BMC Public Health

RESEARCH

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Changes in dementia treatment patterns associated with changes in the National Policy in South Korea among patients with newly diagnosed Alzheimer's disease between 2011 and 2017: results from the multicenter, retrospective CAPTAIN study

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Abstract

Background The South Korean government has been actively involved in plans to combat dementia, implementing a series of national strategies and plans since 2008. In July 2014, eligibility for mandatory long-term care insurance (LTCI) was extended to people with dementia enabling access to appropriate long-term care including the cognitive function training program and home nursing service. This study aimed to investigate changes in treatment patterns for Alzheimer's disease (AD) between July 2011 and June 2017 which spanned the 2014 revision.

Methods This multicenter, retrospective, observational study of patients with newly diagnosed AD analyzed electronic medical records from 17 general hospitals across South Korea. Based on their time of AD diagnosis, subjects were categorized into Cohort 1 (1 July 2011 to 30 June 2014) and Cohort 2 (1 July 2014 to 30 June 2017).

Results Subjects (*N*=3,997) divided into Cohorts 1 (*n*=1,998) and 2 (*n*=1,999), were mostly female (66.4%) with a mean age of 84.4 years. Cohort 1 subjects were significantly older (*P*<0.0001) and had a lower number of comorbidities (*P*=0.002) compared with Cohort 2. Mean Mini-Mental State Examination (MMSE) scores in Cohorts 1 and 2 at the time of AD diagnosis or start of initial treatment were 16.9 and 17.1, respectively (*P*=0.2790). At 1 year, mean MMSE scores in Cohorts 1 and 2 increased to 17.9 and 17.4, respectively (*P*=0.1524). Donepezil was the most frequently administered medication overall (75.0%), with comparable rates between cohorts. Rates of medication persistence were ≥98% for acetylcholinesterase inhibitor or memantine therapy. Discontinuation and switch treatment rates were significantly lower (49.7% *vs.* 58.0%; *P*<0.0001), and mean duration of initial treatment significantly longer, in Cohort 2 *vs.* 1 (349.3 *vs.* 300.2 days; *P*<0.0001).

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Conclusions Comparison of cohorts before and after revision of the national LTCI system for dementia patients found no significant difference in mean MMSE scores at the time of AD diagnosis or start of initial treatment. The reduction in the proportion of patients who discontinued or changed their initial treatment, and the significant increase in mean duration of treatment, were observed following revision of the LTCI policy which enabled increased patient access to long-term care.

Keywords Dementia, Alzheimer's disease, Treatment pattern, Medication persistence, Electronic medical records, National policy, Long-term care insurance, LTCI

Background

The number of people worldwide living with dementia in 2020 was more than 55 million people and numbers are expected to increase to 78 million in 2030 and 139 million in 2050 [1]. In South Korea (henceforth Korea), analysis of big data from the National Health Insurance Service (NHIS) for dementia and hospital utilization for dementia show that the prevalence of dementia has increased significantly in recent years, notably among the elderly population (aged ≥65 years) [2–4]. In 2021, the prevalence of dementia in Korea was estimated to be more than 786,000 with numbers expected to continue to rise over the next two decades or more [5]. The health-economic burden of dementia in Korea is substantial and was estimated at US$6,957 per capita, with indirect costs accounting for 48.0% of the total burden, mainly from loss of productivity for family members and caregivers [6]. The total annual national dementia management cost for dementia patients in 2021 (approx. US$138 billion) accounted for about 0.9% of Korea's GDP and, during a 6-year period from 2017, the cost increased by 31.9% [7].

In Korea, AD medication is available from hospitals and clinics. Data from 2021 for people with dementia in Korea (approx. 1.66 million), show that most treatments received were as outpatients (52.3%), followed by from a pharmacy (35.4%) or as inpatients (12.3%). Many people with dementia (n = 382,155) accessed long-term care insurance services for the elderly in 2021, with over two-thirds choosing to receive care at home (67.5%) rather than in care facilities [7].

The Korean government has been actively involved in plans to combat dementia, implementing a series of national strategies and plans, beginning in 2008 when the first national dementia plan was announced. Both the first and second national dementia plans, the latter being announced in 2012, focused primarily on promoting early detection and diagnosis of dementia by healthcare providers. The Dementia Management Act of 2012 established a statutory basis for the organization of national dementia plans. The third national dementia plan, released in 2016, focused on the community-based prevention and management of dementia and the fourth, released in 2020, deals with the prevention, early detection, and early post-diagnosis management of Alzheimer's disease (AD) [8, 9].

