Can Anti-hypertension Therapy Reverse Vascular Aging and Dementia?

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The Pulse : revived in Asia.
(www.pulseasia.org)

1st the Pulse of Asia, April 17-18th 2009, in Daegu, Korea
Contents:

- Hypertension and vascular aging
- Vascular changes of brain in hypertension
- Hypertension and dementia
- Does Anti-hypertension therapy reverse those changes?
  - Effects of RAS blockade on vascular aging
  - Effect of BP reduction on brain damage and dementia
"Most cardiovascular disease risk factors result in progressive changes in blood vessels, including those of the brain..."
**Arterial changes in Hypertension**

**Normotension**
- Hemodynamic: pressure, flow, cyclic stress
- Structure

**Hypertension**
- Hemodynamic: pressure, flow, cyclic stress
- Structure
  - Extra/intracellular stimuli: Ang II, ET-1, NO^−, O_2^− ...
  - ECM deposition: Collagen↑, Elastin X
  - Large: Hypertrophic remodeling
  - Small: Eutrophic remodeling
  - Endothelial dysfunction
  - Altered vascular mechanics

Park JB and Schiffrin EL. Curr Hypertens Reports 2000
Resistance Artery Study in Human

Gluteal subcutaneous biopsy

Subcutaneous fat

Peripheral resistance artery (150 ~ 350 µm)

Small artery studies (isobaric)

Structure; media to lumen ratio

Function; ach and nitroprusside

Mechanics
- Intraluminal pressure = 3 - 140 mmHg
- Lumen and media measurements

Park JB 1999
Small artery remodeling is the most prevalent (earliest?) form of target organ damage in mild essential hypertension.

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance Artery</td>
<td>63 - 97</td>
</tr>
<tr>
<td>Vascular Remodeling</td>
<td>34 - 58</td>
</tr>
<tr>
<td>- Media/Lumen ratio</td>
<td>No change</td>
</tr>
<tr>
<td>Endothelial Function</td>
<td></td>
</tr>
<tr>
<td>- Ach response</td>
<td></td>
</tr>
<tr>
<td>Vascular Stiffness</td>
<td>26 - 34</td>
</tr>
<tr>
<td>- $E_{inc}$ vs stress</td>
<td></td>
</tr>
<tr>
<td>LV Mass</td>
<td></td>
</tr>
<tr>
<td>ECG/ECHO</td>
<td></td>
</tr>
</tbody>
</table>

Park JB, Schiffrin EL. *J Hypertens* 2001;19:921
Event-free survival in patients with hypertension or diabetes and with a media–lumen (M/L) ratio of small arteries and incidence of CV events.

Central SBP
vascular endothelial damage & mechanical fatigue
atherosclerosis
aortic stiffness & arteriosclerosis
↑ central wave reflection
↑ PP
↑ Central SBP

Large artery, Central Artery Changes

arteriosclerosis
stiffened

stroke
renal failure
IHD…
Park JB 2008
Large/small artery cross-talk

**Target organ damage**
- Myocardial ischemia
- Reduction in GFR
- Microalbuminuria
- White matter lesions

**Small artery remodeling**
- Wall/lumen ratio and rarefaction

**Target organ damage**
- LVH
- Carotid IMT
- Plaque rupture

**Central PP**

**Mean BP**

**Arterial stiffness**

**Large artery remodeling**
Determinants of Arterial Pressure and its Reversal in Hypertension: Pulse and flow

- SBP (PP)
- LV function
- Central artery stiffness
- Endothelial dysfunction
- Pulse wave reflection
- Peripheral Resistance
- Veins Stroke Volume
- D(or M)BP

Park JB 2009
Difference of CVD prediction between systolic and diastolic BP as a function of age

\[ \beta_{(SBP)} - \beta_{(DBP)} \]

Age (year) 25 35 45 55 65 75

2003 JNC VII

Park JB 2006
Disparity of drug on vascular changes will result in different outcome in CVD and stroke?
BP reduction reduces CV risk

1-Year Treatment Effects of Losartan and Atenolol on Small Artery Structure and Function in Hypertension

**Structure**

- Media/Lumen ratio (%)

**Endothelium-dependent relaxation**

- Maximal Acetylcholine Response (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Before</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>8.5</td>
<td>9.1</td>
</tr>
<tr>
<td>Atenolol</td>
<td>8.0</td>
<td>8.5</td>
</tr>
</tbody>
</table>

