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Use of Flutemetamol F 18–Labeled Positron Emission Tomography and Other Biomarkers to Assess Risk of Clinical Progression in Patients With Amnestic Mild Cognitive Impairment

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IMPORTANCE Patients with amnestic mild cognitive impairment (aMCI) may progress to clinical Alzheimer disease (AD), remain stable, or revert to normal. Earlier progression to AD among patients who were β-amyloid positive vs those who were β-amyloid negative has been previously observed. Current research now accepts that a combination of biomarkers could provide greater refinement in the assessment of risk for clinical progression.

OBJECTIVE To evaluate the ability of flutemetamol F 18 and other biomarkers to assess the risk of progression from aMCI to probable AD.

DESIGN, SETTING, AND PARTICIPANTS In this multicenter cohort study, from November 11, 2009, to January 16, 2014, patients with aMCI underwent positron emission tomography (PET) at baseline followed by local clinical assessments every 6 months for up to 3 years. Patients with aMCI (365 screened; 232 were eligible) were recruited from 28 clinical centers in Europe and the United States. Physicians remained strictly blinded to the results of PET, and the standard of truth was an independent clinical adjudication committee that confirmed or refuted local assessments. Flutemetamol F 18–labeled PET scans were read centrally as either negative or positive by 5 blinded readers with no knowledge of clinical status. Statistical analysis was conducted from February 19, 2014, to January 26, 2018.

INTERVENTIONS Flutemetamol F 18–labeled PET at baseline followed by up to 6 clinical visits every 6 months, as well as magnetic resonance imaging and multiple cognitive measures.

MAIN OUTCOMES AND MEASURES Time from PET to probable AD or last follow-up was plotted as a Kaplan-Meier survival curve; PET scan results, age, hippocampal volume, and aMCI stage were entered into Cox proportional hazards logistic regression analyses to identify variables associated with progression to probable AD.

RESULTS Of 232 patients with aMCI (118 women and 114 men; mean [SD] age, 71.1 [8.6] years), 98 (42.2%) had positive results detected on PET scan. By 36 months, the rates of progression to probable AD were 36.2% overall (81 of 224 patients), 53.6% (52 of 97) for patients with positive results detected on PET scan, and 22.8% (29 of 127) for patients with negative results detected on PET scan. Hazard ratios for association with progression were 2.51 (95% CI, 1.57-3.99; $P < .001$) for a positive β-amyloid scan alone (primary outcome measure), 5.60 (95% CI, 3.14-9.98; $P < .001$) with additional low hippocampal volume, and 8.45 (95% CI, 4.40-16.24; $P < .001$) when poorer cognitive status was added to the model.

CONCLUSIONS AND RELEVANCE A combination of positive results of flutemetamol F 18–labeled PET, low hippocampal volume, and cognitive status corresponded with a high probability of risk of progression from aMCI to probable AD within 36 months.

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Mild cognitive impairment (MCI) is a deficit in 1 or more cognitive domains, with relative preservation of functional independence without dementia; patients with MCI may progress to clinical Alzheimer disease (AD), suggesting that MCI (specifically amnestic MCI [aMCI]) is often prodromal AD.[1,2] To better define those most likely to have prodromal AD, a National Institute of Aging-Alzheimer Association working group revised MCI criteria to incorporate AD biomarkers.[2] They proposed that biomarkers measuring β-amyloid and neuronal injury or degeneration increase the likelihood that MCI is due to AD, indicating a higher risk of cognitive decline. Precise quantification of this risk would prove useful for physicians, patients, and families.

We investigated the safety and efficacy of the positron emission tomographic (PET) β-amyloid tracer flutemetamol F 18 for assessing the probability of progression from aMCI to probable AD within 36 months[3]; we also explored combining PET with 2 clinically accessible biomarkers: hippocampal volume (HV; one of the canonical neurodegenerative biomarkers of AD) and severity of memory impairment. Finally, we explored white matter hyperintensities (WMHs) as a biomarker of cerebrovascular disease (the second most common cause of age-associated cognitive impairment after AD)[4] in β-amyloid–negative patients who progressed to dementia (presumably owing to non-AD pathophysiology). The primary objective was to compare the time to progression to probable AD after positive vs negative results detected on PET β-amyloid brain scans at baseline and acquired after the patient received intravenous flutemetamol F 18 (Vizamyl; GE Healthcare). Secondary objectives included safety, interreader agreement, intrareader reproducibility, and progression risk based on quantitative scan analysis.

Key Points

Question How can biomarkers be used to supplement clinical assessments in the workup of patients with amnestic mild cognitive impairment?

Findings In this multicenter cohort study assessing progression from amnestic mild cognitive impairment to probable Alzheimer disease after flutemetamol F 18–labeled positron emission tomography, patients with β-amyloid–positive scans had approximately 2.5 times the risk of progressing to probable Alzheimer disease within 3 years compared with those with negative scan results. Adding the biomarkers of hippocampal volume and cognitive status to the model increased the risk of progression to 8.5:1 during the same observation period.

Meaning Biomarker combinations may have more utility than single diagnostic tests to assist physicians in assessing the risk of future cognitive decline.