Mandatory long-term care insurance (LTCI) was introduced in Korea in 2008 and eligibility was extended in July 2014 to people with dementia (including mild dementia). Prior to the 2014 revision, people with cognitive disorders but without severe physical disability were not eligible for LTCI [8, 10]. The revision enabled access to appropriate long-term care for many dementia patients (including mild AD patients) and their families including the cognitive function training program and home nursing services [11]. National policies continue to play a vital role in dementia care for the elderly, especially those with low income. These policies are essential for supporting the treatment of dementia including medications for AD and dementia.

This study aimed to investigate changes in treatment patterns for AD and assessed their effectiveness during two consecutive 3-year periods (July 2011 – June 2014 and July 2014 – June 2017) which spanned revision of the LTCI system regarding eligibility for dementia patients, in July 2014.

Methods

The multicenter, retrospective, observational CAPTAIN (Change of treatment patterns for newly diagnosed Alzheimer's Disease Patients According to Korean National Policy [Long Term Care Insurance] for dementia) study of patients with newly diagnosed AD analyzed electronic medical records (EMRs) from 17 general hospitals across Korea between July 2011 and June 2017. A complete list of all study sites and corresponding Institutional Review Boards (IRBs) that reviewed and approved the study protocol is provided in Supplementary Table 1. Subjects were categorized into two cohorts based on the time of AD diagnosis: from 1 July 2011 to 30 June 2014 (Cohort 1) and from 1 July 2014 to 30 June 2017 (Cohort 2).

Variables

Data retrieved from patient EMRs included age, highest attained educational level, past medical history including comorbidities defined by MedDRA v24.1 System Organ Class (SOC) and Preferred Term (PT), AD-related

medication history, Mini-Mental State Examination (MMSE) score [12], Clinical Dementia Rating (CDR) [13], and Global Deterioration Scale (GDS) [14].

Inclusion and exclusion criteria

Inclusion criteria were patients who were newly diagnosed with AD between 1 July 2011 and 30 June 2017, attended a general hospital as an outpatient, and started acetylcholinesterase inhibitor (AChEI) or memantine administration during this period. Patients were required to have a verifiable MMSE score within 6 months prior to AD diagnosis or the start of initial treatment.

Exclusion criteria were patients with no records available for MMSE, CDR, and/or GDS between 1 July 2011 and 30 June 2017, and/or with a medication history of AChEI or memantine treatment prior to AD diagnosis.

Objectives

The primary objective of this study was to compare MMSE scores between cohorts at the time of AD diagnosis or start of initial treatment. Secondary objectives were comparisons between cohorts of changes in MMSE scores after 1 year's treatment, initial treatment medication and reasons for the discontinuation or change (add-on, switching) of treatment, and time from initial treatment initiation to diagnosis of depression or prescription of antidepressants.

Statistical analyses

Continuous variables were summarized by mean, standard deviation (SD), median and range; and categorical variables by number and percentage. Statistical comparisons were made using Wilcoxon rank-sum, Chi-square or Fisher's exact tests except for Kaplan-Meier analyses which used log-rank tests. The significance level was set at 0.05 (two sided). All statistical analyses were conducted using SAS version 9.4.

Results

In total, 3,997 subjects were enrolled in the study and there were no exclusions. Based on their time of diagnosis, subjects were divided into Cohort 1 (July 2011 – June 2014; $n = 1{,}998$) and Cohort 2 (July 2014 – June 2017; $n = 1{,}999$). Subjects were mostly female (66.4%) with a mean age of 84.4 years. Subjects in Cohort 1 were significantly older than those in Cohort 2 (mean age 84.9 *vs* 84.0 years; $P < 0.0001$). By age category, Cohort 1 had a lower proportion of subjects in the ≥70 to <80 years (19.3% *vs* 22.4%) and ≥80 to <90 years (46.2% *vs* 51.6%) age groups, but a higher proportion of subjects in the ≥90 years age group (30.2% *vs* 22.3%). The highest educational level attained was significantly different between cohorts ($P < 0.0001$). Approximately three quarters of subjects (75.7%) had one or more comorbidities. By PT, the most common comorbidities were hypertension (45.5%, $n = 1{,}817$) followed by diabetes mellitus (20.5%, $n = 820$) and hyperlipidemia (8.8% $n = 350$). Cohort 1 had a lower proportion of subjects with ≥1 comorbidity compared with Cohort 2 (73.6% *vs* 77.8%; $P = 0.0019$). Cohort 1 had a lower prevalence of depression (11.8% *vs* 14.0%; $P = 0.004$), diabetes mellitus (19.1% vs. 21.9%; $P = 0.0403$) and hypertension (43.8% vs. 47.1%; $P = 0.0289$) compared with Cohort 1; and stroke was more common in Cohort 1 (24.5% *vs* 21.0%; $P = 0.0137$) (Table 1).

