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Cognitive Change in Heart Failure: A Systematic Review

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Abstract

Background—Cognitive impairment (CI), 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 regarding 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 1st, 1980 to September 30th, 2012 that used validated measures to diagnose HF and assess cognitive function two or more times in adults with HF were eligible for inclusion. Change in cognitive function was examined in the context of HF treatments applied (e.g., medication initiation, left ventricular assist device implantation), length of follow-up, and by comparison group. 15 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 (e.g., heart transplant) and among patients examined over short time periods (< 1 year). Studies comparing HF patient to their own baseline tended to report improvements while 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 appears to be modifiable with cardiac treatment. Further research is needed to identify the mechanisms that cause cognitive change in HF.

Keywords

heart failure; cognition; epidemiology

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Disclosures
None

Background

Cognitive impairment (CI) is an important patient factor associated with poor outcomes in HF[1]. CI affects approximately 25–85% of patients with HF and develops earlier in patients with HF than in persons of similar age without HF[2–5]. Patients with HF have up to a 2-fold increased risk of impaired cognitive function compared to age-matched controls, particularly in the domains of memory, psychomotor speed, attention, and executive function[2,6]. Patients with HF and co-occurring CI may have poor somatic awareness and decreased ability to carry out essential self-care activities to manage their disease[7,8], 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 heart failure has been examined in previous systematic reviews, these reviews[4,9] were 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 of 2012. Keywords and Medical Subject Heading (MeSH) terms used in these searches included “cognitive disorder”,” cognition disorder”, “cognition”, “cognitive impairment”, “neurocognitive”,” memory”,” dementia”, “processing speed”, “attention”,” executive function”, “visuospatial”, “ heart failure”, “congestive heart failure”, “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 old), publication date from January 1st, 1980 through September 30th, 2012, published in English, use of validated criteria to diagnose HF, and use of validated neurocognitive measures to assess cognitive function at two or more 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.H.) independently abstracted data from all included studies using a standardized form. Information was abstracted for: study type; number of participants; type of comparator group used (e.g., self at baseline, healthy controls); demographic characteristics (i.e., age, gender, race/ethnicity, and education level); cardiac characteristics (e.g., mean left ventricular ejection fraction); HF diagnostic criteria (e.g., NYHA criteria); cognitive domains assessed and associated neurocognitive tests; frequency and timing of cognitive assessments; type of intervention or treatments applied (e.g., disease management program, heart transplant); and primary results for change in cognitive function.

Definition of Change in Cognitive Function

We defined significant change in cognitive function as a statistically significant ($p<0.05$) change between two 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 (e.g., Mini Mental Status Exam[10]) to domain-specific measures on which performance is measured on a linear scale. All studies reported whether there was significant change in performance over two time points, allowing for comparisons across studies by using this definition. Since many studies examined changes in a single domain of cognition (e.g., 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 & Black criteria[11], which examine validity, bias, power and other study attributes. The Downs & Black scale, developed to assess quality in clinical trials, was modified, based on previous systematic reviews,[12,13] to accommodate the characteristics of observational studies. For example, for non-randomized trials, criteria pertaining to randomization technique were removed. The checklist item about power was dichotomized into sufficient or insufficient power rather than a five-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 based on its design characteristics (maximum=28 for RCTs, 21–26 for non-RCTs) and are reported in percentages. Due to 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 based on title and abstract review. Of the 33 full text articles reviewed, 22 were excluded, the majority due to small sample sizes (n=10) or inability to examine patterns of function in HF patients specifically (n=7). Four additional articles were identified from the references of included articles. Thus this review reports on 15 articles that report on 14 study samples (Figure 1). Characteristics of included articles are detailed in Table 1.

Study Design & Recruitment

The majority of included studies were observational cohort studies (n=13). Two of these cohort studies[14,15] included population-based cohorts in which residents of entire municipalities or countries were eligible for enrollment and eleven studies[16–26] reported on samples recruited from inpatient or outpatient care settings. Two non-randomized trials[27,28] were included.

