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Featured Article

Acetylcholinesterase inhibitors and risk of stroke and death in people with dementia

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Abstract

Introduction: The aim of this study was to investigate the association between acetylcholinesterase inhibitor (AChEI) use and risk of ischemic stroke and death in people with dementia.
Methods: A cohort study of 44,288 people with dementia registered in the Swedish Dementia Registry from 2007 to 2014. Propensity score-matched competing risk regression models were used to compute hazard ratios and 95% confidence intervals for the association between time-dependent AChEI use and risk of stroke and death.
Results: Compared with matched controls, AChEI users had a lower risk of stroke (hazard ratio: 0.85, 95% confidence interval: 0.75–0.95) and all-cause death (hazard ratio: 0.76, 95% confidence interval: 0.72–0.80). After considering competing risk of death, high doses (≥1.33 defined daily doses) of AChEI remained significantly associated with reduced stroke risk.
Discussion: The use of AChEIs in people with dementia may be associated with reduced risk of ischemic stroke and death. These results call for a closer examination of the cardiovascular effects of AChEIs.

Keywords: Cholinesterase inhibitors; Stroke; Dementia; Alzheimer disease; Cohort studies; Registries

1. Introduction

Worldwide, there are more than 46.8 million people with dementia, and this number is projected to increase to 131.5 million by 2050 [1]. In Sweden, an estimated 160,000 individuals have a diagnosis of dementia [2]. Cardiovascular disease (CVD) and its risk factors have been associated with both cognitive impairment and dementia [3]. In particular, people with dementia are at an increased risk of ischemic stroke, with previous studies indicating a twofold greater risk of stroke in people with dementia compared with those without [4–6]. People with dementia who experience a stroke have accelerated functional decline, decreased daily activities, and poorer survival [7–9]. The presence of coexisting stroke in dementia also increases the use and cost of health-care services and increases the burden of care placed on carers and families [10]. In 2015, the total estimated worldwide costs of dementia were US $815 billion [1].

Acetylcholinesterase inhibitors (AChEIs) are indicated for the symptomatic treatment of mild-to-moderate Alzheimer's disease (AD). They inhibit acetylcholinesterase, an enzyme responsible for the breakdown of acetylcholine, a neurotransmitter associated with memory function [11].

Conflicts of interest: The authors have declared that no conflict of interest exists.

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Experimental studies in both animals and humans suggest that these medications have additional endothelial protective effects and anti-inflammatory properties [12,13]. It has been postulated that AChEIs may thus lower the risk of stroke through benefits on endothelial function and inflammatory processes associated with atherosclerosis and ischemic stroke development [8,14].

Our research group has reported that AChEIs reduce the risk of myocardial infarction in people with AD [14]. The aim of this study was to investigate whether AChEIs reduce the risk of ischemic stroke and mortality in people with dementia.

2. Methods

2.1. Data source and study population

This was a cohort study based on people with dementia registered in the Swedish Dementia Registry from 2007 to 2014. The Swedish Dementia Registry is a national quality registry for monitoring the diagnosis, treatment, and care of people with dementia in Sweden [15]. It covers 100% of memory clinics and 75% of primary care units in Sweden. It included a total of 48,133 individuals with newly diagnosed dementia from 2007 to 2014. After excluding those with missing data (n = 3845, 8%), a total of 44,288 people were included in the analyses. Compared with excluded participants, included participants were younger (baseline mean age [standard deviation {SD}]: 79.7 [7.8] years vs. 80.4 [8.6] years, $P < .01$) and had a higher baseline Mini–Mental State Examination (MMSE) (20.4 [6.1] vs. 19.8 [6.3], $P < .01$) but similar distribution of the sexes (women: 59.4% vs. 58.6%, $P = .33$).

2.2. Assessment of demographic, medical, and medication data

Demographic data at baseline were obtained from the Swedish Dementia Registry and included age, sex, MMSE, living situation (institutionalized or living alone vs. living at home with a coresident), home care use, and dementia disorder [15]. Dementia diagnoses were made according to the International Classification of Diseases, Tenth Revision, criteria [16] and coded as AD, vascular dementia, mixed dementia, dementia with Lewy bodies, frontotemporal dementia, Parkinson's disease dementia, unspecified dementia, and other dementia types.

