Clinical Predictors for Mild Cognitive Impairment Progression in a Korean Cohort

Yong S. Shim,1 Dong Won Yang,1 Bora Yoon,2 Yunhwan Lee,3 Chang Hyung Hong,4 Sang Won Seo,6
Soo Jin Yoon,6 Jee Hyang Jeong,7 Moon Ho Park,8 Seong Yoon Kim10

1Department of Neurology, College of Medicine, The Catholic University of Korea, Seoul, Korea
2Department of Neurology, Konyang University College of Medicine, Daejeon, Korea
3Departments of Preventive Medicine and Public Health and Psychiatry, Ajou University School of Medicine, Suwon, Korea
4Department of Neurology, Sungkyunkwan University School of Medicine, Seoul, Korea
5Department of Neurology, Eulji University College of Medicine, Daejeon, Korea
6Department of Neurology, Ewha Womans University School of Medicine, Seoul, Korea
7Department of Neurology, Korea University College of Medicine, Seoul, Korea
8Department of Neurology, Inha University School of Medicine, Incheon, Korea
9Department of Psychiatry, University of Ulsan College of Medicine, Seoul, Korea

Background and Purpose  Patients with mild cognitive impairment (MCI) and their caregivers are concerned with the likelihood and time course of progression to dementia. This study was performed to identify the clinical predictors of the MCI progression in a Korean registry, and investigated the effects of medications without evidence, frequently prescribed in clinical practice.

Methods  Using a Korean cohort that included older adults with MCI who completed at least one follow-up visit, clinical characteristics and total medical expenses including prescribed medications were compared between two groups: progressed to dementia or not. Cox proportional hazards regression analysis was conducted.

Results  During the mean 1.42±0.72 years, 215 (27.63%) of 778 participants progressed to dementia. The best predictors were age (hazard ratio [HR], 1.036; 95% confidence interval [CI], 1.006–1.067; p=0.018), apolipoprotein ε4 allele (HR, 2.247; 95% CI, 1.512–3.337; p<0.001), Clinical Dementia Rating scale-sum of boxes scores (HR, 1.367; 95% CI, 1.143–1.636; p=0.001), Instrumental Activities of Daily Living scores (HR, 1.035; 95% CI, 1.003–1.067; p=0.029), and lower Mini-Mental State Examination scores (HR, 0.892; 95% CI, 0.839–0.949; p<0.001). Total medical expenses were not different.

Conclusions  Our data are in accordance with previous reports about clinical predictors for the progression from MCI to dementia. Total medical expenses were not different between groups with and without progression.

Key Words  cholinesterase inhibitors, dementia, mild cognitive impairment, predictors.

INTRODUCTION

Mild cognitive impairment (MCI) represents an intermediary state between normal aging and dementia.1 Several longitudinal studies have shown that most persons with MCI are at increased risk for the development of dementia.2,3 Especially, when memory loss is the predominant symptom, it is termed “amnestic MCI” and is frequently seen as a prodromal stage of Alzheimer’s disease (AD).4 Therefore, MCI has been receiving considerable attention in clinical practice and research settings.
A question commonly raised by patients with MCI and their family members concerns the likelihood and time course of progression to dementia. Although the general rate of progression among those with a diagnosis of MCI is estimated at 10–15% per year,
1 certain factors predict a more rapid progression. The degree of memory impairment at presentation is a clinical predictor of progression,
2 probably because these patients are closer to the threshold for the diagnosis of dementia. Longitudinal data have shown that the progression to dementia is more rapid among carriers of the apolipoprotein (APOE) ε4 allele than among noncarriers.
3 Other considerations such as old age and low education were also reported.

As MCI may represent a prodromal state to clinical AD, treatments proposed for AD, such as cholinesterase inhibitors (ChEIs), may be considered for MCI, too. However, until now, there is no proven treatment for MCI.
4 Several potential treatments are still under investigation.
5 Although the risk-benefit ratio is questionable, some interventions in patients with MCI are being used in clinical practice without evidence.

We planned this study to investigate the effects of medications without evidence, frequently prescribed in clinical practice, such as ChEIs and neural pills including nootropics and Ginkgo Biloba, on progression to dementia, in addition to determining the potential clinical predictors of progression from MCI in a Korean cohort.

