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Effects of FDA approved medications for Alzheimer's disease on clinical progression

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Abstract

Background—Observational studies suggest cholinesterase inhibitors and/or memantine may delay clinical progression of Alzheimer's disease (AD) in 40% of individuals taking the medications. Given this response and existence of side effects, we sought to quantify medication use and benefits in a population-based study of incident AD cases.

Methods—The Cache County Dementia Progression study (DPS) enrolled and followed a cohort of 327 incident AD cases up to 9 years. Drug exposure was expressed using a persistency index (PI), calculated as total years of drug use divided by total years of observation. Linear mixed effects models examined PI, and interactions with sex and APOE ϵ 4, as predictors of clinical

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progression on the Mini-Mental State Exam (MMSE) and Clinical Dementia Rating-Sum of Boxes (CDR-Sum).

Results—Sixty-nine participants (21.1%) ever used cholinesterase inhibitors or memantine. There was a strong three-way interaction between PI, sex, and time. Among women, a higher PI (i.e. greater duration of use) of cholinesterase inhibitors was associated with slower progression on the MMSE and CDR-Sum, particularly among those with an APOE ϵ 4 allele. In contrast, higher PI was associated with faster progression in males.

Conclusion—A low percentage of individuals with AD in the community are taking cholinesterase inhibitors or memantine. This study suggests that women, particularly those with an APOE ϵ 4 allele, may receive the most benefit from these medications. With the newly approved increased dose of donepezil, it will be imperative to determine whether a higher dose is needed in men or whether other factors warrant consideration.

Keywords

Cholinesterase inhibitor; Memantine; Incident Alzheimer's disease; Population-based; Disease progression; Sex; APOE

1. Introduction

While there is currently no cure for Alzheimer's disease (AD) nor any treatment demonstrated to alter the pathophysiological course of the disease, current therapeutic strategies aimed at treating disease symptoms and delaying cognitive and functional decline include the use of second-generation cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the N-methyl-D aspartate receptor antagonist, memantine. Studies conducted in specialized clinical settings and nursing homes suggest a high prevalence of dementia medication use among those with AD [1–4]. However, this is likely an overestimate of use as many persons with AD in the United States do not seek specialized treatment and are not diagnosed [5]. A study of community-dwelling Medicare beneficiaries reported that only 26% of persons with dementia were prescribed a cholinesterase inhibitor or memantine between 2001 and 2003 [6]. While claims data include information on prescription medications, they lack clinical information and are subject to misclassification biases due to diagnostic errors, especially underdiagnosis. A population-based study of well-characterized participants with incident AD is preferred to characterize patterns of medication use among AD patients.

Cholinesterase inhibitors and memantine are regarded as having very modest symptomatic benefits on cognition and functioning, but are not disease modifying. Observational studies suggest that these drugs may have symptomatic effects that delay cognitive progression for up to a year and may delay the time to nursing home placements [7,8]. However, only 40% are thought to be improved [9,10]. Given this low response, and the existence of side effects, it is important to quantify their benefits in real world settings and to identify predictors of treatment response. While several clinical trials and clinical observational studies have examined such predictors, these have not been examined in a population-based study of well-characterized incident dementia cases. Clinical studies and randomized trials have more stringent criteria for inclusion and findings may therefore not be generalizable to the vast majority of individuals with AD.

The Cache County Dementia Progression study (DPS) has enrolled and followed a population-based cohort of incident dementia cases for more than 9 years. Participants were originally diagnosed from the population-based Cache County Study on Memory and Aging. The aims of these analyses were to 1) describe patterns of use for FDA approved AD

dementia medications (cholinesterase inhibitors and memantine) in this unique population-based sample of incident dementia cases; 2) determine whether persistency of medication use (defined below) is associated with slower dementia progression, as assessed by the Mini-Mental State (MMSE) and Clinical Dementia Rating-Sum of Boxes (CDR-Sum); and 3) examine whether specific participant characteristics previously reported in clinical studies, including APOE ϵ 4 genotype, sex, and onset age affect response to these medications in this cohort.

