An Update on TIA and Minor Stroke

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Disclosures

Dr. Johnston is principal investigator for the POINT trial, sponsored by the NIH but with drug and placebo contributed by Sanofi-Aventis.

The Agenda

• PROGNOSIS
  – SCORES
  – IMAGING
• PATHOPHYSIOLOGY
• GUIDELINES AND PROVEN MANAGEMENT STRATEGIES
• AGGRESSIVE TREATMENT

PROGNOSIS
TIA: Short-Term Prognosis

- Many studies on prognosis, but the immediate period after TIA is often ignored
- California ED TIA Study
  - All Kaiser-Permanente enrollees (N=1,707) given a diagnosis of TIA in the emergency department
  - March 1997 – February 1998
  - Follow-up from record review for 3 months after presentation.

Johnston et al, JAMA 2000;284:2901

ABCD² Score

Score points for each of the following:
- Age ≥60 (1)
- Blood pressure >140/90 on initial evaluation (1)
- Clinical:
  • Focal weakness (2)
  • Speech impairment without weakness (1)
- Duration
  • ≥60 min (2)
  • 10-59 min (1)
- Diabetes (1)

Final Score 0-7


ABCD² Score and Stroke Risks

New Infarction and Stroke Risk

• New infarct on CT as a predictor of stroke:
  – 38% with new infarct had a stroke within 90 days vs. 10% without (p=0.008).
  – OR 4.1 after adjustment for clinical factors.
• New infarct on MRI also shown to be a predictor.
  – 5-fold increase in risk with new lesion on baseline MRI
  – Also, greater risk of in-hospital stroke in a second cohort.

VC Douglas et al. Stroke 2003; 34:2894
SB Coutts et al. Neurology 2005; 65:513
H Ay et al, Ann Neurol 2005; 57:679

Large-Artery Stenosis or Occlusion

• Large-vessel stenosis/occlusion associated with greater risk
  – OR 3.5 in Barcelona (similar for intra- and extra-cranial disease)
  – OR 7.9 in Calgary for intracranial occlusion
  – HR 3.4 in Paris for large artery atherosclerosis

Ois et al, Stroke 2008; 39:1717

Guidelines and Prognostic Scores

• AHA: It reasonable to hospitalize patients with ABCD² ≥3 presenting within 72 hours of symptoms, or with lower scores if workup cannot be done as an outpatient within 2 days or if there is other evidence for focused ischemia.

• NICE: Evaluation by specialist within 24 hours for scores ≥4.

Stroke Risk After TIA

<table>
<thead>
<tr>
<th>Year</th>
<th>N</th>
<th>Stroke Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnston, et al (Kaiser ED) 2000</td>
<td>1707</td>
<td>10.5%/90d</td>
</tr>
<tr>
<td>Eliasew, et al (NASCET) 2004</td>
<td>603</td>
<td>20.1%/90d</td>
</tr>
<tr>
<td>Lovett, et al (Oxfordshire) 2004</td>
<td>209</td>
<td>12%/30d</td>
</tr>
<tr>
<td>Gladstone, et al (Toronto) 2004</td>
<td>371</td>
<td>5%/30d</td>
</tr>
<tr>
<td>Daffertshofer, et al (Grmy) 2004</td>
<td>1150</td>
<td>13%/180d</td>
</tr>
<tr>
<td>Hill, et al (Alberta) 2004</td>
<td>2285</td>
<td>9.5%/90d</td>
</tr>
<tr>
<td>Lisabeth, et al (Texas) 2004</td>
<td>612</td>
<td>4.0%/90d</td>
</tr>
<tr>
<td>Kleindorfer, et al (Ginc) 2005</td>
<td>927</td>
<td>14.6%/90d</td>
</tr>
<tr>
<td>Whitehead, et al (Scotland) 2005</td>
<td>205</td>
<td>7%/30d</td>
</tr>
<tr>
<td>Correia, et al (Portugal) 2006</td>
<td>141</td>
<td>13%/7d</td>
</tr>
<tr>
<td>Tsivgoulis, et al (Greece) 2006</td>
<td>226</td>
<td>9.7%/30d</td>
</tr>
<tr>
<td>Purroy, et al (Spain) 2007</td>
<td>345</td>
<td>4.9%/7d</td>
</tr>
<tr>
<td>AVERAGE</td>
<td></td>
<td>~12% stroke risk in 90 days after TIA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5% in first 2 days</td>
</tr>
</tbody>
</table>
Stroke Risk After Stroke

