Investigation of the association between blood pressure medication use during life and dementia pathology in the brain after death

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Introduction

Dementia is a group of diseases that affect memory, thinking, and behaviour. Currently, there are over 55 million individuals worldwide living with dementia, with more than 60% of them living in low- and middle-income countries[1].

At present, treatments available for dementia have limited effectiveness. Emerging evidence suggest that **angiotensin receptor blockers (ARB),** a medication for treating high blood pressure, may prevent dementia[2].

The two medicines ARBs and **angiotensin converting enzyme inhibitors (ACE)** are similarly effective for treating high blood pressure, but only ARBs are expected to prevent dementia by selectively blocking an inflammatory pathway in the brain.
Therefore, ACE is a suitable medicine to compare with ARB.

Dementia is characterised by abnormal accumulation of proteins in the brain including **amyloid-β, tau, and α-synuclein**. These protein accumulations can be observed under the microscope and classified according to **neuropathological staging systems.**

Aim

Determine whether ARB use during life is associated with lower dementia-related proteins in the brain after death compared to ACE use.

Method

1. All cases with a record of ACE or ARB use, irrespective of dementia neuropathology (n=340) were extracted from the UK Brain Banks Network (UKBBN) dataset.
2. Neuropathological staging systems were binarized into significant and non-significant neuropathology.
3. Binomial logistic regression was carried out to analyse the relationship between ARB use and neuropathology outcomes.
4. In 58 cases, alpha-synuclein, amyloid-beta, and tau staining in the entorhinal cortex and CA1 region of the brain tissue slides were analysed using QuPath software as shown below.


Select brain region   Highlight neuropathology
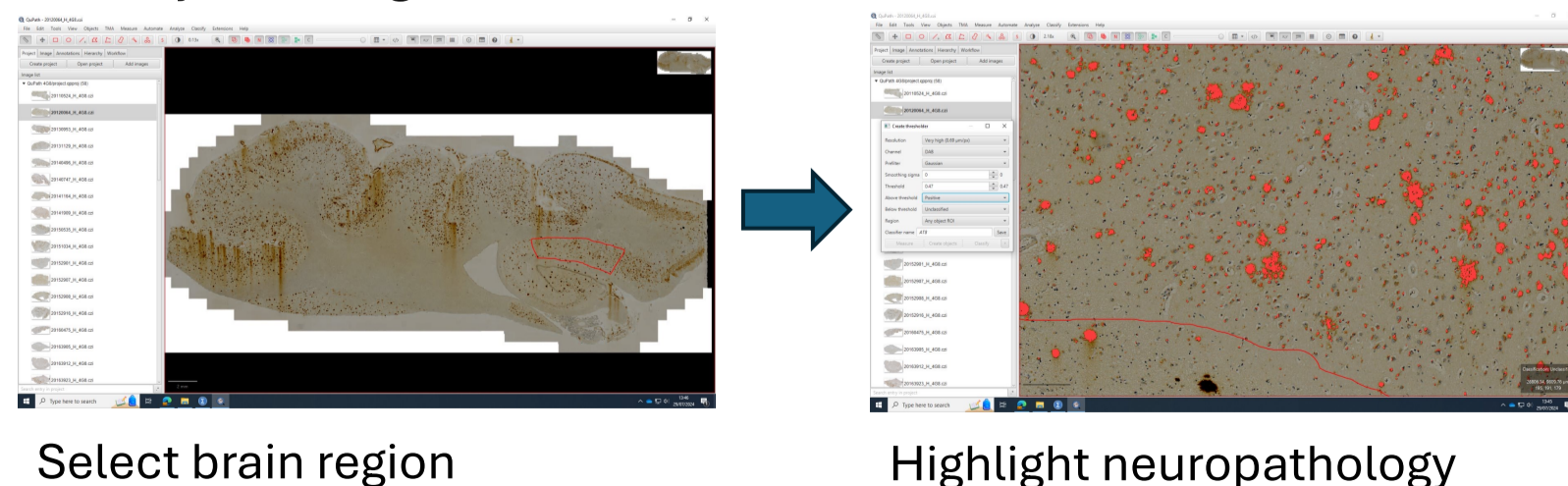
UKBBN Dataset Analysis Results

Table 1. Demographics of the patients selected from the UKBBN dataset.

Covariates	ACE	ARB
n	247	93
Age at death, mean (SD)	84.5 (9.13)	84.9 (9.21)
Sex, % female	44.5	46.2
Baseline MMSE, mean (SD)	23.9 (7.98)	24.8 (7.64)

The age, sex, and baseline memory test score (MMSE) were similar between both groups. More patients were on ACE compared to ARB because ACE were developed earlier and used to be cheaper than ARBs.

