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Cognitive Decline Over Time in Patients with Systolic Heart Failure: Insights from WARCEF

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The investigators in the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) Study Group are listed in the Supplementary Appendix

Conflict of Interest:

Dr. Anker reports being a consultant for Bayer, Boehringer Ingelheim, Novartis, Stealth Peptides, Servier, Vifor, Janssen (all for trial/registry steering committee work), and he has received research grants from Abbott Vascular and Vifor. Dr. Homma reports being a consultant for St. Jude Medical, Daiichi-Sankyo, Bristol Meyers Squibb, Pfizer. Dr. Labovitz has received a research grant from Bristol-Myers Squibb/Pfizer for the AREST trial. Dr. Lip has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo; speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. Dr. Sacco has received research grants from NINDS, NCATS, AHA, Evelyn McKnight Brain Foundation and Boehringer Ingelheim. Dr. Teerlink has received consulting fees/research grants from Actelion, Amgen, Bayer, Cytokinetics, Medtronic, Novartis, St. Jude, Trevena. The other authors have no relations to report.

Clinical Trial Information: The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial has been registered in the database (http://www.ClinicalTrials.gov Trial Reg no.).

Abstract

Objectives: To characterize the cognitive decline (CD) over time and its predictors in patients with systolic heart failure (HF)

Background: Despite the high prevalence of CD and its impact on mortality, predictors of CD in HF have not been established.

Methods: We investigated CD in the Warfarin versus Aspirin in Reduced Ejection Fraction (WARCEF) trial, which performed yearly Mini-Mental State Examination (MMSE; higher scores are better cognitive function; normal score: 24 or higher). We performed longitudinal time-varying analysis between pertinent covariates, including baseline MMSE, and MMSE score during follow-up, analyzed both as a continuous variable and a 2-point decrease. To account for loss to follow-up, data at the baseline and 12-month visit were analyzed separately (sensitivity analysis).

Results: A total of 1846 patients were included. In linear regression, MMSE decrease was independently associated with higher baseline MMSE ($p<0.0001$), older age($p<0.0001$), non-White race/ethnicity ($p<0.0001$), and lower education ($p<0.0001$). In logistic regression, CD was independently associated with higher baseline MMSE (odds ratio 1.13, 95% confidence interval [1.07-1.20], $p<0.001$), older age (1.37 [1.24-1.50], $p<0.001$), non-White race/ethnicity (2.32 [1.72-3.13] for Black, 1.94 [1.40-2.69] for Hispanic vs. White, $p< 0.001$), lower education ($p<0.001$), and NYHA class II or higher ($p=0.03$). Warfarin and other medications were not associated with CD. Similar trends were seen in the sensitivity analysis (N=1439).

Conclusions: CD in HF is predicted by baseline cognitive status, demographic variables and NYHA class. The possibility of intervening on some of its predictors suggests the need for the frequent assessment of cognitive function in HF patients.

Keywords

Longitudinal analysis; Cognitive function; MMSE; Dementia; Comorbidities

INTRODUCTION

Patients with heart failure (HF) often experience cognitive decline (CD) (1); in fact, CD prevalence ranges from 25% to75% (2–4). HF patients with CD experience early death, loss of functional independence, lower adherence to therapy and decreased quality of life (5). The established or postulated mechanisms for CD in HF are: chronic cerebral hypoperfusion, micro emboli from cardiac thrombi, disruptions of blood-brain barrier, vascular remodeling, systemic inflammation and endothelial dysfunction (3).

Although CD has a profound impact on mortality in HF (6), little is known about the extent of changes in cognitive function over time among patients with HF because of the paucity of longitudinal data (1,7–12). Longitudinal studies of CD are challenging, partly because of missing data due to loss to follow-up, which may in part result from the impact of CD itself. First, CD is associated with a greater probability of missing social engagements, including clinic visits (5). Second, since mortality in HF is still high, patients may die before a second assessment of cognitive function can be performed. Third, a relatively long follow-up period,

ideally 18 months, is needed to monitor for development of CD (2), because cognitive changes in HF patients are gradual (9,10).

Hence, the risk factors for CD in HF have not been clearly established. In addition, because chronic cerebral hypoperfusion, microemboli from cardiac thrombi and endothelial dysfunction are postulated as mechanism for CD among HF patients, variables such as severity of HF, anticoagulant therapy, and drug treatment could all affect the trajectory of cognitive function over time; however, they have not been thoroughly examined due to the limited information regarding severity and treatment of HF in previous studies (1,7–10).

The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial (13) was a large randomized clinical trial that tested the effect of warfarin versus aspirin on the risk of death and stroke in 2305 patients with systolic HF in sinus rhythm. The loss to follow-up rate was notably low (1.5%). The WARCEF cohort was followed for an average of 3.5 years, and cognitive function was assessed annually. Previously we reported that shorter six-minute walk distance was an independent predictor for cognitive impairment measured by the Mini-Mental State Examination (MMSE) (14). In the present analysis, we aimed to characterize the frequency and predictors of CD as measured by change in MMSE over time, and to determine whether CD was independently associated with baseline cognitive function, indicators of HF severity and treatment of HF.

METHODS

WARCEF trial

The protocol of the WARCEF trial has been described previously (13) (http://www.ClinicalTrials.gov Trial Reg no.). Briefly, patients with LVEF ≤ 35% who were in sinus rhythm were randomized to receive warfarin or aspirin. Additional eligibility criteria included age ≥ 18 years old, having no contraindications to warfarin, having a modified Rankin score of ≤ 4, and being on evidence-based heart failure medications (beta-blocker, angiotensin-converting enzyme [ACE] inhibitor, or angiotensin II receptor blockers [ARBs], or hydralazine and nitrates). The trial excluded patients if they had a clear indication for warfarin or aspirin, or a condition that conferred a high risk of cardiac embolism. A total of 2,305 patients (warfarin arm, N=1,142; aspirin arm, N=1,163) were enrolled from 168 centers in 11 countries from October 2002 to January 2010. Out of 2305 patients, the number lost to follow-up and withdrawal of consent was 34 (1.5%) and 34 (1.5%), respectively. MMSE assessment, described previously (12) was mandatory at every yearly visit. MMSE is commonly used to estimate the severity of cognitive impairment and to follow the course of cognitive changes in an individual over time. Higher scores are better, and normal cognitive function is set at a score of 24 or higher. In WARCEF, MMSE was administered in a standardized fashion in the native language of each patient by trained staff at each individual site. Mean follow-up was 3.5 ± 1.8 years. Institutional Review Boards at the coordinating centers for all sites approved the study, and all patients provided informed consent.

