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Effects of amyloid and vascular markers on cognitive decline in subcortical vascular dementia

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ABSTRACT

Objective: To determine the independent and synergistic effects of amyloid and small vessel disease (SVD) burden on longitudinal cognitive decline in patients with subcortical vascular dementia (SVaD).

Methods: A longitudinal cohort study was conducted involving patients from outpatient clinics of 2 tertiary referral centers. Sixty-one patients with SVaD were prospectively recruited and underwent MRI, 11C-Pittsburgh compound B (PiB) PET at baseline, and a 3-year annual neuropsychological follow-up. Effects of PiB positivity and SVD markers (white matter hyperintensities [WMH], lacunes, and microbleeds) on longitudinal cognitive decline were evaluated using generalized estimation equation after controlling for age, sex, education, *APOE4* allele, and follow-up interval.

Results: When individual neuropsychological tests were used as outcome measures, PiB positivity was associated with faster cognitive decline in attention, visuospatial, visual memory, and global cognition function. Higher WMH burden was associated with faster cognitive decline in attention, visuospatial, visual recognition memory, and semantic/phonemic fluency function, whereas lacunes and microbleeds had no significant effects. When global dementia rating (Clinical Dementia Rating sum of boxes) was considered as an outcome measure, however, only PiB positivity was associated with faster cognitive decline. Significant interactions between PiB positivity and higher SVD burden were found to affect cognitive decline in semantic word fluency (from WMH burden) and global dementia rating (from microbleed burden).

Conclusions: In SVaD patients, amyloid burden, independently or interactively with SVD, contributed to longitudinal cognitive decline. Amyloid deposition was the strongest poor prognostic factor. ***Neurology*® 2015;85:1687–1693**

GLOSSARY

AD = Alzheimer disease; **AMPETIS** = Amyloid PET Imaging for Subcortical Vascular Dementia; **CDR-SOB** = Clinical Dementia Rating Sum of Boxes; **COWAT** = Controlled Oral Word Association Test; **CVD** = cerebrovascular disease; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders, 4th edition*; **FLAIR** = fluid-attenuated inversion recovery; **GEE** = generalized estimation equation; **MMSE** = Mini-Mental State Examination; **PiB** = Pittsburgh compound B; **RCFT** = Rey-Osterrieth Complex Figure Test; **SVaD** = subcortical vascular dementia; **SVD** = small vessel disease; **WMH** = white matter hyperintensities.

Small vessel disease (SVD) markers observed in brain MRI in patients with subcortical vascular dementia (SVaD) include extensive white matter hyperintensities (WMH), lacunar infarcts and microbleeds.[1–6] Recent studies showed that amyloid deposition, a hallmark of Alzheimer disease (AD), frequently co-occurs with these cerebrovascular disease (CVD) markers in patients with vascular cognitive impairment.[7–9]

To date, no longitudinal studies investigating the natural course of cognitive decline in patients with SVaD have been conducted. Moreover, why some SVaDs take a progressive course

