**Refining Mild-to-Moderate Alzheimer Disease Screening: A Tool for Clinicians**

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**A b s t r a c t**

Objectives: Recent evidence suggests that a substantial minority of people clinically diagnosed with probable Alzheimer disease (AD) in fact do not fulfill the neuropathological criteria for the disease. A clinical hallmark of these phenocopies of AD is that these individuals tend to remain cognitively stable for extended periods of time, in contrast to their peers with confirmed AD who show a progressive decline. We aimed to examine the prevalence of patients clinically diagnosed with mild-to-moderate AD who do not experience the expected clinically significant cognitive decline and identify markers easily available in routine medical practice predictive of a stable cognitive prognosis in this population.

Design: Data were obtained from two independent, longitudinal, observational multicenter studies in patients with mild-to-moderate AD.

Setting: The two studies were the European “Impact of Cholinergic Treatment Use” (ICTUS) and the French “REseau sur la maladie d’Alzheimer FRançais” (REAL.FR).

Participants: We used prospective data of 756 patients enrolled in ICTUS and 340 enrolled in REAL.FR. Measurements: A prediction rule of cognitive decline was derived on ICTUS using classification and regression tree analysis and then cross-validated on REAL.FR. A range of demographic, clinical and cognitive variables were tested as predictor variables.

Results: Overall, 27.9% of patients in ICTUS and 20.9% in REAL.FR did not decline over 2 years. We identified optimized cut-points on the verbal memory items of the Alzheimer Disease Assessment Scale-Cognitive Subscale capable of classifying patients at baseline into those who went on to decline and those who remained stable or improved over the duration of the trial.

Conclusion: The application of this simple rule would allow the identification of dementia cases where a more detailed differential diagnostic examination (eg, with biomarkers) is warranted. These findings are promising toward the refinement of AD screening in the clinic. For a further optimization of our classification rule, we encourage others to use our methodological approach on other episodic memory assessment tools designed to detect even small cognitive changes in patients with AD.

**Introduction**

Recent evidence from in vivo neuroimaging research and post-mortem examinations revealed that a higher than expected proportion of subjects clinically diagnosed with mild-to-moderate probable Alzheimer disease (AD) does not meet established neuropathological guidelines for AD1,2 The misdiagnosis of noneamyloid-dependent dementia, estimated to be approximately 14% 16%, has a detrimental impact both for the clinical management of affected patients and for clinical trials in AD testing the amyloid hypothesis.3,4 Therefore, it is imperative to improve the identification of these clinical phenocopies of AD. Insofar as amyloid biomarker measurements are not available in routine medical practice, a better understanding of the cognitive and behavioral signatures characteristic of this subset of patients with dementia would empower clinicians to refine the screening of AD.

Subjects with a probable AD dementia diagnosis who do not present with neuropathological criteria for the disease have been observed to have slightly but significantly better cognitive performance at baseline compared to subjects who do have AD pathology.1,2 They also tend to show no clinically significant decline over 3 years on a range of neuropsychological tests, in contrast with their peers with neuropathologically confirmed AD.2,5 Therefore, identifying predictors of a stable cognitive prognosis in patients suspected to have mild-to-moderate AD would enable clinicians to detect cases where more detailed differential diagnostic examinations are warranted, possibly involving biomarkers.

Extensive research has been carried out to predict cognitive progression in mild cognitive impairment (MCI) and AD using neuro-psychological tests.6e10 A common approach thus far has been to combine information from neuropsychological tests in sophisticated ways, for example, using multivariate methods to derive latent factors or composite measures predictive of conversion.11,12 Although these techniques have been proven useful in predicting rates of decline, they are arguably too complex to be implemented in clinical routine.

Moreover, to date, most of the literature on cognitive prediction models of decline has focused on conversion from MCI to AD13,14 and on slow versus rapid decline in patients with AD, with an emphasis on the latter group.15 Comparatively little is known regarding the pre-dictive factors of a stable prognosis in patients with dementia.

