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Circulating Progenitor Cells and Cognitive Impairment in Men and Women with Coronary Artery Disease

Kasra Moazzami[a,b], **Matthew T. Wittbrodt**[c], **Bruno B. Lima**[a,b], **Jeong Hwan Kim**[a,b], **Muhammad Hammadah**[a,b], **Yi-An Ko**[d], **Malik Obideen**[a,b], **Naser Abdelhadi**[a,b], **Belal Kaseer**[a,b], **M. Mazen Gafeer**[a,b], **Jonathon A. Nye**[e], **Amit J. Shah**[a,b,f], **Laura Ward**[d], **Paolo Raggi**[a,g], **Edmund K. Waller**[h], **J. Douglas Bremner**[c,e,f], **Arshed A. Quyyumi**[b,1], **Viola Vaccarino**[a,b,1,*]

[a]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA

[b]Department of Medicine, Emory Clinical Cardiovascular Research Institute, Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA

[c]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

[d]Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA, USA

[e]Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, GA, USA

[f]Atlanta VA Medical Center, Decatur, GA, USA

[g]Mazankowski Alberta Heart Institute, University of Alberta, Alberta, Canada

[h]Department of Hematology and Oncology, Winship Cancer Institute, Atlanta, GA, USA

Abstract

Background: Circulating progenitor cells (CPC) have been associated with memory function and cognitive impairment in healthy adults. However, it is unclear whether such associations also exist in patients with coronary artery disease (CAD).

Objective: To assess the association between CPCs and memory performance among individuals with CAD.

Methods: We assessed cognitive function in 509 patients with CAD using the verbal and visual Memory subtests of the Wechsler memory scale-IV and the Trail Making Test parts A and B. CPCs were enumerated with flow cytometry as $CD45^{med}$/CD34+ blood mononuclear cells, those

[*]Correspondence to: Viola Vaccarino, MD, PhD, Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Road NE, Atlanta, GA 30322, USA. viola.vaccarino@emory.edu.

[1]These authors contributed equally to this work.

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co-expressing other epitopes representing populations enriched for hematopoietic and endothelial progenitors.

Results: After adjusting for demographic and cardiovascular risk factors, lower number of endothelial progenitor cell counts were independently associated with lower visual and verbal memory scores (p for all < 0.05). There was a significant interaction in the magnitude of this association with race ($p < 0.01$), such that the association of verbal memory scores with endothelial progenitor subsets was present in Black but not in non-Black participants. No associations were present with the hematopoietic progenitor-enriched cells or with the Trail Making Tests.

Conclusion: Lower numbers of circulating endothelial progenitor cells are associated with cognitive impairment in patients with CAD, suggesting a protective effect of repair/regeneration processes in the maintenance of cognitive status. Impairment of verbal memory function was more strongly associated with lower CPC counts in Black compared to non-Black participants with CAD. Whether strategies designed to improve regenerative capacity will improve cognition needs further study.

Keywords

Circulating progenitor cells; cognitive impairment; coronary artery disease; dementia; memory; trail making tests; Wechsler Memory Scale

INTRODUCTION

Coronary artery disease (CAD) remains a major cause of death and disability worldwide. Cognitive impairment is among the major comorbidities present in this group of patients [1]. Patients with CAD or its risk factors have a greater degree of brain atrophy and microvascular infarcts [2-4] that in turn are associated with memory impairment [2-5] and frank dementia [6, 7]. Possible causes are small vessel microvascular disease [8, 9] and impairments related to coronary bypass surgery and percutaneous coronary intervention procedures [10, 11]. Reduction of cardiovascular risk factors is one preferred strategy for reducing the rate of cognitive decline in this population [12]. However, identification of other biological mechanisms and risk markers for early cognitive changes in these patients is of significant interest.