2. Methods

2.1 Participants and dementia diagnosis

The design and sampling methods of the study have previously been described in detail [11,12]. The DPS originated from the longitudinal, population-based Cache County Study on Memory in Aging (CCSMA), which has examined the prevalence, incidence, and risk factors of dementia in a U.S. county recognized for its residents' longevity. In its first wave, CCSMA enrolled 90% of the 5677 county residents aged 65 years or older. Three triennial incidence waves were subsequently completed, as previously described [11,12]. Briefly, using state of the art diagnostic assessments involving cognitive screening and in-home evaluation by a trained team, a study geropsychiatrist and neuropsychologist reviewed data from each participant at each CCSMA wave and assigned preliminary diagnoses of dementia according to DSM-III-R criteria [13]. Neuroimaging and laboratory studies were used as part of the diagnostic work-up to further define dementia type. The age of dementia onset was the age when the participant unambiguously met DSM-III-R criteria for dementia. Dementia severity was rated on the Clinical Dementia Rating (CDR) [14] and health status according to the General Medical Health Rating [15]. A panel of experts consisting of neurologists, geropsychiatrists, neuropsychologists, and a cognitive neuroscientist reviewed all available clinical and neuropathological data and possible and probable AD was diagnosed according to NINCDS-ADRDA criteria [16]. All study procedures were approved by the institutional review boards of Utah State, Duke, and the Johns Hopkins Universities.

All participants and their caregivers/proxy informants surviving as of 2002 were recruited to participate in the Dementia Progression Study (DPS), a longitudinal study of dementia progression. Participants and their caregivers/proxy informants were visited semi-annually by a nurse and psychometric technician. Participants completed a battery of neuropsychological tests including the MMSE, and underwent a brief physical examine including height and weight check and standardized measurement of blood pressure. A CDR was administered to participants and caregivers. Caregivers were also interviewed regarding the functional status of the care-recipient, and they provided updated information about the participant's health history, psychiatric symptoms, family history of memory problems, medications, quality of life, and use of formal and informal services.

Of the original 581 persons diagnosed with incident dementia in the CCSMA, 358 had at least one follow-up visit either through procedures of the CCSMA or the DPS. The DPS enrolled 88% of the surviving cases of dementia (n=337) and has followed them semiannually over the past eight years. Attrition primarily has been due to death, with less than 5% of subjects refusing follow-up. Those participants diagnosed with Possible or Probable AD were included in the present analyses.

2.2 Measures of dementia progression

Outcomes reflecting progression of AD dementia were the MMSE [17] and the CDR-Sum [14]. The MMSE is a global measure of cognition that is widely used in clinical trials that assess potential treatments on AD progression [18]. Similar to methods previously employed in DPS [12,19], a sensory/motor MMSE adjusted score was calculated by discarding items

missed due to sensory/motor impairment (e.g., severe vision or hearing loss, motor weakness, tremor, etc.), calculating the percent correct, and rescaling the final score on a 30-point scale.

The CDR [14] examines functioning in six domains: memory, orientation, judgment/problem solving, community affairs, home/hobbies, and personal care. The CDR is assessed with a semi-structured interview and has excellent reliability and validity [20]. Scores include a composite score (CDR-composite) and Sum of Boxes (CDR-Sum), which is the sum of ratings in each of six domains with a range of 0 (no impairment) to 30 (maximum impairment in all domains). CDR-Sum was chosen as the principal outcome here, instead of the composite, because of its greater range and demonstrated sensitivity to change in MCI and AD as demonstrated (e.g. [21]).

2.3 Medication ascertainment and calculation of persistency index

Ascertainment of medications in this study has been previously described [22] and relied on visual inspection of all available medication vials at each follow-up. When participants were institutionalized, this information was obtained from nursing home records. We classified current dementia medication use as regular if a medication was being used 4 times per week. We focused on FDA-approved medications: cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and the N-methyl-D-aspartate receptor antagonist, memantine. As the various cholinesterase inhibitors have been shown to have similar efficacy despite different pharmacological properties we examined this drug category rather than each specific drug.

