

# Support for the Vascular Depression Hypothesis in Late-Life Depression

## Results of a 2-Site, Prospective, Antidepressant Treatment Trial

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**Context:** Research on vascular depression has used 2 approaches to subtype late-life depression, based on executive dysfunction or white matter hyperintensity severity.

**Objective:** To evaluate the relationship of neuropsychological performance and white matter hyperintensity with clinical response in late-life depression.

**Design:** Two-site, prospective, nonrandomized controlled trial.

**Setting:** Outpatient clinics at Washington University and Duke University.

**Participants:** A total of 217 subjects aged 60 years or older met DSM-IV criteria for major depression, scored 20 or more on the Montgomery-Asberg Depression Rating Scale (MADRS), and received vascular risk factor scores, neuropsychological testing, and magnetic resonance imaging; they were excluded for cognitive impairment or severe medical disorders. Fazekas rating was conducted to grade white matter hyperintensity lesions.

**Intervention:** Twelve weeks of sertraline treatment, titrated by clinical response.

**Main Outcome Measure:** Participants' MADRS scores over time.

**Results:** Baseline neuropsychological factor scores correlated negatively with baseline Fazekas scores. A mixed

model examined effects of predictor variables on MADRS scores over time. Baseline episodic memory ( $P=.002$ ), language ( $P=.007$ ), working memory ( $P=.01$ ), processing speed ( $P<.001$ ), executive function factor scores ( $P=.002$ ), and categorical Fazekas ratings ( $P=.05$ ) predicted MADRS scores, controlling for age, education, age of onset, and race. Controlling for baseline MADRS scores, these factors remained significant predictors of decrease in MADRS scores, except for working memory and Fazekas ratings. Thirty-three percent of subjects achieved remission ( $MADRS \leq 7$ ). Remitters differed from nonremitters in baseline cognitive processing speed, executive function, language, episodic memory, and vascular risk factor scores.

**Conclusions:** Comprehensive neuropsychological function and white matter hyperintensity severity predicted MADRS scores prospectively over a 12-week treatment course with selective serotonin reuptake inhibitors in late-life depression. Baseline neuropsychological function differentiated remitters from nonremitters and predicted time to remission in a proportional hazards model. Predictor variables correlated highly with vascular risk factor severity. These data support the vascular depression hypothesis and highlight the importance of linking subtypes based on neuropsychological function and white matter integrity.

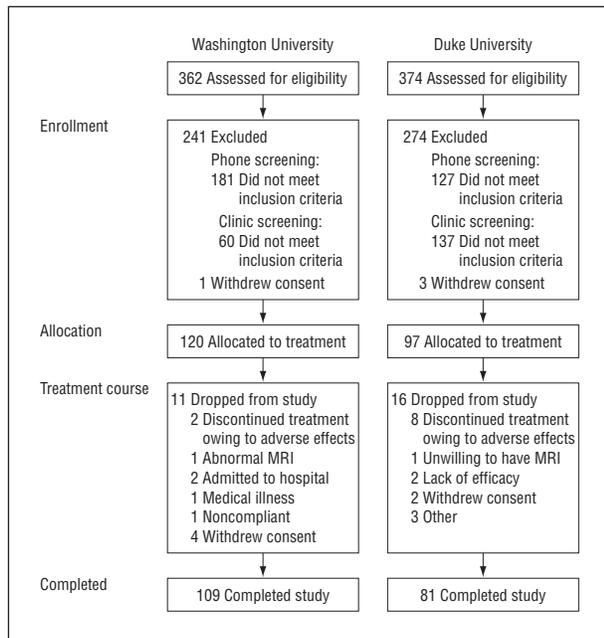
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**L**ATE-LIFE DEPRESSION (LLD) produces significant morbidity and mortality, making it an important public health issue given the growing number of elderly persons. The heterogeneity of LLD has been well described, including the large degree of medical comorbidity, especially vascular risk factors (eg, cardiovascular disease, stroke, hypertension, and diabetes).<sup>1-5</sup> Vascular disease may contribute to LLD by affect-

ing subcortical structures involved in mood regulation and the white matter pathways that connect these structures to frontal cortex.<sup>6</sup> Research on vascular depression has developed 2 ways of subtyping LLD: (1) those identified clinically by neuropsychological characteristics, especially executive dysfunction; and (2) those identified by brain magnetic resonance imaging (MRI) characteristics. In the subtype consisting of patients characterized as having executive dysfunction,<sup>7,8</sup> vascu-

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**Figure 1.** Patient flowchart for Washington University and Duke University sites, indicating the numbers of subjects included in the screening process, enrollment, and final allocation to the study, subjects who dropped out of treatment, and reasons for discontinuation. MRI indicates magnetic resonance image.

lar depression has been characterized clinically as a “depression-executive dysfunction syndrome of late life.”<sup>8</sup> Despite enthusiasm for this theory,<sup>9</sup> few studies have examined the predictive utility of cognitive function in understanding the course and outcome of LLD. A recent study by Alexopoulos et al<sup>10</sup> prospectively examined neuropsychological function in predicting treatment outcome in LLD and found a significant negative effect of executive function on treatment outcome, suggesting an important role for cognitive function in understanding the course of LLD.