*Significant difference

Schiffrin and Park..Circulation 2000
Differential Effects of Antihypertensive Therapy on Small Artery in Hypertension: 1-Year F/U

<table>
<thead>
<tr>
<th>Normotension</th>
<th>Hypertension</th>
<th>ACEi/ARB CCB</th>
<th>Atenolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humoral factor</td>
<td>Blood Pressure</td>
<td>≈</td>
<td>↓</td>
</tr>
<tr>
<td>Tensile stress</td>
<td>Vascular Remodeling</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Cyclic stress</td>
<td>media/lumen ratio</td>
<td>←</td>
<td>←</td>
</tr>
<tr>
<td></td>
<td>Endothelial Dysfunction</td>
<td>↑</td>
<td>←</td>
</tr>
<tr>
<td></td>
<td>Ach response</td>
<td>↓</td>
<td>←</td>
</tr>
<tr>
<td></td>
<td>Vascular Stiffness</td>
<td>↓</td>
<td>←</td>
</tr>
<tr>
<td></td>
<td>stress/strain</td>
<td>↓</td>
<td>←</td>
</tr>
</tbody>
</table>

Park JB and Schiffrin EL et al. Circulation, Hypertension, J Hypertens, Am J Hypertens, Curr Hypertens Reports, J Renin Angiotens System....
**Pharmacological treatment associated with a reduction in arterial stiffness**

<table>
<thead>
<tr>
<th>Antihypertensive treatment</th>
<th>ACE inhibitors/AT1 blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aldosterone blockers</td>
</tr>
<tr>
<td></td>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
</tr>
<tr>
<td></td>
<td>β-Blockers</td>
</tr>
<tr>
<td>Treatment of congestive heart failure</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td></td>
<td>Nitrates</td>
</tr>
<tr>
<td>NO donors</td>
<td>Nitrates</td>
</tr>
<tr>
<td></td>
<td>Sinitrotil</td>
</tr>
<tr>
<td>Phosphodiesterase type-5 inhibitors</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>Hypolipidemic agents</td>
<td>Statins</td>
</tr>
<tr>
<td></td>
<td>Ezetimibe</td>
</tr>
<tr>
<td>Anti-inflammatory drugs</td>
<td>TNFα antagonists</td>
</tr>
<tr>
<td>Antidiabetic agents</td>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>AGE breakers</td>
<td>Alagebrium (ALT-711)</td>
</tr>
</tbody>
</table>
Effect of the 4 main classes of antihypertensive drug on aortic (A) and brachial (B) pressure.

## Comparative effect of drugs on central hemodynamic indices

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Aortic pulse wave velocity</th>
<th>Augmentation index</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>▼</td>
<td>▼ ▼</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>▼</td>
<td>▼ ▼</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>▼ ▼ ▼</td>
<td>↑</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>▼</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>↔</td>
<td>▼</td>
</tr>
<tr>
<td>Nitrates</td>
<td>↔</td>
<td>▼ ▼ ▼</td>
</tr>
<tr>
<td>PD5 inhibitors</td>
<td>▼</td>
<td>▼ ▼ ▼</td>
</tr>
</tbody>
</table>
CAFE: Lower central aortic BP with newer vs older antihypertensive regimen despite similar brachial BP

The ACEi ramipril reduces CV mortality and morbidity in CV high-risk patients

**HOPE**: CV high-risk patients; mean baseline SBP/DBP 139/79 mmHg

- **Composite CV endpoint†**: -22% p<0.001
- **Death from CV causes**: -26% p<0.001
- **MI**: -20% p<0.001
- **Stroke**: -32% p<0.001

Ramipril, n = 4,645
Placebo, n = 4,652

† Composite CV endpoint = death from CV causes + MI + stroke
HOPE = Heart Outcomes Prevention Evaluation

Primary Composite Endpoint

Composite of CV death, stroke and MI

Proportion of patients with first event (%)

Losartan

Atenolol

Adjusted Risk Reduction 13.0%, p=0.021
Unadjusted Risk Reduction 14.6%, p=0.009

ASCOT: Fatal & Nonfatal Stroke

Amlodipine ± perindopril
Amlodipine ± ACEI
Atenolol ± thiazide
Atenolol ± thiazide