Circulatory progenitor cells (CPCs) are mononuclear cells that originate primarily from the bone marrow, which have the potential to differentiate into several lineages which promote vascular repair and regeneration [13-16]. CPCs are frequently identified by the expression of the CD34 hematopoietic stem cell marker (CD34+) [17, 18]. Co-expression of chemokine (C-X-C motif) receptor 4 (CXCR4) further characterizes CPCs with capacity to home to areas of ischemia [19], cardiovascular or cerebrovascular injury where they promote angiogenesis and neurogenesis [20-25]. Additional expression of vascular endothelial growth factor receptor 2 (VEGFR2+) has been proposed to identify a subgroup of CD34+ cells enriched for endothelial progenitors [26]. Finally, cells expressing CD146 are also enriched for endothelial progenitors and have been demonstrated to play a key role in angiogenesis and vessel regeneration [27, 28].

Lower CPC counts are associated with cardiovascular risk factors, higher cardiovascular mortality [17, 24, 25, 29, 30], and cerebrovascular diseases including stroke and Alzheimer's disease [31-33]. CPC levels are considered to reflect reduced endogenous regenerative capacity. These cells have also been shown to be elevated in obese children and to be positively associated with cognitive function [34]. Previous studies in relatively small numbers of subjects with Alzheimer's disease or mild cognitive dysfunction have shown relatively reduced levels of circulating progenitor cells [35], a relationship between lower cell counts and worse memory function [31, 32] and higher cerebrospinal amyloid-β levels [33]. However, others have shown higher number of CPCs in those with moderate to severe dementia, but not in those with mild dementia when compared to healthy controls [36]. We have previously demonstrated in otherwise healthy volunteers, associations between lower CPC counts and greater cognitive decline [37]. However, the relationship between CPC levels in relation to memory performance in CAD patients, a group at particularly high risk for cognitive decline [5, 6], has not been previously studied.

The overall objective of the present study was to assess the association between CPCs and memory performance among subjects with CAD. Our hypothesis was that lower CPC counts, reflecting reduced regenerative capacity, would be linked to cognitive impairment in this population.

METHODS

Study population

Between September 2011 and September 2014, patients with stable CAD were recruited from Emory University affiliated hospitals as part of the Mental Stress Ischemia Mechanisms and Prognosis Study (MIPS) as described elsewhere [38]. From a total number of 659 patients enrolled in MIPS, data on CPC counts and memory function were available in 509 patients, which were included in the current analysis. CAD was defined based on a positive nuclear stress test, presence of angiographic atherosclerosis, or a history of prior myocardial infarction or revascularization. Patients with a history of recent (less than 2 months) acute coronary syndrome or decompensated heart failure, end-stage renal disease, systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg on the day of the test, or unstable psychiatric conditions including schizophrenia, psychotic depression, or bipolar disorder, in the past year were excluded. Data regarding sociodemographic characteristics, medical history, and medication history of all participants were collected using standardized questionnaires, and clinical information was verified by medical record review. The research protocol was approved by the Institutional Review Board, and all participants provided informed consent (IRB00035540).

CPC measurements

Venous blood samples were collected after an overnight fast into EDTA tubes and processed within 4h as previously described [17, 39]. CPCs were enumerated using flow cytometry as $CD45^{med}$ cells co-expressing CD34, CXCR4, VEGFR2, or CD146 epitopes [29, 40]. It has been shown that selection of cells that express low levels of CD45 ($CD45^{med}$) helps eliminate lymphoblasts and non-hematopoietic progenitors including mesenchymal or

osteoprogenitor cells, respectively [41]. For each sample, a total of 300 μL of peripheral blood was incubated with the following fluorochrome-labeled monoclonal anti–human mouse antibodies in the dark for 15 min: FITC-CD34 (BD Biosciences), PerCP-CD45 (BD Biosciences), PE-VEGF2 R (R&D system), and PE-Cy7-conjugated anti-CXCR4 (EBioscience, clone 12G5). This step was followed by adding 1.2 mL of staining medium (PBS with 3% heat inactivated serum and 0.1% sodium azide) to stop the lysing reaction. Samples were then centrifuged at 1500 rpm for 5 min and washed with PBS. Thereafter, cells were mixed and run on flow cytometer (BD FACS Canto II Flow Cytometer). Flow data were analyzed with Flowjo software (Treestar, Inc). The absolute mononuclear cell count was estimated using a Coulter ACT/Diff cell counter (Beckman Coulter), as the sum of lymphocytes and monocytes. The number of CPCs were expressed as cells per micro liter (μL).