Since accumulation of exposure to AD dementia medications may be important to progression, drug exposure was estimated using the Persistency Index (PI) [23]. The PI was calculated as the total years of drug use divided by the total years of observation since AD diagnosis by the study investigators, and ranged from 0–1. A PI of 1 indicates that the person has been taking an AD medication over the entire study duration while a PI of 0.5 would indicate the person was taking it only over half the study duration. Since the DPS sample is an incident sample, all participants with AD had been assessed before the onset of dementia. The use of these medications was first assessed at the visit when dementia diagnosis occurred. Time in the study was from the initial baseline visit (e.g. from the visit of the dementia diagnosis) forward, and in multivariate models we adjusted for the duration of dementia at the time of the diagnostic visit that was determined by the age of onset estimated at the consensus conference. A PI was calculated for any dementia medication use and just for cholinesterase inhibitors (excluding participants ever taking memantine). We did not calculate a PI for memantine-only users because of insufficient numbers.

As we did not have information on medication use between visits, if a person was taking a medication at consecutive visits, we assumed s/he was taking it over the whole time-period between these visits. If an individual was taking the medication at one visit but not at the next consecutive visit, we estimated the time of drug use was half the time between visits. This method was supported by our observation in this study that no individuals went on drug, off drug, and then back on drug over three consecutive visits. Hence, once they started a dementia medication, they tended to stay on a dementia medication, although they may have changed to a different cholinesterase inhibitor or memantine at subsequent visits.

2.4 Statistical analyses

Differences in baseline demographic and health-related characteristics between those who ever regularly used a dementia medication versus irregular (<4 times/week) or never users was examined using Fisher's exact test for categorical variables and Student's t-test for

continuous variables. Similarly these same tests were used to estimate differences between those with only a baseline visit and those with one or more follow-up visits.

To model non-linear effects of medication use (PI) on dementia progression, we examined average change in MMSE and CDR-sum from the visit at which dementia was first diagnosed, using mixed effects models, treating subject-specific intercepts and linear change with time as random effects. This approach, used previously in DPS [12] allows us to assess the effects of key fixed factors, such as age, on average rate of change, while accounting for the dependence between within-subject repeated measures and for *non-linear* change with respect to time. Because our analysis revealed significant non-linear time effects for both the MMSE and CDR-sum, and as we have done before in similar analyses, we included a time-squared term and appropriate time-squared terms in all examined interactions.

The following variables have previously been found to be associated with progression in MMSE and CDR-sum in this population of AD participants [12]. They were, therefore, included as covariates in the current models: baseline age, sex, education, dementia duration at the time from the age of dementia onset to the age when diagnosis was made, and presence of one or two *APOE* ϵ 4 alleles. Education, sex and *APOE* genotype were determined at Wave 1 of the CCSMA. *APOE* genotype was determined from buccal DNA using standard protocol [11]. In addition, we also examined three-way interactions between the PI, time, and sex. The interaction terms were retained in the models if the comparison between likelihood ratio (LR) test statistics between models with and without the interaction terms was significant ($p < 0.05$). All analyses were conducted using STATA Version 10.0 (StataCorp, College Station, TX).

3. Results

3.1 Descriptive

The current analyses included 327 participants diagnosed with incident AD and who had information on medication use. The majority were female (65.8%), Caucasian (99.1%) and had mild impairment (mean global CDR = 1.1, SD = 0.6) at the time of diagnosis. At baseline, 36 (11.0%) were regularly taking a cholinesterase inhibitor and/or memantine: 32 (9.8%) were regularly only taking a cholinesterase inhibitor. Over the course of the follow-up, an additional 26 (8.0%) persons initiated regular cholinesterase use and 7 (2.1%) initiated regular memantine use (see Table 1 for cross-sectional use of dementia medications at each follow-up visit and at which visit each drug was first taken). For persons who took dementia medications at multiple visits, all visits were consecutive (i.e. no person was on a drug at one timepoint, off at another timepoint, then back on the medication again at the next timepoint).

