Prevalence of Memory Disorders in Ambulatory Patients Aged ≥70 Years With Chronic Heart Failure (from the EFICARE Study)

Olivier Hanon, MD, PhD[a,b,*], Jean-Sébastien Vidal, MD, PhD[a,b], Pascal de Groote, MD, PhD[c], Michel Galinier, MD, PhD[d], Richard Isnard, MD, PhD[e,f], Damien Logeart, MD, PhD[g,h], and Michel Komajda, MD[e,f]

The aim of this multicenter observational study conducted in France was to determine the prevalence of memory impairment in ambulatory patients aged ≥70 years with chronic heart failure (HF). Two hundred ninety-one cardiologists recruited 912 ambulatory patients with HF (mean age 79.2 ± 5.8 years) from January to November 2009. Memory was evaluated by the delayed-recall Memory Impairment Screen (MIS-D). Memory impairment was defined as MIS-D score ≤6 and severe memory impairment as MIS-D score ≤4. HF was diagnosed 4.4 ± 4.8 years earlier and mean left ventricular ejection fraction was 43.6 ± 12.0%. Memory impairment was found in 416 subjects (45.6%, 95% confidence interval 42.4 to 48.8) and severe memory impairment in 213 subjects (23.4%, 95% confidence interval 20.6 to 26.1), whereas cardiologists only suspected memory impairment in 109 patients (12%; before evaluation by MIS). Determinants of memory disorders included older age, lower education level, depression, history of stroke, renal failure, and less regular physical activity. The severity of memory impairment increased with increasing severity of HF (New York Heart Association classification; p <0.00001). In conclusion, memory impairment in older patients with HF is common. The use of a simple-to-use tool such as the MIS-D may identify patients at risk and enable implementation of management strategies to improve therapeutic compliance. **(Am J Cardiol 2014;113:1205−1210)**

Both heart failure (HF) and memory disorders are conditions that primarily affect older subjects.[1] However, the relation between HF and memory disorders remains controversial.[2−6] The main objective of the Evaluation of risk Factors for cognitive Impairment in Chronic Ambulatory heart failuRe in the Elderly (EFICARE) study was to determine the usability of the Memory Impairment Screen (MIS) test by cardiologists to assess the prevalence and determinants of memory impairment in a large ambulatory population of subjects ≥70 years with HF in France. The second objective was to compare the cardiologists' clinical global impression with the MIS for the screening of memory disorders.

Methods

EFICARE study is an observational study of ambulatory patients aged ≥70 years with symptomatic HF living in France. Private practice cardiologists were contacted by phone and invited to participate in the study. They were equally distributed by region. To ensure recruitment of a representative population from France as a whole, each cardiologist was asked to recruit the first 4 consecutive patients seen for a routine consultation who met the following criteria: men or women aged ≥70 years, HF diagnosed according to the European Society of Cardiology criteria,[7] and hospitalized for HF in the last 12 months irrespective of left ventricular ejection fraction (LVEF) value. The study complied with the Declaration of Helsinki. The study was approved by local regulatory authorities and each participant signed an informed consent form.

Data were collected from January to November 2009. Demographic characteristics, information on concurrent comorbidities, New York Heart Association (NYHA) classification, and prescribed medications were recorded by the cardiologists. Before the cognitive function evaluation, cardiologists were asked to rate their patients' cognitive status subjectively as normal or impaired. Then they evaluated memory function using the French version of the delayed-recall Memory Impairment Screen (MIS-D).[8] The MIS test, a brief, 4-word, immediate free- and cued-recall memory test, with higher scores indicating better performance, has been developed as a screening tool. The test has been modified by adding a 10-minute delayed recall to the immediate recall (MIS-D). For each word, the patient received a score of 2 for free recall and 1 for cued recall. The

[a]Service de Gérontologie, Hôpital Broca, [e]Service de Cardiologie, Hôpital Pitié-Salpêtrière, and [g]Service de Cardiologie, Hôpital Lariboisière, Assistance Publique−Hôpitaux de Paris, Paris, France; [b]Université Paris Descartes, Sorbonne Paris Cité, Equipe d'Accueil (EA) 4468, Paris, France; [c]Service de Cardiologie, Centre Hospitalier Régional Universitaire de Lille, Lille, France; [d]Service de Cardiologie, Centre Hospitalier Universitaire de Rangueil, Toulouse, France; [f]Université Pierre et Marie Curie, Paris, France; and [h]INSERM U942, Université Paris Diderot, Paris, France. Manuscript received October 9, 2013; revised manuscript received and accepted December 10, 2013.

