ORIGINAL ARTICLE

A Dynamic View of Depressive Symptoms and Neurocognitive Change Among Patients With Coronary Artery Disease

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Context: Older patients with coronary artery disease often experience depressive symptoms and are vulnerable to developing cognitive impairment. Whether depressive symptoms increase their risk of cognitive decline is unknown.

Objectives: To examine the association between the stability of depressive symptoms and cognitive decline for 30 months among patients undergoing coronary angiography and to explore whether any observed associations were modified by the presence of the apolipoprotein E (*APOE*) ε4 allele.

Design: Cohort study.

Setting: Urban tertiary care hospital serving southern Alberta.

Participants: Three hundred fifty patients 60 years or older (73.7% male) undergoing nonemergent catheterization (October 27, 2003, through February 28, 2007) without prior revascularization. We compared a baseline measure of depressive symptoms (Geriatric Depression Scale score ≥5) with a dynamic measure capturing change from baseline to 12 months.

Main Outcome Measures: Mean change in domain (*z* scores for attention/executive function, learning/memory, and verbal fluency) and global (raw Mini-Mental State Examination) cognitive scores from baseline to 6, 12, and 30 months and from 12 to 30 months.

Results: In adjusted models, participants with persistent depressive symptoms (at baseline and ≥1follow-up visit) showed significantly greater declines at 30 months in attention/executive function (mean *z* score change, –0.22), learning/memory (–0.19), verbal fluency (–0.18), and global cognition (mean Mini-Mental State Examination [MMSE] score change, –0.99) compared with participants with no or baseline-only depressive symptoms. Persistent depressive symptoms were associated with significantly greater declines in all cognitive measures from 12 to 30 months after adjusting for sociodemographic and clinical factors. For global cognition, a significantly greater decline was evident for patients with persistent depressive symptoms and the *APOE* ε4 allele (mean MMSE score change, –2.93 [95% CI, –4.40 to –1.45]).

Conclusions: Depressive symptoms persist in some patients with coronary artery disease, placing them at a greater risk for cognitive decline. Whether this decline is additionally modified by the presence of *APOE* ε4 requires further investigation.

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RELATIVELY HIGH RATES OF depressive symptoms have been observed among older patients with coronary artery disease (CAD), including those undergoing coronary interventions.[1-3] Major and minor depression are independent risk factors for all-cause mortality and adverse cardiovascular events.[1,4,5] Older patients with CAD may also be at risk for developing cognitive impairment over time.[6,7] Whether depressive symptoms exacerbate these patients' risk for long-term cognitive decline remains unexplored.

Numerous[8-17] although not all[18,19] prospective studies of older adults support an association between depressive symptoms and cognitive decline. Explanations for this association propose that depressive symptoms represent a psychological reaction to worsening cognition; early preclinical symptoms of a dementia disorder; the consequence of vascular risk factors or disease also predictive of cognitive impairment; or a true causal risk factor linked to the pathophysiological symptoms underlying cognitive decline.[20,21] Depression may also act synergistically with other risk factors (eg, presence of the apolipoprotein E [*APOE*] ε4 allele) to produce even greater cognitive risks.[22-24] For patients undergoing coronary interventions, attention has focused on the poten-

tial confounding effects of depression on cognitive performance test results.[25] Few studies have directly investigated the independent risk posed by depressive symptoms (or potential effect modification by the *APOE* ε4 allele) on subsequent cognitive outcomes, and findings remain inconclusive.[26-31] This research has largely been correlational and limited by small sample sizes, insufficient follow-up, and/or a focus on patients undergoing coronary artery bypass graft (CABG) procedures. Data are scarce for patients undergoing percutaneous coronary intervention (PCI) or medical therapy (MT) after catheterization.

No studies to date have explored the prognostic importance of the stability of depressive symptoms over time on longer-term (beyond 12 months) cognitive decline after revascularization. Emerging evidence suggests that not all depressed patients with CAD may be at risk of adverse health outcomes. Those patients with new-onset or persistent depression (possibly associated with nonresponse to treatment) appear to be at highest risk for subsequent mortality and cardiac events.[4,32-34] Although not yet investigated in patients with CAD, studies of persistent depressive symptoms in older adults have shown an increased risk for cognitive decline.[16,17] Persistent symptoms among patients, as opposed to transient symptoms at the time of catheterization (eg, due to uncertainty about their diagnosis and impending procedure), may be more strongly linked with the pathophysiological mechanism(s) underlying cognitive impairment.[20,21] Prior negative findings may reflect a failure to assess for changes in depressive symptoms over time in relation to adverse health outcomes, including cognitive decline.

The primary aim of this study was to examine the effect of clinically significant depressive symptoms on longer-term (≤30 months after the procedure) changes in select cognitive domains among older patients undergoing coronary catheterization who subsequently received CABG, PCI, or MT. We compared the following 2 measures of depressive symptoms: (1) a binary measure capturing symptoms (present or absent) at baseline (before the procedure) and (2) a dynamic measure capturing the course of depressive symptoms from baseline to 12 months after the procedure. A secondary aim was to investigate whether the *APOE* ε4 allele was an effect modifier of any observed associations.

METHODS

STUDY DESIGN

The Calgary Cardiac and Cognition (3C) Study was a prospective cohort investigation of the effect of neurocognitive and psychological factors on quality of life and functional recovery among older patients with CAD undergoing coronary revascularization. A total of 374 participants 60 years or older were enrolled from October 27, 2003, through May 7, 2007. All underwent coronary angiography at an urban tertiary care hospital providing centralized cardiac services for southern Alberta. After catheterization (performed from October 27, 2003, through February 28, 2007), 128 underwent CABG procedures, 150 underwent PCI, and 96 received MT. Patients presenting for angiography underwent screening for eligibility and were approached by trained cardiovascular research nurses. Exclusion criteria included being younger than 60 years, undergoing emergency catheterization or prior revascularization, and being unable to provide informed written consent or complete the assessment owing to language difficulties or cognitive and/or physical impairments. There was purposeful oversampling of those scheduled to undergo CABG and PCI (for comparison of the study sample with all eligible patients undergoing coronary catheterization during our recruitment period, see the eTable; http://www.archgenpsychiatry.com). Ethics approval was received from the Conjoint Health Research Ethics Board of the University of Calgary.

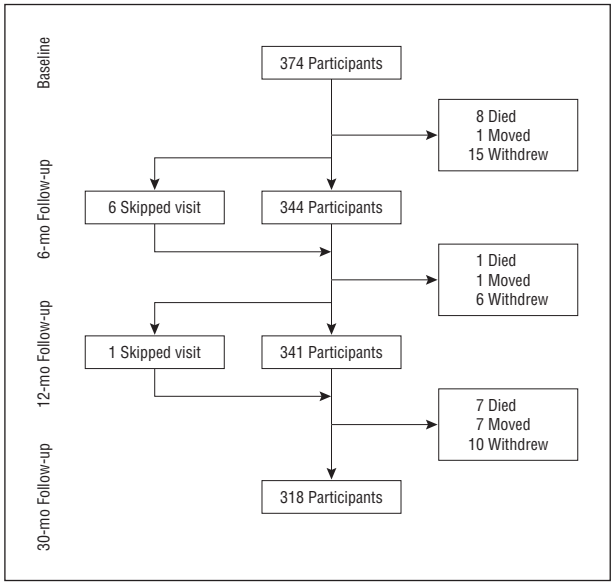

Figure 1. Calgary Cardiac and Cognition Study flowchart. The 6 participants who skipped the 6-month visit returned for the 12-month visit; the 1 participant who skipped the 12-month visit returned for the 30-month visit.

