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Frequent Cognitive Impairment in Patients With Disorders Along the Heart-Brain Axis

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Background and Purpose—Patients with cardiovascular disease are at increased risk for cognitive decline. We studied the occurrence and profile of cognitive impairment in 3 patient groups as exemplar conditions of hemodynamic disturbances at different levels of the heart-brain axis, including patients with heart failure (HF), carotid occlusive disease (COD), and patients with cognitive complaints and vascular brain injury on magnetic resonance imaging (possible vascular cognitive impairment [VCI]).

Methods—In 555 participants (160 HF, 107 COD, 160 possible VCI, 128 reference participants; 68±9 years; 36% F; Mini-Mental State Examination 28±2), we assessed cognitive functioning with a comprehensive test battery. Test scores were transformed into *z*-scores. Compound *z*-scores were constructed for: memory, language, attention/psychomotor speed, executive functioning, and global cognitive functioning. We rated cognitive domains as impaired when *z*-score≤−1.5. Based on the number of impaired domains, patients were classified as cognitively normal, minor, or major cognitive impairment. We used general linear models and χ^2 tests to compare cognitive functioning between patient groups and the reference group.

Results—Age, sex, and education adjusted global cognitive functioning z-score was lower in patients with COD (β [SE]=−0.46 [0.10], *P*<0.001) and possible VCI (β [SE]=−0.80 [0.09], *P*<0.001) compared with reference participants. On all domains, *z*-scores were lower in patients with COD and possible VCI compared with reference participants. Patients with HF had lower z-scores on attention/speed and language compared with reference participants. Cognitive impairment was observed in 18% of HF, 36% of COD, and 45% possible VCI. There was no difference in profile of impaired cognitive domains between patient groups. Memory and attention-psychomotor speed were most commonly affected, followed by executive functioning and language.

Conclusions—A substantial part of patients with HF and COD had cognitive impairment, which warrants vigilance for the occurrence of cognitive impairment. These results underline the importance of an integrative approach in medicine in patients presenting with disorders in the heart-brain axis. **(*Stroke*. 2019;50:3369-3375. DOI: 10.1161/STROKEAHA.119.026031.)**

Key Words: brain ■ cerebral small vessel diseases ■ cognitive impairment ■ dementia ■ heart failure

Increasing age is associated with increasing health problems, such as cardiovascular diseases, cognitive impairment, and dementia.[1,2] These disorders pose a large burden on patients, caregivers, and society.[3,4] Population-based cohorts and cross-sectional studies have shown that cardiovascular factors, such as decreased cardiac functioning, atherosclerotic changes, and arterial stiffness are related to cognitive impairment in the elderly.[5–10] The term vascular cognitive impairment (VCI) has been introduced to describe the complete spectrum of cognitive impairment, including minor and major cognitive impairment, related to vascular brain injury.[3,11] In recent years, attention is shifting to even earlier stages, that is, subjective cognitive decline.[12,13] At this moment, vascular brain injury is the only cause of dementia that might be preventable or modifiable,[14] in contrast to Alzheimer's disease and other neurodegenerative diseases.

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The present study is part of the Heart-Brain Study,[15] which focuses on hemodynamic factors along the heart-brain axis, as a connecting mechanism between cardiovascular diseases and cognitive functioning. The Heart-Brain Study includes patients with heart failure (HF), carotid occlusive disease (COD), and patients with cognitive complaints and vascular brain injury on magnetic resonance imaging (possible VCI), as 3 exemplar conditions of hemodynamic disturbances at different levels of the heart-brain axis. Former studies have investigated the prevalence of cognitive impairment in cardiovascular disorders in isolated patient groups using mostly cognitive screening tests or limited neuropsychological assessment. This hampers comparison of prevalence and profiles of cognitive impairment. In the general population, studies suggest that executive functioning and information processing speed, and to a lesser extent memory, are related to cardiovascular factors.[5–10] Literature in patients with cardiovascular disorders is heterogeneous. In patients with HF, up to 50% of patients may have some degree of cognitive impairment,[16] across different cognitive domains.[16,17] An estimate of 10% has been provided for major cognitive impairment.[18] In population-based studies, it has been found that patients with asymptomatic carotid stenosis are at risk of cognitive impairment,[19–21] which might be stronger related to the left than right internal carotid artery.[22] The profile of cognitive impairment in COD was reported to be diffuse,[23] including most cognitive domains.[24] Former studies are hampered by limited neuropsychological assessment and the focus on a single patient group. In the current study, we aimed to study cognitive functioning with an extensive and standardized neuropsychological examination in 3 patient groups as exemplar conditions of hemodynamic disturbances at different levels of the heart-brain axis. This allowed us to directly compare the occurrence and profile of cognitive impairment across disorders.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request, within the privacy legislation of the Netherlands and after permission of the Heart-Brain Connection steering committee.

