment window to 6 hrs
  – relatively complicated procedure
  – no comparisons with conventional i.v. rt-PA

• endovascular devices to remove embolus
Intensive care management

• blood pressure control
• volume status
• blood glucose control
• therapeutic hypothermia
• decompressive surgery
• management of complications
• high blood pressure (> 140/90 mmHg) present in > 80% patients immediately after AIS
  - pre-existing hypertension
  - stress, raised ICP, neuroendocrine response

• high BP independently associated with poor outcome
  - for every 10-mm Hg increase > 180 mm Hg, the risk of neurological deterioration increases by 40% & risk of poor outcome by 23%

• routine BP lowering is not recommended after AIS

• recent studies are increasingly reassuring about the safety of BP lowering

*Sare et al, Cerebrovasc Dis 2009;27 (Suppl 1):156-61*
<table>
<thead>
<tr>
<th>Trial</th>
<th>Active intervention</th>
<th>Patients</th>
<th>Difference in BP (time)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCESS [23]</td>
<td>oral candesartan</td>
<td>339</td>
<td>none</td>
<td>no effect on functional outcome; reduced cardiac and cerebral events</td>
</tr>
<tr>
<td>BEST [25]</td>
<td>atenolol or propranolol</td>
<td>303</td>
<td>−6 to −9% (24 h)</td>
<td>more early deaths in treatment group</td>
</tr>
<tr>
<td>CHHIPS [21]</td>
<td>oral/IV labetalol, or oral/sublingual lisinopril</td>
<td>179</td>
<td>significant difference</td>
<td>no effect on functional outcome; reduced death</td>
</tr>
<tr>
<td>Eveson [41]</td>
<td>oral lisinopril</td>
<td>40</td>
<td>−19 mm Hg (4 h)</td>
<td>no effect on functional outcome</td>
</tr>
<tr>
<td>GIST [39]</td>
<td>IV glucose/insulin/potassium</td>
<td>933</td>
<td>−9 mm Hg (24 h)</td>
<td>no effect on functional outcome</td>
</tr>
<tr>
<td>GTN 2 [36]</td>
<td>transdermal glyceryl trinitrate</td>
<td>90</td>
<td>−6.7% (mean over 24 h)</td>
<td>no effect on functional outcome</td>
</tr>
<tr>
<td>IMAGES [37]</td>
<td>intravenous magnesium</td>
<td>2,386</td>
<td>−4/−3 mm Hg (mean over 24 h)</td>
<td>no effect on functional outcome</td>
</tr>
<tr>
<td>INTERACT pilot&lt;sup&gt;1&lt;/sup&gt; [49]</td>
<td>intensive versus guideline-based treatment</td>
<td>404</td>
<td>−13 mm Hg (1 h)</td>
<td>no effect on functional outcome; trend to reduced haematoma expansion</td>
</tr>
<tr>
<td>PROFESS [24]</td>
<td>oral telmisartan</td>
<td>8,113</td>
<td>−3.8/2.0 mm Hg (mean over 2.5 years)</td>
<td>no effect on functional outcome; trend to reduced recurrence</td>
</tr>
</tbody>
</table>

<sup>1</sup> Primary intracerebral haemorrhage.

- **ENOS** (n = 5,000)
- **SCAST** (n = 2,500)
- **COSACS** (n = 2,900)
- **INTERACT 2** (n = 2,500)
Blood pressure management

- routine BP lowering is not recommended after AIS (class IV)
- cautious BP lowering in patients with BP >220/120 mmHg (class IV)
- BP >185/110 mm Hg should be lowered before thrombolysis (class IV)
- avoid abrupt BP lowering (Class II)
- low BP should be treated with volume expanders (Class IV)

ESO Writing Committee, Cerebrovasc Dis 2008;25:457-507
Blood glucose

- post-stroke hyperglycaemia is common

![Graph showing incidence of PSH across various stroke studies](image)

**Incidence of PSH across a number of acute stroke studies**

*Note differing definitions of PSH & resulting heterogeneity in reported incidence*

