Cerebrovascular disease and diabetes

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University of Glasgow
European City of Culture 1989

We get tanked up for a scrap on Buckie and Charlie, we've all got blades
Why discuss stroke?

- #1 cause of disability
- 20-30% of stroke patients die within a month
- #3 cause of death (12%)
- 130,000 per year in UK
- Approx £3 billion direct NHS costs annually
- *Almost as much as diabetes*...
- 7% NHS beds
- Reverse the historical perception of stroke…
Diabetes and the burden of stroke

- Effect on stroke risk
- Effect on stroke outcome
- Therapeutic considerations
Diabetes and stroke risk

- Diabetes accounts for 10% of population risk of stroke, and about half of the stroke risk in an individual.
- Diabetes *more than doubles* an individual’s risk of ischaemic stroke correcting for other factors.

157,315 participants

Lancet 2010;375:2215-2222
Diabetes and stroke risk

<table>
<thead>
<tr>
<th></th>
<th>Number of participants</th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>168,191</td>
<td>2,193</td>
<td>2.16 (1.84–2.52)</td>
<td>0.0089</td>
</tr>
<tr>
<td>Female</td>
<td>125,571</td>
<td>1,606</td>
<td>2.83 (2.35–3.40)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at survey</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–59 years</td>
<td>234,263</td>
<td>1,729</td>
<td>3.74 (3.06–4.58)</td>
<td>0.0001</td>
</tr>
<tr>
<td>60–69 years</td>
<td>38,140</td>
<td>1,134</td>
<td>2.06 (1.64–2.58)</td>
<td></td>
</tr>
<tr>
<td>≥70 years</td>
<td>21,359</td>
<td>936</td>
<td>1.80 (1.42–2.27)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottom third</td>
<td>110,044</td>
<td>1,149</td>
<td>1.90 (1.50–2.40)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Middle third</td>
<td>97,478</td>
<td>1,163</td>
<td>2.28 (1.85–2.80)</td>
<td></td>
</tr>
<tr>
<td>Top third</td>
<td>86,240</td>
<td>1,487</td>
<td>2.90 (2.49–3.37)</td>
<td></td>
</tr>
<tr>
<td><strong>Systolic blood</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottom third</td>
<td>113,199</td>
<td>711</td>
<td>3.06 (2.33–4.01)</td>
<td>0.7275</td>
</tr>
<tr>
<td>Middle third</td>
<td>106,966</td>
<td>1,217</td>
<td>2.79 (2.23–3.49)</td>
<td></td>
</tr>
<tr>
<td>Top third</td>
<td>73,597</td>
<td>1,871</td>
<td>2.49 (2.02–3.07)</td>
<td></td>
</tr>
</tbody>
</table>
Diabetes on stroke units

- 20% prevalence in acute cerebrovascular trials
- True prevalence probably approaches 30%
- *Suggestion* that small vessel stroke over-represented
- Longer average length of stay in almost all studies
Ambulatory status at discharge

![Bar graph showing the ambulatory status at discharge with categories 'Able', 'Assistance', and 'Unable'. The graph compares 'DM' and 'No DM' with different colors. The bars for 'Able' are the tallest, followed by 'Assistance', and then 'Unable'.](Stroke%202010%3A41%3Be409-e417)
Delayed stroke recovery

- **Scandinavian Score**

- **Day 0**
- **Day 1**
- **Day 7**
- **Day 14**

- **DM**

- **No DM**

<table>
<thead>
<tr>
<th>Day</th>
<th>DM</th>
<th>No DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>1</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>14</td>
<td>47</td>
<td>49</td>
</tr>
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</table>
10 year survival after stroke

