Cognitive Change in Heart Failure
A Systematic Review

Alexandra M. Hajduk, MPH; Catarina I. Kiefe, MD, PhD; Sharina D. Person, PhD; Joel G. Gore, MD; Jane S. Saczynski, PhD

Background—Cognitive impairment, highly prevalent in patients with heart failure (HF), increases risk for hospitalization and mortality. However, the course of cognitive change in HF is not well characterized. The purpose of this systematic review was to examine the available evidence longitudinal changes in cognitive function in patients with HF.

Methods and Results—A literature search of several electronic databases was performed. Studies published from January 1, 1980, to September 30, 2012, that used validated measures to diagnose HF and assess cognitive function ≥2x in adults with HF were eligible for inclusion. Change in cognitive function was examined in the context of HF treatments applied (eg, medication initiation, left ventricular assist device implantation), length of follow-up, and comparison group. Fifteen studies met eligibility criteria. Significant decline in cognitive function was noted among patients with HF followed up for >1 year. Improvements in cognition were observed among patients with HF undergoing interventions to improve cardiac function (eg, heart transplantation) and among patients examined over short time periods (<1 year). Studies comparing patients’ cognition over time with their own baseline tended to report improvements, whereas studies using a comparison group without HF tended to report declines or stability in cognition over time among patients with HF.

Conclusions—Patients with HF are at increased risk for cognitive decline, but this risk seems to be modifiable with cardiac treatment. Further research is needed to identify the mechanisms that cause cognitive changes in HF. (Circ Cardiovasc Qual Outcomes. 2013;6:451-460.)

Key Words: cognition ■ epidemiology ■ heart failure

Cognitive impairment is an important patient factor associated with poor outcomes in heart failure (HF). Cognitive impairment affects 25% to 85% of patients with HF and develops earlier in patients with HF than in persons of similar age without HF. Patients with HF have up to a 2-fold increased risk of impaired cognitive function compared with age-matched controls, particularly in the domains of memory, psychomotor speed, attention, and executive function. Patients with HF and co-occurring cognitive impairment may have poor somatic awareness and decreased ability to carry out essential self-care activities to manage their disease, leading to worsening of HF, hospitalization, and mortality. However, the course of cognitive change in HF is not well understood.

Understanding the longitudinal course of cognitive function and identifying factors that influence cognition in patients with HF will guide clinicians in identifying patients at risk for poor outcomes and creating treatment plans that improve outcomes and quality of life. Although the relationship between cognitive function and HF has been examined in previous systematic reviews, these reviews focused primarily on cross-sectional studies and did not report on change in cognition over time. Our objective was to conduct a systematic review of the literature evaluating the current evidence about longitudinal changes in cognition among patients with HF.

Methods

Searches to identify relevant articles were performed in Medline, Ovid, and ISI Web of Science in September 2012. Keywords and Medical Subject Heading terms used in these searches included cognitive disorder, cognition disorder, cognition, cognitive impairment, neurocognitive, memory, dementia, processing speed, attention, executive function, visuospatial, HF, congestive HF, cardiovascular disease, longitudinal, time, and follow-up. Bibliographies of eligible articles were searched for additional references.

This review was limited to observational studies and controlled trials investigating changes in cognition over time in humans with HF. Additional inclusion criteria included use of adult sample (>18 years of age); publication date from January 1, 1980, to September 30, 2012; published in English; use of validated criteria to diagnose HF; and use of validated neurocognitive measures to assess cognitive function at ≥2 time points. Editorials, reviews, case studies, and meeting abstracts were excluded, as were studies with n<50 or those using a general sample from which data specific to participants with HF could not be obtained.

Data Collection

We performed an initial review of the titles and abstracts of all articles to exclude any studies that did not meet inclusion criteria. Full review of all remaining studies was undertaken to determine eligibility for inclusion. One author (A.M.H.) independently abstracted data from all included studies using a standardized form. Information was abstracted on study type, number of participants, type of comparator group used (eg, self at baseline, healthy controls), demographic

Received August 25, 2012; accepted June 4, 2013.

From the Departments of Quantitative Health Sciences (A.M.H., C.I.K., S.D.P., J.G.G., J.S.S.) and Medicine (J.G.G., J.S.S.), Meyers Primary Care Institute (A.M.H., J.S.S.), University of Massachusetts Medical School (UMMS), Worcester.

Correspondence to Alexandra Hajduk, MPH, Department of Quantitative Health Sciences, University of Massachusetts Medical School, 55 Lake Ave N, A57-1065J, Worcester, MA 01655. E-mail alexandra.hajduk@umassmed.edu

© 2013 American Heart Association, Inc.