Participants

We included all participants of the baseline assessment (Heart-Brain Connection baseline data version 2, 1-1 2018, *n*=559) of the ongoing Heart-Brain Study[15] with available neuropsychological assessment. Four participants were excluded due to missing neuropsychological assessment. Reasons were: study procedures discontinued due to inability to undergo magnetic resonance imaging (*n*=2), illness (*n*=1), and participant refused neuropsychological assessment (n=1). This yielded a total sample size of 555 participants (160 HF, 107 COD, 160 possible VCI, and 128 reference participants). Patients were recruited from cardiology, memory, and neurology outpatient clinics from 4 hospitals: Leiden University Medical Center in Leiden; Maastricht University Medical Center in Maastricht; University Medical Center Utrecht in Utrecht; and Amsterdam UMC, location VUmc in Amsterdam, the Netherlands. Inclusion criteria for all participant groups were: (1) age 50 years or older, (2) able to undergo cognitive testing, and (3) able to undergo other study procedures, such as imaging, as assessed during history taking. We included patients with HF in accordance with the European Cardiology Society guidelines,[25] irrespective of left ventricular ejection fraction and coronary artery disease and with a stable clinical situation. We included patients with asymptomatic and symptomatic COD with a significant stenosis (>80%) or occlusion of the internal carotid artery as assessed with magnetic resonance angiography. For possible VCI, inclusion criteria were cognitive complaints, a Clinical Dementia Rating scale score of ≤1, and a Mini-Mental State Examination score of ≥20 (ie, we included patients with subjective cognitive decline, mild cognitive impairment, and mild dementia), combined with moderate to severe vascular brain injury on magnetic resonance imaging—operationalized as white matter lesion (Fazekas >1) and/or (lacunar) infarct(s) and/or intracerebral (micro-) hemorrhage(s)—or mild vascular brain injury—operationalized as white matter lesions (Fazekas=1)—with the presence of vascular risk factors. A reference group was recruited through advertisements, for example, in local newspapers, through leaflets, and among spouses of patients. Participants in the reference group had no history of VCI. Group-specific inclusion and exclusion criteria have been described in detail previously.[15] Level of education was assessed with the system of Verhage, ranging from 1 to 7 (low to high education).[26] The presence of cardiovascular risk factors (ie, hypertension, hypercholesterolemia, and diabetes mellitus) were determined based on self-reported medical history and medication use. Smoking status was dichotomized into current versus never or former smoker. Alcohol use was dichotomized into <15 units/wk versus ≥15 units/wk. Finally, body mass index was dichotomized into higher and lower than 30 kg/m^2.

Written informed consent was obtained before participation in the study. The Medical Ethics Review Committee of the Leiden University Medical Center performed central approval. Local medical ethical committees of all sites approved the local performance of the study.