METHODS

Participants

This study was conducted as part of the Clinical Research Center for Dementia of South Korea (CREDOS) study, which is a multicenter hospital-based prospective cohort study. From May 2007 to September 2011, 778 patients who completed at least one follow-up visit were included in the study. The Institutional Review Boards at all participating centers approved this study. Written, informed consent was obtained from patients and caregivers.

All patients with MCI met the following guidelines based on the criteria proposed by Petersen:
6 1) subjective memory complaint, 2) normal general cognitive function as defined by scores on the Korean version of the Mini-Mental State Examination (K-MMSE)
7 ≥-1.0 standard deviation of the norms for age- and education-matched normal subjects, 3) normal activities of daily living (ADL), as judged both clinically and on the ADL scale described below, 4) objective cognitive impairment on at least one of the four domains of comprehensive neuropsychological tests with scores below the 16th percentile, and 5) not demented. Patients with MCI were divided into amnestic or nonamnestic.

Patients with neurological or psychiatric illnesses such as schizophrenia, epilepsy, and encephalitis were excluded. Patients with physical illnesses that could interfere with the clinical study, such as hearing or vision loss, aphasia, malignancy, and hepatic or renal disorders were excluded. Blood tests for excluding medical diseases included a complete blood count, blood chemistry tests, vitamin B12/folate, syphilis serology, and thyroid function tests. Conventional brain magnetic resonance imaging (MRI) scans confirmed the absence of structural lesions such as tumors, traumatic brain injuries, hydrocephalus, or severe white matter hyperintensities (WMHs).

Clinical assessments

We used the Dementia Evaluation Package developed by CREDOS, which is composed of the Clinical Evaluation Form and Caregiver Questionnaire Form.
8 The Clinical Evaluation Form included: 1) the history of cognitive decline from the caregiver, 2) K-MMSE,
9 3) Clinical Dementia Rating (CDR) and CDR Sum of Boxes (CDR-SOB),
10 4) Hachinski ischemia scale,
11 5) body mass index (BMI), 6) neurological examinations, and 7) Geriatric depression scale (GDS).
12 The Caregiver Questionnaire Form included: 1) basic demographic data, 2) medical history, including vascular risk factors, and 3) the Seoul Instrumental ADL (S-IADL).
13 All participants underwent a standardized neuropsychological battery known as the Seoul Neuropsychological Screening Battery.
14 MRI was performed on all participants, based on the protocol of MRI acquisition for CREDOS registration.
15 WMHs were represented by a final ischemia score of minimal, moderate, or severe.
16 Additionally, APOE genotype was determined by polymerase chain reaction.

At the follow-up visit, all cognitive and neuropsychological assessments except laboratory tests and MRI were performed annually. The diagnosis of dementia was based on criteria from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Some other participants remained with MCI or reversed into normal cognition. Specific diagnostic criteria were used for designation of dementia classification. Using the criteria from the National Institute of Neurological and Communication Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association,
17 National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l’Enseignement en Neurosciences,
18 criteria modified from McKeith et al.
19 for Dementia with Lewy Body (DLB), and research criteria for frontotemporal dementia (FTD) proposed by Knopman et al.
20 all dementia participants were assigned to one of the following specific dementia diagnosis classifications: 1) AD; 2) vascular dementia (VaD); 3) DLB; or 4) FTD.
Linkage to the national health insurance claims database

With help of the National Strategic Coordinating Center for Clinical Research, the national health insurance claims database from 2007 to 2011 was analyzed to investigate medications prescribed and total medical costs. The claims data were provided through an IRB approval of the Health Insurance Review and Assessment Service that builds a national claims database for the total population. Using these data files, total medical expenses including medication costs (medicine cost dispensed by prescription) and number of used medical care institutions were analyzed. Total costs only by public health insurance were analyzed. Total medical expenses for 1 year were calculated. Medication domain was classified as ChEIs including donepezil, galantamine, and rivastigmine, and neural pills including acetyl-L-carnitine, choline alphoscerate, nicergoline, oxiracetam, and Ginkgo Biloba extract. All the costs were calculated in Korean Won.

Statistical analyses

SAS (version 9.3; SAS Institute Inc., Cary, NC, USA) and SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL, USA) were used for data analyses. We analyzed the frequencies and the mean values of the variables to determine group differences in total medical expenses as well as demographic and clinical characteristics between the progressed to dementia and not progressed groups. Age and K-MMSE scores were included as covariates for analyses of covariance.