Methods

Patients

Eligible patients were 55 years of age or older; met Petersen and Morris criteria[5] for aMCI; had no vascular, traumatic, or inflammatory causes of aMCI as determined by noncontrast magnetic resonance imaging (MRI); and could comply with study procedures. Additional requirements were a Logical Memory Scale II (LM-II[6]; delayed recall) score of 11 or less for those with 16 years or more of education, a score of 9 or less for those with 8 to 15 years of education, and a score of 6 or less for those with 7 years or less of education (we classified aMCI as early [EMCI] or late [LMCI] based on LM-II scores as per the Alzheimer's Disease Neuroimaging Initiative 2[7]); a Clinical Dementia Rating[8] of 0.5; a Modified Hachinski Ischemic Scale[9] score of 4 or less; a Mini-Mental State Examination[10] score of 24 to 30; and a Hamilton Depression Scale[11] score of 12 or less. This study was conducted in accordance with the Declaration of Helsinki,[12] the International Conference on Harmonisation good clinical practice guidelines, applicable laws, and regulations. The protocol was approved by the Western Institutional Review Board; Johns Hopkins University School of Medicine Institutional Review Board; Michigan State University Biomedical and Health Institutional Review Board; Hammersmith, Queen Charlotte's & Chelsea Research Ethics Committee; Mount Sinai Medical Center Institutional Review Board; University of Michigan Medical School Institutional Review Board; De Videnskabsetiske komiteer i region Hovedstaden; Commission d'éthique bio-médicale hospitalo-facultaire; Regionala Etikprövningsnämnden i Lund; STM/ETENE, TUKIJA; Comité d'éthique hospito-facultaire de l'Université de Liège, Centre hospitalier universitaire; Catholic Healthcare West/St. Joseph's Hospital & Medical Center Institutional Review Board; Medical Ethics Committee UZ KU Leuven/Clinical Research; and the University of Pennsylvania Office of Regulatory Affairs. Participants and/or their legal representatives gave prior written informed consent (NCT01028053).

Interventions

Patients received approximately 185 MBq of intravenous flutemetamol F 18 and approximately 90 minutes later underwent a 30-minute brain scan, collected in six 5-minute frames; the first 2 scans were summed for image reading.[3] Scans were randomized and approximately 10% of the scans were duplicated and randomly combined to measure intrareader reproducibility. At a central review center, 5 trained readers blinded to patient information interpreted the PET scans as positive or negative as per the manufacturer's instructions.[13] High-resolution T1-weighted MRI scans (typically 1-mm isotropic voxels), either previously available within 6 months of PET or newly acquired on 1.5- or 3-T scanners, were used to determine HV. The hippocampus was segmented using a local, patch-based label fusion approach.[14] Mean HVs were adjusted for intracranial volume by multiplying native space volume by a scaling factor estimated from the affine matrix needed to coregister the individual skull to a standard MNI152 reference (eg, the SIENAX approach; https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA). Scaled HVs less than 4.5 cm^3 were considered abnormal based on prior empirical experience with this particular measure. Fluid-attenuated inversion recovery and/or T2 images were reviewed for evidence of vascular disease. White matter hyperintensities were identified using an automated classifier whose results were verified individually by a

human rater (A.C.).[15] Intracranial volume was corrected using the same scaling factor. Data on WNH were log-transformed to account for nonnormality in statistical analyses.

Positron emission tomographic and MRI scans were coregistered to define volumes of interest for quantitative image analysis; standardized uptake volume ratios (SUVRs) were derived from the mean of 5 cortical regions bilaterally (frontal, anterior cingulate, parietal, lateral temporal, and posterior cingulate and precuneus), with the whole cerebellum as a reference.[3] Using a predefined threshold, we dichotomized SUVR values as positive (>1.56) or negative (≤1.56).[3]

For up to 3 years, on-site clinicians (D.A.W., C.S., B.S., J.O.R., R.D., R.P., M. Agronin, J.G., J.S., A.I., L.M., Z.W., S.H., C.H., M.S., M. Albert, A.F., P.L., E.T., K.F., P.H., A.B., R.B., E.S., P.F.S., and F.I.) performed clinical evaluations, including the following neuropsychological assessments every 6 months: Mini-Mental State Examination, activities of daily living,[16] LM-II, Clinical Dementia Rating, Alzheimer Disease Assessment Scale-Cognitive Subscale,[17] Digit Span test,[18] Digit Symbol Substitution Test,[18] Category Fluency Test,[19] and Trail Making Test.[20]

Outcomes

Patient data from each visit were reviewed independently by 2 of a 4-member clinical adjudication committee (CAC) experienced in diagnosing memory disorders. The CAC did not have quantitative imaging results or CSF data and were blinded to PET scan results. The data provided to the CAC for each patient included the medical and neurologic history and the results of examination and psychometric testing, and a clinical assessment form completed by the site investigator at each 6-month follow-up study visit querying about relevant worsening on psychometric or functional evaluation and any intervening neuropsychiatric symptoms or other clinically relevant events. The CAC was also notified of any "triggers" in psychometric testing results: a Clinical Dementia Rating of 1 or greater at any 6-month follow-up visit or a decrease in the Mini-Mental State Examination score from baseline by 4 points or a score below 20 at any time during the study. Diagnoses of probable AD were based on the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[21] The time to probable AD in days was measured from PET scan to the latest visit supporting a diagnosis of probable AD. Censoring time in days was measured from PET scan to the last completed follow-up visit.