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>Lower 95%</th>
<th>Upper 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>0.75</td>
<td>0.51</td>
<td>1.09</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>0.82</td>
<td>0.53</td>
<td>1.28</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>0.49</td>
<td>0.30</td>
<td>0.80</td>
</tr>
<tr>
<td>Other disabling diseases</td>
<td>0.59</td>
<td>0.37</td>
<td>0.92</td>
</tr>
<tr>
<td>Daily alcohol consumption</td>
<td>1.39</td>
<td>0.92</td>
<td>2.11</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.50</td>
<td>0.30</td>
<td>0.82</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>0.52</td>
<td>0.35</td>
<td>0.78</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.46</td>
<td>0.26</td>
<td>0.81</td>
</tr>
<tr>
<td>Stroke subtype</td>
<td>0.34</td>
<td>0.16</td>
<td>0.72</td>
</tr>
</tbody>
</table>
Diabetes and stroke

- Patients with diabetes are:
  - More likely to have a stroke
  - Less likely to do well afterwards

Why?
Mediators of endothelial damage in diabetes

- Hyperglycaemia
- Oxidative stress
- Protein kinase C activation
- Insulin resistance
- Advanced glycation end products
- Dyslipidaemia
  - Small, dense LDL
  - Low HDL
  - Hypertriglyceridaemia

Reduced NO bioavailability

Vascular dysfunction
Vascular dysfunction in diabetes

- Extensively studied in the forearm and other human vascular beds
- The cerebral vasculature behaves very differently...
- ...but it’s harder to study
Carotid blood flow after NOS inhibition

Blunted response to L-NMMA in diabetic subjects, suggesting reduced cerebral NO bioavailability.
Diabetes and stroke

- Patients with diabetes are:
  - More likely to have a stroke
  - Less likely to do well afterwards

- Pathophysiology complex and incompletely understood: chronic vascular dysfunction is likely to be an important factor

What are the practical therapeutic implications?
Treatment of stroke in the diabetic population

- Thrombolytic therapy
- Glycaemic control
- Blood pressure reduction
Thrombolysis

The proven acute pharmacological strategy for ischaemic stroke

Recipients at least 30% more likely to have little or no disability in RCTs
Meta-analysis of IV rt-PA trials

Difference/1000:
- 141 extra alive and independent survivors
- 130 fewer dependent survivors

(P<0.01)
NNT in context

- RCTs: relatively large treatment effect
- Compares favourably with:
  - Other stroke therapies
  - Established coronary interventions
Theoretical concern over lysis of diabetic / hyperglycaemic stroke patients

Admission hyperglycaemia is associated with poor outcome and increased risk for symptomatic intracerebral haemorrhage

Outcomes in diabetic tpa recipients are equivalent to untreated non-diabetic patients

Neurology 2011;77:1866–1872
Effect of thrombolysis: SITS and VISTA

<table>
<thead>
<tr>
<th>Patients’ group</th>
<th>Analyses type</th>
<th>OR (95%CI)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>No diabetes</td>
<td>Unadjusted</td>
<td>1.7 (1.6, 1.8)</td>
<td>23453</td>
</tr>
<tr>
<td></td>
<td>Age and baseline severity adjusted</td>
<td>1.6 (1.5, 1.7)</td>
<td>23246</td>
</tr>
<tr>
<td></td>
<td>Favorable outcome</td>
<td>1.9 (1.8, 2.1)</td>
<td>23246</td>
</tr>
<tr>
<td></td>
<td>Excellent outcome</td>
<td>1.6 (1.5, 1.7)</td>
<td>23246</td>
</tr>
<tr>
<td></td>
<td>Survival</td>
<td>1.2 (1.1, 1.3)</td>
<td>23246</td>
</tr>
<tr>
<td></td>
<td>All adjusted</td>
<td>1.6 (1.5, 1.8)</td>
<td>19621</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Unadjusted</td>
<td>1.3 (1.2, 1.4)</td>
<td>5411</td>
</tr>
<tr>
<td></td>
<td>Age and baseline severity adjusted</td>
<td>1.4 (1.3, 1.6)</td>
<td>5354</td>
</tr>
<tr>
<td></td>
<td>Favorable outcome</td>
<td>1.8 (1.5, 2.0)</td>
<td>5354</td>
</tr>
<tr>
<td></td>
<td>Excellent outcome</td>
<td>1.6 (1.4, 1.8)</td>
<td>5354</td>
</tr>
<tr>
<td></td>
<td>Survival</td>
<td>1.1 (0.9, 1.2)</td>
<td>5354</td>
</tr>
<tr>
<td></td>
<td>All adjusted</td>
<td>1.6 (1.3, 1.8)</td>
<td>4322</td>
</tr>
</tbody>
</table>
Thrombolytic therapy