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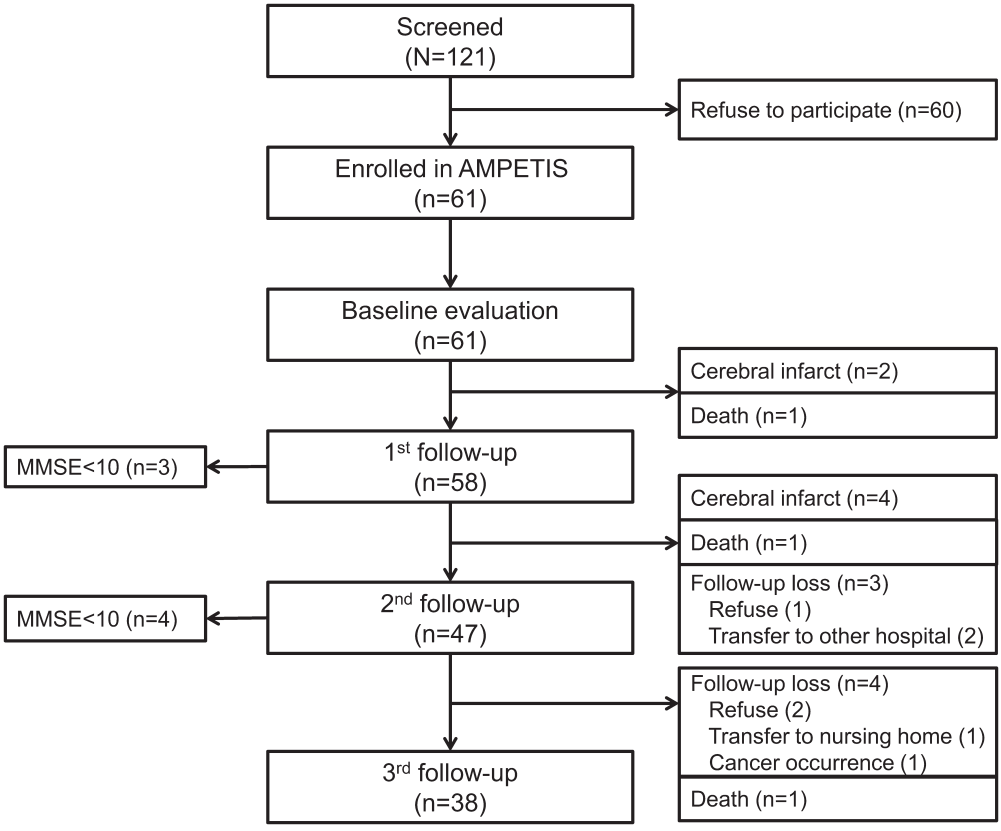
despite vigorous control of risk factors and treatment with antiplatelets or anticoagulants remains largely unanswered. In addition, although previous studies have shown that CVD and AD pathologies influence cognitive dysfunction,[10–14] no studies have investigated the independent effects of CVD and AD pathologies on cognitive decline in patients with SVaD.

In the current study, based on a longitudinal cohort study called Amyloid PET Imaging for Subcortical Vascular Dementia (AMPETIS), we examined the natural course and cognitive trajectories of patients with SVaD in a 3-year follow-up period and investigated the effects of baseline amyloid burden and SVD markers on cognitive decline.

METHODS **Patients.** Participants were prospectively recruited from the memory disorder clinic of Samsung Medical Center and Asan Medical Center, Seoul, Korea. New or followed up SVaD patients were asked to participate in the AMPETIS study from September 2008 to September 2010. All of our SVaD patients had (1) dementia, (2) focal neurologic signs suggestive of CVD, and (3) a severe WMH on MRI defined as a cap or band ≥10 mm and a deep white matter lesion ≥25 mm, fulfilling both *DSM-IV* vascular dementia criteria[15] and the predominantly white matter cases imaging criteria for SVaD by Erkinjuntti et al.[16] (see e-Methods on the *Neurology*® Web site at Neurology.org for details). For longitudinal follow-up, patients were also required to have (1) 50 ≤ age ≤ 85 years and (2) Mini-Mental State Examination (MMSE) score ≥10. A total of 121 patients were diagnosed with SVaD, and after those who did not agree to participate (n = 60) were excluded, 61 participated in the AMPETIS study. Participants had higher MMSE scores than nonparticipants (20.7 ± 4.9 vs 18.8 ± 5.0, $p = 0.033$), but there were no significant differences in demographic features or Clinical Dementia Rating Sum of Boxes (CDR-SOB). At baseline, participants underwent brain MRI, Pittsburgh compound B PET (PiB-PET) scan, and detailed neuropsychological tests. Afterwards, the participants had 3 serial annual follow-ups with the same neuropsychological tests.

As illustrated in figure 1, of the initial 61 patients with SVaD, 7 dropped out from the study (dropout rate 11.5%) for the following reasons: nursing home placement (1/7), follow-up refusal (3/7), transfer to another hospital (2/7), and occurrence of cancer (1/7). Among the remaining 54 patients, 6

Figure 1 **Flow chart of study participant follow-up**



A total of 121 patients were diagnosed with subcortical vascular dementia from September 2008 to September 2010 and were asked to participate in the Amyloid PET Imaging for Subcortical Vascular Dementia (AMPETIS) study. Sixty-one patients agreed to participate in the study. During the 3-year follow-up period, 6 patients had cerebral infarction and 7 patients had a Mini-Mental State Examination (MMSE) score below 10 before their last follow-up. Ten patients dropped out of the study (dropout rate 16.4%). One patient was admitted to a nursing home; 5 patients refused follow-up; 2 patients transferred to another hospital; one patient had subdural hematoma; and one patient developed a cancer.