The present study sought to (1) determine the prevalence of a stable cognitive prognosis over 2 years in patients clinically diagnosed with mild-to-moderate AD, (2) identify cognitive and behavioral markers predictive of a stable prognosis, and (3) operationalize these into a quick and straightforward decision rule to be easily implemented in clinical practice. Differentiating our work from previous research, we focused on the prediction of “non-decline” rather than rate of decline, as a targeted approach to identify dementia cases requiring a more detailed etiological enquiry. Data were obtained from two separate, observational, longitudinal, multicenter cohort studies: Impact of Cholinergic Treatment USe (ICTUS) and REseau sur la mal-adie d’Alzheimer FRançais (REAL.FR). We hypothesized that a rela-tively preserved episodic memory as measured by the verbal memory items of the Mini-Mental State Examination (MMSE) or the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) would be predictive of a stable prognosis.

**Methods**

Study Design and Subjects

ICTUS and REAL.FR have been described elsewhere and were carried out with ethical approval.16,17 In short, ICTUS is a 2-year, prospective, multicenter study, which aimed to investigate the history of AD, its treatment outcomes and its socioeconomic impact on patients and their caregivers. The study enrolled 1376 patients with a clinical diagnosis of mild-to-moderate probable AD recruited at 29 European specialist outpatient memory clinics. REAL.FR is a 4-year, prospective, multicenter study targeting ambulatory community-dwelling patients with probable AD. It was carried out on 686 volunteers recruited in 16 specialized memory clinics across France. Patients in both ICTUS and REAL.FR were diagnosed with probable AD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition18 and the National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria19 and had mild-to-moderate AD (ie, MMSE 10-26/30).17 Due to the observational nature of the studies, patients were allowed to stay on their regular medications, including AD medications.

For the present analyses, patients were categorized as decliners or non-decliners based on their change in MMSE score at the 2-year follow-up visit compared to baseline (non-decliners being defined as presenting a 2-year MMSE change from baseline score 0). We chose the MMSE to define these groups primarily because prediction models of decline have commonly used this variable as outcome measure, providing a reference of what can be considered as a clinically meaningful cognitive decline.20 The MMSE is also frequently used as a screening tool to evaluate patients’ eligibility for entering clinical trials and as an outcome measure to show treatment effects.

We excluded from our analyses subjects who dropped out before that time point or had insufficient data to calculate their MMSE change from baseline score. Overall, we included 756 patients (55%) from ICTUS and 340 (50%) from REAL.FR. Relative to the patients that were included, dropouts and patients with insufficient data were similar in age (76.9 7.5 vs 75.8 7.8; P > .05) but more impaired cognitively and functionally in ICTUS (total ADAS-Cog 22.46 10.3 vs 19.86 8.8 and total IADL 4.6 2.3 vs 5.0 2.2, all P <.01). In REAL.FR, excluded patients were significantly older (78.6 6.6 vs 77.1 7.0; P < .01) and more impaired cognitively and functionally (total ADAS-Cog 19.0 8.9 vs 16.7 7.3 and total IADL 7.57 3.8 vs 9.25 3.3; all P < .01).

Clinical and Cognitive Parameters

In both ICTUS and REAL.FR, the standardized clinical examination included a baseline evaluation of the patients’ medical history (including cardiovascular risk factors and depression), physical disability (as per the Instrumental ADL scale [IADL]), neuropsychiatric symptoms (as per the neuropsychiatric inventory [NPI]), and a comprehensive neuropsychological assessment including the MMSE, the ADAS-Cog, and the Clinical Dementia Rating (CDR) scale. Follow-up of patients included a 6-monthly cognitive assessment for up to 2 years including the MMSE, the ADAS-Cog, and the CDR scale administered by highly trained specialists in the context of expert memory clinics.

The MMSE includes 30 items (range, 0-30) measuring different cognitive aspects (orientation, registration, attention, recall, and language).21 Higher scores indicate better cognitive performance. The ADAS-Cog22 (range, 0-70) represents the most widely adopted cognitive outcome measure in AD trials. It includes 11 items assessing different cognitive domains (memory, language, and praxis). Higher scores indicate worse cognitive performance. The CDR scale23 assesses the severity of the dementia syndrome along five levels of impairment (rated as 0, 0.5, 1, 2 or 3 ranging between no dementia and dementia) in each of six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

The baseline ADAS-Cog and CDR scores were used as predictor variables.

