

Treatment Effects of ARB versus ACEI Initiation on Dementia Subtypes, Evidence from Target Trial Emulation of 2.5 Million US Veterans

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INTRODUCTION

- Hypertension is a modifiable risk factor for dementia, yet it remains unclear whether its effects operate through vascular pathways Alzheimer’s disease (AD) pathology, or both
- ARBs and ACEIs differentially modulate renin-angiotensin signaling and vascular or AD pathways
- ARBs may confer lower risk of specific dementia subtypes than ACEIs

OBJECTIVE

Compare ARB versus ACEI initiation on the cause-specific hazards of three dementia subtypes

METHODS

- Data Source**
- Using longitudinal electronic health records from >2.5 million US Veterans with incident hypertension who initiated ACEI or ARB between 01/01/2000 and 12/31/2017
 - ACEI and ARB use was determined from pharmacy dispensing records
- Target Trial Emulation**
- Aligned the times of treatment initiation, patients’ eligibility, and start of follow-up
 - Minimized selection bias & immortal time bias
- Outcomes** (Identified using ICD 9/10 codes)
- Incident AD; Incident vascular dementia (VCID); Incident other dementia (OD)
- Statistical Methods**
- Over 65 baseline covariates were controlled using inverse probability (IP) weighting
 - Treatment effects were estimated as time-varying hazard ratios from 6 months to 5 years, along with 95% confidence intervals with deaths prior to dementia censored

RESULTS

Table 1. Baseline Characteristics of Veterans Before and After Inverse Probability Weighting. Continuous variables are summarized as mean (SD) and categorical variables as counts (%). Absolute standardized mean differences (ASMD) <0.10 indicate acceptable balance.

Variable	Before IP Weighting			After IP Weighting		
	ARB N = 247,802	ACEI N = 2,329,198	ASMD	ARB	ACEI	ASMD
Age (years)	65 (12)	63 (12)	0.20	64 (12)	63 (12)	0.08
Sex			0.05			0.01
Female	13,616 (5.5%)	101,354 (4.4%)		4.6%	4.4%	
Male	234,186 (95%)	2,227,844 (96%)		95%	96%	
Race/Ethnicity			0.06			0.05
Hispanic	8,973 (3.6%)	107,160 (4.6%)		4%	4.5%	
Non-Hispanic Black	35,398 (14%)	352,508 (15%)		14%	15%	
Non-Hispanic White	162,101 (65%)	1,501,069 (64%)		65%	65%	
Other	41,330 (17%)	368,461 (16%)		17%	16%	
Body mass index, kg/m2	31.2 (5.9)	30.5 (6)	0.12	30.7 (5.8)	30.5 (6)	0.03
Systolic blood pressure, mm Hg	141 (18)	144 (18)	0.14	143 (18)	144 (18)	0.02
Cardiovascular disease	62,336 (25%)	245,541 (11%)	0.39	12%	11%	0.01
Chronic kidney disease	9,743 (3.9%)	65,539 (2.8%)	0.06	3.8%	3%	0.05
Frailty			0.03			0.04
Frail	7,528 (3.0%)	60,055 (2.6%)		3.3%	2.7%	
Non-frail	240,274 (97%)	2,269,143 (97%)		97%	97%	

Figure 2. Inverse Probability of Treatment Weighted Hazard Ratios for Dementia Subtypes. Event rates, HRs, and 95% CIs comparing ARB vs. ACEI initiators for AD, vascular dementia (VCID), and other dementia (OD).

Subtype, Follow-up Period	Number of events (Event rate per 1000 person-years)		Hazard Ratio (95% CI)
	ARB	ACEI	
AD			
0-0.5 year	235 (0.21)	487 (0.38)	0.55 (0.36, 0.85)
0.5-1 year	337 (0.15)	697 (0.28)	0.55 (0.39, 0.78)
1-2 years	1188 (0.28)	1619 (0.33)	0.84 (0.68, 1.04)
2-3 years	1329 (0.21)	1896 (0.26)	0.81 (0.66, 0.98)
3-4 years	1527 (0.19)	2085 (0.22)	0.84 (0.70, 1.01)
4-5 years	1813 (0.19)	2095 (0.19)	1.01 (0.84, 1.20)
VCID			
0-0.5 year	520 (0.47)	730 (0.57)	0.82 (0.58, 1.17)
0.5-1 year	621 (0.28)	797 (0.31)	0.89 (0.64, 1.24)
1-2 years	1102 (0.26)	1613 (0.32)	0.79 (0.63, 1.00)
2-3 years	1003 (0.16)	1509 (0.21)	0.76 (0.59, 0.97)
3-4 years	1021 (0.13)	1562 (0.17)	0.76 (0.59, 0.98)
4-5 years	1213 (0.12)	1553 (0.14)	0.90 (0.71, 1.14)
OD			
0-0.5 year	1273 (1.15)	1721 (1.34)	0.85 (0.69, 1.05)
0.5-1 year	1677 (0.77)	2102 (0.83)	0.92 (0.77, 1.11)
1-2 years	3546 (0.83)	4679 (0.94)	0.87 (0.77, 0.99)
2-3 years	3806 (0.61)	5295 (0.73)	0.83 (0.74, 0.93)
3-4 years	4546 (0.56)	5819 (0.62)	0.90 (0.81, 1.01)
4-5 years	4808 (0.49)	6315 (0.56)	0.88 (0.79, 0.98)

CONCLUSIONS

- Among U.S. Veterans with hypertension, the **associations between initiation of ARB versus ACEI and the risk of dementia may differ across subtypes.**
- Our findings may be influenced by 1) diagnosis codes capturing only one etiology, though most dementia is mixed pathology; 2) dependent censoring of deaths; 3) unmeasured confounding due to missing information on education and baseline cognitive function.
- Future research is needed to **clarify subtype-specific mechanisms underlying the timing and magnitude of potential benefits of antihypertensive therapies.**

CONNECT

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Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Department of Veterans Affairs.

Funding: This work is supported by R01AG74989 and K24AG080168 from the National Institute on Aging (Bethesda, MD).