A comprehensive standardized assessment, including neuropsychological and physical performance tests, sociodemographic items, and measures of health behavior, self-rated health, activities of daily living, and health-related quality of life, was administered at baseline (before the procedure) and at 6, 12, and 30 months after the procedure by trained research nurses/associates. Most baseline assessments (57.8%) were conducted in the hospital; the remainder (and all follow-up assessments) were conducted in the participant's home. All data were entered and audited against the original forms. A trained psychometrician (blinded to patients' clinical characteristics) reviewed and scored all cognitive testing results. A structured interview with the patient's primary caregiver (including section H of the Cambridge Mental Disorders of the Elderly Examination–Revised [CAMDEX-R])[35] was administered at all follow-up times, where possible. The 3C Study database was linked with the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH),[36] a comprehensive registry of all patients undergoing cardiac catheterization in the province, for baseline clinical characteristics and data on repeated revascularizations during follow-up. Three patients could not be linked because of out-of-province catheterizations (n=2) or missing hospital records (n=1).

During the 30-month study period, 31 participants withdrew, 9 participants moved or could not be located, 16 died, and 7 missed the 6- or the 12-month assessment but remained in the study (**Figure 1**). Loss to follow-up at 30 months was 15.0%. The number of participants with minimum outcome data at 6 or 12 months and included in our analyses was 350 (93.6%).

MEASUREMENT OF DEPRESSIVE SYMPTOMS

The 15-item Geriatric Depression Scale[37,38] with a cut point of 5+ was used to define clinically important depressive symptoms. We examined a baseline measure (depressive symptoms [present or absent]) and a dynamic measure[16] with the following categories: (1) no clinically important depressive symptoms (at baseline and 6 and 12 months); (2) baseline-only symptoms (at baseline but not at 6 and 12 months); (3) new-onset symptoms (not at baseline but present at 6 or 12 months); and (4) persistent symptoms (at baseline and at 6 or 12 months).

NEUROCOGNITIVE OUTCOMES

Based on an initial exploration of pairwise Pearson correlations and variable loadings in a factor analysis, 3 domains and 1 global cognitive measure were defined as follows:

- Learning and memory were assessed with the Brief Visuospatial Memory Test–Revised[39] and the Consortium to Establish a Registry for Alzheimer's Disease Test of Verbal Learning and Memory.[40] We calculated *z* scores on the basis of published age-, sex-, and education-specific norms for both tests.[39,40] The mean *z* score for the visuospatial test (trial 3, total and delayed recall scores) and for the verbal test (trial 3 and delayed recall tests) were then averaged together for the mean domain score.
- Verbal fluency was assessed with the Controlled Oral Word Association and Animal Naming tests.[41]
- Attention/executive function was derived from the Trail Making Test, parts A and B.[41] For both the verbal fluency and attention/executive function domains, *z* scores were calculated on the basis of published age-, sex-, and education-specific norms[41,42] and averaged together.
- Global cognition was assessed with the Mini-Mental State Examination (MMSE).[43] Raw scores were used.

OTHER MEASURES

The patients' sociodemographic, health, and lifestyle characteristics were assessed at baseline by study nurses. Self-reported educational level was recorded as the number of full-time completed years of education after kindergarten. Current or past smoking (including cigarettes, cigars, and pipe) was assessed by questions on present and ever smoking patterns. Heavy drinking was indicated by self-reported drinking of at least 2 alcoholic drinks per day or by a positive response to the CAMDEX section H caregiver question,[35] "Did you ever think he/she was a heavy drinker?" Living arrangements (alone vs with a spouse and/or others) were self-reported. Self-reported health was collapsed into a dichotomous variable (fair/poor vs good/very good/excellent). The 8-item Questionnaire for Verifying Stroke-Free Status (QVSFS)[44] was completed at each assessment. Anxiety was assessed with the State-Trait Anxiety Inventory[45] (State form only), with higher scores indicating greater anxiety.

Baseline clinical data from the APPROACH[36] database included admission diagnosis, ejection fraction, high-risk coronary anatomy (ie, double-vessel CAD with proximal left anterior descending artery involvement, any 3-vessel disease, or left main disease), Canadian Cardiovascular Society angina class, acute coronary syndrome, and disease history (cerebrovascular, congestive heart failure, peripheral vascular, diabetes mellitus, hypertension, hyperlipidemia, pulmonary, renal, malignant neoplasm, liver, and gastrointestinal disease).

Blood samples were collected for 357 of the 374 participants (95.5%) at the time of catheterization (for patients receiving MT) or revascularization (for patients who underwent PCI and CABG). For 12 participants with missing blood work, buccal samples were collected for genotyping. We extracted DNA from blood and buccal cell samples using standard practice at the Molecular Diagnostic Laboratory of Alberta Children's Hospital and a nucleic acid purification system (Autopure LS; Gentra Systems, Inc). The *APOE* genotype was identified using TaqMan assays as described by Koch et al[46] and reported as ε2, ε2/ε3, ε2/ε4, ε3, ε3/ε4, or ε4. A dichotomous variable (*APOE* ε4 present vs absent) was used in the analyses.

PREVIOUS AND INTERIM CEREBROVASCULAR EVENTS

To identify patients with stroke and/or transient ischemic attack (TIA) events before baseline and/or from baseline to their 12-month follow-up, 2 clinicians (D.B.H. and A.M.D.) reviewed the following: (1) patients' responses to individual QVSFS items at each assessment; (2) caregivers' responses at each assessment to the CAMDEX questions, "Has he/she ever had a stroke?" and "Has he/she ever passed out and then had a brief weakness or difficulty with speech, memory or vision?" If the answer to either question was yes, the time in months since the first occurrence (at baseline) or from their most recent assessment (at follow-up) was recorded; (3) all clinical notes recorded at each assessment by study nurses, including the patients' score on the National Institute of Health Stroke Scale, assessed for those scoring 1 or more on the QVSFS; and (4) all relevant diagnostic codes available from inpatient hospitalizations from fiscal years 1994-1995 through 2007-2008. Final decisions were by consensus with all uncertain cases and discrepancies verified by medical record review.

MISSING DATA AND VALUE ASSIGNMENT AND IMPUTATION

A neuropsychologist and geriatrician (D.B.H.) reviewed all neurocognitive data for participants with 1 or more missing test values. Twenty-four participants (6.4%) judged unable to complete a test owing to cognitive impairment (determined by consensus decision) were assigned a score approximately 3 SDs below the sex-/age-/education-adjusted mean because this was the low end of the distribution for those who were able to complete the test. Two participants (with dementia at follow-up) unable to answer questions about depressive symptoms were assigned Geriatric Depression Scale scores based on CAMDEX section H caregiver questions[35] about the participant's mood. After these value assignments, 0% to 2% of participants still had missing items, depending on the test and visit. Reasons included refusal, physical impairments, and illiteracy (in 2 cases). We used multiple imputation with Markov chain Monte Carlo methods[47] to impute missing data, so that all data would have a similar sample size within each visit.