Factors were analyzed as predictors of time to dementia diagnosis using a Cox proportional hazard regression model. Covariates included age and baseline K-MMSE scores. To further analyze the best predictors of dementia progression, we re-performed the analyses with factors that showed significance at the first Cox proportional hazard regression model, such as education, APOE ε4 allele, CDR-SOB, S-IADL, BMI, and changes of GDS, as covariates in addition to age and K-MMSE scores. Time to the event was defined as the time from study entry to the follow-up visit during which a first-time diagnosis of dementia was made. Participants that did not progress into AD were treated as censored observations from the time of their final follow-up evaluation.

RESULTS

Of the 778 participants with MCI who completed at least one follow-up visit, 215 (27.63%) progressed to dementia (200 AD, 8 VaD, 4 DLB, and 3 FTD) and 74 (9.51%) reversed to normal cognition. The demographic and clinical characteristics of the participants who progressed into dementia, remained in MCI, and revised into normal cognition, are summarized in Table 1. Mean follow-up duration was 1.42±0.72 years, and not different between groups. Participants who progressed to dementia were older and had lower K-MMSE scores at the baseline evaluation, compared with those who did not progress. Even after adjusting for age and K-MMSE scores, CDR-SOB score, BMI value, and frequency of presence of APOE ε4 allele were different. GDS scores were different at follow-up (p=0.0006), although these were not different at

Table 1. Characteristics of the study population at baseline

|                  | Total (n=778) | Remained MCI (n=489) | To normal (n=74) | To dementia (n=215) | p value |
|------------------|---------------|----------------------|------------------|---------------------|---------|
| Age (years)      | 70.62±7.40    | 70.55±7.45           | 66.82±7.33       | 72.07±6.85          | 0.0001* |
| Sx. duration (months) | 25.00±24.62 | 24.66±23.58          | 28.59±29.81      | 24.61±25.12         | 0.7616  |
| Gender (M:F)     | 264:514       | 175:314              | 22:52            | 67:148              | 0.0366  |
| Education (years)| 8.04±5.09     | 7.84±5.08            | 8.09±4.82        | 8.46±5.21           | 0.227   |
| K-MMSE           | 24.70±3.50    | 24.96±3.30           | 26.47±2.92       | 23.52±3.77          | <0.001* |
| CDR-SOB          | 1.61±0.90     | 1.56±0.87            | 1.07±0.68        | 1.90±0.91           | <0.001* |
| BMI (kg/m²)      | 23.79±3.13    | 23.95±3.08           | 24.56±2.97       | 23.16±3.21          | 0.0042  |
| HIS              | 1.89±1.76     | 1.95±1.85            | 1.70±1.83        | 1.81±1.51           | 0.352   |
| GDS              | 6.22±4.29     | 6.30±4.33            | 6.70±4.29        | 5.87±4.19           | 0.285   |
| Severity of WMHs*| 571:192:15    | 350:129:10           | 62:120:0         | 159:51:05           | 0.239   |

APOE ε4 169/437 (38.67%) 82/266 (30.83%) 6/31 (19.35%) 81/140 (57.86%) 79/128 (61.72%) <0.001*  

Data are mean±SD or n (%) values.  
*Severity of WMHs was represented as minimal: moderate: severe. The analyses were performed by analysis of covariance, adjusted for age and K-MMSE score.  
†Difference between those who remained with MCI and reversed to normal, at the post hoc analysis by using the Scheffe’s method.  
‡Difference between those who remained with MCI and progressed to dementia, at the post hoc analysis by using the Scheffe’s method.

AD: Alzheimer’s disease, APOE: apolipoprotein, BMI: body mass index, CDR-SOB: Clinical Dementia Severity–Sum of Boxes, F: female, GDS: Geriatric Depression Scale, HIS: Hachinski Ischemic Scale, K-MMSE: Korean version of Mini-Mental State Examination, M: male, MCI: mild cognitive impairment, SD: standard deviation, Sx.: symptom, WMHs: white matter hyperintensities.
baseline. The change of GDS scores during follow-up was 1.79±5.11 in participants who progressed to dementia, which was higher compared to -0.28±4.17 in those remained, and -1.24±3.16 in those reversed (p=0.0001). Distribution of other characteristics including family history of dementia and history of concomitant medical diseases was not different.