A second subtype description of vascular depression, “MRI-defined vascular depression,”<sup>11</sup> is defined by the presence and severity of white matter hyperintensities (WMHs), which are thought to be produced by small, silent cerebral infarctions.<sup>12</sup> Increased WMH severity is a well-replicated finding in elderly subject groups with depression,<sup>13-19</sup> although there are negative studies as well.<sup>20,21</sup> Several factors contribute importantly to the pathogenesis of WMH, particularly age<sup>22</sup> and medical comorbidity, especially hypertension<sup>23</sup> diabetes mellitus,<sup>24</sup> cardiovascular disease,<sup>25</sup> and overall higher Framingham risk factor score.<sup>26,27</sup>

Although each of these two ways of subtyping LLD have been shown to have clinical relevance, few studies have attempted to clarify the relationship between neuropsychological function and WMH in predicting course and outcome in LLD. Thus, in the current study, these two different ways of subtyping vascular depression, namely neuropsychological function variables and WMH severity, were used to predict course of illness over 12 weeks of antidepressant treatment in LLD. We hypothesized that impaired baseline neuropsychological performance, particularly processing speed and executive function, would predict poorer

clinical response in a prospective treatment trial using sertraline. In addition, we hypothesized that increased baseline WMH severity would predict worse clinical outcome and that there would be an association between WMH and executive dysfunction in predicting poor treatment response. The study was conducted at 2 sites to increase sample size and our ability to generalize our results to the larger population of LLD.

## METHODS

### SUBJECTS

Patients were recruited for an ongoing National Institute of Mental Health study, Treatment Outcome in Vascular Depression, through advertising and physician referral to Washington University (WU) Medical Center and Duke University Medical Center. Of 362 phone screens at WU and 374 at Duke, there were 181 clinic screenings at WU and 135 at Duke (**Figure 1**). Patients who met *DSM-IV* criteria for major depression by Structured Clinical Interview for Axis I *DSM-IV* Disorders (SCID-IV), given by a research psychiatrist (Y.S., M.D., K.G., or K.G.) were recruited into the study after satisfying exclusionary criteria. Patients were moderately depressed outpatients; no inpatients were included in the study. All patients were screened to rule out severe or unstable medical disorders (eg, myocardial infarction within past 3 months, end-stage cancer, decompensated cardiac failure) and known primary neurological disorders including dementia, delirium, diagnosis of stroke within the past 3 months, Parkinson disease, brain tumors, multiple sclerosis, seizure disorder, conditions or drugs that may cause depression (eg, systemic steroids, pancreatic cancer, uncorrected hypothyroidism), history of other Axis I disorders prior to their depression diagnosed by SCID, current suicidal risk, current episode that failed to respond to adequate trials of 2 prior antidepressants for at least 6 weeks at therapeutic doses, use of psychotropic prescription or nonprescription drugs or herbals (eg, hypericum) within 3 weeks or 5 half-lives, except for limited use of certain hypnotics or in exceptions when the patients' depression was worsening, in which case antidepressant use was tapered off after starting to take sertraline, or a Mini-Mental State Examination (MMSE) score of 21 or lower.<sup>28</sup> Patients were restricted from other therapies during participation. While our criteria excluded those with an MMSE score of less than 21, only 3% of subjects had an MMSE score of less than 24. The exclusionary criteria further reduced the patient study group to 120 patients enrolled at WU and 97 at Duke (n = 217 total). All patients were enrolled in a 12-week treatment trial with sertraline and were restricted from receiving other therapies during participation. At WU, 109 subjects completed the protocol and 11 had early termination, 2 had adverse effects, 2 psychiatric hospitalization, and 1 abnormal MRI; 4 withdrew consent, 1 was noncompliant, and 1 had an unrelated medical illness. At Duke, 81 depressed subjects completed the protocol, and there were 16 with early termination, 8 had adverse effects and 2 lack of efficacy, 1 was unwilling to have MRI, 2 withdrew consent, and 3 had other reasons. Thus, there were a combined 217 intent-to-treat patients and a combined 190 completers. For various data analyses, there were different numbers of subjects included, reflecting the partial missing data on some measures. Written informed consent approved by the relevant institutional review board was obtained for all subjects.

### MEASURES

Data were obtained from evaluations performed by research staff of the clinical research study at each site and included medi-