STATISTICAL ANALYSES

Descriptive analyses were conducted to examine the distribution of the patients' sociodemographic and clinical characteristics overall and by depression status. The 2 measures of depressive symptoms (baseline present or absent and the 4-level categorical measure) were compared with regard to mean change in cognitive score (average *z* scores for the cognitive domains and raw scores for the MMSE) between baseline and 6, 12, and 30 months using linear mixed models with an unstructured correlation matrix (PROC MIXED procedure in SAS; SAS Institute, Inc). For these analyses, the participant was considered to have 3 repeated measurements, with the visit modeled as a categorical variable to allow for nonlinear associations between time and cognitive change. The model included depres-

sion measure, visit, an interaction term between depressive symptoms and visit to assess the differential effect of depressive symptoms over time, and baseline cognition scores, age, sex, and educational level as covariates. The results were summarized in terms of least squares means with standard errors and *P* values and 95% CIs. A secondary analysis using the 4-level categorical depression measure defined as time-changing covariates was explored. Because the results led to similar conclusions, this analysis was not presented.

To examine the relevance of depressive symptom change within the first year to subsequent cognitive decline, linear regression models were used to compare the 4 depressive symptom categories in the prediction of cognitive change from months 12 to 30. We used *APOE* ε4 × depressive symptom interaction terms to calculate unadjusted and adjusted estimates of mean differences in cognitive domain scores (month 30 minus month 12) for those with and without the *APOE* ε4 allele in each of the 4 depressive symptom categories. Adjusted models included the following covariates (identified previously as having clinical and/or methodological significance[6-17]): relevant cognitive test scores (baseline and change scores to 6 months), age, sex, educational level, smoking status, anxiety, treatment group (CABG, PCI, or MT), ejection fraction of less than 50% (includes 21 not performed and 4 missing), high-risk coronary anatomy, acute coronary syndrome, history of stroke and/or TIA (before baseline), interim stroke and/or TIA (baseline to 12 months after the procedure), and comorbidity (history of congestive heart failure, peripheral vascular disease, diabetes mellitus, hypertension, and pulmonary disease). We used various modeling strategies in which covariates were added one at a time to base models (including baseline cognitive scores, depressive symptom category, age, sex, and educational level) and simultaneously with backward elimination. Because these strategies did not alter risk estimates (or standard errors of estimates) for our depressive symptom measure, we presented fully adjusted models stratified by the presence or absence of the *APOE* ε4 allele.

RESULTS

Of the 350 patients, 74 (21.1%) had clinically significant depressive symptoms at baseline. They had lower average levels of education and were more likely to have high-risk coronary anatomy, marked/unstable angina (Canadian Cardiovascular Society class >II), a history of cerebrovascular disease, diabetes, gastrointestinal tract disease, poor self-rated health, and higher anxiety levels than participants without depressive symptoms (**Table 1**).

During 1 year, 248 patients (70.9%) exhibited no significant depressive symptoms, 32 (9.1%) had baseline-only symptoms, 28 (8.0%) had new-onset symptoms (at 6 or 12 months), and 42 (12.0%) showed persistent depressive symptoms. Few baseline sociodemographic, lifestyle, and clinical characteristics varied across the groups (**Table 2**). Compared with participants without significant depressive symptoms at any assessment, (1) those with new-onset symptoms were older, less educated, and more likely to be living alone and more likely to have marked/unstable angina, an acute coronary syndrome, and previous stroke, and (2) those with persistent symptoms were more likely to report poor self-rated health and higher anxiety and more likely to have a history of diabetes, marked/unstable angina, and an acute coronary syndrome. Eight participants (2.3%) experienced a stroke and 4 (1.1%) had a TIA (including 1 patient with both) during the first 12 months after the procedure (data not shown).

ASSOCIATIONS BETWEEN BASELINE DEPRESSIVE SYMPTOMS AND NEUROCOGNITIVE OUTCOMES

Estimates of average change in cognitive domain scores from baseline to each of the follow-up visits (adjusted for baseline cognitive score, age, sex, and educational level) for patients with and without depressive symptoms at baseline are presented in **Figure 2** and **Table 3**. Both groups showed improvement (positive change from baseline) at 6 and 12 months across all cognitive domains. For 3 domains (attention/executive function, learning/memory, and global cognition), this change was followed by decline at 30 months (overall differences among visits, $P<.001$, $P<.001$, and $P=.04$, respectively). For verbal fluency, a decline at 30 months was observed only for those with depressive symptoms. Those with depressive symptoms at baseline showed a greater decline at 30 months in verbal fluency (depression group × visit interaction, $P=.08$) and global cognition ($P=.03$) but did not differ significantly from the group without symptoms on the 2 other domains.

ASSOCIATIONS BETWEEN DEPRESSIVE SYMPTOM CHANGE DURING YEAR 1 AND NEUROCOGNITIVE OUTCOMES

Estimates of average change in cognitive domain scores from baseline to each of the follow-up visits (adjusted for baseline cognitive score, age, sex, and educational level) for patients classified according to depressive symptom change are presented in **Figure 3** and **Table 4**.

For attention/executive function, patients with new-onset or persistent symptoms showed significantly poorer performance compared with those with no or baseline-only symptoms across all visits ($P=.006$). Scores differed significantly overall by visit ($P=.002$). For learning/memory, all 4 groups showed significant improvement for the first 12 months ($P=.005$). This improvement was maintained at 30 months for patients with baseline-only symptoms. For the other 3 groups, declines in learning/memory were observed at 30 months, and this decline was most significant for those with persistent symptoms ($P=.002$). For verbal fluency, those with no or baseline-only depressive symptoms showed improvement at each follow-up, whereas those with new-onset symptoms showed initial improvement followed by decline from 6 to 12 months. Patients with persistent symptoms showed both an initial (at 6 months) and later (at 30 months) decline in verbal fluency ($P=.04$ for the overall difference between groups and $P=.08$ for the group × visit interaction). For global cognition, patients with new-onset symptoms showed a slight decline at 6 months, and those with persistent symptoms showed a significant decline from baseline at 30 months ($P=.009$). Those with no or baseline-only depressive symptoms showed little change over time in global cognition.

