Title: The Prevalence of Cognitive Impairment Among Adults with Incident Heart Failure: The REasons for Geographic and Racial Differences in Stroke (REGARDS) Study

Short Title: Cognitive Impairment in Incident Heart Failure

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Abstract

Background: Cognitive impairment (CI) is estimated to be present in 25%-80% of heart failure (HF) patients, but its prevalence at diagnosis is unclear. To improve our understanding of cognition in HF, we determined the prevalence of CI among adults with incident HF in the REGARDS study.

Methods: REGARDS is a longitudinal cohort study of adults ≥45 years of age recruited from 2003-2007. Incident HF was expert-adjudicated. Cognitive function was assessed with the Six-Item-Screener. The prevalence of CI among those with incident HF was compared to the prevalence of CI among an age, sex, and race-matched cohort without HF.

Results: The 436 participants with incident HF had a mean age of 70.3 years (SD 8.9), 47% were female, and 39% were black. Old age, black race, female gender, less education, and anticoagulation use were associated with CI. The prevalence of CI among participants with incident HF (14.9% [11.7-18.6%]) was similar to the non-HF matched cohort (13.4% [11.6% – 15.4%], p<0.43).

Conclusion: 14.9% of adults with incident HF had CI, suggesting that the majority of cognitive decline occurs after HF diagnosis. Increased awareness of CI among newly diagnosed patients, and ways to mitigate it in the context of HF management, are warranted.

Keywords: heart failure; cognition; cohort study; hospitalization; prevalence

Abbreviations

HF = heart failure

CI = cognitive impairment

SIS = Six-Item Screener

CHD = coronary heart disease

ECG = electrocardiogram

eGFR = estimated glomerular filtration rate

Introduction

Cognitive impairment (CI) is one of the most common comorbid conditions among adults with heart failure (HF) (1, 2) and is associated with poor quality of life (3) and self-care (4), and increased morbidity and mortality (5-7). While prior studies agree that CI is highly prevalent in HF, prevalence estimates vary widely, ranging from 25-80% (1, 7, 8). Additionally, the underlying pathophysiology of CI and its trajectory in HF, remain uncertain (1, 7).

Some uncertainty could be attributed to a lack of understanding of the prevalence of CI among adults with newly diagnosed disease. For example, if CI is prevalent at disease onset, then providers need to screen for cognitive deficits early and advise patients accordingly. If, however, adults with incident HF have similar cognitive profiles to adults without HF, then more attention ought to be focused on mitigating cognitive decline among those with existing HF. Yet, few studies have investigated the prevalence of CI in incident HF.

To fill this gap, we determined the prevalence and correlates of CI among adults with incident HF in the REasons for Geographic and Racial Differences in Stroke (REGARDS) study**,** a national prospective cohort of 30,239 community-dwelling adults in the US aged ≥45 years.

Methods

REGARDS

Details of the REGARDS study have been described previously (9). Briefly, REGARDS is a cohort study that evaluates racial and geographic disparities in cardiovascular disease. Recruitment occurred from 2003 to 2007. Blacks and residents of the Stroke Belt were oversampled by design (9). Participants completed a telephone interview followed by an in-home examination. At six-month intervals, participants are asked about hospitalizations and health status. The study was approved by the institutional review boards of all participating institutions. All participants provided written informed consent.

Study Population

Adults with incident HF who underwent a cognitive assessment more than 1 month but less than 18 months prior to their incident HF diagnosis were included. One month was selected as a cutoff because individuals may experience cognitive changes as HF worsens.

Incident Heart Failure

An incident HF diagnosis was defined as the participant's first hospitalization for HF without a prior history of HF. We included hospitalizations from 2004 to 2016. HF hospitalizations were adjudicated by two experts and disagreements were resolved by committee with $\kappa \geq 0.80$ (10). Since hospitalizations for cardiac events can affect cognition, participants with hospitalizations for other cardiac etiologies known to REGARDS prior to their incident HF hospitalization, were excluded.

Cognition

REGARDS participants undergo global cognitive function assessments annually with the Six-Item Screener (SIS), a validated measure that assesses 3-item recall and orientation to year, month, and day of the week.(11) The SIS, which can be administered easily by telephone, has a sensitivity of 74.2% to 84.0% and specificity of 80.2% to 85.3% in community and clinical samples for a diagnosis of cognitive impairment.(11) Scores for the SIS range from 0-6 and each correctly answered question receives 1 point.(12-15) Similar to other studies, scores were dichotomized; scores of 5 and 6 were normal, whilst scores of 4 and less connoted CI.