Outcomes and covariates

We analyzed CD using change in MMSE in two ways; first as a continuous variable, and second as a discrete 2-point or greater decline from the baseline, a clinically relevant definition based on the previous literature (15,16).

We considered all baseline characteristics available in WARCEF (Table 1) as candidate confounders. These include demographic characteristics such as, age, sex, race/ethnicity, education, geographic location, and clinical characteristics such as vitals (body mass index, pulse rate), lifestyle risk factors (smoking status, alcohol consumption), comorbidities and past medical history, medications, laboratory data, and indices of HF severity (left ventricular ejection fraction [LVEF], New York Heart Association [NYHA] classification, baseline health-related quality of life measured by Minnesota Living with Heart Failure Questionnaire [MLWHFQ] score, and distance covered on 6-minute walk). The definitions of each variable are described in detail elsewhere (13). The missingness of the baseline variables is presented in Supplemental Table 1.

Study Population and Statistical analysis

For the current analysis, we included patients who had at least two MMSE measurements: baseline and another visit at any point during their follow-up (**Main analysis**, N=1846).

Patient characteristics are presented as means ± standard deviations (SD) for continuous variables and as proportions for categorical variables. Kaplan-Meier plots by baseline cognitive function were produced for the time to the first event in the composite end point of ischemic stroke, intracerebral hemorrhage, or death from any cause. Kaplan-Meier estimates of mortality rate were also calculated.

To account for the repeated measurements of cognitive function in each patient, mixed-effects models were used to evaluate the association between baseline covariates and the outcomes of interest (linear model for the change of MMSE score from the baseline and logistic model for decline of ≥ 2 MMSE points from baseline). The mixed-effects models consist of two components, a fixed-effects component that represents the average model in the population, and a random effects component that represents within-individual variation. We used a random intercept to account for individual variation. For each baseline covariate, we first built an individual model with the covariate as an independent variable, adjusting for follow-up time (in months). The final multivariable model was built using backward elimination, adjusting for follow-up time. Aldosterone blocker treatment was removed from the analysis due to the large amount of missing information (Supplemental Table 1).

Among the reasons for missing follow-up mentioned previously, two are relevant to the results of our investigation. One is that patients may have died before the second follow-up visit; the other is that they may have missed the follow-up visits for reasons that include CD. To at least partly address these concerns, we conducted a sensitivity analysis to assess the association between baseline variables and CD observed beyond month 12, only examining patients who had at least three MMSE measurements: baseline, 12-month visit, and another visit at any point after 12 months (**Sensitivity analysis**, N=1439). The same set of analyses was conducted as for the general analysis, except for using CD from 12-month visit (rather

than from baseline) as the outcome. Missing values of baseline variables were imputed using means for continuous variables and modal values for categorical variables. For all statistical analyses, a two-tailed $P < 0.05$ was considered significant. All data analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

All 2305 randomized patients were included in the WARCEF primary analysis. 622 (27.0%) of them had a primary event (stroke, intracerebral hemorrhage, or death) (13), and 2287 (99%) had a baseline MMSE measurement. The current main analysis includes the 1846 patients (80.1%) who had baseline MMSE and at least one follow-up MMSE measurement. The 459 patients who lacked some of this information could not be included. Compared to these, the patients included in the current main analysis were more likely to have better baseline MMSE score, smaller Non-Hispanic Black representation, slower pulse rate, higher education level, fewer comorbidities (hypertension, diabetes, prior stroke and atrial fibrillation), higher rate of beta-blocker treatment, higher hemoglobin level, better kidney function, and lower HF severity (Supplemental Table 2). The baseline MMSE in the study cohort was 28.6 ± 2.0. The numbers of patients with an MMSE score of 30, 27-29, and < 27 were 788, 843, and 215, respectively. Kaplan-Meier estimates of the composite endpoint (ischemic stroke, intracerebral hemorrhage, or death from any cause) with an MMSE score of 30, 27-29 and < 27 were 25.2%, 34.3%, and 37.9% (p =0.023), respectively (Supplemental Figure 1). Kaplan-Meier estimates of death rate were 22.0%, 32.2%, and 32.7% (p =0.018), respectively.

At 12 months, 227 patients out of 1680 with available information (13.6%) showed CD (i.e., decline of ≥ 2 MMSE points from baseline). Among 1224 patients who had at least one MMSE measure after 12 months and did not show CD at 12-month visit, an additional 231 (18.9%) showed CD beyond 12 months. Kaplan-Meier estimates of death with an MMSE decrease of ≥ 2-point, 1-point, and no decrease were 33.4%, 32.1%, and 27.2% (p=0.051), respectively (Figure 1). Table 1 shows patient characteristics in the main analysis (N=1846) and the sensitivity analysis (N=1439). The mean age in the main analysis was 60.8 ± 11.2 years, 80.6% of patients were men, and 98.5 % were on an ACE inhibitor or ARB. Among the 1846 patients in the main analysis, 1439 patients who underwent MMSE measurement at both 12-month visit and a later follow-up visit were included in the sensitivity analysis. The patients included in the sensitivity analysis showed similar baseline MMSE score, racial/ethnic distribution and clinical variables, including HF treatment and severity (Table 1).

In the multivariable model for MMSE change from baseline, we observed that a higher MMSE at baseline, older age, non-White race/ethnicity, lower education level, and higher LVEF were independently associated with MMSE decrease (Table 2). In the sensitivity analysis beyond 12 months (Table 3), MMSE decline was associated with higher MMSE at the 12-month visit, older age, non-White race/ethnicity, lower education level, prior history of stroke/TIA and lower estimated glomerular filtration rate (eGFR).

In the multivariable model for CD (i.e. ≥ 2-point drop in MMSE) from baseline (Main analysis; Table 4), we observed that a higher MMSE at baseline, older age, non-White race/

ethnicity, lower education level, and NYHA class II or higher were independently associated with increased likelihood of CD. In the sensitivity analysis for the CD beyond 12 months (Table 5), CD was associated with the same variable as the main analysis in addition of prior history of stroke/TIA and renal dysfunction.

