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Review Article

Cognitive Impairment in Heart Failure: A Heart Failure Society of America Scientific Statement

PARAG GOYAL, MD MSc[1,*] ROBERT J. DIDOMENICO, PharmD[2] SUSAN J. PRESSLER, PhD, RN[3] CHINWE IBEH, MD[4] CONNIE WHITE-WILLIAMS, PhD, RN[5] LARRY A. ALLEN, MD, MHS[6] and EIRAN Z. GORODESKI, MD, MPH[7,*]

New York, NY; Chicago, IL; Indianapolis, IN; Birmingham, AL; Aurora, CO; and Cleveland, OH

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ABSTRACT

Cognitive impairment is common among adults with heart failure (HF), as both diseases are strongly related to advancing age and multimorbidity (including both cardiovascular and noncardiovascular conditions). Moreover, HF itself can contribute to alterations in the brain. Cognition is critical for a myriad of self-care activities that are necessary to manage HF, and it also has a major impact on prognosis; consequently, cognitive impairment has important implications for self-care, medication management, function and independence, and life expectancy. Attuned clinicians caring for patients with HF can identify clinical clues present at medical encounters that suggest cognitive impairment. When present, screening tests such as the Mini-Cog, and consideration of referral for comprehensive neurocognitive testing may be indicated. Management of cognitive impairment should focus on treatment of underlying causes of and contributors to cognitive impairment, medication management/optimization, and accommodation of deficiencies in self-care. Given its implications on care, it is important to integrate cognitive impairment into clinical decision making. Although gaps in knowledge and challenges to implementation exist, this scientific statement is intended to guide clinicians in caring for and meeting the needs of an increasingly complex and growing subpopulation of patients with HF. (*J Cardiac Fail 2024;30:488–504*)

Key Words: Cognition, heart failure.

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From the [1]Program for the Care and Study of the Aging Heart, Department of Medicine, Weill Cornell Medicine, New York, NY; [2]University of Illinois Chicago College of Pharmacy, Department of Pharmacy Practice, Chicago, IL; [3]Indiana University School of Nursing, Indianapolis, IN; [4]Columbia University Irving Medical Center, New York, NY; [5]University of Alabama at Birmingham Hospital, Birmingham, AL; [6]University of Colorado School of Medicine, Aurora, CO and [7]University Hospitals, Harrington Heart & Vascular Institute, and Case Western Reserve University School of Medicine, Cleveland, OH.

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Reprint requests: Eiran Z. Gorodeski, MD, MPH. Harrington Heart & Vascular Institute, University Hospitals, Lakeside 3rd Floor, 11100 Euclid Avenue, Cleveland, Ohio 44106. E-mail: Eiran.Gorodeski@UHHospitals.org

*Drs. Gorodeski and Goyal contributed equally to this work and are joint corresponding authors.

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Heart failure (HF) is linked with abnormalities in multiple organ systems that go beyond the cardiovascular system. The brain is often negatively impacted in adults with HF. Advanced age, multimorbidity (defined as multiple chronic medical conditions), shared risk factors, and the pathophysiological mechanisms of HF all contribute to alterations in the brain, which can lead to cognitive impairment.[1] The prevalence of cognitive impairment has been reported to be as high as 78% in some subsets of patients with HF.[2,3] Cognition is important because it is critical for a myriad of activities that are necessary to manage HF, including self-care and medication adherence. Cognition also has a major impact on HF prognosis and health-related quality of life.[4,5] Consequently, cognitive impairment has important implications for care and creates a set of unique challenges for patients, family caregivers and clinicians. This scientific statement reviews the epidemiology of cognitive impairment; enumerates its pathophysiologies, risk factors and etiologies; outlines screening tools; and emphasizes treatment and management strategies. This scientific statement serves as a guide to caring for and meeting the needs of an increasingly complex and growing subpopulation of people with HF.

Table 1 Key definitions

Cognition	Cognition, derived from the Latin root cognōscere, meaning *to know*, refers to the mental process of acquiring knowledge and understanding.
Cognitive impairment	Cognitive impairment is an inclusive term that captures the spectrum of deficits in cognition, ranging from mild cognitive impairment to dementia.
Mild cognitive impairment	Mild cognitive impairment is characterized by objective evidence of cognitive impairment with minimal impairment in capacity to conduct instrumental activities of daily living, such as paying bills or managing medications, and no evidence of dementia.
Dementia	Dementia manifests as a severe impairment in cognition, whereby patients experience a significant decline from prior level of function, often with impairments that interfere with their instrumental activities of daily living.
Delirium	Delirium is an acute and transient disturbance in attention and awareness that develops over a short period of time.

Definitions and Epidemiologies of Cognitive Impairment

Cognition, derived from the Latin root *cognōscere*, meaning *to know*, refers to the mental process of acquiring knowledge and understanding it (Table 1).[6] Abnormalities in cognition range from the expected decline in cognition of normal aging to pathological declines that can vary from mild to severe. Mild cognitive impairment (MCI) is characterized by objective evidence of cognitive impairment with minimal impairment in capacity to conduct instrumental activities of daily living (IADLs), such as paying bills or managing medications, and no evidence of dementia.[7] MCI may be subcategorized as amnestic (with evidence of memory impairment) or nonamnestic (with intact memory but impairment in 1 or more of the nonmemory cognitive domains).[7] Dementia manifests as a severe impairment in cognition, whereby patients experience a significant decline from prior levels of function, often with impairments that interfere with their IADLs.[8] Of note, cognitive impairment is distinct from delirium, which is an acute and transient disturbance in attention and awareness that develops over a short period of time.

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) identifies 6 key domains of cognitive function; they include complex attention, executive function, learning and memory, language, perceptual-motor function, and social cognition. *Complex attention* refers to the ability to concentrate selectively on discrete aspects of information while ignoring others; *executive function* refers to cognitive processes that control behavior, including reasoning, problem solving and planning; *learning and memory* refer to the ability to record information and retrieve it at a later time; *language* refers to the ability to communicate through speaking or writing; *perceptual-motor function* refers to the ability to coordinate movements in response to the environment; and *social cognition* refers to the process, recall and use of information in contexts of individual or interpersonal behavior.

HF can affect any of these domains—impairments in learning and memory and executive function are cited frequently[9–12]; and deficits in attention, psychomotor speed, language, or social cognition are encountered in 28%–58% of patients with HF at some point during the course of their disease.[13] The reported prevalence of cognitive impairment among patients with HF ranges from 22%–78%.[2,14] This wide range reflects differences in the definitions and severities of cognitive impairment, the diagnostic tools used to identify impairment and the populations studied. For example, the prevalence of cognitive impairment is higher when using diagnostic tools that can detect a broad range of cognitive impairment, including milder forms such as MCI. In a study of nearly 200 older adults hospitalized with worsening HF, a standardized assessment of cognition (Montreal Cognitive Assessment [MoCA] screening) revealed that 72% met criteria for MCI, while just 2% were detected clinically.[14] Also, the prevalence of cognitive impairment tends to be higher among hospitalized patients compared to those who are ambulatory, due to multiple reasons, such as the acuity of illness and the hospitalization itself.