Table 1. Baseline Characteristics of Patients in the 3C Study by Presence or Absence of Depressive Symptoms Assessed at Baseline Only[a]

Characteristic	Total Sample (N = 350)	Baseline Depressive Symptoms		*P* Value[b]
		Absent (n = 276)	Present (n = 74)	
Age, mean (SD), y	71.3 (5.9)	71.2 (5.9)	71.4 (5.6)	.83
Male sex	258 (73.7)	204 (73.9)	54 (73.0)	.87
Educational level, mean (SD), y	12.8 (3.8)	13.0 (3.9)	11.9 (3.6)	.02
Lives alone	55 (15.7)	40 (14.5)	15 (20.3)	.23
Current or past smoker	249 (71.1)	196 (71.0)	53 (71.6)	.92
Heavy drinker	68 (19.4)	52 (18.8)	16 (21.6)	.59
Treatment group				
CABG	121 (34.6)	90 (32.6)	31 (41.9)	.33
PCI	143 (40.9)	116 (42.0)	27 (36.5)	
MT	86 (24.6)	70 (25.4)	16 (21.6)	
Clinical characteristics[c]				
Admitted with stable angina (vs MI, unstable angina, and other)	227 (65.4)	184 (67.2)	43 (58.9)	.17
Ejection fraction <50%	77 (22.2)	59 (21.5)	18 (24.7)	.57
High-risk coronary anatomy[d]	160 (46.4)	121 (44.3)	39 (54.2)	.05
CCS angina class >II	167 (48.1)	122 (44.5)	45 (61.6)	.01
Acute coronary syndrome	89 (25.6)	64 (23.4)	25 (34.2)	.06
Medical history[c]				
Cerebrovascular disease	34 (9.8)	22 (8.0)	12 (16.4)	.03
Congestive heart failure	33 (9.5)	27 (9.9)	6 (8.2)	.67
Peripheral vascular disease[e]	31 (8.9)	22 (8.1)	9 (12.2)	.46
Type 1 or 2 diabetes mellitus	83 (23.9)	57 (20.8)	26 (35.6)	.01
Hypertension	268 (77.2)	208 (75.9)	60 (82.2)	.26
Hyperlipidemia	290 (83.6)	232 (84.7)	58 (79.5)	.28
Pulmonary disease	76 (21.9)	56 (20.4)	20 (27.4)	.20
Renal disease	10 (2.9)	6 (2.2)	4 (5.5)	.14
Malignant neoplasm	18 (5.2)	14 (5.1)	4 (5.5)	.90
Severe/debilitating liver disease	2 (0.6)	1 (0.4)	1 (1.4)	.31
Severe/debilitating gastrointestinal tract disease	26 (7.5)	16 (5.8)	10 (13.7)	.03
Additional clinical information				
APOE ε4 allele present[f]	90 (26.3)	74 (27.5)	16 (21.9)	.34
Previous stroke	20 (5.7)	13 (4.7)	7 (9.5)	.12
Previous TIA	26 (7.4)	21 (7.6)	5 (6.8)	.80
Previous stroke and/or TIA	43 (12.3)	32 (11.6)	11 (14.9)	.45
Self-rated health fair/poor[g]	80 (22.9)	41 (14.9)	39 (52.7)	<.001
Anxiety level (STAI score), mean (SD)[h]	34.4 (10.3)	32.9 (9.8)	39.6 (10.5)	<.001

Abbreviations: *APOE*, apolipoprotein E; 3C, Calgary Cardiac and Cognition; CABG, coronary artery bypass graft; CCS; Canadian Cardiovascular Society; MI, myocardial infarction; MT, medical therapy; PCI, percutaneous coronary intervention; STAI, State-Trait Anxiety Inventory; TIA, transient ischemic attack.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] Calculated using the unpaired, 2-tailed *t* test with pooled variance for continuous variables and χ^2 test for categorical variables.

[c] Includes Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) variables collected at the time of catheterization (274 patients in the group with no depressive symptoms and 73 in the group with depressive symptoms) unless otherwise noted.

[d] Includes 273 patients in the group with no depressive symptoms and 72 in the group with depressive symptoms.

[e] Includes 273 patients in the group with no depressive symptoms and 74 in the group with depressive symptoms.

[f] Includes 269 patients in the group with no depressive symptoms and 73 in the group with depressive symptoms.

[g] Includes 275 patients in the group with no depressive symptoms and 74 in the group with depressive symptoms.

[h] Includes 274 patients in the group with no depressive symptoms and 74 in the group with depressive symptoms.

DEPRESSIVE SYMPTOM CHANGE OVER 12 MONTHS AS A PREDICTOR OF SUBSEQUENT NEUROCOGNITIVE DECLINE

Across all cognitive domains, patients with persistent symptoms generally showed greater average declines from 12 to 30 months relative to the other 3 depression groups (**Table 5**). For global cognition, there was statistical evidence of an interaction between persistent depressive symptoms and *APOE* genotype ($P = .03$), with significantly greater decline observed among those with persistent symptoms and the *APOE* ε4 allele. Although not statistically significant, a similar pattern emerged for verbal fluency. For learning/memory and attention/executive function, the decline associated with persistent symptoms varied less by patients' *APOE* ε4 status. For learning/memory, those with no depressive symptoms showed a significant decline, whereas those with baseline-only symptoms showed improvement (in the absence of *APOE* ε4) from 12 to 30 months.

The pattern of significant declines noted for participants with persistent symptoms remained after adjusting for sociodemographic and clinical covariates, including baseline cognitive score and change in score from baseline to 6 months, age, sex, educational level, current/past smoking, anxiety, treatment group (CABG, PCI, and

Table 2. Baseline and Follow-up GDS Characteristics of Patients in the 3C Study by Depressive Symptom Change During 1 Year[a]