Medical diagnoses in the cohort at baseline and during follow-up were obtained from the Swedish National Patient Register. The Swedish National Patient Register contains prospectively collected information from all inpatient and specialized outpatient visits in Sweden and is maintained by the Swedish National Board of Health and Welfare. The coverage of inpatient discharges is >99% [17]. The medical diagnoses of all individuals are classified according to the International Classification of Diseases, Tenth Revision. The primary outcome of ischemic stroke was defined as the first occurrence of International Classification of Diseases, Tenth Revision code 163.x. History of CVD at the time of dementia diagnosis included acute myocardial infarction (I21.x, I22.x, I25.2), ischemic heart disease (I20.x–I25.x), cerebrovascular disease (G45.x, G46.x, H34.0, I60.x–I69.x), congestive heart failure (I09.9, I11.0, I13.0, I13.2, I50.x), atrial fibrillation (I48.x), and diabetes (E1x.x). Data on all-cause death were obtained from the Swedish Total Population Register. This register is maintained by Statistics Sweden and covers 100% of all deaths in Sweden [18].

Information on dispensed drugs was extracted from the Swedish Prescribed Drug Register. This register contains data with unique patient identifiers for all prescriptions dispensed by pharmacies to the whole population of Sweden. The register is maintained by the National Board of Health and Welfare, and the coverage is >99% [19]. All drugs are classified according to the Anatomical Therapeutic Chemical code. AChEIs were defined as Anatomical Therapeutic Chemical code N06DA. Doses were expressed as prescribed daily dose (PDD), that is, the proportion of defined daily dose for the respective AChEI taken. Doses were based on the last AChEI dispensing. If more than one AChEI was used, then their PDDs were summed. Doses were categorized according to tertiles as low dose (<0.67 PDD), medium dose (0.67–1.32 PDD), and high dose (≥1.33 PDD). Data on other drugs dispensed within the previous 3 months of baseline were also extracted and included diuretics (Anatomical Therapeutic Chemical code, C03), β blockers (C07), calcium channel blockers (C08), angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists (C09), other antihypertensives (C02), lipid-modifying agents (C10), antithrombotics (B01AA and B01AC), antidiabetics (A10), antipsychotics (N05 A), antidepressants (N06 A), and nonsteroidal anti-inflammatory drugs (M01 A).

2.3. Statistical analysis

Baseline differences in the cohort for those who did and did not use AChEIs were compared using descriptive statistics. As there were differences in baseline covariates between users and nonusers of AChEIs, we performed 1:1 propensity score matching. Where possible, each AChEI user was matched with an AChEI nonuser with a similar propensity score, based on nearest-neighbor matching without replacement, using a caliper width equal to 0.1 of the SD of the logit of the propensity score. Based on this, a propensity score-matched cohort of 23,144 people (11,572 users and 11,572 nonusers of AChEIs) was generated. Standardized mean differences were used to assess balance between the AChEI user and nonuser cohorts after matching, with a standardized mean difference less than 0.1 taken to indicate

balance in covariates between groups [20]. A time-dependent variable for AChEI initiation was used to define current users and nonusers. Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for outcomes of interest according to (1) AChEI use; (2) AChEI dose; and (3) AChEI type over the study period in the matched cohorts. Multivariable models were adjusted for all baseline covariates. Given the high mortality rate in this older cohort, competing risk regression was also performed, with all-cause mortality as the competing risk, yielding a subdistribution hazard ratio (sHR) [21]. Survival time was defined as the time from the date of dementia diagnosis to the date of first stroke, date of death, or December 31, 2014, whichever came first. To further assess the robustness of results, we conducted sensitivity analyses including repeating the analyses before matching and adjusting for propensity scores. We also performed stratification of the matched cohorts according to the following subgroups: sex, age, atrial fibrillation, previous stroke, and dementia disorder. As AChEIs are currently indicated for people with AD, we performed a subgroup analysis limited to those with AD (defined as early-onset, late-onset, and mixed dementia) to confirm results. Using similar analytic methods, we created a propensity score-matched AD cohort and repeated the primary and sensitivity analyses. All analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY) and SAS, version 9.4 (SAS Institute, Cary, NC).