Circ Cardiovasc Qual Outcomes is available at http://circoutcomes.ahajournals.org · DOI: 10.1161/CIRCOUTCOMES.113.000121

451
WHAT IS KNOWN

- Cognitive impairment, common among patients with heart failure (HF), increases risk for poor outcomes, such as hospitalization and mortality.
- Understanding the course of cognitive change in patients with heart failure is important for identifying patients at risk for poor outcomes and developing treatments that may preserve cognitive function. The course of cognitive change in HF over time has not been systematically examined.

WHAT THE STUDY ADDS

- Findings from the 15 studies examined in this systematic review indicate that patients with HF are at higher risk of cognitive decline over time than same-age peers without HF.
- After interventions to improve cardiac function (eg, medications, cardiac resynchronization), cognitive function can stabilize or improve in patients with HF over the short term (ie, up to a year).
- Studies that examine the natural course of cognition in HF for >1 year uniformly show declines among patients with HF.

characteristics (ie, age, sex, race/ethnicity, and education level), cardiac characteristics (eg, mean left ventricular ejection fraction), HF diagnostic criteria (eg, New York Heart Association criteria), cognitive domains assessed and associated neurocognitive tests, frequency and timing of cognitive assessments, type of intervention or treatments applied (eg, disease management program, heart transplantation), and primary results for change in cognitive function.

Definition of Change in Cognitive Function

We define significant change in cognitive function as a statistically significant (P<0.05) change between 2 time points. We chose this definition because of the variability in cognitive tests administered in the included studies, which ranged from tests with standardized cut points for impairment (eg, Mini Mental Status Examination) to domain-specific measures on which performance is measured on a linear scale. All studies reported whether there was significant change in performance >2 time points, allowing for comparisons across studies using this definition. Because many studies examined changes in a single domain of cognition (eg, memory) using several assessment tools, cognitive change was recorded as significant if the results from any test measuring that domain were statistically significant.

Quality Assessment

The quality of each study was assessed using Downs and Black criteria, which examine validity, bias, power, and other study attributes. The Downs and Black scale, developed to assess quality in clinical trials, was modified, on the basis of previous systematic reviews, to accommodate the characteristics of observational studies. For example, for nonrandomized trials, criteria pertaining to randomization technique were removed. The checklist item about power was dichotomized into sufficient or insufficient power rather than a 5-level ordinal item. A quality score for each study was calculated by dividing the total number of points received by the total number of points for which the study was eligible to receive on the basis of its design characteristics (maximum=28 for randomized, controlled trials; 21–26 for observational studies) and are reported in percentages. Because of the heterogeneous nature of the included studies, meta-analyses were not performed.

Results

Study Selection

The literature search yielded 566 articles, from which 254 duplicates were removed, leaving 312 articles for review. Of these, 279 were excluded on the basis of title and abstract review. Of the 33 full-text articles reviewed, 22 were excluded, the majority because of small sample size (n=10) or inability to examine patterns of function in patients with HF specifically (n=7). Four additional articles were identified from the references of included articles. Thus, this review reports on 15 articles of 14 study samples (Figure). Characteristics of included articles are detailed in Table 1.

Study Design and Recruitment

The majority of included studies were observational cohort studies (n=13). Two of these cohort studies included population-based cohorts in which residents of entire municipalities or countries were eligible for enrollment, and 11 studies reported on samples recruited from inpatient or outpatient care settings. Two nonrandomized trials were included.

Six studies recruited individuals without HF to serve as comparison groups. Individuals without HF were recruited from ambulatory or outpatient care settings voluntarily responded to a media campaign, or were recruited as part of a population-based cohort. Individuals without HF were recruited at the same general location (ie, same study sites) and during the same time period as individuals with HF.

Several exclusion criteria that may impact the association between HF and cognitive change were consistently noted in included studies. A number of studies reported excluding participants based on comorbidities of HF that increase with age and may also be associated with cognitive function, such as history of stroke, cerebrovascular disease, severe neurological disease, dementia or other cognitive impairments, recent myocardial infarction, illiteracy, and depression or other psychiatric disorder.

Quality Ratings

Quality ratings, based on modified Downs and Black criteria, ranged from 67.9% to 91.3% (of a possible 100%); the average score was 84.3.

Sample Characteristics

Sample sizes ranged from 54 to 1511 participants. Six studies had <100 participants, 6 studies had 100 to 999 participants, and 3 studies had ≥1000 participants.

Comparison groups ranged widely among the 15 studies. Four studies did not use a comparison group but rather compared participants’ cognitive performance at follow-up with their baseline scores. Eleven studies made formal comparisons with control groups and compared treatment/intervention groups with control participants without HF. Patients with stable HF patients with HF who did not undergo the treatment/intervention under study, or patients with HF who did not respond to the treatment/intervention under study. Eight studies compared change in cognition across multiple comparison groups, including 1
study\textsuperscript{20} that compared cognitive change among participants with decompensated HF, participants with stable HF, and healthy controls.