HR = 0.77 (0.660.89)
p = 0.0003

A, B, C, and D drug in hypertension therapy
Vascular and Tissue Dysfunction in Hypertension

Vascular Dysfunction
- Endothelial Dysfunction
- Remodeling/Hypertrophy
- Fibrosis
- Atherosclerosis

Tissue Dysfunction
- Cell loss
- Fibrosis
- Remodeling
- Ischemia

Hypertension

Genetics,
Risk factors (diabetes, hypercholesterolemia)
Environment (diet, smoking, stress)

ACEi, ARB, CCB…

Stroke
Hypertension
Heart failure
MI
Renal failure

Atherosclerosis*
Vasoconstriction
Vascular hypertrophy
Endothelial dysfunction
LVH
Fibrosis
Remodeling
GFR
Proteinuria
Aldosterone release
Glomerular sclerosis
BP reduction reduces brain damage. But how about on dementia?
Hypertension aggravates dementia

Age & Hypertension

Small vessel disease

Aβ accumulation
Neurofibrillary tangles

Cerebral blood flow ↓

Cholinergic neurotransmission ↓

White matter lesions
Cortical disconnection

Neuronal death
Brain atrophy

Vascular dementia
Alzheimer’s disease
Association of hypertension with prevalence of vascular dementia.

Association of hypertension with incidence of vascular dementia

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Vascular Dementia (n/N)</th>
<th>Control (n/N)</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katzman, et al. 1989</td>
<td>5/15</td>
<td>183/350</td>
<td>7.08 [0.46, 1.36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hérbert, et al. 2000</td>
<td>47/105</td>
<td>270/802</td>
<td>24.38 [1.60, 2.41]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reitz, et al. 2004</td>
<td>31/54</td>
<td>400/856</td>
<td>14.27 [1.54, 2.68]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiang, et al. 2007</td>
<td>15/63</td>
<td>37/249</td>
<td>8.04 [1.79, 3.52]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI)
Total events: 206 (Vascular dementia), 3455 (Control)

Test for heterogeneity: Chi² = 7.98, df = 5 (P = 0.16), I² = 37.4%
Test for overall effect: Z = 4.40 (P < 0.0001)

BP reduction and stroke

Law, BMJ 2009

BP reduction reduces almost 40% of stroke incidence.

Law, BMJ 2009
BP reduction and dementia

Incidence of Dementia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Active treatment</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>HYVET 2008</td>
<td>126</td>
<td>1687</td>
<td>137</td>
<td>1649</td>
</tr>
<tr>
<td>SCOPE 2003</td>
<td>62</td>
<td>2477</td>
<td>57</td>
<td>2460</td>
</tr>
<tr>
<td>SHEP 1991</td>
<td>37</td>
<td>2365</td>
<td>44</td>
<td>2371</td>
</tr>
<tr>
<td>Syst Eur 1997</td>
<td>11</td>
<td>1238</td>
<td>21</td>
<td>1180</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>7767</td>
<td>7660</td>
<td>100.0%</td>
<td>0.89 [0.74, 1.07]</td>
</tr>
</tbody>
</table>

- Total events: 236 events in active treatment and 259 in placebo
- Heterogeneity: Chi² = 3.63, df = 3 (P = 0.30); I² = 17%
- Test for overall effect: Z = 1.25 (P = 0.21)

Cognitive changes from baseline, outcome (MMSE)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Active treatment Mean</th>
<th>SD</th>
<th>Total</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
<th>Mean Difference IV, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYVET 2008</td>
<td>0.7</td>
<td>4</td>
<td>1687</td>
<td>-1.1</td>
<td>3.9</td>
<td>1649</td>
<td>18.9% 1.80 [1.53, 2.07]</td>
<td></td>
</tr>
<tr>
<td>SCOPE 2003</td>
<td>-0.49</td>
<td>4.07</td>
<td>2477</td>
<td>-0.64</td>
<td>4.07</td>
<td>2409</td>
<td>26.1% 0.15 [-0.08, 0.38]</td>
<td></td>
</tr>
<tr>
<td>Syst Eur 1997</td>
<td>0.08</td>
<td>1.76</td>
<td>1238</td>
<td>0.01</td>
<td>2.15</td>
<td>1180</td>
<td>55.1% 0.07 [-0.09, 0.23]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>5402</td>
<td></td>
<td>5238</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.42 [0.30, 0.53]</td>
<td></td>
</tr>
</tbody>
</table>

