Cognitive Decline Over Time in Patients With Systolic Heart Failure: Insights From WARCEF.

Tetz C Lee

Min Qian

Yutong Liu

Susan Graham

Douglas L Mann

See next page for additional authors

Published In/Presented At

Lee, T. C., Qian, M., Liu, Y., Graham, S., Mann, D. L., Nakanishi, K., Teerlink, J. R., Lip, G., Freudenberger, R. S., Sacco, R. L., Mohr, J. P., Labovitz, A. J., Ponikowski, P., Lok, D. J., Matsumoto, K., Estol, C., Anker, S. D., Pullicino, P. M., Buchsbaum, R., Levin, B., … WARCEF Investigators (2019). Cognitive Decline Over Time in Patients With Systolic Heart Failure: Insights From WARCEF. *JACC. Heart failure*, *7*(12), 1042–1053. https://doi.org/10.1016/j.jchf.2019.09.003

JACC: HEART FAILURE VOL. 7, NO. 12, 2019

PUBLISHED BY ELSEVIER

Cognitive Decline Over Time in Patients With Systolic Heart Failure

Insights From WARCEF

Tetz C. Lee, MD, MPH,[a] Min Qian, PhD,[a] Yutong Liu, MS,[a] Susan Graham, MD,[b] Douglas L. Mann, MD,[c] Koki Nakanishi, MD,[a] John R. Teerlink, MD,[d] Gregory Y.H. Lip, MD,[e,f] Ronald S. Freudenberger, MD,[g] Ralph L. Sacco, MD, MS,[h] Jay P. Mohr, MD,[a] Arthur J. Labovitz, MD,[i] Piotr Ponikowski, MD, PhD,[j] Dirk J. Lok, MD,[k] Kenji Matsumoto, MD,[a] Conrado Estol, MD,[l] Stefan D. Anker, MD, PhD,[m,n] Patrick M. Pullicino, MD,[o] Richard Buchsbaum,[a] Bruce Levin, PhD,[a] John L.P. Thompson, PhD,[a] Shunichi Homma, MD,[a] Marco R. Di Tullio, MD,[a] for the WARCEF Investigators

ABSTRACT

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

RESULTS A total of 1,846 patients were included. In linear regression, MMSE decrease was independently associated with higher baseline MMSE score ($p < 0.0001$), older age ($p < 0.0001$), nonwhite race/ethnicity ($p < 0.0001$), and lower education ($p < 0.0001$). In logistic regression, CD was independently associated with higher baseline MMSE scores (odds ratio [OR]: 1.13; 95% confidence interval [CI]: 1.07 to 1.20]; $p < 0.001$), older age (OR: 1.37; 95% CI: 1.24 to 1.50; $p < 0.001$), nonwhite race/ethnicity (OR: 2.32; 95% CI: 1.72 to 3.13 for black; OR: 1.94; 95% CI: 1.40 to 2.69 for Hispanic vs. white; $p < 0.001$), lower education ($p < 0.001$), and New York Heart Association functional class II or higher ($p = 0.03$). Warfarin and other medications were not associated with CD. Similar trends were seen in the sensitivity analysis ($n = 1,439$).

CONCLUSIONS CD in HF is predicted by baseline cognitive status, demographic variables, and NYHA functional class. The possibility of intervening on some of its predictors suggests the need for the frequent assessment of cognitive function in patients with HF. (Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction [WARCEF]; NCT00041938) (J Am Coll Cardiol HF 2019;7:1042–53) © 2019 by the American College of Cardiology Foundation.

From the [a]Columbia University Medical Center, New York, NY; [b]Department of Medicine, State University of New York at Buffalo, Buffalo, New York; [c]Department of Medicine, Washington University School of Medicine, St. Louis, Missouri; [d]Section of Cardiology, San Francisco Veterans Affairs Medical Center and School of Medicine, University of California San Francisco, San Francisco, California; [e]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, United Kingdom; [f]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; [g]Lehigh Valley Hospital, Allentown, Pennsylvania; [h]Department of Neurology, University of Miami, Miami, Florida; [i]Department of Medicine, University of South Florida, Tampa, Florida; [j]Military Hospital, Wroclaw, Poland; [k]Deventer Hospital, Deventer, the Netherlands; [l]Stroke Unit, Sanatorio Guemes, Buenos Aires, Argentina; [m]Division of Cardiology and Metabolism, Department of Cardiology, and Berlin-Brandenburg Center for Regenerative Therapies, Deutsches Zentrum für Herz-Kreislauf-Forschung partner site Berlin; Charité Universitätsmedizin Berlin, Germany; [n]Department of Cardiology and Pneumology, University Medicine Göttingen, Göttingen, Germany; and the [o]Kent Institute of Medicine and Health Science, Canterbury, United Kingdom. The WARCEF trial was supported by U.S. National Institute of Neurological Disorders and Stroke (NINDS) grants U01-NS-043975 (to Dr. Homma) and U01-NS-039143 (to Dr. Thompson). Dr. Anker is a consultant for Bayer,