Cognitive Functioning

All participants underwent an extensive and standardized neuropsychological assessment. We used the neuropsychological measurement set that was developed in the context of the Dutch Parelsnoer Initiative.[27] As cognitive screening instruments, we used the Mini-Mental State Examination[28] and the Clinical Dementia Rating.[29] Memory was assessed with the Rey Auditory Verbal Learning Test,[30,31] immediate recall, delayed recall and recognition, and the Visual Association Test[32] part A. We assessed language with the Visual Association Test-naming condition and the 1-minute animal fluency test.[33,34] The attention and psychomotor speed domain was assessed with digit span forward,[35] the Letter-Digit Substitution Test,[36] Trail Making Test (TMT)[37] A, and the Stroop Color Word Test[38–40] card 1 and 2. Finally, we assessed executive functioning with digit span backward, TMT B/A index, and a Stroop Color Word Test interference score, calculated as card 3/([card 1+card 2]/2). For an overview of the neuropsychological test protocol, see Table I in the online-only Data Supplement. Missing scores on TMT B were 3.4% across all groups (2.7% test aborted, 0.5% test not started, 0.2% otherwise). We replaced missing TMT B scores by imputation of the mean B/A-index multiplied by TMT A, after which missing values were 0.2% on TMT B. Missing values on other tests ranged from 0.2% (digit span and 1-minute animal fluency test) to 3.2% (Stroop interference). These scores were not imputed. To compare test scores between groups, individual test scores were standardized into *z*-scores adjusted for age, sex, and education, and using reference participants as reference group. First, age and education were centered around the mean (value minus mean; step 1). Second, we used multiple linear regression analysis in reference participants to calculate coefficients for age, sex, and education, necessary to calculate expected test scores (step 2). We used the cognitive test scores as dependent variables (separate analysis for each cognitive test). Covariates were age, sex, and education. The regression coefficients of age, sex, and education were used in the next step. Third, in the total group, expected test scores were calculated (step 3) by a regression equation where age, sex, and education were weighted by the estimated regression coefficients that were generated in step 2. Finally, *z*-scores were calculated (step 4) by (actual test score−expected score)/SD of the residuals. Age, sex, education-adjusted compound scores were constructed per cognitive domain. These domain scores were based on available tests. Global cognitive functioning was calculated as an average z-score across domains. Please note that due to use of z-scores, by definition, the reference group has mean 0±SD 1. This further implies that for each cognitive domain 7% of the reference participants is classified as cognitively impaired. Missing scores on cognitive domains were 0.9% on language and 0.7% on memory,

attention-psychomotor speed, and executive functioning as well as global cognitive functioning. We rated a cognitive domain as impaired when the z-score was ≤1.5 or lower; that is, 1.5 SD below the mean. Subsequently, patients were classified as cognitively normal (no impairment), minor cognitive impairment (1 domain impaired), or major cognitive impairment (>1 domain impaired).

Statistical Analysis

For statistical analysis, SPSS 22.0 was used (IBM for Windows, NY). Characteristics and vascular risk factors per patient group were compared with ANOVA and χ^2 tests when appropriate. To compare cognitive domains and global cognitive functioning between patient groups and reference participants, we used general linear models. We used compound z-scores of cognitive domains as dependent variables (each in separate model), and patient group (using dummy variables), age, sex, and educational level as independent variables. To investigate whether center influenced the results, we included center in the model (using dummy variables). When the coefficients for center were not significant, we repeated the analysis without center in the model. We used χ^2 tests to compare classification of cognitive impairment (no, minor, major) between patient groups. In view of the explorative nature of the study, we did not adjust for multiple testing.

Results

Patient characteristics are summarized in Table 1. Patients with HF and possible VCI were older compared with patients with COD and reference participants. Patients with HF and COD were less often women and had a lower education than reference participants. Mean Mini-Mental State Examination was lower in patients with COD and possible VCI than in patients with HF and reference participants. A Clinical Dementia Rating of 0.5 or 1 was more frequent in patient groups than in reference participants, and most frequent in patients with possible VCI. Compared with reference participants, patient groups had more vascular risk factors (ie, hypertension, hypercholesterolemia, and diabetes mellitus) and were more often current smokers.

Cognitive Functioning

Table 2 shows the cognitive domain z-scores per patient group. Raw neuropsychological test scores are presented in Table II in the online-only Data Supplement. Age, sex, and education adjusted global cognitive functioning z-score was lower in patients with COD (β [SE]=−0.46 [0.10], $P<0.001$) and possible VCI (β [SE]=−0.80 [0.09], $P<0.001$) compared with reference participants. No difference was found between patients with HF and reference participants. On all cognitive domains, *z*-scores were lower in patients with possible VCI and COD compared with reference participants (possible VCI: β [SE]=−1.28 [0.20] to −0.49 [0.11], all $P<0.001$ and COD: β [SE]=−0.83 [0.14] to −0.25 [0.12], all $P<0.05$). Patients with HF had lower *z*-scores on attention/psychomotor speed and language compared with reference participants (β [SE]=−0.28 [0.13] to −0.24 [0.10], both P<0.05), but not on memory and executive functioning. We found minor and major cognitive impairment more frequently in all patient groups compared with reference participants (minor cognitive impairment: HF: 14.5%, COD: 26.2%; possible VCI: 22.5%; major cognitive impairment: HF: 3.1%, COD: 9.3%; possible VCI: 22.5%, all $P<0.05$). Figure shows the profile of impaired cognitive domains in all participant groups. On visual inspection, the profile of impaired cognitive domains was similar across participant groups. Overall, the memory and attention-psychomotor speed domain were most commonly affected, followed by executive functioning and language.