Statistical Analysis

Descriptive sociodemographic and clinical characteristics of patients classified into decliners and non-decliners were calculated using mean values and standard deviations or percentages according to the nature of the variables. Baseline differences between decliners and non-decliners were tested using independent-sample t-tests or c2 as appropriate. To identify predictors capable of discriminating between decliners and non-decliners, we used CART. CART is a tree-building technique based on binary recursive partitioning that classifies sub-jects into different categories according to the predictor criterion (in our case, decline vs non-decline). The nodes or variables used to classify subjects are determined following an exhaustive search of all possibilities, including all variables and all possible cut-points for a split. CART analysis has several advantages over other regression methods such as logistic regression24: (1) it is nonparametric, (2) the model creates surrogate values where predictor variables are missing, enabling the inclusion of patients with missing values, and (3) it can deal with complex interactions between the predictor variables. We derived the CART classification rule on the ICTUS database, as it was the larger of the two studies and thus better powered. The splitting was carried out using the Gini index to minimize node impurity, with the minimum number of cases for parent nodes set at 100 and that of child nodes at 50. A 10-fold cross-validation was used to accurately assess its goodness of fit. Sensitivity and specificity of the classification rule were calculated.

Predictor variables entered into the CART analysis included age, gender, education, current AD treatment, and all baseline IADL, CDR, MMSE, and ADAS-Cog item-level scores. Education was operationalized as years of formal education including primary school (range, 0-24). Current AD treatment was coded as a binary variable according to whether patients were on symptomatic treatment with acetyl-cholinesterase inhibitors (AChE-I) at the time of enrollment, or not.

The CART-derived classification rule was subsequently tested in REAL.FR using binary logistic regression using the predicted cognitive course as independent variable (predicted decliners vs non-decliners according to the CART threshold) and the observed cognitive course as outcome (actual decliners vs non-decliners). Analyses included both unadjusted and adjusted models taking into account age, gender, education, current AD treatment, and baseline MMSE. Secondary regression analyses further explored the CART rule in REAL.FR regarding its ability to predict decline versus non-decline (1) in models stratified according to age (tertiles), gender, and CDR, as well as (2) over a more extended period of 3 and 4 years. For the latter analyses, the MMSE change from baseline thresholds were made more lenient to account for the expected decline due to normal aging-related processes (ie, 1 at 3 years and 3 at 4 years). The definition of these MMSE cut-off points were guided by previous reports that even after 4 years of follow-up, some patients diagnosed with probable AD present no clinically meaningful decline defined as a change in initial MMSE score 3.20

Finally, as a precaution, we verified whether the 2-year cognitive course of decliners and non-decliners (as defined by the change in MMSE) could be corroborated by a different cognitive measure. For this purpose, we used the ADAS-Cog (considered to be a more sensitive measure for subtle cognitive changes than the MMSE) in a repeated-measures analysis of variance (ANOVA) with group (decliners vs non-decliners) as a between-subject factor and ADAS-Cog at baseline versus at 2 years as within-subject factor, adjusted for age, sex, education, and AD treatment. Significant group by ADAS-Cog interactions (indicative of a difference between groups in terms of their 2-year cognitive progression) were further explored with paired-sample t-tests.

Statistical analyses were performed on SPSS 22. All tests for significance were two-tailed at a probability level of 0.05.

