Cholinesterase Inhibitors and Neuropathology of Cerebrovascular Disease and Other Dementias in Patients with Alzheimer's Disease: A Study of NACC Autopsy and Medical History Data, 2005 – 2017

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Abstract

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In vitro testing of cholinesterase inhibitors suggested protective effects against neuronal toxicity from multiple sources. Investigations in primates found ChEI restored cerebral blood flow. Work in animals suggests ChEI may have a neuroprotective effect, though not necessarily impacting pathologies associated with Alzheimer's Disease. Imaging studies had inconsistent results. Our objective was to assess the impact of ChEI on cerebrovascular or neurodegenerative pathologies in patients with AD. Using the National Alzheimer's Coordinating Center database, we identified 2245 individuals with at least two annual visits where medications were recorded, an etiologic clinical diagnosis of AD, and who had died and completed neuropathological examination at autopsy. Generalized Estimating Equations were used to calculate the association between use of AD or cardiovascular medications and dementia pathology. Approximately 67% of the study population reported using a ChEI. Microinfarcts were negatively associated with rivastigmine (OR: 0.61; 95% CI: 0.37 – 0.99) and AD pathology was positively associated with use of donepezil (OR: 1.43; 95% CI: 1.04 – 1.96). Our findings suggest some value in further exploring the pathological impacts of ChEI.

Introduction:

Cholinesterase inhibitors (ChEI) are a class of medication used to treat Alzheimer's disease (AD). Donepezil, rivastigmine, and galantamine are three common CHEI drugs for the management of cognitive symptoms AD[1]. For on-label use, patients must experience notable cognitive decline prior to prescription of these agents as they are only approved to slow progression of symptoms, not to modify the disease pathology itself.

The underlying neuropathologic features necessary for a diagnosis of AD neuropathologic change are: (1) A-beta amyloid deposition (as indicated by Thal score-- "A" score)[2]; (2) the frequency and extent of neurofibrillary tangles (per Braak score or "B" score)[3]; and, (3) the occurrence of neuritic plaques as noted by the semi quantitative CERAD neuritic plaque score ("C" score)[4]. The frequency with which the combination of each of these is present in the brain determines the likelihood that an Alzheimer's disease neuropathologic diagnosis is warranted[5]. Evaluation of all are necessary for a pathologic diagnosis i.e., the overall ABC score.

While these pathologic features are indicative of AD itself, regardless of the presence of symptoms, there are frequently other coexisting pathologies. Lewy bodies (primarily aggregated alpha synuclein) are traditionally associated with Parkinson's disease and Dementia with Lewy bodies, but are frequently present along with AD neuropathologic features[2]. There are also several features of cerebrovascular disease that can be present in the brain and also can contribute to cognitive impairment[6,7]. The effect that the AD medications of interest have on these other pathologies is largely unexplored. Although the specific mechanism of ChEI action is at the neuronal synapses, to provide for more neurotransmitter by slowing degradation of acetylcholine through inhibiting acetylcholinesterase, ChEIs may have other actions that impact other disease processes.

Some *in vitro* testing of cholinesterase inhibitors suggested that they may be protective against neuronal toxicity from multiple sources. The toxic effects of exogenous amyloid-beta protein on rat neurons were mitigated by prophylactic exposure to donepezil[8]. Pre-treatment with donepezil was also protective against oxygen-glucose deprivation, an insult mimicking the effects of cerebral ischemia[9]; pre-treated cells were less likely to show signs of oxidative stress, i.e. increased activity of superoxide dismutase, than those without treatment[10]. When the same model of ischemia was used on cultured neurons treated with galantamine and rivastigmine, no protective effects were found[11]. However, the same research suggested that donepezil and galantamine were both protective against glutamate neurotoxicity[11]. Despite all acting on cholinesterase, the pharmacokinetics of these medications differ, meaning that their effects on progression of pathology may differ as well.

To further examine the potential of cholinesterase inhibitors to alter the progression of AD, the medication has been applied to animal models. Transgenic mice treated with donepezil showed improved cognitive abilities, indicating successful treatment of symptoms. They also displayed decreased cholinergic loss compared to those that did not undergo treatment, but no significant difference was found in the severity of tauopathies[12]. Investigations also found that cholinesterase inhibitors restored cerebral blood flow in primates providing additional support for the hypothesis that this class of medications may have some impact on pathology[13,14]. The work in animals suggests that there may be a neuroprotective effect from cholinesterase inhibitors, though they may not impact the pathologies typically associated with AD.