- Magnitude of benefit comparable in patients with and without diabetes
- Aggressive acute provision of lytic therapy in patients with diabetes is warranted
A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

Olvert A. Berkhemer, M.D., Puck S.S. Fransen, M.D., Debbie Beumer, M.D., Lucie A. van den Berg, M.D., Hester F. Lingsma, Ph.D., Albert J. Yoo, M.D., Wouter J. Schonewille, M.D., Jan Albert Vos, M.D., Ph.D., Paul J. Nederkoorn, M.D., Ph.D., Marieke J.H. Wermer, M.D., Ph.D., Marianne A.A. van Walderveen, M.D., Ph.D., Julie Staals, M.D., Ph.D., et al., for the MR CLEAN Investigators*
Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

“Benefits are seen across a wide range of age and initial stroke severity, and apply to patients irrespective of eligibility of IV alteplase”
Treatment of hyperglycaemia

- Present in about 45% of acute stroke patients
- Arguably the most common and treatable abnormality
- Hyperglycaemia causes:
  - Increased substrate for anaerobic glycolysis
  - Increased cortical lactate concentration
  - And is associated with worse outcomes
Short term survival after stroke

BMJ. 1997 May 3; 314(7090): 1303-1306
Hyperglycaemia after stroke

- Intervention with insulin:
  - May reverse this
  - Neuromodulatory effect independent of glycaemia?
  - Seems to work when coronary arteries get blocked...
Glycaemic control post MI

Mortality

30 60

control insulin
Intervention in stroke with GKI – effect on glycaemia and BP

Lancet Neurology 2010;6:397-406
GIST trial

- **Underpowered**
  - 933 of a proposed 2355 patients recruited

- **Similar glycaemic profiles between groups**
  - Absolute reduction in glucose of 0.57 mmol/L induced by insulin infusion. (*cf* 2.1 mmol/L in DIGAMI)

- **Mild hyperglycaemia**
  - Small proportion with baseline blood sugar concentrations >10 mmol/L
In the absence of evidence...

- Guidelines vary:
  - **RCP**
    - “Maintain euglycaemia”
  - **EUSI**
    - “IV insulin if glucose > 10mmol/L”
  - **AHA**
    - “Insufficient evidence to guide management”
Blood pressure control: PROGRESS

- 6105 stroke survivors
- Any type of stroke
- ACEI + Diuretic vs placebo
- 4 year follow up
PROGRESS: overall results

Proportion with stroke

28% RRR

Placebo  Active
PROGRESS: effect on BP
BP reduction and outcomes

- Benefits at least as great in diabetic subgroup

- Subgroups:
  - Recurrent stroke
    - Diabetes
    - No diabetes
  - Any vascular event
    - Diabetes
    - No diabetes

![Graph showing hazard ratio with 95% CI for active and placebo better scenarios. The x-axis represents the hazard ratio ranging from 0.5 to 1.5, with categories for active better and placebo better.]
Blood pressure reduction

- Diuretic plus ACEI mainstay of preventative therapy post stroke for all patients
- Used even in those with “normal” blood pressure
- Benefit at least as great in diabetic population
- Consistent message from many other prevention trials
Summary

- Diabetic patients are very prone to cerebrovascular disease
- Stroke hits diabetic patients harder
- Current acute strategies limited:
  - Thrombolysis works
  - Tight glycaemic control of uncertain benefit
- Secondary prevention strategies:
  - BP lowering particularly effective