Mean ± SD MMSE scores in Cohorts 1 and 2 at the time of AD diagnosis or start of initial treatment were 16.9 ± 6.1 and 17.1 ± 5.8, respectively ($P = 0.2790$). At 1 year, mean ± SD MMSE scores in Cohort 1 ($n = 588$) and Cohort 2 ($n = 707$) were 17.9 ± 6.1 and 17.4 ± 5.5, respectively. Differences in 1-year MMSE between cohorts were not significantly different ($P = 0.1524$). Mean ± SD change in MMSE score from treatment start to end of 1 year's treatment was +0.2 ± 3.6 in Cohort 1 ($n = 588$) and −0.2 ± 3.6 in Cohort 2 ($n = 707$). These differences were not statistically significant ($P = 0.0711$). In subjects stratified by disease severity at baseline [baseline MMSE score: 30-27 (normal), 26-21 (mild), 20-10 (moderate), <10 (severe)], there was a significant difference between cohort subgroups in change in MMSE at 1 year in subjects with mild disease ($P = 0.0021$), but not in subjects with normal, moderate or severe disease status (Supplementary Table 2).

Initial medications administered to AD patients differed significantly between cohorts ($P < 0.0001$). Donepezil monotherapy was the most administered medication overall (75.0%) and the administration rate in Cohort 1 was higher in Cohort 2 (77.1% and 72.9%, respectively). Rivastigmine was more commonly administered to patients in Cohort 1 (12.5% *vs.* 9.0%) while galantamine (6.81% *vs.* 10.91%) and memantine (3.6% *vs.* 3.8%) were more frequently administered to Cohort 2 patients. Combination donepezil + memantine was only administered to Cohort 2 subjects (3.4%) (Table 2). In a subgroup analysis (by 12-month period) of each cohort, donepezil was consistently the most common medication administered with some variation between the 12-monthly periods analyzed. Combination donepezil + memantine was most frequently administered during July 2014–June 2015 (Cohort 2-1) (Supplementary Table 3).

Medication persistence, defined as the proportion of time during the prescribed duration for which patients continued treatment, was high (≥98%) for donepezil, galantamine, rivastigmine and memantine (Table 3). Mean medication persistence was significantly higher in Cohort 1 *vs* 2 for donepezil (98.7 *vs.* 98.4; $P = 0.0001$) and memantine (98.8 *vs.*98.7; $P = 0.0339$). In subjects

Table 1 Demographics and baseline characteristics

	Cohort 1 (*n* = 1,998)	Cohort 2 (*n* = 1,999)	Total (*N* = 3,997)	*P* value*: Cohort 1 *vs* 2
Sex: male/female, n (%)	657 (32.9)/ 1,341 (67.1)	685 (34.3)/ 1,314 (65.7)	1,342 (33.6)/ 2,655 (66.4)	0.3542
Age (years), Mean ± SD	84.9 ± 8.6	84.0 ± 7.5	84.4 ± 8.0	<0.0001
Age range (years)				
<40	1 (0.1)	0 (0.0)	1 (0.0)	<0.0001
≥40 to <50	5 (0.3)	0 (0.0)	5 (0.1)	
≥50 to <60	10 (0.5)	5 (0.3)	15 (0.4)	
≥60 to <70	71 (3.6)	70 (3.5)	141 (3.5)	
≥70 to <80	385 (19.3)	447 (22.4)	832 (20.8)	
≥80 to <90	923 (46.2)	1,031 (51.6)	1,954 (48.9)	
≥90	603 (30.2)	446 (22.3)	1,049 (26.2)	
Highest educational level				
No formal school education	383 (19.2)	471 (23.6)	854 (21.4)	<0.0001
Elementary school or below	544 (27.2)	600 (30.0)	1,144 (28.6)	
Middle school	102 (5.1)	133 (6.7)	235 (5.9)	
High school	111 (5.6)	147 (7.4)	258 (6.5)	
College/graduate school	58 (2.9)	80 (4.0)	138 (3.5)	
Unknown	800 (40.0)	568 (28.4)	1,368 (34.2)	
Past medical history				
Depression, n (%)	235 (11.8)	280 (14.01)	515 (12.9)	0.0040
Diabetes mellitus	382 (19.1)	438 (21.9)	820 (20.5)	0.0403
Hypertension	876 (43.8)	941 (47.1)	1,817 (45.5)	0.0289
Stroke, n (%)	490 (24.5)	419 (21.0)	909 (22.7)	0.0137
≥1 comorbidity, n (%)	1,470 (73.6)	1,555 (77.8)	3,025 (75.7)	0.0019