This study was supported by an unrestricted grant from A. Menarini Industrie Farmaceutiche Riunite Srl, Florence, Italy. Medical writing support was provided by Jenny Grice of *in*Science Communications, Springer Healthcare. This assistance was funded by A. Menarini Industrie Farmaceutiche Riunite Srl.

See page 1209 for disclosure information.

*Corresponding author: Tel: (+33) 1 44 08 30 30; fax: (+33) 1 44 08 35 10.

E-mail address: olivier.hanon@brc.aphp.fr (O. Hanon).

0002-9149/14/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjcard.2013.12.032

Table 1
Comparison of the general characteristics according to cognitive status (MIS-D scores)

General Characteristic	MIS-D$_{[7-8]}$ (n = 496)	MIS-D$_{[5-6]}$ (n = 203)	MIS-D$_{[0-4]}$ (n = 213)	p Value*
Mean age (yrs)	78.1 ± 5.6	79.6 ± 5.7	81.0 ± 5.7	<0.0001
Men	352 (71.0)	113 (55.6)	125 (58.7)	0.002
Higher education	92 (18.7)	19 (9.4)	11 (5.2)	<0.00001
Mean body mass index (kg/m^2)	26.5 ± 4.4	26.4 ± 3.9	25.9 ± 4.2	0.27
Low sodium diet	411 (84.9)	167 (82.2)	167 (78.4)	0.02
At least 1 lifestyle adjustment for HF	421 (89.8)	174 (87.9)	173 (82.4)	0.009
Therapeutic education program for HF	86 (18.2)	27 (13.6)	20 (9.5)	0.06
Regular physical activity	260 (53.6)	74 (36.5)	62 (29.1)	<0.00001
Cognitive impairment according to cardiologists before performing MIS-D	20 (4.1)	17 (8.7)	72 (33.9)	<0.00001
Atrial fibrillation	155 (31.8)	79 (39.3)	79 (37.4)	0.21
Renal failure (eGFR <60 ml/min)	281 (67.9)	135 (78.5)	154 (87.0)	0.009
Diabetes mellitus	116 (23.9)	57 (28.8)	57 (26.9)	0.11
Chronic obstructive pulmonary disease	92 (18.8)	35 (17.6)	38 (17.8)	0.99
Depression	60 (12.5)	34 (17.3)	54 (25.7)	0.0002
Anemia (hemoglobin <11 g/L)	54 (11.0)	35 (17.7)	29 (13.7)	0.20
Previous stroke	51 (10.4)	19 (9.5)	43 (20.3)	0.001
Dysthyroidism	45 (9.2)	17 (8.5)	16 (7.6)	0.30
Fall experienced in the last 12 months	26 (5.4)	12 (6.2)	31 (14.8)	0.006
Cancer	36 (7.4)	10 (5.0)	17 (8.0)	0.39
Malnutrition	15 (3.1)	6 (3.1)	15 (7.2)	0.12
IADL				
4	329 (67.1)	100 (49.8)	46 (21.9)	<0.00001
3	98 (20.0)	48 (23.9)	31 (14.8)	
2	33 (6.7)	25 (12.4)	37 (17.6)	
1	24 (4.9)	21 (10.4)	64 (30.5)	
0	6 (1.2)	7 (3.4)	32 (15.2)	

Data are presented as mean ± SD or n (%).

Higher education is defined as above high school achievement, low sodium diet is defined as a diet containing ≤6 g of salt per day, and dysthyroidism is hyperthyroidism or hypothyroidism.

eGFR = estimated glomerular filtration rate.

* Overall difference among the 3 groups of MIS-D scores adjusted for age and gender.