Statistical Analysis

Statistical analysis was conducted from February 19, 2014, to January 26, 2018, using SAS (SAS Institute Inc). A Cox proportional hazards regression model[22] determined a hazard ratio (HR) for each variable as a measure of the strength of its independent contribution to progression probability. Variables explored in 4 separate Cox proportional hazards regression models were PET scan result (positive or negative) and patient age; PET scan result, age, and apolipoprotein E (*APOE* [OMIM 107741]) genotype; PET scan result, age, and mean HV (normal vs abnormal); and PET scan result, age, mean HV (normal vs abnormal), and aMCI stage (EMCI vs LMCI). Hazard ratios were determined for majority scan interpretations, made independently by at least 3 of 5 readers. Interreader agreement is reported as the Cohen and Fleiss κ with 95% CIs; intrareader reproducibility is reported as the Cohen κ.

Sample size and power calculations assumed, based on prior carbon 11-labeled Pittsburgh compound B studies, that for more than 3 years, 10% of patients with negative scan results and 30% of those with positive scan results would progress to probable AD with an HR of 3.0. The correlation of scan result with any other tested variable was assumed to be 0.2. Assuming a 2-sided α of .05 and a 3-year overall progression rate of 19%, 230 patients would provide 90% power. $P < .05$ (2-sided) was considered significant.

Results

β-Amyloid Status and Outcomes

Screening at 28 European and US centers began November 11, 2009 (imaging from December 1, 2009, to December 30, 2010); the last follow-up visit was January 16, 2014. Of 365 patients screened, 232 were eligible, administered flutemetamol F 18, and evaluable for safety and efficacy. The mean (SD) age was 71.1 (8.6) years; 118 participants were female (50.9%); and 225 were white (97.0%), 5 were black (2.2%), 1 was Asian (0.4%), and 1 was other race/ethnicity (0.4%).

By majority (at least 3 of 5 readers) image interpretation, 134 PET scans (57.8%) were negative and 98 (42.2%) were positive. By study end, 224 patients (127 negative and 97 positive) underwent at least 1 CAC assessment; 81 (36.2%) received a diagnosis of probable AD (none were designated with other forms of dementia). Baseline results of neuropsychological tests (**Table 1**) showed significantly lower immediate and delayed LM-II scores among patients with positive scan results and significantly lower immediate and delayed LM-II, Mini-Mental State Examination, and activities of daily living scores among those who progressed to probable AD. The mean HV was smaller in patients with positive scan results than in patients with negative scan results and was smaller in those who progressed to probable AD vs those who did not.

By study end, rates of progression to a diagnosis of probable AD were 53.6% (52 of 97) for patients with positive scan results and 22.8% (29 of 127) for patients with negative scan results; Kaplan-Meier plots for individual readers were similar to **Figure 1** based on majority image interpretation. Mean annual progression rates were 12.1% overall (27 of 224), 17.5% for patients with positive scan results (17 of 97), and 7.9% for patients with negative scan results (10 of 127).

Flutemetamol F 18–Labeled PET Reader Agreement

Pairwise interreader agreement ranged from 77% (κ = 0.56) to 98% (κ = 0.96), with 73% agreement across all readers (Fleiss κ = 0.76). Pairwise agreement was 90% to 98% among readers 1, 3, 4, and 5 but was 77% to 85% between reader 2 and the other 4 readers. Intrareader reproducibility was 86% to 100% (κ = 0.70-1.00), based on reinterpretation of 21 to 29 scans per reader.