Risk Factors for Cognitive Impairment

The high prevalence of cognitive impairment among adults with HF relates to the concurrence of multiple risk factors for developing cognitive impairment, including aging, comorbid conditions and HF itself (Fig. 1) (Fig. 2). Given the overlapping and interdependent nature of many of these risk factors, separating out the individual contributions of each is, perhaps, less helpful than considering their cumulative burden and various interactions.

Age as a Risk Factor

Normal aging processes contribute to the structural and chemical changes responsible for cognitive impairment, even in the absence of pathological degenerative disease. Aging alters the cellular components and tissue architectures of the brain which, over time, can disrupt the functional interactions involved in cognitive processing.[15] With age, morphological changes are observed in both the white and gray matter, resulting in progressive deterioration of brain architecture. The myelin sheaths of white matter, responsible for insulating neuronal axons and facilitating rapid neurotransmission, begin to degrade at around age 40 through a process that may be accelerated by chronic ischemic injury.[16] Meanwhile, gray-matter volume, which consists of neuronal cell bodies and their dendrites, is believed to start declining at as early as 20 years of age.[17] Although studies have found the prefrontal gray matter to be most susceptible to this form of age-related atrophy, the temporal lobe (including the hippocampus) experiences significant degrees of gray-matter loss over time.[18] Biochemically, age-related alterations in neurotransmitter activity, particularly serotonin and dopamine, may play a role in cognitive impairment. Serotonin levels fall with age and have been shown to contribute to dysregulation of synaptic plasticity and adult neurogenesis.[19] Starting from early adulthood, dopamine levels fall by about 10% per decade and have been associated with declines in motor and cognitive performance.[20]

Changes in neuroplasticity may additionally mediate cognitive impairment. Neuroplasticity is a critical component of cognitive processing that refers to the brain's capacity to alter the cellular and molecular characteristics of synaptic circuits in response to both intrinsic and extrinsic stimuli.[21] Adult neurogenesis (a form of structural neuroplasticity) involves de novo generation and integration of new neurons into existing neural networks. In the mammalian brain, adult neurogenesis is believed to occur primarily in 2 discrete regions—the subventricular zone of the lateral ventricles and the subgranular layer of the dentate gyrus of the hippocampus.[22] Normal age-related decreases in hippocampal neurogenesis, in particular, have been associated with declines in cognitive performance, and several models of neurodegenerative disorders (including Alzheimer's disease) have shown similar patterns of waning neurogenesis.[23–25]

Cardiovascular Comorbid Conditions as Risk Factors

Atherosclerotic vascular disease contributes to both cerebrovascular disease and ischemic heart disease. Cerebrovascular disease that contributes to cognitive impairment is often termed *vascular cognitive impairment*.[26] The mechanisms include vascular causes (large cerebrovascular artery occlusion, cerebral small-vessel disease and cerebral amyloid angiopathy) and parenchymal lesions (brain infarcts, white- and gray-matter loss, enlarged perivascular spaces, lobar or deep hemorrhages, and brain microbleeds).[27] Comorbid conditions, including hypertension, diabetes, hyperlipidemia (as well as suboptimal lifestyle behaviors, such as smoking and physical inactivity) are common among adults with HF and are, therefore, important contributors as shared risk factors for developing vascular cognitive impairment.

Atrial fibrillation is strongly associated with cognitive impairment and HF. In a study of 37,025 consecutive patients from the large, prospective Intermountain Heart Collaborative Study database, atrial fibrillation was independently associated with multiple forms of dementia studied (including vascular and Alzheimer's disease), with greatest risk in the younger cohort ($\leq$ 70 years).[28] Some of this may be attributed to embolic events leading to ischemic strokes. Ischemic stroke, which is more common in adults with HF compared to the general population, more than doubles the risk of new-onset dementia, though this risk varies by the clinical severity, size and location of infarct.[29] Unsurprisingly, infarcts of larger volume and increased number are associated with increased likelihood of dementia in clinical and pathological reports.[30] Importantly, atrial fibrillation can contribute to cognitive impairment even in the absence of stroke. In 2 large community-based analyses, atrial fibrillation was associated with worse cognitive performance and dementia, even after accounting for stroke.[31,32] Purported mechanisms include hippocampal and global atrophy,[33] chronic hypoperfusion and cumulative injury due to microemboli. It is likely that atrial flutter contributes to cognitive impairment via mechanisms similar to those outlined for atrial fibrillation, though risk may not be as significant compared to atrial fibrillation. In a study by a large health insurance registry in Taiwan between 2001 and 2013, the risk of new-onset dementia was 14% higher in patients with atrial fibrillation than in those with atrial flutter.[34]

Although some of the elevated risk for embolic strokes relates to atrial fibrillation, there is an emerging body of evidence indicating that the risk for embolic stroke is elevated in HF in the absence atrial arrhythmias.[35] Abnormal left atrial function, frequently described as left atrial myopathy, has been implicated as a contributing factor when atrial fibrillation is not present.[36] In addition, HF is believed to cause a relative hypercoagulable state via static blood flow and endothelial dysfunction, which subsequently increases risk for stroke.[37,38]