Imaging (specifically MRI) has been used to investigate potential effects of cholinesterase inhibitors on neuronal atrophy as well as vascular indicators. One such study found that randomized use of donepezil didn’t significantly reduce the rate of hippocampal

atrophy[15], while another did find a significant reduction in the rate of hippocampal atrophy[16]. These differences may be the results of differences in methodology; findings were only significant when patients self-selected use of donepezil, rather than being randomly assigned to a treatment group. Additionally, the follow-up time in the study with significant findings was shorter; this could suggest that there is a short-term effect on hippocampal atrophy, but over the long-term the impact of donepezil is insignificant.

PET scans, based on several radio-labeled ligands, now allow for the *in vivo* visualization of the location and severity of amyloid and tau deposits[17]. While the imaging methodology exists, it has not been well utilized to assess the effects of ChEI on pathology. Through a combination of PET imaging and measurements of A-beta and tau from CSF, one study suggested that use of a cholinesterase inhibitor helped to stabilize cerebral metabolic rate for glucose[18]. The sample size in this investigation was very limited implying that further exploration with larger numbers would be beneficial. Though NACC collects some imaging data, there are currently relatively few individuals in the NACC database who have neuropathology data and segmented summary volumes based on MRI calculated and that overlap with the current study series. This makes information collected at autopsy a unique opportunity, even though it is the final stage of pathology rather than progression over time as might be observed through serial imaging.

It is widely accepted in the research community that these medications (ChEI) are not disease modifying with regards to AD pathology[19]. However, we will be able to explore the effects of ChEI on AD as well as other co-occurring pathologies. AD pathology occurs frequently in conjunction with vascular disease and/or Lewy body disease, and it is perhaps the combination of these brain insults that would lead to an earlier or more severe expression of

cognitive symptoms. If the use of cholinesterase inhibitors does play a role modifying vascular disease, Lewy Body pathology or even AD pathology, this would suggest that dementia patients may be receiving unexpected benefit from ChEIs. By introducing medication that would alter progression disease-specific or co-morbid pathologies before substantial advancement of pathology occurs, those with AD pathology could have a delayed onset of dementia thereby granting them a higher quality of life. Given the current evidence that ChEIs appear to have little effect on AD pathology, the more likely path for preventive treatment is through the potential reduction of co-morbid brain pathologies that also contribute to the expression of dementia symptoms.

Methods:

Study Design, Data Sources, and Population:

The National Alzheimer's Coordinating Center (NACC) maintains data from 36 active and inactive, NIA-funded, Alzheimer's Disease Centers (ADC) across the United States. All of the enrollees at each ADC are examined following the annual protocol of the Uniform Data Set (UDS), and the resulting data are uploaded to the NACC database[20]. Demographic characteristics, health history, medication use, and assessments of cognitive status are among data collected from participants both with and without cognitive impairment [20]. Some of the enrolled participants consent and undergo autopsy with standardized neuropathologic exam at the ADCs, allowing for the collection of neuropathology data in a standardized fashion across all ADCs, such that those data are stored in the NACC database. NACC makes deidentified clinical and neuropathologic data available to researchers [21]. This study was exempt from review by the University of Washington Institutional Review Board since NACC is a data repository consistent

with Private Health Information (PHI) restrictions consistent with HIPAA for a Research limited data set and NACC also holds a NIH Certificate of Confidentiality.

Neuropathology data were available for 4819 individuals (approximately 50-60% of all decedents). Patients with fewer than two visits providing medication data were excluded to ensure patients remained on a ChEI (n=1338). Individuals never receiving a dementia diagnosis were also excluded from analysis (n=720), because they would not have been indicated for on-label use of a ChEI. Additionally, persons who did not have a primary or contributing etiologic diagnosis of Alzheimer's disease were not included (n=516). The final study population consisted of 2245 individuals, 1502 of whom reported use of a cholinesterase inhibitor at two or more visits (Figure 1).

