Design of the SARTAN-AD Trial: A Randomized, Open Label, Proof of Concept Study of Telmisartan vs. Perindopril in Hypertensive Mild-Moderate Alzheimer's Disease Patients

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RATIONALE

Alzheimer's Disease (AD) and Hypertension (HTN)

- HTN prevalence is 63% in Canada at age 74 (average age AD patients present to memory clinics)[1]
- HTN is a significant risk factor for AD[2] and is associated with reduced cortical thickness in areas vulnerable to AD in normal elders on Magnetic Resonance Imaging (MRI)[3]
- In the Syst-Eur Study, treating HTN prevented decline to dementia over 4 years[4,5] but other antihypertensive studies, including comparisons of Angiotensin Converting Enzyme inhibitors (ACEIs) and Angiotensin Receptor Blockers (sartans), have been equivocal[6-10], often due to insufficient sample sizes

Repurposing Drugs

- Only 5 drugs have been approved for symptomatic treatment of AD (last one in 2003)
- All attempts to develop a disease-modifying treatment have been unsuccessful, and there are few new drugs in the pipeline considering the magnitude of the problem[11]
- Successfully repurposing existing drugs could save up to 10 years in drug development

ACEIs vs. Sartans

- Centrally-penetrating ACEIs stimulate cholinergic function[12,13] and have been linked to functional[14] and cognitive[8,15] benefits to AD patients, but since ACE catabolizes amyloid-beta (Aß) 40-42, ACE inhibitors may accelerate amyloid deposition in AD[16]
- Centrally-penetrating sartans increase insulin degrading enzyme, which increases Aß breakdown[17]; they facilitate long-term potentiation and memory[18] and may have other neuroprotective effects (telmisartan through the activation of PPAR-gamma[19,20])
- Treatment with sartans versus other antihypertensive drug classes was associated with reduced emergent dementia in a veteran population[21] and, in an autopsy series, resulted in less premorbid cognitive decline and less AD pathology[22]
- A head-to-head trial of a centrally-acting ACEI vs. a centrally-acting sartan is warranted to determine comparative efficacy in slowing progression of AD

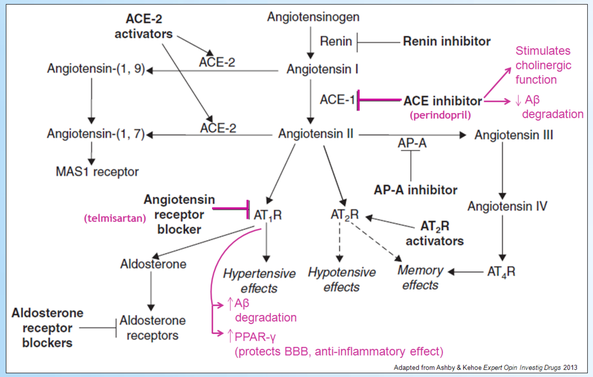

Figure 1. Renin Angiotensin System pharmacological actions, including on the amyloid cascade

PRIMARY OBJECTIVE

- To compare efficacy and safety of perindopril vs. telmisartan in reducing progression of brain atrophy, indexed by ventricular volume change[23] on 3 Tesla MRI, at 12 months in patients with comorbid mild-moderate AD and hypertension

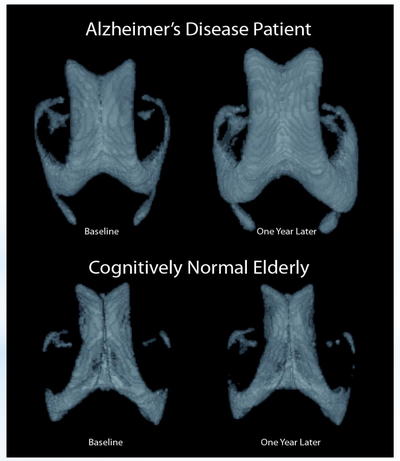

Figure 2. Ventricular expansion over one year
Top view of 3D surface renderings of ventricles from an AD patient (top) and NC subject (bottom), obtained at baseline (left) and 1 year (right). Volumetrics obtained using Lesion Explorer MRI processing pipeline[24].