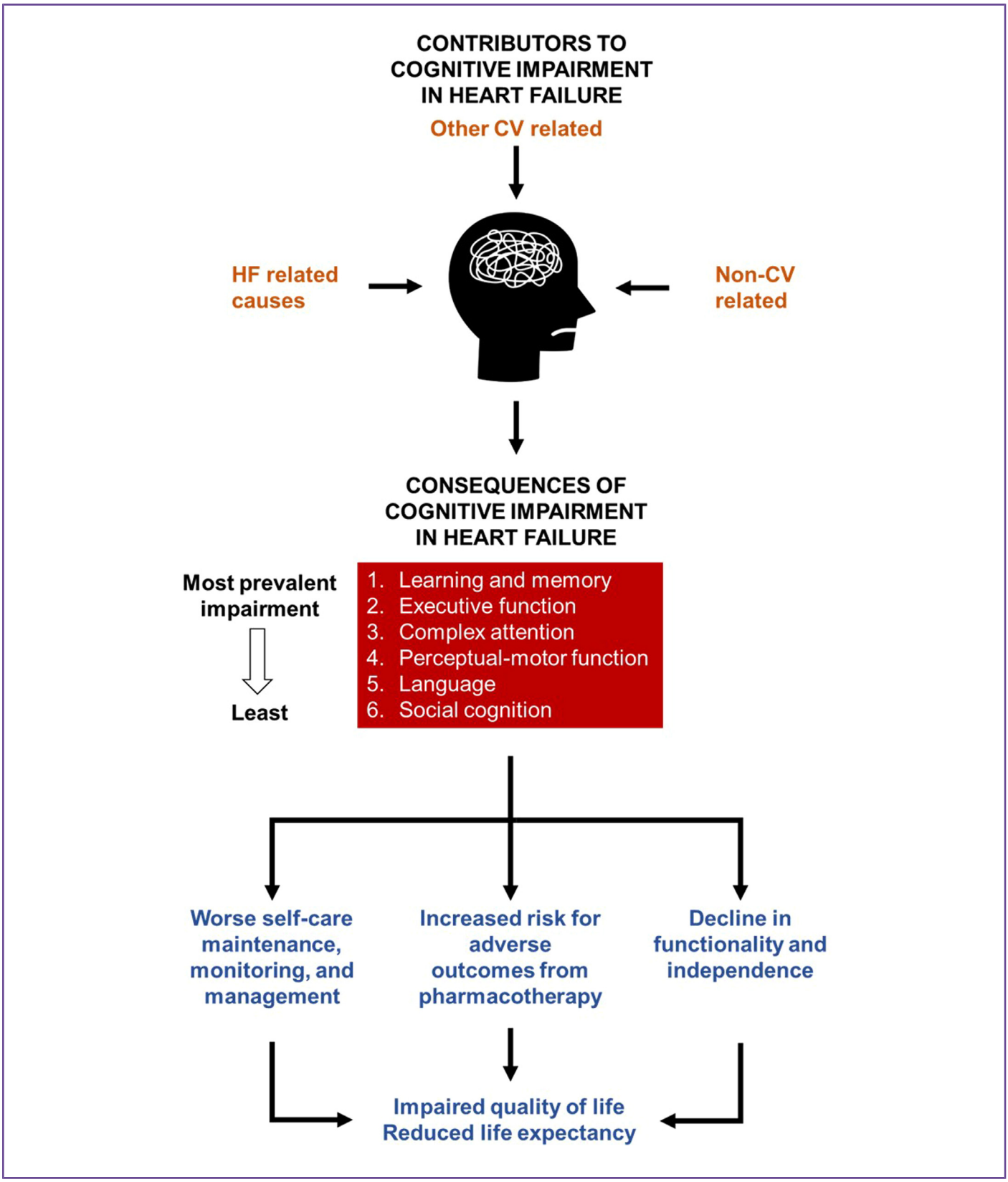


Fig. 1. Contributors, consequences, and management strategies for cognitive impairment.

Hypertension, in addition to being an important cause of HF, is also associated with cognitive impairment and dementia.[39] In a substudy, SPRINT (Systolic Blood Pressure Intervention Trial) found that intense blood pressure control reduced the risk of MCI, though it did not statistically reduce the risk of dementia, an observation that

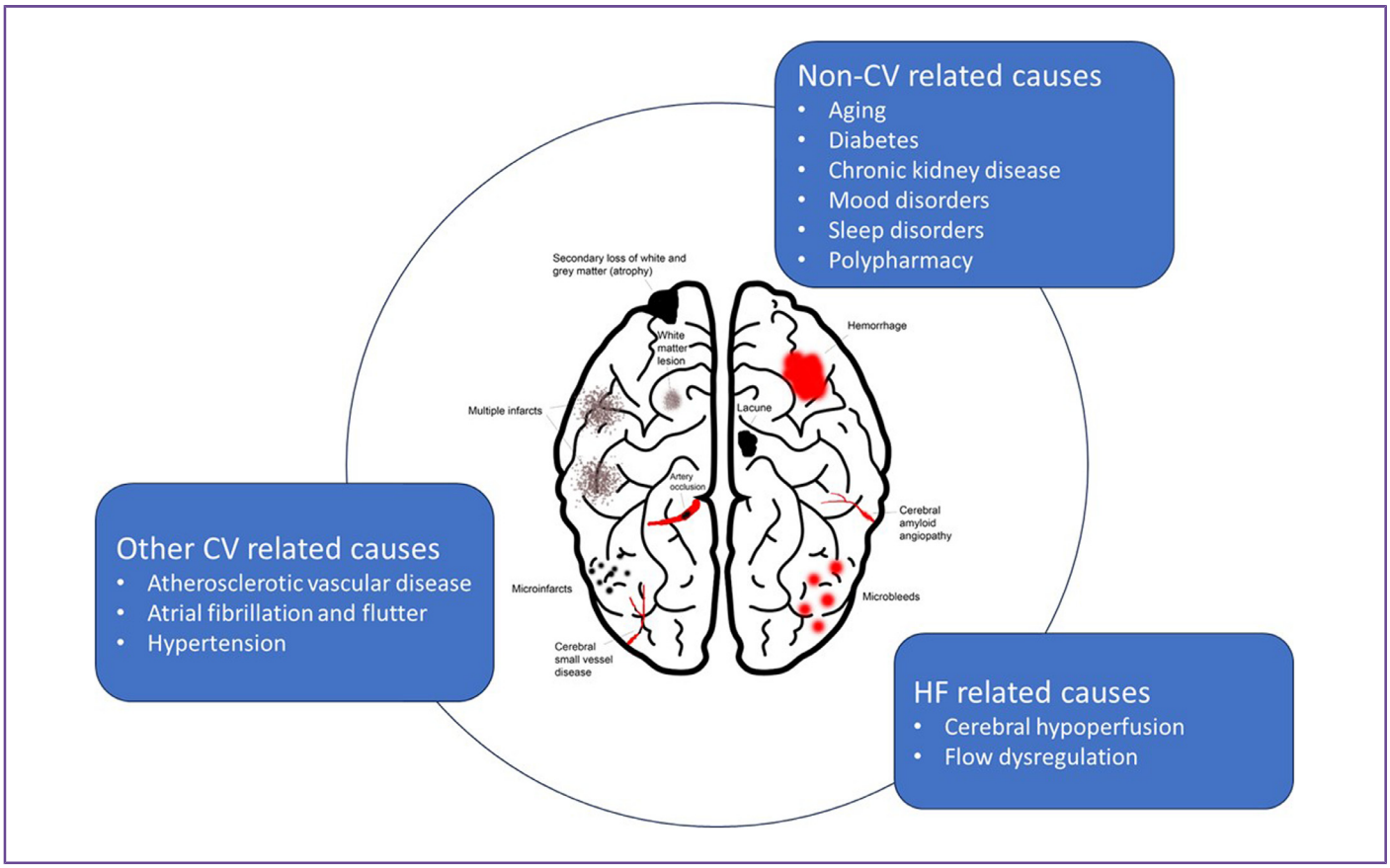


Fig. 2. Risk factors and conditions that result in cognitive impairment in patients with HF (HF-related, other CV-related and non-CV-related causes). CV, cardiovascular; HF, heart failure.

may be a result of being underpowered.[40] Given the relationship of hypertension to stroke, HF and other risk factors for cognitive decline, blood pressure control to < 130 mmHg is recommended for all people.[41] Minimum blood pressure goals for the preservation of long-term cognitive function are less well understood. In very old or frail people, some studies demonstrate a relationship between low blood pressure and worse cognitive function.[42]

Noncardiovascular Comorbid Conditions as Risk Factors

Multiple noncardiovascular conditions have been cited as potential contributors to cognitive impairment in patients with HF. These notably include diabetes, chronic kidney disease, mood disorders, and sleep disorders.

Diabetes is increasingly recognized as an important risk factor for cognitive impairment. Epidemiological studies have demonstrated that patients with type 2 diabetes have significantly higher risks of developing vascular dementia and Alzheimer's disease.[43] Mechanistic studies suggest that vascular disease and alterations in glucose, insulin and amyloid metabolism underlie the pathophysiology, but which of these mechanisms are clinically relevant is unclear, and the cerebral burden of the prototypical Alzheimer's pathologies does not appear to be higher in people with diabetes.[44] Diabetes control, particularly with lifestyle modifications and sodium glucose cotransporter inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists, are likely important for HF management, cognitive preservation and overall cardiovascular health.