Participant Characteristics

Demographic data included age, sex, race, education, annual household income, and region of residence. Clinical data included history of coronary heart disease (CHD) by self-report or electrocardiogram (ECG); diabetes, defined as fasting blood glucose ≥126 mL/dL, non-fasting glucose >200 mL/dL, oral hypoglycemic, or insulin use; history of hypertension, defined as systolic blood pressure ≥140, diastolic blood pressure of ≥90, or medication use for hypertension; history of atrial fibrillation by self-report or by ECG; history of self-reported stroke; chronic kidney disease, defined as eGFR <60ml/min/1.73^2; body mass index; cigarette smoking; high-density lipoprotein and total cholesterol. Left ventricular ejection fraction was abstracted from the most recent echocardiogram. Depressive symptoms were assessed with the 4-item Center for Epidemiological Studies-Depression scale (16). Medication use at baseline was ascertained.

Healthy Comparison Population

To contextualize our findings, we compared the prevalence of CI among adults with incident HF to that of an age, sex, and race-matched group of participants without HF. We matched participants (3:1 ratio) who did not have an adjudicated HF hospitalization or another adjudicated cardiovascular event in REGARDS, and were similar in age (+/- 5 years), gender, race, and year of SIS, to each HF participant. Matching was performed with SAS macro gmatch which uses a "greedy" algorithm approach (17) (18).

Statistical Analysis

The prevalence of CI was determined among participants with incident HF and among the matched control group. First, we examined differences in participant characteristics by CI. Next, we performed multivariable logistic regression to examine associations between participant characteristics

and CI among those with incident HF. Multiple imputation with chained equations was used to account for missing data. Analyses were conducted with STATA and statistical significance for all analyses was set as $P < .05$ (2-sided).

Results

CI in Incident HF

539 participants were hospitalized for incident HF (Supplemental Figure 1). Among them, 103 lacked a SIS, leaving 436 in the final analytic cohort. Of note, there were no clinical differences between this cohort and the 103 who were excluded.

Overall participants had a mean age of 70 (SD±8.9) years, 53.0% were male, 60.6% were white, the majority (82.1%) had ≥ high school education, 77.8% had hypertension, 38.5% had diabetes, and 31.9% had CHD (Table 1). The prevalence of CI was 14.9% [95% CI: 11.7, 18.6%]. Participants with CI were older, male, and less educated than those without CI. The majority of clinical characteristics did not differ by cognition.

Among participants with incident HF, older age (1.04 [1.01, 1.08]), black race (1.88 [1.08, 3.28]), less education (1.89 [1.02, 3.51]), higher SBP (1.01 [1.00,1.02]), and anticoagulant use (3.01 [1.05,8.63]) were associated with higher odds of CI, whereas female sex (0.54 [0.31,0.94]) was associated with lower odds of CI, in an age-adjusted model (Table 2). In a fully adjusted model, age, gender, race, and anticoagulant use remained independently associated with CI.

CI in Healthy Comparison Population

1,307 participants comprised the healthy comparison population (Supplemental Figure 2). Participants with CI were older, male, black, and had less education and income than those without CI (Table 3). Again, hypertension (62.5%), CHD (20%), and Diabetes (20%) were prevalent. The overall prevalence of CI was 13.4% (95% CI: 11.6 – 15.4%), which did not differ from the incident HF cohort ($p<0.43$).

Discussion

Overall, 14.9% of adults with incident HF had CI, indicating that healthcare providers should consider assessing cognition at the time HF diagnosis. Since the prevalence of CI among adults with existing HF ranges between 25% and 80% (1, 19), our results, alongside 2 recent studies in the Cardiovascular Health Study(20, 21), suggest that CI may develop during the course of the disease itself, rather than at the outset or due to CHD risk factors alone (7, 22).

Prior studies have attributed cognitive decline in HF to disease duration and severity (23). Underlying mechanisms include cerebral hypo-perfusion, multiple cardiogenic emboli, and impaired microcirculation (1, 23-26). Thus, among newly diagnosed HF patients, in addition to mitigating CHD risk factors, increased attention to interventions and medications which have the ability to affect these underlying processes may be most important to preserving cognitive function (7).