Although baseline cognitive impairment was associated with 6-minute walk distance in our previous report (14), in the present study neither any MMSE decline nor CD over time was associated with 6-minute walk distance. In the WARCEF trial, the intervention was the administration of warfarin or aspirin in double-blinded fashion. In the multivariable analyses, warfarin treatment was neither associated with CD nor with decrease of MMSE score. Moreover, blockade of renin-angiotensin system (ACE inhibitor or ARB) was also not associated with CD or any MMSE decline in either analysis.

DISCUSSION

In this post-hoc analysis of the WARCEF trial, cognitive impairment at baseline was associated with a higher mortality rate, as previously known (5), thus affecting the ensuing analysis on CD over time. The sample size of our cohort (1,846) was larger than the combined number of HF patients (1,553) included in previous longitudinal studies. In addition, in the present study over 13% of patients showed a decrease in MMSE score of at least 2-point at 12-month visit. In the multivariable analyses, the magnitude of any MMSE score decline was significantly associated with higher baseline MMSE score, older age, non-White race/ethnicity, and lower educational level. In the multivariable analysis that focused on the clinically relevant decline (decline of ≥ 2-point MMSE score), CD was again significantly associated with higher baseline MMSE score, older age, non-White races/ethnicity, lower education level, and also with NYHA class II or higher. Also, CD was not associated with anticoagulation therapy or HF medications. Similar trends were seen in the sensitivity analysis (N=1439), with the addition of renal dysfunction and prior history of stroke/TIA being associated with MMSE decrease and CD.

Few studies have specifically addressed the factors associated with CD among HF patients. There are seven longitudinal studies (a total of 1,553 patients with HF diagnosis) which measured cognitive function repeatedly (1,7–12). However, four of them focused primarily on the incidence or prevalence of CD in patients with and without HF, rather than on the risk factors for CD among HF patients (1,8–10). One study (n= 280, 6-month follow-up) (7) that did examine the risk factors for CD among HF patients provided a detailed assessment of cognitive function, socioeconomic status, and behavioral factors, but its generalizability was limited by its relatively small sample size, short follow-up and limited information regarding HF severity. Another study (N = 382, 18-month follow-up) (11) focused on the prevalence of severe cognitive impairment and its predictors among elderly patients, while our focus was gradual change of cognitive function over time, mostly still remaining within normal limits. Another difference is that the measurement of cognitive function in the previous study was the Hodkinson Abbreviated Mental Test, which has a lower sensitivity and specificity in detecting cognitive impairment than the MMSE (17). Our investigation has a larger sample size, longer follow-up (3.5 ± 1.8 years), and yearly MMSE measurements, which have allowed a time-varying outcome analysis. Also, the larger sample size enabled us to assess

and take into account the potential bias due to missing data. Patients with cognitive impairment are often lost to follow-up, therefore resulting in an artificially lower perceived effect of HF on CD; in fact, we observed a progressive increase in mortality with decreasing baseline MMSE, which led us to try and confirm the main results in the subgroup who had available MMSE data at both baseline and the 12-month visit.

Higher baseline MMSE score was significantly associated with decline of MMSE score as well as CD (≥ 2-point decline of MMSE score) after adjustment of covariates in the main analysis and the sensitivity analysis. Our result is contrary to results from the general population, which showed CD to be associated with low baseline MMSE score (18,19). From a pathophysiology standpoint, our results are plausible because CD in HF patients is conceivably more related to the interaction between heart and brain than in general population (3), which may recognize other predominant risk factors for CD (8,9).

With regard to HF severity and CD, our findings were different from previous studies (1), which consistently showed that NYHA class are not associated with CD in HF patients. In contrast, we showed that NYHA class II or higher was associated with CD after 12 months. Our observation appears in line with the proposed pathophysiology of CD in HF patients: chronic HF leads to a relative loss of gray matter in the brain (12) and, therefore, affects brain function (3). However, other indices of HF severity, such as baseline MLWHFQ score and distance of 6-minute walk were not associated with incident CD in our study. The observed association between CD and HF severity cannot indicate a specific mechanism for CD in HF patients; unfortunately, we did not have data regarding the possible associations between chronic cerebral hypoperfusion and HF severity. Therefore, answering mechanistic questions on CD in HF will require further investigation in appropriately designed studies.

We showed that the decline of cognitive function was not associated with warfarin or aspirin therapy or with HF medications. Since microembolism from a cardiac source is considered another possible mechanism for CD in HF, warfarin treatment might have been expected to decrease the risk of CD. Although our study showed that anticoagulation therapy by warfarin was not associated with protection from CD or any MMSE score decline (Tables 2–5), the possibility that anticoagulation may affect CD development in HF patients would again have to be analyzed in ad hoc studies. Since 98% of patients were receiving an ACE inhibitor or ARB medication, we could not assess the effect of these medications on CD.

Although alcohol consumption is a strong risk factor of CD in general population (20,21), it was not associated with CD in our study. However, this result needs careful interpretation because the much higher mortality rate among HF patients than in general population may have confounded the results. Noncardiovascular comorbidities of HF patients have significant impact on clinical outcomes (22–24). We showed that lower eGFR and the history of stroke/TIA was significantly associated with CD and any decline of MMSE score in the sensitivity analysis (Table 3 and 5). These findings suggest that noncardiovascular comorbidities also play an important role in CD in HF patients, and unlike other predictors such as age and race/ethnicity, represent potential targets for interventions to reduce the incidence of CD in HF patients.

Our results showed that older age, lower education and non-White race/ethnicity were significantly associated with CD and decrease of MMSE score (Table 2–5). These confirm the findings of a previous study in Alzheimer disease. (25) Non-white race/ethnicity was significantly associated with CD even after controlling for other variables, suggesting the existence of racial disparities among patients with HF, in accordance with the ongoing public concerns regarding racial disparities in HF care and outcomes in the US. (26–28) However, given the retrospective nature of our investigation, this interpretation requires caution and should be regarded as exploratory and hypothesis-generating. Also, we could not address the possibility of socioeconomic factors affecting this result, because race/ethnicity is a variable that encompasses a lifelong social experience (29,30), and WARCEF did not collect detailed information of socioeconomic status other than educational level.