Chronic kidney disease is another common comorbidity in HF that is likely to be an independent risk factor for cognitive impairment. Observational studies consistently show that cognitive impairment is more common in patients with renal impairment.[45] In patients with severe chronic kidney disease, cognitive function has been shown to improve with the initiation of dialysis and with renal transplantation.[45,46] With milder degrees of renal dysfunction or dynamic changes due to cardiorenal syndrome, the exact relationships with cognitive function are less well understood.

Anxiety and depression are common among patients with HF, with at least a quarter exhibiting symptoms of both.[47] In a meta-analysis of more than 80,000 patients with HF across multiple settings, the prevalence of depression was approximately 29%.[48] Mood disorders can exacerbate cognitive impairment via diminished ability to concentrate and loss of retentiveness.[21] It has been proposed that mood disorders and cognitive impairment share a pathophysiological mechanism in patients with

HF. Brain-imaging studies of cerebral blood flow have demonstrated that patients with HF who have poor flow to the hippocampus perform worse on memory testing and have higher rates of depression.[1] It is postulated that this is because the hippocampus is the center of emotion, memory and the autonomic nervous system, and it is particularly vulnerable to the cerebral hypoxia and poor cerebral blood flow that can occur in HF.[1] Accordingly, mood disorders can independently exert a negative effect on cognition, or can do so as a direct consequence of HF.

Patients with HF report a high frequency of sleep problems, including poor sleep quality, excessive daytime sleepiness and insomnia. Studies evaluating the association between subjective sleep problems in patients with HF and cognitive impairment have shown mixed results. A systematic review of observational studies by Tang et al. found an inconsistent association between abnormal sleep parameters and dysfunction in a variety of cognitive domains in patients with HF.[49] In a study of patients with HF, there was a significant association between apnea-hypopnea index scores and greater brain-volume reduction as assessed by MRI.[50] This is important because sleep disorders such as sleep apnea are common in patients with HF, affecting 40%−60% of patients with symptomatic HF.[51] There has been a long-standing recognition that central sleep apnea, the temporary withdrawal of central respiratory drive that results in the cessation of respiratory-muscle activity and airflow, is associated with cognitive impairment in patients with HF. A recent review of studies assessing cognitive impairment in obstructive sleep apnea noted that neuropsychological deficits in memory, attention, executive functions, and visuo-constructive abilities were common. Deficits are attributable mainly to decreased daytime vigilance and nocturnal hypoxemia.[52] Unfortunately, studies to date of nocturnal oxygen as well as noninvasive ventilation (continuous positive airway pressure and adaptive support ventilation) have failed to demonstrate improvements in cognition in patients with HF and obstructive sleep apnea.[53]

HF as an Important Etiologic Contributor

Epidemiological observations indicate an association between HF and cognitive impairment. In healthy older adults, decline in cognition may be extremely slow, perceptible only on a time scale of decades,[54] but older adults with incident HF are likely to experience an acceleration in cognitive impairment. This was seen in the Atherosclerosis Risk in Communities Study, where cognitive impairment over a 15-year period was greater in participants with HF compared to those without HF, even after adjustment for comorbid conditions (adjusted relative risk ratio for dementia = 1.60 [1.13, 2.25], and adjusted relative risk ratio for MCI = 1.36 [1.12, 1.64]).[55]

The mechanism of brain injury in HF is multifactorial, and probably involves changes in brain structure via cerebral hypoperfusion and flow dysregulation.[56] Reduced cerebral blood flow caused by low cardiac output can contribute to cognitive deterioration and development of diffuse periventricular white-matter changes.[57] Chronic hypoperfusion and hypoxic injury lead to disruption of the tight junctions that bind together the endothelial cells of the blood/brain barrier.[58] Sustained oxidative damage eventually results in local cerebral cytokine production, increased amyloid precursor protein and amyloid-beta protein deposition, with associated memory impairments.[59,60] Inflammation is yet another mechanism that has been implicated as a contributor to cognitive impairment in HF; HF is known to be a state of increased inflammation and immune response, with multiple reports linking increased levels of interleukin-6, total plasma homocysteine and C-reactive protein in HF to cognitive impairment.[56,61]

Polypharmacy as a Marker of Risk and/or an Etiological Contributor

Polypharmacy is nearly universal in adults with HF.[62,63] This is important because those with polypharmacy (broadly defined as a high burden of medications) are at higher risk of having and/or developing cognitive impairment. There are multiple reasons for this. First, polypharmacy is strongly linked to multimorbidity; a high number of medications is often the result of a high number of comorbid conditions. Many of those comorbid conditions can contribute directly to cognitive impairment, so polypharmacy serves as an important marker of risk for cognitive impairment. Polypharmacy can also serve as an etiological contributor to cognitive impairment. Perhaps the most obvious consequence of a high medication burden is the risk for adverse drug events; such events can result directly from a single agent or from a drug-drug interaction or a drug-disease interaction. With an increased number of medications and (as is often the case) an increased number of medical conditions, the pharmacokinetics and pharmacodynamics of medications (and their subsequent effects) become less predictable. This puts patients at risk for adverse drug events even at low or normal dosages. Adverse drug events can take many forms and can have short-lived or long-term consequences.[64] It is important to recognize that the agents that constitute the medication regimen and the characteristics of the individual patient are the most important determinants of the potential link between polypharmacy and cognitive impairment. For example, noncardiovascular medications, such as anticholinergic and sedative medications, are known to impair cognition.[65,66]

Implications of Cognitive Impairment

Cognitive impairment impacts several domains of health, including self-care, medication management, function

and independence, health-related quality of life, and life expectancy (Fig. 1).

Self-care

Self-care is defined as a process of maintaining health through health-promoting and preventive practices.[67,68] Fig. 1 enumerates the relevant cognitive domains necessary for HF self-care; they include learning and memory, executive function, complex attention, perceptual-motor function, language, and social cognition. When any one of these aspects of cognition is impaired, patients may not be able to engage in critical self-care activities.[69–72] For example, adults with cognitive impairment may struggle with following dietary restrictions (self-care maintenance), tracking symptoms and/or weight changes that could be suggestive of worsening HF or impending HF exacerbation (self-care monitoring), adjusting diuretics when needed and/or seeking care when appropriate (self-care management), and managing other chronic conditions such as diabetes.[67,68] Given their integral role in the management of HF, challenges involving critical aspects of self-care place patients with HF at risk for adverse outcomes ranging from the need for hospitalization to the loss of independence (requiring long-term institutionalization in a nursing home) to reduced life expectancy.