Length of follow-up ranged from 13 days\textsuperscript{26} to 9 years.\textsuperscript{15} The follow-up period was <6 months in over half of the studies,\textsuperscript{17,20-23,28} 6 to 11 months in 2 studies,\textsuperscript{19,24} and ≥1 year in 4 studies.\textsuperscript{14-16,18} Eight studies\textsuperscript{17-19,23-27,28} reported on loss to follow-up. Rates of loss to follow-up (excluding loss to follow-up because of death, which is appreciable in patients with HF) varied widely according to the characteristics of the study sample and length of follow-up time and ranged from <1%\textsuperscript{22} to 66%\textsuperscript{28}; the majority of studies\textsuperscript{17-19,21,23,28} experienced attrition rates >30%.

Mean sample ages ranged from 44.7±10.6\textsuperscript{18} to 84.3±4.1\textsuperscript{14} years; studies examining cognition in the context of standard treatment practices tended to have older participants, whereas studies examining cognition in the context of invasive treatments (eg, heart transplantation) tended to have younger participants, reflecting the patient population typically eligible for such treatments. Cardiovascular disease risk factors common in HF that may contribute to cognitive decline, including hypertension, diabetes mellitus, depression, and smoking history, were accounted for in 12,\textsuperscript{14,15,17,19-22,24-28} 7,\textsuperscript{14,15,20,24-26,28} 5,\textsuperscript{14,16-18,20} and 3\textsuperscript{14,17,20} studies, respectively.

Cognitive Assessments and Outcomes

The majority of studies (n=10)\textsuperscript{16-18,20-23,28} included 2 cognitive assessments, whereas others had 3,\textsuperscript{19,21,22} 4,\textsuperscript{15} or 5\textsuperscript{14} assessments. The cognitive domains most often assessed were global cognition,\textsuperscript{15,16,18,19,22-28} memory,\textsuperscript{14,16,18,20-24} attention,\textsuperscript{16-18,22,24,27} visuospatial ability,\textsuperscript{14,17,21,23,24} processing speed,\textsuperscript{14,20-22} executive function,\textsuperscript{18,20,22} language,\textsuperscript{21,24} and reasoning.\textsuperscript{18,24} Other domains tested less frequently (eg, praxis) were not examined in this review. The studies used a wide variety of neurocognitive tests to assess cognition, with some studies using multiple tests to measure cognition in a single domain. Most studies did not report whether alternative versions of the neurocognitive tests were used to limit the influence of practice effects associated with repeated assessments.

Changes in Cognition According to Comparison Group

Changes in cognitive function among patients with HF differed according to the comparison group against which they were evaluated (Table 2). Studies that compared patients’ follow-up scores on cognitive tests with their baseline scores tended to report significant improvements in performance over time,\textsuperscript{15-19,21,23-26} although several of these studies reported no significant change.\textsuperscript{20,27,28} Conversely, studies that compared change in function with comparison groups of patients without HF were more likely to report declines in cognition over time.\textsuperscript{14-16,20} Results of studies that compared changes in cognition between patients with decompensated HF with other patients with HF differed according to whether the comparison group had stable or decompensated HF. Cognition tended to improve in patients with unstable HF undergoing a treatment or intervention when compared with patients with decompensated HF not receiving or responding to the treatment,\textsuperscript{18,25,26} although this was not observed in 1 study.\textsuperscript{27} When patients with stable HF were used as a comparator group,\textsuperscript{20} cognition in patients with decompensated HF was lower than the comparison group at baseline but often improved up to the level of patients with stable HF upon compensation.

Changes in Cognition According to Length of Follow-up

Cognitive changes in patients with HF were also related to length of study follow-up time (Table 3). Three\textsuperscript{14-26} of 4 studies
### Table 1. Characteristics of the 16 Studies Included in the Systematic Review of Cognitive Change in HF