Limitations

Our study is a post-hoc analysis and the results do not establish a causal relation between the explored variables and CD. Second, possible selection bias might limit the interpretation. The MMSE measurement took place annually, and we analyzed only patients who had multiple MMSE measurements. The exclusion of patients who died or were lost to follow-up before the second MMSE measurement may have led to an underestimation of CD in our study (Supplemental Table 1). Third, we could not analyze the possible impact on CD of underlying silent atrial fibrillation. Fourth, the WARCEF data do not allow differentiation between patients with CD and patients with depression or patients who had changes in manifestations of depression.

Conclusion

CD over time was present in a sizeable portion of the cohort and was significantly associated with patients' baseline cognitive function, demographics and NYHA class II or higher. The high impact of CD on clinical outcomes and the possibility of intervening on some of its clinical predictors suggests the need for the frequent assessment of cognitive function in HF patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS LIST

HF	heart failure
CD	cognitive decline

MMSE	Mini-Mental State Examination
WARCEF trial	The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction trial
SD	standard deviations
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
MLWHFQ	Minnesota Living with Heart Failure Questionnaire score
eGFR	estimated glomerular filtration

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CLINICAL PERSPECTIVES

Clinical relevance

Although cognitive decline is common among patients with heart failure, the risk factors for it have not yet been established due to the paucity of longitudinal data. The present study showed that cognitive decline was associated with better baseline cognitive function, older age, non-White race/ethnicity, lower education level, and also NYHA class, prior stroke and renal dysfunction in the longer term. Medical treatment of HF and anticoagulation were not associated with cognitive decline. Considering the high impact of cognitive impairment on mortality, and the possibility to act on some of its predictors, clinicians who treat HF patients should assess cognitive function frequently.

Translational outlook

The present study showed that cognitive decline took place in a sizeable portion of patients with systolic HF, and its predictors could be identified among a host of demographic and clinical variables. Despite the high prevalence of cognitive impairment and its impact on mortality among HF patients, possible measures to prevent or delay cognitive deterioration are not established and will require further focused investigation.

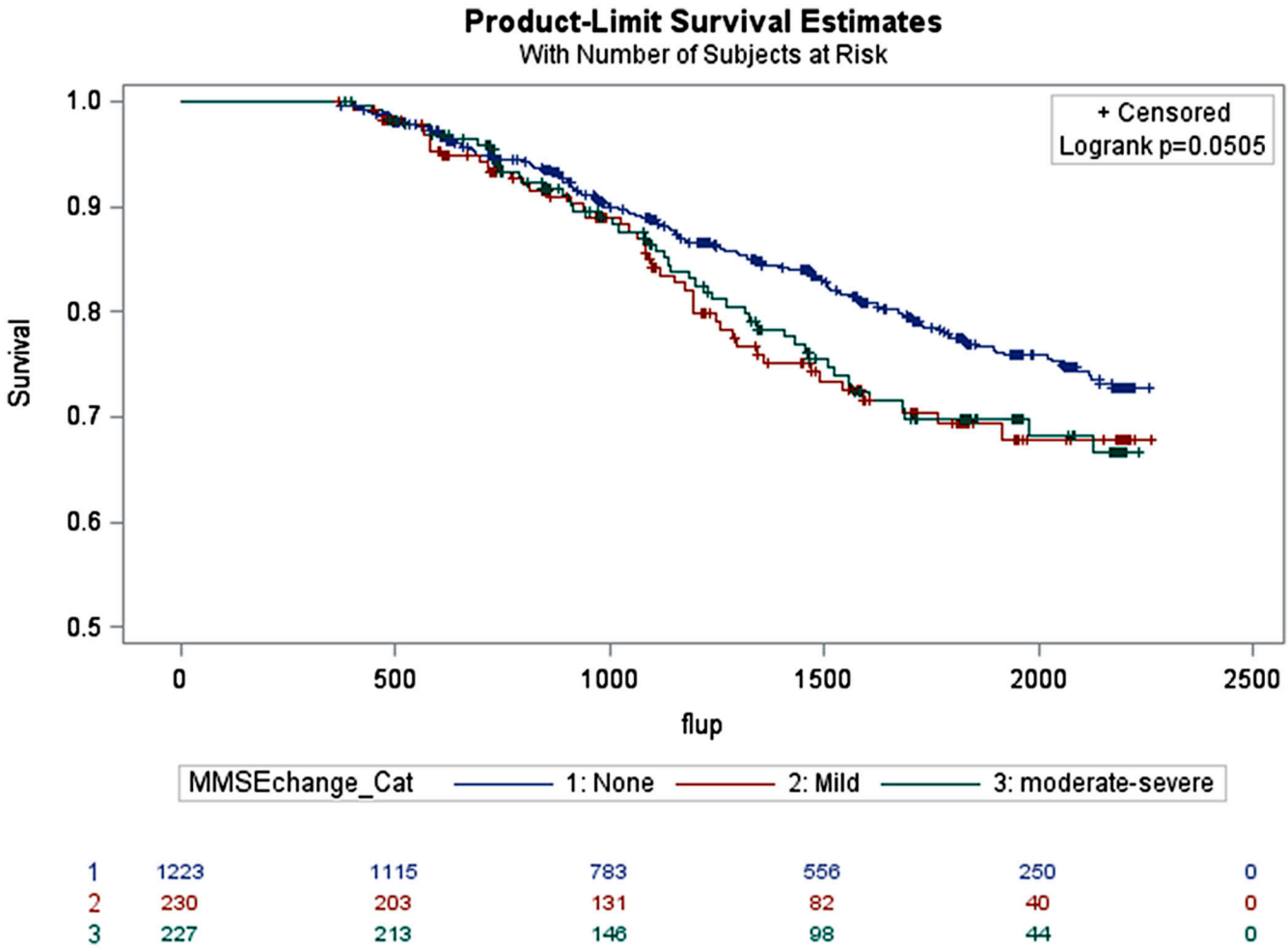
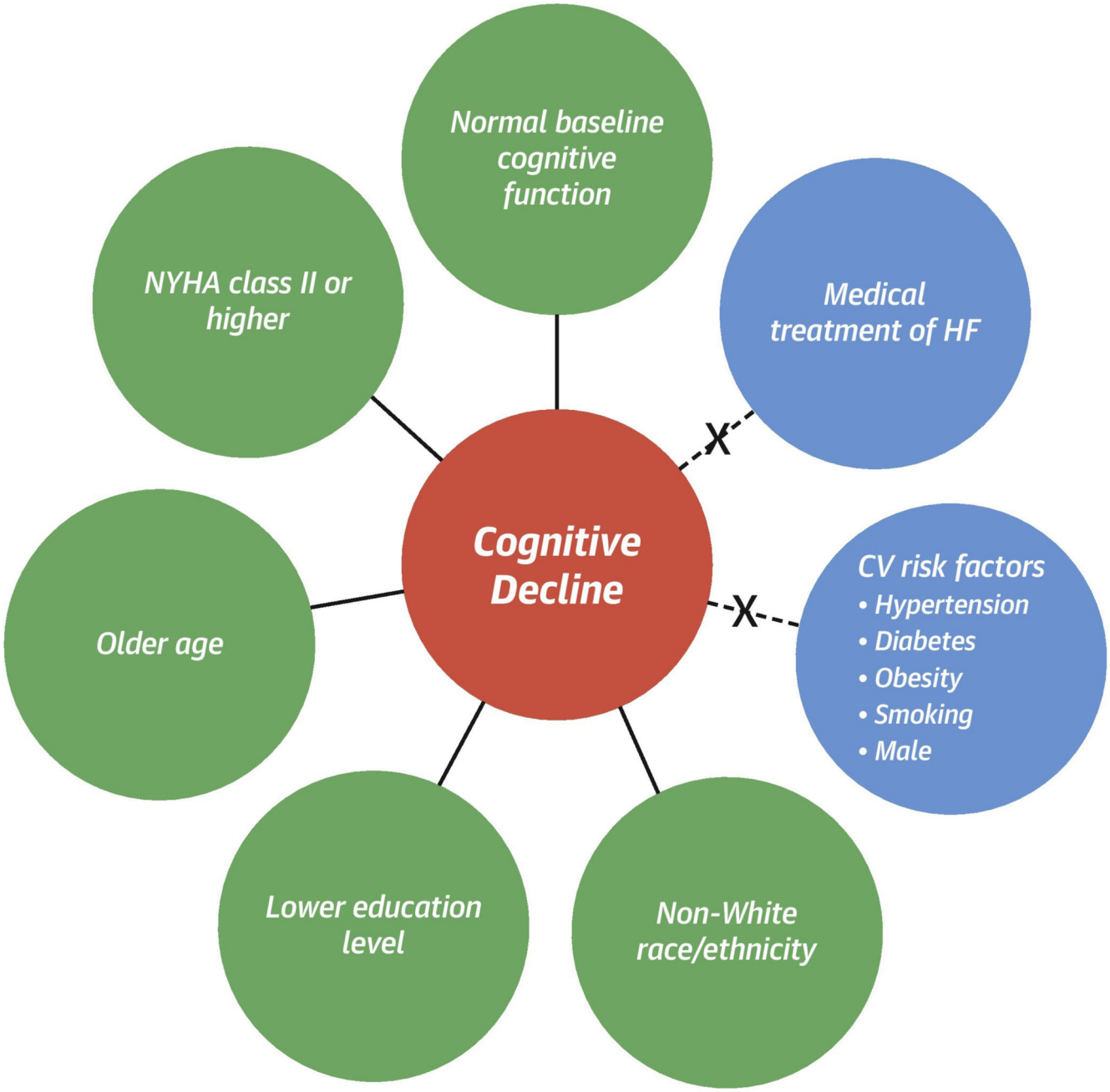