Medication Management

The complexity of the medication regimen experienced by adults with HF (due to polypharmacy) may be problematic for adults with cognitive impairment because of difficulties in reading/understanding prescription labels, opening safety caps and/or filling weekly pill boxes. This complexity is further compounded by medications that require multiple doses in a day, the need to cut pills in half, special rules about dosing (ie, requirement to take with a meal), and dosing adjustments based on clinical status (weight-based diuretic dosing). Consequently, adults with HF and cognitive impairment are particularly vulnerable to knowledge-based mistakes,[73] which can lead to medication errors and adverse drug events that contribute to unplanned hospitalizations.[74,75] Cognitive impairment can also lead to worse outcomes through medication nonadherence, which is reported to be as high as 58% in community-based adults with HF.[76,77] Nonadherence is important, because failure to take prescribed medications undermines the opportunity to derive the many benefits of indicated medications such as guideline-directed medical therapy.

Function and Independence

Cognitive impairment is associated with loss of independence, because higher-order cognitive processes and executive functioning are necessary to carry out complex activities such as meal preparation (considered part of IADLs) as well as more basic activities such as bathing (considered part of basic activities of daily living). When coupled with the negative effects of HF on independence and health-related quality of life, cognitive impairment can lead to precipitous reductions in health-related quality of life and accelerate need for long-term nursing-home care, an outcome described by many adults with HF to be worse than death itself.[78,79]

Life Expectancy

Cognitive impairment is associated with reduced life expectancy among adults with HF. It is frequently difficult to discern whether cognitive impairment is the primary driver or tracks with other important markers of risk, such as multimorbidity and frailty.[1] Regardless, recognizing this association is important because it impacts the risk/benefit ratio of many therapeutic interventions. The benefits of pharmacotherapy and procedural interventions may be limited if patients do not live long enough to derive benefit. For example, if life expectancy is limited to less than 1 year, the likelihood of benefit from an implantable cardioverter-defibrillator is low and would, therefore, not be indicated (class III indication suggesting potential for harm). Without incorporating cognitive impairment (and resulting impact on life expectancy and impact on health priorities), there is risk for suboptimal decisions leading to futile therapeutic interventions and/or interventions whose risks outweigh potential benefits.

Screening/Assessment

Clinicians caring for patients with HF should be attuned to clinical clues present at medical encounters that suggest the presence of cognitive impairment (Table 2). Gaps

Table 2 Clues to cognitive impairment

Domain	Specific Activities
Difficulty with activities of daily living	Forgets to shower or bathe Wears the same clothes Difficulty with walking, shopping
Difficulty with devices	Unable to use phone, television remote or household appliances
Financial management	Difficulty counting money Difficulty balancing checkbook No concept of money amount
Difficulty with numbers, dates	Difficulty with recipes Unable to remember birthdays, anniversaries
Medication management	Forgets to take medicine Runs out of medicine
Safety	Experiences more falls

and/or errors in patients' self-reported histories of present illness could be indicative of short-term memory loss and related cognitive impairment. Missed doses and/or medication errors could be indicative of cognitive impairment; nonadherence may not always represent an explicit unwillingness to or disinterest in taking medications according to instructions and may, in fact, be inadvertent due to impairments in cognition. Limited health literacy (especially if a decline is noted over time) may be a clue to cognitive impairment.[80] Finally, new deficits in IADLs (manifested as increased dependence on others for assistance with various tasks such as managing finances) could indicate cognitive impairment. When any of the aforementioned clinical clues emerge during medical encounters, it is important to inquire further about potential impairment in cognition and consider referral for additional testing.

Patients, themselves, may not fully appreciate the true extent of their impairment and/or may withhold this information from their health care team due to the threat of lowering their self-esteem, the need for additional testing and/or losing their independence. It may be important to ask family caregivers explicitly about behaviors that could indicate cognitive impairment as a fairly simple strategy to screen informally for cognitive impairment. Relatives and friends may report longitudinal changes in memory and behavior that patients themselves may not recognize or report explicitly. Subjective short-term memory deficits, especially those reported by family members, probably indicate pathological cognitive processes and support caregivers' inquiries as a routine screening strategy.

Although there is no consensus about which formal screening tools[81,82] should be used to assess cognition in patients with HF, several exist and can be incorporated into routine practice, depending on the time and resources available. Tools include the Mini-Cog, Mini Metal State Exam and MoCA for their utility, practicality, recognition/awareness, and prognostication. Details of each tool are provided in Table 3. Tools used in routine practice should be chosen based on available time and personnel. However, clinicians should also note differences in diagnostic performance. The Mini-Cog can be administered in 3 minutes but may not be sufficiently sensitive to detect mild cognitive impairment, whereas the MoCA may be better at detecting MCI, but takes 10 minutes (or longer in cognitively impaired individuals) to administer.

Clinicians who screen for cognitive impairment should be aware of several potential confounders that may mimic or exacerbate cognitive impairment in patients with HF. Confounders include mood disorders, such as anxiety and depression, sleep disorders, delirium, and sensory deficits. Screening and treating for mood disorders as well as sleep apnea are warranted, as they can clarify the diagnosis and potentially improve cognition. Delirium (acute and transient disturbance in attention and awareness that develops over a short period of time) is another important confounder that is common in the hospital, especially at a time of acutely decompensated HF. To diagnose delirium, validated tools such as the Confusion Assessment Method,[83] which is part of routine care in some hospitals and intensive care units, can be helpful. Given the risk of delirium, the contribution of acute medical conditions and reductions in sleep and physical activity common during hospitalization, an assessment of cognition during a hospitalization may substantially differ from assessment of cognition in the ambulatory setting. It may be wise to repeat cognitive testing in the ambulatory setting to better understand long-standing deficits. It is similarly important to consider whether hearing or vision impairment is present, because intact hearing and vision are necessary for cognitive screening. Sensory impairment can also contribute to increased risk for cognitive impairment.[84] Finally, it is important to be aware of the impact that social determinants of health might have on the diagnostic performance of screening tools. For example, it has been observed that declines in cognition occur more frequently in those with less education compared to those with more education. One theory is that this reflects a notion known as *cognitive reserve*, which refers to a reservoir of knowledge and education that can compensate for declines in cognitive health.[85] Alternatively, limited education and/or health literacy could negatively impact performance in cognitive assessments, even when cognition is actually intact.[86] It is similarly important to consider whether there are intellectual disabilities at baseline, because this can influence the performance of screening tools for cognition; in this specific scenario, diagnostic tools specifically designed for those with intellectual disabilities are preferred.[87]

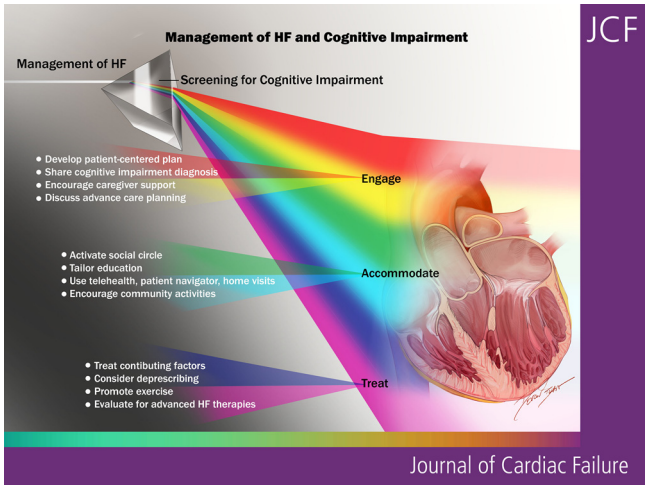
If cognitive impairment is suspected, it may be reasonable to refer to a specialist for imaging and neuropsychological testing, which can provide a definitive diagnosis and characterization. Neuropsychological testing usually examines multiple domains, including intelligence, memory, language, executive function, and visuospatial function; it is administered by specialized neuropsychologists and can last up to 2−4 hours.