Cognitive testing

All patients were administered four subtests from the Wechsler Memory Scale (WMS) - Fourth Edition [42]. Specifically, we administered the Visual Reproduction subtests to evaluate immediate and delayed visuospatial memory, and the Verbal Memory subtest to evaluate immediate and delayed verbal declarative memory. For immediate recalls, participants replicated a line drawing after viewing it for 10 s (immediate visual memory), or recalled details of a short story immediately after it was read to them (immediate verbal memory). For delayed recall subsets, recall was probed 20 min after the immediate condition with different pictures and stories. Scores were given from 1 to 20 on the accuracy of the drawn lines or retelling of the story. Memory consolidation was calculated as the ratio of delayed to immediate recall scores multiplied by 100, to express the percentage of retained memory (percent retention). The term consolidation used in this paper is derived from the field of cognitive psychology and refers to the aftermath of the encoding period when memories are strengthened or eliminated. Immediate recall on the WMS is a combined measure of attention and memory while delayed recall and percent retention measure memory consolidation, or the ability to retain information once learned. Verbal declarative memory consolidation as measured with the WMS had been correlated with neuronal number in the hippocampus in patients with epilepsy undergoing surgical treatment for their disorder [43, 44]. A higher score in verbal and logical memory scales indicates a better cognitive function.

The Trail Making Test parts A and B was also administered to test attention and executive function, respectively [45]. Briefly, Trail-A requires an individual to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper, whereas the more complex Trail-B requires rapidly switching between numbers and letters. The score on each part represents the amount of time (in min) required to complete the task. Lower scores on the Trail-A and B tests indicate better cognitive function.

Statistical analysis

Continuous variables are presented as means (SD) and categorical variables as proportions (%). Linear regression analysis was used to determine the bivariate association between memory scores and baseline demographics, cardiovascular risk factors, and CPC counts.

Multivariable regression models were constructed to explore the independent association between log-transformed CPC levels and memory scores (outcome variable). Since CPC values were not-normally distributed, the base-2 logarithm transformation was used for regression analysis. The β coefficient of 1 in this analysis can be therefore interpreted as every unit increase in each memory score corresponding to a doubling of CPC counts. All models were adjusted for demographic factors (age, sex, race/ethnicity, education), and cardiovascular risk factors and comorbidities (body mass index, glomerular filtration rate, hypertension, obesity, hyperlipidemia, diabetes, smoking, previous myocardial infarction, previous coronary artery bypass grafting, presence of angiographic atherosclerosis, left ventricular ejection fraction, history of a positive stress test, of heart failure, and of atrial fibrillation). Sensitivity analyses were conducted for each memory subtest and according to patients' sex, age (<60 and ≥60 years), and race/ethnicity after adjusting for the same characteristics, and interaction effects were tested. All analyses were conducted using Stata 14 (StataCorp., College Station, Texas). As a result of multiple testing, a *p*-value of <0.0125 (0.05/4) was considered statistically significant.

RESULTS

The baseline characteristics of the sample are shown in Table 1. The mean age was 62 years, 71% were male, and 32% Black. The most common comorbidity was history of dyslipidemia, followed by obesity and hypertension (Table 1). On bivariate analysis, the CD34+ and CD34+ CXCR4+ subsets were positively associated with male gender and glomerular filtration rate, and inversely associated with older age and black race (Table 2). The CD34+/VEGFR2+ subset was associated with the presence of atrial fibrillation, while the CD34+/CD146+ subset was associated with angiographic evidence of atherosclerosis (Table 2).

Circulating progenitor cells and memory

Bivariate associations between memory tests and CPC counts are shown in Table 2. No significant association (at $p < 0.012$) was found between CD34+ and CD34+/CXCR4+ subsets and any of the memory domains. However, CPC subsets expressing the endothelial markers VEGFR2 or CD146 were positively associated with higher memory performance in both visual and verbal memory domains (Table 2). As shown in Table 3, after adjusting for demographic factors, cardiovascular risk factors and comorbidities, presence of angiographic atherosclerosis, history of positive stress test, and left ventricular ejection fraction, the CD34+/CD146+ subgroup was independently associated with visual and logical memory tests, both for immediate and delayed memory, while the CD34+/VEGFR2+ subset was found to be independently associated with delayed visual memory test (Table 3). There were no associations between CPC subsets with attention and executive function (trail making test). For every unit increase in CD34+/VEGFR2+ and CD34+/CD146+ cells, the delayed visual memory increased by 1.3 and 3.1 units, respectively.