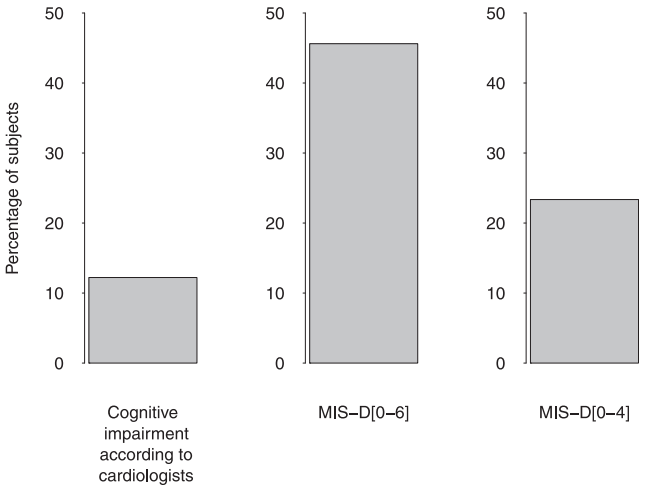

Figure 1. Cognitive impairment according to cardiologists' assessment (before performing MIS-D) and according to MIS-D scores.

maximal score for MIS-D is 8. An MIS-D score ≤6 indicates memory impairment and an MIS-D recall score ≤4 suggests severe memory impairment.[8] Before its administration to subjects, cardiologists received a training session on MIS test by phone or in person. Autonomy was assessed using the 4-item version of the instrumental activities of daily living (IADL) scale.[9] Subjects were scored according to their highest level of functioning in each category, with a total score ranging from 0 (low function, dependent) to 4 (high function, independent).

Higher education level was defined as above high school achievement. Regular physical activity was defined as moderate daily physical activity.[7] Lifestyle adjustments for HF were defined as low sodium diet (diet containing ≤6 g of salt per day), regular physical activity, and following a HF management program.[7] Depression was defined as use of antidepressant medications or diagnosis of depression made by the subjects' psychiatrist or general practitioner. Renal failure was defined as a creatinine clearance of <60 ml/min as calculated with Cockcroft formula. Hypertension was defined as a history of hypertension or blood pressure ≥140/90 mm Hg.

Results are presented as means and SD for quantitative variables and as the number of subjects and percentage for categorical variables. Demographic and clinical characteristics were compared among the 3 groups of subjects, that is, MIS-D score >6 (MIS-D$_{[7-8]}$), MIS-D ≤6 and >4 (MIS-D$_{[5-6]}$), and MIS-D ≤4 (MIS-D$_{[0-4]}$), using analysis of variance for quantitative data and chi-square test or Fisher's exact test for categorical variables. Correlation of MIS-D and IADL was tested using Kendall τ statistic. Univariate analysis was performed for each variable using a logistic regression

Table 2
Comparison of the cardiovascular characteristics according to cognitive status (MIS-D scores)

Cardiovascular Characteristic	MIS-D$_{[7-8]}$ (n = 496)	MIS-D$_{[5-6]}$ (n = 203)	MIS-D$_{[0-4]}$ (n = 213)	p Value*
Mean duration of HF disease (yrs)	4.24 ± 5.05	4.62 ± 5.14	4.62 ± 4.00	0.50
Mean time since last hospitalization (mo)	4.35 ± 3.20	4.64 ± 3.23	4.14 ± 3.10	0.30
Hypertension	381 (77.1)	162 (80.2)	165 (77.5)	0.67
Coronary heart disease	263 (53.2)	102 (50.5)	117 (55.2)	0.46
Dilated cardiomyopathy	189 (38.3)	72 (35.6)	75 (35.5)	0.98
Severe valvulopathy	94 (19.0)	42 (20.8)	56 (26.4)	0.42
NYHA classification				
Class I	40 (8.1)	6 (3.0)	3 (1.4)	<0.00001
Class II	293 (59.4)	117 (57.6)	106 (49.8)	
Class III	149 (30.2)	76 (37.4)	86 (40.4)	
Class IV	11 (2.2)	4 (1.9)	18 (8.4)	
Mean systolic blood pressure (mm Hg)	129.7 ± 18.0	131.5 ± 16.7	132.0 ± 19.2	0.54
Mean diastolic blood pressure (mm Hg)	75.7 ± 10.0	77.2 ± 10.0	76.1 ± 11.1	0.27
Mean LVEF (%)	43.4 ± 12.2	44.1 ± 12.1	43.4 ± 11.5	0.50
Mean heart rate (beats/min)	70.7 ± 14.2	74.2 ± 13.7	73.2 ± 16.2	0.05
Cardiovascular treatment				
β Blockers	396 (80.5)	167 (82.2)	164 (77.0)	0.53
Angiotensin-converting enzyme inhibitors	331 (67.0)	124 (61.4)	135 (63.4)	0.64
Antiplatelet therapy	262 (54.5)	110 (55.8)	123 (59.4)	0.37
Vitamin K antagonists	200 (41.2)	87 (43.5)	85 (40.7)	0.85
Angiotensin II receptor blockers	120 (24.4)	59 (29.1)	61 (28.6)	0.37
Aldosterone antagonists	134 (27.2)	49 (24.3)	38 (17.9)	0.11
Calcium channel blockers	73 (15.1)	29 (14.6)	34 (16.1)	0.90
Thiazide diuretics	29 (5.9)	17 (8.4)	16 (7.5)	0.56
Loop diuretics	429 (87.2)	171 (84.2)	190 (89.2)	0.40
Nitroglycerin (glyceryl trinitrate)	91 (18.8)	30 (15.2)	44 (20.1)	0.37
Digoxin	67 (13.6)	33 (16.3)	41 (19.3)	0.43

