CO110

Evaluating the Repurposing Potential of Statins: Association Between Statin Use and Cognitive Decline in Patients with Mild-to-Moderate Alzheimer's Disease

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BACKGROUND

- Current treatments for Alzheimer's disease (AD) provide limited clinical benefit or have safety concerns, prompting interest in repurposing existing drugs.
- Statins exhibit pleiotropic effects, including the reduction of amyloid-beta (Aβ) plaques and neurofibrillary tangle (NFT) formation, potentially targeting core pathological features of AD.[1]
- Evidence on cognitive effects of statin use in AD is mixed: some studies suggest potential benefits,[2,3] while others report null or inconclusive results.[4,5]

OBJECTIVES

To evaluate the impact of statins on cognitive function among patients with mild to moderate AD under the treatment of cognitive enhancers.

METHODS

- **Data source:** NTUH-iMD electronic health records database
- **Study design:** Sequential target trial emulation (STTE) design with incidence-density sampling approach (To distinguish person-trial from most STTE, these trials are called "**Episodes**") **(Figure 1)**
- **Study population:**

Inclusion criteria:
(1) **mild-moderate AD (MMSE 10-26, CDR 0.5-2)**
(2) aged ≥ 65 years
(3) under acetylcholinesterase inhibitors (AChEI) treatment between Jan 2007 and Dec 2022

Exclusion criteria:
(1) statin use within 365 days prior to the index date
(2) missing baseline MMSE/ CDR* assessment

- **Exposures: Initiation of statin therapy post-AChEI initiation**
- **Study outcome**:
  - Cognitive decline (ΔMMSE score ≥2 points, ΔCDR ≥1 from baseline)
- **Follow-up period: up to 8 years from index date**
- **Covariates:** demographics, comorbidities, concomitant medication†, LDL-C level† and AD-related factors†
- **Statistical analysis**:
  - Per-protocol effect estimated after **propensity score matching (PSM)** (SMD‡ < 0.1 as negligible)
  - **Inverse probability of censoring weighting (IPCW)** applied for censoring events: (1) all-cause death, (2) end of study period (Dec 2023), (3) discontinuation of AChEI, (4) discontinuation of statin§, (5) completion of 8-year follow-up, and (6) missing MMSE/CDR follow-up
  - **Cox proportional hazards model** were used to estimate hazard ratios (HR) with robust standard errors for 95% confidence intervals (CIs)

* MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating.
† These were considered as time-varying covariates in per-protocol analyses.
‡ SMD, standard mean difference.
§ Treatment deviations were considered in the per-protocol analyses, not in ITT analysis.

RESULTS

- A total of 80,374 episodes were enrolled in this cohort. After PSM, 234 episodes with statin initiation and 906 episodes without statin initiation following AChEI initiation were identified (**Figure 2**).
- Baseline covariates—including demographics, comorbidities, concomitant medications, laboratory data, and AD-related factors—were well balanced between the two groups after matching (**Table 1**).
- Compared with non-initiators (median follow-up: 621 days), statin initiators (median follow-up: 600 days) experienced fewer episodes of cognitive decline (15.4% vs. 25.8%), corresponding to a crude hazard ratio (HR) of 0.70 (95% CI: 0.51–0.95). However, after adjusting for censoring events, this apparent protective effect was attenuated (weighted HR: 0.98; 95% CI: 0.94–1.02) (**Table 2**).
- Subgroup analyses: No significant association between statin use and cognitive decline across sex or baseline severity strata.
- Sensitivity analyses: Findings were robust across alternative definitions of cognitive decline and ITT analysis, showing no significant differences between statin users and non-users.