* Chi-square tests except Wilcoxon rank-sum test for mean age

Table 2 Initial medications administered

	Cohort 1 (*n* = 1,998) n (%)	Cohort 2 (*n* = 1,999)	Total (N = 3,997)	*P* value*: Cohort 1 *vs* 2
Donepezil	1,541 (77.1)	1,457 (72.9)	2,998 (75.0)	<0.0001
Rivastigmine	250 (12.5)	180 (9.0)	430 (10.8)	
Galantamine	136 (6.8)	218 (10.9)	354 (8.9)	
Memantine	71 (3.6)	76 (3.8)	147 (3.7)	
Combination donepezil + memantine	0 (0.0)	68 (3.4)	68 (1.7)	

* Chi-square test

stratified by disease severity at baseline, medication persistence for ChEIs or memantine was significantly different in mild (galantamine: $P = 0.0285$), moderate (donepezil: $P = 0.0023$; memantine: $P = 0.0230$), and severe (donepezil: $P = 0.0424$) AD subgroups (Supplementary Table 2).

Overall, the mean ± SD time from AD diagnosis to the start of initial therapy was 8.3 ± 39.6 days. Time to the start of therapy was significantly shorter in Cohort 1 (7.8 ± 41.0 days) compared with Cohort 2 (8.8 ± 38.2 days) ($P = 0.0007$). In subjects stratified by disease severity at treatment start, this difference was statistically significant in patients in the mild ($P = 0.0427$) and moderate ($P = 0.0034$) AD subgroups (Supplementary Table 2).

Discontinuation and adjustment of initial treatment rates were significantly lower in Cohort 2 *vs.* Cohort 1 (49.7% *vs.* 58.0%; $P < 0.0001$). In subjects stratified by disease severity at baseline, this difference was statistically significant in the moderate AD subgroup ($P < 0.0001$) (Supplementary Table 2). For subjects who discontinued

Table 3 Medication persistence[a] (%)

		Cohort 1	Cohort 2	Total	*P* value†: Cohort 1 *vs* 2
Donepezil	n	1,514	1,473	2,987	
	Mean ± SD	98.7 ± 7.3	98.4 ± 6.8	98.57 ± 7.0	0.0001
Rivastigmine	n	249	178	427	
	Mean ± SD	98.3 ± 10.6	99.8 ± 2.8	98.9 ± 8.3	0.0500
Galantamine	n	136	215	351	
	Mean ± SD	98.7 ± 5.9	99.5 ± 3.8	99.2 ± 4.7	0.0785
Memantine	n	71	142	213	
	Mean ± SD	98.8 ± 7.2	98.7 ± 6.8	98.7 ± 6.9	0.0339

[a] Medication persistence is defined as the proportion of time during the prescribed duration for which patients continued treatment, calculated as:

$$\text{Medication Possession Ratio (MPR)} = \frac{\text{Actual number of days of taking medication*}}{\text{Planned number of days of taking medication**}} \times 100$$

*Treatment end date (end date of administration or end date of follow-up specified in the electronic medical record) - treatment start date (start date of administration)

**Number of prescribed days X times of prescription (in case the number of prescribed days were different, each number of prescribed days was added)

†Wilcoxon rank-sum test

or changed their initial treatment, the mean ± SD overall duration of initial treatment was 324.8 ± 315.0 days. Kaplan-Meier analysis of initial treatment duration in Cohorts 1 and 2 who discontinued or changed their initial treatment is shown in Fig. 1. Mean duration of initial treatment was significantly longer in Cohort 2 (349.8 ± 316.1 days) than Cohort 1 (300.2 ± 312.0 days) (Log-rank test $P < 0.0001$). In subjects stratified by disease severity at treatment start, statistically significant differences were observed in the mild ($P = 0.0317$), moderate ($P < 0.0001$), and severe ($P = 0.0286$) AD subgroups (Supplementary Table 2).

Treatment interruption/discontinuation occurred in 2,190 subjects: 1,159 subjects in Cohort 1 (52.9%) and 1031 in Cohort 2 (47.1%). Overall, 1,587 subjects were lost to follow-up (39.7% of all subjects) and included 901 (45.1%) and 686 (34.3%) in Cohorts 1 and 2, respectively. The most frequent reason for discontinuation or change of initial treatment was lack of effectiveness (8.1%*vs* 11.1%, respectively), followed by adverse effects (2.3% *vs* 3.2%) and death (0.3% *vs* 0.7%) (Table 4). In subgroup analysis (by 12-month periods) of each cohort, interruption/discontinuation due to lack of effectiveness was higher during the first 12 months although numbers