Significant pathology were defined as: Thal amyloid phase >3, Braak neurofibrillary tangle stage >3, CERAD neuritic plaque score 'moderate density' or 'high density', and Braak Lewy body stage >0.

Figure 1. Bar chart of % significant neuropathology by neuropathological staging system. Binomial logistic regression was conducted with age at death and sex accounted for.
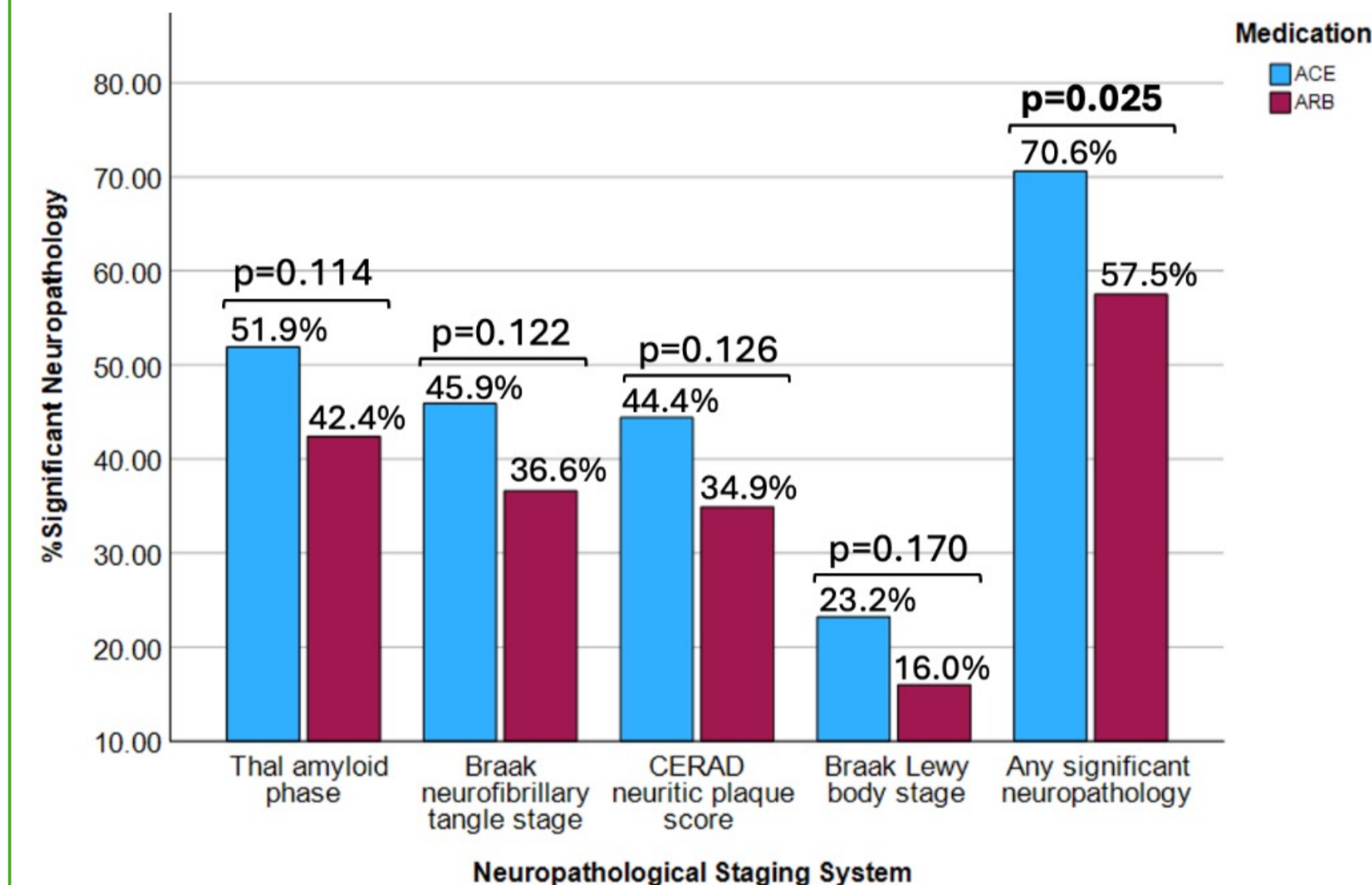
ARB group had lower % cases with significant neuropathology compared to ACE group in all neuropathological staging systems. A possible reason that only 'any significant neuropathology' had a statistically significant difference is because it accounts for several types of dementia associated with higher scores in different neuropathological staging systems.

Brain Tissue Image Analysis Results

Covariates	ACE	ARB
n	39	19
Age at death, mean (SD)	83.6 (9.8)	85.6 (10.7)
Sex, % female	53.8	63.2
Baseline MMSE, mean (SD)	25.4 (7.54)	25.6 (8.38)

Table 2. Demographics of the patients included in the brain tissue image analysis. Age at death and % female were slightly higher in the ARB group; both are associated with increased dementia risk.