<table>
<thead>
<tr>
<th>References</th>
<th>Study Type</th>
<th>Sample Size and Comparison Group</th>
<th>Sample Demographics</th>
<th>Frequency and Timing of Cognitive Assessments</th>
<th>Cognitive Domains Assessed</th>
<th>Treatments/Interventions</th>
<th>Change in Cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almeida et al16</td>
<td>Observational cohort</td>
<td>N=231</td>
<td>Mean age (SD): HF group=68.4 (10.2)</td>
<td>2-Baseline, 2 y</td>
<td>Global Memory Attention</td>
<td>None (standard clinical treatment assumed)</td>
<td>Patients with HF declined in global cognition faster than healthy controls but not compared with CVD controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HF group: n=77</td>
<td>CVD group: n=73</td>
<td>Healthy controls: n=81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HF group compared with their own, CVD group, and healthy controls at f/u</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almeida and Tamai17</td>
<td>Observational cohort</td>
<td>N=81</td>
<td>Mean age (SD): CHF=67.3 (0.9) Controls=76.7 (1.5)</td>
<td>2-Baseline, 6 wk</td>
<td>Attention Visuospatial</td>
<td>None (standard treatment assumed)</td>
<td>Patients with HF improved on some attention tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HF group: n=50 (31 with complete f/u) Elderly controls: n=31</td>
<td>% Men: CHF=76.0 Controls=66.7</td>
<td></td>
<td></td>
<td></td>
<td>HF group had similar scores for all attention tests at f/u as controls at baseline</td>
</tr>
<tr>
<td>Bornstein18</td>
<td>Observational cohort</td>
<td>N=62 (preoperative)</td>
<td>Mean age: 44.7 (10.6) y 75.8% men</td>
<td>2-Baseline, 36 mo (25 mo for transplantation recipients)</td>
<td>Global cognition Memory Reasoning/concept formation Mental flexibility/response Fluency (executive function) Attention/concentration Other</td>
<td>Heart transplantation</td>
<td>Transplanted patients showed 11.6% mean improvement in cognition, controls showed 0% change</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intervention group: n=7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Transplanted patients had improvements or less decline in memory, mental flexibility, and attention than nontransplanted pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control group: n=4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transplantation recipients compared with nonrecipients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Of the two groups, but differences between experimental groups NS</td>
</tr>
<tr>
<td>Ghali et al27</td>
<td>Randomized, controlled trial</td>
<td>N=170</td>
<td>Mean age (SD): Lixivaptan group=69.1 (11.8) Placebo group=70.6 (11.2)</td>
<td>2-Baseline, 4 wk</td>
<td>Global Attention</td>
<td>Treatment with lixivaptan (vasopressin receptor antagonist)</td>
<td>Global function and attention improved in both groups, but difference between experimental groups NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lixivaptan group: n=111</td>
<td>Placebo group: n=59</td>
<td></td>
<td></td>
<td></td>
<td>Improvements in global cognition, but attenuated in cyclosporine users</td>
</tr>
<tr>
<td>Grimm et al39</td>
<td>Observational cohort</td>
<td>N=110 (baseline) 55 heart transplantation candidates 55 healthy controls N=19 (end of f/u) HF pts’ baseline served as own controls at f/u</td>
<td>Mean age=54.8 (9.2) 92.7% men</td>
<td>3-Baseline, 4 and 12 mo after transplantation</td>
<td>Global cognition Other</td>
<td>Heart transplantation</td>
<td></td>
</tr>
<tr>
<td>Hjelm et al44</td>
<td>Observational population-based cohort</td>
<td>N=702</td>
<td>Mean age, y: HF=84.3 (4.1) % men: HF=67 no-HF=67 100% white</td>
<td>5-Baseline, 2, 4, 6, and 8 y</td>
<td>Memory Processing speed Visuospatial</td>
<td>None (standard treatment assumed)</td>
<td>Pts with HF consistently performed lower on almost all cognitive tests</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HF=variable, n=66–147 No-HF=variable, n=301–511</td>
<td>No-HF=83.3 (2.9)</td>
<td></td>
<td></td>
<td></td>
<td>Pts with HF declined faster than patients without HF in memory</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HF pts compared with no-HF pts and their own baseline data at f/u</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pts without HF cognitively caught up with patients with HF by end of study</td>
</tr>
</tbody>
</table>