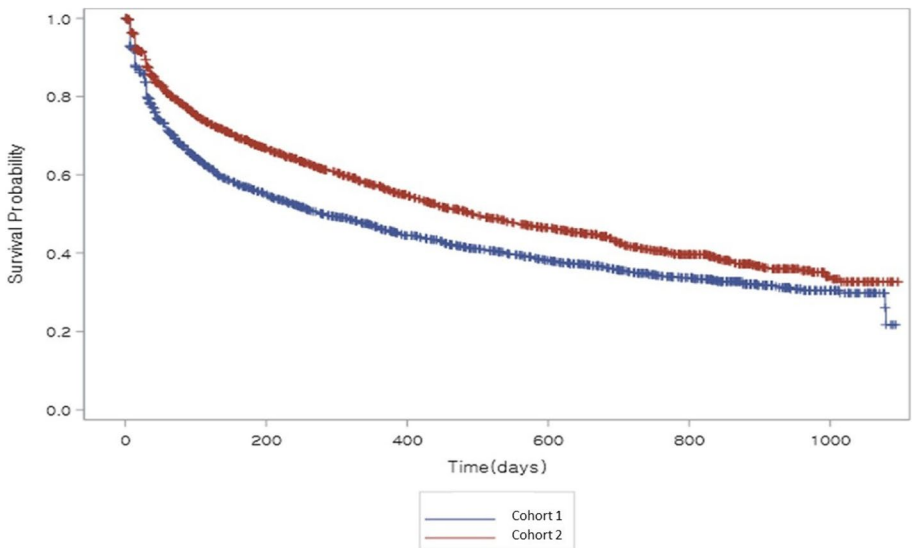

Fig. 1 Kaplan-Meier analysis of initial treatment duration in subjects who discontinued or changed their initial treatment

Table 4 Reasons for discontinuation or change of initial treatment in Cohorts 1 and 2

	Cohort 1 ($n = 1,998$) n (%)	Cohort 2 ($n = 1,999$)	Total ($N = 3,997$)
Lost to follow-up	901 (45.1)	686 (34.3)	1,587 (39.7)
Lack of effectiveness	161 (8.1)	222 (11.1)	383 (9.6)
Adverse effects	45 (2.3)	63 (3.2)	108 (2.7)
Death	6 (0.3)	13 (0.7)	19 (0.5)
Economic burden	1 (0.1)	2 (0.1)	3 (0.1)
Symptom improvement	1 (0.1)	0 (0.0)	1 (0.0)
Other	44 (2.2)	45 (2.3)	89 (2.2)
Total	1,159 (58.0)	1,031 (51.6)	2,190 (54.8)

Percentages shown are for the proportion of subjects in each cohort

of subjects in each subgroup are low (Supplementary Table 4).

Overall, 136 patients added therapy due to lack of effectiveness of initial treatment medication: 29 subjects in Cohort 1 and 107 in Cohort 2. Change to add-on therapy occurred in most subjects during the first 12 months of analysis in both cohorts: 69.0% ($n = 20$) in Cohort 1-1 (July 2011–June 2012) and 67.3% ($n = 72$) in Cohort 2-2 (July 2014–June 2015).

In total, 335 subjects (8.38%) switched AD medication: 169 (8.5%) in Cohort 1 and 166 (8.3%) in Cohort 2. In Cohort 1, the most common reason for switching drugs was lack of effectiveness ($n = 120$; 6.0%), followed by adverse effects ($n = 38$; 1.9%), other ($n = 10$; 0.5%) and economic burden ($n = 1$; 0.1%). In Cohort 2, reasons for switching were lack of effectiveness ($n = 103$; 5.2%), adverse effects ($n = 49$; 2.5%), and other ($n = 14$; 0.7%). Differences between cohorts regarding reasons for switching medication were not statistically significant ($P = 0.1866$).

In subgroup analysis of Cohort 1, most subjects switched medications due to lack of effectiveness ($n = 119$) during the first year (Cohort 1-1, 57.1%), compared with the second (Cohort 1-2; 33.6%), and third year of