**Table 1. Demographics Characteristics and z Scores**

Demographic Variables	Mean (SD)			P Value <sup>a</sup>
	All Participants (n=217)	Dropouts (n=27)	Completers (n=190)	
White race, No. (%)	198 (91.2)	25 (92.6)	173 (91.1)	>.99
Sex male, No. (%)	96 (44.2)	13 (48.2)	83 (43.7)	.68
Late age of onset <sup>b</sup> (≥age 60 y) (n=199)	90 (45.2)	7 (38.9)	83 (45.9)	.63
Age, y	68.4 (7.2)	67.8 (6.3)	68.6 (7.3)	.79
Age at onset, y (n=199)	53.6 (17.2)	53.4 (15.7)	53.6 (17.3)	.86
Education, y	14.2 (3.1)	13.2 (3.1)	14.4 (3.1)	.09
MMSE score (n=216)	27.7 (2.0)	27.4 (2.3)	27.8 (2.0)	.43
VRF (n=211)	11.7 (4.6)	11.6 (4.6)	11.7 (4.6)	.96
Baseline MADRS score	26.0 (4.4)	25.1 (4.5)	26.1 (4.4)	.25
Episodic memory (n=198)	-0.34 (3.1)	-0.03 (2.8)	-0.37 (3.2)	.66
Language processing (n=193)	-0.10 (2.3)	0.12 (2.2)	-0.12 (2.4)	.45
Working memory (n=197)	-0.04 (2.3)	-0.74 (2.1)	0.03 (2.3)	.10
Processing speed (n=192)	0.004 (2.5)	0.54 (2.3)	-0.05 (2.6)	.31
Executive function (n=184)	-0.10 (3.3)	0.12 (3.2)	-0.12 (3.4)	.80
Total Fazekas score (n=184)	4.2 (2.4)	4.5 (2.5)	4.2 (2.3)	.56
Total Fazekas categorical score, No. (%) (total Fazekas score >2) (n=184)	127 (69.0)	8 (80.0)	119 (68.4)	.73
Last sertraline dose, mg (n=204)	114.0 (54.2)	72.2 (38.2)	118.0 (53.9)	<.001

Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; MMSE, Mini-Mental State Examination; VRF, vascular risk factor.

<sup>a</sup>Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

<sup>b</sup>Defined as 60 years or older.

cal, psychiatric, demographic, MRI, and neuropsychological measures. Demographic variables (**Table 1**) were age, education, sex, race, depression symptom severity (scored on the Montgomery-Asberg Depression Rating Scale [MADRS]),<sup>29</sup> age of depression onset, MMSE score, final dose of sertraline, and vascular risk factor (VRF), as defined by the Framingham study.<sup>25</sup> The Framingham study uses a stroke risk prediction assessment tool that includes the following VRFs to predict 10-year risk of stroke in both men and women: age, systolic blood pressure, use of antihypertensive therapy, diabetes mellitus, cigarette smoking, cardiovascular disease (coronary heart disease, cardiac failure, or intermittent claudication), atrial fibrillation, and left ventricular hypertrophy by electrocardiogram. As expected, the stroke risk increased with increasing age. In our sample, subjects who were younger than 65 years had a mean VRF score of 9.0, indicating a 10-year stroke risk of 8% (average risk for age group, 7%); for those aged 65 to 74 years, the VRF was 12.2, indicating a 10-year risk of 13.5% (average risk, 11%); for those aged 75 to 84 years, the VRF was 16.2, indicating a risk of 23% (average risk, 20%); and for those aged 85 years or older, the mean VRF was 19.3, with a risk of 34% (average risk, 13.7%). Thus, based on mean VRF scores, our population had a higher 10-year probability of stroke compared with the average stroke risk per age in the general population. The relative increase in stroke risk in our population is as follows: 14% for those younger than 65 years; 22.7%, 65 to 74 years; 14.4%, 75 to 84 years; and 148.1%, 85 years and older.

Age at onset was ascertained from the SCID-IV and available medical and psychiatric records. Neuropsychological testing was performed by a highly trained examiner who was supervised by a PhD-level psychologist (D.B. and K.W.B.). Patients were tested prior to the initiation of antidepressant medication and were psychotropic free.

### Outcome Measures

Montgomery-Asberg Depression Rating Scale<sup>29</sup> scores were obtained at baseline and weekly for 12 weeks by a research psy-

chiatrist. Prior to study initiation, a start-up meeting was held with all investigators from both sites that included training to standardize MADRS ratings across sites. For purposes of data analysis, given variable patient schedules for completing the study, completion was defined as more than 8 weeks in the study. Remission was defined in patients who remained in the trial at least 8 weeks (completers) and had a final MADRS score of 7 or lower. Nonremitters were defined as patients who stayed in the trial at least 8 weeks but did not have a final MADRS score of 7 or lower. The comparison between remitters and nonremitters is shown in **Table 2**. While many studies have used a final MADRS score of 10 or lower to define remission, we chose a more stringent value based on evidence from a meta-analysis<sup>30</sup> supporting a lower cut-off.

### Sertraline Treatment

The initial sertraline dose was 25 mg for 1 day to rule out drug sensitivity, then 50 mg daily, with subsequent dose changes at 2 weeks (to 100 mg/d), 4 weeks (to 150 mg/d), and 6 weeks (to 200 mg/d) based on treatment response and adverse effects. Adverse effects were assessed at each visit using a checklist. At any point, patients who had adverse effects could be given titrated doses to reach a lower dose. Medication adherence was assessed at each visit by self report. Final doses and number of participants at each dose were as follows: less than 100 mg, n=64; 100 to 125 mg, n=60; 150 to 175 mg, n=46; 200 mg, n=34 (mean [SD] final dose, 114.0 [54] mg).