Table 1. Baseline Neurologic Test Results

Test	No. of Patients				
	Overall	Positive Scan	Negative Scan	Progression to Probable AD[a]	Nonprogression to Probable AD[b]
Mini-Mental State Examination score	232	98	134	81	151
Mean (SD)	27.09 (2.15)	26.80 (2.11)	27.31 (2.17)	26.15 (2.10)	27.60 (2.01)
Median (range)	27.0 (18-30)	27.0 (22-30)	28.0 (18-30)	26.0 (18-29)	28.0 (18-30)
95% CI	26.8-27.4	26.4-27.2	26.9-27.7	25.7-26.6	27.3-27.9
P value	NA	.08		<.001	
Hamilton Depression Scale score	231	97	134	80	151
Mean (SD)	2.00 (2.23)	1.88 (1.83)	2.08 (2.49)	2.20 (2.24)	1.89 (2.23)
Median (range)	1.0 (0-11)	2.0 (0-7)	1.0 (0-11)	2.0 (0-11)	1.0 (0-8)
95% CI	1.7-2.3	1.5-2.2	1.7-2.5	1.7-2.7	1.5-2.2
P value	NA	.49		.31	
Activities of Daily Living score	232	98	134	81	151
Mean (SD)	73.78 (4.15)	74.30 (3.76)	73.40 (4.39)	72.27 (4.81)	74.58 (3.51)
Median (range)	75.0 (57-78)	75.5 (61-78)	75.0 (57-78)	73.0 (57-78)	76.0 (61-78)
95% CI	73.2-74.3	73.5-75.0	72.6-74.1	71.2-73.3	74.0-75.1
P value	NA	.10		<.001	
Logical Memory II score immediately after story	232	98	134	81	151
Mean (SD)	9.04 (3.55)	7.90 (3.78)	9.88 (3.14)	7.48 (3.59)	9.88 (3.25)
Median (range)	9.0 (0-20)	8.0 (0-17)	10.0 (1-20)	8.0 (0-17)	10.0 (1-20)
95% CI	8.6-9.5	7.1-8.7	9.3-10.4	6.7-8.3	9.4-10.4
P value	NA	<.001		<.001	
Logical Memory II score 30 min after story	231	97	134	81	150
Mean (SD)	5.81 (3.30)	4.27 (3.33)	6.93 (2.79)	4.46 (3.32)	6.54 (3.06)
Median (range)	6.0 (0-13)	4.0 (0-11)	7.0 (0-13)	5.0 (0-11)	7.0 (0-13)
95% CI	5.4-6.2	3.6-4.9	6.4-7.4	3.7-5.2	6.0-7.0
P value	NA	<.001		<.001	
Hippocampal volume, cm^3	229	98	131	79	149
Mean (SD)	3.36 (0.56)	3.13 (0.46)	3.54 (0.56)	2.99 (0.51)	3.56 (0.48)
Median (range)	3.35 (1.91-4.54)	3.13 (2.19-4.39)	3.61 (1.91-4.54)	2.95 (1.91-4.43)	3.58 (2.44-4.54)
95% CI	3.29-3.44	3.03-3.22	3.44-3.64	2.88-3.10	3.49-3.65
P value	NA	<.001		<.001	
Modified Hachinski Ischemic Scale score	231	97	134	80	151
Mean (SD)	0.57 (0.74)	0.65 (0.85)	0.51 (0.63)	0.60 (0.76)	0.55 (0.73)
Median (range)	0.0 (0-4)	0.0 (0-4)	0.0 (0-3)	0.0 (0-3)	0.0 (0-4)
95% CI	0.5-0.7	0.5-0.8	0.4-0.6	0.4-0.8	0.4-0.7
P value	NA	.15		.62	

Abbreviations: AD, Alzheimer disease; NA, not applicable.

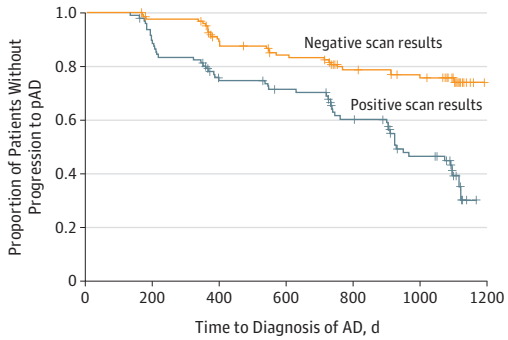
[a] Progression to probable AD denotes patients whom the clinical adjudication committee determined to have progressed to probable AD during the study.

[b] Nonprogression to probable AD denotes patients whom the clinical adjudication committee determined not to have progressed to probable AD or who withdrew prior to first clinical adjudication committee evaluation.

Association Based on β-Amyloid Status

The probability of progression at 36 months was 70% for patients with positive scan results and 26% for patients with negative scan results. In the Cox proportional hazards regression analysis, the majority interpretations of flutemetamol F 18-labeled PET scan results were significantly associated with progression to dementia (HR, 2.51; 95% CI, 1.57-3.99; $P < .001$); the HR of 2.51 indicates approximately 2.5 times risk that a patient with scan results visually confirmed to be positive would progress to probable AD earlier than those with negative scan results (**Table 2**). Age was also significantly associated with progression to dementia (HR, 1.05; 95% CI, 1.02-1.08; $P < .001$); the HR of 1.05 indicates that the risk of progression per unit time increases approximately 5% per year, doubling approximately every 14 years of age. Results for individual readers were similar, with HRs ranging from 2.0 to 3.4 (median HR, 2.6). Scan classification by SUVR gave results nearly identical to the majority image interpretation (scan: HR, 2.50; 95% CI, 1.57-3.98; $P < .001$; age: HR, 1.05; 95% CI, 1.02-1.08; $P = .002$).

Figure 1. Survival (Nonprogression) Probabilities Over Time for Patients With Positive or Negative Flutemetamol F 18–Labeled Positron Emission Tomographic Scans



No. at risk

Positive scan results	97	85	67	62	48	32
Negative scan results	127	121	105	97	82	76

Scan results assessed as positive or negative for β-amyloid by majority interpretation. Crosses are censored patients. Each vertical line marks 1 or more individuals who progressed to probable Alzheimer disease (pAD). The median time to progression to pAD was 928 days (95% CI, 760-1115) in the group with positive scan results but could not be estimated in the group with negative scan results, owing to a progression rate of less than 50%.