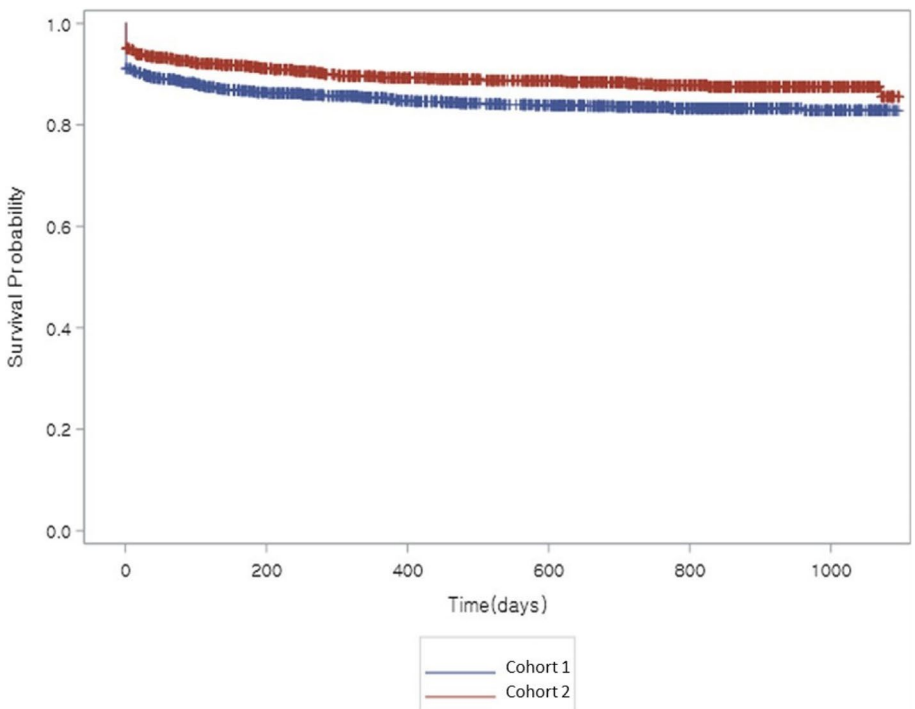

Fig. 2 Kaplan-Meier analysis of time from initial Alzheimer's disease treatment to diagnosis of depression or antidepressant prescription

study (Cohort 1-3; 9.2%); and rates for switching due to adverse effects ($n = 38$) in Cohorts 1-1, 1-2 and 1-3 were 63.2%, 10.5% and 26.3%, respectively. In subgroup analysis of Cohort 2, rates of subjects switching medications due to lack of effectiveness ($n = 102$) in Cohorts 2-1, 2-2 and 2-3 were 38.2%, 39.2% and 22.6%, respectively; and for those switching due to adverse effects ($n = 49$) were 49.0%, 24.5% and 26.5%, respectively.

Overall, mean ± SD time from initial AD treatment to diagnosis of depression or antidepressant prescription was 517.0 ± 350.4 days ($n = 3,222$). Kaplan-Meier analysis of time from initial AD treatment to diagnosis of depression or antidepressant prescription in Cohorts 1 and 2 is shown in Fig. 2. Mean ± SD time to depression diagnosis/antidepressant prescription was significantly prolonged in Cohort 2 ($n = 1,586$) compared with Cohort 1 ($n = 1,636$): 530.8 ± 352.6 *vs* 503.6 ± 347.9 days (Log-rank test $P < 0.0001$). In subjects stratified by disease severity at baseline, Cohort 2 prolongation of time to depression diagnosis/antidepressant prescription was found in the mild ($P = 0.0001$) and moderate ($P = 0.0209$) AD subgroups (Supplementary Table 2).

In patients who did not have a diagnosis of depression at baseline, time from initial treatment of AD to diagnosis of depression or antidepressant prescription for each medication is shown in Table 5. Mean time to diagnosis of depression or antidepressant prescription was significantly longer in Cohort 2 *vs* Cohort 1 for donepezil (521.9 *vs* 520.7 days; $P = 0.0026$) and rivastigmine (678.7 *vs* 505.8 days; $P = 0.0220$).

Discussion

This retrospective cohort study investigated changes in treatment patterns for subjects with newly diagnosed AD in Korea during two consecutive 3-year periods which were before (Cohort 1) and after (Cohort 2) the July 2014 revision of the national LTCI system regarding eligibility for dementia patients.

At baseline, a higher proportion of patients in Cohort 2 (July 2014 – June 2017) than Cohort 1 (July 2011 – June 2014) had one or more comorbidities which may reflect increased diagnosis and treatment of dementia in clinics visited for evaluation of non-dementia conditions. Depression was more commonly diagnosed in Cohort 2 which may reflect increased recognition of cognitive disturbances associated with depressive symptoms [15]. In contrast, stroke was less common in Cohort 2 and the reasons for this are unclear. Although stroke mortality in Korea has steadily decreased from 2010 to 2019 (by 12.8% from 2014 to 2019) due to better management of risk factors and improved medical interventions, the absolute number of incident strokes increased by 29.7% from 2014 to 2019 [16]. Moreover, based on an analysis of health insurance big data, the female incidence of stroke has decreased in Korea [17] and, as the AD patient population in our study was predominantly female, this may account for the observed decrease in stroke between Cohort 1 and Cohort 2.

Mean MMSE scores at the time of AD diagnosis or start of initial treatment were not significantly different between cohorts but, as there were significant differences in mean age and age category, then it is possible that age-related MMSE scores may differ for some age groups. These analyses remain to be done. Similarly, no significant difference was found in 1-year MMSE scores between cohorts and a "trend" of statistical significance was observed for change in MMSE scores from treatment start to 1 year's end of treatment.