### Neuropsychological Test Performance in LLD

All participants were given a large battery of neuropsychological tests that covered cognitive domains relevant to understanding late-life depression. We grouped the cognitive tasks into rationally motivated domains, described below, based on literature regarding the cognitive processes assessed by each of the tasks.<sup>31</sup> To combine the tasks, we created z scores for

**Table 2. Comparison of Remitters vs Nonremitters**

Demographic Variable	Mean (SD)		P Value <sup>a</sup>
	Nonremitter (n=118)	Remitter (n=72)	
White race, No. (%) (n=190)	109 (92.4)	64 (88.9)	.44
Sex male, No. (%) (n=190)	52 (44.1)	31 (43.1)	>.99
Late age at onset, No. (%) (n=181)	51 (45.5)	32 (46.4)	>.99
Age, y (n=190)	69.2 (7.7)	67.6 (6.7)	.21
Age at onset, y (n=181)	53.5 (17.9)	53.7 (16.6)	.93
Education, y (n=190)	14.2 (2.9)	14.7 (3.4)	.19
MMSE score (n=189)	27.6 (1.9)	28.0 (2.1)	.06
VRF (n=188)	12.3 (4.5)	10.6 (4.6)	.01
Baseline MADRS score (n=190)	26.6 (4.5)	25.2 (4.1)	.06
Episodic memory (n=180)	-0.82 (3.2)	0.37 (3.1)	.005
Language processing (n=175)	-0.50 (2.5)	0.47 (2.1)	.004
Working memory (n=179)	-0.09 (2.3)	0.20 (2.2)	.42
Processing speed (n=174)	-0.56 (2.8)	0.74 (1.9)	<.001
Executive function (n=167)	-0.58 (3.4)	0.61 (3.2)	.02
Total Fazekas score (n=174)	4.4 (2.5)	3.8 (2.1)	.09
Categorical Fazekas (total Fazekas score >2), n (%) (n=174)	76 (72.4)	43 (62.3)	.18
Last sertraline dose, mg (n=186)	125.7 (56.9)	105.9 (46.6)	.02

Abbreviations: MADRS, Montgomery-Asberg Depression Rating Scale; MMSE, Mini-Mental State Examination; VRF, vascular risk factor.  
<sup>a</sup>Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

**Table 3. Correlations Between VRF and Predictor Variables**

Other Predictors	VRF Pearson Correlations	
	Correlation Coefficient (r)	P Value
Episodic memory (n = 194)	-0.22	.002
Language processing (n = 189)	-0.19	.01
Working memory (n = 193)	-0.12	.11
Processing speed (n = 188)	-0.35	<.001
Executive function (n = 181)	-0.28	<.001
Fazekas categorical score (n = 183)	0.26	<.001

Abbreviation: VRF, vascular risk factor.

the primary dependent measure of interest at baseline across all participants and then summed the z scores. Follow-up waves used items normalized using the mean and standard deviation at baseline. Variables in which good performance was represented by lower values rather than higher (such as Trail Making Tests A and B) were reverse scored to insure that higher z scores represented better performance for all variables. Cronbach  $\alpha$  (a measure of internal consistency) was computed for each domain. As seen in **Table 3**, neuropsychological variables as well as white matter hyperintensities were correlated with vascular risk factors.

**Executive Function.** This domain included verbal fluency (total phonological and semantic), Trails B (reverse scored time to completion), the color-word interference condition of the Stroop test (number completed), the Initiation and Perseveration sub-

scales of the Mattis Dementia Rating Scale, and categories completed from the Wisconsin Card Sorting Test. The  $\alpha$  for this domain was .73.

**Processing Speed.** This domain included Symbol-digit modality (number completed), the color naming condition of the Stroop test (number completed), and Trails A (reverse scored time to completion). The  $\alpha$  for this domain was .80.

**Episodic Memory.** This domain included word list learning (total correct), logical memory (total correct immediate), constructional praxis (memory performance), and the Benton Visual Retention Test (total correct). The  $\alpha$  for this domain was .76.

**Language Processing.** This domain included the Shipley Vocabulary Test (number correct), the Boston Naming Test (number correct), and the Word reading condition of the Stroop test (number completed). The  $\alpha$  for this domain was .67.

**Working Memory.** This domain included digit span forward (number of trials correctly completed), digit span backward (number of trials correctly completed), and ascending digits (number of trials correctly completed). The  $\alpha$  for this domain was .68.

### Magnetic Resonance Imaging

Magnetic resonance images were collected using a MAGNETOM Sonata 1.5 T scanner (Siemens, Munich, Germany) at WU. Three-dimensional, T1-weighted (T1W) scans were acquired with magnetization-prepared rapid acquisition gradient echo: time to repetition (TR), 1900 milliseconds; echo time (TE), 4 milliseconds; time following inversion pulse (TI), 1100 milliseconds; and  $222 \times 256 \times 128$  pixels ( $1 \times 1 \times 1.25$  mm). Axial T2-weighted (T2W) scans were acquired using 2-dimensional turbo spin echo: TR, 4000 milliseconds; TE, 97 milliseconds; 17 echoes; thickness, 2 mm; 10-mm gap; 6 interleaves;  $256 \times 256$  mm; and 108 slices ( $1 \times 1 \times 2$  mm). To improve signal-to-noise ratio, 4 T1W images were obtained and averaged for each subject.