**Results**

Characterization of Decliners and Non-Decliners in ICTUS and REAL.FR

Overall, 27.9% of patients in ICTUS and 20.9% of patients in REAL.FR showed no decline at the 2-year follow-up visit. Table 1 shows the demographic and clinical characteristics of decliners and non- decliners in both studies. Patients grouped according to their cognitive course were similar in terms of age, sex, education, AD treatment, and neuropsychiatric symptoms, with the only exception that non-decliners in ICTUS had a higher level of education compared to the decliners (P ¼.01). The non-decliners performed significantly better at the ADAS-Cog (P ¼ .01 and P ¼ .04 in ICTUS and REAL.FR, respectively), but not at the MMSE (P > .05). In ICTUS, non-decliners were also less severely functionally impaired at baseline. Regarding the medical history, non-decliners in ICTUS had significantly higher rates of hypercholesterolemia (P < .01), hypertension (P ¼ .04), and stroke (P < .01) compared to decliners, while no group differences were observed for diabetes and depression. No group differences in terms of medical history were detected in REAL.FR, a result that calls for caution due to low sample sizes, particularly in the group of non-decliners.

As shown in Table 2, non-decliners were almost equally distributed across all CDR categories.

CART Analysis in ICTUS

Figure 1 shows the tree yielded by the CART analysis that best discriminates between decliners and non-decliners in ICTUS. The tree is composed of two nodes: the ADAS-Cog Word Recall item with a cut-point of 6/10, and the ADAS-Cog Word Recognition item with a cut-point of 4/12. A description of these items is provided in Figure 2. A classification rule derived from these cut-points revealed a sensitivity of 41.2% and a specificity of 78.7% to identify non-decliners in ICTUS.

Cross-Validation of the CART-Derived Classification Rule in REAL.FR

times more likely to decline (adjusted OR, 95%; CI, 4.57 [1.30-16.06], P ¼ .02). The model run in patients with a CDR 2 did not yield interpretable results due to the low number of non-decliners.

Finally, we examined the ability of the classification rule to predict decline over 3 and 4 years. As shown in Table 4, patients with no clinically meaningful decline over 3- versus 4-year follow-up were three and a half versus two and a half times more likely to be classified as actual non-decliners according to the CART rule (OR, 95%; CI, 3.52 [1.52-8.20], P < .01 versus 2.50 [1.10-5.67], P ¼ .03).

We next examined the ability of the previously mentioned CART-derived thresholds to differentiate decliners and non-decliners using longitudinal data from REAL.FR. Table 3 shows the odds ratios (ORs) and 95% confidence intervals (CIs) for the ability of the ADAS-Cog verbal memory cut-points to predict whether patients actually declined over the 2-year follow-up. We set predicted non-decliners as the reference group, given that the CART rule was found to have low sensitivity but high specificity for the identification of non-decliners. Patients classified as predicted decliners according to the rule were more likely to actually decline (OR, 95%; CI, 2.74 [1.43-5.23], P < .01 adjusted for age, sex, education, AD treatment, and baseline MMSE). Further exploratory analyses examined the rule on patients stratified by age tertiles, sex, and CDR category. The ORs were consistently high (ranging between 2.18 and 4.60) and reached levels of significance or showed suggestive trends. It is noteworthy that patients aged 76 to 80 classified as predicted decliners were up to four and a half times more likely to decline (adjusted OR, 95%; CI, 4.57 [1.30-16.06], P ¼ .02). The model run in patients with a CDR 2 did not yield interpretable results due to the low number of non-decliners.

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Verification of Patients’ Cognitive Decline (as per the MMSE) Using the ADAS-Cog

We verified whether patients classified into decliners and non-decliners according to the MMSE were also significantly different on the ADAS-Cog. There was a significant interaction between group and longitudinal ADAS-Cog in the repeated measures ANOVA (P < .01). Performance on the ADAS-Cog significantly worsened for decliners (paired-sample t-test P < .01) but not for non-decliners (P ¼ .47).

**Discussion**

The prevalence rate of a stable cognitive prognosis over 2 years in patients clinically diagnosed with mild-to-moderate AD ranged be-tween 20.9% and 27.9% in two independent multicenter observational studies. According to previous research, patients diagnosed with probable AD who are found to not fulfill the neuropathological criteria for the disease tend to not show the expected clinically significant decline. Building on this evidence, the current study sought to refine the screening of mild-to-moderate AD through the identification of clinical markers predictive of a stable prognosis. Using a relatively novel data mining approach and cross-validating results on two in-dependent cohorts, we identified a quick and simple rule capable of classifying patients at baseline into decliners versus non-decliners over the following 2 years. Specifically, the rule classified patients according to their baseline scores on the two verbal memory items of the ADAS-Cog. These results are in line with previous recommendations to use episodic verbal memory tests such as the Free and Cued Selective Reminding Test for the early identification of AD.25,26 In the present study, the rule proved suitable across the severity spectrum.