Table 2. Cox Proportional Hazards Regression Models for Prediction of Progression to Clinical Alzheimer Disease[a]

Model Parameters	*P* Value	Hazard Ratio (95% CI)
Model 1		
β-Amyloid status	<.001	2.51 (1.57-3.99)
Age	<.001	1.05 (1.02-1.08)
Model 2		
β-Amyloid status	<.001	2.35 (1.45-3.80)
Neurodegeneration status	.005	2.01 (1.24-3.26)
Age	.01	1.04 (1.01-1.07)
Model 3		
β-Amyloid status	.003	2.09 (1.28-3.42)
Neurodegeneration status	.04	1.70 (1.04-2.79)
Mild cognitive impairment status	.006	2.03 (1.23-3.36)
Age	.02	1.04 (1.01-1.07)

[a] The Cox proportional hazards regression model included β-amyloid status (negative or positive; reference, negative), neurodegeneration status (negative or positive; reference, negative), mild cognitive impairment (MCI) status (early MCI or late MCI; reference, EMCI), and age (years).

Of 193 patients (83.2%) genotyped for *APOE*, 63 (32.6%) were ε4 heterozygous and 13 (6.7%) were ε4 homozygous. Of 81 patients with positive scan results, 51 (63.0%) had at least 1 ε4 allele, compared with 25 of 112 (22.3%) of patients with negative scan results. However, the *APOE* genotype was not significant in the Cox proportional hazards regression model including PET scan result and age, but *APOE* and scan status were strongly associated.

Association Based on β-Amyloid and Neurodegeneration Status

Following the logic of the National Institute of Aging-Alzheimer Association criteria's incorporation of biomarkers for determining the likelihood that MCI is due to AD,[2] we classified patients as positive (A+) or negative (A−) for β-amyloid based on majority visual image interpretation and as positive (N+) or negative (N−) for neurodegeneration based on HV. **Table 3** shows that the A+N+ group (high likelihood of MCI due to AD, based on 2011 criteria[2]) had the poorest memory, including lowest memory retention consistent with a temporal limbic amnesia, and highest rate of progression to probable AD. The A−N− group (unlikely due to AD) had the best memory and lowest rate of progression. The other 2 groups (intermediate likelihood of MCI due to AD) displayed intermediate cognitive performance and rate of progression. Mean (SD) HV did not differ with age as a covariate in the N+ groups (A+N+ mean, 2.90 [0.39]; A−N+ mean, 3.02 [0.49]; $P = .22$) but did differ between the N− groups (A+N− mean, 3.46 [0.36]; A−N− mean, 3.80 [0.39]; $P = .03$), with the A+N− group having somewhat smaller hippocampi.

A Cox proportional hazards regression analysis that included neurodegeneration status (N+ vs N−) showed that β-amyloid status and neurodegeneration each contributed significantly to the association with progression (PET β-amyloid status: HR, 2.35; 95% CI, 1.45-3.80; $P < .001$; MR-based neurodegeneration status: HR, 2.01; 95% CI, 1.24-3.26; $P < .001$) (Table 2). Age remained significantly associated (HR, 1.04; 95% CI, 1.01-1.07; $P = .01$). An overall HR of 5.60 (95% CI, 3.14-9.98; $P < .001$) was found for A+N+ vs A−N− without age, indicating 5.6 times increased risk that those in the A+N+ group would progress earlier than those in the A−N− group (**Figure 2**).

Association Based on β-Amyloid, Neurodegeneration, and MCI Severity

A clinically accessible potential association not captured by the current criteria is the overall degree of cognitive impairment. We followed the Alzheimer's Disease Neuroimaging Initiative definition of EMCI and LMCI based on LM-II performance. A Cox proportional hazards regression analysis showed that β-amyloid status (HR, 2.09; 95% CI, 1.28-3.42; $P = .003$), neurodegeneration status (HR, 1.70; 95% CI, 1.04-2.79; $P = .04$), MCI status (HR, 2.03; 95% CI, 1.23-3.36; $P = .006$), and age (HR, 1.04; 95% CI, 1.01-1.07; $P = .02$) were all significant (Table 2). Omitting age, comparison of the A+N+ LMCI group with the A−N− EMCI group had an HR of 8.45 (95% CI, 4.40-16.24; $P < .001$), indicating an 8.5 times risk that the former group would progress earlier than the latter (Figure 2B).

White Matter Hyperintensities

Given the relatively high rate of progression in the A− group (particularly those in the A−N+ group), and prior work suggesting that such patients have increased cerebrovascular disease,[23] the association between WMHs and neurodegeneration in the A− groups was explored. As Table 3 shows, WMH volume was larger in A−N+ patients than in A−N− patients, after log transformation for normality and including age as a covariate (A−N+ median, 7.7 cm^3 [range, 0.9-68.4 cm^3]; A−N− median, 2.7 cm^3 [range, 0-55.6 cm^3]; $P = .03$). However, within the A+ groups, there was no significant difference (A+N+ median, 5.1 cm^3 [range, 0.3-55.4 cm^3]; A+N− median, 3.8 cm^3