Magnetic resonance images were collected using a 1.5 T scanner (General Electric, Schenectady, New York) at Duke University. The equivalent sagittal T1W sequence was conducted using a 3-dimensional inversion recovery-prepared spoiled gradient recalled scan: TR, 8.3 milliseconds; TE, 3.3 milliseconds; TI, 300 milliseconds  $256 \times 256 \times 124$  pixels. The axial T2W scan was a 2-dimensional fast spin echo: TR, 4000 milliseconds; TE2, 105 milliseconds; thickness, 5 mm; field of view,  $150 \times 200$  mm; and 20 slices ( $1 \times 1 \times 5$  mm). Axial fluid-attenuated inversion recovery images were obtained at both sites. This T2W sequence allows translation to most clinical sites: TR, 9.99 seconds; TE, 105 milliseconds; TI=2300 milliseconds; slices, 20; thickness, 5 mm; and interleaved acquisitions with no gap.

To correct for head movement and improve signal-to-noise ratio, the 4 T1W scans were coregistered using standard 12-parameter affine transform to create a single average image.<sup>32</sup> The 6 T2W images were collated and fused and then coregistered with the T1W scans. Both T1W and T2W images were then resampled to a common Talairach stereotaxic atlas (T88) using 1-mm<sup>3</sup> voxels. To correct for magnetic field inhomogeneities, a parametric bias field correction was used to correct both T1W and T2W image intensities.<sup>33,34</sup>

### T2W Hyperintensities

Hyperintensities were assessed blind to treatment data using the modified Fazekas criteria. All ratings were conducted at WU by R.C.M. and Y.I.S. using fluid-attenuated inversion recovery

**Table 4. Mixed Models Predicting MADRS Score**

Predictor	Model 1 <sup>a,b</sup>		Model 2 <sup>a,c</sup>	
	Regression Parameter (SE)	P Value	Regression Parameter (SE)	P Value
Episodic memory (n = 192)	-0.45 (0.14)	.002	-0.35 (0.13)	.008
Language processing (n = 187)	-0.54 (0.20)	.007	-0.39 (0.18)	.03
Working memory (n = 191)	-0.48 (0.19)	.01	-0.25 (0.17)	.15
Processing speed (n = 186)	-0.72 (0.18)	.001	-0.59 (0.17)	<.001
Executive function (n = 179)	-0.45 (0.14)	.002	-0.33 (0.13)	.01
Total Fazekas categorical score (n = 182)	1.85 (0.93)	.05	1.19 (0.85)	.16
VRF score (n = 209)	0.12 (0.10)	.25	0.20 (0.09)	.03
Last sertraline dose, mg (n = 192)	0.05 (0.007)	<.001	0.03 (0.007)	<.001

Abbreviations: SE, standard error; VRF, vascular risk factor.

<sup>a</sup>The effect of each predictor was analyzed separately.

<sup>b</sup>Main effect (across all times), controlling for time, age, age at onset, race, education.

<sup>c</sup>Main effect (across all times), controlling for time, age, age at onset, race, education, baseline time, and baseline Montgomery-Asberg Depression Rating Scale score.

and T2-weighted images in a side-by-side review. The modified Fazekas criteria<sup>35</sup> describe MRI hyperintensities in 3 regions and follow an ascending degree of severity. The criteria assess periventricular hyperintensities (0, absent; 1, caps; 2, smooth halo; and 3, irregular and extending into deep white matter). Deep WMH were scored as follows: 0, absent; 1, punctate foci; 2, beginning confluence of foci; 3, large confluent area; subcortical gray matter lesions: 0, absent; 1, punctate; 2, multipunctate; 3, diffuse. Interrater reliability was calculated separately for the 3 Fazekas ratings: periventricular hyperintensities, 0.73; deep WMH, 0.86; subcortical gray matter lesions, 0.94; in all cases of disagreement, a follow-up consensus rating was conducted. In addition, a total Fazekas rating ("Total Fazekas score") was created by summing the 3 ratings from deep white matter, subcortical gray matter, and periventricular ratings, producing a score that ranged from 0 to 9. From this total score, a categorical Fazekas score ("Total Fazekas categorical") was created: 3 or more, high, and 2 or less, low.

## STATISTICAL ANALYSIS

Pearson product moment correlations were used to investigate the relationship between baseline neuropsychological function and WMH (Fazekas scores). In addition, Pearson correlations were conducted between the Framingham VRF scores and the predictor variables.

The change in MADRS scores over 12 weeks was assessed. To accommodate missing values owing to missed appointments and censoring owing to dropout, a mixed model<sup>36</sup> was used. Three different mixed models were then used to predict treatment outcome. For model 1, separately for each predictor measure, neuropsychological cognitive function and WMH measures were used to predict MADRS scores following treatment, controlling for time, age, education, race, and age of onset (not accounting for initial MADRS). For model 2, the same predictor variables and covariates were used as in model 1 but the model also controlled for baseline MADRS score as well as these variables to assess whether cognitive function or WMH predicted the magnitude of change from baseline to endpoint MADRS. For model 3, to assess the difference in trajectories, in a third analysis, the variable  $\times$  time interaction was incorporated into the model to assess whether cognitive function or WMH predicted the speed of change as well as the magnitude of change from baseline to endpoint.

