

Losartan to slow the progression of mild-to-moderate Alzheimer's disease through angiotensin targeting: the RADAR RCT

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Declared competing interests of authors: Patrick G Kehoe has previously undertaken advisory work for Novartis in the development and use of dual-acting inhibitors of angiotensin receptors and neprilysin for the treatment of different forms of cardiovascular disease. He is also an unfunded co-investigator of the ongoing Alzheimer's Association (USA)-funded HEART Phase 1b study of telmisartan and its use as an intervention against the renin-angiotensin system in non-dementia African Americans at risk of developing dementia by parental history. Carole H Sudre was a recipient of an Alzheimer's Society Junior Fellowship (AS-JF-17-011) during the conduct of the study.

J Athene Lane is a co-director of a Clinical Trials Unit (CTU) that receives National Institute for Health Research (NIHR) CTU infrastructure support and is a member of the NIHR CTU Standing Advisory Committee. Peter Passmore received honoraria for talks on a variety of antihypertensive medications over a number of years. This included losartan (losartan potassium; Teva Pharmaceuticals Industries Ltd, Petah Tikva, Israel) and similar medications. Nick Fox reports personal fees from Biogen Inc. (Cambridge, MA, USA), GE Healthcare (Chicago, IL, USA) and Lilly (Hampshire, UK) and Roche (Roche Diagnostics, Hertford, UK), outside the submitted work. Yoav Ben-Shlomo has received funding from the NIHR HTA programme as a co-investigator of the CHolinesterase Inhibitors to prEvent Falls in Parkinson's Disease (CHIEF-PD) trial. He is a member of the NIHR Parkinson's Portfolio Development Group (PDG) and the Care, Implementation and Public Health Grant Advisory Board for the Alzheimer's Society and is the cohort representative for the Caerphilly Prospective Study (CaPS) that is part of the Dementia Platform UK collaboration.

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Plain English summary

The RADAR RCT

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Plain English summary

Alzheimer's disease is a disorder of memory in older individuals. High blood pressure in mid-life increases the risk of developing Alzheimer's disease. We and others have found that a biochemical pathway in the brain, which also influences blood pressure, may be more relevant in Alzheimer's disease than changes to blood pressure. This pathway, the renin-angiotensin system, includes a small molecule called angiotensin II that is raised in brain tissue from people with Alzheimer's disease. As well as raising blood pressure, angiotensin II influences inflammation and chemical stress in brain cells and stops the release of chemicals involved in memory. Angiotensin II also enhances the production of key proteins (amyloid- β and tau) that damage brain tissue in Alzheimer's disease. All of these damaging characteristics point to angiotensin II being a detrimental factor in Alzheimer's disease.

We conducted a multicentre randomised clinical trial to test whether or not losartan, the first drug developed to reduce the function of angiotensin II, could slow the progression of Alzheimer's disease compared with placebo. We believed that reducing angiotensin II function would slow brain cell damage, brain shrinkage and memory problems in Alzheimer's disease while improving brain blood flow. We recruited 211 participants and their study partners through 23 centres across Great Britain and Northern Ireland. We used brain imaging techniques, 12 months apart, to measure changes in brain volume and, in a subset of people, levels of brain-related vascular damage and brain blood flow as indicators of disease. We also used established questionnaires to assess memory and thinking, quality of life and activities of daily living to explore if losartan brought any benefits. Unfortunately, we found no evidence that 12 months' treatment with losartan slowed the progression of Alzheimer's disease according to our main study measures. Although losartan was unsuccessful in this study design, other study designs testing related drugs may still be successful.

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