Published in final edited form as:

Int J Geriatr Psychiatry. 2023 September ; 38(9): e6000. doi:10.1002/gps.6000.

Functional, Cognitive, and Cerebrovascular Aspects of Depression before Coronary Artery Bypass Graft Surgery: Testing the Vascular Depression Hypothesis

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Abstract

Objective: Depression in patients undergoing coronary artery graft bypass (CABG) surgery is associated with morbidity and mortality, making its early identification and clinical management crucial. Vasculopathy and older age, hallmarks of patients requiring CABG, are also features of vascular depression. In this study, we assess for features of vascular depression in patients undergoing CABG surgery.

Methods: This is a cross-sectional analysis of a single-site prospective observational cohort study of patients undergoing CABG surgery. Subjects were assessed preoperatively using the Depression Interview and Structured Hamilton (DISH), depression scales, transcranial Doppler, neuropsychological testing, and Clinical Dementia Rating (CDR).

Results: Of 161 subjects (mean age 66.2 ± 9.3, female 25%) who completed DISH, 18 had major or minor depression, 17 of whom had a past history of major or minor depression (mean age of onset 35.8 years-old). Pre-CABG depression was associated with greater functional impairment on CDR Sum of Boxes (*OR* = 3.7, 95% CI: 1.4, 9.7) and worse performance on letter fluency test (OR = 0.90, 95% CI: 0.81, 0.99) and trail-making tests (A: OR = 1.06, 95% CI: 1.01, 1.12; B: OR 1.02, 95% CI: 1.01, 1.04). Pre-CABG depression was not associated with middle cerebral artery stenosis.

Conclusions: Pre-CABG depression is associated with cognitive and functional impairment similar to vascular depression, but we did not find evidence of an association with older age of onset and middle cerebral artery stenosis. Further studies on white matter disease in this population is needed to examine the vascular depression hypothesis for pre-CABG depression.

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Disclosure: The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Conflict of interest: The authors report no relevant conflicts of interest.

Ethics approval statement: The study was approved by the Yale University Human Investigation Committee and registered with the National Institutes of Health (study identifier: NCT01838356).

Keywords

vascular depression; cognitive impairment; functional status; cardiovascular disease; cerebrovascular disease; CABG surgery

Introduction

Performed almost 400,000 times annually, coronary artery bypass graft (CABG) surgery is one of the most common major operations in the United States.[1] According to a 2020 systematic review and meta-analysis, an estimated 19–37% of patients undergoing CABG had depression as measured by validated scales.[2] This is two to four times greater than the 8.5% estimated 1-year prevalence of depression in U.S adults from 2017 to 2018.[3] Furthermore, pre-CABG depression is associated with increased risk of all-cause mortality,[4,5] adverse cardiac events, readmission, persistent surgical pain, and impaired physical recovery.[6,7] Better recognition and targeted intervention for pre-CABG depression could lead to reduced morbidity and mortality among CABG patients, but lack of knowledge about the etiogenesis and symptom profile of pre-CABG depression remains a barrier to developing effective strategies.

The advanced age and high prevalence of cerebrovascular risk factors among patients undergoing CABG suggests a potential overlap in etiopathogenesis between pre-CABG depression and vascular depression, which is defined as late-life depression attributed to the effects of cerebrovascular disease.[8] The vascular depression hypothesis posits that "cerebrovascular disease may predispose, precipitate or perpetuate some geriatric depressive syndrome."[8] Clinically defined vascular depression is associated with greater cognitive impairment and functional disability than non-vascular depression. Whereas the mechanism by which vascular depression develops is not clearly understood, it is postulated that strategic lesions or an accumulation of lesions in neural pathways critical to mood regulation results in depression.

Despite these indirect reasons suggesting that pre-CABG depression may be explained, at least in part, by cerebrovascular disease, direct evidence of this relationship is lacking. This study aims to characterize pre-CABG depression directly in relation to the vascular depression hypothesis. We predicted that cerebrovascular disease, measured by the degree of cerebral artery stenosis on transcranial Doppler (TCD), is positively correlated with the presence of clinical depression in pre-CABG depression. Also, consistent with the proposed diagnostic criteria for vascular depression by Steffens and Krishnan,[9] we also hypothesized that late age of onset (after age 50), lack of family history of mood disorders, and depressive symptoms that include anhedonia and psychomotor retardation along with cognitive and functional impairment would be more common among those with depression. Here, we present a cross-sectional analysis of pre-CABG neuropsychiatric profiles and cerebrovascular disease burden among the participants of the Neuropsychiatric Outcomes After Heart Surgery (NOAHS) study.[10].