Discussion

The main finding of this study is that a substantial part of patients with HF and COD have cognitive impairment. The profile of impaired cognitive domains in patients with HF and COD was similar to that in patients with possible

Table 1. Characteristics in Patients With Heart Failure, Carotid Occlusive Disease, Possible Vascular Cognitive Impairment, and Reference Participants

n=555	Reference Participants (n=128)	HF (n=160)	COD (n=107)	Possible VCI (n=160)
Age, y	65.6 (7.4)*†	69.6 (9.8)‡§	66.2 (8.0)*†	68.8 (8.4)‡§
Women, n (%)	60 (46.9)*§	53 (33.1)‡	25 (23.4)‡†	61 (38.1)§
Education,‖ score	5.4 (1.1)*§	5.0 (1.3)‡†	5.0 (1.2)‡	5.3 (1.2)*
Mini-Mental State Examination, points	28.8 (1.3)§†	28.6 (1.3)§†	27.7 (2.2)‡*	27.4 (2.7) ‡*
Clinical dementia rating scale ≥0.5, n (%)	6 (4.8)*§†	27 (16.9) ‡§†	39 (37.1)‡*†	113 (70.6)‡*§
Vascular risk factors				
Hypertension, n (%)	36 (28.1)*§†	128 (80.0)‡	83 (77.6)‡	119 (74.4)‡
Hypercholesterolemia, n (%)	39 (30.5)*§†	103 (64.4)‡§	99 (92.5)‡*†	117 (74.1)‡§
Diabetes mellitus, n (%)	3 (2.3)*§†	29 (18.1)‡§	31 (29.0)‡*†	19 (11.9)‡§
Currently smoking, n (%)	8 (6.3)*§†	23 (14.4)‡§	30 (28.0)‡*	29 (18.1)‡
Alcohol ≥15 units, n (%)	12 (9.4)§	14 (8.8)§	25 (23.4)‡*†	21 (13.1)§
BMI≥30 kg/m^2, n (%)	20 (15.6)*§	42 (26.4)‡	29 (27.1)‡	28 (17.6)

Data are presented as mean (SD) and number (percentage). Continuous variables analyzed with ANOVA. Categorical variables with χ^2 tests. Presence of vascular risk factors was determined based on self-reported medical history and medication use. BMI indicates body mass index; COD, carotid occlusive disease; HF, heart failure; and VCI, vascular cognitive impairment.

$P<0.05$: ‡≠reference participants, *≠HF, §≠COD, †≠VCI. No correction for multiple testing was used.

‖Education was assessed with the system of Verhage, ranging from 1–7 (low to high education).

Table 2. Cognitive Domain *z*-Scores of Patients With Heart Failure, Carotid Occlusive Disease, and Possible Vascular Cognitive Impairment

n=555	Reference Participants (n=128)	HF (n=160)	COD (n=107)	Possible VCI (n=160)
		β (SE)	β (SE)	β (SE)
Global cognitive functioning, *z*-score†	Ref	−0.17 (0.09)	−0.46 (0.10)**	−0.80 (0.09)**
Memory, *z*-score‡	Ref	−0.13 (0.20)	−0.50 (0.22)*	−1.28 (0.20)**
Attention/speed, *z*-score¶	Ref	−0.28 (0.13)*	−0.83 (0.14)**	−0.83 (0.12)**
Language, *z*-score‖	Ref	−0.24 (0.10)*	−0.26 (0.10)*	−0.59 (0.09)**
Executive functioning, *z*-score#	Ref	−0.10 (0.11)	−0.25 (0.12)*	−0.49 (0.11)**

Data are represented as β (SE). General linear models, adjusted for age, sex, and educational level. COD indicates carotid occlusive disease; HF, heart failure; and VCI, vascular cognitive impairment.

*P<0.05, **P<0.001. No correction for multiple testing was used.

†Global cognitive functioning is the average z-score across the compound z-scores of memory, language, attention/speed, and executive functioning. Z-scores were individually adjusted for age, sex, and educational level, using reference participants as reference group.

‡Memory is based on the Rey Auditory Verbal Learning Test immediate and delayed recall, and recognition, and Visual Association Test A.