Figure 1.

Kaplan-Meier plot of all-cause death according to the change of MMSE score from baseline (N=1846)

MMSE, Mini-Mental State Examination

The outcome of the Kaplan-Meier plot was the time to death from any cause. Kaplan-Meier estimates of mortality rate with an MMSE score change of ≥2, 1, and non-drop (labeled as moderate-severe, mild, and none in the figure) were 33.4%, 32.1%, and 27.2% (p =0.051), respectively.



Central Illustration. Predictors of cognitive decline in systolic heart failure

NYHA, New York Heart Association; HF, heart failure; CV, cardiovascular.

Demographic and clinical variables (green circles) associated with cognitive decline during follow-up

Table 1.

Patients' characteristics

Variables	Main Analysis (N=1846)	Sensitivity Analysis (N=1439)
Location		
Argentina	76/1846 (4.1)	59/1439 (4.1)
Europe	904/1846 (49.0)	728/1439 (50.6)
North America	866/1846 (46.9)	652/1439 (45.3)
Baseline MMSE score	28.56 ± 2.05	28.62 ± 1.97
Age – year	60.8 ± 11.2	60.6 ± 11.0
Male sex	1487/1846 (80.6)	1163/1439 (80.8)
Race or ethnic group		
Non-Hispanic white	1424/1846 (77.1)	1138/1439 (79.1)
Non-Hispanic black	234/1846 (12.7)	158/1439 (11.0)
Hispanic & Other	188/1846 (10.2)	143/1439 (9.9)
Mean Body-mass index	29.2 ± 5.9	29.4 ± 5.9
Systolic blood pressure - mmHg	124.0 ± 18.7	124.0 ± 18.5
Pulse - beats/min	71.7 ± 11.9	71.7 ± 11.8
Educational level		
< High school	786/1843 (42.6)	613/1436 (42.7)
High-school graduate or some college	751/1843 (40.7)	575/1436 (40.0)
College graduate or postgraduate	306/1843 (16.6)	248/1436 (17.3)
Smoking status		
Current smoker	327/1845 (17.7)	252/1438 (17.5)
Former smoker	942/1845 (51.1)	747/1438 (51.9)
Never smoked	576/1845 (31.2)	439/1438 (30.5)
Alcohol Consumption		
Current consumption, >2 oz/day	470/1846 (25.5)	388/1439 (27.0)
Previous consumption, >2 oz/day	399/1846 (21.6)	305/1439 (21.2)
Never consumed alcohol	977/1846 (52.9)	746/1439 (51.8)
Hypertension	1072/1793 (59.8)	835/1405 (59.4)
Diabetes Mellitus	556/1843 (30.2)	420/1439 (29.2)
Ischemic Cardiomyopathy	793/1843 (43.0)	614/1439 (42.7)
Pacemaker or defibrillator	436/1844 (23.6)	343/1439 (23.8)
Prior stroke or TIA	217/1844 (11.8)	158/1438 (11.0)
Atrial Fibrillation	60/1844 (3.3)	41/1439 (2.8)
Warfarin	907/1846 (49.1)	704/1439 (48.9)
ACE inhibitor or ARB	1816/1844 (98.5)	1415/1437 (98.5)
Beta-blocker	1674/1845 (90.7)	1312/1438 (91.2)
Aldosterone blocker	657/1108 (59.3)	510/884 (57.7)
Hemoglobin - g/dL	14.1 ± 1.5	14.2 ± 1.5
eGFR	69.0 ± 20.1	69.1 ± 20.1
LV ejection fraction - %	24.8 ± 7.5	25.0 ± 7.7