Outcomes:

Neuropathologic features were assessed at autopsy applying a standardized neuropathologic examination for all subjects; such data were captured by the Neuropathology Data Set and stored in the NACC database. Our primary outcomes of interest were cerebrovascular pathologies: infarcts and hemorrhages (any or none), microinfarcts (any or none), arteriolosclerosis (moderate/severe or none/mild), and cerebral amyloid angiopathy (moderate/severe or none/mild). Alzheimer's disease pathology was also assessed. Consistent with the NIA-AA criteria, Alzheimer's disease pathology was defined as having Braak stage of three or higher and a CERAD neuritic plaque score of two or greater[5]. Lewy Bodies were an additional pathology of interest and analysis assessed presence of any Lewy Bodies at autopsy.

Exposures and Potential Confounders:

The primary medications (exposures) of interest were rivastigmine, galantamine, and donepezil; these are also referred to as cholinesterase inhibitors (ChEI). Memantine is also given for moderate dementia symptoms, most often in conjunction with ChEIs, but focuses on glutamate and NMDA receptors instead of acetylcholinesterase. We also included memantine in analysis to account for its potential effect. Other medications of interest included ACE inhibitors, beta-blockers, calcium channel inhibitors, vasodilators, angiotensin II inhibitors, lipid lowering medications, and anticoagulants, primarily because of their known impact on vascular disease. Individuals tend to stay on ChEIs and the vascular medications, once they are prescribed and if they are well tolerated. Thus, we considered persons exposed (to each) if they reported use of the medication at two or more annual visits. Persons reporting use of medications for only one visit were considered unexposed as discontinuation in the interval until next annual follow-up was likely due to intolerance.

Several potential confounders were identified *a priori*. Participants' sex, age at death, age at symptom onset, race (white or other), APOE E4 carrier status (at least one e4 allele), education (no completion of high school, high school diploma, bachelor's degree, or advanced degree), and marital status (married/domestic partner, widowed, or divorced/separated) were all considered. Education is thought to affect the occurrence and progression of symptoms through the ability to cope with cognitive problems (a.k.a., cognitive reserve) as well as the likelihood of receiving ChEIs; marital status potentially influences use of ChEIs. Though there was concern that use of Carbidopa-Levodopa would be a confounding factor, none of the participants in the final study population reported use for more than one visit.

Statistical Analyses:

Logistic regression using general estimating equations to account for clustering by ADC yielded odds ratios and confidence intervals measuring the association between medication and pathology[22]. The relationship was assessed separately for each of the neuropathologic features. The covariance was assumed to have an exchangeable correlation structure. The analyses were conducted in R (version 3.4.3) through the RStudio interface (version 1.1.419). Most *a priori* confounders were included in final adjusted model, though race was excluded as less than 1% of the population was non-white. Final models also included medications of interest if they were associated with the outcome at $p < 0.10$ in a bivariate analysis.

Results:

Among the 2245 participants, 67% reported having used a cholinesterase inhibitor. Participants that had used a cholinesterase inhibitor tended to be younger at symptom onset and younger at time of death (Table 1). They were also more likely to be male (59% vs 49%) and a APOE E4 carrier (57% vs 45%). Users of cholinesterase inhibitors were also more likely to use memantine (64% vs 16%), lipid lowering medications (48% vs 31%), and anticoagulants (45% vs 36%).

Cerebrovascular Pathology:

In this study, 449 autopsies revealed infarcts or hemorrhages (Table 2A). This pathology was more common among individuals had used beta-blockers (adjusted OR: 1.31; 95% CI: 1.02 – 1.67), but was not significantly associated with use of ChEI. Microinfarcts were identified in 457 individuals (Table 2B), and the final model showed a negative association with use of rivastigmine (AOR: 0.61; 95% CI: 0.37 – 0.99). However, microinfarcts were positively

associated with the use of anticoagulants (AOR: 1.30; 95% CI: 1.04 – 1.62). Arteriolosclerosis was more common in the population, affecting 942 individuals (Table 2C), but there were no significant associations with any of the medications of interest. Cerebral amyloid angiopathy occurred in 840 participants (Table 2D) and was positively associated with the APOE E4 allele (AOR: 2.00; 95% CI: 1.58 – 2.54).