Initial medications administered to AD patients differed significantly between cohorts, and donepezil was

Table 5 Time from initial treatment (days) of Alzheimer's disease to diagnosis of depression or antidepressant prescription

		Cohort 1	Cohort 2	Total	*P* value*: Cohort 1 *vs* 2
Donepezil	n	1,406	1,335	2,741	
	Mean ± SD	520.7 ± 343.7	521.9 ± 353.8	521.3 ± 348.6	0.0026
Rivastigmine	n	247	162	409	
	Mean ± SD	505.8 ± 368.7	678.7 ± 316.4	574.3 ± 358.6	0.0220
Galantamine	n	134	213	347	
	Mean ± SD	433.2 ± 353.1	460.4 ± 314.0	449.9 ± 329.4	0.1065
Memantine	n	71	73	144	
	Mean ± SD	380.8 ± 314.6	449.5 ± 348.1	415.6 ± 332.6	0.3086
Combination donepezil + memantine	n		68	68	
	Mean ± SD	—	723.7 ± 366.7	723.7 ± 366.7	—

* Log-rank test. Mean (± SD) time from initial treatment to diagnosis of depression or antidepressant prescription is shown

most frequently administered – to more than three-quarters of patients. Combination AChEI + memantine was only given to Cohort 2 patients as insurance coverage for combination therapy was only available from October 2014. Recent results from the Observational Medical Outcome Partnership Common Data Model (OMOP CDM) which analyzed data from five hospitals in Korea during 2009-2019 also found that donepezil was the most prescribed anti-dementia medication (48.8%) among patients with newly diagnosed AD (n = 8,653), followed by memantine (18.1%), rivastigmine (9.0%), and galantamine (5.7%) [18].

Low medication persistence and/or adherence represents a significant challenge in treating patients with chronic diseases, including those with dementia [19, 20]. Medication persistence rates in the present study for donepezil, galantamine, rivastigmine and memantine were all high (≥98%). For comparison, the OMOP CDM study reported 12-month persistence rates of approximately 50% for donepezil and memantine and around 40% for rivastigmine and galantamine [18]. Differences in persistence rates may be due to differences in definitions of persistence and in study populations. Although mean medication persistence in our study was statistically higher in Cohort 1 *vs* 2 for donepezil and memantine, this was not clinically meaningful. Data indicate that several factors may influence persistence with dementia pharmacotherapy, including patient age, sex, ethnic/racial background, socioeconomic status, and region-specific reimbursement criteria, in addition to the extent and quality of interactions among patients, caregivers, and providers [20].

Depressive symptoms are common in AD, occurring in approximately 15% of patients [21]. Mean time to depression diagnosis/antidepressant prescription was significantly prolonged in Cohort 2 compared with Cohort 1. The prescription of depressive drugs other than those issued by psychiatry departments was more tightly regulated in earlier years which may have contributed to these results. In addition, prescriptions were checked only in EMRs from neurology departments. Mean time to diagnosis of depression or antidepressant prescription was significantly longer for donepezil (by approximately 1 day) and rivastigmine (by nearly 173 days).

The mean time from AD diagnosis to the start of initial therapy was slightly longer (by approximately 1 day) in Cohort 2 compared with Cohort 1. This may be due to a strain on AD diagnostic facilities due to increased patient numbers. However, in patients who discontinued or changed their initial treatment, the mean duration of treatment was significantly longer in Cohort 2 (by 49 days). This likely reflects the change in LTCI policy which enabled increased access to long-term care for patients. Introduction of the national LTCI-funded cognitive function training program was also associated with a significant reduction in the decline of cognitive function in older people with mild dementia after, compared to before, its introduction [11].

The proportion of patients who discontinued or changed their initial treatment was also significantly lower in Cohort 2 and appear to be associated with the policy revision in 2014. Lack of effectiveness and adverse effects were the main reasons for discontinuing or changing treatment, but as many subjects (n = 1,587; 39.7% of all subjects) were lost to follow-up, differences between cohorts were limited by relatively low numbers of patients. Predictors of discontinuation or change in therapy was beyond the scope of this study. However, a 2-year European prospective cohort study of patients with mild-to-moderate AD initiating AChEIs (n = 557) reported that predictors of discontinuation were behavioral disturbances, decline in MMSE score, AD-related hospitalization, low body mass index (BMI) and falls; and predictors of switching treatment were MMSE score, decline in activities of daily living score, shorter AD duration, aberrant motor behavior, and higher nurse resource use [22].