Data are presented as mean ± SD or n (%).
Severe valvulopathy is defined as severe mitral or aortic valve regurgitation and/or severe mitral or aortic valve stenosis.
* Overall difference among the 3 groups of MIS-D scores adjusted for age and gender.

model adjusted for age and gender in which the reference group was composed of subjects with MIS-D$_{[7-8]}$.

All variables associated with memory impairment ($p < 0.15$) were entered into multivariate multinomial logistic regression models to identify those associated independently with memory impairment. A stepwise backward selection method of the clinical variables was used to obtain the final model. Finally, in subjects of MIS-D$_{[0-6]}$ group (i.e., cognitively impaired), we analyzed demographic and clinical characteristics according to the cardiologists' subjective cognitive status assessment. In a sensitivity analysis, we performed a hierarchical model to take into account the correlation between patients seen by the same cardiologist, comparing MIS-D$_{[5-6]}$ group with MIS-D$_{[7-8]}$ group and MIS-D$_{[0-4]}$ group with MIS-D$_{[7-8]}$ group, including the same variables as the final multivariate model. Statistical analysis was performed with the R statistical software.[10] In all analyses, the 2-sided α level of 0.05 was used for significance testing.

Two hundred eighty-nine cardiologists (259 men [90%], 30 women [10%], mean age 51.7 ± 7.5 years) agreed to participate and recruited 1,054 patients. Seventy-four subjects were excluded because of protocol deviations (date of inclusion before January 1, 2009 [n = 1], last hospitalization >1 year ago [n = 59], or no data provided [n = 14]) leaving 980 patients. Compared with excluded subjects, the 980 included subjects had higher systolic (136.8 ± 18.3 vs 130.6 ± 18.0 mm Hg, p = 0.0007) and diastolic blood pressures (79.1 ± 10.3 vs 76.1 ± 10.3 mm Hg, p = 0.004) and lower LVEF (43.6 ± 12.0% vs 45.6 ± 11.6%, p = 0.01). They also used beta blockade more frequently (80% vs 66%, p = 0.0005) and thiazide diuretics less often (6.8% vs 15.7%, p = 0.002). Cardiologists successfully evaluated with MIS-D 93% (n = 912) of the 980 included subjects. Errors with MIS-D were mainly in scoring the test: 2 points per free recall items and 1 point for cued recall item that had not been free recalled. There were no significant differences in general characteristics between the 912 subjects included in the analysis and those with missing MIS-D (results not shown).

Results

General characteristics of the population (n = 912) at baseline are listed in Table 1. Mean age was 79.1 ± 5.8 years and 590 subjects (65%) were men. Compared with patients with MIS-D$_{[7-8]}$, subjects with MIS-D$_{[0-6]}$ were older, more often women, and had a lower education level. They were also more likely to have renal failure, a history of stroke, depression, and at least 1 fall in the last 12 months and were less likely to be physically active. As expected, level of functional impairment (IADL score) was strongly associated with MIS-D, with the lowest score in subjects with MIS-D$_{[0-4]}$ (Kendall's correlation coefficient $\tau = 0.38$, $p < 0.0001$).