(Courtesy of Dr. J. Ramirez, Sunnybrook HSC)

STUDY INTERVENTION

- **Perindopril** 2-8mg/day OR **Telmisartan** 40-80mg/day
  - Both drugs demonstrate equal cardiovascular protection and blood pressure control
  - Both thought to be best in their class for CNS effects
- Patients are titrated appropriately, with protocols for adjustment to maintain target pressures
- 240 subjects recruited from 10-12 sites across Ontario
- 12-18 months accrual, 12 months follow-up
- First patient randomized Spring 2014
- The study is randomized, open-label but rater-blinded for the primary outcome measure

SECONDARY AND EXPLORATORY OBJECTIVES

- Compare outcomes in executive function, cortical thickness, hippocampal volume (Figure 3) and small vessel disease
- Compare treatment responsiveness of other cognitive (e.g. ADAS-Cog), neurobehavioural (e.g. NPI), and functional measures
- Compare treatment responsiveness of multi-modal MRI measures including Diffusion Tensor Imaging (DTI) and resting-state functional MRI (rsfMRI)
- Compare treatments on economically important parameters including caregiver burden, health-related quality of life, and resource utilization
- Obtain data needed to power future studies if warranted

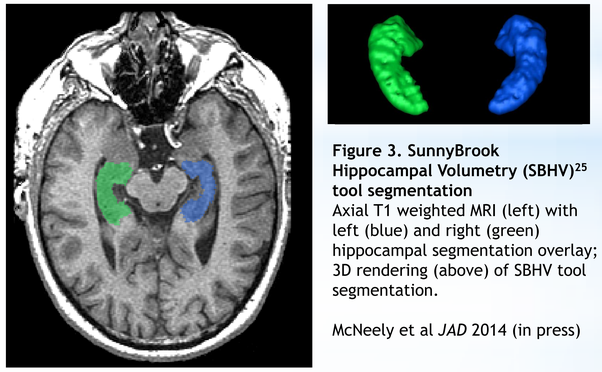

Figure 3. SunnyBrook Hippocampal Volumetry (SBHV)[25] tool segmentation
Axial T1 weighted MRI (left) with left (blue) and right (green) hippocampal segmentation overlay; 3D rendering (above) of SBHV tool segmentation.

McNeely et al *JAD* 2014 (in press)

KEY INCLUSION CRITERIA

- Probable AD with mild untreated or mild-moderate treated HTN, MMSE score 16-27
- Age ≥55, otherwise healthy
- Non-specific white matter changes allowed
- Stable type 2 DM allowed (HbA1C <8.5%)
- Stable dose of ChEI and/or memantine for 3 months

KEY EXCLUSION CRITERIA

- Blood pressure >160/100 mmHg (>180/100 mmHg if over 80)
- Treatment with a sartan within past 12 months
- Significant kidney or liver dysfunction
- Intolerance/contraindication to study medications or MRI
- Major depression or score >18 on Cornell Scale

STUDY EVENTS

- 3T structural, DTI, and resting-state fMRI scans are obtained at baseline and 1 year with cognitive testing, mood/behaviour and economic impact questionnaires at baseline, 6 and 12 months
- Regular blood tests, clinic visits and phone checks for the purposes of medication management and safety are also scheduled
- Patients are given a home blood pressure cuff and asked to record their blood pressure daily and to share this information with the study team

CONCLUSION

- ACEIs and sartans may be more beneficial to brain health than other antihypertensives, while being equally effective for cardiovascular health
- A head-to-head proof of concept trial in AD is warranted to assess comparative efficacy
- Using ventricular size, a valid objective neuro-degenerative biomarker, to quickly assess potential will hopefully be a cost-effective, efficient process to guide further action

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