Table 1 Demographic, clinical, and MRI characteristics of PiB(+) and PiB(−) patients

	Total (n = 61)	PiB(+) (n = 20)	PiB(−) (n = 41)	*p* Value[a]
Female	36 (59.0)	15 (75.0)	21 (51.2)	0.076
Baseline age, y	74.1 ± 7.1	79.2 ± 3.8	71.7 ± 7.0	<0.001
Disease duration, y	4.8 ± 3.7	5.2 ± 3.8	4.7 ± 3.7	0.603
Education, y	9.3 ± 5.1	9.6 ± 5.9	9.2 ± 4.8	0.774
Risk factors				
DM	18 (29.5)	6 (30.0)	12 (29.3)	0.953
HTN	49 (80.3)	17 (85.0)	32 (78.0)	0.734
Hyperlipidemia	25 (41.0)	6 (30.0)	19 (46.3)	0.223
Cardiac disease	8 (13.1)	2 (10.0)	6 (14.6)	>0.999
Previous stroke	19 (31.1)	3 (15.0)	16 (39.0)	0.057
Geriatric Depression Scale	16.4 ± 8.2	16.4 ± 8.2	16.3 ± 8.3	0.970
WMH volume, mL	41.7 ± 17.7	45.0 ± 24.6	40.1 ± 13.3	0.318
Number of lacunes	16.3 ± 16.8	7.5 ± 7.1	20.6 ± 18.5	<0.001
Number of microbleeds	10.0 ± 18.3	12.5 ± 28.8	8.8 ± 10.3	0.588
APOE4 allele, %[b]	58	20	38	0.006
Carrier	16 (27.6)	10 (50.0)	6 (15.8)	
Noncarrier	42 (72.4)	10 (50.0)	32 (84.2)	
Hippocampal volume	2.8 ± 0.6	2.7 ± 0.4	2.9 ± 0.6	0.459
Intracranial volume ($\times 10^3$ mL)	1.4 ± 0.1	1.4 ± 0.2	1.4 ± 0.1	0.785
Follow-up information				
Incident stroke	6 (9.8)	0	6 (14.6)	0.165
MMSE <10 during follow-up	7 (11.5)	4 (20.0)	3 (7.3)	0.203
Dropout	7 (11.5)	1 (5.0)	6 (14.6)	0.409
Cancer occurrence	1 (1.6)	0	1 (2.4)	>0.999
Death	3 (13.1)	2 (10.0)	1 (2.4)	0.248

Abbreviations: DM = diabetes mellitus; HTN = hypertension; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; WMH = white matter hyperintensities.
Data are expressed as mean ± SD or n (%).
[a] *p* Values are results of independent *t* tests or χ^2 tests.
[b] *APOE* genotypes were analyzed in 58 patients because 3 patients refused the test.

patients experienced acute cerebral infarctions, 7 patients scored below 10 on the MMSE (severe cognitive deterioration) during the follow-up period, and 3 patients died. We did not consider these 16 patients as dropouts but regarded them as having reached the endpoint of the current study. Therefore, we included their neuropsychological data in the analysis obtained prior to the event (stroke or death). The mean follow-up duration was 2.58 ± 1.02 years (median 2.97 years, interquartile range 1.99–3.25 years). Among the 7 dropouts, 4 patients had 2 annual follow-ups and 3 had 1 follow-up. The dropout and remaining patients did not differ in age, sex, education, baseline MMSE, or baseline CDR-SOB.

During the study period, 59 patients were treated with antiplatelet agents, 1 with anticoagulants, and 1 patient had a large unruptured cerebral aneurysm.

Standard protocol approvals, registrations, and patient consents. We obtained written consent from each participant and the Institutional Review Board of Asan Medical Center and Samsung Medical Center approved the study protocol.