Six studies recruited individuals without HF to serve as comparison groups. Individuals without HF were recruited from ambulatory or outpatient care settings[16,17,20,24], voluntarily responded to a media campaign[16], or were recruited as part of a population-based cohort[14,15]. Individuals without HF were recruited at the same general location (i.e., 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, or severe neurologic disease[16–18,24–27], dementia or other cognitive impairments[15,16,22,24–26], recent myocardial infarction[16,17,27], illiteracy[16,17] and depression or other psychiatric disorder[16,20,22,24].

Quality Ratings

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

Sample Characteristics

Sample sizes ranged from 54 to 1511 participants. Six studies[17,18,20,21,23,24] had less than one hundred participants, six studies[14,16,19,22,27,28] had 100–999 participants, and three studies[15,25,26] had ≥1,000 participants.

Comparison groups ranged widely among the 15 studies. Four studies[19,21–23] did not use a comparison group but rather compared participants' cognitive performance at follow-up to their baseline scores. Eleven studies made formal comparisons to control groups[9,14–16,18,20,24–28] and compared treatment/intervention groups to control participants without HF,[14–17,20,24] stable HF patients,[20] HF patients who did not undergo the treatment/intervention under study,[18,26–28], or HF patients who did not respond to the treatment/intervention under study[25]. Eight studies[17,18,20,24–28] compared change in cognition across multiple comparison groups, including one study[20] that compared cognitive change among participants with decompensated HF, participants with stable HF, and healthy controls. Length of follow-up ranged from thirteen days[26] to nine years[15]. The follow-up period was less than six months in over half of the studies[17,20–23,25–28], 6–11 months in two studies[19,24],and ≥1 year in four studies[14–16,18]. Eight studies[17–19,21–23,27,28] reported on loss to follow-up. Rates of loss to follow-up (excluding loss to follow-up due to 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 less than 1%[22] to 66%[28]; the majority of studies[17–19,21,23,28] experienced attrition rates greater than 30%.

Mean sample ages ranged from 44.7 ±10.6[18] to 84.3 ±4.1[14] years; studies examining cognition in the context of standard treatment practices tended to have older participants, while studies examining cognition in the context of invasive treatments (e.g., heart transplant) 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, depression, and smoking history were accounted for in twelve[14,15,17,19,20,21,22,24,25,26,27,28], seven[14,15,20,24,25,26,28], five[14,16,17,18,20], and three[14,17,20] studies, respectively.

Cognitive Assessments & Outcomes

The majority of studies (n=10)[16–18,20,23–28] included two cognitive assessments, while others had three[19,21,22], four[15] or five[14] assessments;. The cognitive domains most often assessed were: global cognition[15,16,18,19,22–28], memory[14,16,18,20–24], attention[16–18,22,24,27], visuospatial ability[14,17,21,23,24], processing speed[14,20–22], executive function[18,20,21], language[21,24], and reasoning[18,24]. Other domains tested less frequently (e.g., 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

Results for change in cognitive function among patients with heart failure differed according to the comparison group to which they were evaluated (Table 2). Studies that compared patients' follow-up scores on cognitive tests to their baseline scores tended to report significant improvements in performance over time[17–19,21,23–26], although several of these studies reported no significant change[20,23,27,28]. Conversely, studies that compared change in function to comparison groups of patients without HF were more likely to report significant declines in cognition over time[14–16,20]. Results of studies that compared changes in cognition among decompensated heart failure patients to other heart failure patients 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 to patients with decompensated HF not receiving or responding to the treatment[18,25,26], although this was not observed in one study[27]. When stable HF patients were used as a comparator group[20], cognition in decompensated HF patients was lower than the comparison group at baseline but often improved up to the level of stable HF patients 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[14–16] out of four studies that followed participants for one year or more reported cognitive decline among HF patients, while only one[20] of eleven studies that followed patients for less than one year reported cognitive decline. One study[14] which followed patients for eight 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 (≤12months)[17,19–28] tended to report improvements[17,19,21,25–27] or no change[22–24,28] in cognition. This finding implies that cognition remains stable over short periods and may even improve, particularly among HF patients 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 transplant[18,19,23], left ventricular assist device (LVAD) implantation[21] , a nurse-led HF management program[28], various medications[26,27] and standard in-hospital treatments[17,20,25] on cognitive change in patients with HF. Five studies[14–16,22,24] 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 surgeries[18,19,21,23] tended to report improvements in cognition among patients who had severe heart failure at baseline. One study[28] reporting on change following a non-invasive intervention (i.e., 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 six-months of follow-up. Studies examining the influence of compensation of HF among acutely decompensated patients through standard in-hospital treatments[17,20,25] reported improvements in cognition that brought them up similar to scores of patients with stable HF, with the exception of one randomized controlled trial assessing the influence of a vasopressin receptor antagonist among HF patients[27] that found no significant change in cognition over time despite improvements in edema. The majority (3 of 5)[14–16] of studies assessing the natural course of cognition if HF documented declines. Findings from the only study[24] to report improvements in cognitive function in the