According to the classification rule, patients were more likely to decline over the next 2 years if they (1) retrieved a mean of 3/10 words on verbal recall or (2) retrieved a mean of 4/10 words on verbal recall but recognized a maximum of 7/12 words on verbal recognition. The observed low sensitivity of this rule to detect non-decliners was expected, because they were less represented in the population than decliners.6 On the other hand, the specificity of nearly 80% implies that the rule is suitable to identify patients who go on to decline (ie, patients who are particularly likely to have AD pathology). In the clinical context, specificity is generally considered more important than sensitivity, as the use of a too-sensitive cut-point can lead to the examination of an unacceptable number of false-positive cases.27

In addition to the low representation of non-decliners in our sample, a further explanation for the relatively low sensitivity is that the MMSE may not have properly captured slight worsening over time. We addressed this point by using the ADAS-Cog (which is considered to be a more sensitive tool to detect subtle cognitive decline) to corroborate that decliners and non-decliners as defined by the MMSE had a different cognitive course. Performance on the ADAS-Cog significantly worsened for decliners but not for non-decliners, supporting the utility of the MMSE for the purpose of our study. Nevertheless, the use of other episodic memory tests more sensitive to subtle changes in cognition than the MMSE would likely increase the sensitivity of a CART-derived classification rule. Of course, although in our context, specificity is arguably more important than sensitivity, ideally a good classification rule should have both high specificity and sensitivity.

Non-decliners in the better-powered European longitudinal study had significantly higher rates of cardiovascular events and risk factors in their medical histories compared to decliners (stroke, hypertension, and hypercholesterolemia). While speculative, the potential implications of this finding merit some consideration. Autopsy and neuro-imaging studies have revealed that the majority of dementia cases involve brain lesions of both cerebrovascular etiology (such as macro-and microinfarcts) and neurodegenerative etiology (such as neuritic plaques and neurofibrillary tangles).28 The distinct cardiovascular profile and stable cognitive trajectory we observe in the non-declining patient group suggests that the underlying cause for their dementia, at least for a proportion of these patients, might have been primarily vascular. Their cognitive trajectory would thus be expected to be characterized by stepwise decrements temporally linked with cardiovascular events, interspersed with periods of cognitive stability and even cognitive amelioration. Although the current study did not allow verifying this with biomarkers, our interpretation is further supported by the superior performance of non-decliners on the verbal memory items of the ADAS-Cog, suggestive of a selective sparing of medial temporal lobe structures. A wealth of studies have shown that, compared to patients with AD, patients with vascular dementia perform better on a range of verbal learning and memory tests.29 Moreover, while histopathological studies point to the trans-entorhinal cortex, entorhinal cortex and hippocampus among the first anatomical targets of AD pathology, these brain regions are frequently intact in those with vascular dementia.29

Our findings have important implications both for the clinic and for research. The ADAS-Cog is an inexpensive tool commonly used in clinical research and in specialized clinical settings. Even though this instrument is typically considered as a whole, our algorithm suggests that the verbal memory items by themselves might be of specific in-terest for AD screening. Whereas administration of the whole ADAS-Cog typically takes 30 to 45 minutes, the selective administration of the two verbal memory items would significantly shorten this time making it more feasible in clinical practice. On one hand, the rule could be used to ascertain the diagnosis of probable AD through the identification of patients who are at increased risk of declining over the next 2 years (supported by the high specificity of the rule). On the other hand, it would allow the identification of those patients whose AD-like symptoms might potentially be caused by a noneamyloid-dependent pathology that should be examined in more detail, such as subclinical cardiovascular disease. In research, our classification rule could enable the enrichment of AD patient cohorts through the exclusion of volunteers who are unlikely to decline during the duration of the trial, thereby (1) maximizing the power to detect treatment-related changes in the rates of decline and (2) enhancing the effect size of specific AD medications.