The main limitations of the current study reflect those associated with the retrospective nature of the study design which analyzed data from EMRs. Data pre-processing and data quality (e.g. incomplete, inaccurate and/or missing data) challenges, and the potential for limited generalizability, are recognized challenges encountered when using EMR data for secondary research purposes [23]. For example, this may have impacted findings relating to medication persistence because it was not possible to differentiate between patients who actually took the medication and those who did not. There may also be differences in patient care between hospitals such as neuropsychological examinations, interval between examinations etc. although all patients were treated by neurologists. Antidepressants are often prescribed by psychiatrists due to insurance regulations, and this may have also led to differences in care of patients between hospitals. As there were a number of policy changes over several years, only large changes to policy were considered. Finally, as the primary aim of the study was to examine change in treatment patterns between cohorts, in depth statistical analyses such as Cox regression to account for confounding factors for differences in MMSE were not performed. However, we are planning more detailed *post-hoc* analyses (including Cox regression) for a subsequent publication.

Conclusions

This study compared cohorts before and after revision of the national LTCI system for dementia patients in Korea and found no significant difference between cohorts in mean MMSE scores at the time of AD diagnosis or start of initial treatment. The reduction in the proportion of patients who discontinued or changed their initial treatment, and the significant increase in mean duration of treatment, were observed following revision of the LTCI policy including national dementia management, which enabled increased access to long-term care for patients with dementia and positive effects on care of depression. Large-scale research projects including long-term prospective studies are needed to continue to monitor the care of dementia patients in Korea.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-024-17671-2.

Additional file 1: Supplementary Table 1. List of study sites and corresponding Institutional Review Boards (IRB) that reviewed and approved the study protocol.

Additional file 2: Supplementary Table 2. Change in MMSE, treatment duration, discontinuation/changing treatment, medication persistence and time to diagnosis of depression/ prescription of antidepressants by severity of Alzheimer's disease (AD) at baseline.

Additional file 3: Supplementary Table 3. Initial treatment medication in Cohort subgroups (analyzed by 12-month periods).

Additional file 4: Supplementary Table 4. Reasons for discontinuation/interruption of initial treatment in Cohort subgroups (analyzed by 12-month periods).

Acknowledgements

We thank the following investigators for assistance with data gathering: Hyung-Gyun Oh (Gwangju Veterans Hospital), Sae-Hoon Lee (Chamjoeun Hospital), Seong-Hee Kim (Changwon Fatima Hospital), Kyung-Yeol Cheon (Hallym Hospital), and Sung-Man Jun (BongSeng Memorial Hospital). Editorial assistance was provided by Robert A. Furlong PhD and David P. Figgitt PhD, ISMPP CMPP™, Content Ed Net, with funding from Eisai Korea Inc.

Authors' contributions

Young Jin Kim: data gathering as a Principal Investigator (PI) and publication drafting; Ki- Yoon So: data gathering as a PI; Hyo Min Lee: data gathering as a PI; Changtae Hahn: data gathering as a PI; Seung-Hoon Song: data gathering as a PI; Yong-Seok Lee: data gathering as a PI; Sang Woo Kim: data gathering as a PI; Heui Cheun Park: data gathering as a PI; Jaehyung Ryu: data gathering as a PI; Jung Seok Lee: data gathering as a PI; Min Ju Kang: data gathering as a PI; Jun Hong Lee: data gathering as a PI; JinRan Kim: project management, publication support; Yoona Lee: project management. All authors provided critical input on draft versions of the manuscript and approved the final manuscript prior to submission.

Funding

This work was supported by Eisai Korea Inc.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to ethical constraints but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Institutional Review Board (IRB) and regulatory authority review and approval of the study protocol were obtained according to local laws and regulations, as applicable. A complete list of all study sites and corresponding IRBs is provided in Supplementary Table 1. The following IRBs reviewed and approved the study protocol and waived the need for informed consent: Sungae Hospital IRB, Gwangju Veterans Hospital IRB, The Public Institutional Review Board (Public IRB), Daegu Fatima Hospital IRB, Daejeon St. Mary's Hospital IRB, Seoul Metropolitan Government-Seoul National University Boramae Medical Center IRB, Busan St. Mary's Hospital IRB, Andong Medical Group Hospital IRB, Jeju National University Hospital IRB, Veterans Healthcare Medical Center IRB, Changwon Fatima Hospital IRB, National Health Insurance Service Ilsan Hospital IRB, BongSeng Memorial Hospital IRB. This was a retrospective observational study and because the study did not involve more than minimum risks to subjects, the need for informed consent was not required by any of the IRBs that reviewed and approved the study protocol. The study was conducted in compliance with the relevant regulations provided by the Declaration of Helsinki and International Conference for Harmonization (ICH) Good Clinical Practice guidelines. Anonymity of subjects was maintained rigorously throughout the study.

Consent for publication

Not applicable.

Competing interests

JinRan Kim and Yoona Lee are both employees of Eisai Korea Inc. The other authors declare that they have no competing interests.

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Received: 26 June 2023 Accepted: 4 January 2024
Published online: 12 January 2024

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