natural course of HF must be interpreted with caution due to potential bias introduced by lack of information on patients' treatments, the exclusion of patients with cognitive impairment at baseline, and the use of complete case analysis.

Association of Changes in Clinical Parameters and Cognitive Function

Eight[16–19,25–28] of fifteen studies included information on changes in cardiac function concomitant with changes in cognitive function. Five studies[16,18,19,25,27] reported that changes in clinical parameters at least partially correlated with changes in cognitive function. Three studies[17,26,28] reported that improvements in LVEF and blood pressure did not correlate with changes in cognitive function. These mixed findings and the absence of reports on correlations between changes in clinical and cognitive parameters in almost half of the studies in this review makes it difficult to draw conclusions about the association between changes in physical and cognitive health among patients with HF.

Discussion

In this review, we found evidence for significant decline in cognitive function in patients with HF followed for 11 months or more. We also found that over shorter periods of follow-up and in 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[4] that suggested cognitive impairment could be reversed in patients with heart failure through heart transplantation, although the data available at the time was 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 to 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 heart failure influences cognition: (1) via decreased cerebral blood perfusion, resulting in microvascular changes in the brain, and (2) cerebral emboli, both attributable to cardiac insufficiency[29]. 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 (e.g., 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 transplant recipients. However, not all studies examining this association, even in the context of heart transplant, 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 HF patients 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 (e.g.,hypertension, diabetes, depression, 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 HF patients varied according to the groups to which these changes were compared. Generally, 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 HF patients 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 stable HF patients. 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 HF patients in comparison to 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 measures of HF disease severity (such as 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 one 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 (i.e., longer than one year), while 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 less than one 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 stable HF patients 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 are not sustainable and HF patients remain at risk for long-term decline, especially as HF severity progresses. However, heterogeneity of the relatively small number of studies with long follow-up time precludes making broad conclusions about the temporality of cognitive decline in HF; more studies examining longitudinal trajectories of cognition in HF patients over long periods of time are warranted to confirm our 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 (i.e, 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[14–16,22,24] characterized as "no treatment specified" (i.e., 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, 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 feasible that many participants involved in these non-interventional observational studies received treatments similar to those reported to positively influence cognition in other studies, such as ACE inhibitors[26], 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 HF patients may actually be more conservative than what occurs among HF patients not receiving any treatment for their disease. Therefore, it is important for future non-interventional 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[30]. *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 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 due to these reasons may have had poorer physical and cognitive health than those who persisted in the study. Understandably, research in HF patients is difficult and there is bound to be significant attrition due to 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.

Lastly, since 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 the mechanisms by which heart failure affects cognition and provide clinicians with opportunities to improve cognition through cardiac treatments.

Clinical Implications

Based on the findings of this review, change in cognitive function is common among patients with HF. Clinicians should routinely assess cognition in HF patients using the aforementioned recommended batteries[30], especially during crucial times when changes in cognition may occur due to 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 regarding treatment options may be positively influenced by the possibility of cognitive improvement. It is known that treatments such as surgery[31], lifestyle maintenance programs[32], and medications[33] improve physical function in patients with heart failure; findings from this review suggest these treatments may also improve cognitive function, which may make them more attractive to patients and their families.

Limitations

This systematic review had a number of limitations. This review was limited to studies published in English, potentially introducing publication bias. Also, due to 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 to 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 HF patients to identify patients at risk for poor health outcomes and those whose physical and cognitive health may benefit from optimal 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.