¶Attention/speed is based on digit span forward, Letter-Digit Substitution Test, Trail Making Test A, and the mean of Stroop I and II.

‖Language is based on Visual Association Test naming and 1-minute animal fluency.

#Executive functioning is based on digit span backward, Trail Making Test B/A index, and Stroop interference.

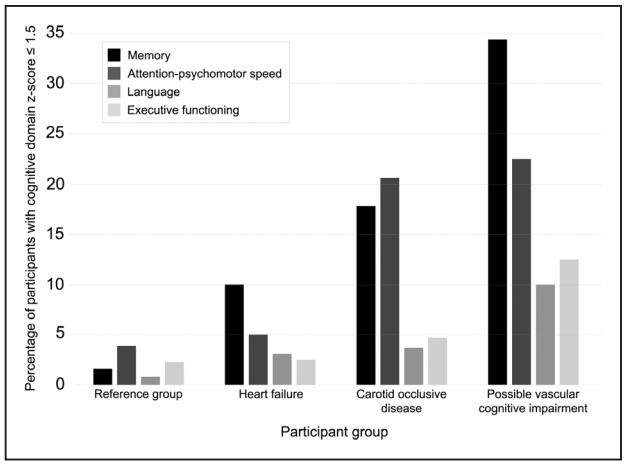

Figure. Profile of impaired cognitive domains in patients with heart failure, carotid occlusive disease, possible vascular cognitive impairment, and reference participants. Bars represent the percentage of participants with a cognitive domain z-score of −1.5 or lower.

VCI, with the memory and attention-psychomotor speed domain most commonly affected. We found that 18% of patients with HF and 36% of patients with COD had cognitive impairment. The occurrence of cognitive impairment in patients with HF and COD was lower in our study than in previous studies. Occurrence of cognitive impairment was previously reported in up to 50% in HF,[16,18] and in half to two-thirds of patients with COD.[23,24] The differences in occurrence of cognitive impairment between studies can be explained by differences in demographics, but also by varying neuropsychological (screening) tests and cutoff scores between studies. In the present study, we performed an extensive neuropsychological assessment, standardized between patient groups, with a performance of ≤1.5 SD below the mean as cutoff demarcating cognitive impairment. Other studies might have used more lenient cutoffs (ie, ≤1 SD), which may lead to higher estimated prevalence of cognitive impairment.[41] In addition, we included relatively young and stable patients with HF, which could explain the lower prevalence of cognitive impairment in this patient group. Nevertheless, with our stringent cutoff, we found high occurrence of cognitive impairment in both patients with HF and COD. This calls for further evaluation and warrants vigilance for the occurrence of cognitive impairment in these patient groups, especially in elderly patients. As a first step, during history taking physicians could ask patients with cardiovascular diseases whether they have memory complaints. In addition, brief cognitive screening tools could be helpful in determining who needs more thorough cognitive evaluation. Patients who score below the cutoffs of these tests should be investigated in more detail, with a neuropsychological test battery covering the major cognitive domains, for instance, similar to the protocol used in this study. Subsequent management of cognitive functioning could include the optimization of medications for both the heart and the brain. The question if optimization of cardiovascular factors may have direct cognitive benefit, apart from preventing stroke, is still unanswered, although there is emerging evidence that this may be the case.[42] Ongoing clinical trials are addressing for example if increasing cardiovascular fitness through aerobic exercise benefits brain perfusion and cognition[43] or if revascularization in patients with COD has cognitive benefit.[44,45]

In patients with possible VCI, we reported cognitive impairment in about half of the patients. This reflects our inclusion criteria that allowed the participation of patients regardless of the severity of cognitive impairment. Hence, our sample also included patients with evidence of vascular brain injury on magnetic resonance imaging and cognitive complaints that could not be objectified by neuropsychological assessment.[12] The rationale behind our approach is that patients with cognitive complaints as a results of vascular brain injury may not always develop cognitive deficits that are severe enough to be classified as mild cognitive impairment. Even more, literature indicates that patients with cognitive complaints and white matter hyperintensities are at risk for clinical progression to mild cognitive impairment or dementia.[13]

We found similar profiles of impaired cognitive domains across patients with HF, COD, and possible VCI. Using an extensive and standardized neuropsychological assessment, we found in all patient groups that domains of memory and attention-psychomotor speed were most commonly affected.