Prior to entering predictor variables, we first examined the effect of covariates on MADRS using a mixed model to deter-

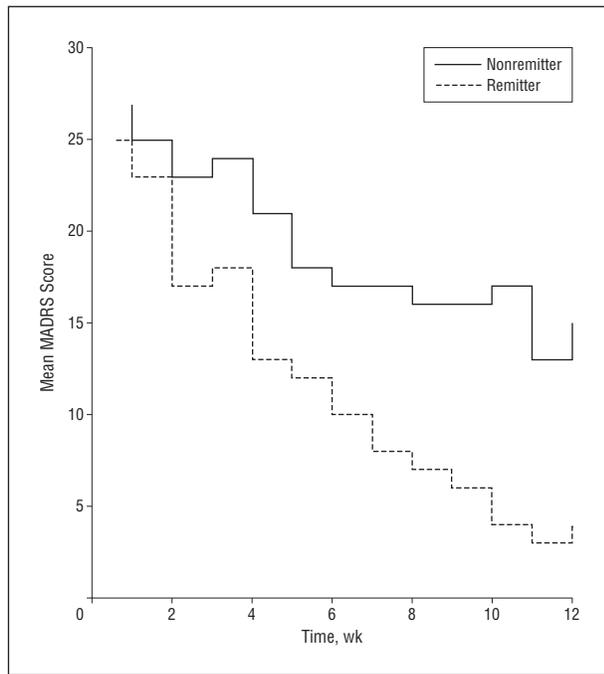
mine the results in the unadjusted model (not shown) where we only adjusted for that covariate and time. The covariates had the following bearing on the outcome: age was borderline significant ( $P = .06$ ); race was not significant ( $P = .8$ ); education was borderline significant ( $P = .06$ ); and age of onset was not significant ( $P = .3$ ). These results are not displayed in **Table 4**. The unadjusted model for memory ( $P < .001$ ), language ( $P = .002$ ), working memory ( $P = .004$ ), processing speed ( $P < .001$ ), executive function ( $P < .001$ ), and categorical Fazekas score ( $P = .02$ ) indicates that all hypothesized covariates had a slightly larger magnitude effect in the unadjusted model, and the effect slightly weakened as more covariates were added to the model, as shown in models 1 and 2 in Table 4. All of the hypothesized covariates were significant for the unadjusted model.

In addition, a Cox proportional hazards model<sup>37</sup> analyzed time to remission and was used to predict the remitter survival given baseline predictor variables and further adjusting for covariates.

## RESULTS

Demographic variables used as predictor variables of treatment outcome were age, education, race, age at onset, and depression symptom severity on the MADRS. The number, mean, and standard deviation of these variables are shown in Table 1 and were used as covariates in the analyses. The number and percentage of patients with early-onset vs late-onset depression ( $\geq 60$  years) is also shown in Table 1. The MMSE scores were included and, as shown in Table 1, the mean was relatively high (27.7). In addition, the mean (SD) of each of the neuropsychological factor scores, the Fazekas score and the VRF score, as defined by the Framingham study,<sup>25</sup> are shown in Table 1. Table 1 shows the demographic data for the patients who completed at least 8 weeks of the 12-week trial (completers) vs the patients who failed to complete at least 8 weeks (dropouts). Comparing the groups, the variable that was different for dropouts was final dose of sertraline, which was significantly lower.

Of subjects who completed at least 8 weeks of treatment, Table 2 compares those with remission of depression vs nonremitters. As shown in Table 2, 33% of sub-



**Figure 2.** Montgomery-Asberg Depression Rating Scale (MADRS) scores over the 12-week course of treatment are plotted separately for subjects who achieved remission of depression and those who did not. All subjects in this analysis remained in the study for at least 8 weeks.

jects achieved remission of depression ( $\leq 7$  on MADRS). The *P* values indicate statistically significant differences in variables between subjects who achieved remission (remitters) vs those who did not (nonremitters). Interestingly, compared with remitters, the nonremitters had a higher final dose of sertraline, indicating that an attempt had been made to increase the dose to a level that would achieve remission and that the difference in remission was not simply a matter of underdosing. **Figure 2** graphically displays the MADRS scores from baseline to 12 weeks of treatment for the remitters vs nonremitters.

As shown in Table 3, using a Pearson correlation, the Framingham vascular risk factor scores were statistically significantly correlated with all of the predictor variables except for working memory. In addition, we determined correlations between the categorical Fazekas score (high vs low) with neuropsychological factor scores (data not shown). Fazekas scores were statistically significantly correlated with all of the baseline neuropsychological factor scores: executive function ( $r = -0.27$ ;  $P < .001$ ), cognitive processing ( $r = -0.27$ ;  $P < .001$ ), episodic memory ( $r = -0.21$ ;  $P = .004$ ), language ( $r = -0.15$ ;  $P = .05$ ), and working memory ( $P = .003$ ).