Methods

Study design

We conducted an analysis of pre-CABG data from the NOAHS study, a prospective observational cohort study of patients undergoing CABG surgery at Yale-New Haven Hospital in New Haven, Connecticut. Eligible subjects were adults 40 years old or older, English-speaking and with a reliable collateral source (e.g. family or friend). Exclusion criteria were prior CABG surgery, history of dementia or cognitive impairment, auditory or visual impairment that would interfere with study procedures, active alcohol or substance abuse (i.e. CAGE-AID ≥ 2), severe mental illness, and life expectancy less than 1 year. The study was approved by the Yale University Human Investigation Committee and registered on ClinicalTrials.gov (NCT01838356).

Pre-CABG Assessments

Baseline demographics were obtained, and Charlson comorbidity index was calculated for each subject. A trained clinician administered the Depression Interview and Structured Hamilton (DISH) assessment.[11] Based on the results of DISH, subjects were determined to have major, minor, or no depression as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV*).[12] Two additional depression scales were administered: Patient Health Questionnaire (PHQ-9) and Geriatric Depression Scale (GDS).

Cerebrovascular disease was assessed by measuring the degree of middle cerebral artery (MCA) stenosis per TCD, a tool which has been validated for detection of intracranial atherosclerosis against the gold standard method, catheter angiography.[13] While TCD does not directly measure white matter disease burden, TCD measurements have been shown to be associated with depression,[14] and TCD is non-invasive and less burdensome than the traditional angiography to patients who are sick and in urgent need of CABG surgery. Using a validated scoring system,[15] each subject was identified as having ≥ 50% or < 50% stenosis in right, left, bilateral, or either middle cerebral artery (MCA). For subjects whose TCD could not be completed before surgery, TCD was completed within 2 days of surgery. No subjects had neurologic exam consistent with new-onset MCA occlusion or stroke at the time of TCD.

Functional assessment included Clinical Dementia Rating (CDR), a semi-structured interview conducted by trained clinicians.[16] CDR global score ≥ 1 indicates presence of dementia and excluded potential study subjects from enrollment. Higher CDR Sum of Boxes (SB) score indicates greater severity of cognitive and functional impairment. Additional assessment included the Lawton instrumental activities of daily living (IADL) scale. Medical outcomes study (MOS) Social Support Survey was administered to assess the degree of social support.[17]

Neuropsychological battery included the following tests: Wechsler Memory Scale (WMS) - Visual Reproduction, Hopkins Verbal Learning Test (HVLT), Wechsler Adult Intelligence Scale (WAIS)-IV Digit Symbol Coding, WAIS-IV Digit Span Sequencing, Wide Range

Achievement Test (WRAT) Word Reading, Letter Fluency Test, Trail Making Test (TMT) Part A and B, and Neuropsychological Assessment Battery (NAB) Mazes.

Statistical Analysis

The study sample was stratified by presence or absence of pre-CABG depression. Subjects with minor or major depression based on DISH assessment comprised the study group. Baseline sociodemographic variables and cardiovascular risk factors were compared between the depressed group and non-depressed group using independent *t*-tests and Mann Whitney *U* tests, depending on distributions for continuous variables, and chi-square and Fisher's exact tests for categorical variables. Logistic regression was used to examine the association of risk factors on depression, controlling for sociodemographic variables (age, gender, years of education). Data was analyzed using SPSS Statistics version 28.0 (IBM; Armonk, NY). By convention, alpha was set at 0.05.

Results

Baseline characteristics

Of those who completed DISH assessment ($n = 161$), 18 met criteria for pre-CABG major or minor depression (Table 1). Those with depression were more likely to be younger (60.3 ± 10.7 vs. 66.9 ± 8.9; $p = 0.005$), have a past history of depression (94.4% vs. 28.7%; $p < 0.001$), and a family history of depression (64.7% vs. 31.1%; $p = 0.006$). Of the 18 patients with pre-CABG depression, 17 reported having past history of major (n = 4) or minor (n = 14) depressive episode. Twelve of the 17 patients reported the age of first depressive episode (35.8 ± 25.84). The one patient with pre-CABG depression without past depression was aged 86 at the time of the study. On PHQ-9, the depressed group endorsed anhedonia but not psychomotor retardation/agitation at significantly higher rates. Both the depressed and non-depressed groups were similar in years of education and in marital status. The gender distribution, degree of social support on MOS survey, and employment status did not differ between the two groups.