Sensitivity analysis

Formal analysis of interaction produced little evidence of significant heterogeneity, except for race and both CD34+/VEGFR2+ and CD34+/CD146+ subsets (p <0.01). As shown

in Table 4, after adjusting for age, sex, and education levels, CD34+/VEGFR2+ counts showed strong positive associations with delayed verbal memory among Blacks, but was weaker among non-Blacks (Table 4). Similar results were observed for the CD34+ CD146+ subgroup. Additional adjustments for the aforementioned comorbidities did not change the results.

DISCUSSION

To our knowledge, the present study is the first to show that lower counts of CPC subsets enriched for endothelial progenitors (VEGFR2 and CD146) are associated with worse memory performance and cognitive impairment in patients with CAD. Lower levels of circulating endothelial progenitor cells were associated with poorer verbal and visual memory, even after adjusting for demographic and cardiovascular risk factors. For the verbal memory domain, these observations were most robust in Black patients.

Small previous studies have shown that patients with either mild cognitive impairment or dementia have shown lower CPC counts compared to control populations [31-33, 35]. A previous longitudinal study of predominantly healthy employees from our group revealed protective effects of higher hematopoietic CPC against the risk of cognitive decline in the executive function and working memory domains during a 4-year follow-up period [37]. Results from experimental studies have also shown that transplantation of endothelial enriched progenitor cells improves memory impairment and outcomes in rodent models of Alzheimer's disease and stroke, respectively [20-23, 37]. However, no prior study has investigated the link between CPCs and memory function of patients with CAD. Our results expand upon the previous literature by suggesting a protective role of higher endothelial CPC counts against memory loss in participants with CAD.

Endothelial progenitor cells have shown to play important roles in reestablishing the endothelial integrity of vessels in animal models by promoting focal angiogenesis and neurogenesis [46, 47]. Accumulating evidence suggests that vascular dysfunction plays an important role in the development and progression of cognitive impairment and Alzheimer's disease [48, 49]. Accumulation of abnormal amyloid-β has shown to be toxic to the vascular endothelium *in vitro*, causing destruction of the neurovascular units, inducing blood-brain barrier permeability, and eventually leading to accelerated cell senescence and death [50, 51]. Therefore, endothelial progenitor cells can improve cognitive performance by restoring the integrity of the vascular endothelium and preventing neuronal loss.

In the present study, while both visual and verbal memory subtests were linked to CPC counts, no associations were found for Trail Making Test A or B. The Trail Making Tests are measures of executive functioning, mental flexibility, and psychomotor speed, rather than declarative memory function [52]. Anatomically, executive functions are associated with activation in the dorsolateral and medial prefrontal cortex (including supplementary motor area/dorsal anterior cingulate), and the parietal cortex, areas which are also activated during Trail Making Tests [53, 54]. In contrast, visual and verbal memory have been more strongly related with structures of the medial temporal lobe with known involvement in memory function, especially the hippocampal formation and the entorhinal cortex [55, 56]. Larger

hippocampal and entorhinal volumes have been related to better memory performance among healthy adults [57, 58], and loss of neurons in the hippocampus was correlated with impairments in verbal declarative memory consolidation as measured with the Wechsler Memory Scale [43, 44].

There are several possible explanations for the association between CPCs and memory function but not attention/executive function in this study. CPCs may be a proxy for or co-vary with precursor cells in the brain that are primarily located in the hippocampus, which is known from multiple lines of evidence to play a critical role in verbal declarative memory. Studies have demonstrated that neurogenesis continues to occur in the adult human hippocampus [59-61]. Hippocampal neurogenesis is susceptible to environmental effects, and stress and deprived environments can result in decreased neurogenesis [61-65], while enriched environment and even physical activity have shown to promote neurogenesis in animal models [60, 66]. Positive correlations have been reported between CD34+ cell counts and hippocampal perfusion [67-69], which can indicate potential relationships between CPC counts and both function and structure of the hippocampus [35]. However which subset of CPCs are associated with hippocampal function, requires further exploration