(Continued)
Table 1.  Continued

<table>
<thead>
<tr>
<th>References</th>
<th>Study Type</th>
<th>Sample Size and Comparison Group</th>
<th>Sample Demographics</th>
<th>Frequency and Timing of Cognitive Assessments</th>
<th>Cognitive Domains Assessed</th>
<th>Treatments/Interventions</th>
<th>Change in Cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karlsson et al28</td>
<td>Randomized clinical trial</td>
<td>N=208 (randomized)</td>
<td>Mean age=76 (7.5)% men=56</td>
<td>2-Baseline, 6 mo</td>
<td>Global</td>
<td>Nurse-based HF management program</td>
<td>No significant improvement in cognition found in intervention group vs control group % impaired decreased over time (12%–4%)</td>
</tr>
<tr>
<td>Kindermann20</td>
<td>Observational cohort</td>
<td>N at baseline=70 N at f/u=60</td>
<td>Mean age=50 (14) y % men=81</td>
<td>3-Baseline, 2 weeks (14±7 days)</td>
<td>Memory</td>
<td>Standard clinical treatment</td>
<td>Memory, processing speed, executive function improved in decompensated HF group to level of stable HF group, but not to level of healthy controls</td>
</tr>
<tr>
<td>Petrucci et al21</td>
<td>Observational cohort</td>
<td>N=93 (baseline) N=28 (complete data at end of f/u)</td>
<td>Mean age, y; HF=83.3 (5.4) No-HF=81.2 (4.8)</td>
<td>4-Baseline, 4, 6, and 9 y (mean f/u= 5.02 y)</td>
<td>Memory</td>
<td>LVAD implantation</td>
<td>Vissuospatial perception, memory, and processing speed improved in pts with complete data</td>
</tr>
<tr>
<td>Qiu et al15</td>
<td>Observational population-based cohort</td>
<td>N=1301 HF: n=205 No-HF: n=1096</td>
<td>Mean age= y; HF=83.3 (5.4) No-HF=81.2 (4.8)</td>
<td>4-Baseline, 4, 6, and 9 y (mean f/u= 5.02 y)</td>
<td>Global cognition</td>
<td>None (standard treatment assumed)</td>
<td>HF at baseline associated with HR of 1.84 for dementia at f/u compared with pts without HF Use of antihypertensives attenuated dementia risk</td>
</tr>
<tr>
<td>Riegel et al22</td>
<td>Observational cohort</td>
<td>N=279 Average processing speed group: n=114 Below average processing speed group: n=165</td>
<td>Mean average age (SD): Average PS group=56.1 (12.1) Below average PS group=66.3 (11.9) 64% men</td>
<td>3-Baseline, 3 and 6 mo</td>
<td>Global Memory attention processing speed</td>
<td>None (standard treatment assumed)</td>
<td>No significant changes in cognition</td>
</tr>
<tr>
<td>Schall et al23</td>
<td>Observational cohort</td>
<td>N=54 (pretransplantation) N=20 (posttransplantation)</td>
<td>Mean age, y=46 (11) % men=81.5%</td>
<td>2-Baseline, 7.7 mo (range=3–15)</td>
<td>Global cognition Memory Vissuospatial Other</td>
<td>Heart transplantation</td>
<td>No change in cognition (except other)</td>
</tr>
<tr>
<td>Stanek et al24</td>
<td>Observational cohort</td>
<td>N=70 (complete cases) HF: n=40 No-HF: n=35 HF pts' scores compared with pts without HF scores and their own baseline</td>
<td>Mean age, y=70.7 (7.7) % men=63</td>
<td>2-Baseline and 12 mo</td>
<td>Global cognition Memory Attention Verbal fluency Vissuospatial Planning/reasoning</td>
<td>None (standard clinical treatment assumed)</td>
<td>Pts with HF global cognition, attention, verbal fluency, planning/reasoning improved at f/u</td>
</tr>
</tbody>
</table>

(Continued)
Table 1. Continued

<table>
<thead>
<tr>
<th>References</th>
<th>Study Type</th>
<th>Sample Size and Comparison Group</th>
<th>Sample Demographics</th>
<th>Frequency and Timing of Cognitive Assessments</th>
<th>Cognitive Domains Assessed</th>
<th>Treatments/ Interventions</th>
<th>Change in Cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zuccala et al25</td>
<td>Observational cohort</td>
<td>N=1511 Pts with HF compared at t/u according to their normalization status on clinical tests</td>
<td>Mean age, y: Impaired=82 (8) Not impaired=76 (10) % men: Impaired=39 Not impaired=50</td>
<td>2-Baseline and immediately before hospital discharge (mean=15±10 days)</td>
<td>Global cognition</td>
<td>None (standard clinical treatment)</td>
<td>Normalization of hypo/hyperglycemia, hypo/hyperkalemia, and anemia associated with improved global cognition</td>
</tr>
<tr>
<td>Zuccala et al26</td>
<td>Observational cohort</td>
<td>N=1220 ACEI group: n=446 No-ACEI group: n=774 Pts on (ACEI) compared with patients not on ACEI</td>
<td>Mean age, y: ACEI=79(9) No-ACEI=79 (9) % men: ACEI=43 No-ACEI=47</td>
<td>2-Baseline and immediately before hospital discharge (mean=13 [IQR=8–20] days)</td>
<td>Global cognition</td>
<td>Standard treatment with ACEI</td>
<td>ACEI pts experienced greater improvement in global cognition than no-ACEI pts</td>
</tr>
</tbody>
</table>

ACE-I indicates angiotensin-converting-enzyme inhibitor; CVD, cardiovascular disease; t/u, follow-up; HF, heart failure; HR, hazard ratio; pts, patients; IQR, interquartile range; and LVAD, left ventricular assist device.

that followed participants for ≥1 year reported cognitive decline among patients with HF, whereas only 1 of 11 studies that followed patients for <1 year reported cognitive decline. One study14 that followed patients for 8 years reported that cognitive decline occurred faster and at a younger age in patients with HF than those without HF. Studies that examined cognitive change over shorter time periods (≤12 months)17,19–28 tended to report improvements17,19,21,25–27 or no change22–24,28 in cognition. These findings imply that cognition remains stable over short periods and may even improve, particularly among patients with HF whose baseline assessments were during hospitalization for HF decompensation. However, over longer periods of follow-up (>12 months), cognitive function tends to decline.