Table 2 shows the differences of total medical expenses including medication costs and number of used medical institutions, and the prescription frequency of ChEIs and neural pills during follow-up. During the follow-up period, neural pills were prescribed to 539 (69.28%) MCI participants and ChEIs were used by 395 (50.77%). ChEIs were prescribed to 172 (80.00%) participants with progression to dementia, 208 (42.54%) remained, and 15 (20.27%) reversed (p<0.001). Other differences were not observed.

Initial Cox proportional hazard models, adjusted for age and K-MMSE score, revealed that some factors were associated with a higher risk of MCI progression: lower education years, lower BMI values, amnesia, higher CDR-SOB and S-IADL scores at baseline, increased GDS scores during follow-up, and presence of APOE ε4 allele, in addition to older age and lower K-MMSE score at baseline (Table 3). To further analyze the best predictors of dementia progression, we performed Cox proportional hazard analyses entering all the above factors showing significance at the initial analysis. Older age [hazard ratio (HR), 1.036; 95% confidence interval (CI), 1.006–1.067; p=0.018], APOE ε4 allele (HR, 2.247; 95% CI, 1.512–3.337; p<0.001), higher CDR-SOB score (HR, 1.367; 95% CI, 1.143–1.636; p=0.001), higher S-IADL score (HR, 1.035; 95% CI, 1.003–1.067; p=0.029), and lower K-MMSE score (HR, 0.892; 95% CI, 0.839–0.949; p<0.001) predicted greater hazard (Table 3).

**DISCUSSION**

This study shows the risk of progression from MCI to dementia and its underlying predictors, in a clinical Korean cohort for dementia research. Older age, worse baseline cognitive and global function, and presence of the APOE ε4 allele are the best predictors. Additionally, lower education years, lower BMI values, presence of amnesia at baseline, and increased GDS scores during follow-up had some influence on the progression to dementia. The present findings are in agreement with those from previous studies. Furthermore, with linkage to the national health insurance claims database, we show that total medical expenses are not different between MCI participants who progressed to dementia and those who did not. Although it was based on a clinical cohort, we believe that the present evidence will add to the existing knowledge
on the risk of dementia, especially AD, in Korea, which has been accumulated mostly from epidemiological studies in this country.21

At present, there has been no medication approved for the treatment of MCI. In several placebo-controlled clinical trials, there was no significant reduction in the rates of progression to dementia among MCI patients who were treated with ChEIs.6,25-27 In one trial, donepezil significantly reduced the risk of progression to AD for the first 12 months of the study (and for up to 24 months in subgroups who were carriers of APOE ε4) but had no significant effect on the risk of AD at 36 months, which was the primary study outcome.6 The present study showed that, at the initial Cox proportional hazard models, HR for ChEIs during follow-up was 3.546 (95% CI, 2.48–5.08, p<0.001). However, the result was not significant after multivariate analysis. We do not suggest that ChEIs might make patients with MCI progress rapidly. During the follow-up of mean 1.42 years, 396 (50.77%) participants with MCI were prescribed with ChEIs. Eighty percent of MCI participants who progressed into dementia were prescribed with ChEIs, which was higher than in those who did not progress. During follow-up, changes in K-MMSE, CDR-SOB, and S-IADL scores were more severe in participants who progressed to dementia. We do not have information on whether the participants were already taking ChEIs before being enrolled into the claims database. However, mean age at the initial visit was older, and initial and follow-up scores of K-MMSE were lower in participants prescribed with ChEIs during follow-up. Our findings might indicate that substantial MCI patients in Korea, who were considered as severe as dementia by clinicians, could be prescribed with ChEIs, but this medication could not prevent the progression to dementia. In our cohort data, the annualized rate of progression to AD in our study (17.49%) was slightly higher than the original estimate (10 to 15% per year) by Petersen et al.1 Another study performed in Korea showed the annual conversion rate of 15.48%.28