ISSN 2213-1779/$36.00 https://doi.org/10.1016/j.jchf.2019.09.003

Patients with heart failure (HF) often experience cognitive decline (CD) (1). In fact, CD prevalence ranges from 25% to 75% (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, microemboli from cardiac thrombi, disruptions of blood-brain barrier, vascular remodeling, systemic inflammation, and endothelial dysfunction (3).

SEE PAGE 1054

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, because 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 patients with HF 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 mechanisms for CD among patients with HF, variables such as severity of HF, anticoagulant therapy, and drug treatment could all affect the trajectory of cognitive function over time; however, these mechanisms have not been thoroughly examined due to the limited information regarding severity and treatment of HF in previous studies (1,7–10).

The WARCEF (Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction) trial (13) was a large randomized clinical trial that compared the effects of warfarin with those of aspirin on the risk of death and stroke in 2,305 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. A previous study by the present authors reported that a shorter 6-min walk distance was an independent predictor for cognitive impairment measured by the Mini-Mental State Examination (MMSE) (14). The aim of the present analysis was to characterize the frequency and predictors of CD as measured by changes in MMSE over time and to determine whether CD was independently associated with baseline cognitive function, indicators of HF severity and treatment of HF.

ABBREVIATIONS AND ACRONYMS

CD = cognitive decline

HF = heart failure

NYHA = New York Heart Association

METHODS

WARCEF TRIAL. The protocol of the WARCEF trial has been described previously (13). Briefly, patients with left ventricular ejection fraction ≤35% who were in sinus rhythm were randomized to receive warfarin or aspirin. Additional eligibility criteria included age ≥18 years old, no contraindications to warfarin, a modified Rankin score of ≤4, and taking 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. Of 2,305 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,

Boehringer Ingelheim, Novartis, Stealth Peptides, Servier, Vifor, and Janssen; and has received research support from Abbott Vascular and Vifor. Dr. Homma is a consultant for St. Jude Medical, Daiichi-Sankyo, Bristol-Myers Squibb, and Pfizer. Dr. Labovitz has received research support from Bristol-Myers Squibb/Pfizer. Dr. Lip is a consultant for Bayer/Janssen, Bristol-Myers Squibb/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo; and is a speaker for Bayer, Bristol-Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. Dr. Sacco has received research support from grants from NINDS, National Center for Advancing Translational Sciences, American Heart Association, the Evelyn McKnight Brain Foundation, and Boehringer Ingelheim. Dr. Teerlink is a consultant for and has received research support from Actelion, Amgen, Bayer, Cytokinetics, Medtronic, Novartis, St. Jude Medical, and Trevena. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 12, 2019; revised manuscript received August 28, 2019, accepted September 10, 2019.