Management of Cognitive Impairment

Although authors of treatment guidelines for cognitive impairment do not recommend specific interventions to improve cognition or delay progression, HF clinicians can adopt strategies to provide the best care to adults with HF and cognitive impairment,[7] specifically, by treating underlying contributors to cognitive impairment and providing accommodation for the resulting deficits. As shown, it is important to consider HF management through the prism of cognitive impairment (Take Home Visual).

Table 3 Cognitive impairment screening tools

Test	License/Training Required to Administer?	Cognitive Domains Assessed	Validation Populations	Complexity of Training and Deployment	Activities Required	Number of Items	Scoring Range, Cutoff Point Indicating Cognitive Impairment	Expected Length of Time to Complete (min)
The Mini-Cog	No	Memory Executive functioning Visuo-construction	Inpatient prior to discharge	Simple	Drawing	2	Range of 0–5 points, score of 2 or less indicates cognitive impairment	~ 3
Mini-Mental State Exam (MMSE)	Yes (license required)	Orientation Attention/working memory Language Visuospatial	Inpatient and outpatient settings	Moderate	Drawing Writing Reading Counting	11	Range of 0–30 points; score <24 indicates cognitive impairment	~ 8
Montreal Cognitive Assessment (MoCA)	Yes (training and certification required)	Short-term memory Orientation/attention Visuospatial Executive functioning Language Working memory/concentration	Inpatient and outpatient settings	Moderate/complex	Drawing Counting	16	Range of 0–30 points, score <26 indicates cognitive impairment	~ 10
Saint Louis University Mental Status (SLUMS) Examination	No	Orientation Memory Attention Executive Function	Any clinical setting	Moderate	Drawing Recall Orientation Calculations Naming	11	Range of 0–30 points, score <27 indicates cognitive impairment	~ 10



Take Home Visual.

Treatment of Underlying Causes/Contributors

HF itself contributes to cognitive impairment, so optimal management may prevent or even reverse cognitive impairment. In patients with HF, optimizing Guideline-Directed Medical Therapy (GDMT) may improve cognitive deficits, though decisions about GDMT must also consider the attendant risks of each agent and of polypharmacy in the setting of cognitive impairment. Prior work has shown that SGLT2is can improve cognition, but there are limited data concerning other GDMT agents.[66] Historically, there has been some concern about the negative effects of beta-blockers on cognition; however, a recent study of older adults with HF suggested that beta-blockers were beneficial (at least in those with HF with reduced ejection fraction) in the setting of Alzheimer's disease and related dementias.[88] For patients hospitalized for acutely decompensated HF, a tailored approach based on clinical and hemodynamic subsets (eg Forrester classification) has been proposed to maximize end-organ perfusion, including the brain.[89] Decongestive therapies (eg, diuretics, vasodilators, renal-replacement therapies) are beneficial in patients with evidence of volume overload, and therapies to improve cardiac output and support blood pressure (eg, inotropes, vasopressors, mechanical circulatory support) can be used in patients with evidence of low cardiac output. Restoration of metabolic derangements has been shown in some patients to partially reverse cognitive deficits observed upon hospital admission.[90,91] Advanced HF therapies, such as cardiac resynchronization therapy, left ventricular assist device (LVAD) implantation, enhanced external counterpulsation, and heart transplantation have been associated with improvements in cognition, though cognitive impairment adds complexity to patient selection (See "Integration of cognitive impairment in complex decision making" section below for more details).[92–95]

Management of contributing comorbid conditions can potentially prevent cognitive impairment or at least attenuate a decline. Treating hypertension has been associated with a decreased risk of dementia or vascular dementia and may have a modest effect in preventing cognitive impairment.[40,96,97] Controlling blood pressure in patients with HF and uncontrolled hypertension is a reasonable treatment goal. Although data are limited largely to observational studies, effective oral anticoagulation in patients with atrial fibrillation may have a modest effect in preventing cognitive impairment and/or dementia compared to patients treated with antiplatelets or no oral anticoagulation.[98–100] Rhythm control using catheter ablation was associated with lower rates of dementia in patients with atrial fibrillation, though further study is required.[101] Taken together, for adults with HF and cognitive impairment who have atrial fibrillation, it is reasonable to consider anticoagulation and possibly pursue a rhythm-control strategy to reduce the risk of cognitive impairment. Clinicians should also screen for and manage other potentially reversible causes of cognitive impairment in patients with HF, including mood disorders, obstructive sleep apnea, hypothyroidism, vitamin B-12 deficiency, infection, and impaired hearing and vision.[102]

Exercise

There is a rationale and early supportive evidence for the ways in which exercise could improve cognition, though definitive mechanisms are yet to be determined.[103–105] Tanne and colleagues conducted a hypothesis-generating study to evaluate an 18-week supervised exercise-training intervention in cognitive function in 20 patients with severe HF (New York Heart Association class 3; LVEF $\leq$ 35%).[10] Compared with the control group (5 patients with HF who did not receive the intervention), participants in the exercise-training group had significantly improved cognition according to 3 neuropsychological tests (Trail Making Tests A and B, Stroop test). In a small study of 69 participants with HF, Redwine and colleagues studied the effects of 2 different 16-week exercise regimens (tai chi and resistance band) compared to usual care, and showed significant improvements in cognitive function as measured by the MoCA test.[106] On the other hand, Kitzman and colleagues did not find that a 12-week progressive physical rehabilitation intervention improved cognition as measured by the MoCA test in a randomized control trial involving 349 patients hospitalized for acute decompensated HF, though cognitive function was measured as an exploratory outcome.[107] To date, it is unclear whether the changes in cognition are durable. Gary and colleagues conducted a pilot study among 69 participants with HF to evaluate the effects of a combined exercise and computerized cognitive-training intervention on cognition and showed improved verbal memory scores at 3 months but not at 6 months.[104] Taken together, there are promising data for the potential benefit of exercise, but large-scale studies and further investigation into biological mechanisms are needed.

Medication Management/Optimization

Given the complexity of the medication regimens and frequency of medication challenges in patients with HF and cognitive impairment, clinicians should carefully review and reconcile medication regimens. Strategies to improve outcomes in the setting of cognitive impairment could include deprescribing, the process of stopping a medication with supervision.[64] Candidate agents for deprescribing could include medications known to exacerbate HF[108–111] and/or medications that appear on the Beers criteria, a list of medications whose risks often outweigh benefits in most older adults, in part due to their potential to impact cognition negatively.[112] Clinicians can incorporate screening tools and/or involve pharmacists to identify and deprescribe agents that worsen outcomes; this approach has been shown to safely reduce overall medication burden and has the potential to improve mortality rates,[113] though its impact on cognition and clinical outcomes, specifically in adults with HF, remains uncertain.

