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)

- 63% of Canadians aged 74 (average age of AD patients presenting to memory clinics) have hypertension[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]
- Other antihypertensive studies, including comparisons of Angiotensin Converting Enzyme inhibitors (ACEIs) and Angiotensin Receptor Blockers ("sartans"), have been equivocal[6-10]; this is often due to insufficient sample sizes

Repurposing Drugs

- Only 5 drugs have been approved for symptomatic treatment of AD (last one in 2003)
- Attempts to develop a disease-modifying treatment have been unsuccessful, and there are not many 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; however, as 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 also 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 incident dementia in a veteran population[21]; similarly, it was associated with less premorbid cognitive decline and less AD pathology in an autopsy series[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

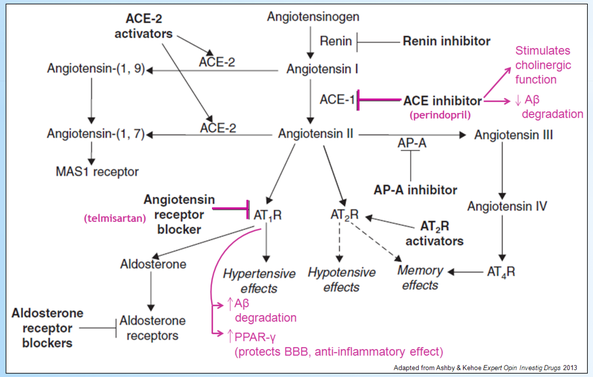

Figure 1. Renin Angiotensin System pharmacological actions, including on the amyloid cascade

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

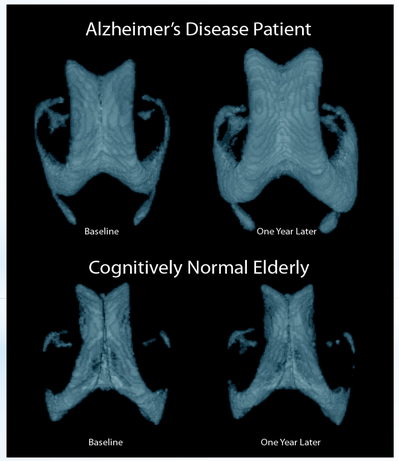

Figure 2. Ventricular expansion over one year

Top view of 3D surface renderings of ventricles from an AD patient (top) and a normal control (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

- **Participants randomized to 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 Canada
- First patient randomized Spring 2014
- The study is open-label but rater-blinded for the primary outcome measure

SECONDARY AND EXPLORATORY OBJECTIVES

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

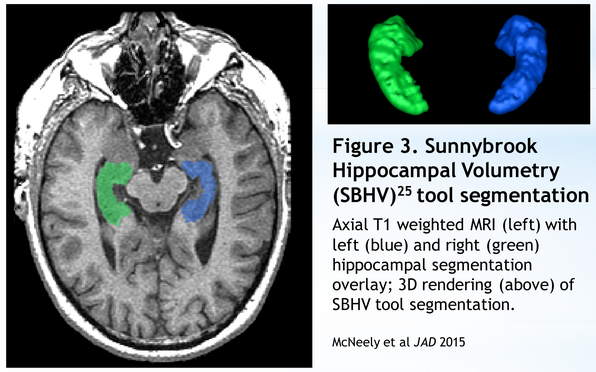

Figure 3. Sunnybrook Hippocampal Volumetry (SBHV)[25] tool segmentation

Axial T1 weighted MRI (left) with left (blue) and right (green) hippocampal segmentation overlay; 3D rendering (above) of SBHV tool segmentation.

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KEY INCLUSION CRITERIA

- Probable AD (McKhann 2011) with treated HTN
- MMSE score 16-27
- Age ≥55, otherwise healthy
- Stable dose of ChEI and/or memantine for 3 months
- Stable type 2 DM allowed (HbA1C <8.5%)
- Non-specific white matter changes allowed if not severe (periventricular Fazekas score <3)

KEY EXCLUSION CRITERIA

- Treatment with a sartan within past 12 months
- Significant systemic illness (particularly kidney or liver dysfunction) or nervous system illness
- 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 (ADAS-Cog), 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 neurodegenerative biomarker, to quickly assess potential will hopefully be a cost-effective, efficient process to guide further action

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