Other Pathology:

In this data set, 1751 participants had AD pathology (Table 3A). Among individuals with AD pathology, the APOE E4 allele was more common (AOR: 2.92; 95% CI: 2.18 – 3.91) as expected. Donepezil (AOR: 1.43; 95% CI: 1.04 – 1.96) and memantine use (AOR: 1.81; 95% CI: 1.38 – 2.37) were also associated with AD pathology (as clinical AD symptoms were necessary for their prescription). Lewy body pathology was present in 865 people (Table 3B). These participants were also more likely to be carriers of the APOE E4 allele (AOR: 1.28; 95% CI: 1.01 – 1.57) and to have used memantine (AOR: 1.29; 95% CI: 1.03 – 1.61), but they were less likely to have used angiotensin II inhibitors (AOR: 0.59; 95% CI: 0.45 – 0.79) or anticoagulants (AOR: 0.83; 95% CI: 0.71 – 0.98). Autopsy revealed neocortical Lewy Bodies in 320 individuals (Table 3C); their presence was not significantly associated with any of the exposures of interest.

Discussion:

In this study of AD patients, ChEI was associated with variations in some forms of vascular neuropathology. Individuals that had reported use of rivastigmine were less likely to have microinfarcts identified at autopsy. Additionally, cardiovascular medications were

associated with neurodegenerative pathologies; the autopsies of persons having used angiotensin II inhibitors or anticoagulants showed Lewy bodies less frequently.

Congruent with the theory supported by *in vitro* studies and the results of animal studies, vascular pathology (e.g. microinfarcts) were less common among individuals using rivastigmine[13,14]. Other vascular pathology was also associated with medication exposure. Evidence of infarcts or hemorrhages and microinfarcts were more common among individuals using some cardiovascular medications, beta-blockers and anticoagulants, respectively. This is possibly the result of confounding by indication; prior vascular events or risk factors that may have resulted in the cerebrovascular pathology also indicated use of these medications. Cerebral amyloid angiopathy was associated with having one or more APOE E4 alleles. Because this pathology is caused by amyloid deposition[23], this is not entirely unsurprising; however, it is worth noting that this relationship was observed even after adjusting for the presence of typical AD pathology. This may indicate that the impact of APOE E4 on cerebral amyloid angiopathy go beyond what is mediated by AD pathology.

Among other dementia pathologies, there were several significant associations. One or more APOE E4 alleles, use of donepezil, and use of memantine were all more common among those with AD pathology. This is not particularly surprising as the relationship between APOE E4 and AD pathology is well documented[24,25]. Like vascular pathology, one would expect that there is also some confounding by indication in the association between use of memory enhancing medications (i.e. donepezil and memantine) and AD pathology. One might expect that more severe pathology would indicate use of one of these medications and their role in AD pathology is by no means causal. Lewy body pathology was more common with APOE E4, even after adjustment for the presence of AD pathology, but less common among users of angiotensin

II inhibitors and anticoagulants. Prior investigations have similarly found a relationship between APOE E4 and dementia with Lewy bodies[26,27]. Some previous work has found a similar relationship between reduced α-synuclein aggregation and anticoagulants[28], though this was dependent on the type of anticoagulant as heparin and other glycosaminoglycans were associated with increased α-synuclein in other *in vitro* research[29].

There are limitations to this study. Because the outcome data is measured only at autopsy, we have no way to see how ChEI may impact the development of pathology or rate of onset. It is possible that while pathology was not markedly different at the time of death, use of ChEI may have temporarily slowed the progress of pathology. In this instance, the ChEI would in fact be modifying disease progression, even if the pathology was ultimately similar. An additional limitation is confounding by indication, that another condition that indicated use of medication could be associated with pathology or the symptoms of the pathology indicated use of the medication. While some specific instances of this type of confounding are previously noted, this is still an important potential source of bias to consider when interpreting other results. Finally, these analyses only address final occurrence of pathology; several of the *in vitro* investigations suggested that ChEI were protective against the damage that the pathology may cause, though not necessarily the pathology itself[8–11]. As the cross-sectional nature of the outcome data limits our ability to measure damage that may occur over time, these potential benefits could not be adequately explored in this analysis.

Our findings suggest that there may be value in further exploring the pathological impacts of ChEI through imaging. Imaging technology would allow for the investigation of pathologic changes over time and may provide more insight into some of the mechanisms. Additionally, despite usually being reserved for patients with an AD diagnosis, these analyses

suggest that there may be a potential benefit in using ChEI in patients for whom the primary concern is cerebrovascular disease. Taken with the prior literature, it also suggests potential benefits of anticoagulants against aggregation of α-synuclein. Though other factors should be considered before prescribing these medications for off-label use, it may be worthwhile to further evaluate the potential neuropathologic benefits of some of these medications.