Changes in Cognition According to Treatment

Most studies included in this review examined the effects of treatments and interventions, such as heart transplantation,18,19,23 left ventricular assist device implantation,21 a nurse-led HF management program,28 various medications,26,27 and standard in-hospital treatments17,20,25 on cognitive change in patients with HF. Five studies14–16,22,24 examined the natural course of cognitive change among patients with HF. Evidence from included studies suggests that the direction of cognitive change varied according to the type of treatment or intervention applied (Table 4). Studies assessing the influence of invasive surgeries18,19,21,23 tended to report improvements in cognition among patients who had severe HF at baseline. One study28 reporting on change after a noninvasive intervention (ie, disease management program) found no significant improvements in cognitive function over time but did report that the proportion of the study sample with cognitive impairment (defined as a Mini Mental State Examination score of ≤24) decreased from 12% at baseline to 4% at the end of 6 months of follow-up. Studies examining the influence of compensation of HF among acutely decompensated patients through standard in-hospital treatments17,20,25 reported improvements in cognition that brought them up to scores similar to patients with stable HF, with the exception of 1 randomized, controlled trial assessing the influence of a vasopressin receptor antagonist among patients with HF27 that found no significant change in cognition over time, despite improvements in edema. The majority (3 of 5)14–16...
Table 3. Change in Cognition According to Length of Follow-up

<table>
<thead>
<tr>
<th>Length of Follow-Up</th>
<th>Studies</th>
<th>Cognitive Change Over Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤6 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almeida and Tamai17</td>
<td>81</td>
<td>Improvement*, stable†</td>
</tr>
<tr>
<td>Ghali et al20</td>
<td>170</td>
<td>Improvement*, stable‡</td>
</tr>
<tr>
<td>Karlsson et al28</td>
<td>146</td>
<td>Stable*‡</td>
</tr>
<tr>
<td>Kindermann et al20</td>
<td>70</td>
<td>Improvement*, stable‡, decline†</td>
</tr>
<tr>
<td>Petrucci et al21</td>
<td>93</td>
<td>Improvement*</td>
</tr>
<tr>
<td>Riegel et al22</td>
<td>279</td>
<td>Stable*</td>
</tr>
<tr>
<td>Schall et al23</td>
<td>54</td>
<td>Stable*</td>
</tr>
<tr>
<td>Zuccala et al25</td>
<td>1151</td>
<td>Improvement‡</td>
</tr>
<tr>
<td>Zuccala et al28</td>
<td>1220</td>
<td>Improvement‡</td>
</tr>
<tr>
<td>6 to ≤12 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grimm et al18</td>
<td>110</td>
<td>Improvement*</td>
</tr>
<tr>
<td>Stanek et al24</td>
<td>70</td>
<td>Improvement*, stable†</td>
</tr>
<tr>
<td>&gt;12 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almeida et al19</td>
<td>231</td>
<td>Decline†</td>
</tr>
<tr>
<td>Bornstein et al18‡</td>
<td>62</td>
<td>Improvement‡</td>
</tr>
<tr>
<td>Hjelm et al14</td>
<td>702</td>
<td>Decline†</td>
</tr>
<tr>
<td>Qi et al15</td>
<td>1301</td>
<td>Decline†</td>
</tr>
</tbody>
</table>

*Compared with self at baseline.
†Compared with a control group of participants without HF.
‡Compared with a control group of patients with heart failure (HF) who did not receive the treatment/intervention under study, did not respond to an intervention under study, or patients with stable HF for which the intervention under study was not indicated.
§Statistical significance of comparisons not reported.

Discussion

In this review, we found evidence for significant decline in cognitive function in patients with HF followed for >11 months. We also found that over shorter periods of follow-up and the setting of interventions aimed at improving cardiac function, cognition can improve in patients with HF.

Our findings are consistent with those of a previous systematic review that suggested cognitive impairment could be reversed in patients with HF through heart transplantation, although the data available at the time of this review were too sparse to draw any firm conclusions. Furthermore, this previous review only examined changes in cognitive function in HF in the context of treatments and did not include studies that examined the natural course of cognition in HF. The current review expands our understanding of longitudinal changes in cognitive function in patients with HF by examining this relationship in comparison with cognitive changes observed in samples without HF and in relation to length of study follow-up time and various treatments.