In our study, Black patients showed stronger correlations between the delayed and percentage of the retained logical memory and both VEGFR2+ and CD146+ CPC subsets. It has previously been shown that Black subjects have lower numbers of all subtypes of CPCs compared to non-Blacks, which may partly account for their increased risk of cardiovascular disease [70]. This could be partly related to lower levels of matrix metalloproteinases-9 (MMP-9) levels in Black individuals [70]. MMP-9 is a chemokine that plays an important role in releasing CPCs from the bone marrow into the peripheral circulation [71]. While the reasons for these differences are poorly understood, our findings suggest that a lower endothelial regenerative capacity in Blacks may make them more susceptible to memory impairment.

Strengths of our study include the relatively large sample of CAD patients, the use of state-of-the-art methods for quantification of CPCs, exploration of a wide range of CPC subpopulations, and multi-domain assessment of cognition. Limitations include the cross-sectional nature of the study which precludes any determination of causality between the CPC counts and memory impairment. Despite these caveats, our study contributes important new data supporting a relationship between endothelial-enriched CPCs and memory function among patients with CAD.

In conclusion, our findings indicate that lower levels of CPCs enriched for endothelial progenitors are associated with impairments in the visual and verbal memory domains, suggesting a potential role for reduced regenerative capacity in the circulatory system and neurocognitive aging in individuals with CAD. These findings have important clinical implications, as they point to the potential importance of therapeutic approaches that enhance endogenous regenerative capacity in the vasculature in order to mitigate the progression of cognitive decline in those at risk.

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Table 1

Baseline characteristic of the study population (N = 509)

Demographics	All Patients (509)
Mean age, y (SD)	62 (9.2)
Male, N (%)	365 (71.7)
Education, y (SD)	15 (3)
Medical History	
Dyslipidemia, N (%)	428 (84.0)
Obesity, N (%)	412 (80.9)
Hypertension, N (%)	401 (78.7)
Diabetes mellitus, N (%)	161 (31.6)
History of heart failure, N (%)	67 (13.1)
History of myocardial infarction, N (%)	186 (36.6)
Presence of angiographic atherosclerosis, N (%)	31 (13.1)
Presence of positive stress test, N (%)	270 (53.0)
Atrial fibrillation, N (%)	23 (4.5)
Mean body mass index (SD)	29.6 (5.0)
Mean glomerular filtration rate (mL/min) (SD)	94.8 (31.2)
Mean left ventricular ejection fraction, (SD)	53.0 (11)
Median number of diseased coronary arteries (IQR)	1 (1–2)
Mean Gensini angiographic severity score, (SD)	44 (51)
Medications, N (%)	
Aspirin	430 (84.4)
B-Blocker	382 (75.3)
Statins	437 (85.8)
Angiotensin-converting enzyme inhibitors	250 (49.1)
Circulating progenitor cell counts (cells/mL), mean (SD)	
CD34+	1972 (1402)
CD34+/CXCR4+	862 (721)
CD34+/VEGFR2+	12 (9)
CD34+/CD146+	10 (8)

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Demographics	All Patients (509)
Memory Function, mean (SD)	
Immediate Verbal Memory (score points)	10.4 (3.3)
Delayed Verbal Memory (score points)	7.5 (3.7)
Verbal Memory consolidation, %	68.2 (18.2)
Immediate Visual Reproduction (score points)	8.7 (4.7)
Delayed Visual Reproduction (score points)	8.3 (4.7)
Visual Reproduction consolidation, %	86.3 (15)
Trail-A (s)	42 (19)
Trail-B (s)	101 (49)

Immediate Verbal Memory (minimum 2.1, maximum 20), Delayed Verbal Memory (minimum 2.1, maximum 20), Verbal Memory consolidation (minimum 0, maximum 100), Immediate Visual Reproduction (minimum 0, maximum 20), Delayed Visual Reproduction (minimum 0, maximum 19.5), Visual Reproduction consolidation (minimum 0, maximum 100), Trail-A (minimum 15, maximum 164), Trail-B (minimum 20, maximum 503). A higher score in verbal and logical memory scales indicates a better cognitive function, while lower scores on the Trail-A and B tests indicate better cognitive function.