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Table 1 – Descriptive Statistics by Cholinesterase Inhibitor Use

	No Single Cholinesterase Inhibitor for Two or More Visits (n = 743)	Rivastigmine (n=162)	Galantamine (n=237)	Donepezil (n=1111)	Total* (n = 2245)
Age at Autopsy (mean (sd))	83.7 (10.6)	79.4 (9.7)	80.6 (9.9)	80.6 (10.1)	81.5 (10.4)
Age at Diagnosis (mean(sd))	72.6 (11.2)	68.7 (9.9)	69.3 (9.8)	69.9 (10.1)	70.5 (10.5)
Male	367 (49.4%)	96 (59.3%)	154 (65.0%)	635 (57.2%)	1245 (55.5%)
APOE E4 (at least one allele)	297 (45.3%)	88 (57.5%)	132 (59.7%)	580 (56.6%)	1094 (53.5%)
Race					
White	738 (99.3%)	161 (99.4%)	235 (99.2%)	1105 (99.5%)	2232 (99.4%)
Other	5 (0.7%)	1 (0.6%)	2 (0.8%)	6 (0.5%)	13 (0.6%)
Education					
No Diploma	52 (7.1%)	7 (4.3%)	20 (8.4%)	72 (6.5%)	147 (6.6%)
High School	290 (39.5%)	58 (36.0%)	84 (35.4%)	415 (37.6%)	848 (38.1%)
Bachelor's Degree	194 (26.4%)	56 (34.8%)	63 (26.6%)	318 (28.8%)	625 (28.1%)
Advanced Degree	199 (27.1%)	40 (24.8%)	70 (29.5%)	298 (27.0%)	608 (27.3%)
Marital Status					
Married/Domestic Partner	649 (87.3%)	150 (92.6%)	218 (92.0%)	1013 (91.2%)	2021 (90.0%)
Widowed	58 (7.8%)	8 (4.9%)	11 (4.6%)	58 (5.2%)	136 (6.1%)
Divorced/Separated	36 (4.8%)	4 (2.5%)	8 (3.4%)	40 (3.6%)	88 (3.9%)
Other Medication Use					
Memantine Use	121 (16.3%)	113 (69.8%)	161 (67.9%)	700 (63.0%)	1082 (48.2%)
Any Hypertensives	398 (53.6%)	101 (62.3%)	140 (59.1%)	634 (57.1%)	1267 (56.4%)
Anticoagulants	268 (36.1%)	83 (51.2%)	114 (48.1%)	493 (44.4%)	944 (42.0%)
Lipid Lowering Medication	232 (31.2%)	83 (51.2%)	114 (48.1%)	523 (47.1%)	945 (42.1%)

*Numbers in table may not sum to total as some participants were users of multiple cholinesterase inhibitors.

Table 2A – Infarcts and Hemorrhages in relation to memory medication and cardiovascular medication

	No Infarcts or Hemorrhages	Infarct or Hemorrhage	Odds Ratio (95% CI)	
	n = 1790 | %	n = 449 | %	Crude	Adjusted*
At Least One APOE E4 Allele	875 (53.5%)	218 (53.8%)	1.04 (0.85 - 1.27)	-
Dementia Medication				
Rivastigmine	126 (7.0%)	36 (8.0%)	1.24 (0.85 - 1.81)	-
Galantamine	191 (10.7%)	46 (10.2%)	1.00 (0.73 - 1.38)	-
Donepezil	910 (50.8%)	199 (44.3%)	0.80 (0.66 - 0.97)	0.93 (0.77 - 1.13)
Memantine	890 (49.7%)	279 (62.1%)	0.80 (0.64 - 1.02)	1.04 (0.78 - 1.37)
Cardiovascular Medication				
ACE Inhibitor	316 (17.7%)	106 (23.6%)	1.47 (1.17 - 1.84)	1.26 (0.95 - 1.66)
Calcium Channel Blocker	263 (14.7%)	87 (19.4%)	1.37 (1.06 - 1.75)	1.04 (0.75 - 1.44)
Beta-Blockers	364 (20.3%)	128 (28.5%)	1.55 (1.21 - 1.99)	1.31 (1.02 - 1.67)
Vasodilators	50 (2.8%)	21 (4.7%)	1.66 (1.04 - 2.65)	1.22 (0.60 - 2.50)
Angiotensin II Inhibitors	137 (7.7%)	36 (8.0%)	1.00 (0.72 - 1.38)	-
Lipid Lowering	746 (41.7%)	198 (44.1%)	1.17 (0.95 - 1.43)	-
Anticoagulants	721 (40.3%)	222 (49.4%)	1.47 (1.24 - 1.76)	1.09 (0.88 - 1.36)