Reconsidering the risk-benefit ratio of medications may be reasonable when cognitive impairment is detected. For example, the use of aspirin in those without known coronary artery disease may be less beneficial in some, especially those with higher degrees of cognitive impairment whose life expectancy is limited. There is evidence of the short-term safety of deprescribing statins in those with limited life expectancy (including those with significant cognitive impairment).[114] Given the risks associated with withdrawal of GDMT in HF,[115] routine deprescribing of GDMT is probably not the optimal strategy, even in the setting of cognitive impairment, especially because GDMT can help with symptoms and quality of life. However, depending on the specific clinical circumstance and health priorities, deprescribing GDMT may be reasonable for selected patients[116] who have limited life expectancy, severe functional impairment and/or those with poor quality of life who seek a palliative approach.

Finally, new medications are available to treat specific subtypes of cognitive impairment. Cholinesterase inhibitors (donepezil, rivastigmine, galantamine) are currently recommended to treat mild to moderate dementia due to Alzheimer's disease or Lewy bodies.[117] However, in the absence of Alzheimer's disease or Lewy bodies, the benefit of cholinesterase inhibitors to treat cognitive impairment is questionable; the risk of adverse events (eg, gastrointestinal, cardiac) is increased, and the quality of evidence varies.[118–120] Thus, consensus recommendations do not endorse the use of cholinesterase inhibitors to treat cognitive impairment unrelated to Alzheimer's disease or Lewy bodies. In fact, consensus recommendations include deprescribing cholinesterase inhibitors in patients with cognitive impairment unrelated to Alzheimer's disease or Lewy bodies and informing patients that such use is off-label and not evidence-based.[7,121,122] More recently, disease-modifying monoclonal antibodies have been approved to treat patients with mild cognitive impairment and mild dementia due to Alzheimer's disease. In phase 3 clinical trials, both aducanumab-avwa and lecanemab-irmb have been shown to reduce amyloid-beta plaques in the brain, leading to moderate reductions in the decline of cognition and function. However, both medications are associated with an increased risk of amyloid-related imaging abnormalities, which can include cerebral microhemorrhages, cerebral macrohemorrhages, superficial siderosis, brain edema, or sulcal effusion.[123,124] Given the high prevalence of antiplatelet and anticoagulation use in adults with HF, these monoclonal antibodies should be used with caution and reserved for selected patients with cognitive impairment resulting from Alzheimer's disease and only in conjunction with shared decision making, where the risks of stopping antiplatelet agents and/or anticoagulation are discussed explicitly.

Accommodation of Deficiencies in Self-Care

The best approach to accommodating deficiencies in self-care is to activate a patient's social circle. This could include engaging family, friends and/or other potential caregivers who may be available to assist with various aspects of self-care. Involvement of others can ensure that the necessary tasks of managing HF at home are understood, that instructions are followed and that tasks are completed. For example, family caregivers can remind patients to take their medications as prescribed and help them to follow dietary restrictions, help patients to track their symptoms and weight so as to maintain euvolemia, and assist with diuretic adjustment and/or correspondence with the patients' clinicians, when necessary. Activation of the social circle can identify people who can aid with transportation needs (to appointments or tests), mitigating challenges of accessing care that are common among adults with cognitive impairment. The burden of caregiving for patients with HF is high, especially in those with cognitive impairment, and it is a recognized source of stress and depressive symptoms in family caregivers.[125]

In a setting where self-care is substantially impaired to the point where there are limitations in the person's ability to engage in instrumental activities of daily living and/or basic activities of daily living, it is critically important to consider strategies to ensure basic care. Safety is an important aspect to consider when cognitive impairment is present. Even when activities of daily living are intact, forgetfulness leading to situations such as leaving an unattended stove on or getting lost on the way home should prompt further discussion about strategies to ensure safety. Strategies to ensure care and safety could involve additional help at home or the need to move from an independent dwelling to an assisted-living facility or long-term care facility, depending on individual circumstances and preferences.

Table 4 Strategies for optimizing self-care in patients with cognitive impairment

	Strategy
Education Materials[98–100]	• Use materials set at appropriate reading levels
	• Use teach-back methods to check for understanding
Medication Management[101–103]	• Simplify medication regimens (reducing frequency; avoiding the need for pill cutting)
	• Fill pill boxes for patients
	• Prescribe to pharmacies that can provide medication blister-packs organized by day and time
	• Help patients to develop reminder systems in their daily routines
	• Use pharmacist-led medication-management services
Technology[104,105]	• Leverage remote-monitoring technology and mobile health
	• Use blood pressure cuffs, scales and glucometers with remote-monitoring capabilities
Support[106,107]	• Employ advance-practice nurses, patient navigators and/or community health workers
	• Use home visits
	• Use team-based care
	• Include community activities and support
	• Employ cardiac rehabilitation
	• Contact social workers and case managers
	• Contact palliative care teams

Unfortunately, some adults do not have access to a social circle that can provide support. Absence of a social circle with reduced social interaction is associated with further cognitive impairment.[126] Clinicians should be sensitive to patients with limited social circles and should accommodate patients as much as possible (Table 4). More broadly, greater attention should be paid to the social determinants of health, which have been implicated as important contributors to cognitive impairment and have a profound impact on patients' capacities to manage when cognitive impairment is present.[127]

Integration of Cognitive Impairment in Complex Decision Making

Given its impact on self-care and life expectancy, integrating cognitive impairment into clinical decision making is a complex, yet critical part of caring for adults with HF and cognitive impairment. The following section outlines an overall approach to decision making for adults with HF and cognitive impairment and includes a special section on decision making for advanced therapies, which is especially challenging.

Approach to Decision Making

Effective communication is critical to facilitating decision making and implementing optimal management strategies for patients with HF and cognitive impairment.[128] First, it is important for clinicians to share explicitly the diagnosis of cognitive impairment, its implications for care and the resulting uncertainties related to prognosis with patients and their care partners. In addition, it may be helpful for clinicians to provide information about follow-up assessments to determine the cause and the treatment plan for managing both HF and cognitive impairment. When necessary, the need for referral to other specialties merits explanation. Incorporating family members and caregivers in the discussion can be helpful, given the importance of their support from a psychological and emotional standpoint and also from a logistical and financial standpoint. Because family members may experience increased caregiver burden,[129] communication may include information regarding available resources to support their efforts.[130]

The creation of care plans that are both evidence-based and patient-centered can seem difficult or even contradictory, as guideline stacking in older patients with multiple chronic conditions can lead to polypharmacy and accumulating side effects while health status wanes and life expectancy shortens.[131] To address this, decisions should align with patients' values, goals and preferences and should incorporate multiple domains of health (medical, psychological/emotional, physical/function, social environment).[1] Treatment plans should subsequently reflect the greatest expected benefit-to-harm ratio.