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Table 2

Unadjusted linear regression analysis for predictors of CPC subsets

Variable	CD34+*	CD34+/CXCR4+*	CD34+/VEGFR2+*	CD34+/CD146+*
		β (95% Confidence Interval)		
Male sex	0.12 (0.04, 0.19)	**0.06 (0.007, 0.12)**	−0.009 (−0.007, 0.003)	−0.005 (−0.01, 0.004)
Age	**−0.009 (−0.01, −0.005)**	**−0.005 (−0.008, −0.002)**	0.003 (−0.002, 0.005)	0.012 (−0.02, 0.03)
Black race	**−0.16 (−0.23, −0.08)**	**−0.08 (−0.14, −0.03)**	−0.003 (−0.008, 0.001)	−0.001 (−0.10, 0.007)
Education level	−0.01 (−0.03, 0.01)	−0.007 (−0.02, 0.01)	0.001 (−0.002, 0.003)	0.002 (−0.0007, 0.005)
Hypertension	0.04 (−0.03, 0.12)	0.02 (−0.03, 0.08)	−0.003 (−0.009, 0.001)	−0.001 (−0.01, 0.02)
Dyslipidemia	0.03 (−0.05, 0.12)	0.02 (−0.04, 0.08)	−0.003 (−0.009, 0.002)	−0.004 (−0.01, 0.02)
Diabetes	−0.01 (−0.09, 0.05)	−0.003 (−0.05, 0.05)	−0.001 (−0.006, 0.003)	−0.004 (−0.01, 0.004)
Myocardial infarction	0.02 (−0.05, 0.09)	−0.018 (−0.07, 0.03)	−0.002 (−0.007, 0.002)	0.001 (−0.10, 0.007)
Heart failure	−0.10 (−0.20, −0.007)	−0.03 (−0.11, 0.03)	−0.001 (−0.005, 0.007)	−0.001(−0.01, 0.01)
Body mass index	0.001 (−0.005, 0.007)	0.001 (−0.003, 0.006)	0.005 (−0.002, 0.010)	0.001 (−0.001, 0.001)
Presence of angiographic atherosclerosis	−0.07 (−0.20, 0.05)	−0.042 (−0.13, 0.052)	0.007 (0.001, 0.013)	**0.01 (0.003, 0.018)**
Presence of positive stress test	0.009 (−0.089, 0.091)	−0.014 (−0.080, −0.53)	0.001 (−0.004, 0.005)	0.003 (−.002, 0.008)
Atrial Fibrillation	0.11 (−0.08, 0.30)	0.02 (−0.12, 0.16)	**0.01 (0.002, 0.019)**	0.009 (−0.001, 0.020)
Left ventricular ejection fraction	0.001 (−0.003, 0.006)	0.002 (−0.001, 0.005)	0.001 (−0.0001, 0.003)	0.002 (−0.001, 0.003)
Number of diseased coronary arteries	0.004 (−0.04, 0.053)	−0.007 (−0.042, 0.028)	0.001 (−0.001, 0.003)	0.001 (−0.002, 0.003)
Glomerular filtration rate (mL/min)	**0.002 (0.001, 0.003)**	**0.002 (0.001, 0.003)**	0.001 (−0.001, 0.002)	−0.006 (−0.010, 0.001)
Medications				
Aspirin	−0.05 (−0.15, 0.05)	−0.05 (−0.12, 0.02)	−0.003 (−0.009, 0.004)	0.007 (−0.005, 0.018)
B-Blocker	**0.08 (0.001, 0.16)**	0.02 (−0.03, 0.08)	−0.004 (−0.10, 0.001)	0.002 (−0.008, 0.012)
Statins	0.009 (−0.08, 0.10)	−0.008 (−0.07, 0.06)	0.001 (−0.006, 0.007)	−0.002 (−0.014, 0.010)
ACEI	0.003 (−0.004, 0.01)	**0.01 (0.001, 0.019)**	0.001 (−0.001, 0.008)	−0.001 (−0.10, 0.007)
Gensini score	0.001 (−0.001, 0.001)	−0.002 (−0.001, 0.003)	−0.002 (−0.004, 0.001)	−0.001 (−0.002, 0.001)
Visual Memory				
Immediate	0.003 (−0.004, 0.01)	0.01 (0.001, 0.019)	0.001 (−0.001, 0.008)	**0.006 (0.001, 0.013)**
Delayed	0.005 (−0.002, 0.01)	0.008 (0.0007, 0.01)	**0.001 (0.0001, 0.003)**	**0.009 (0.003, 0.010)**
Consolidation	0.001 (−0.0005, 0.002)	0.001 (−0.002, 0.002)	0.001 (0.0001, 0.002)	0.001 (−0.0007, 0.02)
Verbal Memory				