Variables	Main Analysis (N=1846)	Sensitivity Analysis (N=1439)
NYHA classification		
I	264/1838 (14.4)	220/1433 (15.4)
II	1033/1838 (56.2)	821/1433 (57.3)
III	523/1838 (28.5)	381/1433 (26.6)
IV	18/1838 (1.0)	11/1433 (0.8)
Baseline MLWHFQ score	32.7 ± 23.1	31.8 ± 22.7
Distance covered on 6-minute walk - m	357.2 ± 144.3	366.5 ± 141.6

Values are mean ± SD or n (%)

MMSE, Mini-Mental State Examination; TIA, transient ischemic attack; ACE, angiotensin-converting-enzyme; ARB, Angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; LV, left ventricular; NYHA, New York Heart Association; MLWHFQ, The Minnesota Living with Heart Failure Questionnaire

Main analysis was performed with patients who had a baseline MMSE measurement and at least one record of MMSE (n=1846) during follow up. Sensitivity analysis (N=1439) was performed on a subset of patients from the main analysis, who had at least three MMSE measurements: baseline, 12-month visit, and another visit at any point after 12 months. Lost follow-up group were the WARCEF patients who were not included in the main analysis.

Table 2.

Main analysis: association between decline of MMSE score from baseline and clinical factors at baseline (N=1846)

	Individual model (adjusted for month)				Multivariable LMM model			
		95 % CI				95 % CI		
Variables	**β**	**Lower Limit**	**Upper Limit**	**P value**	**β**	**Lower Limit**	**Upper Limit**	**P value**
Month	−0.003	−0.005	−0.001	0.013	−0.003	−0.01	−0.001	0.005
Continent (ref = North America)				0.49				0.01
Argentina	−0.22	−0.62	0.18	0.28	−0.48	−0.87	−0.08	0.02
Europe	−0.06	−0.21	0.10	0.47	−0.15	−0.29	−0.0002	0.05
MMSE at month 12	0.45	0.42	0.48	<0.0001	0.49	0.46	0.52	<.0001
Age - 10 years	0.07	0.002	0.14	0.04	0.18	0.12	0.24	<.0001
Male (ref = 0)	−0.02	−0.21	0.17	0.85				
Ethnicity/Race (ref = Non-Hispanic white)				0.73				<.0001
Non-Hispanic black	−0.03	−0.26	0.20	0.78	0.40	0.19	0.60	0.0002
Hispanic & Other	0.09	−0.16	0.35	0.48	0.60	0.34	0.86	<.0001
BMI	0.00	−0.01	0.01	0.82	−0.01	−0.02	−0.0002	0.05
Systolic BP- 10 mmHg	−0.01	−0.05	0.03	0.64				
Pulse rate - 10 beats/min	−0.10	−0.17	−0.04	0.00				
Education Level (ref = < High school)				0.49				<.0001
High-school graduate or some college	0.00	−0.16	0.17	0.99	−0.23	−0.37	−0.09	0.002
College graduate or postgraduate	−0.12	−0.34	0.10	0.27	−0.48	−0.66	−0.29	<.0001
Smoking Status (ref = Never smoked)				0.49				
Former smoker	0.10	−0.08	0.27	0.28				
Current smoker	0.01	−0.22	0.23	0.95				
Alcohol Consumption (ref = Never consumed)				0.18				
Previous consumption >2 oz/day	−0.10	−0.30	0.09	0.29				
Current consumption >2 oz/day	0.10	−0.08	0.29	0.26				
Hypertension	0.00	−0.15	0.15	1.00				
Diabetes Mellitus	0.10	−0.06	0.27	0.22				
Ischemic Cardiomyopathy	0.01	−0.15	0.16	0.94				
Device	0.02	−0.16	0.20	0.85				
Prior stroke or TIA	−0.28	−0.51	−0.04	0.02				
Atrial Fibrillation	0.14	−0.30	0.57	0.53				
Warfarin	−0.02	−0.17	0.13	0.78				
ACE inhibitor or ARB	0.23	−0.40	0.85	0.47				
Beta blockers	0.06	−0.20	0.33	0.64				
Hemoglobin - g/dL	0.00	−0.05	0.06	0.90				
Estimated GFR	0.00	−0.01	0.001	0.12				
LV ejection fraction - %	0.01	0.001	0.02	0.03	0.01	0.001	0.02	0.03

	Individual model (adjusted for month)				Multivariable LMM model			
		95 % CI				95 % CI		
Variables	**β**	**Lower Limit**	**Upper Limit**	**P value**	**β**	**Lower Limit**	**Upper Limit**	**P value**
NYHA classification (ref = class I)				0.07				
II	0.11	−0.12	0.33	0.35				
III and IV	−0.05	−0.29	0.20	0.70				
Baseline MLWHF score	−0.004	−0.01	−0.001	0.02				
Distance on 6-minute walk −100m	0.03	−0.02	0.09	0.26				

CI, confidence interval; MMSE, mini mental state exam; TIA, temporary ischemic attack; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; GFR, glomerular fraction rate; LV, left ventricular; NYHA, New York Heart Association; MLWHFQ, Minnesota Living with Heart Failure Questionnaire.

For the Main analysis, we included patients who had at least two MMSE measurements: baseline and another visit at any point during their follow-up. Mixed effect linear regression models for MMSE change from baseline (time-varying outcome) is presented. Individual model: For month, a random intercept model with month as covariate was fitted; for each baseline covariate, a random intercept model with this covariate and month was fitted. β (95% CI) and p-value of the covariate is reported. Multivariable model: a random intercept model that include month, with covariates selected using backward elimination.

Table 3.