Neuropsychological tests. All patients underwent neuropsychological tests using a standardized Seoul Neuropsychological Screening Battery, which is described in detail elsewhere[17,18] and in the e-Methods.

MRI acquisition. All patients were referred to Samsung Medical Center for MRI using identical imaging protocols on a 3.0T MRI scanner (Achieva, Philips 3.0T; Eindhoven, Netherlands). Three-dimensional T1 turbo field echo (TFE), fluid-attenuated inversion recovery (FLAIR), T1, T2, and fast field echo were performed on all study participants. Detailed imaging parameters are described in e-Methods.

Measurement of WMH volume and rating of lacunes and microbleeds on MRI. We used FLAIR images to quantify WMH volume through fully automated segmentation and classification of WMH, as described previously[19] and in e-Methods. Details of lacune and microbleed counting are also described in e-Methods.

[^{11}C] PiB-PET. [^{11}C] PiB-PET scanning was performed at Samsung Medical Center or Asan Medical Center using a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, WI). The detailed methods for PiB-PET scanning and the calculation of global PiB retention ratio are described in a previous study[9] and in e-Methods. We defined the global PiB retention ratio as a continuous variable representing amyloid burden. Patients were considered PiB(+) if their global PiB retention ratio was more than 2 SDs (PiB retention ratio >1.5) from the mean of the normal controls.[9]

Statistical analyses. Descriptive statistics of the baseline workup were performed using χ^2 and Student *t* tests when appropriate. To explore the association of SVD markers and PiB retention with longitudinal changes in neuropsychological scores, the generalized estimation equation (GEE) was used.[20] The GEE treated individual neuropsychological scores as dependent variables and the interaction between the follow-up interval from the baseline and variables including SVD markers and PiB retention as predictors. Correlation between successive measures in each patient was accommodated using an unstructured (or autoregressive) correlation structure. Due to the positive skewness of SVD markers, we treated them as dichotomized variables using the second tertile as cutoffs. Patients with SVaD were therefore divided into higher WMH burden (n = 21) and lower WMH burden (n = 40, WMH volume < cutoff, 47 mL); higher lacunar burden (n = 23) and lower lacunar burden (n = 38, number of lacunes < cutoff, 14); and higher microbleed burden (n = 20) and lower microbleed burden (n = 41, number of microbleeds < cutoff, 7). Comparisons of clinical, neuropsychological, and MRI characteristics between patients with higher and lower SVD burden are also summarized in tables e-1 and e-2.

Two GEE models were applied to determine independent predictors of longitudinal cognitive decline. In model 1, to test univariate association between each predictor and longitudinal cognitive decline, interaction between interval and each independent variable was individually tested after controlling for baseline age, sex, education, *APOE4* genotype (*APOE4* carrier vs noncarrier), and interval (table e-3). Among SVD markers and PiB positivity, variables interacting with an interval at a *p* value <0.1 were selected for the second GEE model (model 2), in which the selected independent variables were simultaneously entered. In model 1, possible interaction between PiB positivity and SVD markers on longitudinal cognitive decline was also tested using 3-way interaction among PiB positivity, SVD markers, and interval

(table e-4), and those with $p < 0.05$ were included as predictors in model 2. Therefore, model 2 tested the independent and interaction effect of PiB positivity and SVD markers on longitudinal cognitive decline. Because GEE model 2 had different predictors and interaction terms for each neuropsychological test, and in order to reduce the chances of missing important associations during the early stage of analysis, we used a statistical significance level of 0.05 with no correction for multiple comparisons. All statistical analyses were performed using the Statistical Package for the Social Sciences 18.0 (SPSS Inc., Chicago, IL).

