Effect of Renin-Angiotensin System Inhibitors on Alzheimer's Disease: A Population-Based Cohort Study

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INTRODUCTION

Alzheimer's Disease (AD)

- Cognitive or behavioral impairment severe enough to affect behavior, feelings, and relationships and interfere with daily activities
- The most common cause of dementia, accounting for 60~80% of all cases

Renin-Angiotensin System (RAS)

- A hormone system responsible for regulating systemic blood pressure, electrolyte homeostasis, and vascular resistance.

Central RAS and Neurodegeneration

- RAS in central nervous system (CNS) is known to involve in oxidative stress, neuroinflammation, and apoptosis of the brain
- RAS may play a role in both neurodegeneration or neuroprotection
- Relationships between the blood-brain barrier (BBB) permeability of RAS inhibitors and increased neuroprotection are inconclusive

OBJECTIVES

- To assess the effects of different types of RAS inhibitors on the risk of AD
- To compare RAS inhibitors using the BBB permeability and cumulative duration-response relationship

METHODS

A Population-Based Retrospective Cohort Study (Figure 1)

- Patients aged 60 or older and diagnosed with ischemic heart disease (IHD) in the year 2009 using the Korean national health insurance claims database between 2008 and 2019
- First use of RAS inhibitors in the year 2010
- Applied 1-year lag time to minimize reverse causality of AD

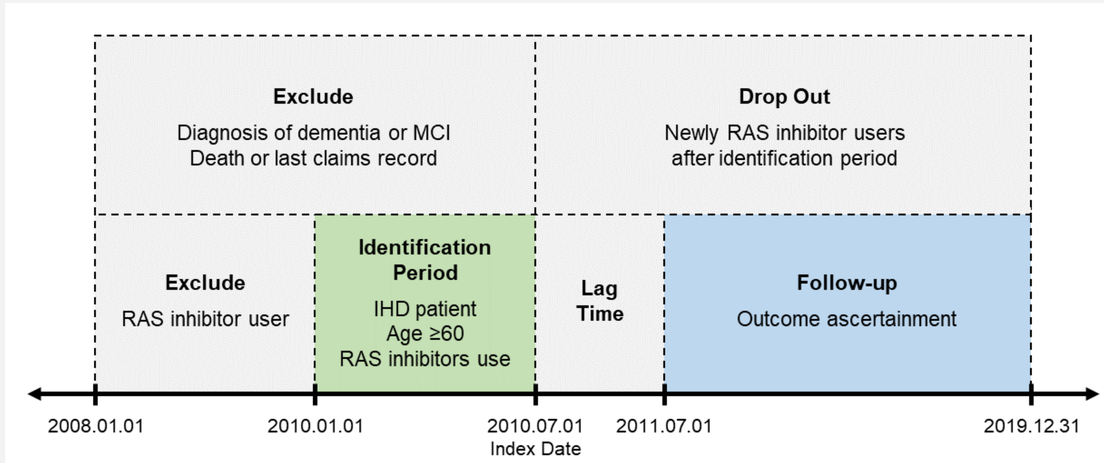

Figure 1. Study design and study population

Exclusion Criteria

- Patients who had :
  - ✓ First use of RAS inhibitors before or after the identification period
  - ✓ Death or last claims record prior to follow-up
  - ✓ Diagnosis of dementia or mild cognitive impairment before follow-up

Multivariate Cox Proportional Hazard Regression Model

- The association between the RAS inhibitors use and AD incidence
- 1:1 propensity score matching
- Adjusted for age, sex, type of insurance, comorbid diseases, and concomitant medications
- Individuals were categorized into 2×2 groups according to :
  - ✓ Classification of RAS: 1) Angiotensin-converting enzyme inhibitors (ACEI), and 2) angiotensin II receptor blockers (ARB)
  - ✓ Potential BBB permeability

RESULTS

- Of the 82,456 subjects identified, 9,682 were new users of RAS inhibitors and 72,774 were non-users (Figure 2).