* Adjusted for age at symptom onset, age at death, education, marital status, NIA center, presence of Alzheimer's Disease pathology, presence of Lewy Body pathology, and present variables significant at 0.10 in univariate analysis

Table 2B – Microinfarcts in relation to memory medication and cardiovascular medication

	No Microinfarcts	Microinfarcts	Odds Ratio (95% CI)	
	n = 1786 | %	n = 457 | %	Crude	Adjusted*
At Least One APOE E4 Allele	866 (53.2%)	227 (54.7%)	1.07 (0.87 - 1.31)	-
Dementia Medication				
Rivastigmine	138 (7.7%)	24 (5.3%)	0.71 (0.49 - 1.01)	0.61 (0.37 - 0.99)
Galantamine	192 (10.8%)	45 (9.8%)	0.92 (0.62 - 1.37)	-
Donepezil	905 (50.7%)	206 (45.1%)	0.79 (0.66 - 0.96)	0.79 (0.62 - 1.00)
Memantine	879 (49.2%)	203 (44.4%)	0.82 (0.66 - 1.01)	1.06 (0.81 - 1.39)
Cardiovascular Medication				
ACE Inhibitor	334 (18.7%)	90 (19.7%)	1.16 (0.89 - 1.50)	-
Calcium Channel Blocker	264 (14.8%)	86 (18.8%)	1.43 (1.16 - 1.76)	1.10 (0.80 - 1.51)
Beta-Blockers	384 (21.5%)	108 (23.6%)	1.16 (0.97 - 1.38)	-
Vasodilators	60 (3.4%)	11 (2.4%)	0.87 (0.51 - 1.47)	-
Angiotensin II Inhibitors	132 (7.4%)	41 (9.0%)	1.22 (0.85 - 1.77)	-
Lipid Lowering	738 (41.3%)	207 (45.3%)	1.28 (1.04 - 1.59)	1.18 (0.93 - 1.50)
Anticoagulants	704 (39.4%)	240 (52.5%)	1.67 (1.40 - 1.98)	1.30 (1.04 - 1.62)

* Adjusted for age at symptom onset, age at death, education, marital status, NIA center, presence of Alzheimer's Disease pathology, presence of Lewy Body pathology, and present variables significant at 0.10 in univariate analysis

Table 2C – Arteriosclerosis in relation to memory medication and cardiovascular medication

	No Arteriolosclerosis	Arteriolosclerosis	Odds Ratio (95% CI)	
	n = 1043 | %	n = 942 | %	Crude	Adjusted*
At Least One APOE E4 Allele	487 (52.1%)	469 (54.7%)	1.02 (0.90 - 1.16)	-
Dementia Medication				
Rivastigmine	74 (7.1%)	72 (7.6%)	1.10 (0.85 - 1.43)	-
Galantamine	108 (10.4%)	90 (9.6%)	0.87 (0.62 - 1.21)	-
Donepezil	529 (50.7%)	458 (48.6%)	0.94 (0.77 - 1.15)	-
Memantine	520 (49.9%)	455 (48.3%)	0.86 (0.68 - 1.09)	-
Cardiovascular Medication				
ACE Inhibitor	185 (17.7%)	197 (20.9%)	1.30 (1.10 - 1.53)	1.18 (0.96 - 1.45)
Calcium Channel Blocker	147 (14.1%)	155 (16.5%)	1.48 (1.22 - 1.81)	1.11 (0.89 - 1.39)
Beta-Blockers	204 (19.6%)	224 (23.8%)	1.44 (1.20 - 1.72)	1.22 (0.97 - 1.52)
Vasodilators	33 (3.2%)	28 (3.0%)	1.15 (0.80 - 1.66)	-
Angiotensin II Inhibitors	79 (7.6%)	81 (8.6%)	1.21 (0.94 - 1.57)	-
Lipid Lowering	441 (42.3%)	410 (43.5%)	1.17 (0.99 - 1.37)	1.10 (0.92 - 1.33)
Anticoagulants	441 (42.3%)	410 (43.5%)	1.20 (1.03 - 1.40)	0.97 (0.78 - 1.19)