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What is known

1. Cognitive impairment, common among patients with heart failure, increases risk for poor outcomes such as hospitalization and mortality.
2. 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 heart failure over time has not been systematically examined.

What this article adds

1. 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.
2. Following interventions to improve cardiac function (e.g., medications, cardiac resynchronization), cognitive function can stabilize or improve in patients with HF over the short-term (i.e., up to a year).
3. Studies that examine the natural course of cognition in HF for more than one year uniformly show declines among patients with heart failure.

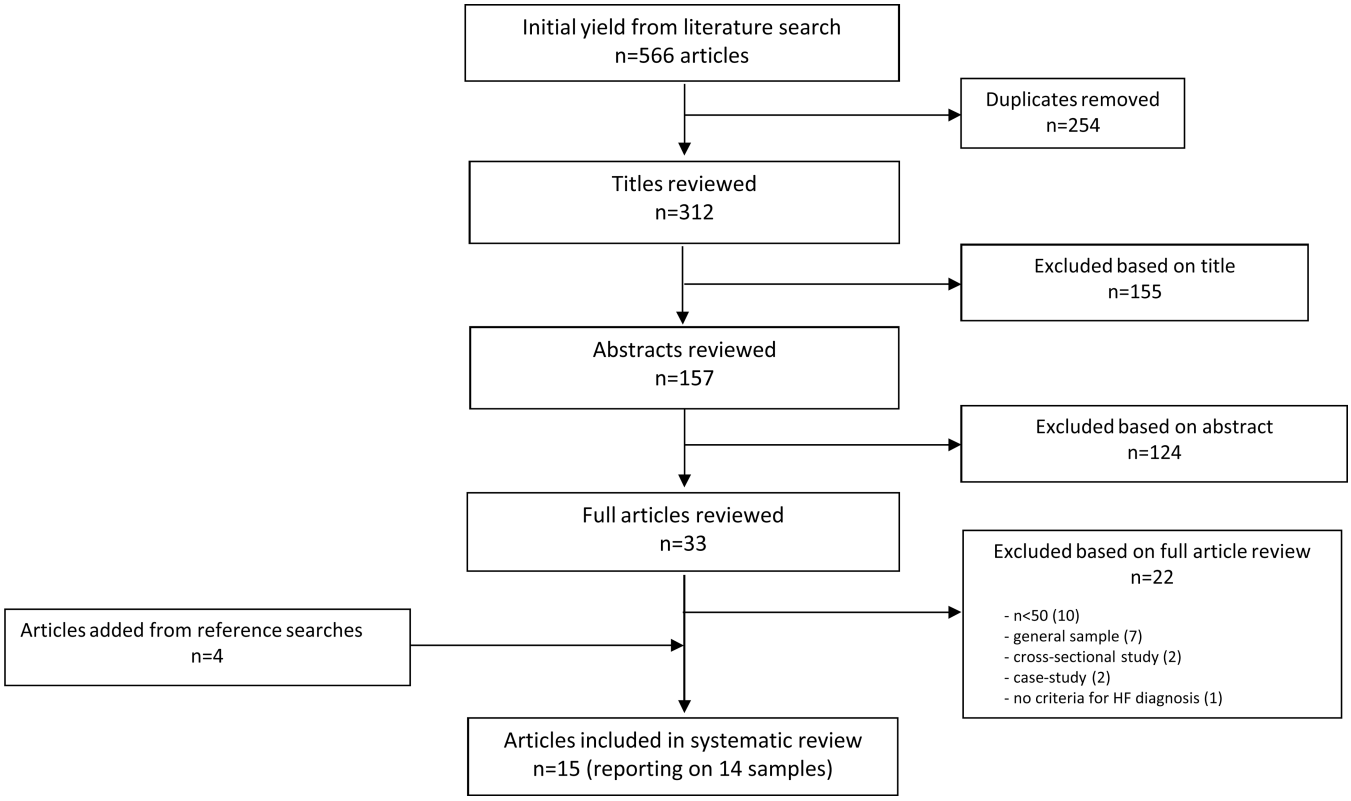

Figure 1.
Article Selection Process

Table 1

Characteristics of the 16 Studies Included in the Systematic Review of Cognitive Change in Heart Failure