Sensitivity analysis: association between decline of MMSE score from the 12-month visit and clinical variables (N=1439)

	Individual model for month				Multivariable LMM model			
		95 % CI				95 % CI		
Variables	β	Lower Limit	Upper Limit	P value	β	Lower Limit	Upper Limit	P value
Month	−0.002	−0.01	0.001	0.21	−0.002	−0.01	0.001	0.16
Continent (ref = North America)				0.56				
Argentina	−0.19	−0.63	0.25	0.41				
Europe	−0.07	−0.23	0.09	0.41				
MMSE at month 12	0.39	0.35	0.42	<0.0001	0.42	0.38	0.46	<0.0001
Age - 10 years	0.07	−0.002	0.14	0.06	0.14	0.08	0.21	<.0001
Male (ref = 0)	−0.04	−0.24	0.16	0.68				
Ethnicity/Race (ref = Non-Hispanic white)				0.07				<.0001
Non-Hispanic black	0.30	0.04	0.55	0.02	0.55	0.33	0.77	<.0001
Hispanic & Other	0.08	−0.19	0.35	0.55	0.41	0.18	0.64	0.001
BMI	0.0002	−0.01	0.01	0.97				
Systolic BP- 10 mmHg	−0.01	−0.05	0.03	0.69				
Pulse rate - 10 beats/min	−0.04	−0.10	0.03	0.27				
Education Level (ref = < High school)				0.17				0.03
High-school graduate or some college	0.17	−0.01	0.34	0.06	−0.06	−0.21	0.09	0.43
College graduate or postgraduate	0.09	−0.13	0.31	0.43	−0.26	−0.45	−0.07	0.01
Smoking Status (ref = Never smoked)				0.23				
Former smoker	0.15	−0.03	0.32	0.11				
Current smoker	0.03	−0.21	0.26	0.83				
Alcohol Consumption (ref = Never consumed)				0.65				
Previous consumption >2 oz/day	−0.08	−0.28	0.12	0.42				
Current consumption >2 oz/day	−0.07	−0.25	0.12	0.49				
Hypertension	0.05	−0.11	0.21	0.57				
Diabetes Mellitus	0.06	−0.11	0.23	0.51				
Ischemic Cardiomyopathy	0.06	−0.09	0.22	0.43				
Device	−0.02	−0.21	0.16	0.82				
Prior stroke or TIA	0.20	−0.05	0.45	0.12	0.40	0.18	0.61	0.0003
Atrial Fibrillation	0.49	0.02	0.96	0.04				
Warfarin	−0.01	−0.17	0.14	0.88				
ACE inhibitor or ARB	0.05	−0.60	0.69	0.89				
Beta blockers	0.16	−0.12	0.44	0.27				
Hemoglobin - g/dL	0.00	−0.06	0.05	0.96				
Estimated GFR	−0.01	−0.01	−0.004	<0.0001	−0.01	−0.01	−0.001	0.01
LV ejection fraction - %	0.002	−0.01	0.01	0.68				

	Individual model for month				Multivariable LMM model			
		95 % CI				95 % CI		
Variables	β	Lower Limit	Upper Limit	P value	β	Lower Limit	Upper Limit	P value
NYHA classification (ref = class I)				0.50				
II	0.00	−0.23	0.22	0.98				
III and IV	−0.11	−0.36	0.14	0.39				
Baseline MLWHF score	−0.001	−0.004	0.003	0.63				
Distance on 6-minute walk −100m	0.06	0.01	0.12	0.03				

CI, confidence interval; MMSE, mini mental state exam; TIA, temporary ischemic attack; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; GFR, glomerular fraction rate; LV, left ventricular; NYHA, New York Heart Association; MLWHFQ, Minnesota Living with Heart Failure Questionnaire.

For the Sensitivity analysis, we included patients who had at least three MMSE measurements: baseline, 12-month visit, and another visit at any point after 12 months. Mixed effects linear regression models for MMSE decline from 12-month visit (time-varying outcome) is presented. Individual model: For month, a random intercept model with month as covariate was fitted; for each baseline covariate, a random intercept model with this covariate and month was fitted. β (95% CI) and p-value of the covariate is reported. Multivariable model: a random intercept model that include month, with covariates selected using backward elimination.

Table 4.

Main analysis: association between cognitive decline (2-point MMSE drop) from baseline and clinical factors at baseline (N=1846)

	Individual model (adjusted for month)				Multivariable model			
		95 % CI				95 % CI		
Variables	**OR**	**Lower Limit**	**Upper Limit**	**P value**	**OR**	**Lower Limit**	**Upper Limit**	**P value**
Month	1.00	0.99	1.00	0.2719	1.00	0.99	1.00	0.68
Continent (ref = North America)				0.30				
Argentina	1.01	0.57	1.79	0.97				
Europe	0.86	0.70	1.05	0.13				
MMSE at baseline	1.05	1.00	1.11	0.05	1.13	1.07	1.20	<.0001
Age - 10 years	1.03	1.02	1.04	<.0001	1.37	1.24	1.50	<.0001
Male (ref = 0)	1.05	0.81	1.34	0.73				
Ethnicity/Race (ref = Non-Hispanic white)				<.0001				<.0001
Non-Hispanic black	1.71	1.29	2.28	0.0002	2.32	1.72	3.13	<.0001
Hispanic & Other	1.67	1.21	2.30	0.00	1.94	1.40	2.69	<.0001
BMI	0.98	0.96	1.00	0.02				
Systolic BP- 10 mmHg	0.99	0.94	1.05	0.79				
Pulse rate - 10 beats/min	0.93	0.86	1.01	0.10				
Education Level (ref = < High school)				<.0001				<.0001
High-school graduate or some college	0.77	0.62	0.96	0.02	0.74	0.60	0.93	0.01
College graduate or postgraduate	0.49	0.36	0.67	<.0001	0.47	0.34	0.64	<.0001
Smoking Status (ref = Never smoked)				0.38				
Former smoker	0.93	0.74	1.16	0.49				
Current smoker	0.81	0.60	1.09	0.16				
Alcohol Consumption (ref = Never consumed alcohol)				0.79				
Previous consumption >2 oz/day	1.02	0.79	1.31	0.91				
Current consumption >2 oz/day	1.09	0.86	1.37	0.50				
Hypertension	1.19	0.97	1.45	0.10				
Diabetes Mellitus	1.27	1.02	1.57	0.03				
Ischemic Cardiomyopathy	1.06	0.87	1.30	0.55				
Device	1.10	0.87	1.38	0.45				
Prior stroke or TIA	1.26	0.93	1.71	0.14				
Atrial Fibrillation	1.27	0.73	2.23	0.40				
Warfarin	0.88	0.72	1.07	0.19				
ACE inhibitor or ARB	1.45	0.58	3.64	0.43				
Beta blockers	0.81	0.57	1.13	0.21				
Hemoglobin - g/dL	0.93	0.87	1.00	0.04				
Estimated GFR	0.99	0.99	1.00	0.03				
LV ejection fraction - %	1.01	1.00	1.03	0.07				
NYHA classification (ref = class I)				0.07				0.03