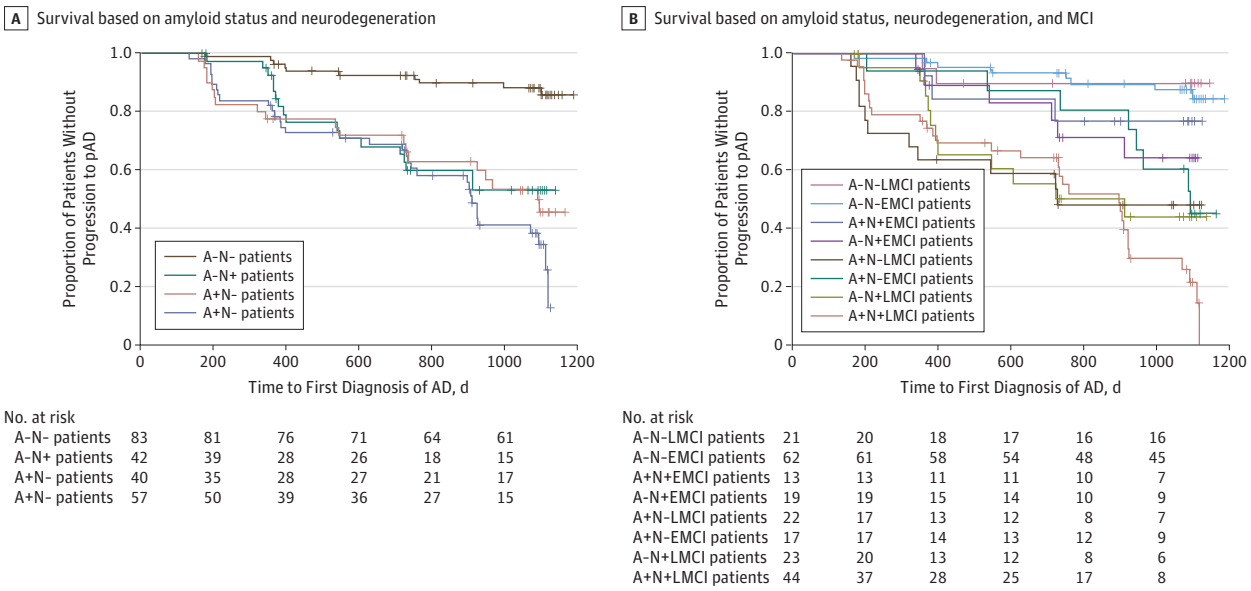
Table 3. Demographic, Cognitive, and Biomarker Data on 229 Patients With Mild Cognitive Impairment (MCI) Classified by β-Amyloid and Neurodegeneration Status

Characteristic	A+N+ Patients	A+N− Patients	A−N+ Patients	A−N− Patients
No. (%)	58 (25.3)	40 (17.5)	44 (19.2)	87 (38.0)
Age, mean (SD), y	73.8 (8.3)	72.4 (7.2)	74.8 (8.4)	66.5 (7.5)
APOE ε4, %	64.7	60.0	20.6	23.7
MCI Status, % EMCI	22.4	43.6	47.7	75.6
MMSE score, mean (SD)	26.5 (2.1)	27.3 (2.1)	27.6 (2.0)	27.3 (2.1)
LM-II immediate score, mean (SD)	7.2 (3.9)	8.8 (4.4)	8.3 (3.1)	10.8 (3.0)
LM-II delayed score, mean (SD)	3.5 (3.2)	6.2 (4.6)	5.6 (2.7)	7.4 (2.5)
LM-II retention, %	48.6	70.5	67.5	68.5
Progression to Alzheimer disease, %	57.9	47.5	40.4	12.0
Hippocampal volume,[a] mean (SD), cm^3	2.90 (0.39)	3.46 (0.36)	3.02 (0.49)	3.80 (0.39)
SUVR, mean (SD)	2.13 (0.36)	2.01 (035)	1.30 (0.19)	1.23 (0.12)
WMH volume, median (range), cm^3	5.1 (0.3-55.4)	3.8 (0.2-56.2)	7.7 (0.9-68.4)	2.7 (0-55.6)

Abbreviations: A+, positive for β-amyloid; A−, negative for β-amyloid; EMCI, early MCI; LM-II, Logical Memory–II test; MMSE, Mini-Mental State Examination; N+, positive for neurodegeneration; N−, negative for neurodegeneration; SUVR, standardized uptake volume ratio; WMH, white matter hyperintensities.

[a] Hippocampal volumes are presented prior to application of intracranial volume scaling factor.

