Clinical Investigations

Incident Heart Failure and Cognitive Decline: The Atherosclerosis Risk in Communities Study

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ABSTRACT

Background: Cognitive impairment is found in a significant proportion of patients with heart failure (HF). Although cognitive impairment may be a consequence of HF, early signs of cognitive impairment may also indicate subclinical vascular disease, and thus a risk factor for future cardiovascular events.

Methods and Results: The Atherosclerosis Risk in Communities Study is a prospective cohort study of the development of atherosclerosis. Cox proportional hazards regression was used to examine the association between mean 6-year change in cognitive function and incident HF in 7962 white and 1933 African-American men and women aged 46 to 70 years and free of clinical stroke. Scores were obtained for the Delayed Word Recall Test, the Digit Symbol Substitution Test (DSST), and the Word Fluency Test. There was a significantly increased risk of developing HF during the mean 12.6-year follow-up period after adjustment for age, gender, race, and education for those in the quartile with the greatest decline in DSST scores (hazard ratio [HR] = 1.17, $P = .009$), and in the quartile with the lowest baseline DSST scores (HR = 1.43, $P < .001$).

Conclusions: The results suggest that relatively low performance on a test of information processing speed may serve as an indicator of HF risk in middle age. (*J Cardiac Fail 2017;23:47–55*)

Key Words: Epidemiology, cognition.

Heart failure (HF) is a major cause of hospitalization and mortality in the United States, estimated to affect more than 6 million adults in 2010.[1] The lifetime risk of developing HF for both men and women was reported to be 1 in 5 at 40 years of age in the Framingham Heart Study.[2] Major risk factors for HF include coronary heart disease, hypertension, left ventricular hypertrophy, abnormal heart valves, diabetes, cigarette smoking, obesity, and lack of physical activity.[3,4]

An estimated 25% to 50% of patients with HF have cognitive impairment, with decreased attention and executive function, reduced processing speed, and memory loss as the most frequent deficits.[5–7] In a systematic review of mostly cross-sectional studies including 2937 patients with HF and 14,848 controls, the odds ratio for cognitive impairment was 1.62 ($P < .0001$) for individuals with HF.[8] Cerebral hypoperfusion secondary to reduction in cerebral blood flow is suggested as the primary physiological mechanism linking HF and impaired cognitive function.[9]

Although cognitive impairment may be a downstream consequence of HF, early signs of cognitive impairment may also be an indication of subclinical vascular disease and thus a risk factor for future clinically apparent cardiovascular disease. In a previous investigation carried out in the Atherosclerosis Risk in Communities (ARIC) study, Elkins et al tested the hypothesis that poor performance on tests of cognitive function may be used to identify individuals who are particularly

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susceptible to developing myocardial infarction and stroke and found that lower cognitive scores predicted a greater risk of cardiovascular events over a 6.4-year period.[10] Similar results have recently been reported for 5292 participants in the Whitehall II study, in which lower scores on tests of vocabulary and verbal and mathematical reasoning were associated with an increased incidence of coronary heart disease during 6 years of follow-up,[11] and in the Health and Retirement Study and a study of Swedish men in which lower scores on tests of delayed word recall or executive function, respectively, were shown to predict risk of incident stroke.[12,13] The aim of the current study was to determine whether performance on 3 neurocognitive tests administered at baseline or change in cognitive function measured over 6 years were associated with incident HF in white and African-American participants in the ARIC study.