2.4. Ethical considerations

This study was approved by the regional human ethics committee in Stockholm (approval number 2015/743-31/4) and registered with the Monash University Human Research Ethics Committee. Data were coded and anonymized before statistical analyses.

3. Results

3.1. Study population characteristics

The study cohort consisted of 44,288 people with a mean age of 79.7 (SD 7.8) years at baseline and the majority being female (59.4%). A total of 25,166 (56.8%) patients received at least one prescription for an AChEI during the study period. The median (quartiles) interval between the first and last dispensing of AChEIs was 595 (189–1165) days. Compared with nonusers, AChEI users were more likely to be younger and female, have higher MMSE scores, live at home with a coresident and were less likely to receive homecare, have a history of CVD, or concomitant use of medications. Regarding dementia disorders, those who used AChEIs were more likely to have AD, mixed dementia, dementia with Lewy bodies, and Parkinson's disease dementia. Of the AChEIs used, donepezil was the most commonly used (54.0%), followed by rivastigmine (24.3%) and galantamine (21.7%). After propensity score matching, we identified 11,572 AChEI users and 11,572 matched controls with similar baseline characteristics. Detailed information regarding demographics of these cohorts is presented in Table 1.

3.2. Risk of ischemic stroke and all-cause mortality in the dementia cohort

During the follow-up period (mean [SD] 836.9 [611.6] days; median [quartiles] 715 [345–1300] days), 2084 people had a stroke, and 11,276 people died. AChEI users had a lower incidence rate of ischemic stroke than matched controls (1.42/100 person-years vs. 2.91/100 person-years) (Table 2). AChEI users in the matched case-control cohort had a lower risk of ischemic stroke (adjusted HR 0.85, 95% CI 0.75–0.95) and all-cause death (aHR 0.76, 95% CI 0.72–0.80) in comparison with matched AChEI nonusers (Table 3). However, after adjusting for all-cause mortality as a competing risk, the association with ischemic stroke was no longer statistically significant.

Of the types of AChEIs, rivastigmine and galantamine were associated with a reduced risk of stroke compared with the matched controls (aHR 0.79, 95% CI 0.65–0.97 and aHR 0.81, 95% CI 0.66–0.99, respectively) (Table 3); however, this did not remain significant when considering the competing risk of death. All AChEI types were associated with a reduced risk of all-cause mortality.

We found a dose-response association between AChEI use and mortality, with risk of death decreasing with increasing AChEI dose. Those patients taking the highest doses of AChEI ($\geq$1.33 PDD) had the lowest risk of stroke (aHR 0.71, 95% CI 0.60–0.84) and all-cause death (aHR 0.60, 95% CI 0.56–0.65) compared with matched nonusers (Table 3). The association between high doses of AChEI and reduced stroke risk remained significant after adjusting for the competing risk of all-cause mortality (sHR 0.78, 95% CI 0.66–0.93). Sensitivity analyses conducted before propensity score matching produced similar results (Supplementary Table A.1).

Stratified analyses of the propensity score-matched cohort revealed that the association between AChEI use and incident ischemic stroke remained significant only in the female, younger age ($<$80 years), and lower MMSE score ($<$21 points) subgroups, including after considering death as a competing risk (sHR 0.83, 95% CI 0.71–0.98, sHR 0.80, 95% CI 0.66–0.97, and sHR 0.79, 95% CI 0.67–0.93), respectively (Table 4).

3.3. Risk of ischemic stroke and all-cause mortality in the AD subgroup

A total of 22,367 people were included in the AD subgroup analysis. Of these, 16,939 (75.7%) were prescribed

Table 1
Characteristics of the dementia cohort according to acetylcholinesterase inhibitor (AChEI) use