RESULTS

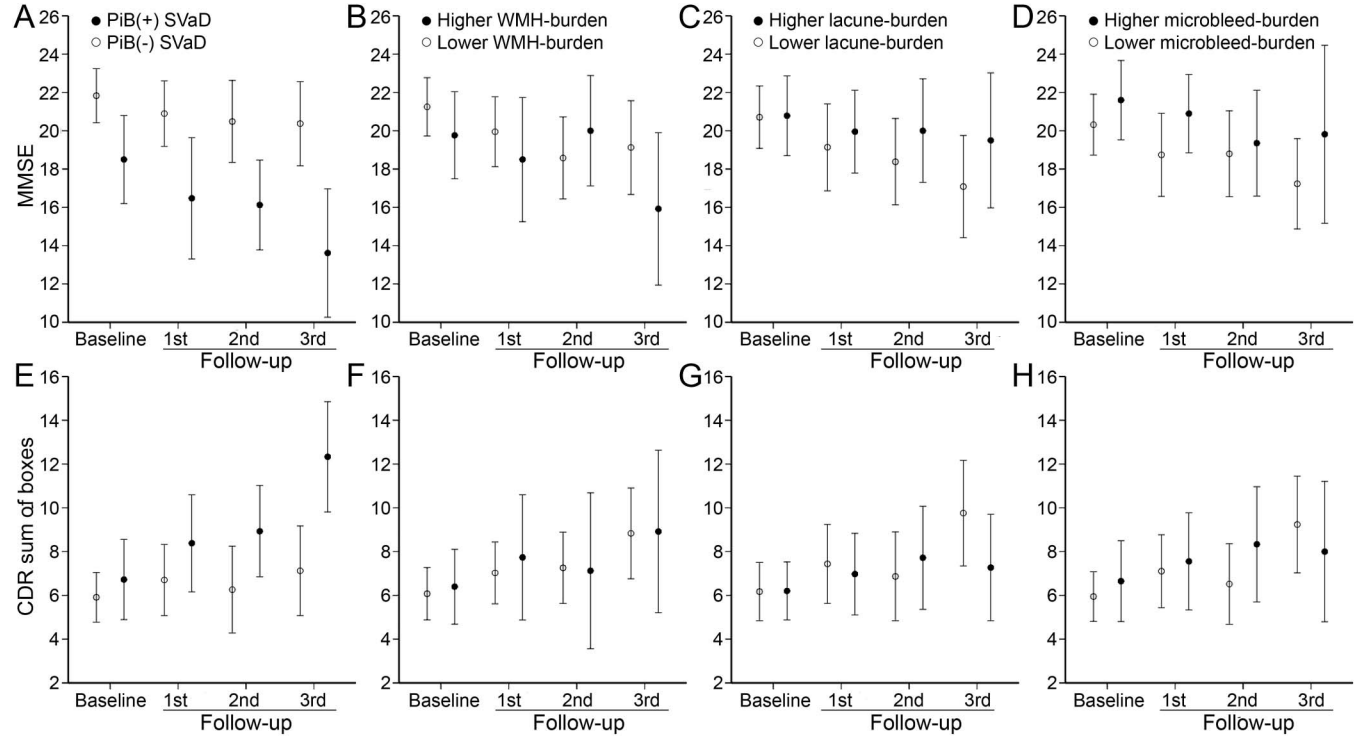
Natural course of SVaD. During the 3-year follow-up period, 6 patients experienced ischemic cerebral infarction and all 6 patients were PiB(−). Among them, 3 patients had territorial infarctions and the other 3 lacunar infarctions. The MMSE score was 20.7 ± 4.9 at baseline and 18.0 ± 6.2 at the third follow-up. The CDR-SOB score was 6.2 ± 3.7 at baseline and 8.9 ± 5.2 at the third follow-up. The mean rate of MMSE change was 0.91 per year and the mean rate of CDR-SOB change was 0.9 per year.

Comparisons of clinical, neuropsychological, and MRI characteristics and longitudinal cognitive decline between groups based on PiB positivity and SVD markers. A total of 20 (32.8%) participants tested positive for PiB retention. PiB(+) and PiB(−) SVaD groups differed in terms of age, the number of lacunes, and the proportion of *APOE4* carriers (table 1). The PiB(+) group was older and had a higher proportion of *APOE4* carriers, while the PiB(−) group had a greater number of lacunes. There were no significant differences in vascular risk factors.