Table 1. Baseline characteristics of eligible episodes after PS matching

Characteristics	Statin Initiators (n=234)	Non-initiators (n=906)	SMD
Gender (Male), n (%)	82 (35.0)	314 (34.7)	0.01
Age, mean (SD), yr	77.6 (6.2)	77.6 (6.4)	-0.01
Baseline MMSE scores, median (Q1-Q3)	17.0 (13.0-21.0)	18.0 (13.0-22.0)	-0.05
Baseline severity, n (%)			0.08
Mild	146 (62.4)	599 (66.1)	
Moderate	67 (28.6)	233 (25.7)	
Cognitive decline history, n (%)			0.05
Missing or unknown	86 (36.8)	357 (39.4)	
No	85 (36.3)	316 (34.9)	
Yes	63 (26.9)	233 (25.7)	
Education level, n (%)			0.05
Missing or unknown	3 (1.3)	15 (1.7)	
Illiterate	24 (10.3)	99 (10.9)	
Elementary school	97 (41.5)	370 (40.8)	
High school	69 (29.5)	256 (28.3)	
College and above	41 (17.5)	166 (18.3)	
LDL-C, n (%)			0.08
Missing or unknown	159 (67.9)	633 (69.9)	
LDL-C ≤70 mg/dL	5 (2.1)	20 (2.2)	
LDL-C 71-100 mg/dL	10 (4.3)	35 (3.9)	
LDL-C 101-129 mg/dL	22 (9.4)	95 (10.5)	
LDL-C ≥130 mg/dL	38 (16.2)	123 (13.6)	
Comorbidities, n (%)			
Anxiety	21 (9.0)	77 (8.5)	0.02
Coronary artery disease	46 (19.7)	168 (18.5)	0.03
Depression	28 (12.0)	108 (11.9)	0
Diabetes mellitus	66 (28.2)	250 (27.6)	0.01
Hyperlipidemia	66 (28.2)	231 (25.5)	0.06
Hypertension	111 (47.4)	419 (46.2)	0.02
Malignancy	24 (10.3)	97 (10.7)	-0.01
Mild cognitive impairment	19 (8.1)	72 (7.9)	0.01
Parkinson's disease	52 (22.2)	208 (23.0)	-0.02
Stroke	22 (9.4)	94 (10.4)	-0.03
Vascular dementia	9 (3.8)	36 (4.0)	-0.01
CCI in categories, n (%)			0.08
0	11 (4.7)	40 (4.4)	
1	103 (44.0)	411 (45.4)	
2	65 (27.8)	222 (24.5)	
≥3	55 (23.5)	233 (25.7)	
Comedication, n (%)			
Anticholinergic agents	4 (1.7)	16 (1.8)	0
Anticoagulants	42 (17.9)	174 (19.2)	-0.03
Antidepressants	81 (34.6)	322 (35.5)	-0.02
Antidiabetic medications	13 (5.6)	34 (3.8)	0.09
Antihypertension drugs	89 (38.0)	327 (36.1)	0.04
Antipsychotics	47 (20.1)	174 (19.2)	0.02
Diuretics	14 (6.0)	55 (6.1)	0

Figure 1. Design of sequential target trial emulation with incidence density sampling approach