TABLE 1 Patient Characteristics

	Main Analysis (n = 1,846)	Sensitivity Analysis (n = 1,439)
Location		
Argentina	76/1,846 (4.1)	59/1,439 (4.1)
Europe	904/1,846 (49.0)	728/1,439 (50.6)
North America	866/1,846 (46.9)	652/1,439 (45.3)
Baseline MMSE score	28.56 ± 2.05	28.62 ± 1.97
Age, yrs	60.8 ± 11.2	60.6 ± 11.0
Males	1,487/1,846 (80.6)	1,163/1,439 (80.8)
Race or ethnic group		
Non-Hispanic white	1,424/1,846 (77.1)	1,138/1,439 (79.1)
Non-Hispanic black	234/1,846 (12.7)	158/1,439 (11.0)
Hispanic and other	188/1,846 (10.2)	143/1,439 (9.9)
Mean body-mass index	29.2 ± 5.9	29.4 ± 5.9
Mean systolic blood pressure, mm Hg	124.0 ± 18.7	124.0 ± 18.5
Pulse, beats/min	71.7 ± 11.9	71.7 ± 11.8
Educational level		
<High school	786/1,843 (42.6)	613/1,436 (42.7)
High-school graduate or some college	751/1,843 (40.7)	575/1,436 (40.0)
College graduate or postgraduate	306/1,843 (16.6)	248/1,436 (17.3)
Smoking status		
Current smoker	327/1,845 (17.7)	252/1,438 (17.5)
Former smoker	942/1,845 (51.1)	747/1,438 (51.9)
Never smoked	576/1,845 (31.2)	439/1,438 (30.5)
Alcohol consumption		
Current consumption, >2 oz/day	470/1,846 (25.5)	388/1,439 (27.0)
Previous consumption, >2 oz/day	399/1,846 (21.6)	305/1,439 (21.2)
Never consumed alcohol	977/1,846 (52.9)	746/1,439 (51.8)
Hypertension	1,072/1,793 (59.8)	835/1,405 (59.4)
Diabetes mellitus	556/1,843 (30.2)	420/1,439 (29.2)
Ischemic cardiomyopathy	793/1,843 (43.0)	614/1,439 (42.7)
Pacemaker or defibrillator	436/1,844 (23.6)	343/1,439 (23.8)
Prior stroke or TIA	217/1,844 (11.8)	1,58/1,438 (11.0)
Atrial fibrillation	60/1,844 (3.3)	41/1,439 (2.8)
Warfarin	907/1,846 (49.1)	704/1,439 (48.9)
ACE inhibitor or ARB	1,816/1,844 (98.5)	1,415/1,437 (98.5)
Beta-blocker	1,674/1,845 (90.7)	1,312/1,438 (91.2)
Aldosterone blocker	657/1,108 (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
NYHA functional classification		
I	264/1,838 (14.4)	220/1,433 (15.4)
II	1,033/1,838 (56.2)	821/1,433 (57.3)
III	523/1,838 (28.5)	381/1,433 (26.6)
IV	18/1,838 (1.0)	11/1,433 (0.8)
Baseline MLWHFQ score	32.7 ± 23.1	31.8 ± 22.7
Distance covered on 6-min walk, m	357.2 ± 144.3	366.5 ± 141.6

Values are n/N (%) or mean ± SD. Main analysis was performed in patients who had a baseline MMSE measurement and at least 1 record of MMSE (n = 1,846) during follow-up. Sensitivity analysis (n = 1,439) was performed in a subset of patients from the main analysis who had at least 3 MMSE measurements: baseline, 12-month visit, and another visit at any point after 12 months.

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

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.

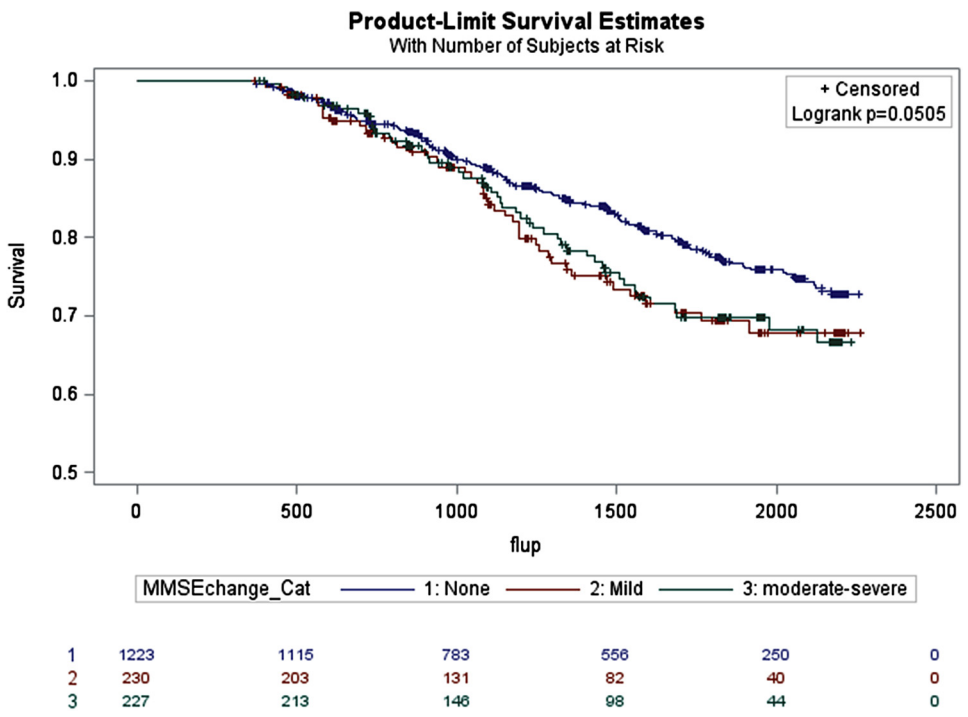
OUTCOMES AND COVARIATES. We analyzed CD by using changes in MMSE in 2 ways; first as a continuous variable and second as a discrete 2-point or greater decline from the baseline, a clinically relevant definition based on published reports (15,16).