Next, using mixed models, we examined the effect of our predictor neuropsychological measures, Fazekas scores, VRF, and last sertraline dose on the trajectory of treatment response. Of note, there were different numbers of subjects in these analyses owing to the different numbers of subjects completing the separate measures. We used 3 prediction models to assess the effect of baseline variables on treatment outcome. We first used a mixed model to assess the effect of predictor variables (cognitive function, Fazekas scores, VRF, and last dose of sertraline) on MADRS scores, with time, age, education, age

of onset, and race as covariates. The following measures produced a statistically significant effect on the MADRS scores (Table 4, model 1): episodic memory ( $P = .002$ ), language ( $P = .007$ ), working memory ( $P = .01$ ), processing speed ( $P < .001$ ), executive function ( $P = .002$ ), and categorical Fazekas score ( $P = .05$ ). In addition, a higher last dose of sertraline predicted worse outcome, indicating that nonremitters received a higher dose in an attempt to adequately treat their depression.

After controlling for baseline MADRS score (model 2), episodic memory ( $P = .008$ ), processing speed ( $P < .001$ ), executive function ( $P = .01$ ), language scores ( $P = .03$ ), VRF scores ( $P = .03$ ), and last dose of sertraline ( $P < .001$ ) all produced a statistically significant effect on MADRS scores, indicating that these variables predicted higher or lower levels of MADRS scores during the course of treatment. It was actually higher sertraline doses that predicted worse outcome. Fazekas scores and working memory scores did not significantly predict change in MADRS scores once baseline MADRS values were entered into the model.

The predictors reported in Table 4 were analyzed in separate models (in contrast to conducting a model with all predictors entered at once). As shown in Table 4, all neuropsychological factor scores had a negative relationship with MADRS score. Episodic memory, language, working memory, and executive function had similar relationships in magnitude and direction to MADRS. The relationship between processing speed and MADRS had a larger effect than found with the other neuropsychological predictors. As the neuropsychological factor scores increased (indicating higher function), there was a decrease in the MADRS score. The relationship between total Fazekas categorical score and MADRS was positive, indicating that those with a Fazekas value of at least 3 (more severe WMH) had a larger MADRS score than those with a Fazekas value of less than 3. As noted in the "Statistical Analysis" section, the magnitude for all the predictors of interest (WMH and neuropsychological covariates) slightly decreased from the model controlling for time only (not shown in Table 4) to the model controlling for time, age, age of onset, race, and education (Table 4, model 1). When further adjusting for baseline time and baseline MADRS (Table 4, model 2), the magnitude of the effect for all of the neuropsychological factor scores and WMH decreased even more. This finding makes intuitive sense because it would be expected that controlling for the baseline outcome value would account for some of the variability in the regression portion of the mixed model. The effect for working memory and total Fazekas categorical score was decreased by almost half when adjusting for baseline time and baseline MADRS; however, the standard error remained about the same, leading to nonsignificant results.

Neither neuropsychological factors nor Fazekas scores interacted with time to predict MADRS scores (results not shown), controlling for age, race, education, age of onset, baseline time, and baseline MADRS scores. This result indicates that, while many of the neuropsychological variables predicted the overall magnitude of MADRS score change, they did not predict the rate of change (slope).

Examining the probability of remission using a Cox proportional hazards model, controlling for age, age of onset, education, and race, the factors that predicted the remitter survival were episodic memory ( $P=.006$ ), cognitive processing speed ( $P=.001$ ), executive function ( $P=.01$ ), and language function ( $P=.05$ ), but not working memory or Fazekas scores.

## COMMENT

The principal finding of this prospective antidepressant treatment study of late-life depression was that both baseline neuropsychological function and WMH scores predicted MADRS scores over a 12-week course of treatment and that neuropsychological function and WMH scores were correlated. Further, all of these predictor variables were highly correlated with the Framingham VRF scores, indicating a strong association with vascular disease. Several studies have shown that a large number of patients with late-life depression fail to respond or respond only partially to treatment, particularly those with executive impairment.<sup>7,10</sup>

While some studies support the preeminence of executive dysfunction,<sup>9</sup> cross-sectional assessments of cognitive function in LLD have yielded variable findings about the specificity of deficits to executive function.<sup>38-41</sup> Of the studies using a matched control group, many<sup>38-40</sup> suggested the presence of disturbances across a range of cognitive domains in LLD. However, in recent studies,<sup>31,41</sup> disturbances occurred across a broad range of domains and could be best explained by core deficits in cognitive processing speed that influenced performance in a range of cognitive domains. Thus, it is not clear whether cognitive deficits in vascular depression are specific to executive dysfunction or representative of more general disturbances in neuropsychological function that may, in part, reflect slowed processing speed. As noted, compared with the number of studies examining cross-sectional neuropsychological function in LLD, there are few prospective studies of treatment outcome. The current study used a comprehensive neuropsychological battery and was thus able to simultaneously assess multiple domains of cognitive function. In the current study, even after controlling for baseline depression severity, cognitive processing speed was still strongly predictive of MADRS scores ( $P<.001$ ), whereas executive function was less highly significant ( $P=.01$ ). There was also a strong predictive effect for episodic memory ( $P=.008$ ). Our results add to the literature demonstrating that neuropsychological function predicts MADRS scores in LLD. They expand on prior research by elucidating the relationship of neuropsychological function and WMH in MADRS score change. Furthermore, examining treatment remission, there was a strong effect of baseline cognitive processing speed, executive function, episodic memory, and language processing as well as VRF score comparing patients who achieved depression remission vs those who did not.