Sixty-nine participants (21.1%) ever used a cholinesterase inhibitor or memantine from the time of diagnosis to the last follow-up. Differences in baseline demographic and other health-related characteristics between the 69 persons who ever regularly took a cholinesterase inhibitor and/or memantine during the study and the 258 who did not are shown in Table 2. Those who ever took an FDA approved AD medication were younger (81.2 vs. 87.1, $p < 0.001$), had more years of education (14.0 vs. 13.0, $p = 0.014$), and were more likely to be *APOE* ϵ 4 allele carriers (68.1% vs. 39.1%, $p < 0.001$) compared to those who never regularly used a cholinesterase inhibitor and/or memantine. There were no differences in baseline MMSE or CDR-Sum scores, dementia duration, or other health-related characteristics, including medical co-morbidities.

Of the 327 participants at baseline, 216 had at least one follow-up visit and could be analyzed longitudinally; 191 participants were included in the calculation of the

cholinesterase inhibitor-only Persistency Index (PI) after excluding those ever taking memantine. One hundred eleven individuals (33.9%) lacked any follow-up, the majority (n = 88, 79.3%) due to death. As previously reported [12], these individuals were older and had a lower MMSE at diagnosis compared to those with follow-up data. Of the 216 participants with follow-up data, average time in the study was 3.3 years (SD = 2.2; max = 9.9 years) with 4.2 study visits (SD = 2.4; max = 11 visits). The mean (SD) of the overall PI among the 62 persons in the longitudinal sample taking any FDA approved AD medication was 0.64 (SD=0.31, range 0.07–1.0), meaning they were taking such a medication for 64% of the time under observation. For the 37 participants only taking a cholinesterase inhibitor (excluding anyone taking memantine) the mean PI was 0.63 (SD = 0.31, range = 0.07–1).

3.2 Persistency index

For individuals taking any FDA approved AD medication or for those taking cholinesterase inhibitors only, a higher PI (i.e., use of one of these medications for longer periods under observation) was not associated with better performance over time on either the MMSE or CDR-Sum (Table 3). However, there was a strong three-way interaction between PI, sex, and time, particularly when examining cholinesterase inhibitor use only (MMSE LR $\chi^2 = 9.26$, 2 df, $p < 0.01$; CDR-Sum LR $\chi^2 = 6.40$, 2 df, $p < 0.05$), for which there was more power, due to the greater number of individuals taking these medications as compared to memantine (Table 4). Women with a PI of 1 compared to a PI of 0 did better on the MMSE and CDR-Sum over time. In contrast, men with a PI of 1 compared to a PI of 0 did worse over time.

We further explored the effect of the APOE $\epsilon 4$ allele on the 3-way interaction, stratifying the above models by the presence of any vs. none $\epsilon 4$ alleles. While the results are based on a small sample number as there were only 19 females and 10 males with a PI>0 and an $\epsilon 4$ allele, the relationship between cholinesterase inhibitor use and MMSE and CDR trajectories appeared to be limited to $\epsilon 4$ carriers for each sex; such that women with a high PI did better over time if they had an $\epsilon 4$ allele while men did worse. Table 5 shows this association in greater detail and displays the amount of progression on both the MMSE and CDR-Sum at 1, 3, and 5 years after baseline. For example, after 5 years, women with a PI of 1 and an APOE $\epsilon 4$ allele had a 2.6-point decline (95% CI: -9.11, 3.96) on the MMSE, which was significantly less than the 20.9-point decline among women with a PI of 1 and without an APOE $\epsilon 4$ allele. Similarly, after 5 years, men with a PI of 1 and an APOE $\epsilon 4$ allele had a 19.7-point MMSE decline (95% CI: -28.87, -10.22), which was significantly more than the 6.4-point decline among men with a PI of 1 and without an APOE $\epsilon 4$ allele.