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

STUDY POPULATION AND STATISTICAL ANALYSIS. For the current analysis, patients were included who had at least 2 MMSE measurements: from baseline and from another visit at any point during their follow-up (main analysis: n = 1,846). Patient characteristics are presented as mean ± 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 endpoint of ischemic stroke, intracerebral hemorrhage, or death from any cause. Kaplan-Meier estimates of rate of mortality 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 2 components, a fixed effects component that represents the average model in the population, and a random effects component that represents within-individual variation. A random intercept was used to account for individual variation. For each baseline covariate, first an individual

FIGURE 1 Kaplan-Meier Plot of All-Cause Death According to the Change of MMSE Score From Baseline



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 and 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 ($n = 1,846$). MMSE = Mini-Mental State Examination.

model was built with the covariate as an independent variable, adjusting for follow-up time (in months). The final multivariate model was built using backward elimination, adjusting for follow-up time. Treatment with an aldosterone blocker was removed from the analysis due to the large amount of missing information (Online Table 1).

Among the reasons for missing follow-up mentioned previously, two reasons are relevant to the results of this investigation. One reason is that patients might have died before the second follow-up visit; the other reason is that they might have missed the follow-up visits for reasons that include CD. To at least partly address these concerns, a sensitivity analysis was conducted to assess the association between baseline variables and CD observed beyond month 12, examining only patients who had at least 3 MMSE measurements: at baseline, at 12-month visit, and at another visit at any point after 12 months (sensitivity analysis: $n = 1,439$). The same set of analyses was conducted as for the general analysis, except for using CD from the 12-month visit (rather than from baseline) as the outcome. Missing baseline variable values were imputed using means for continuous variables and modal values for categorical variables. For all statistical analyses, a 2-tailed p value < 0.05 was considered significant. All data analyses were conducted using SAS version 9.4 software (SAS Institute Inc., Cary, North Carolina).

RESULTS

All 2,305 randomized patients were included in the WARCEF primary analysis. A total of 622 patients (27.0%) had a primary event (stroke, intracerebral hemorrhage, or death) (13), and 2,287 (99%) had a baseline MMSE measurement. The current main analysis included the 1,846 patients (80.1%) who had baseline MMSE and at least 1 follow-up MMSE measurement. The 459 patients who lacked some of this information could not be included. Compared to those patients, the patients included in the current main analysis were more likely to have better baseline MMSE scores, smaller non-Hispanic black representation, slower pulse rate, higher education level, fewer comorbidities (hypertension, diabetes, prior

TABLE 2 Main Analysis: Association Between Decline of MMSE Score From Baseline and Clinical Factors at Baseline (n = 1,846)

	Individual Model (Adjusted for Month)				Multivariate LMM Model			
		95% CI				95% CI		
	β Value	Lower Limit	Upper Limit	p Value	β Value	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	<0.0001
Age, 10 yrs	0.07	0.002	0.14	0.04	0.18	0.12	0.24	<0.0001
Males (ref. = 0)	−0.02	−0.21	0.17	0.85				
Ethnicity/race (ref. = non-Hispanic white)				0.73				<0.0001
Non-Hispanic black	−0.03	−0.26	0.20	0.78	0.40	0.19	0.60	0.0002
Hispanic and other	0.09	−0.16	0.35	0.48	0.60	0.34	0.86	<0.0001
BMI	0.00	−0.01	0.01	0.82	−0.01	−0.02	−0.0002	0.05
Systolic BP, 10 mm Hg	−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				<0.0001
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	<0.0001
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				
Pacemaker or Defibrillator	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
NYHA functional class (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-min walk, 100 m	0.03	−0.02	0.09	0.26				

For the main analysis, patients were included who had at least 2 MMSE measurements: at baseline and at another visit at any point during their follow-up. Mixed-effects 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 were fitted. β (95% CI) and p values of the covariate are reported. Multivariate model was a random intercept model that included month, with covariates selected using backward elimination.

CI = confidence interval; LMM = linear mixed model; other abbreviations as in Table 1.

stroke, and atrial fibrillation), higher rate of beta-blocker treatment, higher hemoglobin levels, better kidney functions, and lower HF severity (Online Table 2).

The baseline MMSE in the study cohort was 28.6 ± 2.0. The numbers of patients with MMSE scores of 30, 27 to 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 to 29, or <27 were 25.2%, 34.3%, and 37.9% (p = 0.023), respectively (Online Figure 1). Kaplan-Meier estimates of death rates were 22.0%, 32.2%, and 32.7% (p = 0.018), respectively.