Similar to other studies (27, 28), we found older age, black race, and less education to be associated with CI, indicating that certain patient subgroups may require targeting at diagnosis. Interestingly, many clinical characteristics known to be associated with CI in HF were not associated with CI in incident HF. This may be due to our relatively small sample size and because the severity of some

factors may be less at HF onset. In addition, index event bias may support these unanticipated observations (29).

The prevalence of CI (13.4%) among a matched sub-cohort without HF did not differ significantly from the incident HF cohort, and was comparable to other populations of similar age and comorbidity status (30, 31). This finding supports our main finding, but also speaks to the accumulating evidence which has shown CHD and CHD risk factors to be associated with the development of CI (15, 30-33).

Strengths of our study include a geographically and racially diverse cohort, expert-adjudicated outcomes, and the measurement of cognition prior to an incident HF hospitalization, which minimizes the bias of clinical deterioration on cognition. Limitations include that cognition was assessed with 1 screener; although the SIS is brief, reliable, and validated against the MMSE (11), it is less sensitive for the detection of mild CI (34-36). Additionally, we did not study other cognitive domains which are relevant to self-care (34, 36). Finally, incident HF diagnoses made in the ambulatory setting were not included, which limits the generalizability.(37)

Conclusion

14.9% of adults hospitalized for incident HF had CI in a range consistent with varying levels of CHD risk in a similarly aged group of adults. The majority of the cognitive decline previously reported in HF may occur over the course of the disease rather than prior to presentation. Increased awareness of the prevalence of CI among newly diagnosed HF patients, and ways to mitigate cognitive decline in the context of HF management, are warranted.

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Table 1. Baseline Characteristics of REGARDS participants with Incident Heart Failure by Cognitive Status

Characteristic	**All Participants (n = 436)**	**No Cognitive Impairment (n = 371)**	**Cognitive Impairment (n=65)**	**P-value**
Prevalence of Cognitive Impairment: 14.9% (95% CI: 11.7-18.6%)				
Demographic Characteristics				
Age, years(SD)	70.31 (8.98)	69.81 (8.94)	73.14 (8.73)	0.006*
Gender, n (%)				0.02*
Male	231 (53.0%)	188 (50.7%)	43 (66.2%)	
Female	205 (47.0%)	183 (49.3%)	22 (33.8%)	
Race, n (%)				0.14
White	264 (60.6%)	230 (62.0%)	34 (52.3%)	
Black	172 (39.4%)	141 (38.0%)	31 (47.7%)	
Education, n (%)				0.03*
Less than high school	78 (17.9%)	60 (16.2%)	18 (27.7%)	
High school or higher	358 (82.1%)	311 (83.8%)	47 (72.3%)	
Income, n (%)				0.87
< $35K	234 (53.7%)	202 (54.4%)	32 (49.2%)	
≥ $35K	147 (33.7%)	126 (34.0%)	21 (32.3%)	
Region of Residence, n (%)				0.79
Belt	166 (38.1%)	139 (37.5%)	27 (41.5%)	
Buckle	94 (21.6%)	80 (21.6%)	14 (21.5%)	
Non-belt	176 (40.4%)	152 (41.0%)	24 (36.9%)	
Clinical Characteristics				
Heart Failure Type, n (%)				0.76

HFrEF <50	198 (45.4%)	168 (45.3%)	30 (46.2%)	
HfpEF ≥50	178 (40.8%)	153 (41.2%)	25 (38.5%)	
Coronary Heart Disease, n (%)	139 (31.9%)	116 (31.3%)	23 (35.4%)	0.51
Diabetes Mellitus, n (%)	168 (38.5%)	142 (38.3%)	26 (40.0%)	0.93
Hypertension, n (%)	339 (77.8%)	288 (77.6%)	51 (78.5%)	0.91
Stroke, n (%)	50 (11.5%)	41 (11.1%)	9 (13.8%)	0.52
Atrial Fibrillation, n (%)	18 (4.1%)	15 (4.0%)	3 (4.6%)	0.82
Chronic Kidney Disease, n (%)	113 (25.9%)	93 (25.1%)	20 (30.8%)	0.34
Depressive symptoms, n (%)	60 (13.8%)	55 (14.8%)	5 (7.7%)	0.12
General Health, n (%)				0.68
Poor	23 (5.3%)	20 (5.4%)	3 (4.6%)	
Fair	112 (25.7%)	98 (26.4%)	14 (21.5%)	
Good	161 (36.9%)	136 (36.7%)	25 (38.5%)	
Very good	102 (23.4%)	83 (22.4%)	19 (29.2%)	
Excellent	38 (8.7%)	34 (9.2%)	4 (6.2%)	
Body Mass Index (kg/m2), mean (SD)	30.2 (6.6)	30.3 (6.7)	29.8 (6.5)	0.56
Waist circumference (cm), mean (SD)	102.2 (16.7)	101.91 (16.11)	103.87 (19.8)	0.39
Systolic blood pressure (mmHg), mean, (SD)	134.4 (19.0)	133.9 (18.8)	137.4 (19.5)	0.17
Total Cholesterol (mg/dL), mean (SD)	184.8 (41.9)	186.0 (41.9)	177.9 (42.0)	0.15
HDL Cholesterol (mg/dL), mean (SD)	47.1 (14.2)	47.4 (14.4)	45.8 (13.0)	0.43
				Health Behaviors
Smoking History, n (%)				0.88
Never	182 (41.7%)	157 (42.3%)	25 (38.5%)	