MCA stenosis

Table 2 depicts the results of TCD for MCA. We did not find a statistical correlation between degree of MCA stenosis (right, left or bilateral) and presence of pre-CABG depression. Of unclear significance, the direction of association between depression and stenosis were inconsistent between right (OR = 0.5, 95% CI: 0.1, 4.4, $p = 0.58$) and left MCA (OR = 3.1, 95% CI: 0.8, 12.6, $p = 0.06$).

Functional assessment

Lawton IADL scores were similar between the depressed and non-depressed groups, with insignificantly greater functional impairment among those with depression (Table 3). However, pre-CABG depression was associated with statistically higher CDR-SB indicative of greater clinical impairment. This association remained significant when adjusting for age and gender ($OR = 3.7$, 95% CI: 1.4, 9.7) (Table 4).

Neuropsychological assessment

On bivariate analysis, pre-CABG depression was statistically associated with poorer performance on total letter fluency and WAIS-IV Digit Span Sequencing (Table 3). When adjusted for age, gender, and years of education, letter fluency test score remained statistically associated with pre-CABG depression (OR = 0.90, 95% CI: 0.81, 0.99) whereas Digit Span Sequencing was no longer significant (Table 4). Unlike the unadjusted scores, TMT A and B scores adjusted for the same three variables resulted in significant correlations with pre-CABG depression (TMT A: OR = 1.06, 95% CI: 1.01, 1.12; TMT B: OR 1.02, 95% CI: 1.01, 1.04) (Table 4). The depressed and non-depressed groups did not differ in the results of the remaining neuropsychological tests (WMS-visual reproduction, HVLT, WAIS-IV Digit Symbol Coding, WRAT Word Reading and NAB mazes; data not shown).

Discussion

Our analysis provides divergent lines of evidence for the vascular depression hypothesis as a potential explanation for the etiopathology of pre-CABG depression (Table 5). The high prevalence of functional disability and neuropsychological impairment, notably in executive function, among patients with pre-CABG depression support the hypothesis, whereas the natural history of depression among these patients differs from the criteria proposed by Steffens and Krishnan, such as late-onset depression and absence of family history of mood disorders.

A key feature shared by vascular depression and pre-CABG depression in this study population is impaired cognition. The specific cognitive domains that are impaired in vascular depression are not clearly defined, but executive function, processing speed and memory are thought to be principally involved[7,8,11]. Accordingly, our analysis found that patients with pre-CABG depression were more likely to have decreased executive dysfunction (total letter fluency and trail-making test B) and processing speed (trail-making test A), though no differences were seen tests of either verbal or visual memory (HVLT and WMS-visual reproduction). The relatively modest adjusted odds ratios could mean that this association is of only limited clinical importance. Alternatively, pre-CABG depression could be heterogeneous, with only a portion of these patients' depression being mediated by cerebrovascular disease thereby reducing the apparent strength of association.

Further evidence for the cognitive profile of vascular depression is derived from the CDR scores, which evaluate three cognitive domains (memory, orientation, judgment and problem solving) and three functional domains (community affairs, home and hobbies, personal care).[12] We report the results of CDR-SB as it is provides a more nuanced gradient of functional status than global CDR scores, with higher CDR-SB scores indicating greater overall cognitive and functional impairment. Patients with pre-CABG depression had higher CDR-SB scores than those without pre-CABG depression, which means that depression in this population is directly associated with clinically evident functional impairment. Pre-CABG depression was previously found to predict post-CABG delirium in this cohort[13], and this current finding further suggests that pre-CABG depression should be understood as an index for cognitive vulnerability in patients with advanced coronary heart disease. Such an interpretation is consistent with the vascular depression hypothesis.