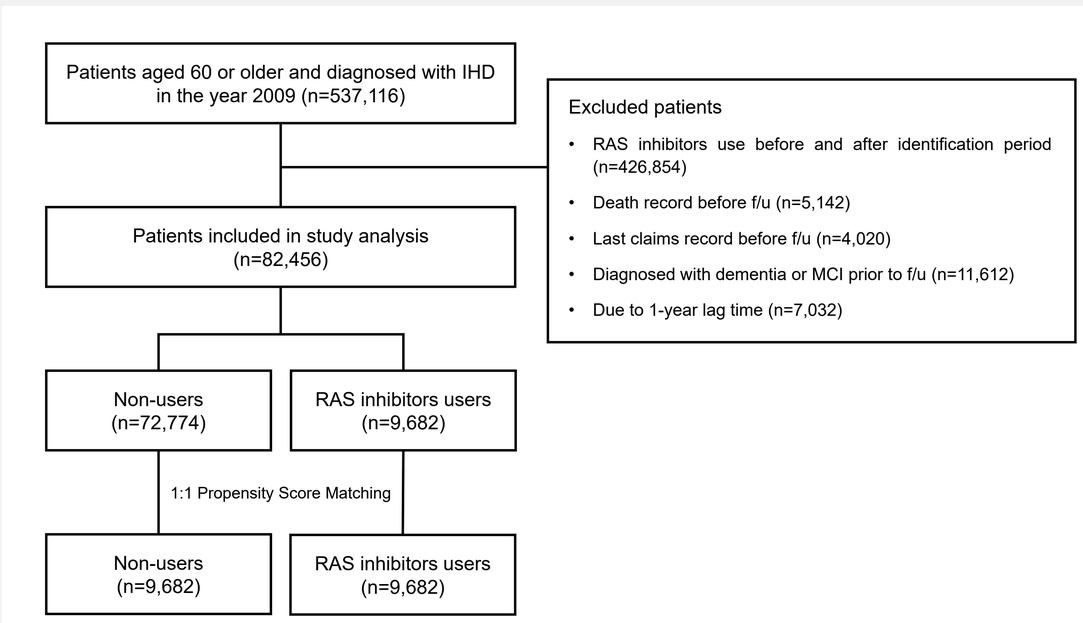

Figure 2. Flow chart of study population inclusion

Effects of RAS Inhibitors on AD

- Among 19,364 matched individuals, a total of 2,427 AD cases were observed and overall incidence was 15.6 per 1,000 person-years.
- The use of RAS inhibitors (aHR 1.02; 95% CI 0.94-1.11), ACEI (aHR 1.04; 95% CI 0.92-1.19), and ARB (aHR 0.99; 95% CI 0.91-1.08) were not significantly associated with the risk of AD occurrence.

Table 1. Cox regression analysis on the association of incident AD with RAS inhibitors and BBB permeability

	Subjects	Person-years	Events	Incidence rate	aHR (95% CI)
RAS inhibitors	9682	77572	1212	15.6	1.02 (0.94-1.11)
ACEI	2221	17228	298	17.3	1.04 (0.92-1.19)
ARB	9190	74053	1128	15.2	0.99 (0.91-1.08)
BBB-crossing RAS	6940	56613	818	14.4	0.90 (0.82-0.99)
BBB-crossing ARB	6142	50698	691	13.6	0.81 (0.73-0.90)

BBB Permeability and AD Risk

- The use of BBB-crossing RAS inhibitors showed a significantly reduced risk of incident AD (aHR 0.90; 95% CI 0.82-0.99).
- Specifically, the BBB permeable ARB users had a significantly lower risk of developing AD compared to non-users (aHR 0.81; 95% CI 0.73-0.90).

CONCLUSIONS

- The findings from this study highlight the potential neuroprotective effect of targeting CNS RAS for reducing the risk of AD.
- This study suggests the BBB-crossing ARB as one of the disease-modifying treatment options for reducing AD risks in patients with cardiovascular diseases.

References

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