	Individual model (adjusted for month)				Multivariable model			
		95 % CI				95 % CI		
Variables	**OR**	**Lower Limit**	**Upper Limit**	**P value**	**OR**	**Lower Limit**	**Upper Limit**	**P value**
II	1.43	1.05	1.94	0.02	1.51	1.11	2.05	0.01
III and IV	1.35	0.97	1.88	0.07	1.50	1.07	2.10	0.02
Baseline MLWHF score	1.00	1.00	1.00	0.79				
Distance on 6-minute walk -100m	0.91	0.84	0.97	0.01				

OR, odds ratio; CI, confidence interval; MMSE, mini mental state exam; TIA, temporary ischemic attack; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; GFR, glomerular fraction rate; LV, left ventricular; NYHA, New York Heart Association; MLWHFQ, Minnesota Living with Heart Failure Questionnaire.

For the Main analysis, we included patients who had at least two MMSE measurements: baseline and another visit at any point during their follow-up. Mixed effect logistic regression models for cognitive decline from baseline (time-varying outcome) is presented. Individual model: For month, a random intercept model with month as covariate was fitted; for each baseline covariate, a random intercept model with this covariate and month was fitted. OR (95% CI) and p-value of the covariate is reported. Multivariable model:a random intercept model that include month with covariates selected using backward elimination.

Table 5.

Sensitivity analysis: association between cognitive decline (2-point MMSE drop) from the 12-month visit and clinical factors at 12 months (N=1439)

	Individual model adjusted for month				Multivariable model			
		95 % CI				95 % CI		
Variables	**OR**	**Lower Limit**	**Upper Limit**	**P value**	**OR**	**Lower Limit**	**Upper Limit**	**P value**
Month	1.00	0.99	1.01	0.75	1.00	0.99	1.01	0.71
Continent (ref = North America)				0.03				
Argentina	1.18	0.56	2.49	0.66				
Europe	0.73	0.56	0.93	0.01				
MMSE at month 12	1.02	0.95	1.09	0.63	1.09	1.01	1.17	0.02
Age - 10 years	1.22	1.09	1.37	0.001	1.20	1.06	1.36	0.01
Male	1.00	0.73	1.37	1.00				
Ethnicity/Race (ref = Non-Hispanic white)				<.0001				<.0001
Non-Hispanic black	2.18	1.52	3.13	<.0001	2.59	1.77	3.79	<.0001
Hispanic & Other	2.74	1.88	3.99	<.0001	3.00	2.05	4.39	<.0001
BMI	0.99	0.97	1.01	0.49				
Systolic BP- 10 mmHg	0.98	0.92	1.05	0.62				
Pulse rate - 10 beats/min	0.89	0.80	0.99	0.03				
Education Level (ref = < High school)				0.04				0.01
High-school graduate or some college	0.90	0.69	1.17	0.42	0.80	0.60	1.06	0.11
College graduate or postgraduate	0.62	0.42	0.90	0.01	0.55	0.37	0.80	0.002
Smoking Status (ref = Never smoked)				0.29				
Former smoker	1.18	0.89	1.57	0.25				
Current smoker	0.93	0.63	1.37	0.71				
Alcohol Consumption (ref = Never consumed alcohol)				0.59				
Previous consumption >2 oz/day	0.88	0.65	1.18	0.81				
Current consumption >2 oz/day	1.04	0.76	1.42	0.39				
Hypertension	1.09	0.84	1.40	0.52				
Diabetes mellitus	1.26	0.97	1.65	0.09				
Ischemic cardiomyopathy	1.27	0.99	1.62	0.07				
Device	0.96	0.71	1.30	0.80				
Prior stroke or TIA	1.67	1.16	2.40	0.01	1.61	1.11	2.34	0.01
Atrial fibrillation	1.70	0.87	3.31	0.12				
Warfarin	0.84	0.66	1.08	0.18				
ACE inhibitor or ARB	0.85	0.31	2.30	0.74				
Beta blockers	0.92	0.59	1.43	0.70				
Hemoglobin - g/dL	0.94	0.86	1.03	0.16				
Estimated GFR	0.99	0.98	0.99	0.0002	0.99	0.98	1.00	0.004
LV ejection fraction - %	1.01	0.99	1.02	0.53				
NYHA classification (ref = class I)				0.37				

	Individual model adjusted for month				Multivariable model			
		95 % CI				95 % CI		
Variables	**OR**	**Lower Limit**	**Upper Limit**	**P value**	**OR**	**Lower Limit**	**Upper Limit**	**P value**
II	1.29	0.89	1.87	0.18				
III and IV	1.30	0.87	1.96	0.20				
Baseline MLWHF score	1.00	1.00	1.01	0.52				
Distance on 6-minute walk -100m	0.97	0.89	1.07	0.57				

OR, odds ratio; CI, confidence interval; MMSE, mini mental state exam; TIA, temporary ischemic attack; ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; GFR, glomerular fraction rate; LV, left ventricular; NYHA, New York Heart Association; MLWHFQ, Minnesota Living with Heart Failure Questionnaire.

For the Sensitivity analysis, we included patients who had at least three MMSE measurements: baseline, 12-month visit, and another visit at any point after 12 months. Mixed effect logistic regression models for cognitive decline from baseline (time-varying outcome) is presented. Individual model: For month, a random intercept model with month as covariate was fitted; for each baseline covariate, a random intercept model with this covariate and month was fitted. OR (95% CI) and p-value of the covariate is reported. Multivariable model: a random intercept model that include month with covariates selected using backward elimination.