Similar to the effect of neuropsychological function on treatment outcome, in some studies, severity of WMH has been associated with poor antidepressant treatment

response.<sup>42-44</sup> In contrast, a study<sup>45</sup> that measured WMH failed to find a relationship with treatment outcome in LLD, and there are clearly subjects with treatment-resistant LLD without VRFs. However, because WMH severity was not quantified in most treatment studies, it was not possible to compare the influence of WMH across studies. Further, very few studies have examined this question prospectively. We now add to the literature by demonstrating that WMH severity predicted MADRS scores, although not after controlling for depression severity, indicating that WMH severity was highly correlated with depression severity as well as with neuropsychological impairment. The apparently poorer performance of the Fazekas rating scale than the cognitive measures in predicting MADRS does not exclude the possibility that more sophisticated methods that include the volume of lesions and/or their location could perform better. We further note that the severity of WMH in the current study is less than in most studies that examined MRI-defined vascular depression; however, a strength of the current study is that, by using a continuous rather than categorical approach, we are able to examine the effect of several predictors at the same time.

Vascular disease appears to contribute to LLD by affecting frontal white matter pathways and subcortical structures involved in mood regulation. In the current study, we showed that vascular risk factors were highly correlated with both WMH and neuropsychological function, indicating that both sets of abnormalities have a vascular component. Extensive literature has provided support for the importance of WMH in LLD,<sup>11,14-19</sup> including an effect on worsening of treatment outcome.<sup>42-44,46</sup> There is some suggestion<sup>34</sup> that specific pathways are more likely to be affected in patients with vascular depression who have increased burden of WMH in those specific white matter tracts that underly brain regions important in cognition and emotion. In addition, normal-appearing white matter may be involved in vascular depression, as manifested in diffusion tensor imaging studies.<sup>47-49</sup> We now demonstrate using a mixed model approach that there is a significantly worse effect of high vs low WMH load on depression outcome. In our study, those with lowest WMH severity (total Fazekas score 0-2) on the categorical Fazekas score differed from those with higher WMH burden (Fazekas scores 3-9). It is interesting that the difference in outcome appeared to select low vs any severity of ischemic lesion severity rather than to emphasize the more severe end of the spectrum, as was hypothesized in the concept of "MRI-defined subcortical ischemic depression."<sup>50</sup> Differences in etiology have been postulated<sup>51</sup> for subcortical ischemic depression and depression-executive syndrome; it has been proposed that subcortical ischemic depression is due to vascular disease, whereas depression-executive dysfunction is due to aging-related changes and degenerative brain disease as well as vascular disease. In the current study, most patients had vascular disease, as evidenced by their Framingham scores; however, it was not sufficiently severe to cause subcortical disease, as indicated by the relatively low scores on the Fazekas subcortical gray matter index. Nonetheless, the degree of WMH predicted MADRS scores, with having some degree of WMH vs none seeming to be the

most important indicator. Further, we found that worse function in all neuropsychological domains was significantly correlated with Fazekas scores. Thus, in our study, there appears to be broad involvement of neuropsychological function in predicting MADRS scores as well as in association with WMH.

An important aspect of our study is that it carefully screened for and excluded subjects with dementia, using an MMSE cutoff of 21, clinical dementia rating score of 0, and National Institute of Neurological Disorders and Stroke and *DSM-IV* criteria to exclude dementia. In our study, most subjects had MMSE scores of 28 to 30, and only 3% scored lower than 24. Because we have previously seen a high degree of correlation between WMH and microstructural abnormality in normal-appearing white matter, which further correlated with neuropsychological function,<sup>49</sup> we suggest that a fundamental aspect of vascular depression may be the disruption of normal white matter integrity, which then results in deficits in neuropsychological function. Our data support the concept that the subtypes of vascular depression defined by neuropsychological function and WMH severity overlap, and that the same etiological mechanisms may account for both sets of findings. In conclusion, this study supports the importance of both the depression-executive dysfunction syndrome of late life as well as the MRI-defined vascular depression subtypes of vascular depression, suggesting that both affect treatment outcome and that they describe different aspects of the same disease. A refinement suggested by our study is that that vascular disease affects neuropsychological function more broadly than just executive dysfunction, that all WMH except the least severe have a negative effect on depression outcome, and that, together, both deficits in neuropsychological function and severity of WMH predict worse outcome.

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### Correction

**Error in Byline and Author Affiliations.** In the article "Support for the Vascular Depression Hypothesis in Late-Life Depression: Results of a 2-Site, Prospective, Antidepressant Treatment Trial" by Sheline et al, published in the March issue of the *Archives* (2010;67[3]:277-285), there were errors in the byline and Author Affiliations. In the byline on page 277, the name Kathleen Welsh-Boehmer, PhD, should appear as Kathleen Welsh-Bohmer, PhD. On page 284, in the Author Affiliations, Dr Welsh-Boehmer should appear as Dr Welsh-Bohmer.