As illustrated in figure 2, the mean rate of MMSE decline was 1.63 per year for the PiB(+) SVaD and 0.48 per year for the PiB(−) SVaD group. The mean rate of CDR-SOB increase was 1.87 per year for the PiB(+) SVaD and 0.40 per year for the PiB(−) SVaD group. Figure 2 also illustrates MMSE and CDR-SOB trajectories according to the higher and lower groups of each SVD marker. The rates of MMSE decline and CDR-SOB increase are described in e-Methods.

Effects of amyloid burden and SVD MRI markers on longitudinal neuropsychological changes. PiB positivity predicted faster decline in digit span backward, Rey-Osterrieth Complex Figure Test (RCFT) copy, RCFT delayed recall, and CDR-SOB scores. Higher WMH burden was independently associated with steeper cognitive decline in digit span forward, Rey copy, RCFT recognition, Controlled Oral Word Association Test (COWAT) supermarket, and COWAT phonemic scores, whereas the

Figure 2 Trajectories of cognitive decline over the 3-year follow-up



Trajectories of Mini-Mental State Examination (MMSE) (A) and Clinical Dementia Rating Sum of Boxes (CDR-SOB) (E) for patients with Pittsburgh compound B (PiB)–positive and PiB-negative subcortical vascular dementia (SVaD) are represented. Trajectories of MMSE and CDR-SOB for patients with higher small vessel disease (SVD) burden and those with lower SVD burden are also represented for white matter hyperintensities (WMH) (B and F), lacunes (C and G), and microbleeds (D and H). Circles denote mean values and whiskers represent the 95% confidence intervals for each mean.

Table 2 Independent and interaction effects of baseline PiB positivity and the burden of small vessel disease MRI markers on neuropsychological change

Neuropsychological test	Predictor	β (SE)	*p* Value
Digit span forward	PiB positivity	−0.07 (0.06)	0.221
	Higher WMH burden	−0.08 (0.02)[b]	0.002[b]
	Interaction (PiB × WMH)	0.12 (0.06)	0.046
Digit span backward	PiB positivity	−0.09 (0.05)[a]	0.039[a]
	Higher lacunar burden	0.07 (0.04)	0.085
K-BNT	PiB positivity	−0.08 (0.05)	0.093
	Higher lacunar burden	0.02 (0.03)	0.392
RCFT copy	PiB positivity	−0.19 (0.08)[a]	0.024[a]
	Higher WMH burden	−0.18 (0.08)[b]	0.017[b]
SVLT immediate recall	PiB positivity	−0.07 (0.08)	0.372
	Higher lacunar burden	0.03 (0.06)	0.660
	Interaction (PiB × lacunar)	−0.24 (0.10)[c]	0.018[c]
SVLT delayed recall	PiB positivity	0.94 (0.23)	<0.001
	Higher lacunar burden	−0.03 (0.17)	0.881
	Interaction (PiB × lacunar)	−1.70 (0.48)[c]	<0.001[c]
SVLT recognition	PiB positivity	0.02 (0.04)	0.663
	Higher lacunar burden	−0.03 (0.03)	0.375
	Interaction (PiB × lacunar)	−0.13 (0.05)[c]	0.005[c]
RCFT delayed recall	PiB positivity	−0.42 (0.21)[a]	0.046 [a]
RCFT recognition	Higher WMH burden	−0.05 (0.02)[b]	0.006[b]
COWAT animal	PiB positivity	0.05 (0.08)	0.559
	Higher WMH burden	−0.05 (0.06)	0.384
	Interaction (PiB × WMH)	−0.26 (0.12)[c]	0.032[c]
COWAT supermarket	PiB positivity	−0.05 (0.11)	0.621
	Higher WMH burden	−0.18 (0.08)[b]	0.027[b]
	Higher lacunar burden	0.10 (0.06)	0.102
	Interaction (PiB × WMH)	−0.34 (0.16)[c]	0.033[c]
COWAT phonemic	Higher WMH burden	−0.36 (0.10)[b]	<0.001[b]
	Higher lacunar burden	0.09 (0.07)	0.196
MMSE	PiB positivity	−0.07 (0.04)	0.088
	Higher WMH burden	−0.07 (0.04)	0.076
	Higher microbleed burden	0.05 (0.03)	0.095
	Interaction (PiB × microbleed)	−0.13 (0.09)	0.139
CDR-SOB	PiB positivity	0.13 (0.04)[a]	0.003[a]
	Higher microbleed burden	−0.02 (0.05)	0.607
	Interaction (PiB × microbleed)	0.17 (0.06)[c]	0.005[c]

Abbreviations: CDR-SOB = Clinical Dementia Rating Sum of Boxes; COWAT = Controlled Oral Word Association Test; K-BNT = Korean version of the Boston Naming Test; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B; RCFT = Rey-Osterrieth Complex Figure Test; SVLT = Seoul Verbal Learning Test; WMH = white matter hyperintensities.