Current	66 (15.1%)	56 (15.1%)	10 (15.4%)	
Former	186 (42.7%)	157 (42.3%)	29 (44.6%)	
Alcohol Use, n (%)				0.84
Never	143 (32.8%)	122 (32.9%)	21 (32.3%)	
Current	191 (43.8%)	164 (44.2%)	27 (41.5%)	
Past	102 (23.4%)	85 (22.9%)	17 (26.2%)	
Medication Use				
*Anti-platelet**, n (%)*	239 (54.8%)	204 (55.0%)	35 (53.8%)	0.86
Anticoagulation, n (%)	17 (3.9%)	11 (3.0%)	6 (9.2%)	0.02*
Statin, n (%)	170 (39.0%)	147 (39.6%)	23 (35.4%)	0.52
Anti-Hypertensive, n (%)	298 (68.3%)	255 (68.7%)	43 (66.2%)	0.92
Insulin, n (%)	52 (11.9%)	45 (12.1%)	7 (10.8%)	0.75

*Significant at p<0.05; missing values included income (n=55), Heart failure type (n=60), coronary heart disease (n=7), diabetes (n=11), hypertension (n= 11), stroke(n=1), atrial fibrillation (n=3), Chronic kidney disease (n=15), depressive symptoms (n=2), waist circumference (n=3), systolic blood pressure (n=1), total cholesterol (n=15), HLD (n=17), smoking status (n=2), aspirin (n=1), anti-hypertensives (10)

**Includes aspirin and clopidogrel

Table 2. Association Between Baseline Characteristics of REGARDS Participants with Incident Heart Failure and the Odds of Cognitive Impairment

Characteristic	Model 1 (Age-adjusted) OR (95% CI)	Model 2 OR (95% CI)
Age	1.04 [1.01,1.08]	1.05 [1.02,1.09]
Female	0.54 [0.31,0.94]	0.48 [0.27,0.85]
Black	1.88 [1.08,3.28]	1.83 [1.01,3.32]
Less than high school education	1.89 [1.02,3.51]	1.79 [0.92,3.46]
Region of residence		
Belt	ref	ref
Buckle	0.89 [0.44,1.81]	0.85 [0.41,1.76]
Non-belt	0.72 [0.39,1.32]	0.62 [0.33,1.16]
Systolic blood pressure	1.01 [1.00,1.02]	1.01 [0.99,1.02]
Anticoagulation use	3.01 [1.05,8.63]	3.00 [1.00,8.99]

*p<0.05; Model 1: Age-adjusted; Model 2: Fully adjusted

Table 3. Baseline Characteristics of a Matched Cohort of REGARDS Participants Without Heart Failure

Characteristic	**All Participants (n =1307)**	**Cognitively Intact (n = 1132)**	**Cognitively Impaired (n=175)**	**P-value**
Prevalence of Cognitive Impairment: 13.4% (95% CI: 11.6 – 15.4%)				
Demographic Characteristics				
Age, years(SD)	70.28 (8.94)	69.56 (8.90)	74.99 (7.67)	<0.001*
Gender, n (%)				<0.001*
Male	692 (52.9%)	575 (50.8%)	117 (66.9%)	
Female	615 (47.1%)	557 (49.2%)	58 (33.1%)	
Race, n (%)				<0.001*
White	791 (60.5%)	707 (62.5%)	84 (48.0%)	
Black	516 (39.5%)	425 (37.5%)	91 (52.0%)	
Education, n (%)				<0.001*
< High school	200 (15.3%)	145 (12.8%)	55 (31.4%)	
≥ High school	1106 (84.6%)	987 (87.2%)	119 (68.0%)	
Income, n (%)				<0.001*