First Author, Publication Year, (Reference number)	Study Type	Sample Size and Comparison Group	Sample Demographics	Frequency and Timing of Cognitive Assessments	Cognitive Domains Assessed	Treatments/ Interventions	Change in Cognition
Almeida, et al., 2012 (16)	Observational cohort	N=231 HF group: 77 CVD group= 73 Healthy controls=81 - HF group compared to their own, CVD group, and healthy controls at f/u	Mean age(SD): HF group= 68.4 (10.2) CVD, no HF group= 67.8 (9.5) Healthy controls= 69.3 (11.3)	2- baseline,2 years	Global Memory Attention	None (standard clinical treatment assumed)	-HF patients declined in global cognition faster than healthy controls, but not compared to CVD controls - no changes in other domains
Almeida & Tamai, 2001 (17)	Observational cohort	N=81 HF group: 50 (31 with complete f/u)Elderly controls: 31 - Pts' f/u scores compared to their own and controls' baseline scores	Mean age(SD): CHF=67.3(0.9) Controls=76.7(1.5) % Male: CHF=76.0 Controls=66.7	2- baseline, 6 weeks	Attention Visuospatial	None (standard clinical treatment assumed)	-HF patients improved on some attention tests -HF group had similar scores for all attention tests at f/u as controls at baseline
Bornstein et al, 1995 (18)	Observational cohort	N=62 (pre-operative) Intervention group: n=7 Control group: n=4 -transplant recipients compared to non-recipients	Mean age: 44.7 (10.6) yrs 75.8% male	2- baseline, 36-months (25-months for transplant recipients)	Global cognition Memory Reasoning/ Concept Formation Mental Flexibility/ Response Fluency (executive function) Attention/ Concentration Other	Heart transplant	-transplanted patients showed 11.6% mean improvement in cognition, controls showed 0% change. - transplanted patients had improvements or less decline in memory, mental flexibility, and attention than non-transplanted pts
Ghali, et al., 2012 (27)	Randomized controlled trial	N=170 Lixivaptan group= 111 Placebo group=59	Mean age(SD): Lixivaptan group=69.1(11.8) Placebo group= 70.6 (11.2) 64% male	2- baseline, 4 weeks	Global Attention	Treatment with lixivaptan (vasopressin receptor antagonist)	-global function and attention improved in both groups, but difference between experimental groups NS
Grimm et al., 1996 (19)	Observational cohort	N=110 (baseline) - 55 heart transplant candidates - 55	Mean age=54.8 (9.2) 92.7% male	3- baseline, 4 and12 months post-transplant	Global cognition Other	Heart Transplant	- improvements in global cognition -improvements in cognition attenuated

First Author, Publication Year, (Reference number)	Study Type	Sample Size and Comparison Group	Sample Demographics	Frequency and Timing of Cognitive Assessments	Cognitive Domains Assessed	Treatments/ Interventions	Change in Cognition
		healthy controls N=19 (end of f/u) -HF pts' baseline served as own controls at f/u					by in cyclosporine users
Hjelm et al., 2011 (14)	Observational population-based cohort	N=702 -HF=variable, 66–147 -no-HF=variable, 301–511 -HF pts compared to no-HF pts and their own baseline data at f/u	Mean age, yrs: -HF=84.3 (4.1) -no-HF=83.3 (2.9) % male: -HF=67 -no-HF=67 100% White	5- baseline, 2, 4, 6 and 8 years	Memory Processing speed Visuospatial	None (standard treatment assumed)	- HF pts consistently performed lower on almost all cognitive tests -HF pts declined faster than no-HF pts in memory -no-HF pts cognitively "caught up" with HF patients by end of study
Karlsson et al., 2005 (28)	Randomized clinical trial	N=208 (randomized) N=146 (baseline) -intervention=72 -control=74 N=90 (f/u) -pts compared to controls and their own baseline data at f/u	Mean age=76 (7.5) % male=56	2- baselin, 6 months	Global	Nurse-based HF management program	-no significant improvement in cognition found in intervention group vs. control group -% impaired decreased over time (12% to 4%)
Kindermann, et al., 2012 (20)	Observational cohort	N at baseline=70 N at f/u=60 Decompensated HF group=20 Stable HF group=20 Healthy controls=20 -decompensated HF group compared to stable HF and healthy control groups at f/u	Mean age (SD): Decompensated HF group= 60.4(16.4) Stable HF group= 60.6 (16.6) Healthy controls=61.6 (15.4) 75% male	2- baseline, two weeks (14±7 days)	Memory Processing speed Executive function	Standard clinical treatment	-memory, processing speed, executive function improved in decompensated HF group to level of stable HF group, but not to level of healthy controls