Preexisting models of care such as the previously published Domain Management Approach[1] can assist clinicians with developing patient-centered care plans. The domain management approach provides a framework that outlines the importance of multiple domains of health that are necessary to provide optimal care to adults with HF.[1] These 4 key domains are: medical domain (which includes HF etiology and severity, multimorbidity, polypharmacy, malnutrition); mind and emotion (which includes cognition and mood); physical function (which includes frailty, function defined by activities of daily living and instrumental activities of daily living, mobility and falls); and social environment (which, most notably, includes social support). When cognitive impairment is present, it is especially important to consider these other domains and subdomains of health, because when 1 deficit is present, the likelihood of other deficits becomes increasingly common. Indeed, when cognitive impairment is present, clinicians should be on high alert for multimorbidity, malnutrition, frailty, and social isolation, among several others. Given their prevalence in the setting of cognitive impairment, their synergistic effects on prognosis and the subsequent complexity of decision making, applying the domain management approach may be especially important when cognitive impairment is present.

Advance Care Planning

Advance care planning is particularly important in patients with 2 life-limiting conditions that can negatively impact decision-making capacity over time—HF and cognitive impairment. The purpose of advance-care planning is to promote and sustain value-concordant care over the course of a disease. Key elements of advance-care planning include understanding and sharing of their values, goals and preferences regarding future potential medical care decisions; choosing and preparing a trusted person (s) to make medical decisions; and documenting these wishes so that they can be enacted when future medical decisions need to be made.[132] Given the high number of medical options and the day-to-day management involved in HF care, loss of decision-making capacity can pose a serious problem for adults with HF. Anticipatory planning related to decisions about deprescribing, avoidance of certain care (mechanical ventilation, feeding tubes and cardiopulmonary resuscitation), deactivation of defibrillator function, and pursuit of a palliative approach is, thus, critical for adults with HF and cognitive impairment so as to ensure value-concordant care.[108]

Advance care planning is ideally started early in a disease, with loved ones involved in the conversation, and then revisited at least annually and when conditions progress and life experiences evolve. To guide these potentially difficult discussions, patient-decision aids such as Five Wishes (https://www.fivewishes.org/for-myself/) and Prepare for Your Care (https://prepareforyourcare.org/) can assist. Patient-decision aids tailored to specific decisions (implantable cardioverter-defibrillator deactivation, enrollment in hospice, etc.) could also be helpful; many of these can be found at the International Patient Decision Aid Standards website (http://ipdas.ohri.ca/), A-Z inventory (https://decisionaid.ohri.ca/AZinvent.php) and/or the Colorado Program for Patient Centered Decisions (https://patientdecisionaid.org/).

Decision Making for Advanced Therapies

Cardiac transplantation and LVADs have high upfront surgical risks, have substantial postoperative burdens and require a high level of adherence and follow-up (rejection surveillance and immunosuppressive monitoring for transplant; device and battery management, driveline care, and anticoagulation monitoring with LVADs). They are, therefore, considered major resource investments. A comprehensive evaluation of candidacy is critical; candidates must be able to participate in shared decision making about treatment options,[133] demonstrate an ability to engage with treatment needs and have a reasonably high likelihood of multiple-year survival with reasonable quality of life. Cognitive impairment has important implications for decision making related to advanced HF therapies, such as cardiac transplantation and LVAD implantation. Cognitive impairment increases risks of morbidity and mortality following cardiac transplantation[134] and LVAD implantation.[135] Reasons for this are multifactorial and are likely to include the following contributors that have prompted guidelines to consider impaired cognitive function as an important contraindication to advanced therapies[108,136]: (1) irreversible structural changes to the brain, which reduce overall life expectancy (predating advanced therapies, but also possibly exacerbated by cardiac bypass[137]); (2) presence of other comorbid conditions that reduce life expectancy; (3) challenges with self-care, which are critical for cardiac transplantation and LVADs. When cognitive impairment is a result primarily of advanced HF, cognitive function can improve with transplantation[138] or LVAD implantation.[139] Post device placement or transplantation, patients have had continued gains in cognition over time.[140,141]

The selection of patients with HF and cognitive impairment for cardiac transplantation and/or LVAD implantation is very challenging. When considering cognition in the setting of advanced therapies, an important aspect of the evaluation is to determine the extent to which HF itself contributes to cognitive impairment (eg, cerebral and end-organ hypoperfusion leading to delirium and encephalopathy) and its reversibility. Although there are no proven strategies to determine whether cognition will improve with advanced HF therapies, assessing the effects of improving cardiac output via inotropic support on cognition could be helpful, but data supporting this approach are limited.[142] It is prudent to evaluate patients across multiple health domains (medical, psychological/emotional, physical/function, social environment)[1] in conjunction with cognitive impairment when assessing candidacy.

Current Gaps in Knowledge and Challenges to Implementation

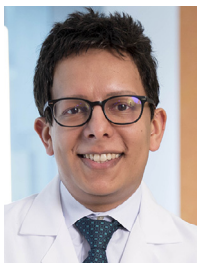
There are a number of ongoing gaps in knowledge and implementation related to providing care to adults with HF and cognitive impairment. Approaches are needed for earlier detection and characterization of cognitive impairment in patients with HF, so that care can be appropriately tailored. In addition, there is a need to develop modalities that can predict reversibility of cognitive impairment, especially among those who are potential candidates for advanced HF therapies. Mechanistic studies are needed to better understand the underlying pathophysiology of cognitive impairment among adults with HF; the link with Alzheimer's disease and other pathological processes of the brain are not well understood. The link between social determinants of health and brain health (with proposed solutions) requires further investigation.[127] Furthermore, understanding (and ultimately improving on) the diagnostic performance of cognitive-screening tools across key demographic factors and social determinants of health is critical to ensure that enhanced

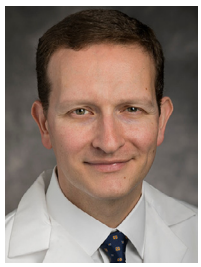
approaches to care do not exacerbate health disparities. Models for implementing routine assessment and integration of cognitive assessments (within the broad context of assessing multiple domains of health) into routine clinical care are needed as well. Finally, there is a need to better understand how to prevent cognitive impairment in the first place.

Conclusions

In summary, cognitive impairment is common in adults with HF due to the concurrence of multiple contributing factors leading to pathological alterations in brain structure. Cognitive impairment has major clinical implications and has important effects on self-care, medical management, function, health-related quality of life, and life expectancy. Management of cognitive impairment should focus on efforts to treat underlying causes and contributors, to optimize medication regimens so as to mitigate risks of medication challenges, and to accommodate deficiencies in self-care. Cognitive impairment must also be integrated into decision making within the broader context of health and patient priorities, especially when advanced therapies, such as cardiac transplantation and LVAD implantation, are being considered. Gaps related to understanding underlying pathophysiological mechanisms, optimal approaches to screening and reversing cognitive impairment are important areas of future work. By addressing these gaps, the field has an opportunity to further improve the care provided by 1 of the most vulnerable segments of the population.

Parag Goyal Eiran Gorodeski





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PARAG GOYAL: Writing – original draft. **ROBERT J. DIDOMENICO:** Writing – review & editing. **SUSAN J. PRESSLER:** Writing – review & editing. **CHINWE IBEH:** Writing – review & editing. **CONNIE WHITE-WILLIAMS:** Writing – review & editing. **LARRY A. ALLEN:** Writing – review & editing. **EIRAN Z. GORODESKI:** Writing – original draft.

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