* Adjusted for age at symptom onset, age at death, education, marital status, NIA center, presence of Alzheimer's Disease pathology, presence of Lewy Body pathology, and present variables significant at 0.10 in univariate analysis

Table 2D – Cerebral Amyloid Angiopathy in relation to memory medication and cardiovascular medication

	No Cerebral Amyloid Angiopathy	Cerebral Amyloid Angiopathy	Odds Ratio (95% CI)	
	n = 1350 | %	n = 840 | %	Crude	Adjusted*
At Least One APOE E4 Allele	553 (44.9%)	507 (67.1%)	2.37 (1.88 - 2.99)	2.00 (1.58 - 2.54)
Dementia Medication				
Rivastigmine	91 (6.7%)	69 (8.2%)	1.14 (0.86 - 1.51)	-
Galantamine	152 (11.3%)	74 (8.8%)	0.72 (0.58 - 0.91)	0.77 (0.58 - 1.01)
Donepezil	625 (46.3%)	458 (54.5%)	1.39 (1.08 - 1.80)	1.20 (0.95 - 1.52)
Memantine	626 (46.4%)	429 (51.1%)	1.19 (0.95 - 1.48)	-
Cardiovascular Medication				
ACE Inhibitor	266 (19.7%)	147 (17.5%)	0.86 (0.72 - 1.01)	0.92 (0.75 - 1.13)
Calcium Channel Blocker	222 (16.4%)	118 (14.0%)	0.89 (0.69 - 1.14)	-
Beta-Blockers	314 (23.3%)	163 (19.4%)	0.86 (0.71 - 1.05)	-
Vasodilators	48 (3.6%)	19 (2.3%)	0.69 (0.45 - 1.06)	0.68 (0.37 - 1.24)
Angiotensin II Inhibitors	108 (8.0%)	61 (7.3%)	0.94 (0.69 - 1.28)	-
Lipid Lowering	578 (42.8%)	344 (34.0%)	1.00 (0.83 - 1.21)	-
Anticoagulants	598 (44.3%)	331 (39.4%)	0.92 (0.78 - 1.09)	-

* Adjusted for age at symptom onset, age at death, education, marital status, NIA center, presence of Alzheimer's Disease pathology, presence of Lewy Body pathology, and present variables significant at 0.10 in univariate analysis

Table 3A – Alzheimer Disease pathology in relation to memory medication and cardiovascular medication

	No AD Pathology	AD Pathology	Odds Ratio (95% CI)	
	n = 476 | 21.4%	n = 1751 | 78.6%	Crude	Adjusted†
At Least One APOE E4 Allele	147 (34.2%)	942 (58.9%)	2.71 (1.97 - 3.73)	2.92 (2.18 - 3.91)
Dementia Medication				
Rivastigmine	28 (5.9%)	133 (7.6%)	1.24 (0.84 - 1.83)	-
Galantamine	51 (10.7%)	184 (10.5%)	1.17 (0.81 - 1.69)	-
Donepezil	165 (34.7%)	940 (53.7%)	1.96 (1.52 - 2.53)	1.43 (1.04 - 1.96)
Memantine	159 (33.4%)	916 (52.3%)	2.07 (1.48 - 2.89)	1.81 (1.38 - 2.37)
Cardiovascular Medication				
ACE Inhibitor	92 (19.3%)	330 (18.8%)	0.94 (0.74 - 1.20)	-
Calcium Channel Blocker	93 (19.5%)	255 (14.6%)	0.79 (0.56 - 1.12)	-
Beta-Blockers	126 (26.5%)	362 (20.7%)	0.78 (0.59 - 1.02)	0.83 (0.62 - 1.11)
Vasodilators	27 (5.7%)	43 (2.5%)	0.57 (0.39 - 0.84)	0.72 (0.37 - 1.37)
Angiotensin II Inhibitors	42 (8.8%)	131 (7.5%)	0.81 (0.53 - 1.22)	-
Lipid Lowering	205 (43.1%)	732 (41.8%)	0.89 (0.68 - 1.17)	-
Anticoagulants	217 (45.6%)	718 (41.0%)	0.84 (0.67 - 1.05)	-

† Adjusted for age at symptom onset, age at death, education, marital status, NIA center, presence of Lewy Body Pathology, microinfarcts, arteriolosclerosis, and present variables