An important strength of the current study was the use of two separate prospective multi-center cohorts for the development and independent cross-validation of the prediction model. The model was derived using CART, a method reported to be suitable for the development of clinical decision rules using variables that are rapidly and easily achievable in daily routine practice. A further advantage of this method was its ability to identify optimized cut-points for predictor variables. In neurology, CART has been successfully used, for example, to identify prognostic variables of outcome in head injury,30 stroke,31 or coma,32 or to differentiate specific neurological disorders from other related conditions.33 More recently, it has been used to predict conversion from MCI to AD.34,35

The reduced power to test the CART-derived classification rule in patients stratified by age, gender, and CDR represents a limitation. Nevertheless, it is striking that the OR for the relationships between predicted and observed decline remained consistently high even after stratifying patients into subgroups. Additionally, the classification rule proved equally suitable for the prediction of decline over 3 and 4 years, with the caveat that dropouts throughout the extended duration of the study might have increasingly biased the representativeness of the AD sample. Collectively, this evidence suggests that despite the aforementioned limitations, the classification rule was relatively robust. A feature of CART that could arguably be considered as a limitation is that it treats outcomes as binary (decliners vs non-decliners) and does not model time to the outcome.35 Therefore, this method does not allow a more refined prediction of decline onset, which was, however, beyond the scope of our study. It also does not allow adjusting for the exclusion of subjects for whom change in MMSE could not be calculated due to premature dropout. Finally, despite the wide use of the MMSE in the literature on prediction models of cognitive decline in AD, the aforementioned limitation of this scale to detect subtle changes in cognition is a weakness of our study. It would be desirable for future studies to apply the methodological approach we present here on other cognitive assessment tools designed to measure small changes in episodic memory, allowing optimized specificity and sensitivity.

**Conclusions**

Using a relatively novel data-mining technique, we identified specific cut-points on the verbal memory items of the ADAS-Cog that were capable of predicting whether a patient with a clinical diagnosis of mild-to-moderate probable AD was likely to experience cognitive decline over the next two years or not. This finding represents a window of opportunity to identify via a clinically friendly tool and in the absence of biomarkers, patients whose dementia profile warrants a more detailed differential diagnostic examination. We encourage others to replicate our findings in combination with biomarker in-formation and use our methodological approach on other episodic memory assessment tools potentially better suited to detect cognitive decline in individuals with AD.

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Table 1. Baseline SocioDemographic and Clinical Characteristics of Mild-to-Moderate AD Patients From ICTUS (n ¼ 756) and REAL.FR (n ¼ 340) Divided Into Two Groups According to Their MMSE Change From Baseline Score Over 2 Years: Decliners (>0) and Non-Decliners ( 0)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ICTUS |  |  |  |  | REAL.FR |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  | Decliners | Non-Decliners | P | Decliners | Non-Decliners | P |
|  | (n ¼ 545, 72.1%) | (n ¼ 211, 27.9%) |  |  | (n ¼ 269, 79.1%) | (n ¼ 71, 20.9%) |  |  |
| Age | 75.5 | (7.9) | 76.6 | (7.6) | 0.07 | 76.8 | (7.1) | 78.2 | (6.5) | .15 |  |
| Sex (female) | 65% |  | 59% |  | 0.13 | 73% |  | 76% |  | .63 |  |
| Education[\*](#page7) | 7.9 | (4.4) | 8.9 | (4.9) | 0.01 | 3.0 | (0.7) | 2.8 | (0.7) | .30 |  |
| AchE-I treatmenty | 92% |  | 87% |  | 0.75 | 91% |  | 94% |  | .37 |  |
| MMSE total | 20.8 | (3.8) | 20.7 | (3.9) | 0.74 | 20.5 | (4.0) | 20.3 | (4.2) | .63 |  |
| ADAS-Cog total | 20.6 | (8.8) | 17.9 | (8.5) | <0.01 | 17.1 | (7.3) | 15.1 | (6.7) | .04 |  |
| IADL | 4.8 | (2.1) | 5.5 | (2.3) | <0.01 | 9.3 | (3.3) | 9.0 | (3.1) | .57 |  |
| NPI | 11.6 | (12.3) | 11.8 | (13.4) | 0.84 | 15.2 | (15.2) | 12.3 | (9.0) | .12 |  |
| Medical historyz |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Diabetes | 11.9% | 12.3% | 0.48 | 9.4% | 6.7% | .35 |  |
| Hypercholesterolemia | 26.6% | 36% |  | <0.01 | 27.7% | 26.2% | .48 |  |
| Hypertension | 37.1% | 44.5% | 0.04 | 42.7% | 50.8% | .15 |  |
| Strokex | 6.1% | 12.3% | <0.01 | n/ax |  | n/a |  | n/a |
| Depression | 25.7% | 26.1% | 0.49 | 41.2% | 40% |  | .49 |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |

AChE-I, Acetylcholinesterase inhibitors; AD, Alzheimer disease; ADAS-Cog, Alzheimer Disease Assessment Scale-Cognitive Subscale; IADL, Instrumental ADL scale; ICTUS, Impact of Cholinergic Treatment USe; MMSE, Mini-Mental State; NPI, neuropsychiatric inventory; REAL.FR, REseau sur la maladie d’Alzheimer FRançais.

Values are shown as mean values and standard deviations or percentages according to the nature of the variable. P values correspond to the baseline differences between declining versus non-declining patients (independent-sample t-tests or c2).

\*Variable operationalized as number of years of formal education including primary school (range, 0-24) in ICTUS and level of education according to French system (range, 1-4: 1,elementary or illiterate; 2, primary school certificate; 3, early secondary education; 4, Technical (high school certificate or higher) in REAL.FR.

yBinary variable indicating whether patients were on AchE-I treatment at baseline.

zCompleteness of reported medical history data was 100% in ICTUS and ranged between 86% to 89% in REAL.

xData completeness for history of stroke in REAL was 45% and hence is not reported.

Table 2. Percent of Non-Decliners Stratified by CDR

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Percent of | ICTUS | REAL.FR |  |  |  |
| Non-Decliners |  |  |  |  |  |  |  |  |
| SampleY2 | SampleY2 | SampleY3 | SampleY4 |
| as a Fraction of: |
| (Sampleinitial) | (Sampleinitial) (Sampleinitial) (Sampleinitial) |
|  |  |
| All CDR | 27.9 (15.3) | 20.9 | (10.3) | 18.7 (6.9) | 29.9 (8.0) |  |
| CDR ¼ 0.5 | 32.6 (19.0) | 21.1 | (12.0) | 19.5 (9.4) | 26.4 (9.9) |  |
| CDR¼1 | 23.7 (13.0) | 24.1 | (12.2) | 19.6 (6.6) | 37.3 (8.7) |  |
| CDR | 2 | 25.9 (11.4) | 11.7 | (4.3) | 10.5 (2.5) | 18.5 (3.1) |  |
|  |  |  |  |  |  |  |  |  |  |

CDR, Clinical Dementia Rating scale; ICTUS, Impact of Cholinergic Treatment USe; MMSE, Mini-Mental State Examination; REAL.FR, REseau sur la maladie d’Alzheimer FRançais.

Percentages are expressed as a fraction of: (Sampleinitial) ¼ Number of observations available at baseline.

SampleY2, SampleY3 and SampleY4 ¼ Number of observations available at year 2, 3 and 4, respectively. The MMSE change from baseline threshold used to define non-decliners was: 0 at 2 years, 1 at 3 years and 3 at 4 years.