- Heterogeneity: Chi² = 126.25, df = 2 (P < 0.00001); I² = 98%
- Test for overall effect: Z = 7.03 (P < 0.00001)

⇒ anti-HTN medication failed to show overall benefit over placebo in new dementia and worsening cognition
Mixed results on anti-hypertension drug on dementia & cognition

- Diuretics and β-B were neutral in developing cognitive impairment in SHEP (1991, 1994) and MRC Older (1996, 1997).

- Antihypertensive therapy might even reverse hypertension-related cognitive impairment (Starr et al., 1996).

- BP lowering in patients without prior cerebrovascular disease did not prevent cognitive impairment or dementia (2004).

- CCBs and ARBs have shown more positive outcomes, (Syst-Eur, 1998 and SCOPE, 2003) along with preliminary data from OSCAR study (2007).

- Meta-analysis of 3 trials suggests a significant benefit with respect to cognition (2008).

- Use of antihypertensive drugs in a longitudinal study was associated with an 8% reduced risk per year for dementia and AD for people <75 years of age (2009).
Effects of RAS blockage on cognition and dementia in Hypertension?
Survival function for incident Alzheimer’s disease and incident dementia in prospective study cohorts

Population: 819,491 predominantly male (98%) aged 65 or more with cardiovascular disease.

Nien-Chen Li et al.
BMJ 2010;340:b5465
Cox proportional hazard model for association between ARBs and incidence of Alzheimer’s disease or dementia

<table>
<thead>
<tr>
<th>Variables</th>
<th>Incidence of Alzheimer’s disease</th>
<th>Incidence of dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate (SE)</td>
<td>P value</td>
</tr>
<tr>
<td>Angiotensin receptor blocker v lisinopril</td>
<td>-0.213 (0.089)</td>
<td>0.016</td>
</tr>
<tr>
<td>Angiotensin receptor blocker v cardiovascular comparator</td>
<td>-0.171 (0.085)</td>
<td>0.045</td>
</tr>
<tr>
<td>Lisinopril v cardiovascular comparator</td>
<td>0.043 (0.029)</td>
<td>0.145</td>
</tr>
<tr>
<td>Age</td>
<td>0.101 (0.001)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>-0.011 (0.017)</td>
<td>0.505</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.039 (0.020)</td>
<td>0.049</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.694 (0.018)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for age, stroke, cardiovascular disease, and diabetes.

BMJ 2010;340:b5465
Effect of ARB dosage (high v low) on incidence of dementia

<table>
<thead>
<tr>
<th>Angiotensin receptor blocker</th>
<th>Estimate (SE)</th>
<th>P value</th>
<th>Hazard rate* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>-0.322 (0.076)</td>
<td>&lt;0.001</td>
<td>0.73 (0.62 to 0.84)</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>-0.174 (0.044)</td>
<td>&lt;0.001</td>
<td>0.84 (0.77 to 0.92)</td>
</tr>
<tr>
<td>Losartan</td>
<td>-0.200 (0.066)</td>
<td>0.0025</td>
<td>0.82 (0.72 to 0.93)</td>
</tr>
<tr>
<td>Valsartan</td>
<td>-0.103 (0.198)</td>
<td>0.602</td>
<td>0.91 (0.61 to 1.33)</td>
</tr>
</tbody>
</table>

*Cox proportional hazard model adjusted for age, cardiovascular disease, diabetes, and stroke.

BMJ 2010;340:b5465
Additive effects of ARB and ACE inhibitors compared with single drug use. Hazard rates are adjusted for age, stroke, diabetes, and cardiovascular disease.