Table 3B – Any Lewy Body Pathology in relation to memory medication and cardiovascular medication

	No Lewy Body Pathology	Any Lewy Body Pathology	Odds Ratio (95% CI)	
	n = 1367 | 61.2%	n = 865 | 38.8%	Crude	Adjusted‡
At Least One APOE E4 Allele	615 (49.5%)	474 (59.8%)	1.42 (1.18 - 1.71)	1.28 (1.04 - 1.57)
Dementia Medication				
Rivastigmine	83 (6.1%)	78 (9.0%)	1.39 (1.08 - 1.79)	1.29 (0.91 - 1.81)
Galantamine	131 (9.6%)	105 (12.1%)	1.20 (0.93 - 1.55)	-
Donepezil	651 (47.6%)	455 (52.6%)	1.18 (0.97 - 1.43)	1.14 (0.95 - 1.36)
Memantine	608 (44.5%)	470 (54.3%)	1.37 (1.12 - 1.66)	1.29 (1.03 - 1.61)
Cardiovascular Medication				
ACE Inhibitor	275 (20.1%)	146 (16.9%)	0.81 (0.67 - 0.99)	0.94 (0.75 - 1.18)
Calcium Channel Blocker	217 (15.9%)	129 (14.9%)	0.93 (0.71 - 1.22)	-
Beta-Blockers	326 (23.8%)	163 (18.8%)	0.74 (0.60 - 0.92)	0.84 (0.63 - 1.13)
Vasodilators	44 (3.2%)	26 (3.0%)	1.01 (0.58 - 1.77)	-
Angiotensin II Inhibitors	119 (8.7%)	53 (6.1%)	0.66 (0.47 - 0.94)	0.59 (0.45 - 0.79)
Lipid Lowering	562 (41.1%)	376 (43.5%)	1.12 (0.94 - 1.33)	-
Anticoagulants	595 (43.5%)	344 (39.8%)	0.86 (0.73 - 1.00)	0.83 (0.71 - 0.98)

‡ Adjusted for age at symptom onset, age at death, education, marital status, NIA center, presence of Alzheimer's Disease pathology, cerebral amyloid angiopathy, microinfarcts, arteriolosclerosis, and present variables

Table 3C – Neocortical Lewy Bodies in relation to memory medication and cardiovascular medication

	No Neocortical Lewy Bodies	Neocortical Lewy Bodies	Odds Ratio (95% CI)	
	n = 1912 | 85.7%	n = 320 | 14.3%	Crude	Adjusted‡
At Least One APOE E4 Allele	912 (52.3%)	177 (60.8%)	1.38 (1.09 - 1.75)	1.32 (0.98 - 1.77)
Dementia Medication				
Rivastigmine	138 (7.2%)	23 (7.2%)	0.97 (0.62 - 1.50)	-
Galantamine	197 (10.3%)	39 (12.2%)	1.19 (0.87 - 1.62)	-
Donepezil	931 (48.7%)	175 (54.7%)	1.25 (1.03 - 1.51)	1.18(0.91 - 1.52)
Memantine	909 (47.5%)	169 (52.8%)	1.18 (0.90 - 1.54)	-
Cardiovascular Medication				
ACE Inhibitor	370 (19.4%)	51 (15.9%)	0.79 (0.59 - 1.05)	-
Calcium Channel Blocker	298 (15.6%)	48 (15.0%)	0.96 (0.70 - 1.31)	-
Beta-Blockers	432 (22.6%)	57 (17.8%)	0.73 (0.52 - 1.04)	0.77 (0.51 - 1.16)
Vasodilators	59 (3.1%)	11 (3.4%)	1.14 (0.46 - 2.84)	-
Angiotensin II Inhibitors	153 (8.0%)	19 (5.9%)	0.71 (0.44 - 1.16)	-
Lipid Lowering	780 (40.8%)	158 (49.4%)	1.40 (1.12 - 1.75)	1.34 (0.99 - 1.81)
Anticoagulants	797 (41.7%)	142 (44.4%)	1.11 (0.91 - 1.35)	-

‡ Adjusted for age at symptom onset, age at death, education, marital status, NIA center, presence of Alzheimer's Disease pathology, cerebral amyloid angiopathy, microinfarcts, arteriolosclerosis, and present variables

Figure 1. Inclusion criteria and study participants