Antihypertensive drug repurposing for dementia prevention: target trial emulations in two large-scale electronic health record systems

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Background. Alzheimer's disease (AD)—the most common type of dementia—affects 5.7 million people in the US and costs about $250 billion annually. Since there are no disease-modifying therapies to date, repurposing FDA-approved drugs preventing dementia onset offers an expedited path to reduce the impact of this epidemic. Beyond age, type 2 diabetes and hypertension are two major risk factors for dementia onset. However, mixed results are emerging from prior observational studies contrasting various antihypertensive drug classes, including Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARB), and Calcium Channel Blockers (CCB). A Mendelian Randomization study recently published in *Neurology Genetics* found that lower expression levels of the ACE gene in the cortex were associated with higher systolic blood pressure and, independently, with an increased risk of Alzheimer's disease but not of other neurodegenerative diseases.

Methods. To address this complexity and evaluate the repurposing potential of antihypertensives with different mechanisms of action, we deployed a causal inference approach accounting for the competing risk of death in emulated clinical trials using two distinct electronic health record (EHR) systems, one from the UK Clinical Research Practice Datalink (CPRD) and the other from the US Research Patient Data Registry (RPDR). We performed intention-to-treat analyses among patients aged 50 or older at baseline, applying Inverse Propensity score of Treatment Weighting to balance the two treatment arms with respect to a set of confounders curated by cardiologists and neurologists. Specifically, we compared antihypertensive treatment initiation with any of seven ARBs (losartan, candesartan, eprosartan, irbesartan, olmesartan, telmisartan, valsartan) vs any of eleven ACE inhibitors (lisinopril, benazepril, captopril, enalapril, fosinopril, moexipril, perindopril, quinapril, ramipril, sacubitril, trandolapril).

Results. In the US RPDR database, a total of 52,026 patients were eligible to participate in the emulated target trial. Treatment initiation with any of the seven ARBs was associated with lower hazard of all-cause mortality (HR=1.14 [95% CI: 1.09-1.20]) and lower cause-specific hazard of dementia onset (HR=1.37 [95% CI: 1.31-1.45]) in cause-specific Cox Proportional Hazards (PH) models, after accounting for prolonged survival, relative to treatment initiation with any of the eleven ACE inhibitors. In addition, within the ARB drug class, the gap in the dementia risk difference over time was more pronounced among patients initiating on compounds that cross the blood-brain barrier (BBB). Results of the competing risks analysis were robust to the structure of the outcome models (i.e., Cox PH vs nonparametric). The directionality and strength of our findings were similar in the UK CPRD database.

Conclusion. Target trial emulations in two large-scale EHR systems suggest that treatment initiation with BBB-crossing ARBs might reduce the risk of dementia among hypertensive patients. In future, we will conduct a mediation analysis in the two considered cohorts to assess the role played by enhanced blood pressure control towards dementia prevention.