Figure 2. Box and whisker plot of amyloid-β, tau, and α-synuclein % area of the brain tissue images. Mann-Whitney U Test was conducted.

There is a similar pattern of difference between ACE and ARB group in the entorhinal cortex and hippocampal CA1 region. The % α-synuclein area is lower in the ARB group compared to the ACE group in a statistically significant manner.
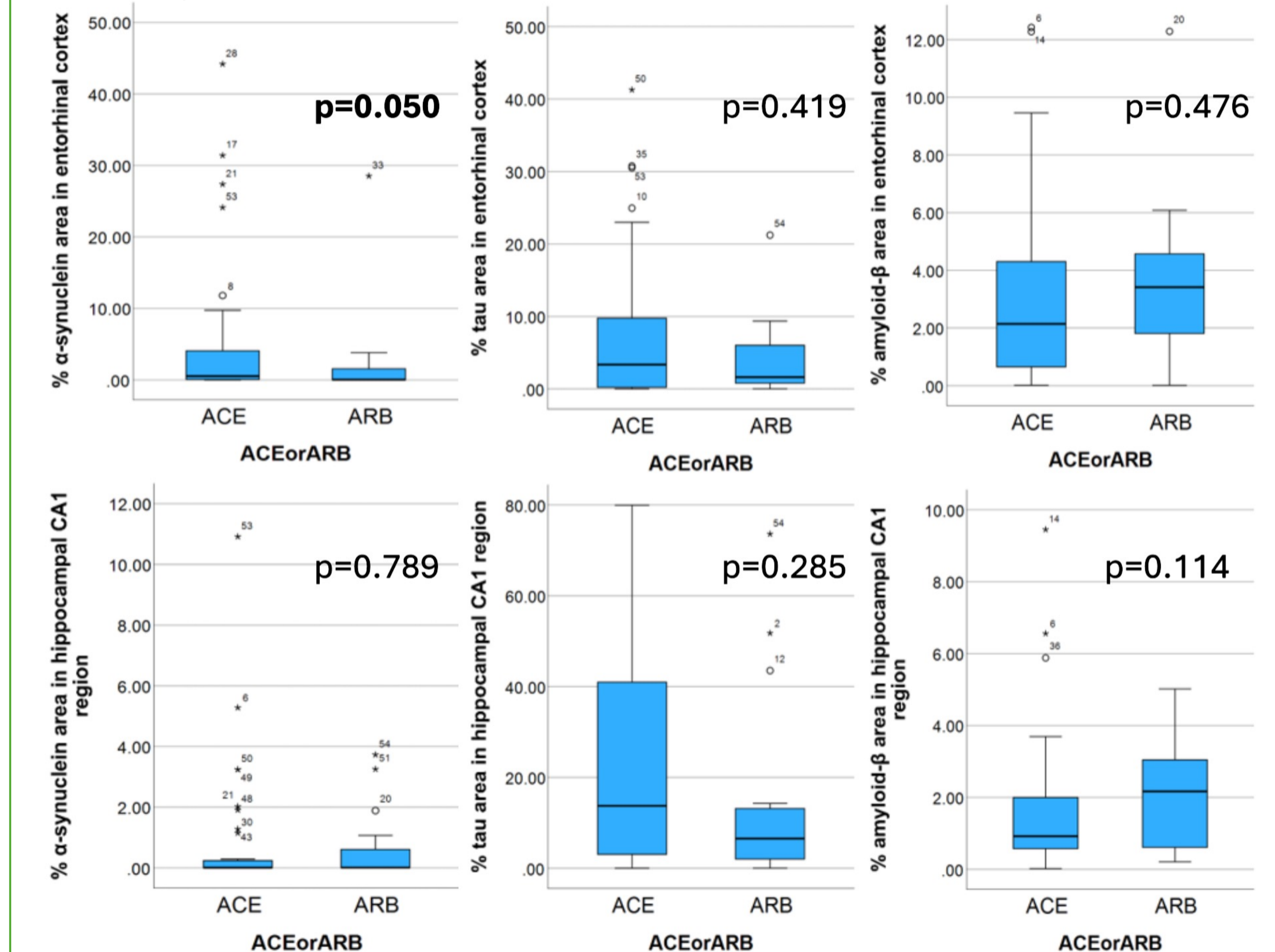
Conclusion

- This study provides evidence that ARB use may be associated with lower levels of dementia neuropathology, particularly alpha-synuclein.
- The results suggest that ARB could be an affordable and readily available medicine to prevent and possibly treat dementia, that benefit patients globally, including in low-income countries.
- The correlation between ARB use and dementia will be further explored by analysing larger datasets and measuring the dementia-related proteins in other relevant regions of the brain.

References
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