Characteristic	Depressive Symptom Category				*P* Value[b]
	None (n = 248)	Baseline Only (n = 32)	New Onset (n = 28)	Persistent (n = 42)	
Age, mean (SD), y	70.1 (5.8)	71.0 (6.1)	74.3 (6.5)	71.7 (5.3)	.03
Age >75 y	57 (23.0)	7 (21.9)	9 (32.1)	12 (28.6)	.11
Male sex	186 (75.0)	23 (71.9)	18 (64.3)	31 (73.8)	.67
Educational level, mean (SD), y	13.2 (3.8)	11.5 (2.7)	11.4 (4.3)	12.2 (4.2)	.01
Lives alone	31 (12.5)	8 (25.0)	9 (32.1)	7 (16.7)	.02
Current or past smoker	176 (71.0)	23 (71.9)	20 (71.4)	30 (71.4)	>.99
Heavy drinker	48 (19.4)	8 (25.0)	4 (14.3)	8 (19.0)	.77
Treatment group					
CABG	80 (32.3)	13 (40.6)	10 (35.7)	18 (42.9)	.66
PCI	107 (43.1)	13 (40.6)	9 (32.1)	14 (33.3)	
MT	61 (24.6)	6 (18.8)	9 (32.1)	10 (23.8)	
Clinical characteristics[c]					
Admitted with stable angina (vs MI, unstable angina, and other)	168 (68.3)	19 (61.3)	16 (57.1)	24 (57.1)	.37
Ejection fraction <50%	53 (21.5)	9 (29.0)	6 (21.4)	9 (21.4)	.82
High-risk coronary anatomy[d]	105 (42.7)	19 (61.3)	16 (59.3)	20 (48.8)	.17
CCS angina class >II	104 (42.3)	19 (61.3)	18 (64.3)	26 (61.9)	.01
Acute coronary syndrome	53 (21.5)	9 (29.0)	11 (39.3)	16 (38.1)	.04
Medical history[c]					
Cerebrovascular disease	20 (8.1)	4 (12.9)	2 (7.1)	8 (19.0)	.14
Congestive heart failure	22 (8.9)	3 (9.7)	5 (17.9)	3 (7.1)	.45
Peripheral vascular disease[e]	21 (8.6)	2 (6.3)	1 (3.6)	7 (16.7)	.57
Type 1 or 2 diabetes mellitus	52 (21.1)	11 (35.5)	4 (14.3)	15 (35.7)	.05
Hypertension	185 (75.2)	27 (87.1)	23 (82.1)	33 (78.6)	.44
Hyperlipidemia	207 (84.1)	24 (77.4)	25 (89.3)	34 (81.0)	.62
Pulmonary disease	48 (19.5)	7 (22.6)	8 (28.6)	13 (31.0)	.31
Renal disease	5 (2.0)	2 (6.5)	1 (3.6)	2 (4.8)	.45
Malignant neoplasm	12 (4.9)	1 (3.2)	2 (7.1)	3 (7.1)	.84
Severe/debilitating liver disease	1 (0.4)	1 (3.2)	0	0	.23
Severe/debilitating gastrointestinal tract disease	14 (5.7)	3 (9.7)	2 (7.1)	7 (16.7)	.09
Additional clinical information					
APOE ε4 allele present[f]	67 (27.6)	9 (29.0)	7 (26.9)	7 (16.7)	.51
Previous stroke	9 (3.6)	3 (9.4)	4 (14.3)	4 (9.5)	.05
Previous TIA	20 (8.1)	1 (3.1)	1 (3.6)	4 (9.5)	.60
Previous stroke and/or TIA	27 (10.9)	4 (12.5)	5 (17.9)	7 (16.7)	.57
Self-rated health fair/poor[g]	34 (13.8)	16 (50.0)	7 (25.0)	23 (54.8)	<.001
Anxiety level (STAI score), mean (SD)[h]	32.7 (9.7)	35.1 (9.2)	35.2 (10.2)	43.1 (10.2)	<.001
Baseline and follow-up GDS score					
Baseline GDS score, mean (SD)	1.76 (1.28)	6.22 (1.64)	2.39 (1.37)	7.60 (2.67)	<.001
30-mo GDS score, mean (SD)	1.20 (1.46)	3.11 (2.25)	3.41 (2.89)	7.70 (3.70)	<.001

Abbreviations: See Table 1. GDS, Geriatric Depression Scale.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] Calculated using the *F* test for continuous variables and χ^2 test for categorical variables.

[c] Includes Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) variables collected at the time of catheterization (246 patients in the group with no depressive symptoms and 31 in the group with symptoms at baseline only unless otherwise noted).

[d] Includes 27 patients in the new-onset group and 41 in the group with persistent depression.

[e] Includes 245 patients in the group with no depressive symptoms.

[f] Includes 243 patients in the group with no depressive symptoms, 31 in the baseline-only group, and 26 in the new-onset group.

[g] Includes 247 patients in the group with no depressive symptoms.

[h] Includes 246 patients in the group with no depressive symptoms.

MT), history of stroke and/or TIA, interim stroke and/or TIA, and all other disease and medical characteristics assessed at the time of catheterization. Treatment group was not a significant predictor of cognitive change scores for any of the domains examined.

COMMENT

This study is one of the first to explore the association between changes in depressive symptoms over time and long-term neurocognitive decline among older patients with CAD who are undergoing CABG, PCI, or MT. Relative to a baseline-only assessment, a dynamic measure capturing the persistence of depressive symptoms during the first year after the procedure better differentiated risk of decline across several cognitive domains during the 30-month study.

At baseline, average cognitive domain scores were consistently lower among patients who were subsequently identified as having persistent depressive symptoms relative to other symptom groups. In longitudinal models adjusted for age, sex, educational level, and baseline cog-

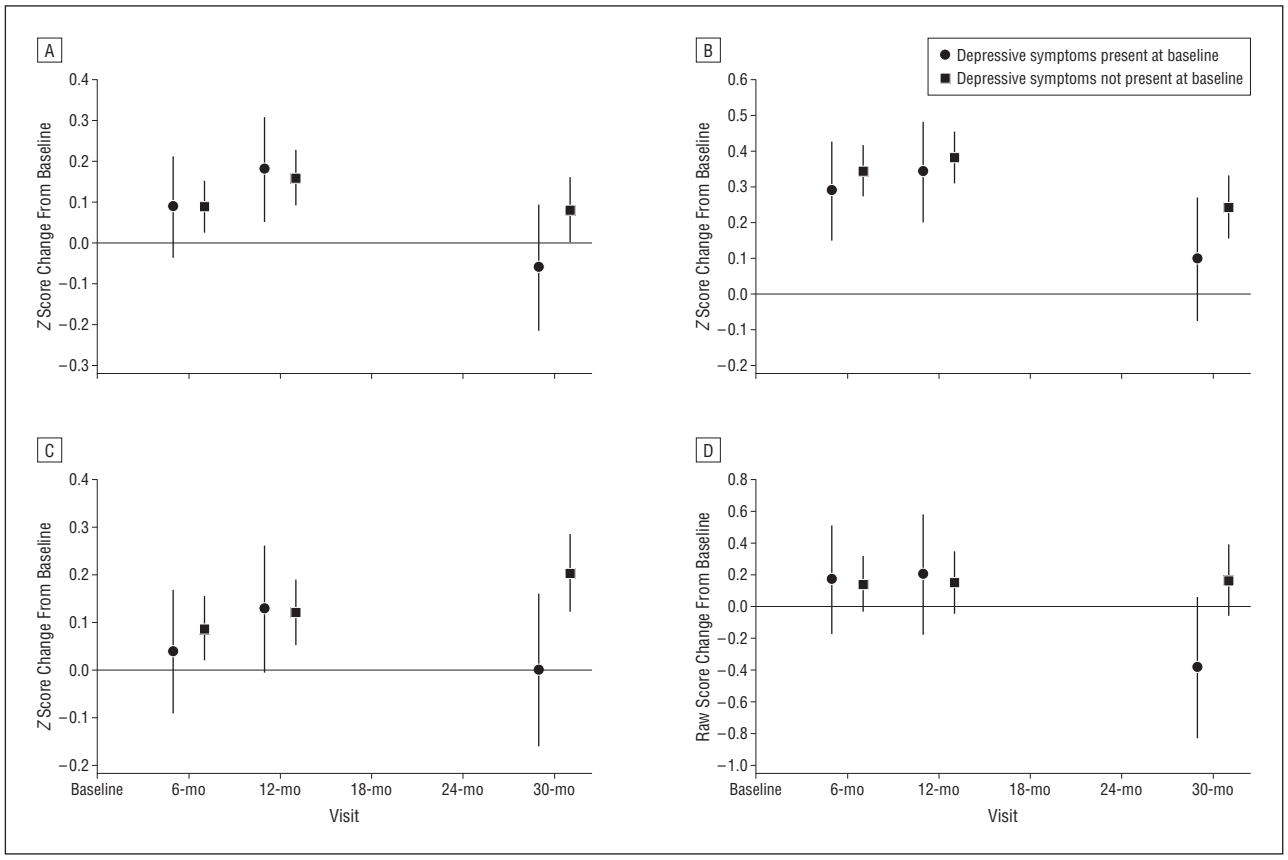

Figure 2. Least-squares mean change (95% CI) in cognitive measures from baseline at each follow-up visit by presence or absence of baseline depressive symptoms. Changes for attention/executive function (A), learning/memory (B), and verbal fluency (C) are expressed as *z* scores; for global cognition (D), changes are expressed as raw scores. Changes are adjusted for baseline cognitive score, age, sex, and educational level.