This study has some limitations. The first is regarding the rates of progression to dementia or reversion to normal cognition observed in our study. Within the mean 1.5 years of follow-up, 27.63% of participants progressed to dementia, which represents an annual conversion rate slightly higher than those found by most studies, generally ranging from 10 to 15% (1–3). This might be due to a selection bias. We investigated only those participants with follow-up evaluations. Several individuals who had MCI at baseline were excluded from our analyses for missing a follow-up evaluation. These individuals differed significantly from those remaining in the study. Patients without cognitive decline would not visit the clinic for a follow-up evaluation. Moreover, 9.51% participants showed reversion to normal cognition, which could be by seeking help for their cognitive difficulties through higher cognitive, physical, and social activities. Consequently, we may be reporting an overestimated prevalence of reversion. An association between age and reversion was not found in this study, but there are reports that individuals younger than 70 years may show different predictors of reversion.29 Moreover, the relatively

### Table 3. Cox proportional hazards models

| Variable                          | HR    | 95% CI     | p value |
|-----------------------------------|-------|------------|---------|
| Age (years)                       | 1.362 | 1.277–1.451| <0.001* |
| Education (years)                 | 0.921 | 0.893–0.95  | <0.001  |
| Sx. duration (months)             | 1.938 | 1.575–2.381| <0.001  |
| Amnesia                           | 2.101 | 1.277–3.46  | 0.004   |
| APOE ε4                           | 2.883 | 2.013–4.127| <0.001* |
| K-MMSE                            | 0.871 | 0.839–0.904| <0.001* |
| CDR-SOB                           | 1.329 | 1.134–1.557| <0.001* |
| S-IADL                            | 1.038 | 1.015–1.063| 0.002*  |
| BMI (kg/m²)                       | 0.91  | 0.87–0.952  | <0.001  |
| GDS                               | 0.969 | 0.936–1.003 | 0.078   |
| Change of GDS                     | 1.066 | 1.036–1.092 | <0.001  |
| ChEIs prescribed during the follow-up | 3.546 | 2.481–5.076 | <0.001  |

*After the initial Cox proportional hazard regression analysis, adjusted for age and K-MMSE score, the second Cox proportional hazard analysis entering all the above factors showing significance at the initial analysis was performed to further analyze the best predictors for dementia progression.

**Abbreviations:** HR: hazard ratio, CI: confidence interval, S-IADL: Seoul-Instrumental Activities of Daily Living, Sx.: symptom.
short duration of follow-up in this study provides only a narrow window of investigation. A longer follow-up period is needed to determine the extent to which unstable MCI represents a very early MCI stage of serious cognitive decline. A final limitation is our lack of consideration of transitory cognitive impairment associated with factors like stress, acute illness, or poor motivation, with MCI diagnosed under such conditions at greater than normal chances of reversion to normal cognition.8,9,10 Additionally, we could not exclude the possibility that MCI patients who progressed to dementia already took ChEIs or neural pills at other clinics (not in the database) before the baseline enrollment in the database. K-MMSE score at initial visit was lower in participants prescribed with ChEIs during the follow-up. Although adjustment for K-MMSE score was performed, matching the baseline cognitive status between those who were prescribed with and without ChEIs could further evaluate the effect of ChEIs on the rate of cognitive decline.

However, this Korean multi-hospital based cohort database showed that 215 (27.63%) of 778 participants with MCI progressed to dementia including 200 AD, during mean 1.42±0.72 years of follow-up duration, and the best predictors for progression were older age, lower K-MMSE scores, higher CDR-SOB, and S-IADL scores, and APOE ε4 allele. Lower education years, lower BMI values, and increased GDS scores during follow-up can have some effect on the prognosis.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgements

This study was supported by grants of the Korea Healthcare technology R&D Project, Ministry of Health and Welfare, Republic of Korea (HI10C2020) and the National Strategic Coordinating Center for Clinical Research, and partly by grants of the Korea Healthcare technology R&D Project, Ministry of Health and Welfare, Republic of Korea (HI12C0713) and the Original Technology Research Program for Brain Science through the National Research Foundation of Korea funded by the Korean government (No. 2014M3C7A1064752).

The authors thank Mr. Min-Kyu Park for the statistical help for this study.