BMJ 2010;340:b5465
Major Studies in RAS-Inhibition
(HOPE Composite) Global Protection

Proportion of Patients

Days of follow-up

Telmisartan/Ramipril
Telmisartan
Ramipril
Placebo

HOPE
ONTARGET
TRANSCEND
<table>
<thead>
<tr>
<th></th>
<th>Telmisartan</th>
<th>Placebo</th>
<th>Telmisartan vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>OR (95% CI) p value</td>
</tr>
<tr>
<td>Number randomised</td>
<td>2954</td>
<td>2972</td>
<td>••</td>
</tr>
<tr>
<td>Number with MMSE</td>
<td>2642</td>
<td>2589</td>
<td>••</td>
</tr>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive impairment*</td>
<td>239/2694 (9%)</td>
<td>245/2689 (9%)</td>
<td>0·97 (0·81–1·17)</td>
</tr>
<tr>
<td>Cognitive decline†</td>
<td>454/2642 (17%)</td>
<td>412/2589 (16%)</td>
<td>1·10 (0·95–1·27)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive decline or impairment‡</td>
<td>520/2914 (18%)</td>
<td>487/2909 (17%)</td>
<td>1·08 (0·94–1·24)</td>
</tr>
<tr>
<td>Cognitive impairment or stroke</td>
<td>318/2694 (12%)</td>
<td>330/2689 (12%)</td>
<td>0·96 (0·81–1·13)</td>
</tr>
<tr>
<td>Cognitive impairment, MMSE score &lt;18§</td>
<td>127/2917 (4%)</td>
<td>111/2932 (4%)</td>
<td>1·16 (0·89–1·50)</td>
</tr>
</tbody>
</table>

Lancet Neurol 2011; 10: 43–53
Effects of BP lowering on cognitive impairment

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Control</th>
<th>Relative risk, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive impairment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADVANCE</td>
<td>39</td>
<td>37</td>
<td>1.05 (0.67–1.65)</td>
</tr>
<tr>
<td>HYVET-COG</td>
<td>126</td>
<td>137</td>
<td>0.90 (0.71–1.13)</td>
</tr>
<tr>
<td>PROGRESS</td>
<td>193</td>
<td>217</td>
<td>0.89 (0.74–1.07)</td>
</tr>
<tr>
<td>PROFESS</td>
<td>1178</td>
<td>1162</td>
<td>1.01 (0.94–1.09)</td>
</tr>
<tr>
<td>SCOPE</td>
<td>62</td>
<td>57</td>
<td>1.08 (0.76–1.54)</td>
</tr>
<tr>
<td>SHEP</td>
<td>37</td>
<td>44</td>
<td>0.84 (0.55–1.30)</td>
</tr>
<tr>
<td>Syst-Eur</td>
<td>11</td>
<td>21</td>
<td>0.50 (0.24–1.03)</td>
</tr>
<tr>
<td>TRANSCEND</td>
<td>239</td>
<td>245</td>
<td>0.97 (0.82–1.15)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td>0.98 (0.92–1.04)</td>
</tr>
</tbody>
</table>

Test for homogeneity: $\chi^2=6.44; \text{df}=7$ (p=0.49)

Test for overall effect: Z=0.63 (p=0.53)

Head to head

ONTARGET (ARB vs ACEI)* | 584 | 7897 | 326 | 3933 | 0.90 (0.79–1.03) |

ONTARGET (ARB+ACEI vs ACEI)* | 618 | 7807 | 326 | 3933 | 0.96 (0.84–1.09) |

Total | 3087 | 42424 | 2572 | 34566 | 0.97 (0.92–1.01) |

Test for homogeneity: $\chi^2=7.73; \text{df}=9$ (p=0.56)

Test for overall effect: Z=1.39 (p=0.17)

Lancet Neurol 2011; 10: 43–53
Effects of BP lowering on cognitive decline

<table>
<thead>
<tr>
<th>Cognitive decline</th>
<th>Active Event</th>
<th>Active n</th>
<th>Control Event</th>
<th>Control n</th>
<th>Relative risk, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active vs placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADVANCE</td>
<td>633</td>
<td>5569</td>
<td>640</td>
<td>5571</td>
<td>0.99 (0.89–1.10)</td>
</tr>
<tr>
<td>HYVET-COG</td>
<td>485</td>
<td>1687</td>
<td>486</td>
<td>1649</td>
<td>0.98 (0.88–1.08)</td>
</tr>
<tr>
<td>PROGRESS</td>
<td>276</td>
<td>3051</td>
<td>334</td>
<td>3054</td>
<td>0.83 (0.71–0.96)</td>
</tr>
<tr>
<td>PRoFESS</td>
<td>795</td>
<td>7739</td>
<td>832</td>
<td>7518</td>
<td>0.95 (0.87–1.05)</td>
</tr>
<tr>
<td>SCOPE</td>
<td>113</td>
<td>2477</td>
<td>125</td>
<td>2409</td>
<td>0.90 (0.70–1.16)</td>
</tr>
<tr>
<td>TRANSCEND</td>
<td>454</td>
<td>2694</td>
<td>412</td>
<td>2589</td>
<td>1.08 (0.96–1.22)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>2276</td>
<td>26820</td>
<td>2829</td>
<td>22790</td>
<td>0.97 (0.91–1.03)</td>
</tr>
</tbody>
</table>