Results are a summary of the generalized estimation equations of cognitive change. Covariates included baseline age, sex, education, *APOE4* allele, and follow-up interval from baseline. Predictors were variables with $p < 0.1$ in table e-3 and interactions with $p < 0.05$ in table e-4. The burden of small vessel disease markers was dichotomized using the second tertile of WMH volume and the number of lacunes and microbleeds as cutoff values. Regression coefficients (β), standard errors (SE), and *p* values for the interaction between predictors and follow-up interval are presented.

[a]Significant detrimental effects of PiB positivity, [b]small vessel disease marker, and [c]their synergistic interaction.

number of lacunes or microbleeds did not affect cognitive decline.

PiB positivity and higher WMH burden were interactively associated with faster cognitive decline in COWAT animal and COWAT supermarket scores; PiB positivity and higher lacunar burden were in the immediate recall, delayed recall, and recognition items of SVLT; and PiB positivity and higher microbleed burden were in MMSE and CDR-SOB (table 2). We confirmed these interaction effects by testing the effect of PiB positivity in the subgroup with higher SVD burden and in the subgroup with lower SVD burden, respectively (table e-5).

Sensitivity analysis. First, we used global PiB retention ratio as a predictor instead of PiB positivity to test the effect of PiB retention as a continuous variable (table e-6). The detrimental effect of global PiB retention ratio was observed in general cognition (MMSE) and global dementia rating (CDR-SOB).

Data loss ratio was more than 30% at the third follow-up, and patients with SVaD without the third follow-up data (see figure 1, n = 9: follow-up loss [4], death [1], and MMSE <10 [4]) had more microbleeds than those who completed all the follow-ups (9.0 ± 17.2 vs 24.1 ± 28.5, $p = 0.044$). We then performed a sensitivity analysis excluding the third follow-up data (table e-7). PiB positivity still showed significant detrimental effects on digit span forward, Korean version of the Boston Naming Test, MMSE, and CDR-SOB, but detrimental effect of SVD was observed only in COWAT animal (from microbleed burden). Also, the synergistic interaction effect was observed only in COWAT phonemic (between PiB positivity and WMH burden) but not in general cognition or global dementia rating.

DISCUSSION

The first major finding of our study was concerned with tracking the natural course of SVaD. Approximately 10% of the patients experienced cerebral infarction during the 3-year follow-up, with an equal number of territorial and lacunar infarction. Interestingly, only PiB(−) patients developed cerebral infarction. Despite treating patients with antiplatelet agents or anticoagulants, no patient developed intracranial macrohemorrhage. Overall mean rates of MMSE decline in patients with SVaD was 0.91 per year and CDR-SOB increase was 0.9 per year, which were less steep than those of patients with AD from our previous study (−1.69 per year for MMSE and 1.54 per year for CDR-SOB).[21] However, the rates of decline in MMSE and CDR-SOB in PiB(+) patients with SVaD patients were similar to those of patients with AD.

The second major finding was that PiB uptake had more powerful independent effects on longitudinal

cognitive decline than SVD markers. Although both PiB uptake and WMH volume were associated with cognitive decline when individual cognitive tests were used as outcome measures, only PiB positivity was significant when global dementia rating (CDR-SOB) was considered as an outcome measure. This finding suggests that relentless cognitive decline in patients with SVaD despite treatment with antiplatelets and management of cardiovascular risk factors is primarily driven by additive amyloid burden superimposed on vascular burden or their synergistic effects. Our finding is consistent with a prior study showing that amyloid burden may be a major determinant of cognitive impairment overwhelming the effect of SVD markers in patients with dementia.[14] These findings, therefore, suggest that evaluation of amyloid deposition may be important when formulating treatment plans for patients with SVaD and anti-amyloid agents may be needed for treating PiB(+) patients with SVaD. Conversely, PiB negativity in patients with SVaD necessitates tight measures of stroke prevention because only PiB(−) patients with SVaD experienced cerebral infarctions in our study.