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients with DM/total patients in trial</th>
<th>Proportion with DM, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMAGES</td>
<td>413/2,386</td>
<td>17.3</td>
</tr>
<tr>
<td>GAIN-I</td>
<td>310/1,523</td>
<td>20.4</td>
</tr>
<tr>
<td>LUB-INT</td>
<td>405/1,785</td>
<td>22.7</td>
</tr>
<tr>
<td>CLASS</td>
<td>292/1,198</td>
<td>24.4</td>
</tr>
<tr>
<td>NINDS</td>
<td>85/624</td>
<td>13.6</td>
</tr>
<tr>
<td>ECASS-II</td>
<td>169/800</td>
<td>21.1</td>
</tr>
<tr>
<td>MAST-E</td>
<td>33/310</td>
<td>10.6</td>
</tr>
<tr>
<td>SAINT I</td>
<td>343/1,705</td>
<td>20.1</td>
</tr>
<tr>
<td>SAINT II</td>
<td>792/33,241</td>
<td>24.4</td>
</tr>
<tr>
<td>Combined</td>
<td>2,842/13,572</td>
<td>20.9</td>
</tr>
</tbody>
</table>

**Prevalence of DM in cohorts of patients recruited to acute stroke trials**

*Quinn & Lees, Cerebrovasc Dis 2009;27 (Suppl 1):148-55*
Blood glucose & outcome

- **GLIA**
  - serum glucose > 8.6mmol/l in first 48 hrs associated with 2.7 x increased risk of poor 3-month outcome
  
  *Fuentes al, Stroke 2006; 37:625*

- **GIST-UK**
  - tight glucose control (4.0-7.0 mmol/l) vs. placebo
  - no difference in 3-month mortality (insulin vs. control: odds ratio 1.14; 95% CI: 0.86–1.51)
  - no difference in 3-month outcome in survivors
  - higher mortality in patients with decrease in serum glucose > 2 mmol/l (34 vs. 22%, p = 0.009)

*Gray et al, Lancet Neurol 2007; 6:397-406*
Blood glucose management

- no RCT data on impact of glucose normalisation on stroke outcome
- optimal serum glucose unknown
  - European Union Stroke Initiative < 10 mmol/l
  - American Stroke Association <16.6 mmol/l
- many units target serum glucose 4.0-7.0 mmol/l & should review their practice
- consider intervention if serum glucose >10 mmol/l & avoid hypoglycaemia

ESO Writing Committee, Cerebrovasc Dis 2008;25:457-507
Therapeutic hypothermia

• one of the most effective neuroprotective strategies in animals
  – most beneficial if applied early

• disappointing results from stroke studies
  – heterogeneity of study design
  – application in late neuroprotective period

• fever
  – present in >25% patients in first 28 hrs after AIS
  – associated with worse outcome
  – thorough evaluation of its source
  – prompt treatment
Decompressive surgery

- acute brain swelling
  - raised ICP
  - herniation

- surgery provides a treatment option
  - mortality reduction from 76 to 32%
  - 66% survivors had good outcome

Steiner et al, Neurology 2001; 57:S61-8

  - RCTs to determine balance between reduction in mortality vs. major disability in survivors

Study protocol

Hemicraniectomy after middle cerebral artery infarction with life-threatening Edema trial (HAMLET). Protocol for a randomised controlled trial of decompressive surgery in space-occupying hemispheric infarction

HAMLET investigators, Trials 2006: 7: 29-35
 Decompressive surgery

• acute brain swelling
  – raised ICP
  – herniation

• surgery provides a treatment option
  – mortality reduction from 76 to 32%
  – 66% survivors had good outcome

  Steiner et al, Neurology 2001; 57:S61-8

  – RCTs to determine balance between reduction in mortality vs.
    major disability in survivors

• posterior fossa stroke
  – potential for rapid decline and death
  – 80% mortality for comatose patients
  – 32% mortality after posterior fossa decompression
Early complications

• pneumonia
  – occurs in 12-24% stroke patients
  – longer ICU stay and worse outcome
  – 10% of early stroke mortality related to pneumonia

• cardiovascular disease
  – arrhythmias, myocardial ischaemia
  – sudden cardiovascular death in 6% stroke patients

• haemorrhagic transformation

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Risk of symptomatic haemorrhagic transformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>No thrombolytic therapy</td>
<td>0.6%</td>
</tr>
<tr>
<td>Intravenous r-PA</td>
<td>6.4%</td>
</tr>
<tr>
<td>Intraarterial rt-PA</td>
<td>10.0%</td>
</tr>
<tr>
<td>Intraarterial rt-PA &amp; clot disruption</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Summary

• improved outcomes
  – new therapies
  – early cerebral reperfusion
  – improved understanding of post-stroke complications

• ICU management
  – close monitoring
  – control of systemic physiological variables
  – optimisation of medical condition