IST 3.3%/3m  
CAST 1.6%/3m  
TOAST 5.7%/3m  
NASCET 2.3%/3m

AVERAGE ~4% stroke risk in 90 days after stroke

PATHOPHYSIOLOGY

Pathophysiology

• Short-term risk of stroke:
  – After TIA (12%) > after stroke (4%)
• Possible explanation
  – Tissue still at risk: unstable situation
    • More thrombo-embolic events
    • Events more apparent

Johnston, NEJM 2002; 347:1687

Possible Explanation: Instability
The Case for Urgency

- Events can only be prevented if you act before they occur.
- Urgency in:
  - Evaluation
  - Initiation of proven therapies
  - Initiation of aggressive treatment
  - Hospitalization

Guideline Recommendations: Evaluation

- Urgent evaluation: usually emergency department.
- ECG.
- Routine labs.
- Head imaging (CT or MRI)
- Carotid imaging.
- Observation for high risk patients.
Carotid Artery Atherosclerosis

- Accounts for about 11% of TIAs.
- Short-term stroke risk appears to be greater
  - 20% at 90-days in one study

Importance of Timing

- Absolute risk reduction at 5 y for stroke or operative death:
  - >50%, < 2 weeks: 20%
  - >50%, >=2 weeks: 0.8%

- NSA Guidelines: Endarterectomy recommended as soon as possible (preferably within 2 weeks) for those with symptomatic 70-99% stenosis and for those with 50-69% who can be treated with <6% risk of perioperative stroke or death.

Guideline Recommendations: Treatment

- Start an antiplatelet agent immediately
  - Aspirin, clopidogrel, aspirin-dipyridamole all acceptable alternatives.
  - OR anticoagulation for atrial fibrillation.
- Start a statin.
- Start an antihypertensive agent.
- Treat diabetes if present.
- Treat carotid disease as soon as possible.
Rationale of Two Large-Scale Trials: CHANCE & POINT

- Treat TIA as an acute condition
  - Begin treatment rapidly (within 12-24 hours)

- Choose an agent that is likely to be effective regardless of underlying cause
  - Clopidogrel, on background of aspirin

CHANCE Trial

- Randomized, double-blind, placebo controlled trial of acute TIA or minor ischemic stroke
  - Clopidogrel (300 load then 75/day) vs. placebo
  - Background aspirin at dose 75/day

- Inclusion criteria:
  - TIA (classic def) <24 hours, ABCD²≥4
  - OR, minor ischemic stroke with NIHSS≤3

- Outcome: 90-day stroke rate
- 5170 patients at 114 centers in China

CHANCE Primary Outcome: Stroke

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Aspirin (N=2586)</th>
<th>Clopidogrel-Aspirin (N=2584)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event No.</td>
<td>Event Risk</td>
<td>Event No.</td>
<td>Event Risk</td>
</tr>
<tr>
<td>Any Bleeding</td>
<td>41</td>
<td>1.6%</td>
<td>60</td>
</tr>
<tr>
<td>Severe Bleeding</td>
<td>4</td>
<td>0.2%</td>
<td>4</td>
</tr>
<tr>
<td>Moderate Bleeding</td>
<td>4</td>
<td>0.2%</td>
<td>3</td>
</tr>
<tr>
<td>Mild Bleeding</td>
<td>19</td>
<td>0.7%</td>
<td>30</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>10</td>
<td>0.4%</td>
<td>10</td>
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POINT Trial

- Similar trial in the US and several other countries.
- Sponsored by US NIH.
- DSMB met in early May and says continue now.
- Anticipated completion 2016.

Conclusions

- TIAs and minor ischemic strokes are ominous
  - Justifies acute interventions, including hospitalization
  - Opportunity to prevent injury but trials are needed
- Scores may help with prognostician but they are far from perfect
- Secondary prevention is key
  - Carotids should be treated right away
  - Proven treatments should be started immediately
- CHANCE is suggestive but needs confirmation