Proposed Mechanisms of Change in Cognition in HF

Several included studies posited mechanisms by which HF influences cognition: (1) via decreased cerebral blood perfusion resulting in microvascular changes in the brain, and (2) cerebral emboli, both attributable to cardiac insufficiency. As evidenced by the handful of studies that reported change in cardiac function during follow-up, the development of HF or worsening of HF severity may be associated with declines in cognition. Conversely, improvements in cardiac parameters (eg, ejection fraction, cardiac index) as a result of treatments or interventions may improve cognition; this association was most apparent in...
studies documenting dramatic improvements in cardiac function, such as those evaluating heart transplantation recipients. However, not all studies examining this association, even in the context of heart transplantation, reported significant correlations between changes in clinical and cognitive parameters, so the link between cardiac and cognitive function cannot be confirmed. Future studies that measure changes in cardiac and cerebrovascular function of patients with HF are necessary to clarify how cardiac function, especially factors related to systemic circulation, may influence cognition in the HF population. In addition, information on cardiovascular disease risk factors (eg, hypertension, diabetes mellitus, depression, and smoking) that are common among patients with HF and are known to impact cognition should be collected and accounted for in statistical models to determine the independent effect of HF on cognitive change over time.

Comparison Group
Changes in cognition among patients with HF varied according to the groups to which these changes were compared. In general, cognitive scores tended to decline more or remain lower among patients with HF when compared with changes in samples without HF that were matched or adjusted for age, suggesting that patients with HF are at greater risk for cognitive decline than their healthy counterparts. However, studies comparing cognitive change in patients with decompensated HF to those with stable HF found that patients with decompensated HF had lower cognitive scores than those with stable HF at baseline and that compensation of HF among decompensated patients was associated with improvements in cognition up to the level of patients with stable HF. This finding suggests that there is room for improvement in cognition among patients with decompensated or poorly controlled HF, although the potential for improvement is probably not large enough to bring HF patients’ cognition up to the level of age-matched people without HF. Studies assessing changes in cognition in patients with HF in comparison with samples with other types of cardiovascular disease did not find significant differences, suggesting that these cognitive changes may not be specific to HF but rather general deficits in cardiovascular function. This is further corroborated by the inconsistent results found between changes in some measures of HF disease severity (eg, left ventricular ejection fraction) and changes in cognition.

Studies that did not use comparison groups to evaluate changes in cognitive function often reported improvements in cognition. However, the absence of a control group in these studies may have introduced bias by not accounting for changes in cognitive scores attributable to Hawthorne, placebo, or practice effects. These threats to validity may be appreciable especially when we consider that, with 1 exception,19 studies did not use alternative forms of neurocognitive tests to limit bias from learning effects. Inclusion of comparison groups and the use of alternative test forms may increase the quality of future studies and make drawing conclusions about the causes of cognitive change over time easier.

Study Follow-up Time
Cognitive decline among patients with HF was reported in studies that assessed changes in cognition over long periods of time (ie, >1 year), although improvements or stability in cognitive scores were more often reported in studies that followed patients for shorter periods of time. Improvements in cognition were especially apparent in studies that followed patients for <1 month, such as those that followed patients admitted to a hospital for acute HF decompensation until discharge; some of these studies found improvement in patients who were quite physically and cognitively ill at baseline whose cognitive scores improved up to the level of patients with stable HF by time of hospital discharge. These findings suggest that cognition may be amenable to improvement in the short term among patients with HF, but that these improvements may not be sustainable and patients with HF remain at risk for long-term decline, especially as HF severity progresses. However, heterogeneity in more studies examining longitudinal trajectories of cognition in patients with HF over long periods of time is warranted to confirm these findings.

Treatments
The majority of studies included in this review examined the association of cognition with some type of treatment or intervention for HF and generally found that patients who underwent these treatments experienced improvements in cognition. Conversely, studies that examined the natural course (ie, no treatments or interventions specified) of cognitive change in patients with HF were more likely to report declines. These findings provide promising evidence that changes in cardiac or overall health brought on by these treatments may improve cognition. However, the use of studies characterized as no-treatment specified (ie, not receiving treatment) as the reference group for the purposes of this examination presents some problems. Realistically, we must assume that the vast majority, if not all, of patients involved in these observational studies received some type of treatment for their HF, but these studies provided little or no information about the medications or other treatments patients received. It is possible that many participants involved in these noninterventional observational studies received treatments similar to those reported to positively influence cognition in other studies, such as angiotensin-converting-enzyme inhibitors, which may affect our characterization of cognitive change among these patients. However, if the no-treatment specified group of studies did encounter this contamination from treatment, it would likely bias our results toward the null, so our findings for decline in the no-treatment specified group of patients with HF may actually be more conservative than what occurs among patients with HF not receiving any treatment for their disease. Therefore, it is important for future noninterventional observational studies to transparently document any treatments being received by the study participants so that we can gain a more comprehensive understanding of how these treatments and interventions affect cognition in HF.