The prevalence of abnormal delayed MIS (MIS-D$_{[0-6]}$) was 45.6% (n = 416) with 95% confidence interval 42.4 to

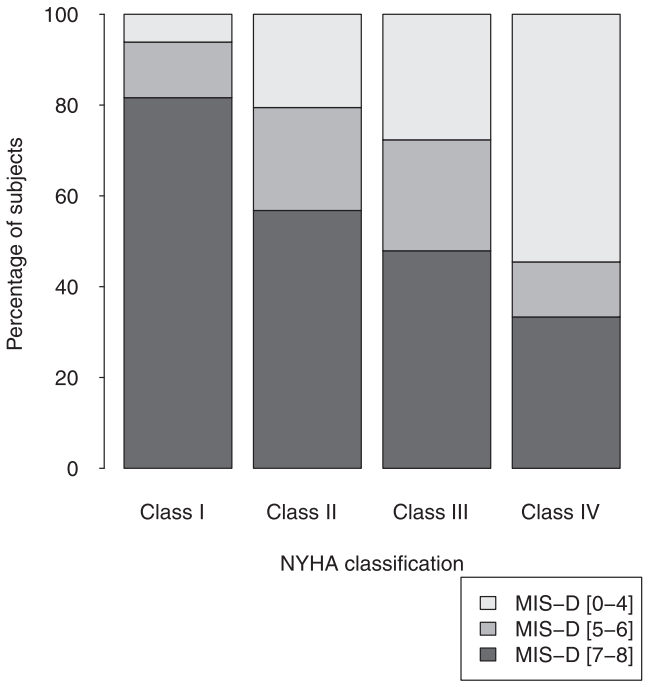

Figure 2. Proportion of cognitive impairment according to NYHA stages. Chi-square p <0.00001 difference of proportion of MIS-D categories by NYHA categories.

Table 3
Multivariate analyses of factors associated with cognitive status (MIS-D scores)

Characteristic	MIS-$D_{[5-6]}$		MIS-$D_{[0-4]}$	
	OR (95% CI)	p Value*	OR (95% CI)	p Value*
Age	1.05 (1.01−1.09)	0.01	1.07 (1.04−1.11)	0.0001
Male	0.66 (0.44−1.00)	0.048	1.05 (0.69−1.61)	0.81
Higher education	0.56 (0.31−1.00)	0.05	0.23 (0.11−0.50)	0.0002
Physical activity	0.60 (0.40−0.88)	0.01	0.47 (0.31−0.72)	0.0004
Depression	1.30 (0.77−2.20)	0.33	2.04 (1.25−3.34)	0.005
History of stroke	0.81 (0.44−1.50)	0.51	1.78 (0.05−3.00)	0.03
Heart rate	1.02 (1.00−1.03)	0.01	1.01 (0.99−1.02)	0.31
Renal failure (eGFR <60 ml/min)	1.21 (0.75−1.95)	0.27	2.12 (1.23−3.64)	0.007

Higher education is defined as above high school achievement.

CI = confidence interval; eGFR = estimated glomerular filtration rate; OR = odds ratio.

* Multinomial logistic regression with subjects with MIS-D >6 as reference group.

48.8. MIS-$D_{[5-6]}$ was found in 203 subjects (22.2%, 95% confidence interval 19.5 to 25.5) and MIS-$D_{[0-4]}$ in 213 subjects (23.4%, 95% confidence interval 20.6 to 26.1; Figure 1 and Table 1). Meanwhile, cardiologists spontaneously suspected cognitive impairment in 109 subjects (12%) before the cognitive evaluation (8.7% of subjects with MIS-$D_{[5-6]}$ and 34% of subjects with MIS-$D_{[0-4]}$; Figure 1).

Subjects had been diagnosed with HF on average 4.4 ± 4.8 years earlier (Table 2). The most frequent underlying cardiovascular diseases were hypertension (59%), coronary heart disease (53%), dilated cardiomyopathy (37%), and atrial fibrillation (35%). Mean LVEF was 44 ± 12.0% and 24% patients had preserved ejection fraction (LVEF ≥50%). None of the treatments for HF was associated with memory impairment. Subjects had an average of 4.4 ± 1.3 different cardiac medications and 43% of them had at least 5 different cardiovascular drugs.