REFERENCES

1. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303-308.
2. Busse A, Hensel A, Gühme U, Angermeyer MC, Riedel-Heller SG. Mild cognitive impairment: long-term course of four clinical subtypes. Neurology 2006;67:2176-2185.
3. Manly JI, Tang MX, Schapf N, Stern Y, Vonsattel JP, Mayeux R. Frequency and course of mild cognitive impairment in a multiethnic community. Ann Neurol 2008;63:494-506.
4. Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett DA, et al. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. Arch Neurol 2004;61:59-66.
5. Dickerson BC, Sperling RA, Hyman BT, Albert MS, Blacker D. Clinical prediction of Alzheimer disease dementia across the spectrum of mild cognitive impairment. Arch Gen Psychiatry 2007;64:1443-1450.
6. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 2005;352:2379-2388.
7. Beydoun MA, Beydoun HA, Garnaldo AA, Teel A, Zonderman AB, Wang Y. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. BMC Public Health 2014;14:643.
8. Cooper C, Li R, Lyketsos C, Livingston G. Treatment for mild cognitive impairment: systematic review. Br J Psychiatry 2013;203:255-264.
9. Karakaya T, Fuller F, Schröder J, Pantel J. Pharmacological treatment of mild cognitive impairment as a prodromal syndrome of Alzheimer’s disease. Curr Neuropharmacol 2013;11:102-108.
10. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183-194.
11. Kang Y, Na DL, Han S. A validity study on the Korean Mini-Mental State Examination (K-MMSE) in dementia patients. J Korean Neurol Assoc 1997;15:300-308.
12. Park HK, Na DL, Han SH, Kim JY, Cheong HK, Kim SY, et al. Clinical characteristics of a nationwide hospital-based registry of mild-to-moderate Alzheimer’s disease patients in Korea: a CREDOS (Clinical Research Center for Dementia of South Korea) study. J Korean Med Sci 2011;26:1219-1226.
13. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993;43:2412-2414.
14. Parnetti L, Inzitari D. Hachinski’s ischemic score and the diagnosis of vascular dementia: a review. Ital J Neurol Sci 1993;14:539-546.
15. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982-1983;17:37-49.
16. Ku HM, Kim JH, Kwon EJ, Kim SH, Lee HS, Ko HJ, et al. A study on the reliability and validity of Seoul-Instrumental Activities of Daily Living (S-IADL). J Korean Neuropsychiatr Assoc 2004;43:189-199.
17. Kang Y, Na DL. Seoul Neuropsychological Screening Battery (SNSB). 1st ed. Incheon: Human Brain Research & Consulting Co., 2003.
18. Nolt Y, Lee Y, Seo SW, Jeong JH, Choi SH, Back JL, et al. A new classification system for ischemia using a combination of deep and periventricular white matter hyperintensities. J Stroke Cerebrovasc Dis 2014;23:636-642.
19. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer’s disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease. Neurology 1984;34:939-944.
20. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 1993;43:250-260.
21. McKeith IG, Dickson DW, Lowe I, Emre M, O’Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863-1872.
22. Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, et al. Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. Brain 2008;131(Pt 11):2957-2968.
23. Pankratz VS, Roberts RO, Mielke MM, Knopman DS, Jack CR Jr, Geda YE, et al. Predicting the risk of mild cognitive impairment in the Mayo Clinic Study of Aging. Neurology 2015;84:1433-1442.
24. Kim S, Kim MJ, Kim S, Kang HS, Lim SW, Myung W, et al. Gender
differences in risk factors for transition from mild cognitive impairment to Alzheimer’s disease: A CREDOS study. Compr Psychiatry 2015;62:114-122.

25. Feldman HH, Ferris S, Winblad B, Sifkas N, Mancione L, He Y, et al. Effect of rivastigmine on delay to diagnosis of Alzheimer’s disease from mild cognitive impairment: the InDEx study. Lancet Neurol 2007;6:501-512.

26. Winblad B, Gauthier S, Scinto L, Feldman H, Wilcock GK, Truyen L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology 2008;70:2024-2035.

27. Doody RS, Ferris SH, Salloway S, Sun Y, Goldman R, Watkins WE, et al. Donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. Neurology 2009;72:1555-1561.

28. Han JW, Kim TH, Lee SB, Park JH, Lee JJ, Huh Y, et al. Predictive validity and diagnostic stability of mild cognitive impairment subtypes. Alzheimers Dement 2012;8:553-559.

29. Olazarán J, Torrero P, Cruz I, Aparicio E, Sanz A, Mula N, et al. Mild cognitive impairment and dementia in primary care: the value of medical history. Fam Pract 2011;28:385-392.

30. Koepsell TD, Monsell SE. Reversion from mild cognitive impairment to normal or near-normal cognition: risk factors and prognosis. Neurology 2012;79:1591-1598.