Table 3. Least-Squares Mean Change in Cognitive Measures From Baseline at Each Follow-up Visit by the Presence or Absence of Baseline Depressive Symptoms[a]

	Baseline Score, Mean (SE)	Least Squares Change, Mean (SE)			*P* Value		
		6 mo[b]	12 mo[c]	30 mo[d]	Between Groups	Among Visits	Group × Visit Interaction
Attention/executive function							
Depressive symptoms	–0.45 (0.10)	0.09 (0.06)	0.18 (0.06)	–0.06 (0.08)	.52	<.001	.14
No depressive symptoms	–0.30 (0.05)	0.09 (0.03)	0.16 (0.03)	0.08 (0.04)			
Learning/memory							
Depressive symptoms	–0.75 (0.11)	0.29 (0.07)	0.34 (0.07)	0.10 (0.09)	.25	<.001	.52
No depressive symptoms	–0.42 (0.05)	0.34 (0.04)	0.38 (0.04)	0.24 (0.05)			
Verbal fluency							
Depressive symptoms	–0.76 (0.09)	0.04 (0.06)	0.13 (0.07)	0.00 (0.08)	.20	.23	.08
No depressive symptoms	–0.47 (0.05)	0.09 (0.03)	0.12 (0.03)	0.20 (0.04)			
Global cognition (MMSE)							
Depressive symptoms	27.6 (0.26)	0.17 (0.17)	0.20 (0.19)	–0.38 (0.23)	.38	.04	.03
No depressive symptoms	28.3 (0.09)	0.14 (0.09)	0.15 (0.10)	0.17 (0.11)			

Abbreviation: MMSE, Mini-Mental State Examination.
[a] Data are expressed as changes in raw scores for global cognition (MMSE) and as *z* scores for all others, adjusted for baseline cognitive score, age, sex, and educational level.
[b] Includes 73 patients with and 271 without depressive symptoms.
[c] Includes 74 patients with and 267 without depressive symptoms.
[d] Includes 65 patients with and 253 without depressive symptoms.

nitive performance, those with persistent symptoms exhibited significantly greater decline at 30 months (relative to baseline) in attention/executive function, learning/memory, verbal fluency, and global cognition compared with those with no or baseline-only depressive symptoms. The presence of persistent symptoms within the first year was also a significant risk factor for subsequent decline (from 12 to 30 months) across all 4 cog-

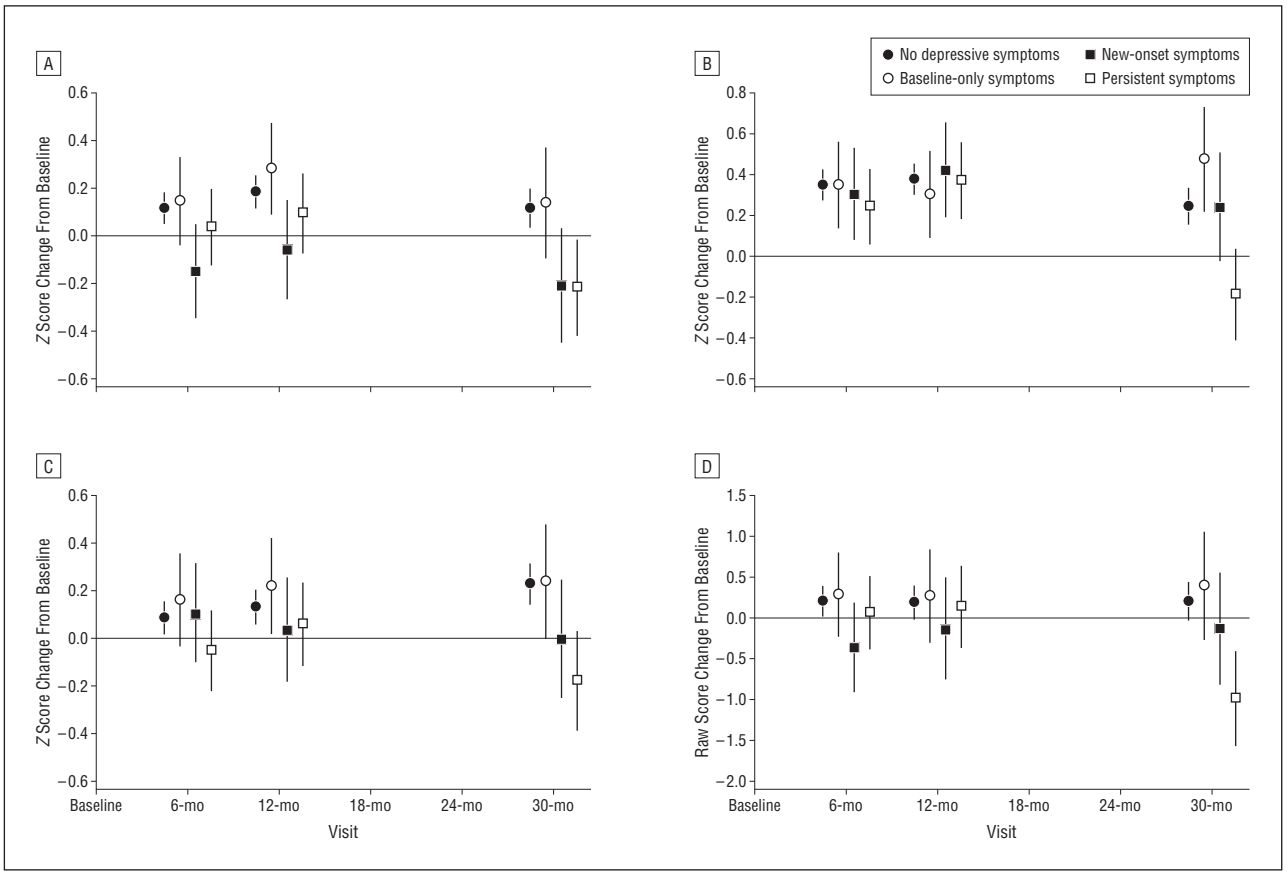

Figure 3. Least-squares mean change (95% CI) in cognitive measures from baseline at each follow-up visit by changes in depressive symptoms during 1 year. Changes for attention/executive function (A), learning/memory (B), and verbal fluency (C) are expressed as z scores; for global cognition (D), changes are expressed as raw scores. Changes are adjusted for baseline cognitive score, age, sex, and educational level.

nitive measures. These associations were essentially unchanged in fully adjusted models. For global cognition (and to a lesser extent, verbal fluency), the magnitude of this decline was greater for those with the *APOE* ε4 allele.

