Effects of Candesartan vs Lisinopril on Neurocognitive Function in Older Adults with Executive Mild Cognitive Impairment

BACKGROUND:

• Studies have shown that there is a potential neuroprotective effect when reducing blood pressure in patients without cognitive impairment. It is unclear if there is also a neuroprotective effect of lowered blood pressure in patients who already have some mild cognitive impairment (MCI). Additionally, it is unclear if the neuroprotective effect is solely due to the blood pressure lowering or if there is some other pleiotropic effect of some classes of antihypertensives. HTN medications that modulate the RAS system (specifically ARBs) may produce a larger neuroprotective effect.

OBJECTIVE:

• To compare the neurocognitive effects of candesartan vs lisinopril in older adults who already have mild cognitive impairment (MCI)

METHODS:

- **Design:** A single center, randomized, double-blind study. **Duration:** 1 year
- **Inclusion-** Patients aged 55 or older with MCI of executive or mixed type and a history of hypertension. Hypertension was defined as systolic BP 140 mmHg or higher, diastolic BP of 90 mmHg or higher, or receiving antihypertension medications. Executive MCI was defined by meeting 3 criteria: Montreal Cognitive Assessment score of at least 26, performance in at least the 10^{th} percentile on at least 1 of 5 screening tests and preserved functional ability with a score of 7 or lower by a functional assessment questionnaire.
- **Exclusion-** Intolerance to any ACEi or ARB, systolic BP higher than 200 mmHg or diastolic Bp higher than 110 mmHg, serum creatinine of >1.99, serum potassium >5.5, any medical condition that requires medical attention or deemed a safety risk by the physician (heart failure, recent stroke, hematologic disease, etc.), confirmed diagnosis of dementia, and inability to perform study procedures
- There was a total of 76 patients enrolled
    - 87 patients received candesartan
    - 89 patients received lisinopril
        - Patients received either candesartan 8 mg, 16 mg, or 32 mg or lisinopril 10 mg, 20 mg, or 40 mg. Patients were titrated to reach a goal BP of less than 140/90. If maximum dosages of the study drugs were reached an additional medication: either HCTZ 12.5 and 25, Amlodipine 2.5, 5, and 10, or Metoprolol XL 12.5, 25, and 50 were added until the target BP was reached
- **Primary Outcomes-** Executive function (measured by the Trail Making Test (TMT) and Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research executive composite score) at baseline, 6months, and 12 months
- **Secondary Outcomes-** Episodic memory, other cognitive domains, and brain MRI
- **Power-** A sample size of 140 would give 80% power to detect an effect size (ES) of 0.24 on executive function (TMT Part B-A). The study planned to enroll 175 participants to account for a 20% dropout rate
- Data handling method used- Intention to treat

RESULTS:

- 77 participants were analyzed in the candesartan group and 64 participants were analyzed in the lisinopril group
- **Primary Outcomes-** At 12 months TMT Part B and B − A were improved in the candesartan group compared with the lisinopril group (TMT Part B: mean [SE] score, 128.3 [5.4] seconds vs 150.2 [5.9] seconds; difference, 22.3 [95% CI, 7.3 to 37.3] seconds; P = .004; TMT Part B − A: mean [SE] score, 87.2 [5.5] seconds vs 111.4 [5.9] seconds in the candesartan and lisinopril groups respectively; difference, 24.6 [95% CI, 9.5 to 39.7] seconds). There was no difference between the treatment groups in the Executive Abilities composite scores (ES = −0.03 [95% CI, −0.08 to 0.03] seconds; P = 0.31)
- **Secondary Outcomes-** Candesartan had improved effects on episodic memory measured by delay recall with an ES of 0.4 (95% CI, 0.02 to 0.8); P = .04 and retention with an ES of 5.1 (95% CI, 0.7 to 9.5); P = .02. Brain MRI results showed there was no significant difference in hippocampal volume or cerebral perfusion between treatment groups (although both groups showed a significant loss of hippocampal volume from baseline). The candesartan group had less white matter lesion accumulation after correcting for baseline values (change in candesartan group: 0.1 [95% CI, −0.3 to 0.5] mm3; change in the lisinopril group: 0.6 [95% CI, 0.2 to 1.0] mm3; ES = −0.2 [95% CI, −0.5 to 0]) but the difference was not statistically significant
- **Authors stated conclusions-** Candesartan is superior to lisinopril on executive function and memory outcomes in MCI. The effects are independent of but likely additive to their BP-lowering effects

STRENGTHS:

- Compared two active controls
- Multiple tests used to determine the extent of MCI

LIMITATIONS:

- Short study duration (1 year)
- Compliance was not assessed
- Limited to one health care center
- Small sample size of 141 participants analyzed
- Standard error used to report variability in the primary outcomes
- Other HTN and CV (statins) drugs used and dosing of those drugs could be confounding factors
- Difference in adverse effects could lead to unblinding
- Some differences in baseline characteristics could have affected study results (% with MCI, family history of dementia, CV disease)
- Not clear if both groups were followed similarly (could be differences in number of study visits)
- Failed to show improvement in both measures used to assess executive function

CONCLUSIONS:

- This study showed that candesartan may have some neuroprotective effects in patients with MCI. However, the study had mixed results when comparing the two primary outcome measures, which makes it difficult to assess if there truly is a treatment difference. Furthermore, the potential confounding variables and potential differences in number of study visits between the groups could have influenced the results of this study. Further studies that account for the confounding factors would be needed to confirm if ARBs (specifically candesartan) provide a better neuroprotective

effect than ACEis (specifically lisinopril). The study would need to be done in more regions of the world to be more ethnically inclusive and have a longer study duration.

Reference:
Hajjar I, Okafor M, McDaniel D, et al. Effects of Candesartan vs Lisinopril on Neurocognitive Function in Older Adults with Executive Mild Cognitive Impairment. JAMA Network Open. 2020;3(8):e2012252. doi:10.1001/jamanetworkopen.2020.12252.

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