	Total cohort			Case-control cohort		
Characteristic	AChEI (n = 25,166)	No AChEI (n = 19,122)	SMD	AChEI (n = 11,572)	No AChEI (n = 11,572)	SMD
Female	15,237 (60.5)	11,057 (57.8)	0.056	6834 (59.1)	6908 (59.7)	−0.013
MMSE	21.3 ± 5.4	19.1 ± 6.7	0.403	20.1 ± 6.0	19.8 ± 6.0	0.038
Age	78.4 ± 7.5	81.4 ± 7.9	−0.399	80.5 ± 7.0	80.8 ± 8.1	−0.040
Residency						
Living alone/institutionalized	11,246 (44.7)	11,381 (59.5)	−0.298	6174 (53.4)	6509 (56.2)	−0.058
Home care	6232 (24.8)	7989 (41.8)	−0.394	4161 (36.0)	4289 (37.1)	−0.026
Dementia disorder						
AD	11,624 (46.2)	2363 (12.4)	0.689	2552 (22.1)	2351 (20.3)	0.037
MixD	5315 (20.7)	3065 (16.0)	0.125	2848 (24.6)	2799 (24.2)	0.010
VaD	1354 (5.4)	6900 (36.1)	−1.361	1353 (11.7)	1551 (13.4)	−0.076
DLB	826 (3.3)	119 (0.6)	0.149	183 (1.6)	119 (1.0)	0.031
FTD	117 (0.5)	478 (2.5)	−0.299	117 (1.0)	117 (1.0)	0.000
PDD	443 (1.8)	203 (1.1)	0.053	204 (1.8)	194 (1.7)	−0.007
Other/unspecified	5487 (21.8)	5994 (31.3)	−0.231	4315 (37.3)	4441 (38.4)	−0.026
Cardiovascular disease at baseline						
Acute myocardial infarction	2193 (8.7)	2882 (15.1)	−0.225	1398 (12.1)	1414 (12.2)	−0.005
Ischemic heart disease	4310 (17.1)	4947 (25.9)	−0.232	2557 (22.1)	2537 (21.9)	−0.005
Atrial fibrillation	3190 (12.7)	4416 (23.1)	0.386	2067 (17.9)	2114 (18.3)	−0.012
Heart failure	1852 (7.4)	3230 (16.9)	−0.365	1395 (12.1)	1435 (12.4)	−0.013
Cerebrovascular disease	3789 (15.1)	5882 (30.8)	−0.439	2517 (21.8)	2591 (22.4)	−0.018
Diabetes	2745 (10.9)	3525 (18.4)	−0.241	1688 (14.6)	1725 (14.9)	−0.010
Drugs at baseline						
Lipid-modifying agents	6263 (24.9)	5312 (27.8)	−0.067	3132 (27.1)	2975 (25.7)	0.031
Antithrombotic agents	10,015 (39.8)	9869 (51.6)	−0.241	5530 (47.8)	5452 (47.1)	0.014
Diuretics	4849 (19.3)	6029 (31.5)	−0.311	3010 (26.0)	3074 (26.6)	−0.014
β-blockers	6834 (27.2)	7244 (37.9)	−0.241	3907 (33.8)	3873 (33.5)	0.007
Calcium channel blockers	4193 (16.7)	3821 (20.0)	−0.089	2203 (19.0)	2196 (19.0)	0.002
ACEIs/ARBs	7157 (28.4)	6738 (35.2)	−0.151	3800 (32.8)	3752 (32.4)	0.009
Other antihypertensives	100 (0.4)	102 (0.5)	−0.022	62 (0.5)	54 (0.5)	0.011
Antidiabetics	2302 (9.1)	2688 (14.1)	−0.170	1356 (11.7)	1381 (11.9)	−0.007
Antipsychotics	1309 (5.2)	1635 (8.6)	−0.151	818 (7.1)	863 (7.5)	−0.018
Antidepressants	6788 (27.0)	5841 (30.5)	−0.081	3467 (30.0)	3352 (29.0)	0.022
NSAIDs	1387 (5.5)	823 (4.3)	0.053	573 (5.0)	5403 (4.7)	0.012

Abbreviations: SMD, standardized mean difference; MMSE, Mini–Mental State Examination; AD, Alzheimer's disease; MixD, mixed dementia; VaD, vascular dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; PDD, Parkinson's disease dementia; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2
Incident rates of ischemic stroke and death in users and nonusers of AChEIs in the dementia cohort