At 12 months, 227 of 1,680 patients with available information (13.6%) showed CD (i.e., decline of ≥2 MMSE points from baseline). Among 1,224 patients who had at least 1 MMSE measurement after 12 months

TABLE 3 Sensitivity Analysis: Association Between Decline of MMSE Score From the 12-Month Visit and Clinical Variables (n = 1,439)

	Individual Model for Month				Multivariate LMM Model			
		95% CI				95% CI		
	β Value	Lower Limit	Upper Limit	p Value	β Value	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 yrs	0.07	−0.002	0.14	0.06	0.14	0.08	0.21	<0.0001
Males (ref. = 0)	−0.04	−0.24	0.16	0.68				
Ethnicity/race (ref. = non-Hispanic white)				0.07				<0.0001
Non-Hispanic black	0.30	0.04	0.55	0.02	0.55	0.33	0.77	<0.0001
Hispanic and 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 mm Hg	−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				
Pacemaker or Defibrillator	−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				
NYHA functional 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-min walk, 100 m	0.06	0.01	0.12	0.03				

For the sensitivity analysis, patients were included who had at least 3 MMSE measurements: at baseline, at the 12-month visit, and at another visit at any point after 12 months. The mixed effects linear regression models for MMSE decline from the 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 values of the covariate are reported. Multivariate model: a random intercept model that included month, with covariates selected using backward elimination.

BP = blood pressure; other abbreviations as in Tables 1 and 2.

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 points, 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 = 1,846) and the sensitivity analysis (n = 1,439). The mean age in the main analysis was 60.8 ± 11.2 years old, 80.6% of patients were men, and 98.5% were taking an ACE inhibitor or ARB. Among the 1,846 patients in the main analysis, 1,439 patients who underwent MMSE measurement at both the 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 scores, racial/ethnic distributions, and clinical variables, including HF treatment and severity (Table 1).

TABLE 4 Main Analysis: Association Between Cognitive Decline (2-Point MMSE Drop) From Baseline and Clinical Factors at Baseline (n = 1,846)

	Individual Model (Adjusted for Month)				Multivariate Model			
		95% CI				95% CI		
	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	<0.0001
Age, 10 yrs	1.03	1.02	1.04	<0.0001	1.37	1.24	1.50	<0.0001
Male (ref. = 0)	1.05	0.81	1.34	0.73				
Ethnicity/Race (ref. = non-Hispanic white)				<0.0001				<0.0001
Non-Hispanic black	1.71	1.29	2.28	0.0002	2.32	1.72	3.13	<0.0001
Hispanic and other	1.67	1.21	2.30	0.00	1.94	1.40	2.69	<0.0001
BMI	0.98	0.96	1.00	0.02				
Systolic BP, 10 mm Hg	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)				<0.0001				<0.0001
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	<0.0001	0.47	0.34	0.64	<0.0001
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				
Pacemaker or Defibrillator	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 functional class (ref. = class I)				0.07				0.03
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-min walk, 100 m	0.91	0.84	0.97	0.01				

For the main analysis, patients were included who had at least 2 MMSE measurements: at baseline and at another visit at any point during their follow-up. Mixed effect logistic regression models for cognitive decline from baseline (time-varying outcome) are 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. Multivariate model: a random intercept model that include month with covariates selected using backward elimination.

OR = odds ratio; other abbreviations as in Tables 1 and 3.

In the multivariate model for MMSE changes from baseline, a higher MMSE at baseline, older age, nonwhite race/ethnicity, lower education level, and higher LVEF were observed to be 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, nonwhite race/ethnicity, lower education level, history of stroke/transient ischemic attack (TIA) and lower estimated glomerular filtration rate.

In the multivariate model for CD (i.e., ≥2-point drop in MMSE) from baseline (main analysis) (Table 4), a higher MMSE at baseline, older age, non-white race/ethnicity, lower education level, and NYHA functional class II or higher was observed to be independently associated with increased likelihood of CD. In the sensitivity analysis for the CD beyond

TABLE 5 Sensitivity Analysis: Association Between Cognitive Decline (2-Point MMSE Drop) From the 12-Month Visit and Clinical Factors at 12 Months (n = 1,439)

	Individual Model Adjusted for Month				Multivariate Model			
		95% CI				95% CI		
	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 yrs	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)				<0.0001				<0.0001
Non-Hispanic black	2.18	1.52	3.13	<0.0001	2.59	1.77	3.79	<0.0001
Hispanic and Other	2.74	1.88	3.99	<0.0001	3.00	2.05	4.39	<0.0001
BMI	0.99	0.97	1.01	0.49				
Systolic BP, 10 mm Hg	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				
Pacemaker or Defibrillator	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 functional classification (ref. = class I)				0.37				
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-min walk, 100 m	0.97	0.89	1.07	0.57				