Material and Methods

The ARIC Study

The ARIC study is a prospective longitudinal investigation of the development of atherosclerosis and its clinical sequelae in which 15,792 individuals aged 45 to 64 years were enrolled at baseline. A detailed description of the ARIC study has been reported previously.[14] At the inception of the study in 1987–1989, participants were selected by probability sampling from 4 communities in the United States: Forsyth County, NC; Jackson, MS (African-Americans only); the northwestern suburbs of Minneapolis, MN; and Washington County, MD. Four examinations were carried out at 3-year intervals (examination 1, 1987–1989; examination 2, 1990–1992; examination 3, 1993–1995; examination 4, 1996–1998), and subjects are contacted annually to update their medical histories between examinations. A fifth clinical examination has recently been completed (2011–2013). Cognitive testing was performed at visits 2, 4, and 5 in all participants. Individuals were not included in this analysis if they were neither African-American nor white (n = 48), were African-Americans from the Minnesota or Maryland field centers because of the small numbers of individuals recruited from these sites (n = 55), had a history of physician-diagnosed stroke (n = 272) or unknown history of stroke (n = 31) before visit 2, did not attend visit 2 (n = 1432), did not attend visit 4 (n = 1769), had HF (n = 530) or an unknown history of HF (n = 233) at the first clinical examination, or developed HF before the second clinical examination (n = 71) or between examinations 2 and 4 (n = 631). Additional exclusions were made for incident definite or probable stroke verified by ARIC clinicians from medical records between visit 2 and 4 (n = 365), missing cognitive data for all 3 neuropsychological tests at either visit 2 or visit 4 (n = 287), if hospitalized for dementia before visit 4 and identified using International Classification of Diseases, ninth edition (ICD-9) codes (Alzheimer's disease [331.0]; vascular dementia [290.4]; or other forms of dementia [290.0, 290.1., 290.2, 290.3, 290.9, 294.1, 294.2, 294.8, 294.9, 331.1, 331.2, 331.8, 331.9] (n = 6), for missing information concerning the highest level of education completed (n = 16), or for missing covariates (n = 151). The final study sample consisted of 7962 white and 1933 African-American men and women. Written informed consent was provided by all study participants, and the study design and methods were approved by institutional review boards at the collaborating medical centers.

Cognitive Tests

Cognitive function was assessed by 3 neuropsychological tests at the second and fourth clinical examinations that have been described previously:[15] (1) The Delayed Word Recall Test (DWRT) is a test of verbal learning and recent memory in which the participant is required to use each of 10 common nouns in a sentence. After a 5-minute delay in which another test is given, the participant is asked to recall the 10 nouns. The DWRT score is the number of correct words recalled (range, 0–10);[16] (2) The Digit Symbol Substitution Test (DSST) is a subtest of the Wechsler Adult Intelligence Scale-Revised involving timed translation of numbers to symbols using a key with paired symbols and digits and measures psychomotor performance,[17,18] and the total number of correct translations within 90 seconds determines the score (range, 0–93);[17] and (3) The Word Fluency Test (WFT) is a measure of executive function. In 3 separate 1-minute trials, the subject is asked to generate as many words as possible beginning with the letters F, A, and S.[18] The score is the combined total of correct words produced.[19] The tests were administered by trained interviewers in a standardized order and were given in a single session. The testing sessions were monitored by tape recorder and a sample of sessions was evaluated to confirm that there were no systematic differences in mean test scores obtained by different interviewers.

For all of the neuropsychological tests, lower scores indicate a lower measure of cognition. Six-year change in cognitive function was analyzed as the difference between the test score obtained at the later of the 2 clinic visits and the test score obtained at the earlier examination for each neuropsychological test.

Clinical and Laboratory Measurements

The clinical and laboratory measurements used for this study were assessed during the second clinical examination with the exception of education, which was evaluated at the baseline examination. Education was included as a covariate in regression models as an ordinal variable based on the highest level attained (≤11 years, 12–16 years, >17 years). Incident HF was defined as the first HF hospitalization (ICD-9 code 428 in any position), or any deaths in which the death certificate included an HF code (code 428, ICD-9 or 150, ICD-10, in any position). Exclusion for HF was based on self-reported current medication use for HF, or having manifest HF as defined by Gothenburg criteria stage 3. The Gothenburg criteria are based on a cardiac score (ie, history of coronary heart disease, angina, or atrial fibrillation), pulmonary score (ie, history of asthma or bronchitis), and therapy