On the contrary, the natural history of pre-CABG depression contrasts with that of vascular depression. Notably, all but 1 patient with pre-CABG depression had past history of depression. Twelve out of 18 patients reported their age of depression onset, which included only 3 patients whose first lifetime episode of depression took place after age 50. One would expect that some episodes of pre-CABG depression are unrelated to cerebrovascular disease, and so this finding might suggest that pre-CABG depression represents a mixed cohort of vascular and non-vascular depression. Further, some patients with a prior episode of depression prior to the age of 50 could have also developed cerebrovascular disease subsequently, contributing to etiologic uncertainty. Of note, the retrospective nature of self-reported age of first depressive episode is a limitation. Additionally, we are unable to account for the lifetime course of depression in these patients as this information was not collected; however, future studies should consider also examining depression course, including proximity of most recent depressive episode, in relation to assessments at the time of CABG. In particular, three patients reported their first depressive episode to have taken during their childhood, which introduces greater risk of recall bias.

Additionally, the fact that patients with depression in this sample had a higher rate of family history of depression than those without depression is inconsistent with prior reports of vascular depression. This too might be explained in part by the fact that several patients with pre-CABG depression likely had non-vascular depression, again introducing heterogeneity into this association.

This study did not find a correlation between MCA stenosis and pre-CABG depression. While MCA stenosis is not a direct measure of white matter disease in the brain, it was used in our study as a proxy measure for severity of cerebrovascular disease. One possible explanation is that this restricted measure of MCA does not reflect global cerebrovascular disease. While TCD exam of MCA was a convenient measurement due to the availability of validated protocols to link the MCA morphology with degree of stenosis,[15] it does not necessarily reflect other major cerebral vasculature. Additionally, TCD does not detect microvascular stenosis that is better appreciated with higher resolution imaging methods such as computerized tomography angiography or magnetic resonance angiography. As vascular depression is linked to microvascular disease of vessels smaller than the MCA[8,18], future studies utilizing higher resolution images of microvasculature are needed to investigate this potential association. Nevertheless, it is intriguing that the association between left MCA and depression trends in an opposition direction from that of right MCA and depression; specifically, the degree of left MCA stenosis and pre-CABG depression are positively associated. While this left-right difference may simply reflect inadequate power, prior studies on post-stroke literature suggests association between left hemisphere stroke and depression.[19–22] A larger study with greater sample size and higher resolution imaging methods might be needed to examine the potential association between left MCA stenosis and pre-CABG depression.

It is also important to consider the definition of major and minor depression used to define the depressed and non-depressed groups. The depressed group in this analysis is comprised of those with major or minor depression as defined by the *DSM-IV* on the DISH assessment.[11] Minor depression is uncommonly used in clinical practice and is defined by

having “one or more periods of depressive symptoms that are identical to Major Depressive Episodes in duration, but which involve fewer symptoms” (at least two but less than five) and less impairment.[12] The relatively low total scores of PHQ-9, in the total sample and both depressed and non-depressed groups, indicate that the severity of depression across both groups is mild to moderate. The limited presence of more severe depression may explain the attenuated or absent correlations between pre-CABG depression and cognitive function, as well as MCA stenosis. Additionally, it may also account in part for the relatively lower rate of depression in our study sample (11%) compared to the rate of 19–37% described in literature.[1] On the other hand, the fact that even mild depression is associated with cognitive and functional vulnerability in this cohort attests to the apparently outsized importance of depression in this population.

In summary, pre-CABG depression shares only parts of the defining features of vascular depression according to the model by Steffens and Krishnan[9] and otherwise appears similar to early-life depression. This implies that pre-CABG depression may not be as treatment resistant as vascular depression, which should encourage clinicians to treat it. Furthermore, the association between pre-CABG depression and post-CABG delirium[23] and cognitive decline[24] render its treatment more imperative.

In addition to the limitations cited above, another key limitation is the small sample size of the depressed group, which constrains statistical power. Relatedly, these current analyses are *post hoc* and examine potential sources of evidence in support of the vascular depression hypothesis. As such, they are not definitive. Although the associations between pre-CABG depression and cognitive impairment appear consistent across current analyses, the lack of associations between depression and MCA stenosis could represent type II error as this study was designed and powered to evaluate baseline cerebrovascular disease in relation to depression evident over the year after CABG surgery, rather than at baseline alone. Therefore, larger studies may be needed to investigate such cross-sectional relationships. The overall higher socioeconomic status and social support could also affect depression prevalence in this cohort and limit generalizability. Lastly, the cross-sectional nature of the analysis does not allow us assess the full range of core characteristics of vascular depression, namely treatment resistance and association with increased morbidity and mortality. The primary analysis of the NOAHS study, which is forthcoming, will examine cerebrovascular disease in relation to the longitudinal course of depression after surgery.