< $ 35K	619 (47.4%)	520 (45.9%)	99 (56.6%)	
≥ $35k	482 (36.9%)	439 (38.8%)	43 (24.6%)	
Region of Residence, n(%)				0.03*
Belt	436 (33.4%)	372 (32.9%)	64 (36.6%)	
Buckle	303 (23.2%)	276 (24.4%)	27 (15.4%)	
Non-belt	568 (43.5%)	484 (42.8%)	84 (48.0%)	
Clinical Characteristics				
Heart Disease, n (%)	262 (20.0%)	212 (18.7%)	50 (28.6%)	0.002*
Diabetes Mellitus, n (%)	261 (20.0%)	219 (19.3%)	42 (24.0%)	0.14
Hypertension, n (%)	817 (62.5%)	705 (62.3%)	112 (64.0%)	0.68
Stroke, n (%)	92 (7.0%)	75 (6.6%)	17 (9.7%)	0.14
Atrial Fibrillation, n (%)	50 (3.8%)	42 (3.7%)	8 (4.6%)	0.59
Chronic Kidney Disease, n (%)	200 (15.3%)	154 (13.6%)	46 (26.3%)	<0.001*
Depressive symptoms, n (%)	139 (10.6%)	113 (10.0%)	26 (14.9%)	0.05*
General Health, n (%)				
Poor	34 (2.6%)	29 (2.6%)	5 (2.9%)	0.35
Fair	192 (14.7%)	158 (14.0%)	34 (19.4%)	
Good	462 (35.3%)	404 (35.7%)	58 (33.1%)	
Very good	417 (31.9%)	366 (32.3%)	51 (29.1%)	
Excellent	197 (15.1%)	174 (15.4%)	23 (13.1%)	
Body Mass Index (kg/m2), mean (SD)	28.4 (5.4)	28.5 (5.4)	27.5 (4.9)	0.02*
Waist circumference (cm), mean (SD)	95.6 (13.9)	95.5 (14.2)	96.4 (12.7)	0.41
Systolic blood pressure	129.7 (17.1)	129.4 (17.1)	131.9 (17.3)	0.06

(mmHg), mean, (SD)				
Total Cholesterol (mg/dL), mean (SD)	189.9 (40.4)	190.7 (40.4)	185.2 (40.2)	0.11
HDL Cholesterol (mg/dL), mean (SD)	51.7 (16.7)	52.2 (16.7)	48.6 (16.4)	0.01*
Health Behaviors				
Smoking History, n (%)				0.26
Never	568 (43.5%)	487 (43.0%)	81 (46.3%)	
Current	161 (12.3%)	146 (12.9%)	15 (8.6%)	
Former	566 (43.3%)	489 (43.2%)	77 (44.0%)	
Alcohol Use, n (%)				0.02*
Never	405 (31.0%)	338 (29.9%)	67 (38.3%)	
Current	639 (48.9%)	570 (50.4%)	69 (39.4%)	
Former	263 (20.1%)	224 (19.8%)	39 (22.3%)	
Medication Use				
*Anti-platelet**, n (%)*	615 (47.1%)	537 (47.4%)	78 (44.6%)	0.48
Anticoagulation, n (%)	41 (3.1%)	34 (3.0%)	7 (4.0%)	0.48
Statin, n (%)	429 (32.8%)	367 (32.4%)	62 (35.4%)	0.43
Anti-Hypertensive, N (%)	709 (54.2%)	616 (54.4%)	93 (53.1%)	0.82
Insulin, n (%)	33 (2.5%)	29 (2.6%)	4 (2.3%)	0.83

*significant at p<0.05; missing values included education(n=1), income (n=206), coronary heart disease (n= 26), diabetes (n=44), hypertension (n=2), stroke(n=3), atrial fibrillation (n=18), Chronic kidney disease (n=52), depressive symptoms (n=14), waist circumference (n=6), systolic blood pressure (n= 2), total cholesterol (n=52), HDL (n=58),smoking status (n=12), aspirin (n=2), anti-hypertensives (n=37)

**includes aspirin and clopidogrel