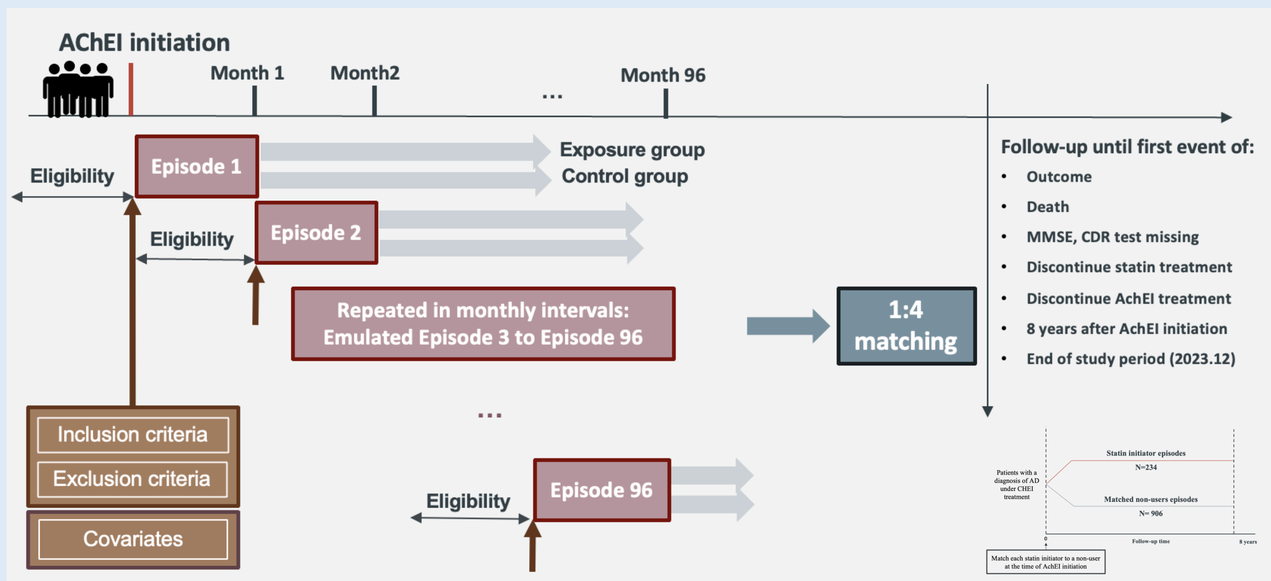

Figure 2. Study flow of eligible episode selection

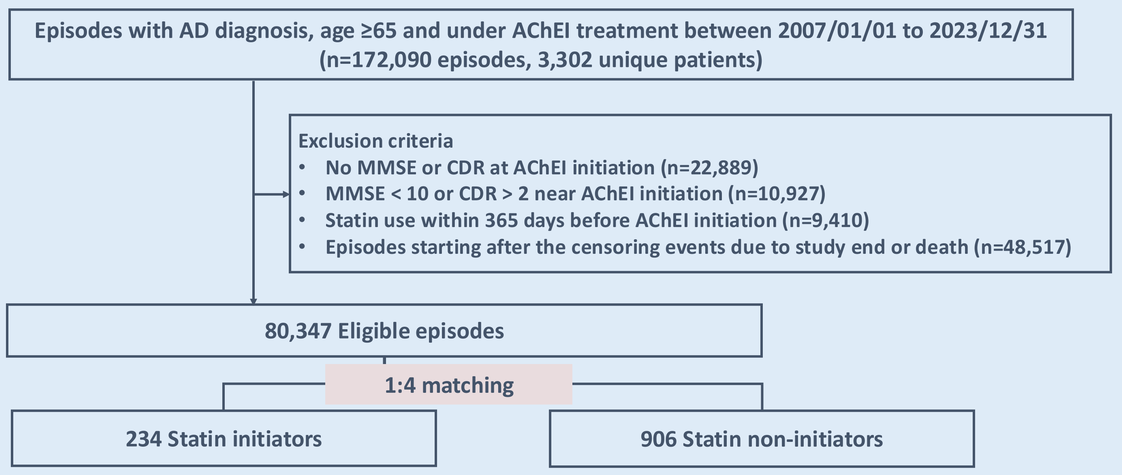

Table 2. Cox proportional hazards model

		Number of events/episodes	Median (Q1-Q3) follow-up, days	Crude HR	Weighted HR
Main analysis	Initiators	36/ 234	600 (212-984)	0.850 (0.615, 1.175)	0.978 (0.936, 1.022)
	Non-initiators	234/ 906	621 (316-1160)	Ref	Ref
Sex					
Male	Initiators	14/ 80	635 (221-1085)	0.996 (0.634, 1.565)	0.997 (0.966, 1.092)
	Non-initiators	80/ 300	666 (336-1217)	Ref	Ref
Female	Initiators	23/ 151	555 (199-942)	0.847 (0.560, 1.281)	1.006 (0.987, 1.026)
	Non-initiators	127/ 578	691 (327-1245)	Ref	Ref
Severity					
Mild	Initiators	23/ 145	616 (236-1044)	0.937 (0.589, 1.491)	0.969 (0.914-1.027)
	Non-initiators	128/ 550	724 (325-1185)	Ref	Ref
Moderate	Initiators	11/ 64	539 (193-971)	0.579 (0.320, 1.046)	1.012 (0.983-1.042)
	Non-initiators	59/ 249	636 (309-1100)	Ref	Ref
Sensitivity analyses					
ITT analysis	Initiators	43/ 234	600 (212-984)	0.697 (0.514, 0.945)	0.850 (0.615, 1.175)
	Non-initiators	237/ 906	621 (316-1160)	Ref	Ref
ΔMMSE ≥3, ΔCDR ≥1	Initiators	36/ 234	600 (212-984)	1.051 (0.771, 1.435)	0.967 (0.927, 1.009)
	Non-initiators	159/ 906	640 (320-1156)	Ref	Ref
ΔMMSE ≥2	Initiators	38 / 238	583 (217-983)	0.725 (0.543, 0.968)	1.015 (0.990, 1.031)
	Non-initiators	250/ 927	616 (313-1059)	Ref	Ref
ΔCDR ≥1	Initiators	9/ 266	575 (294-1098)	1.000 (0.535, 1.868)	1.000 (0.993, 1.007)
	Non-initiators	34/ 1023	605 (218-1033)	Ref	Ref

CONCLUSIONS

- No significant association was observed between statin initiation and the risk of cognitive impairment.
- Apparent crude differences were likely due to baseline confounding and differential censoring among statin users.
- Larger studies with longer follow-up are warranted to confirm findings.

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References:
1. Kemp EC, Ebner MK, Ramanan S, et al. Statin Use and Risk of Cognitive Decline in the ADNI Cohort. *Am J Geriatr Psychiatry*. 2020;28(5):507-517.
2. Murphy C, Dyer AH, Lawlor B, Kennelly SP; NILVAD study group. What is the impact of ongoing statin use on cognitive decline and dementia progression in older adults with mild-moderate Alzheimer's disease?. *PLoS One*. 2023;18(5):e0285529.
3. Lin FC, Chuang YS, Hsieh HM, et al. Early Statin Use and the Progression of Alzheimer Disease: A Total Population-Based Case-Control Study. *Medicine* (Baltimore). 2015;94(47):e2143.
4. Petek B, Häbel H, Xu H, et al. Statins and cognitive decline in patients with Alzheimer's and mixed dementia: a longitudinal registry-based cohort study. *Alzheimers Res Ther*. 2023;15(1):220.
5. Chadha B, Frishman WH. Review of the Protective Effects of Statins on Cognition. *Cardiol Rev*. 2021;29(6):328-335.