Patients with new-onset depressive symptoms showed significant decline from baseline in attention/executive function (at multiple follow-up visits) but exhibited a less consistent pattern of decline in verbal fluency and global cognition. Participants exhibiting no or baseline-only depressive symptoms generally showed little change (or some improvement) over time in adjusted average difference scores for all cognitive domains. One exception was the significantly greater decline in learning/memory observed from 12 to 30 months for participants without depressive symptoms, suggesting an overall vulnerability of our cohort to memory decline, possibly influenced by other factors, including the *APOE* ε4 allele.[16]

Our findings are consistent with other observational studies of older adults.[8-15] The growing literature highlights the risks posed by persistent depressive symptoms in relation to cognitive and functional decline.[16,17,48] Memory[16,17] and aspects of executive function[49,50] may be especially vulnerable to the effects of depressive symptoms, although the extent and nature of the associations remain to be elucidated. The vulnerability for executive dysfunction may place some of these patients at further risk for functional disability[48] and poor antidepressant treatment response, early relapse, and recurrence of depression.[51]

Variation in findings across studies may reflect differences in the measures used to assess depression and neurocognitive deficits, the study design and sample characteristics, analytical approach, and length of follow-up. Our findings illustrate the potential for masking important changes in cognitive function among patients with depression when analyses are restricted to a baseline assessment of symptoms, a single cognitive domain, and/or a relatively short follow-up period. The findings observed for persistent symptoms may reflect the fact that this group captured patients with a "true" or more severe depressive disorder as opposed to those with brief or transient circumstantial symptoms.[12,48] Significant declines in the cognitive domains were generally observed only at 30 months and not within the first year after the procedure. In fact, improvement during the first year was evident for participants without depressive symptoms and with baseline-only symptoms in attention/executive function, learning/memory, and verbal fluency. This improvement (and subsequent decline) parallels findings reported in other long-term investigations of patients undergoing coronary interventions. Selnes et al[7] showed improved cognitive function among patients undergoing CABG and those in the control groups (MT and PCI) from baseline to 12 months but a slight decline in pa-

Table 4. Least-Squares Mean Change in Cognitive Measures From Baseline at Each Follow-up Visit by Depressive Symptom Change During 1 Year[a]

	Baseline Score, Mean (SE)	Least-Squares Change, Mean (SE)			*P* Value		
		6 mo[b]	12 mo[c]	30 mo[d]	Between Groups	Among Visits	Group × Visit Interaction
Attention/executive function							
No depressive symptoms	−0.24 (0.05)	0.12 (0.03)	0.18 (0.04)	0.12 (0.04)	.006	.002	.31
Baseline-only symptoms	−0.19 (0.11)	0.15 (0.09)	0.28 (0.10)	0.14 (0.12)			
New-onset symptoms	−0.33 (0.16)	−0.15 (0.10)	−0.06 (0.11)	−0.21 (0.12)			
Persistent symptoms	−0.70 (0.15)	0.04 (0.08)	0.09 (0.09)	−0.22 (0.10)			
Learning/memory							
No depressive symptoms	−0.34 (0.06)	0.35 (0.04)	0.38 (0.04)	0.24 (0.05)	.19	.005	.002
Baseline-only symptoms	−0.57 (0.15)	0.35 (0.11)	0.30 (0.11)	0.47 (0.13)			
New-onset symptoms	−0.76 (0.18)	0.31 (0.11)	0.42 (0.12)	0.24 (0.14)			
Persistent symptoms	−0.91 (0.16)	0.24 (0.09)	0.37 (0.10)	−0.19 (0.11)			
Verbal fluency							
No depressive symptoms	−0.47 (0.05)	0.09 (0.04)	0.13 (0.04)	0.23 (0.04)	.04	.63	.08
Baseline-only symptoms	−0.71 (0.13)	0.16 (0.10)	0.22 (0.11)	0.24 (0.12)			
New-onset symptoms	−0.33 (0.16)	0.11 (0.11)	0.04 (0.11)	0.00 (0.13)			
Persistent symptoms	−0.82 (0.12)	−0.05 (0.09)	0.06 (0.09)	−0.18 (0.11)			
Global cognition (MMSE)							
No depressive symptoms	28.5 (0.08)	0.20 (0.09)	0.18 (0.11)	0.20 (0.12)	.10	.22	.009
Baseline-only symptoms	27.8 (0.35)	0.29 (0.26)	0.27 (0.29)	0.39 (0.34)			
New-onset symptoms	27.6 (0.43)	−0.36 (0.28)	−0.13 (0.32)	−0.13 (0.35)			
Persistent symptoms	27.2 (0.40)	0.06 (0.22)	0.13 (0.26)	−0.99 (0.29)			

Abbreviation: MMSE, Mini-Mental State Examination.
[a] Data are expressed as changes in raw scores for global cognition (MMSE) and as *z* scores for all others, adjusted for baseline cognitive score, age, sex, and educational level.
[b] Includes 243 patients with no depressive symptoms, 31 with baseline-only symptoms, 28 with new-onset symptoms, and 42 with persistent symptoms.
[c] Includes 240 patients with no depressive symptoms, 32 with baseline-only symptoms, 27 with new-onset symptoms, and 42 with persistent symptoms.
[d] Includes 226 patients with no depressive symptoms, 28 with baseline-only symptoms, 27 with new-onset symptoms, and 37 with persistent symptoms.

tients' performance during the subsequent 4 years. They reported no statistically significant difference in the rate of cognitive decline or in the incidence of clinically significant impairment between treatment groups. Similarly, we found that treatment group was not a significant predictor of cognitive decline. The improvement in cognitive performance during the first year after the procedure may reflect a positive response to treatment and/or learning effects associated with repeated testing. However, we observed initial improvement in cognitive performance even for those domains (eg, learning/memory) for which alternative test versions were used at later examinations.

POSSIBLE EXPLANATIONS FOR OBSERVED ASSOCIATIONS

Various explanations have been proposed for the association between depression and cognition.[20,21] The debate concerning whether depression is a cause or a consequence of cognitive decline has been clouded by inconsistent findings[18,19] and complicated by the potential for multidirectional relationships among depression, cognition, and underlying vascular disease.[9,20,21] For some of our findings (eg, the early declines observed for patients with new-onset depressive symptoms), it is difficult to determine the direction of association given that both variables were assessed concurrently. However, the long-term decline (≤30 months) in cognitive performance associated with the new-onset (eg, in attention/executive function) and persistent depression groups (all domains) and the consistent finding of a strong independent association between persistent depressive symptoms (assessed during the first year) and decline from 12 to 30 months suggest that persistently elevated (and possibly new-onset) depressive symptoms among patients with CAD may have prognostic importance. Evidence from longitudinal investigations[13-17,52] suggests that persistent (or major) depression is likely a risk factor for cognitive decline rather than a reaction to or an early manifestation of a cognitive disorder.