	AChEI users			AChEI nonusers		
Outcome	No of events	Follow-up person-years	Annual rate*	No of events	Follow-up person-years	Annual rate*
Total study cohort						
Before matching						
Ischemic stroke	954	67,355.43	1.42	1130	38,862.81	2.91
All-cause death	5425	67,355.43	8.05	5851	38,862.81	15.06
After matching						
Ischemic stroke	524	28,656.61	1.83	621	24,212.57	2.56
All-cause death	2881	28,656.61	10.05	3307	24,212.57	13.66
AD subgroup						
Before matching						
Ischemic stroke	623	47,081.94	1.32	300	10,630.78	2.82
All-cause death	3607	47,081.94	7.66	1822	10,630.78	17.14
After matching						
Ischemic stroke	236	12,463.39	1.89	281	10,098.08	2.78
All-cause death	1459	12,463.39	11.71	1621	10,098.08	16.05

Abbreviations: AChEI, acetylcholinesterase inhibitor; AD, Alzheimer's disease.
*Per 100 person-years.

Table 3
Association between time-dependent acetylcholinesterase inhibitor use and risk of stroke and death during follow-up in matched cohort (N = 23,144)

	Ischemic stroke				All-cause mortality	
	Adjusted		Competing risk		Adjusted	
AChEI use	HR	95% CI	sHR	95% CI	HR	95% CI
Ever use of AChEI	0.85	0.75–0.95*	0.91	0.81–1.02	0.76	0.72–0.80†
Type						
No use	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Donepezil	0.88	0.77–1.02	0.95	0.83–1.09	0.73	0.69–0.78†
Rivastigmine	0.79	0.65–0.97‡	0.83	0.68–1.02	0.88	0.82–0.96*
Galantamine	0.81	0.66–0.99‡	0.90	0.74–1.10	0.71	0.65–0.77†
Dose						
No use	1.00 (reference)		1.00 (reference)		1.00 (reference)	
Low dose	0.88	0.75–1.03	0.93	0.79–1.08	0.89	0.83–0.95†
Medium dose	1.01	0.85–1.21	1.09	0.91–1.30	0.80	0.74–0.87†
High dose	0.71	0.60–0.84†	0.78	0.66–0.93*	0.60	0.56–0.65†

Abbreviations: HR, hazard ratio; CI, confidence interval; sHR, subdistribution hazard ratio; AChEI, acetylcholinesterase inhibitor.
*$P < .01$.
†$P < .001$.
‡$P < .05$.

an AChEI at least once during the study period. After propensity score matching, 5057 people were identified as AChEI users and 5057 as matched controls with similar baseline characteristics (Supplementary Table A.2). The incidence rate of ischemic stroke was 1.89/100 person-years in AChEI users compared with 2.78/100 person-years in matched controls (Table 2).

Compared with matched controls, users of AChEIs were at a lower risk of all-cause death (aHR 0.72, 95% CI 0.67–0.77) and ischemic stroke (aHR 0.77, 95% CI 0.65–0.92), and the association with ischemic stroke remained significant after considering the competing risk of death (sHR 0.84, 95% CI 0.71–1.00) (Supplementary Table A.3). While all types of AChEI were associated with a reduced risk of all-cause death, only donepezil and galantamine were associated with a reduced risk of ischemic stroke (aHR 0.78, 95% CI 0.63–0.98 and aHR 0.70, 95% CI 0.53–0.91, respectively). However, this association did not remain significant after adjusting for the competing risk of death. A dose-response relationship was also found in the AD subgroup, with increasing dose of AChEI associated with decreasing risk of all-cause death. High doses of AChEI were associated with a reduced risk of ischemic stroke, even after adjusting for death as a competing risk (sHR 0.66, 95% CI 0.50–0.87). Sensitivity analyses conducted before propensity score matching in the AD cohort produced consistent findings (Supplementary Table A.4).