Among SVD markers, higher WMH burden was associated with faster cognitive decline in attention, visuospatial, visual recognition memory and semantic fluency scores, but not in global dementia indices. Previous longitudinal studies involving elderly participants without dementia showed that WMH volume at baseline could predict future cognitive decline, not only in memory function[22] and frontal executive but also general cognitive function.[4] Higher burden of SVD, further adjustment for amyloid effect, and inclusion of patients with dementia in our study could explain the discrepancy of WMH effects on general cognition between previous studies and our results.

The third major finding was that PiB uptake and SVD markers had significant synergistic interaction such that the effect of amyloid burden and SVD markers on cognitive decline through an interaction was greater than the effect of either one added together. More specifically, PiB positivity and SVD markers had synergistic interactions for semantic fluency tests and CDR-SOB. Previous preclinical studies using animal models showed that chronic cerebral hypoperfusion and amyloid toxicity interact deleteriously on cognition.[23,24] However, all prior human studies but one[25] failed to reveal synergistic interaction between amyloid burden and SVD markers on cognition.[13,26–28] This discrepancy between our study and most prior studies could be attributed to the fact that when compared to prior studies, our study was longitudinal in design and our patients probably had more severe ischemic changes and cognitive dysfunction.

Our study has several limitations. First, patients with SVaD were recruited through a memory clinic. It is likely that patients with SVaD with predominant motor symptoms visit a stroke clinic more often than our memory disorder clinic, and vice versa for patients with SVaD with predominant cognitive symptoms, which may limit generalizability of our results. Second, because we only included the neuropsychological data obtained prior to stroke, we could not assess the influence of overt vascular events. Given that stroke occurred only in the PiB(−) group, the rate of cognitive decline in the PiB(−) group could have been underestimated. Third, we cannot exclude the possibility that patients with cerebral amyloid angiopathy have been included in our sample, although there were only 5 patients who had strictly lobar microbleeds. Fourth, the cutoff for PiB positivity may be arbitrary. However, when the global PiB retention ratio was treated as a continuous variable, the results were largely unchanged (table e-6). Fifth, data loss ratio at the third follow-up was significant (more than 30%). This significant follow-up loss might have resulted in an underestimation of the detrimental effects of SVD markers, because the patients who dropped out at the third follow-up had more microbleeds than those who completed all the follow-up. However, when we performed the same analyses after exclusion of the third follow-up data, detrimental effects of PiB positivity were still robust, although detrimental effects of SVD and the synergistic effect between PiB and SVD markers became less robust (table e-7). Sixth, because 61 patients with SVaD who participated in the current study had higher baseline MMSE scores than 60 patients who did not agree to participate, we cannot exclude the possibility of selection bias, which might limit the generalizability of our results. Finally, since we did not do multiple comparison corrections for repeated statistical testing of a large number of neuropsychological tests, the meaning of individual tests may be questionable.

AUTHOR CONTRIBUTIONS

Dr. Duk L. Na and Dr. Jae-Hong Lee had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Byoung Seok Ye, Duk L. Na, and Jae-Hong Lee. Acquisition, analysis, or interpretation of data: Sang Won Seo, Jung-Hyun Kim, Geon Ha Kim, Hanna Cho, Young Noh, Hee Jin Kim, Cindy W. Yoon, Sook-young Woo, Sook Hui Kim, Hee Kyung Park, Sung Tae Kim, Yearn Seong Choe, Kyung Han Lee, Jae Seung Kim, Seung Jun Oh, and Changsoo Kim. Critical revision of the manuscript for important intellectual content: Jae-Hong Lee, Michael Weiner, and Duk L. Na. Drafting of the manuscript: Byoung Seok Ye and Duk L. Na.

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DISCLOSURE

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