4. Discussion

In this population-based study of an incident cohort of persons with AD we found that: 1) only 21.1% of persons diagnosed with AD ever regularly used a cholinesterase inhibitor or memantine; 2) Participants who used these medications tended to be younger, were more highly educated, and were more likely to have an APOE $\epsilon 4$ allele, but they were no more or less likely to have medical co-morbidities; 3) Among all participants, a higher persistency index (PI) was not significantly associated with progression in the MMSE or CDR-Sum. However, among women, longer periods of cholinesterase inhibitor use were associated with slower progression on both the MMSE and CDR-Sum, particularly among those women with an APOE $\epsilon 4$ allele. In contrast, among men, longer periods of cholinesterase inhibitor use were associated with a faster progression, particularly among those with an APOE $\epsilon 4$ allele.

Some studies from clinical settings have reported a high prevalence of dementia medication use [1,4]. For example, Zhu et al., [4] reported that almost 80% of persons in the Predictors

2 cohort used cholinesterase inhibitors or memantine. In contrast, in this population-based cohort of incident AD, just over 21% of participants used one of these FDA approved AD medications. Our finding is similar to a study of Medicare beneficiaries, which reported that 26% of persons with an AD diagnosis had filled prescriptions for either type of medication [6]. As claims data often underestimate the prevalence of dementia, the percentage of persons with dementia who were taking a dementia medication is likely lower than 26%. Thus, there is a large discrepancy between the prevalence of use in clinical observational studies and use at the population-level. Notably, study of Medicare beneficiaries described usage between 2001–2003, and the DPS began enrolling incident dementia cases in 2002. Thus, it is possible that the low frequency could be attributable to the timing of the medication assessments because rivastigmine and galantamine were only approved in 2000 and 2001, respectively. However, as the Predictors 2 cohort recruited the majority of participants prior to 2002, and median follow-up was four years, this timing cannot completely explain the differences in percentages.

While reasons for this discrepancy are not readily clear, it is not surprising that persons who are younger and more educated are more likely to be on a medication. However, since APOE ϵ 4 status obtained in the Cache County Study was not released to any community physician or participant at any point in the study, and information on APOE ϵ 4 status was not included in the clinical consensus diagnosis of dementia type, it is surprising that persons with an APOE ϵ 4 allele were almost twice as likely to have taken a dementia medication. It is possible ϵ 4 allele carriers were more clear-cut cases of AD and, thus, easier for physicians to recognize. However, there were no differences between ϵ 4 allele carriers and non-carriers in the prevalence of vascular factors and other comorbidities at baseline, which may complicate the diagnosis of AD. While African Americans and Hispanics have a lower prevalence of dementia medication use [6,24], this factor cannot explain the finding in this study because 99% of participants were Caucasian. Thus, additional research examining factors associated with use of dementia medications in community settings are needed.

We used the persistency index (PI) [23] to quantify exposure to FDA approved AD medications during the study. The PI is the total years of drug use divided by the total years of observation. The advantage of using this index was twofold: it allowed for the quantification of the medication duration of exposure and accounted for variations in the period of observation due to the high rate of mortality-related attrition. Rountree et al [23] previously reported that higher PIs were associated with better performance on cognitive and functional outcomes. In this study, we did not find an association between PI and decline among the entire sample. However, there was a strong sex interaction such that women with a higher PI had a slower decline compared to women not taking these medications, particularly women carrying an APOE ϵ 4 allele. This is interesting in light of the fact that women with AD have been found to decline faster than men when cholinesterase use is not considered [12,25]. In contrast, men with a high PI and an APOE ϵ 4 allele did significantly worse compared to men with a low PI or with men, regardless of PI, with no APOE ϵ 4 allele. This explains our lack of finding when a gender interaction was not included. Further, this suggests that only sub-groups of the population may be benefiting from these drugs at the currently approved doses. Given that some side effects do exist, it is important to further determine, in additional population-based studies, which people might most benefit from these medications.