Table 4
Stratified analysis for the effect of AChEI use in the matched cohort for all with dementia (N = 23,144)

	Ischemic stroke				All-cause mortality	
	Adjusted		Competing risk		Adjusted	
Subgroups	HR	95% CI	sHR	95% CI	HR	95% CI
Female (n = 13,742)	0.73	0.66–0.91*	0.83	0.71–0.98†	0.71	0.67–0.76‡
Male (n = 9402)	0.94	0.79–1.12	1.01	0.85–1.20	0.82	0.76–0.89‡
Age <80 years (n = 8854)	0.76	0.62–0.92†	0.80	0.66–0.97†	0.76	0.69–0.84‡
Age ≥80 years (n = 14,290)	0.91	0.78–1.05	0.98	0.85–1.13	0.77	0.72–0.81‡
MMSE <21 (n = 10,639)	0.74	0.63–0.88‡	0.79	0.67–0.93‡	0.74	0.68–0.81‡
MMSE ≥ 21 (n = 12,505)	0.96	0.82–1.14	1.04	0.88–1.22	0.79	0.74–0.84‡
Atrial fibrillation (n = 4181)	0.88	0.71–1.09	0.97	0.78–1.19	0.77	0.69–0.85‡
No atrial fibrillation (n = 18,963)	0.84	0.73–0.96†	0.90	0.78–1.03	0.76	0.72–0.81‡
Previous ischemic stroke (n = 2429)	0.80	0.63–1.02	0.85	0.67–1.08	0.87	0.75–1.01
No previous ischemic stroke (n = 20,715)	0.89	0.77–1.01	0.96	0.84–1.09	0.75	0.71–0.79‡

Abbreviations: HR, hazard ratio; CI, confidence interval; sHR, subdistribution hazard ratio; AChEI, acetylcholinesterase inhibitor; MMSE, Mini–Mental State Examination.
*$P < .01$.
†$P < .05$.
‡$P < .001$.

Stratified analyses of the propensity score-matched AD cohort found that the association between AChEI use and incident ischemic stroke remained significant in those younger than 80 years (sHR 0.67, 95% CI 0.49–0.95), those with a MMSE score less than 21 points (sHR 0.64, 95% CI 0.50–0.82), those with a previous history of ischemic stroke (sHR 0.41, 95% CI 0.27–0.62), and those with mixed dementia (sHR 0.76, 95% CI 0.61–0.94), after considering death as a competing risk (Supplementary Table A.5).

4. Discussion

Our study found that AChEI use in people with dementia was associated with a reduced risk of ischemic stroke and all-cause death compared with matched controls. However, the association with ischemic stroke did not remain significant after considering the competing risk of death. High doses of AChEI were associated with the lowest risk of stroke. Results were similar in our AD subgroup analysis.

A recent Taiwanese study [8] investigated the association between AChEI use and risk of stroke in a smaller cohort of people with dementia. The incident rates of ischemic stroke in AChEI users and matched controls reported in their study (1.60 vs. 2.41/100 person-years, respectively) were similar, albeit slightly lower, to our study. Based on propensity score-matched Cox proportional hazard models with competing risk adjustment, Lin et al. reported a sHR for ischemic stroke risk of 0.51 (95% CI 0.43–0.59). Conversely, after considering competing risk of death, the association between AChEI use and risk of stroke was no longer significant in our study. In contrast to our study, Lin et al. found no significant difference in all-cause mortality in users and nonusers of AChEIs. Higher mortality rates in people with dementia in Taiwan compared with Sweden, as well as differences in study characteristics, may explain reported differences in stroke and death risk associated with AChEI use [8].

Our findings also complement results from a previous study conducted by this research group, which found that AChEI use was associated with a 38% reduced risk of myocardial infarction and 36% lower risk of death in Swedish patients with AD [14]. Whether AChEIs reduce the risk of ischemic stroke and myocardial infarction via similar mechanisms remains to be explored.

Similar to the previously mentioned studies, a dose-response relationship was observed with higher doses of AChEI associated with lower risk of cardiovascular outcomes and death [8,14]. In our study, high doses ($\geq$1.33 PDD) were equivalent to $\geq$10 mg donepezil, $\geq$12 mg rivastigmine, and $\geq$21 mg galantamine per day. We did not observe any differences in stroke risk between the different types of AChEI used, and this is consistent with previous findings [8]. While the different AChEI types have slightly different mechanisms of action, they have been shown to have similar cardiovascular risk profiles [22]. Subgroup analysis revealed that the association between AChEI use and stroke risk reduction remained in women, patients less than 80 years, and those with MMSE scores less than 21 at baseline. In those with AD, the association was also significant in those with mixed pathology and a prior history of stroke. These findings may suggest possible use of AChEIs in secondary stroke prevention in people with AD, especially in those with coexistent vascular pathology.