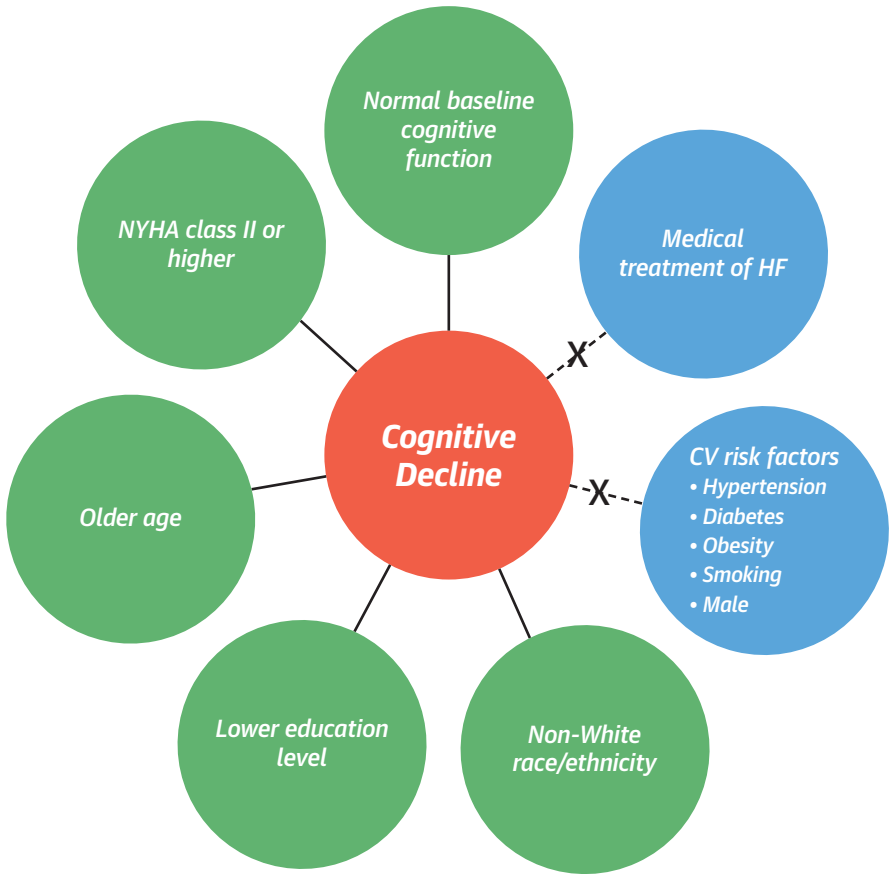
For the sensitivity analysis, patients were included who had at least 3 MMSE measurements: at baseline, at the 12-month visit, and at another visit at any point after 12 months. Mixed effect logistic regression models for cognitive decline from baseline (time-varying outcome) is presented. Individual 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. Multivariate model: a random intercept model that include month with covariates selected using backward elimination.

Abbreviations as in Tables 1, 3, and 4.

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-min walk distance in the authors' previous report (14), in the present study, neither any MMSE decline nor CD over time were associated with 6-min walk distance. In the WARCEF trial, the intervention was the administration of warfarin or aspirin in double-blinded fashion. In the multivariate analyses, warfarin treatment was associated with neither CD nor decrease in MMSE score.

CENTRAL ILLUSTRATION **Predictors of Cognitive Decline in Systolic Heart Failure**



Lee, T.C. et al. J Am Coll Cardiol HF. 2019;7(12):1042–53.

Demographic and clinical variables **(green circles)** associated with cognitive decline during follow-up. CV = cardiovascular; HF = heart failure; NYHA = New York Heart Association.

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 of CD over time. The sample size of the present cohort (n = 1,846) was larger than that of the combined number of patients with HF (n = 1,553) included in previous longitudinal studies. In addition, in the present study more than 13% of patients showed a decrease in MMSE score of at least 2 points at the 12-month visit. In the multivariate analyses, the magnitude of any decline in MMSE score was significantly associated with higher baseline MMSE score, older age, nonwhite race/ethnicity, and lower educational level. In the multivariate analysis, which focused on the clinically relevant decline (decline of ≥2-point MMSE score), CD was again significantly associated with higher baseline MMSE score, older age, nonwhite races/ethnicity, lower education level, and also with NYHA functional class II or higher. Also, CD was not associated with anticoagulation therapy or HF medications. Similar trends were seen in the sensitivity analysis (n = 1,439), with the addition of renal dysfunction and prior history of stroke/TIA being associated with MMSE decrease and CD (**Central Illustration**).