While reasons for the slower decline among women with a higher PI are not exactly known, this sex specific benefit of these medication has been reported in some clinical trials [26], but not others [27]. In animal studies, sex differences have been found for nearly all cholinergic markers including acetylcholinesterase activity, acetylcholine and acetylcholine receptor distribution [28,29,30,31]. Further, testosterone may interfere with the effects of

cholinesterase inhibitors by decreasing the amount of drug that reaches the brain or by modifying the interaction of the cholinesterase inhibitor with cholinesterase [32,33]. Thus, it is possible that men either have less benefit overall or would need a higher dose to have the same benefit from the medications as women. In light of recent approval of a higher dose of donepezil by FDA it would be interesting to find out whether there are sex differences in tolerability and efficacy. It is also notable that the benefit to women was among those taking cholinesterase inhibitors only and not memantine.

Limitations to this study warrant consideration. First, we did not have information on pharmacy claims to directly ascertain whether an individual was a regular user and continuously refilled their prescription. Thus, we may have either overestimated or underestimated use if a medication was started and stopped between waves. Second, we did not have information on dose. However, it is unlikely that doses for women would have been higher than men, and thus explain the beneficial effect in women; if anything we might expect women to be on lower doses due to less tolerability of higher doses because of smaller body size. Third, the number of women and men who were APOE ϵ 4 carrier and taking cholinesterase inhibitors was quite small and necessitates the need for replication in a larger study of incident AD cases. Finally, the Cache County population is primarily Caucasian and of northern European descent. Thus, these results may not generalize to populations with different ethnic representation. Strengths of the study include its population base, its focus on incident cases, the extended follow-up after dementia onset, and the high participation rates observed in dementia ascertainment and over the period of observation.

In conclusion, a low percentage of persons with AD in the community are taking cholinesterase inhibitors or memantine for treatment of AD. As these drugs may benefit a subset of AD patients, [9,10], it is important to further ascertain the reasons for the low prevalence of use. Lastly, this study suggests that women on dementia medications have a slower decline compared to men. With the newly approved increased dose of donepezil, it will be imperative to determine whether a higher dose is needed in men or whether other factors warrant consideration.

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Table 1

Regular use and starting visit of cholinesterase inhibitors and memantine over the DPS follow-up

	Baseline (n=327)	Visit 2 (n=216)	Visit 3 (n=140)	Visit 4 (n=110)	Visit 5 (n=84)	Visit 6 (n=60)	Visit 7 (n=35)	Visit 8 (n=23)	Visit 9 (n=16)	Visit 10 (n=11)	Visit 11 (n=3)
Dementia Medication	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cholinesterase Inhibitor Only											
Use	32 (9.8%)	33 (15.3%)	27 (19.3%)	22 (20.0%)	14 (16.7%)	7 (11.7%)	2 (5.7%)	1 (4.4%)	0	0	0
Visit Started	32 (9.8%)	14 (6.5%)	7 (5.0%)	4 (3.6%)	0	1 (1.7%)	0	0	0	0	0
Memantine Only											
Use	1 (0.3%)	2 (0.9%)	3 (2.1%)	2 (1.8%)	2 (2.4%)	2 (3.3%)	1 (2.9%)	0	1 (6.3%)	0	0
Visit Started	1 (0.3%)	2 (0.9%)	2 (1.4%)	1 (0.9%)	1 (1.2%)	1 (1.7%)	0	0	0	0	0
Both											
Use	3 (0.9%)	3 (1.4%)	7 (5.0%)	8 (7.3%)	9 (10.7%)	8 (13.3%)	4 (11.4%)	2 (8.7%)	2 (12.5%)	2 (18.2%)	1 (33.3%)
Visit Started	3 (0.9%)	2 (0.9%)	6 (4.2%)	2 (1.8%)	4 (4.8%)	2 (3.3%)	0	0	1 (6.3%)	0	0
Any Medication Use	36 (11.0%)	38 (17.6%)	37 (27.2%)	32 (29.0%)	25 (29.8%)	17 (28.3%)	7 (20.6%)	3 (13.6%)	3 (18.8%)	2 (18.2%)	1 (33.3%)

Table 2

Baseline characteristics of regular dementia medication users at any examination over the follow-up and non-users.

