Centrally-acting ACE inhibitors

George Heckman
HYVET-Cog Meta-analysis
Peters et al Lancet Neurology 2008

<table>
<thead>
<tr>
<th>Study</th>
<th>Active (N/n)</th>
<th>Placebo (N/n)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROGRESS RR</td>
<td>3051/193</td>
<td>3054/217</td>
<td>0.89 (0.74-1.07)</td>
</tr>
<tr>
<td>Syst-Eur RR</td>
<td>1238/11</td>
<td>1180/21</td>
<td>0.50 (0.25-1.02)</td>
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<tr>
<td>SHEP RR</td>
<td>2365/37</td>
<td>2371/44</td>
<td>0.84 (0.55-1.30)</td>
</tr>
<tr>
<td>HYVET RR</td>
<td>1687/126</td>
<td>1649/137</td>
<td>0.90 (0.71-1.13)</td>
</tr>
<tr>
<td>Combined (random)</td>
<td></td>
<td></td>
<td>0.87 (0.76-1.00)</td>
</tr>
</tbody>
</table>

Cochran Q=2.409; p=0.491
Test for overall effect; p=0.045
More than just BP?
Savaskan et al Neurobiol Aging 2001; Wright at al Neurosci Biobehav Rev 2002

- Case control post-mortem study
- 9 AD and 9 non-AD
- Parietal cortex; RAAS stains
- Angiotensin II inhibits Acetylcholine release, increase vascular tone, smooth muscle hypertrophy, hyperplasia
- RAAS activation may impair neural plasticity and memory consolidation
6 year cohort study of 1054 older adults treated for HTN, 414 on ACE inhibitors [centrally active: captopril, fosinopril, lisinopril, perindopril, ramipril, trandolapril; non-centrally active: enalapril, quinapril, benzapril, moexipril]

- Measured incident cases of dementia, 3MSE scores and IADL disability
  - ACE inhibitors as a class vs other anti-HTN classes not associated with reduction in the risk of dementia (158 cases)
  - Centrally active ACE inhibitors → 65% reduction in cognitive decline
  - Non-centrally active ACE inhibitors → 73% greater risk of incident dementia and 56% greater risk of IADL disability compared to other HTN-drugs

"the direction of results for all outcomes favored ACE inhibitors that cross the blood-brain barrier."
RCT evidence
Ohru et al Neurology 2004

- 162 pts with mild-mod AD, MMSE 13-23, no stroke or diabetes, MRIs clear of stroke, no HF, psychiatric dx
- BP > 140/90
  - Group 1: 51 to brain penetrating ACEi (perindopril 2 mg/day or captopril 37.5 mg/day), mean age 76±2
  - Group 2: 53 to non brain-penetrating ACE inhibitor (enalapril 5 mg/day or imidapril 5 mg/day), mean age 77±3
  - Group 3: n=58, calcium-channel blocker (nifedipine 20 mg/day or nilvadipine 4 mg/day), mean age 75±2
RCT

- No difference in baseline characteristics or ultimate BP control or MMSE
- F/u 1 year
- Mean 1-year decline in MMSE scores
  - Group 1 = 0.6±0.1
  - Group 2 = 4.6±0.3 (p=0.0023)
  - Group 3 = 4.9±0.3 (p<0.001)
Perindopril and physical function
Sumakudas et al CMAJ 2007

Fig. 3. Change in 6-min walking distance in perindopril and placebo groups from baseline to 10 wk and 20 wk. (From Sumukadas D, Witham MD, Struthers AD, McMurdoo ME. Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. CMAJ 2007;177(8):867–74; with permission.)
Conclusion

- Pretty darn interesting...

- Brain penetrating ACEi
  - Perindopril
  - Ramipril
  - Captopril
  - Fosinopril
  - Lisinopril
  - Trandolapril