Several potential mechanisms may explain the stroke-reducing effects of AChEIs. First, atherosclerosis is an inflammatory disease [23], and AChEIs exhibit anti-inflammatory effects through reduced acetylcholine breakdown [14,24]. Both animal and human studies have shown that AChEIs can reduce peripheral cytokine production [12,13,25]. Second, AChEIs may exert protective effects on endothelial dysfunction in people with AD [26]. Experimental studies have shown that AChEIs have angiogenesis-accelerating properties and antiapoptotic effects on endothelial cells [8,27,28]. Third, AChEIs may lower heart rate by potentiating cardiac vagal activity [29]. It is possible that this may attenuate atrial fibrillation, which is a major cause of stroke. These effects may thus explain the possible reduced risk of ischemic stroke with use of AChEIs.

4.1. Strengths and limitations

This study has several strengths and limitations. Strengths lie in the large, representative cohort of people with dementia, which includes all memory clinics and 75% of primary care clinics across Sweden. In addition, a wider range of dementia disorder subtypes were included compared with other studies. The ascertainment of medical diagnoses and medications used national registers that were complete and allowed for follow-up of individuals which eliminated potential for attrition or recall bias. Although we know that medications were dispensed and collected from pharmacies, we did not investigate the impact of medication adherence. Information on education level, which is a significant protective factor for dementia, was not available and thus could not be controlled. The individuals excluded due to missing values differed slightly from the study population in age and MMSE which may have introduced selection bias. We cannot exclude the possibility of bias due to unmeasured confounding, in particular, confounding by indication. It is likely that people who were perceived to experience therapeutic benefit were more likely to be prescribed an AChEI. This means that certain people, such as those who are older, have more severe coexisting diseases, and more severe cognitive impairment are less likely to be prescribed an AChEI. We tried to address this issue by using propensity score matching to balance baseline covariates associated with stroke risk across cohorts. Although we adjusted for a range of

covariates, it was not possible to control for all factors that may influence a physician's decision to prescribe an AChEI. In addition, those individuals who were prescribed higher doses of AChEIs may have had characteristics that made them less likely to experience an event compared with those using lower doses of AChEIs or nonusers. Users of AChEIs were defined based on instance of first prescription; however, it is possible that participants did not persist with therapy during the time of the outcome. Doses of AChEIs were based on the last dispensed prescription, and this may not be reflective of the doses used throughout the entire study period. The use of cumulative exposure may better capture dose and duration, and this should be used in future studies where possible. In contrast to most previous studies, we addressed issues of potential survival bias by conducting competing risks regression.

5. Conclusions

In conclusion, AChEI use was associated with a reduced risk of ischemic stroke and death in people with dementia. A dose-response relationship was observed with only high doses of AChEI remaining significantly associated with lower stroke risk after adjusting for competing risk of death. Given that CVD is a major cause of death worldwide, including in people with dementia, further research into the cardiovascular benefits of AChEIs is needed.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2018.02.011.

RESEARCH IN CONTEXT

1. Systematic review: The authors searched conventional databases (e.g., PubMed) for relevant literature. Acetylcholinesterase inhibitors (AChEIs) have vagotonic, anti-inflammatory, and endothelial protective properties which may lower the risk of stroke. Few studies have investigated the association between AChEI use and ischemic stroke in people with dementia. Relevant studies have been cited appropriately.
2. Interpretation: In this nationwide cohort of people with dementia, AChEI use was associated with a reduced risk of ischemic stroke and death, especially at higher doses. In those with Alzheimer's disease, the association remained significant in people <80 years, those with a history of previous ischemic stroke, and those with a mixed dementia diagnosis.
3. Future directions: This study highlights the potential for AChEIs to lower ischemic stroke risk. These findings may inform future intervention studies of AChEIs in stroke prevention in people with dementia.

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