Baseline Variable	Regular Use (n=69)		No/Irregular Use (n=258)		p-value
	n(%) or mean (SD)	n(%) or mean(SD)	n(%) or mean(SD)	n(%) or mean(SD)	
Age (yrs)	81.2 (5.4)	87.1 (5.9)			<0.001
Female	42 (60.9%)	173 (67.1%)			0.392
Education	14.0 (3.0)	13.0 (2.9)			0.014
APOE E4 allele	47 (68.1%)	100 (39.1%)			<0.001
Stroke	1 (1.5%)	15 (5.8%)			0.209
CABG	3 (4.4%)	16 (6.2%)			0.774
MI	10 (14.5%)	36 (14.0%)			1.000
Diabetes	7 (10.1%)	47 (18.2%)			0.143
Anti-hypertensive Medication Use	35 (50.7%)	119 (46.3%)			0.587
Dementia Duration	1.9 (1.2)	1.6 (1.3)			0.099
GMHR: Poor	0	1 (0.4%)			0.371
Fair	18 (26.1%)	91 (35.3%)			
Good	44 (63.8%)	134 (51.9%)			
Excellent	7 (10.1%)	32 (12.4%)			
MMSE	22.6 (4.3)	21.7 (4.7)			0.168
CDR-Sum	6.1 (3.3)	5.9 (3.4)			0.696

Abbreviations: CABG=Coronary artery bypass surgery; MI=Myocardial infarction; GMHR=General Medical Health Rating scale; MMSE=Mini-mental state examination; CDR-Sum=Clinical dementia rating scale -- sum of boxscores.

Table 3

Examination of the dementia medication persistency index (PI) as a predictor of progression on the MMSE and CDR-Sum.

PI	MMSE ^{*,†}			CDR-Sum ^{*,†}		
	n	b (95% CI)	LR test	n	b (95% CI)	LR test
Any Dementia Medication	200			216		
PI* time		0.01 (-0.98, 1.00)	$\chi^2 = 1.26, 2 \text{ df}, p = 0.533$		0.01 (-0.82, 0.84)	$\chi^2 = 3.28, 2 \text{ df}, p = 0.194$
PI* time ²		0.06 (-0.08, 0.21)			-0.09 (-0.21, 0.04)	
Cholinesterase Inhibitor Only	175			191		
PI* time		0.25 (-1.20, 1.71)	$\chi^2 = 0.27, 2 \text{ df}, p = 0.874$		-0.19 (-1.43, 1.05)	$\chi^2 = 0.12, 2 \text{ df}, p = 0.941$
PI* time ²		-0.07 (-0.35, 0.20)			0.01 (-0.22, 0.25)	

Abbreviations: PI = Persistency Index; CI = confidence interval; MMSE=Mini-mental State Examination; CDR-Sum = Clinical Dementia Rating Scale - Sum of Boxscores

* Using Mixed Effects Regression, all models adjusted for time, time², baseline age, sex, education, dementia duration at baseline, and any APOE E4 allele.

† A positive coefficient for MMSE represent a better performance whereas a negative coefficient for CDR-Sum represents a better performance.

Examination of an interaction between the dementia medication persistency index (PI) and sex as a predictor of progression on the MMSE and CDR-Sum.