The severity of the HF (NYHA classification) increased with lowering MIS-D score (Table 2 and Figure 2). In contrast, we did not find any relation between MIS-D groups and the underlying cause of HF, the level of blood pressure, or LVEF when analyzed as a continuous variable or with the threshold of 50%. There was a marginal association with heart rate. There were no differences in HF treatments in the 3 groups.

When variables associated with MIS-D groups (with p <0.15) were entered simultaneously in a multinomial logistic model with backward elimination, older age, low education level, low regular physical activity, depression, history of stroke, and renal failure were independent determinants of memory impairment (Table 3). Female gender and higher heart rate were only significantly associated with MIS-$D_{[5-6]}$. Hierarchical models were used to adjust for the effect of individual cardiologists, but there were no substantial differences in results compared with the overall multinomial model (results not shown).

Among subjects with MIS-$D_{[0-6]}$, those perceived to be cognitively normal by cardiologists were younger and with less functional impairment measured by IADL compared with those perceived to be cognitively impaired. Moreover, they had, on average, a less severe overall condition: with less frequent history of stroke, fall, depression, renal failure, peripheral arterial disease, and malnutrition. Those differences were no longer significant after adjustment to the subjects' IADL score.

Discussion

In this large sample of community-dwelling patients aged ≥70 years with HF, we showed that 46% of patients had memory impairment as identified by MIS-D. In contrast, only 12% of the patients were considered to have memory impairment based on the subjective evaluation by their cardiologists Severity of memory impairment increased with increasing severity of HF. Age, lower education level, low physical activity, depression, history of stroke, and renal failure were independently associated with memory impairment.

In the general older population, the prevalence of cognitive impairment ranges from 10% to 25%[11,12] and is much lower than that of our sample of patients with HF. These findings suggest an increased risk of cognitive impairment in HF. Our results agree with already published data on cognitive impairment in subjects with HF for whom prevalence ranges from 25% to 74%.[13,14] The very wide range of this prevalence can be explained not only by the different characteristics of the populations studied but also by differences in the tests and cutoffs used to assess and define the cognitive impairment.

For detection of memory impairment, we chose the MIS test that has been reported as one of the most usable screening tools for the detection of cognitive impairment by the Alzheimer's Association's workgroup of the Alzheimer's Association for Assessment of Cognition[15] and by

the French guidelines for diagnosis and management of Alzheimer disease.[16] Our study highlights the high usability of the MIS-D, with 93% of the cardiologists being able to administer the MIS-D to their patients.

The detection of cognitive deficits is important because a significant increase of 1-year mortality and an increased likelihood of functional disability have been found in subjects with HF with cognitive impairment.[3,17] Management of HF involves complex pharmacological therapy, diet and fluid restrictions, monitored physical activity, and patient education that can be difficult to understand, remember, and manage for patients with cognitive impairment, with consequent suboptimal management and more frequent health complications.[18] Memory deficit has been associated with reduced medication and appointment adherence and difficulty in making diet changes.[19,20] Early identification of memory changes would enable cardiologists to set up strategies to improve drug compliance (pillbox, nurse visits, education of the caregiver, intervention, and so forth).[21] Meanwhile, cardiologists significantly underestimated memory impairment among their patients, similar to reports for nonspecialists who also underestimate the cognitive decline in patients.[22] In this study, cardiologists mainly underestimated memory impairment in subjects with preserved activities of daily living who might appear less impaired even if their memory was severely affected.

As expected, we confirm an association between memory impairment and age, lower education level, low physical activities, depression,[23] and history of stroke[24] that has already been reported in the HF population.[25] Although subjects with memory impairment had hypertension more often, the relation was no longer significant when the analysis was adjusted for age and gender. Furthermore, only a weak association was found with diabetes. Our results could also be explained by selection of our population in which, by definition, the prevalence of those vascular risk factors was very high.

Interestingly, regular physical activity was more frequent among cognitively normal subjects. A beneficial effect of physical activity on cognition has already been shown in older adults[26] and only in a very small sample in subjects with chronic HF.[27] Alternatively, subjects with memory disorders may exercise less than subjects without memory disorders.

As already described, we observed an association between the severity of HF and the severity of memory impairment even when age and gender were taken into account.[4] However NYHA stage was no longer significant when the model was further adjusted for education, physical activity, presence of depression, history of stroke, heart rate, and renal failure, suggesting that the association of HF severity and memory deficit was confounded by these factors.