Figure 2. Survival Curves Based on β-Amyloid Status, Neurodegeneration, and Cognition



A, Survival curves by majority flutemetamol F 18 visual image interpretation (either β-amyloid positive [A+] or β-amyloid negative [A−]) and hippocampal volume (either neurodegeneration positive [N+] or neurodegeneration negative [N−]) combinations. The median time to progression to probable Alzheimer disease (pAD) was 911 days (95% CI, 735-1093) in the A+N+ group and 1092 days (95% CI, 730 to NE) in the A+N− group. Other groups could not be estimated owing to a progression rate of less than 50% during the course of the study. B, Survival curves by majority flutemetamol F 18 visual image interpretation (either A+ or A−), hippocampal volume (either N+ or N−), and severity of mild cognitive impairment (MCI) (early MCI [EMCI] or late MCI [LMCI]) combinations. The vertical order of the group labels corresponds to the probability of progression, least to highest. The median time to progression to pAD was 730 days (95% CI, 205 to NE) in the A+N−LMCI group, 900 days (95% CI, 630-926) in the A+N+LMCI group, 913 days (95% CI, 393 to NE) in the A−N+LMCI group, and 1097 days (95% CI, 925 to NE) in the A+N−EMCI group. The median time to progression to pAD for other groups were not able to be estimated owing to a progression rate of less than 50%; upper limits are not able to be estimated (NE) in some cases owing to sparse data. Crosses are censored patients.

[range, 0.2-56.2 cm^3]; $P = .16$). Moreover, WMH load was significantly inversely correlated with mean HV in the A− group ($r = -0.34$; $P < .001$) but not in the A+ group ($r = -0.16$; $P = .11$). However, including age as a covariate reduced correlation in both groups (A− group, $r = -0.15$; $P = .09$; A+ group, $r = -0.04$; $P = .74$). Finally, with age as a covariate, WMH load in the A− group was higher in those who progressed vs those who did not (progressor median, 5.7 cm^3 [range, 1.1-68.3 cm^3]; nonprogressor median, 3.0 cm^3 [range, 0-54.4 cm^3]; $P = .007$), compared with no difference in the A+ group (progressor median, 3.8 cm^3 [range, 0.2-56.2 cm^3]; nonprogressor median, 4.6 cm^3 [range, 0.3-43.1 cm^3]; $P = .81$).

Discussion

Although use of AD biomarkers in research criteria and clinical trials is advancing,[2,24,25] practical application in the clini-

cal context to individual patients has not been fully realized. Nonetheless, incorporation of these measures is already occurring in the clinical setting, such as the use of β-amyloid PET in the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) study (https://www.ideas-study.org). The present study examined the association of several such biomarkers in aMCI with the progression to probable AD that might be relatively easy to implement in the clinical setting: visual image interpretation of β-amyloid PET scans, HV, and degree of memory impairment.

Visual interpretations of flutemetamol F 18-labeled PET scans correlated significantly with the risk of progression to clinical probable AD, with patients with positive scan results being approximately 2.5 times more likely to develop dementia per unit time than patients with negative scan results. Scan classification using SUVR gave similar results. Our overall annual progression rate of 12% is consistent with prior reports (7.5%-16.5% for clinic patients and 5.4%-11.5% for community samples).[26]

The unique aspects of this study, compared with studies of similar design,[27-34] are the relatively large sample size, longer follow-up, and use of a central CAC to adjudicate the diagnosis of probable AD. Because the Cox proportional hazards regression model and Kaplan-Meier analyses account for varying times of follow-up and varying times to progression through censoring, caution should be exercised in comparing the results of the present study with the results of other studies that did not use a time-to-event analysis because of the bias these approaches may generate, depending on how patients who were lost to follow-up were handled. The HR found for a positive scan result (2.51) in this study is similar to, but slightly lower than, the HR reported by Jack et al[31] (3.2), based on pooled Pittsburgh compound B and cerebrospinal fluid β-amyloid data from the Alzheimer's Disease Neuroimaging Initiative.

Regardless, β-amyloid status alone produced modest precision of likely progression, approximately 75% likelihood of developing dementia in A+ patients vs approximately 30% in A– patients (Figure 1). Addition of HV refined this association such that patients in the A+N+ group were approximately 5.6 times more likely to progress to dementia per unit time than those in the A–N– group, so that by 3 years, approximately 85% of those in the A+N+ group and approximately 15% of those in the A–N– group would be expected to develop dementia (Figure 2A). Although more limited precision could be applied to the A+N– and A–N+ groups (approximately 50% progression for each group after 3 years), the A+N+ and A–N– groups represent 140 of the cohort of 222 individuals in whom more precise information could be provided. Although automated methods for hippocampal measurement are relatively straightforward to implement and there are commercial tools available, methods for semiquantitative visual estimates of medial temporal atrophy may produce similar results and allow for even greater adoption in clinical practice.[35]

Several studies reported a relatively high association of cognitive measures with progression to dementia in MCI.[36,37] We classified patients as having EMCI or LMCI based on education-adjusted LM-II delayed-recall performance. Inclusion of this variable gave an overall HR of 8.45 between the A+N+LMCI vs A–N–EMCI groups. Closer examination reveals that the A–N– group, regardless of degree of memory impairment, had a low rate of progression after 3 years (12.0% [10 of 83]; Figure 2B); conversely, nearly all A+N+LMCI patients developed dementia. Although probability of progression in other groups is mixed, 57.5% of patients (127 of 221) fall into 1 of the 3 groups in which there is relatively high certainty of association between variables and progression to AD that could be conveyed to patients. Given that psychometric data were available to the CAC, it is possible that this could lead to an overestimation of its weight in assessing progression to AD. However, such information is almost always available to clinicians in practice.