Conclusion

The NOAHS study cohort demonstrates that pre-CABG depression shares certain features of vascular depression, with the strongest similarities being cognitive and functional impairment, chiefly affecting executive function and processing speed. Pre-CABG depression in this study differs from vascular depression in that it was associated with the presence of past episodes of depression prior to age 50 and family history of depression. This suggests that pre-CABG depression could represent a mixed cohort of vascular and non-vascular forms of depression. The study was unable to find an association between MCA stenosis and pre-CABG depression. Adequately powered future studies with a wider

range of depressive symptom severity and an assessment of the microvasculature and white matter disease in the brain are needed.

Funding sources:

The NOAHS study was supported by R01 MH085740 awarded to H. Benjamin Lee, primary investigator. The sponsor had no role in the oversight of this present analysis. Mark Oldham is supported by the National Institute on Aging of the National Institutes of Health under Award Number K23AG072383. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data availability statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Key-points:

1. Pre-CABG depression is associated with cognitive and functional impairment in domains that are also impaired in vascular depression.
2. Unlike vascular depression, pre-CABG depression is associated with history of early-life depression and presence of family history of depression.
3. Pre-CABG depression is not associated with the degree of middle cerebral artery stenosis as measured by transcranial Doppler.
4. Future study is needed with a direct measurement of white matter disease and a wider range of depression severity to test the vascular depression hypothesis of pre-CABG depression.

Table. 1

Patient Demographics, by Depression

Characteristic	Total (N = 161)		Depression (n =18)		Not Depression (n = 143)		Test[a]
	M/Med	*SD/Var*	*M/Med*	*SD/Var*	*M/Med*	*SD/Var*	*p*-value
Age, years	66.2	9.3	60.3	10.7	66.9	8.9	.005
Years of education[b]	14.0	11.3	13.0	10.6	14.0	11.2	.119
MOS Social Support Total Score,[c]	91.0	309.6	87.0	578.0	92.0	275.8	.105
GDS total score	2.82	2.67	6.94	3.7	2.4	2.0	<0.001
PHQ-9 total score[d]	5.28	5.04	13.4	3.5	4.3	4.3	<0.001
Anhedonia[d]	.56	0.93	1.69	1.20	0.42	0.80	<0.001
Psychomotor	0.16	0.56	0.56	1.03	0.11	0.45	0.103
	n	**%**	***n***	**%**	***n***	**%**	***p*-value**
Gender: Female	40	24.8	8	44.4	32	22.4	.078
Race							
White	146	90.7	15	83.3	131	91.6	.380
African-American	9	5.6	1	5.6	8	5.6	
Other	6	3.7	2	11.1	4	2.8	
Married[e]	93	58.1	9	50.0	84	59.2	.458
Employment[e]							
Employed	68	42.5	7	38.9	61	43.0	.742
Retired	73	45.6	5	27.8	68	47.9	
Unemployed	19	11.9	6	33.3	13	9.2	
Past history of depression	58	36.0	17	94.4	41	28.7	< .001
Family history of depression[f]	53	34.9	11	64.7	42	31.1	.006

Note:

[*] Mean and standard deviation displayed for age, median and variance for years of education and MOS Score.

[a] *T*-test for age, Mann Whitney *U* test for years of education, MOS Score; Chi-square test for categorical variables, married, employment status (employed – other than employed), family history of depression; Fisher's exact test for female gender, race (white – other than white), past history of depression.

[b] Missing $n = 2$.

[c] Missing $n = 19$.

[d] Missing $n = 10$.

[e] Missing $n = 1$.

[f] First degree relative only, missing $n = 9$.

Abbreviations: CABG, coronary artery bypass graft; GDS, Geriatric Depression Scale; MOS, Medical Outcomes Study; PHQ-9, Patient Health Questionnaire.

Table 2.