Variable	CD34+*	CD34+/CXCR4+*	CD34+/VEGFR2+*	CD34+/CD146+*
		β (95% Confidence Interval)		
Immediate	0.01 (−0.002, 0.02)	0.004 (−0.001, 0.01)	**0.004 (0.0001, 0.009)**	**0.008 (0.004, 0.012)**
Delayed	0.006 (−0.004, 0.01)	0.007 (0.001, 0.013)	**0.005 (0.001, 0.009)**	**0.008 (0.004, 0.013)**
Consolidation	0.0003 (−0.001, 0.002)	0.001 (0.0004, 0.002)	**0.006 (0.002, 0.01)**	**0.003 (0.001, 0.008)**
Trail-A	−0.001 (−0.004, 0.0005)	−0.001 (−0.003, 0.0003)	0.001 (−0.001, 0.002)	−0.0001 (−0.003, 0.001)
Trail-B	−0.007 (−0.001, 0.001)	−0.0005 (−0.001, 0.0001)	0.005 (−0.002, 0.01)	−0.0002 (−0.003, 0.0002)

All values expressed as β, and 95% confidence interval. Bolded numbers indicate a *p*-value of <0.012.

*All subsets of CPCs are Log_2 transformed, indicating that each unit increase in the Log_2 CD34+ subgroup represents a doubling of cell count. A higher score in verbal and logical memory scales indicates a better cognitive function, while lower scores on the Trail-A and B tests indicate better cognitive function. ACEI, angiotensin-converting enzyme inhibitors.

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Table 3

Multivariate analysis investigating the association between cognitive function (outcome) and CPC subgroups

Variable	CD34+	CD34+/CXCR4+	CD34+/VEGFR2+	CD34+/CD146+
		β (95% Confidence Interval)		
Visual Memory				
Immediate	−0.13 (−0.44, 0.17)	0.10 (−0.48, 0.69)	1.2 (1.46, 3.21)	**3.06 (1.33, 4.79)**
Delayed	−0.05 (−0.37, 0.26)	0.36 (−0.23, 0.96)	**1.33 (0.17, 2.17)**	**3.14 (1.38, 4.90)**
Consolidation	3.96 (−1.21, 6.33)	2.84 (−0.23, 5.74)	**0.78 (0.12, 1.35)**	1.21 (−1.4, 1.85)
Verbal Memory				
Immediate	0.10 (−0.11, 0.32)	0.38 (−0.02, 0.79)	1.14 (−8.35, 10.64)	1.00 (−0.20, 2.23)
Delayed	0.03 (−0.21, 0.28)	0.35 (−0.11, 0.82)	1.47 (0.41, 3.50)	**2.05 (0.66, 3.43)**
Consolidation	0.16 (−1.61, 1.87)	1.18 (−1.57, 3.95)	3.91 (1.42, 5.31)	**1.6 (0.36, 1.95)**
Trail-A	0.41 (−0.71, 1.54)	−0.08 (−2.27, 2.05)	1.31 (−3.51, 6.30)	−3.42 (−9.61, 2.77)
Trail-B	0.84 (−2.08, 3.71)	0.18 (−5.35, 5.74)	4.85 (−7.91, 17.52)	−8.02 (−24.5, 8.25)