The association of LMCI and hippocampal atrophy with earlier progression to probable AD suggests that both measures reflect disease severity and relative proximity to crossing the threshold to clinical dementia. However, their independence in the model suggests that they may provide complementary information in this regard. Not surprisingly, age was significantly associated with risk, with risk increasing approximately 4% for every year. Given that this effect was independent of β-amyloid, MCI, and hippocampal status, it may reflect diminishing brain or cognitive reserve with age, contributing to more rapid progression to AD dementia in older individuals with MCI-level impairment.

The study results support using β-amyloid PET to identify patients with aMCI who are at increased risk for relatively near-term progression to dementia. Furthermore, when used with MRI (routinely performed for these patients) and a standard psychometric measure of memory, more precision in the likelihood of progression may be achieved for a significant proportion of patients. Improved identification of at-risk patients may result in more appropriate use of health care resources, by focusing more intense monitoring on and earlier treatment of at-risk patients, and may assist families in future planning. Furthermore, β-amyloid PET may help us select patients with cerebral β-amyloid for clinical trials of therapeutic drugs, resulting in cohorts more likely to develop clinical dementia within a relatively short time.

Limitations

A limitation of this study is a relatively higher (23%) progression rate among patients with negative scan results compared with previously published rates of approximately 10% to 20%.[32,33] This finding could indicate false-positive diagnoses of probable AD by the CAC (eg, patients who developed dementia from another possible cause) and/or false-negative PET scan interpretations. There are inherent weaknesses in the clinical diagnostic process conducted by the CAC, which applied the NINCDS-ADRDA criteria to data obtained from reviews of medical records rather than direct examination of patients. The CAC may enhance uniformity of applied diagnostic criteria but also may reduce reliability relative to an experienced clinician directly evaluating a patient. Regardless, compared with autopsy, the NINCDS-ADRDA criteria for probable AD have a specificity of 56% to 100% (median specificity, 83%),[38-43] giving a 17% median false-positive rate. Therefore, a proportion of the patients with negative scan results progressing to prob-

able AD are likely to have non-AD dementia. Probable AD is a clinical diagnosis, and the field is moving more toward biological definitions of AD, requiring the presence of β-amyloid and tau pathology, regardless of the presence of clinical symptoms.[44,45] In fact, the label of *probable AD* applied here is really synonymous with a multidomain amnestic dementia, which is likely enriched in those with AD pathologic findings, but in which other pathologic characteristics may also be the primary driver.

Jack et al[46] proposed the term *SNAP* (suspected non-Alzheimer pathophysiology) for cognitively normal individuals who are β-amyloid negative by use of PET but have evidence of neurodegeneration by other biomarkers. More recently, SNAP has been applied to β-amyloid-negative patients with MCI who have evidence of AD-like neurodegenerative changes (eg, on fluorodeoxyglucose-labeled PET scans or structural imaging). In some, but not all, studies,[23] this group may have a relatively high risk for progression to dementia (often classified as probable AD), similar to β-amyloid-positive patients with MCI.[47,48] Of the β-amyloid-negative patients in this study, those with evidence of concomitant neurodegeneration had a much higher likelihood of progression than those without concomitant neurodegeneration (Figure 2A).

Although patients with SNAP (A–N+) are likely an etiologically heterogeneous group, the current data offer clues about underlying pathologic characteristics. One possibility is that patients with SNAP have false-negative β-amyloid scans, potentially because they fall just below the threshold for β-amyloid positivity. Although this remains a possibility, our A–N+ group's mean SUVR did not significantly differ from that of the A–N– group, despite being based on visual image interpretation, and was well below a previously determined SUVR threshold (1.56). Furthermore, the mean SUVR did not differ significantly between those who progressed (1.29) and those who did not (1.30) in the A–N+ group. Some evidence suggests that SNAP may be associated with increased cerebrovascular disease.[23,49] In the present study, patients with SNAP had the highest WMH burden, significantly higher than patients without β-amyloid and hippocampal atrophy. Moreover, WMH burden in β-amyloid-negative individuals was inversely correlated with HV, suggesting a potential mechanism for this neurodegeneration and consistent with other work supporting a link between cerebrovascular disease and hippocampal integrity.[50,51] This association was not observed in the β-amyloid-positive group, possibly reflecting AD-related pathologic characteristics obscuring any effect from cerebrovascular disease. One caveat is that while WMH is often considered a surrogate for cerebrovascular disease, recent work has suggested that it also may be associated with neurodegeneration.[52]

Conclusions

Flutemetamol F 18-labeled PET scans correlated well with the relative rates of progression from aMCI to dementia, clinically classified as probable AD. Moreover, adding a neurodegeneration biomarker and cognitive severity may further refine the association in this population. A potential weakness of this study is that it limited the cohort to include those without significant cerebrovascular disease (Modified Hachinski Ischemic Scale score of ≤4) or significant depression; it may be the case that biomarkers would have a different value in cohorts with other comorbities that may affect cognition, and future work should apply measures such as those used here to more diverse clinical populations. Nontheless, relatively simple dichotomous measures such as those used here are clinically practical and, in many cases, could enhance the precision with which one can determine the likelihood of functional decline, which is of considerable importance to patients with mild cognitive symptoms.

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