First Author, Publication Year, (Reference number)	Study Type	Sample Size and Comparison Group	Sample Demographics	Frequency and Timing of Cognitive Assessments	Cognitive Domains Assessed	Treatments/ Interventions	Change in Cognition
Petrucci et al., 2009 (21)	Observational cohort	N=93 (baseline) N=28 (complete data at end of f/u) -pts' f/u scores compared to baseline	Mean age=50 (14) yrs % male=81	3-1-month (served as baseline), 3and 6 months	Memory Visuospatial Language Processing Speed Executive Function	Left Ventricular Assist Device (LVAD) implantation	-visuospatial perception, memory, and processing speed improved in pts with complete data
Qiu et al., 2006 (15)	Observational population-based cohort	N=1301 -HF=205 -no-HF=1096 -HF pts compared to no-HF pts and their own baseline data at f/u	Mean age, yrs: -HF=83.3 (5.4) -no-HF=81.2 (4.8) % male: -HF=20 -no-HF=74	4- baseline, 4, 6, and 9 years (mean f/u= 5.02 years)	Global cognition (dementia diagnosis)	None (standard treatment assumed)	-HF at baseline associated with HR of 1.84 for dementia at f/u compared to no-HF pts -use of antihypertensives attenuated dementia risk
Riegel, et al., 2012 (22)	Observational cohort	N=279 Average processing speed group=114 Below average processing speed group=165	Mean age (SD): Average PS group=56.1(12.1) Below average PS group=66.3(11.9) 64% male	3- baseline, 3 and 6 months	Global Memory Attention Processing speed	None (standard treatment assumed)	- no significant changes changes in cognition
Schall, et al., 1989 (23)	Observational cohort	N=54 (pre-transplant) N=20 (post-transplant) -patients served as own controls	Mean age, yrs =46 (11) %male= 81.5%	2- baseline, 7.7 months (range=3–15)	Global cognition Memory Visuospatial Other	Heart Transplant	-No change in cognition (except "other")
Stanek, et al., 2009 (24)	Observational cohort	N=70 (complete cases) -HF=40 -no-HF=35 -HF pts' scores compared to no-HF patients' scores and their own baseline	Mean age, yrs=70.7 (7.7) % male= 63	2- baseline and 12 months	Global cognition Memory Attention Verbal fluency Visuospatial Planning/reasoning	None (standard clinical treatment assumed)	-HF pts' global cognition, attention, verbal fluency, planning/reasoning improved at f/u
Zuccala, et al., 2005 (25)	Observational cohort	N=1511 -HF pts compared at f/u according to their "normalization"	Mean age, yrs: -impaired=82 (8) -not impaired=76 (10) % male: -impaired=39	2- baseline and immediately before hospital discharge (mean=15 +/− 10 days)	Global cognition	None (standard clinical treatment)	-Normalization of hypo/hyperglycemia, hypo/hyperkalemia, and anemia associated with

First Author, Publication Year, (Reference number)	Study Type	Sample Size and Comparison Group	Sample Demographics	Frequency and Timing of Cognitive Assessments	Cognitive Domains Assessed	Treatments/ Interventions	Change in Cognition
		status on clinical tests	-not impaired=50				improved global cognition
Zuccala, et al., 2005 (26)	Observational cohort	N=1220 -ACI-inhibitor (ACEI) group=446 -no-ACEI group=774 -pts on (ACEI) compared to patients not on ACEI	Mean age, yrs: -ACEI=79(9) -no-ACEI=79 (9) % male: -ACEI=43 -no-ACEI=47	2- baseline and immediately before hospital discharge [mean=13 (IQR=8–20) days]	Global cognition	Standard treatment with ACEI	-ACEI pts experienced greater improvement in global cognition than no-ACEI pts