Research Implications
Measurement of cognitive function in older and acutely ill patients is difficult, and often global tests of cognitive function are used. These tests may not be sensitive to subtle changes in cognitive function or may not adequately measure domains of cognition known to decline in cardiovascular disease, such as
executive function. Domain-specific measures, when included, were not standardized across studies, limiting the ability to compare results across studies. Recently, Hachinski et al., in collaboration with the National Institute for Neurological Disorders and Stroke and the Canadian Stroke Network, encouraged the use of standardized 5-, 30-, and 60-minute cognitive testing protocols consisting of well-validated and standardized measures that assess multiple domains of cognitive function known to be affected in patients with cardiovascular disease. Most of the recommended measures have standardized cut-off scores for cognitive impairment that allow for easy interpretation of test scores. The consistent use of these recommended measures in future research will help to facilitate comparisons across studies and inform the development of brief assessments of cognitive function that can be used in clinical settings by identifying which measures are most sensitive to changes in cognition among patients with HF.

Loss to follow-up and attrition rates were appreciable in a number of studies, and not all studies reported information about attrition rates, reasons for attrition, or baseline characteristics of patients who were lost to follow-up. Large rates of loss to follow-up and omission of information about follow-up may introduce selection bias or healthy survivor bias, as it is reasonable to believe that patients who dropped out because of these reasons may have had poorer physical and cognitive health than those who persisted in the study. Understandably, research in patients with HF is difficult, and there is bound to be significant attrition because of death and disability. Future work should explicitly report loss to follow-up and examine differences between initial and follow-up samples to improve the validity of studies and make study findings easier to interpret.

Finally, because the mechanisms of cognitive change in HF remain poorly understood, future studies should aim to recruit diverse samples of patients that traverse the spectra of cardiac disease severity and cognitive ability and track changes to patients’ cardiac and cognitive function over time. Uncovering correlations between change in cardiac function and change in cognitive function may help to improve our understanding of the mechanisms by which HF affects cognition and provide clinicians with opportunities to improve cognition through cardiac treatments.

Clinical Implications
On the basis of findings of this review, change in cognitive function is common among patients with HF. Clinicians should routinely assess cognition in patients with HF using the aforementioned recommended batteries, especially during crucial times when changes in cognition may occur because of changes in cardiac function, such as at diagnosis, during hospitalization, and during initiation or discontinuation of treatment. Longitudinal follow-up of patients’ cognitive status may provide clues about changes in the patient’s ability to adequately perform self-care, which is essential for maintaining disease stability and preventing poor outcomes. Also, patients’ and family members’ perspectives on treatment options may be positively influenced by the possibility of cognitive improvement. It is known that treatments, such as surgery, lifestyle maintenance programs, and medications, improve physical function in patients with HF; findings from this review suggest that these treatments may also improve cognitive function, potentially making them more attractive to patients and their families.

Limitations
This systematic review had a number of limitations. It was limited to studies published in English, potentially introducing publication bias. Also, because of heterogeneity of study designs and treatment methods, a quantitative meta-analysis could not be performed.

Conclusions
Short-term (≤12 months) stabilization or improvement in cognition is common with treatment in HF; however, patients with HF remain at risk of greater cognitive decline over the long term compared with patients without HF. Clinical interventions that improve cardiac function may also improve cognitive function, which has implications for the health and quality of life of patients and their families. Cognition should be assessed regularly along with cardiac function in patients with HF to identify patients at risk for poor health outcomes and those whose physical and cognitive health may benefit from optimized disease management and treatments. Future investigations with non-HF comparator groups, long follow-up periods, and clear descriptions of treatments are warranted to further clarify the association between HF and changes in cognition over time.

Source of Funding
National Institutes of Health/ National Heart, Lung, and Blood Institute U01HL105268-01, National Institutes of Health/National Center for Research Resources U54RR026088, and National Institute of Aging K01AG033643.

Disclosures
None.

References


Cognitive Change in Heart Failure: A Systematic Review
Alexandra M. Hajduk, Catarina I. Kiefe, Sharina D. Person, Joel G. Gore and Jane S. Saczynski

Circ Cardiovasc Qual Outcomes. 2013;6:451-460; originally published online July 9, 2013; doi: 10.1161/CIRCOUTCOMES.113.000121
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/6/4/451

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Quality and Outcomes can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Quality and Outcomes is online at:
http://circoutcomes.ahajournals.org//subscriptions/