Table 3. Logistic Regression Analyses Testing the Ability of the CART-Derived Classification Rule (Using Non-Decliners as Reference) to Predict Decline Versus Non-Decline Over the 2-Year Follow-up in REAL.FR. Separate Models were Run in All Patients (Bold) and in Subgroups of Patients Stratified by Age Tertiles, Gender and CDR

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Unadjusted |  |  |  | Adjusted[\*](#page7) |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | ny | OR (95% CI) | P | ny | OR (95% CI) | P |
| All Patients | 266/70 | 1.96 | (1.15-3.34) | 0.01 | 241/64 | 2.74 | (1.43-5.23) | < .01 |  |
| 75 y |  | 103/23 | 2.17 | (0.86-5.47) | 0.10 | 101/23 | 2.18 | (0.79-5.97) | .13 |  |
| 76-80 y | 90/24 | 2.28 | (0.90-5.76) | 0.08 | 81/21 | 4.57 | (1.30-16.06) | .02 |  |
| 81 y |  | 73/23 | 1.67 | (0.64-4.37) | 0.29 | 57/19 | 2.58 | (0.72-9.27) | .15 |  |
| Female |  | 194/53 | 1.48 | (0.80-2.72) | 0.21 | 180/51 | 2.27 | (1.09-4.70) | .03 |  |
| Male |  | 72/17 | 4.8 | (1.15-15.20) | <0.01 | 56/9 | 4.60 | (0.95-22.26) | .06 |  |
| CDR ¼ 0.5 | 104/28 | 3.11 | (1.10-8.85) | 0.03 | 91/25 | 4.13 | (1.26-13.61) | .02 |  |
| CDR | 1 | 108/34 | 2.11 | (0.96-4.65) | 0.06 | 96/27 | 3.20 | (1.26-8.15) | .02 |  |
| CDR | 2z | 53/7 | - |  | 0.99 | 47/2 | - |  | .99 |  |
| AD, Alzheimer disease; CDR, Clinical Dementia Rating scale; CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio. |  |  |
| \*Adjusted models include the following covariates: Age, sex, level of education, AD treatment and total MMSE at baseline. |  |  |  |  |
| yn represents number of patients for each group (decliners/non-decliners). |  |  |  |  |  |  |  |
| zORs for CDR | 2 were not calculated due to small sample size. |  |  |  |  |  |  |  |

Table 4

Logistic Regression Analyses Testing the Ability of the CART-Derived Classification Rule (Using Non-Decliners as Reference) to Predict Decline Versus Non-Decline Over the 3-Versus 4-Year Follow-Up in REAL.FR

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Unadjusted |  |  | Adjusted[\*](#page7) |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  | ny | OR (95% CI) | P | ny | OR (95% CI) | P |
| At 3 yearsz | 189/40 | 2.22 (1.10-4.48) | 0.03 | 171/38 | 3.52 (1.52-8.20) | <.01 |  |
| At 4 yearsx | 115/48 | 1.79 (0.89-3.59) | 0.99 | 96/42 | 2.50 (1.10-5.67) | .03 |  |

CART, classification and regression tree; CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio.

\*Adjusted models include the following covariates: Age, sex, level of education, AD treatment and total MMSE at baseline.

yn represents number of patients for each group (decliners/non-decliners).

zNon-decliners at 3 years defined as 1-point change in MMSE.

xNon-decliners at 4 years defined as 3-point change in MMSE.

Fig. 1. Optimal tree found by CART analysis to predict decline versus non-decline in patients with AD. The top pie chart shows the percentage of patients within each group (decliners in light gray vs non-decliners in dark gray). The first node of the tree splits the sample into two subgroups based on patients’ performance on the Word Recall item of the ADAS-Cog, with a cut-point of 6/10 (the left child node corresponding to patients able to recall a mean of four words or more over the three attempts). The second node further splits the left child node using additional information from the ADAS-Cog Word Recognition item, with a cut-point of 4/12 (the left child node corresponding to patients able to recall eight words or more). The pie chart in the bottom right box illustrates the performance of the classification rule.



Fig. 2. (A) Brief description of the ADAS-Cog verbal memory item procedures and score calculation. (B) Schematic representation of the classification rule using the verbal memory item cut-points derived from the CART analysis.