Table 4

PI	MMSE ^{*,†}			CDR-Sum ^{*,†}		
	n	b (95% CI)	LR test	n	b (95% CI)	LR test
Any Dementia Medication	200			216		
PI * Male * time		0.94 (-1.05, 2.94)	$\chi^2 = 3.54, 2 \text{ df}, p = 0.171$		-0.49 (-2.16, 1.17)	$\chi^2 = 3.29, 2 \text{ df}, p = 0.193$
PI * Male * time ²		0.10 (-0.20, 0.39)			-0.11 (-0.36, 0.15)	
Cholinesterase Inhibitor Only	175			191		
PI * Male * time		1.02 (-2.08, 4.14)	$\chi^2 = 9.26, 2 \text{ df}, p = 0.010$		0.71 (-2.02, 3.44)	$\chi^2 = 6.40, 2 \text{ df}, p = 0.041$
PI * Male * time ²		0.42 (-0.18, 1.03)			-0.52 (-1.06, 0.03)	

Abbreviations: PI = Persistency Index; CI = confidence interval; MMSE=Mini-mental State Examination; CDR-Sum = Clinical Dementia Rating Scale - Sum of Boxscores

^{*}Using Mixed Effects Regression, all models adjusted for time, time², baseline age, sex, education, dementia duration at baseline, and any APOE E4 allele.

[†]A positive coefficient for MMSE represent a better performance whereas a negative coefficient for CDR-Sum represents a better performance.

Table 5

Amount of progression on the MMSE and CDR-SB at 1, 3, and 5 years after baseline by sex, APOE ϵ 4 status, and Persistency Index (PI)

	After 1 Year b (95% CI)	After 3 Years b (95% CI)	After 5 Years b (95% CI)
<i>MMSE</i>			
Male			
no ϵ 4 allele			
PI=0	-0.50 (-1.30, 0.30)	-2.20 (-4.28, -0.11)	-4.82 (-8.05, -1.58)
PI=1	-1.12 (-4.90, 2.66)	-3.59 (-10.89, 3.71)	-6.36 (-19.28, 6.55)
1 or 2 ϵ 4 alleles			
PI=0	-0.96 (-1.88, -0.04)	-3.38 (-5.82, -0.95)	-6.50 (-10.41, -2.59)
PI=1	-1.36 (-3.71, 0.99)	-7.91 (-13.23, -2.59)	-19.55 (-28.87, -10.22)
Female			
no ϵ 4 allele			
PI=0	-2.43 (-3.02, -1.84)	-6.99 (-8.49, -5.50)	-11.16 (-13.49, -8.83)
PI=1	-0.95 (-5.30, 3.40)	-7.69 (-15.66, 0.27)	-20.89 (-39.12, -2.65)
1 or 2 ϵ 4 alleles			
PI=0	-1.44 (-2.12, -0.76)	-5.38 (-7.18, -3.58)	-10.72 (-13.66, -7.79)
PI=1	-1.03 (-2.55, 0.49)	-2.32 (-6.17, 1.52)	-2.58 (-9.11, 3.96)
<i>CDR-Sum</i>			
Male			
no ϵ 4 allele			
PI=0	0.40 (-0.29, 1.09)	1.66 (-0.15, 3.47)	3.54 (0.74, 6.33)
PI=1	1.19 (-2.13, 4.51)	0.90 (-5.42, 7.22)	-2.93 (-14.12, 8.27)
1 or 2 ϵ 4 alleles			
PI=0	1.10 (0.37, 1.84)	3.38 (1.53, 5.23)	5.74 (2.91, 8.57)
PI=1	0.27 (-1.74, 2.28)	6.04 (1.90, 10.18)	18.79 (11.83, 25.75)
Female			
no ϵ 4 allele			
PI=0	1.68 (1.18, 2.18)	5.05 (3.79, 6.31)	8.46 (6.50, 10.41)
PI=1	-0.76 (-3.83, 2.31)	0.76 (-5.82, 7.34)	6.34 (-5.26, 17.93)
1 or 2 ϵ 4 alleles			
PI=0	0.77 (0.23, 1.32)	3.44 (2.08, 4.80)	7.60 (5.47, 9.74)
PI=1	1.31 (0.10, 2.52)	3.21 (0.25, 6.17)	4.14 (-0.66, 8.95)

Abbreviations: MMSE=Mini-mental state examination; CDR-Sum = Clinical Dementia Rating scale - Sum of boxscores; PI=Persistency Index