The mechanisms underlying cognitive impairment in patients with HF remain poorly understood. The association could be related to (1) common risk factors between HF and dementia such as hypertension, diabetes, or dyslipidemia, (2) focal brain vascular lesions and/or chronic ischemia more frequent among patients with HF,[28,29] and (3) decreased cardiac output leading to inadequate cerebral perfusion.[30] In our study, however, NYHA stage and low LVEF values were not independently associated with memory deficit,[25] so it is unlikely that it is purely decreased cardiac output that caused the memory deficit.

The strength of the study lies in the large number of subjects with definite chronic HF diagnosis that is likely to be representative of the general HF population as it only included patients in ambulatory care.

Our study has also several limitations. First the cross-sectional design precludes any assessment of the temporal relationship of HF and memory impairment. Second, memory assessment only relied on a global memory score using a screening test. Other domain-specific cognitive impairment such as attention deficit and executive function that are frequently associated with HF were not assessed. No formal diagnosis of dementia was performed, but memory deficit is among the earliest affected markers of cognitive decline and the strong correlation between MIS-D and IADL favors the hypothesis that subjects detected with severe memory impairment probably had dementia.

This study found that memory impairment was frequent in patients with chronic HF and often underrecognized by cardiologists. Memory impairment can be detected easily using a simple test, which is important because memory deficits may have implications for drugs and lifestyle compliance.

Acknowledgment: Data quality control was performed by Axonal S.A., Nanterre, France.

Disclosures

Drs. Hanon, De Groote, Galinier, Isnard, Logeart, and Komajda have received honoraria from Menarini as consultants for the conception and design of the study. Dr. Vidal has no conflict of interest.

1. Bleumink GS, Knetsch AM, Sturkenboom MCJM, Straus SMJM, Hofman A, Deckers JW, Witteman JCM, Stricker BHC. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure. The Rotterdam Study. *Eur Heart J* 2004;25:1614−1619.
2. Vogels RLC, Oosterman JM, van Harten B, Scheltens P, van der Flier WM, Schroeder-Tanka JM, Weinstein HC. Profile of cognitive impairment in chronic heart failure. *J Am Geriatr Soc* 2007;55:1764−1770.
3. Zuccala G, Onder G, Pedone C, Cocchi A, Carosella L, Cattel C, Carbonin PU, Bernabei R. Cognitive dysfunction as a major determinant of disability in patients with heart failure: results from a multicentre survey. On behalf of the GIFA (SIGG-ONLUS) Investigators. *J Neurol Neurosurg Psychiatry* 2001;70:109−112.
4. Trojano L, Antonelli Incalzi R, Acanfora D, Picone C, Mecocci P, Rengo F. Cognitive impairment: a key feature of congestive heart failure in the elderly. *J Neurol* 2003;250:1456−1463.
5. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. *Arch Intern Med* 2006;166:1003−1008.
6. Okonkwo OC, Cohen RA, Gunstad J, Tremont G, Alosco ML, Poppas A. Longitudinal trajectories of cognitive decline among older adults with cardiovascular disease. *Cerebrovasc Dis* 2010;30:362−373.
7. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology.

Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;29:2388−2442.
8. de Rotrou J, Battal-Merlet L, Wenisch E, Chausson C, Bizet E, Dray F, Lenoir H, Rigaud AS, Hanon O. Relevance of 10-min delayed recall in dementia screening. *Eur J Neurol* 2007;14:144−149.
9. Barberger-Gateau P, Dartigues JF, Letenneur L. Four Instrumental Activities of Daily Living Score as a predictor of one-year incident dementia. *Age Ageing* 1993;22:457−463.
10. R Core Team (2013). R: A Language and Environment for Statistical Computing, Vienna, Austria. URL *http://www.R-project.org/*.
11. Schonknecht P, Pantel J, Kruse A, Schroder J. Prevalence and natural course of aging-associated cognitive decline in a population-based sample of young-old subjects. *Am J Psychiatry* 2005;162:2071−2077.
12. Unverzagt FW, Gao S, Baiyewu O, Ogunniyi AO, Gureje O, Perkins A, Emsley CL, Dickens J, Evans R, Musick B, Hall KS, Hui SL, Hendrie HC. Prevalence of cognitive impairment: data from the Indianapolis Study of Health and Aging. *Neurology* 2001;57:1655−1662.
13. Gure TR, Blaum CS, Giordani B, Koelling TM, Galecki A, Pressler SJ, Hummel SL, Langa KM. Prevalence of cognitive impairment in older adults with heart failure. *J Am Geriatr Soc* 2012;60:1724−1729.
14. Vogels RLC, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: a systematic review of the literature. *Eur J Heart Fail* 2007;9:440−449.
15. Cordell CB, Borson S, Boustani M, Chodosh J, Reuben D, Verghese J, Thies W, Fried LB. Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. *Alzheimers Dement* 2013;9:141−150.
16. HAS Recommandations professionnelles. Diagnostic et prise en charge de la maladie d'Alzheimer et des maladies apparentées. *Rev Neurol (Paris)* 2008;164:754−774.
17. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006;355:260−269.
18. Riegel B, Moser DK, Anker SD, Appel LJ, Dunbar SB, Grady KL, Gurvitz MZ, Havranek EP, Lee CS, Lindenfeld J, Peterson PN, Pressler SJ, Schocken DD, Whellan DJ. State of the science: promoting self-care in persons with heart failure: a scientific statement from the American Heart Association. *Circulation* 2009;120:1141−1163.
19. Insel K, Morrow D, Brewer B, Figueredo A. Executive function, working memory, and medication adherence among older adults. *J Gerontol B Psychol Sci Soc Sci* 2006;61:P102−P107.
20. Heckman GA, Patterson CJ, Demers C, St Onge J, Turpie ID, McKelvie RS. Heart failure and cognitive impairment: challenges and opportunities. *Clin Interv Aging* 2007;2:209−218.
21. Barnason S, Zimmerman L, Hertzog M, Schulz P. Pilot testing of a medication self-management transition intervention for heart failure patients. *West J Nurs Res* 2010;32:849−870.
22. Kaduszkiewicz H, Zimmermann T, Van den Bussche H, Bachmann C, Wiese B, Bickel H, Mosch E, Romberg H, Jessen F, Cvetanovska-Pllashniku G, Maier W, Riedel-Heller SG, Luppa M, Sandholzer H, Weyerer S, Mayer M, Hofmann A, Fuchs A, Abholz H, Pentzek M. Do general practitioners recognize mild cognitive impairment in their patients? *J Nutr Health Aging* 2010;14:697−702.
23. van den Kommer T, Comijs H, Aartsen M, Huisman M, Deeg D, Beekman A. Depression and cognition: how do they interrelate in old age? *Am J Geriatr Psychiatry* 2012;21:398−410.
24. Schneider JA, Wilson RS, Cochran EJ, Bienias JL, Arnold SE, Evans DA, Bennett DA. Relation of cerebral infarctions to dementia and cognitive function in older persons. *Neurology* 2003;60:1082−1088.
25. Riegel B, Lee CS, Glaser D, Moelter ST. Patterns of change in cognitive function over six months in adults with chronic heart failure. *Cardiol Res Pract* 2012;2012:631075.
26. Erickson KI, Kramer AF. Aerobic exercise effects on cognitive and neural plasticity in older adults. *Br J Sports Med* 2009;43:22−24.
27. Carles SJ, Curnier D, Pathak A, Roncalli J, Bousquet M, Garcia J, Galinier M, Senard J. Effects of short-term exercise and exercise training on cognitive function among patients with cardiac disease. *J Cardiopulm Rehabil Prev* 2007;27:395−399.
28. Kuller LH, Margolis KL, Gaussoin SA, Bryan NR, Kerwin D, Limacher M, Wassertheil-Smoller S, Williamson J, Robinson JG. Relationship of hypertension, blood pressure, and blood pressure control with white matter abnormalities in the Women's Health Initiative Memory Study (WHIMS)-MRI trial. *J Clin Hypertens (Greenwich)* 2010;12:203−212.
29. Hanon O, Leys D. Cognitive decline and dementia in the elderly hypertensive. *J Renin Angiotensin Aldosterone Syst* 2002;3:S32−S38.
30. Massaro AR, Dutra AP, Almeida DR, Diniz RVZ, Malheiros SMF. Transcranial Doppler assessment of cerebral blood flow: effect of cardiac transplantation. *Neurology* 2006;66:124−126.