Patients with cardiovascular diseases, such as heart failure and carotid stenosis or occlusion, show a wide range of cognitive impairment including memory impairment.[17,20,21,23,24] Patients with vascular brain injury are typically thought to show impairments in executive functioning,[11] while patients with Alzheimer's disease are thought to have prominent memory impairments. However, these specific cognitive profiles do not do justice to reality. As patients with Alzheimer's disease may also present with executive functioning impairments, and patients with vascular pathology with memory impairments. Moreover, vascular and Alzheimer pathology may co-occur, which may contribute to the profile of and may even have an additive effect on cognitive functioning.[46,47]

The similarity in the profile of impaired cognitive domains between patient groups provides support for the notion of a heart-brain connection. Disorders that hinder cerebral perfusion along the heart-brain axis may contribute to cognitive impairment. Moreover, several cardiac and vascular factors along this axis, such as cardiac failure, stiffening of the aorta, or atherosclerotic disease of cerebropetal arteries, may adversely affect the brain by compromising perfusion, disturbing vascular reactivity, or otherwise causing downstream tissue damage. In addition, vascular injury in the brain itself, such as small vessel disease, may increase the vulnerability of the brain to changes in perfusion pressure. All these factors may contribute to cognitive impairment.[3] These mechanisms might act synergistically; however, if and how these mechanisms interact, and how they result in cognitive impairment is currently unknown. Nonetheless, these results underline the importance of minding the brain in patients presenting with disorders in the heart-brain axis and call for a more integrative approach in medicine.

Among the strengths of this study are the large cohort of patients that represent with exemplar conditions of hemodynamic disturbances of different levels of the heart-brain axis, whereas earlier studies mainly focused on single patient groups. In addition, most studies used global cognitive screening tests or limited neuropsychological assessment, whereas this study used a comprehensive and standardized neuropsychological test battery in all participants. Our data on cognitive functioning were nearly complete, with only few missing values meaning that potential bias that might have been introduced is minor. The use of cognitive domain *z*-scores enables comparison of cognitive functioning and cognitive profiles between patient groups.[48] Furthermore, the use of cognitive domain scores decreases the risk of multiple testing as it reduces the number of comparisons. On the contrary, by using domain scores, information of individual neuropsychological tests is combined, neglecting differences that may exist between neuropsychological tests within a domain. Also, the choice of including a particular test into a cognitive domain is arbitrary to a certain extent.

Also, some limitations have to be taken into consideration. First, the categorization of no, minor, and major cognitive impairment was based solely on neuropsychological testing. This method reflects a more actuarial neuropsychological method to define cognitive impairment with a cutoff demarcating cognitive impairment.[41] This categorization is not synonymous with a clinical diagnosis of mild cognitive impairment and dementia, as additional information on (instrumental) activities of daily living is needed, derived from history taking as well as the assessment of the development of symptoms over time.[49] Second, our patients with possible VCI were not included based on any of the established VCI criteria,[3,11,50] since we also included patients without cognitive impairment. Third, some of our inclusion criteria may have introduced bias. We included patients with HF, who were relatively young and with a stable clinical situation, this may have given rise to a selection bias, as we did not include frail patients with HF. As a result, the observed prevalence of cognitive impairment may even be an underestimation. In the reference group, we also included spouses of patients. Using spouses has probably contributed to the sex differences between the reference group and the participants groups. However, spouses included on average 20% in all houses, so other factors contributed to the sex difference as well. We did not have information on ethnic background available. Finally, this study is cross-sectional of nature, precluding statements on the course of cognitive impairment over time. However, the present study is part of a larger Heart-Brain Study with follow-up after 2 years.[15] Future research will focus on the development of cognitive impairments over time in the Heart-Brain study cohort, the mechanisms underlying the association between cardiovascular disorders and vascular cognitive impairment, also in collaboration with other Dutch cohorts,[51,52] and with a focus on the possible modifying effect of sex, as it has been shown that heart disease may manifest very differently in women than in men. Furthermore, we will study cognitive impairment in a wider study population, including participants with atrial fibrillation and kidney disease.

Summary/Conclusions

A substantial part of patients with HF and COD had cognitive impairment, which warrants vigilance for the occurrence of cognitive impairment in these patient groups. The profile of impaired cognitive domains in patients with HF and COD was similar to that in patients with possible VCI, with memory and attention-psychomotor speed most commonly involved. These results underline the importance of minding the brain in patients presenting with disorders in the heart-brain axis and call for a more integrative approach in medicine.

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