Stenosis, by Depression*

Artery	Total (*n* = 128)	Depression (*n* = 11)	No Depression (n = 117)	Odds Ratios[b]					
	n (%)	*n* (%)	*n* (%)	Crude *OR*	95% CI	*p*-value	Adjusted *OR*	95% CI	*p*-value
R MCA	19 (14.8)	1 (9.1)	18 (15.4)	0.6	0.1, 4.6	.580	0.5	0.1, 4.4	.517
L MCA[a]	20 (15.7)	4 (36.4)	16 (13.8)	3.6	0.9, 13.6	.062	3.1	0.8, 12.6	.111
Bilateral[a]	4 (3.1)	1 (9.1)	3 (2.6)	3.8	0.4, 39.6	.269	2.5	0.2, 31.9	.474

Note:

*Table displays participants with assessed stenosis status.

[a]Total for L MCA and Bilateral data n = 127.

[b]Adjusted for gender and age.

Abbreviations: CABG, coronary artery bypass graft; L MCA, left middle cerebral artery; R MCA, right middle cerebral artery

Table 3.

Functional and cognitive assessment by depression, bivariate analysis

	Total				Depression				No Depression				Test[a]
	Med	***Var***	***M***	***SD***	***Med***	***Var***	***M***	***SD***	***Med***	***Var***	***M***	***SD***	***p*-value**
Functional assessment													
Lawton IADL (n = 156)	0.0	4.5	0.5	2.1	0.0	14.1	1.1	3.7	0.0	3.3	0.5	1.8	.151
CDR-SB (n = 155)	0.0	0.2	0.2	0.4	0.5	0.4	0.5	0.6	0.0	0.2	0.2	0.4	.016
Neuropsychological battery													
Total letter fluency raw (n = 97)	33.0	127.5	34.3	11.3	29.0	109.2	26.7	10.5	34.5	122.9	35.3	11.1	.009
TMT A time raw (n = 90)	36.5	258.9	40.8	16.1	38.0	754.9	47.1	27.5	36.0	207.4	40.1	14,4	.423
TMT B time raw (n = 87)	94.0	2373.6	102.0	48.7	116.0	3395.6	128.9	58.3	90.5	2204.2	98.9	46.9	.078
WAIS-IV DSpan raw (n = 95)	8.0	4.4	7.9	2.1	7.0	2.0	6.8	1.4	8.0	4.6	8.1	2.1	.028

Note:

[a] Mann Whitney U test result.

Abbreviations: CABG, coronary artery bypass graft; CDR-SB, clinical dementia rating sum of boxes; IADL, Instrumental Activities of Daily Living; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale

Table 4.

Functional and cognitive assessment by depression, unadjusted and adjusted

Functional assessment	Crude *OR*	95% CI	*p*-value	Adjusted *OR*	95% CI	*p*-value
Lawton IADL (*n* = 156)	1.1	0.9, 1.3	.280	1.1[a]	0.9, 1.4	.199
CDR-SB (*n* = 155)	2.5	1.1, 5.9	.031	3.7[a]	1.4, 9.7	.006
Neuropsychological battery						
Total letter fluency (*n* = 97)	0.93	0.87, 0.99	.022	0.90[b]	0.81, 0.99	.023
TMT A (*n* = 90)	1.02	0.99, 1.06	.225	1.06[b]	1.01, 1.12	.018
TMT B (*n* = 87)	1.01	1.00, 1.02	.099	1.02[b]	1.01, 1.04	.008
WAIS-IV Digit Span (*n* = 95)	0.75	0.55, 1.02	.068	0.76[b]	0.55, 1.06	.104

Note:

[a]Adjusted for gender and age;

[b]Adjusted for gender, age, and years of education.

Abbreviations: CABG, coronary artery bypass graft; CDR-SB, clinical dementia rating sum of boxes; IADL, Instrumental Activities of Daily Living; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale

Table 5.

Comparison between vascular and pre-CABG depression.

Vascular Depression	Pre-CABG Depression
Diagnostic criteria	
Major Depression	Mostly minor depression
Neuroimaging of cerebrovascular disease or Neuropsychological impairment	Neuroimaging: Not measured in this study Neuropsychological impairment: Yes
Clinical cerebrovascular symptoms	Not measured in this study
White or gray matter hyperintensity	Not measured in this study
Cognitive impairment: Executive function Memory Processing speed	Yes (except memory impairment)
Supportive Features	
Depression onset > 50 years of age Or Changes in depressive symptoms after onset of vascular disease	No
Anhedonia	Yes
Psychomotor retardation	No
Lack of family history of mood disorders	No
Marked disability in instrumental or self-maintenance activities of daily living	Yes