*All subsets of CPCs are Log_2 transformed, indicating that each unit increase in the Log_2 CD34+ subgroup represents a doubling of cell count. All values expressed as β, and 95% confidence interval. Bolded numbers indicate a *p*-value of <0.012. A higher score in verbal and logical memory scales indicates a better cognitive function, while lower scores on the Trail-A and B tests indicate better cognitive function. All models were adjusted for demographic factors (age, sex, race/ethnicity, education), and cardiovascular risk factors and comorbidities (body mass index, glomerular filtration rate, hypertension, obesity, hyperlipidemia, diabetes, smoking, previous myocardial infarction, previous coronary artery bypass grafting, presence of angiographic atherosclerosis, left ventricular ejection fraction, history of a positive stress test, of heart failure, and of atrial fibrillation.

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Table 4

Subgroup analysis investigating the association between memory performance (outcome) and CPC subsets in non-Blacks and Blacks

	All patients* (β, *p*)	Non-Blacks (β, *p*)	Blacks (β, *p*)	*p* for Interaction with Race
		CD34+		
Logical Memory				
Immediate	−0.13 (0.40)	0.17 (0.16)	−0.35 (0.10)	0.23
Delayed	−0.05 (0.72)	0.06 (0.64)	−0.30 (0.22)	0.52
Consolidation (%)	3.96 (0.45)	0.39 (0.63)	1.21 (0.50)	0.41
Visual Memory				
Immediate	0.10 (0.34)	−0.12 (0.48)	0.30 (0.37)	0.62
Delay	0.03 (0.79)	0.01 (0.91)	0.03 (0.32)	0.21
Consolidation (%)	0.16 (0.82)	0.12 (0.43)	0.22 (0.69)	0.82
		CD34+/CXCR4+		
Logical Memory				
Immediate	0.10 (0.73)	0.45 (0.06)	−0.05 (0.89)	0.31
Delayed	0.36 (0.23)	0.39 (0.16)	0.03 (0.98)	0.19
Consolidation (%)	2.84 (0.21)	1.21 (0.44)	3.43 (0.95)	0.56
Visual Memory				
Immediate	0.38 (0.06)	0.10 (0.75)	0.17 (0.77)	0.21
Delay	0.35 (0.14)	0.43 (0.22)	0.13 (0.83)	0.61
Consolidation (%)	1.18 (0.39)	1.25 (0.25)	0.84 (0.83)	0.10
		CD34+/VEGFR2+		
Logical Memory				
Immediate	1.2 (0.02)	1.48, $p = 0.77$	4.52, $p = 0.24$	0.18
Delayed	**1.33 (0.03)**	2.46, $p = 0.68$	**15.81, p = 0.001**	**0.009**
Consolidation (%)	**0.78 (0.03)**	2.31, $p = 0.34$	**12.12, p = 0.003**	**0.004**
Visual Memory				
Immediate	1.14 (0.81)	0.89, $p = 0.22$	3.41, $p = 0.10$	0.42
Delay	1.47 (0.15)	1.05, $p = 0.02$	4.32, $p = 0.03$	0.23
Consolidation (%)	3.91 (0.22)	3.01, $p = 0.60$	2.91, $p = 0.03$	0.08
		CD34+/CD146+		

	All patients* (β, *p*)	Non-Blacks (β, *p*)	Blacks (β, *p*)	*p* for Interaction with Race
Logical Memory				
Immediate	**3.06 (0.002)**	0.98, $p = 0.17$	5.61, $p = 0.42$	0.17
Delayed	**3.14 (0.001)**	1.65, $p = 0.06$	**11.43, p = 0.01**	**0.03**
Consolidation (%)	1.21 (0.85)	0.12, $p = 0.06$	**3.12, p = 0.001**	**0.02**
Visual Memory				
Immediate	1.00 (0.10)	1.91, $p = 0.06$	**6.75, p < 0.001**	**0.042**
Delay	**2.05 (0.004)**	1.91, $p = 0.03$	**8.24, p < 0.001**	0.03
Consolidation (%)	**1.6 (0.005)**	4.45, $p = 0.60$	6.21, $p = 0.39$	0.44

All models adjusted for age, sex, and level of education. A higher score in verbal and logical memory scales indicates a better cognitive function, while lower scores on the Trail-A and B tests indicate better cognitive function.