Test for homogeneity: $\chi^2=7.85; \text{df}=5 (p=0.17)$

Test for overall effect: $Z=1.10 (p=0.27)$

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Head to head

<table>
<thead>
<tr>
<th>Head to head</th>
<th>Active Event</th>
<th>Active n</th>
<th>Control Event</th>
<th>Control n</th>
<th>Relative risk, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONTARGET (ARB vs ACEI)*</td>
<td>1279</td>
<td>7566</td>
<td>657</td>
<td>3801</td>
<td>0.98 (0.90–1.07)</td>
</tr>
<tr>
<td>ONTARGET (ARB+ACEI vs ACEI)*</td>
<td>1240</td>
<td>7461</td>
<td>657</td>
<td>3801</td>
<td>0.96 (0.88–1.05)</td>
</tr>
<tr>
<td>Total</td>
<td>5275</td>
<td>37923</td>
<td>4143</td>
<td>30392</td>
<td>0.97 (0.93–1.01)</td>
</tr>
</tbody>
</table>

Test for homogeneity: $\chi^2=7.73; \text{df}=9 (p=0.56)$

Test for overall effect: $Z=1.39 (p=0.17)$

---

Lancet Neurol 2011; 10: 43–53
Association of reduction in SBP with risk reduction for cognitive impairment

Reduction in risk for each 5 mm Hg reduction
3.4% (95% CI –6.6 to 10.9), p=0.40

HYVET-COG
PROGRESS
ADVANCE
PRoFESS
ONTARGET (ARB vs ACEI)
ONTARGET (ARB+ACEI vs ACEI)
SCOPE
TRANSCEND

Lancet Neurol 2011; 10: 43–53
Association of reduction in SBP with risk reduction for cognitive decline

Reduction in risk for each 5 mm Hg reduction 1.0% (95% CI -3.4 to 5.2), p=0.66

HYVET-COG
ADVANCE
TRANSCEND
SCOPE
PROFESS
ONTARGET (ARB vs ACEI)
ONTARGET (ARB+ACEI vs ACEI)

Difference in reduction in SBP (mm Hg)

Relative risk (95% CI)

Lancet Neurol 2011; 10: 43–53
Summary I: Brain and hypertension

- Hypertension is vascular damages in brain.
  - Atherosclerosis, in middle-sized arteries (ICA, MCA...)
  - Arteriolosclerosis, small arterioles (LS aa, perforating aa)

- Small-vessel disease in hypertension
  - Leukoaraiosis
  - Lacunar infarction
  - Cerebral microbleeds

- Cognitive decline in elderly
  - worsening under hypertension
Summary II: Brain and hypertension

- BP reduction is not a skeleton key for the reduction of cognitive impairment and dementia, even though hypertension treatment decrease stroke and CVD incidence.
  - No overall benefit of dementia incidence by hypertension treatment
  - Suggestive of worsening cognitive deficit by BP lowering?
- RAS blockade, esp. ARB may be better?
Mechanisms of the potential superior effects of ARBs on cognition

- Restoring proper central endothelial function,
- Decreasing inflammation,
- Preventing neuronal degeneration through the selective non-inhibition of the type 2 angiotensin receptors in the brain.

Dr. Hajjar et al. *Arch Intern Med.* 2012;172:442-444
In conclusion,

some anti-hypertension therapies reverse vascular aging,

but still not significantly dementia.
The 26th International Society of Hypertension Biennial Scientific Meeting 2016

September 24(Sat) – 29(Thu), 2016
COEX, Seoul, Korea

Please be safe from
- Earthquake
- Tsunami
- Tornado
- Flood
- ...
- Hypertension
- Dementia
Thank you!