Although the biological mechanisms underlying this association are likely complex and remain poorly understood,[13,20,21] several plausible pathways are being investigated. Early work emphasized the role of vascular disease and associated risk factors (eg, hypertension and diabetes mellitus) as possible common underlying causes of depression and cognitive impairment (ie, the vascular depression hypothesis).[53] However, in several studies,[9,17] including ours, depressive symptoms remained strongly predictive of cognitive decline after adjustment for cardiovascular disease and vascular risk factors. Other possible pathways include (hyper)activation of the hypothalamic-pituitary-adrenal axis with subsequent glucocorticoid-related atrophy of the hippocampus,[14,15] chronic low-level activation of inflammatory mediators and processes, and an increased susceptibility to or shared causal pathways with genetic risk factors including the *APOE* ε4 genotype.[22] Although not consistently reported by others,[16,22-24] our finding of a significant inter-

Table 5. Adjusted Mean Difference in Cognitive Scores (Month 30 Minus Month 12) by Depressive Symptom Change During 1 Year and *APOE* ε4 Status

Cognition Measure[a]	Adjusted Mean Difference (95% CI)[b]	
	APOE ε4 Absent	*APOE* ε4 Present
Attention/executive function		
No depressive symptoms	−0.08 (−0.18 to 0.02)	−0.03 (−0.19 to 0.13)
Baseline-only symptoms	0.04 (−0.24 to 0.32)	−0.37 (−0.83 to 0.09)
New-onset symptoms	−0.11 (−0.41 to 0.18)	0.06 (−0.43 to 0.55)
Persistent symptoms	−0.29 (−0.53 to −0.05)[c]	−0.50 (−1.01 to −0.002)[c]
Learning/memory		
No depressive symptoms	−0.13 (−0.23 to −0.03)[c]	−0.20 (−0.37 to −0.04)[c]
Baseline-only symptoms	0.25 (−0.05 to 0.55)[d]	0.03 (−0.45 to 0.52)
New-onset symptoms	−0.06 (−0.37 to 0.25)	−0.41 (−0.92 to 0.10)
Persistent symptoms	−0.55 (−0.80 to −0.30)[c]	−0.44 (−0.96 to 0.08)[d]
Verbal fluency		
No depressive symptoms	0.07 (−0.04 to 0.18)	0.03 (−0.15 to 0.20)
Baseline-only symptoms	0.10 (−0.22 to 0.42)	−0.08 (−0.61 to 0.44)
New-onset symptoms	0.08 (−0.26 to 0.41)	0.06 (−0.50 to 0.62)
Persistent symptoms	−0.19 (−0.46 to 0.08)	−0.62 (−1.19 to −0.05)[c]
Global cognition (MMSE)[b]		
No depressive symptoms	−0.09 (−0.38 to 0.20)	−0.05 (−0.51 to 0.41)
Baseline-only symptoms	−0.27 (−1.10 to 0.57)	0.61 (−0.75 to 1.96)
New-onset symptoms	0.10 (−0.80 to 0.99)	0.27 (−1.17 to 1.71)
Persistent symptoms[e]	−0.55 (−1.25 to 0.16)	−2.93 (−4.40 to −1.45)[c]

Abbreviations: *APOE*, apolipoprotein E; MMSE, Mini-Mental State Examination.

[a] Data are expressed in raw scores (MMSE) and as average *z* scores for all other tests.

[b] Adjusted for baseline cognitive score (and change from baseline to 6 months), age, sex, educational level, smoking status, baseline anxiety, treatment plan, presence of a baseline ejection fraction of less than 50%, high-risk coronary anatomy, acute coronary syndrome, peripheral vascular disease, congestive heart failure, diabetes mellitus, hypertension, cardiopulmonary disease, stroke or transient ischemic attack (TIA) before baseline, and stroke or TIA from baseline to 12 months.

[c] $P < .05$.

[d] $P < .10$.

[e] For persistent depressive symptom × *APOE* ε4 interaction, $P < .05$.

action between the *APOE* ε4 allele and persistent depressive symptoms in relation to decline in global cognition (and possibly verbal fluency) suggests an area for future investigation. The findings presented for the *APOE* ε4 genotype should be interpreted as exploratory and hypothesis generating given the small cell sizes and multiple comparisons. Unfortunately, the lack of neuroimaging and physiological measures in the present study prevents us from speculating further about underlying mechanisms.

STUDY STRENGTHS AND LIMITATIONS

A particular strength of our study is the relatively large sample of older patients with CAD, including those undergoing CABG, PCI, and MT, followed up for a 30-month period with few participants lost to follow-up. In addition to incorporating detailed neurocognitive testing of multiple domains at baseline (before the procedure) and at several follow-up intervals, we examined an extensive list of sociodemographic and clinical covariates (including genetic factors) allowing for a greater opportunity to explore possible effect modification and confounding. Because the Geriatric Depression Scale primarily captures cognitive-affective symptoms rather than somatic ones, it offered a reliable and valid measure of depressive symptoms among our older sample.[38]

At the same time, our interpretations are limited by the observational nature of our study, absence of a clinical diagnosis of depressive disorders, and lack of information on antidepressant use at baseline. Generally, others have not found antidepressant use to be a relevant confounding or effect-modifying variable,[9,10] although this requires further investigation. Our findings illustrate the importance of uncontrolled depressive symptoms (with or without therapy). In addition to the absence of specific diagnostic data, our ability to capture changes in depressive symptoms was limited by our assessment times and the sensitivity of the Geriatric Depression Scale. Without information on history and the date of the first episode of depressive symptoms, we are also unable to comment on the relevance of recurrent depressive episodes. The clinical significance of the lower average cognitive domain scores observed for participants with persistent depression remains unclear. The magnitude of difference in MMSE scores during the 30 months for those with persistent compared with no depressive symptoms (approximately 2-3 points) would generally be viewed as clinically meaningful. We included the MMSE because it is a commonly used measure of global cognition. However, we acknowledge that it provides a poor measure of domains likely to be vulnerable to the effects of depressive symptoms.

The generalizability of our study findings to other patient populations and possibly to the larger CAD population is limited. All our patients underwent catheterization. The eTable compares the baseline characteristics of our study sample with those of the 6594 patients under-

going coronary catheterization at our center who fulfilled eligibility criteria (ie, age ≥60 years and no prior PCI or CABG procedure) during the recruitment period. A higher proportion of patients undergoing CABG and PCI (compared with overall population distributions) and those with stable angina at the time of the baseline assessment were purposefully enrolled, which explains many of the differences observed.

CLINICAL AND TREATMENT IMPLICATIONS

We found that older patients with CAD who had persistent depressive symptoms experienced significantly greater declines in cognitive performance during the 30 months than those with baseline-only or no symptoms during follow-up. Consequently, a 1-time assessment of depressive symptoms may be inadequate for detecting those at risk of longer-term adverse cognitive and functional outcomes.[48] These findings illustrate the need for longer-term monitoring of depressive symptom severity and change by clinicians and other caregivers.

Research directed at elucidating the temporal associations among depressive symptoms, vascular risk factors, cognitive (and functional) impairment, and relevant underlying mechanisms will inform the search for possible treatment opportunities. Two recent randomized trials have shown that treating depression after CABG procedures may improve aspects of health-related quality of life, physical functioning, and mood at 8 to 9 months after the procedure.[54,55] Such findings suggest that depressive symptoms may be one of the more prevalent and potentially amenable factors involved in the pathway leading to cognitive decline and limited functional recovery of older patients with CAD who undergo coronary interventions.

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