Few studies have specifically addressed the factors associated with CD among patients with HF. There are 7 longitudinal studies (a total of 1,553 patients with HF diagnosis) which measured cognitive function repeatedly (1,7–12). However, 4 of those studies

focused primarily on the incidence or prevalence of CD in patients with and without HF, rather than on the risk factors for CD among patients with HF (1,8–10). One study (n = 280, 6-month follow-up) (7) that did examine the risk factors for CD among patients with HF 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, whereas the present focus was gradual change of cognitive function over time, mostly remaining within normal limits. Another difference is that the measurement of cognitive function used 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 the authors 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, a progressive increase was observed in mortality with decreasing baseline MMSE, which prompted an attempt to 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. Present results contrasted with those from the general population, which showed CD to be associated with a low baseline MMSE score (18,19). From a pathophysiology standpoint, the present results are plausible because CD in patients with HF is conceivably more related to the interaction between heart and brain than in the general population (3), which may recognize other predominant risk factors for CD (8,9).

With regard to HF severity and CD, the present findings were different from those of previous studies (1), which consistently showed that NYHA functional classes are not associated with CD in patients with HF. In contrast, the present study showed that NYHA functional class II or higher was associated with CD after 12 months. This observation appears to be in line with the proposed pathophysiology of CD in patients with HF: chronic HF leads to a relative loss of grey 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-min walk were not associated with incident CD in this study. The association observed between CD and HF severity cannot indicate a specific mechanism for CD in patients with HF. Unfortunately, this study did not have data regarding the possible associations between chronic cerebral hypoperfusion and HF severity. Therefore, answering mechanistic questions about CD in HF will require further investigation in appropriately designed studies.

The study showed that the decline in cognitive function was not associated with warfarin or aspirin therapy or with HF medications. Because 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 the present study showed that anticoagulation therapy using warfarin was not associated with protection from CD or any decline in MMSE score (**Tables 2 to 5**), the possibility that anticoagulation may affect CD development in patients with HF would again have to be analyzed in AD hoc studies. Because 98% of patients were receiving an ACE inhibitor or ARB medication, the effects of these medications on CD could not be assessed.

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

These results showed that older age, lower education, and nonwhite race/ethnicity were significantly associated with CD and decrease of MMSE score (**Tables 2 to 5**). These confirm the findings of a previous study in Alzheimer disease (25). Nonwhite 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 United States (26–28). However, given the retrospective nature of our investigation, this interpretation requires caution and should be regarded as exploratory and hypothesis-generating. Also, the possibility of socioeconomic factors affecting this result could not be addressed, because race/ethnicity were variables that encompass a lifelong social experience (29,30), and WARCEF did not collect detailed information of socioeconomic status other than education level.

STUDY LIMITATIONS. This 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 may 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 might have led to an underestimation of CD (Online Table 1). Third, the possible impact on CD of underlying silent atrial fibrillation could not be analyzed. Fourth, the WARCEF data do not allow differentiation among patients with CD and patients with depression or patients who had changes in manifestations of depression.

CONCLUSIONS

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

ADDRESS FOR CORRESPONDENCE: Dr. Marco R. Di Tullio, Department of Medicine, Columbia University Irving Medical Center, 630 West 168th Street, New York, New York 10032. E-mail: md42@cumc.columbia.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: 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 functional 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 patients with HF 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 patients with HF, possible measures to prevent or delay cognitive deterioration are not established and will require further focused investigation.

REFERENCES

1. Hammond CA, Blades NJ, Chaudhry SI, et al. Long-term cognitive decline after newly diagnosed heart failure: longitudinal analysis in the CHS (Cardiovascular Health Study). Circ Heart Fail 2018;11:e004476.

2. Cannon JA, Moffitt P, Perez-Moreno AC, et al. Cognitive impairment and heart failure: systematic review and meta-analysis. J Card Fail 2017;23:464–75.

3. Doehner W, Ural D, Haeusler KG, et al. Heart and brain interaction in patients with heart failure: overview and proposal for a taxonomy. A position paper from the Study Group on Heart and Brain Interaction of the Heart Failure Association. Eur J Heart Fail 2018;20:199–215.

4. Ampadu J, Morley JE. Heart failure and cognitive dysfunction. Int J Cardiol 2015;178:12–23.

5. Zuccala G, Pedone C, Cesari M, et al. The effects of cognitive impairment on mortality among hospitalized patients with heart failure. Am J Med 2003;115:97–103.

6. O'Donnell M, Teo K, Gao P, et al. Cognitive impairment and risk of cardiovascular events and mortality. Eur Heart J 2012;33:1777–86.