Table 2

Change in Cognition According to Comparison Group

Comparison Group Lead Author(reference #)	n	Cognitive Change over Time
Self at Baseline		
Almeida & Tamai[17]	81	Improvement
Bornstein, et al.[18]	62	Improvement
Ghali, et al.[27]	170	Stable
Grimm, et al.[19]	62	Improvement
Karlsson, et al.[28]	146	Stable
Kindermann, et al.[20]	70	Stable
Petrucci, et al.[21]	93	Improvement
Riegel, et al.[22]	279	Stable
Schall, et al.[23]	54	Stable
Stanek, et al.[24]	70	Improvement
Zuccala, et al.[25]	1151	Improvement
Zuccala, et al.[26]	1220	Improvement
HF Control		
Bornstein, et al.¶[18]	62	Improvement
Ghali, et al.[27]	170	Stable
Karlsson, et al.[28]	146	Stable
Kindermann, et al.[20]	70	Stable
Zuccala, et al.[25]	1151	Improvement
Zuccala, et al.[26]	1220	Improvement
Controls without HF		
Almeida, et al.[16]	231	Decline
Almeida & Tamai[17]	81	Stable
Hjelm, et al.[14]	702	Decline
Kindermann, et al.[20]	70	Decline
Qiu, et al.[15]	1301	Decline
Stanek, et al.[24]	70	Stable

¶statistical significance of comparisons not reported

Table 3

Change in Cognition According to Length of Follow-up

Length of Follow-up Lead Author(reference #)	n	Cognitive Change over Time
≤ 6 months		
Almeida & Tamai[17]	81	Improvement†*, Stable‡
Ghali, et al.[27]	170	Improvement†*, Stable†
Karlsson, et al.[28]	146	Stable*†
Kindermann, et al.[20]	70	Improvement†*, Stable†, Decline‡
Petrucci, et al.[21]	93	Improvement†*
Riegel, et al.[22]	279	Stable*
Schall, et al.[23]	54	Stable*
Zuccala, et al.[25]	1151	Improvement†*†
Zuccala, et al.[26]	1220	Improvement†*†
6 to ≤12 months		
Grimm, et al.[19]	110	Improvement†*
Stanek, et al.[24]	70	Improvement†*, Stable‡
>12 months		
Almeida, et al.[16]	231	Decline‡
Bornstein, et al.¶[18]	62	Improvement†*†
Hjelm, et al.[14]	702	Decline‡
Qiu, et al.[15]	1301	Decline‡

* compared to self at baseline

† compared to a control group of HF patients who did not receive the treatment/intervention under study, did not respond to an intervention under study, or stable HF patients for which the intervention under study was not indicated

‡ compared to a control group of participants without HF

¶ statistical significance of comparisons not reported

Table 4

Change in Cognition According to Treatment or Intervention

Intervention Lead Author(reference #)	n	Change in Cognition
Heart Transplant		
Bornstein, et al.¶[18]	62	Improvement*†
Grimm, et al.[19]	110	Improvement*
Schall, et al.[23]	54	Stable*
LVAD Implantation		
Petrucci, et al.[21]	93	Improvement*
Disease Management Program		
Karlsson, et al.[28]	146	Stable*†
Clinical/Pharmacological Treatment		
Almeida & Tamai[17]	61	Improvement*, Stable‡
Ghali, et al.[27]	170	Improvement*, Stable†
Kindermann, et al.[20]	70	Improvement*, Stable†, Decline‡
Zuccala, et al.[25]	1151	Improvement*†
Zuccala, et al.[26]	1220	Improvement*†
No Treatment Specified (Standard Treatment Assumed)		
Almeida, et al.[16]	231	Decline‡
Hjelm, et al.[14]	702	Decline‡
Qiu, et al.[15]	1301	Decline‡
Riegel, et al.[22]	279	Stable*
Stanek, et al.[24]	70	Improvement*, Stable‡

*compared to self at baseline

†compared to control group of HF patients who did not receive the treatment/intervention under study, did not respond to intervention under study, or stable HF patients

‡compared to a control group without HF