7. 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.

8. 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;166:1003–8.

9. Hjelm C, Dahl A, Brostrom A, Martensson J, Johansson B, Stromberg A. The influence of heart failure on longitudinal changes in cognition among individuals 80 years of age and older. J Clin Nurs 2012;21:994–1003.

10. Almeida OP, Beer C, Lautenschlager NT, Arnolda L, Alfonso H, Flicker L. Two-year course of cognitive function and mood in adults with congestive heart failure and coronary artery disease: the Heart-Mind Study. Int Psychogeriatr 2012;24:38–47.

11. Huijts M, van Oostenbrugge RJ, Duits A, et al. Cognitive impairment in heart failure: results from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) randomized trial. Eur J Heart Fail 2013;15:699–707.

12. Almeida OP, Garrido GJ, Etherton-Beer C, et al. Brain and mood changes over 2 years in healthy controls and adults with heart failure and ischaemic heart disease. Eur J Heart Fail 2013;15:850–8.

13. Homma S, Thompson JL, Pullicino PM, et al. warfarin and aspirin in patients with heart failure and sinus rhythm. N Engl J Med 2012;366:1859–69.

14. Graham S, Ye S, Qian M, et al. Cognitive function in ambulatory patients with systolic heart failure: insights from the warfarin versus aspirin in reduced cardiac ejection fraction (WARCEF) trial. PloS One 2014;9:e113447.

15. Stein J, Luppa M, Maier W, et al. Assessing cognitive changes in the elderly: reliable change indices for the mini-mental state examination. Acta Psychiatrica Scandinavica 2012;126:208–18.

16. Hensel A, Angermeyer MC, Riedel-Heller SG. Measuring cognitive change in older adults: reliable change indices for the Mini-Mental State Examination. J Neurol Neurosurg Psychiatry 2007; 78:1298–303.

17. Woodford HJ, George J. Cognitive assessment in the elderly: a review of clinical methods. QJM 2007;100:469–84.

18. Lopez OL, Jagust WJ, Dulberg C, et al. Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. Arch Neurol 2003;60:1394–9.

19. Ravaglia G, Forti P, Maioli F, et al. Conversion of mild cognitive impairment to dementia: predictive role of mild cognitive impairment subtypes and vascular risk factors. Dement Geriatr Cogn Disord 2006;21:51–8.

20. Sabia S, Elbaz A, Britton A, et al. Alcohol consumption and cognitive decline in early old age. Neurology 2014;82:332.

21. Schwarzinger M, Pollock BG, Hasan OSM, et al. Contribution of alcohol use disorders to the burden of dementia in France 2008–2013: a nationwide retrospective cohort study. Lancet Public Health 2018;3:e124–32.

22. Sharma A, Zhao X, Hammill BG, et al. Trends in noncardiovascular comorbidities among patients hospitalized for heart failure: insights from the Get With The Guidelines-Heart Failure Registry. Circ Heart Fail 2018;11: e004646.

23. Ather S, Chan W, Bozkurt B, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol 2012;59: 998–1005.

24. Bozkurt B, Aguilar D, Deswal A, et al. Contributory risk and management of comorbidities of hypertension, obesity, diabetes mellitus, hyperlipidemia, and metabolic syndrome in chronic heart failure: a scientific statement from the American Heart Association. Circulation 2016; 134:e535–78.

25. Weuve J, Barnes LL, Mendes de Leon CF, et al. Cognitive aging in black and white Americans: cognition, cognitive decline, and incidence of Alzheimer disease dementia. Epidemiology 2018; 29:151–9.

26. Lewis EF. Are hospitalizations for heart failure the great equalizer? J Am Coll Cardiol HF 2015;3: 539–41.

27. Vivo RP, Krim SR, Cevik C, Witteles RM. Heart failure in Hispanics. J Am Coll Cardiol 2009;53: 1167–75.

28. Qian F, Parzynski CS, Chaudhry SI, et al. Racial differences in heart failure outcomes: evidence from the Tele-HF trial (Telemonitoring to Improve Heart Failure Outcomes). J Am Coll Cardiol HF 2015;3:531–8.

29. Cooper RS, Nadkarni GN, Ogedegbe G. Race, ancestry, and reporting in medical journals. JAMA 2018;320:1531–2.

30. Williams DR, Wyatt R. Racial bias in health care and health: challenges and opportunities. JAMA 2015;314:555–6.

KEY WORDS cognitive function, comorbidities, dementia, longitudinal analysis, Mini-Mental State Examination

APPENDIX For supplemental tables and figures, please see the online version of this paper.