REVIEW ARTICLE

Heart Failure and Cognitive Impairment: Clinical Relevance and Therapeutic Considerations

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Abstract: Heart failure (HF) is a devastating condition characterized by poor quality of life, numerous complications, high rate of readmission and increased mortality. HF is the most common cause of hospitalization in the United States especially among people over the age of 64 years. The number of people grappling with the ill effects of HF is on the rise as the number of people living to an old age is also on the increase.

Several factors have been attributed to these high readmission and mortality rates among which are; poor adherence with therapy, inability to keep up with clinic appointments and even failure to recognize early symptoms of HF deterioration which may be a result of cognitive impairment.

Therefore, this review seeks to compile the most recent information about the links between HF and dementia or cognitive impairment. We also assessed the prognostic consequences of cognitive impairment complicating HF, therapeutic strategies among patients with HF and focus on future areas of research that would reduce the prevalence of cognitive impairment, reduce its severity and also ameliorate the effect of cognitive impairment coexisting with HF.

1. INTRODUCTION

Heart failure (HF) is a devastating condition characterized by poor quality of life, numerous complications, high rate of hospital readmissions and mortality [1-3]. HF is the most common cause of hospitalization in the United States especially among people over the age of 64 years [1-4]. The number of people grappling with the ill effects of HF is on the rise as the number of people living to old age is also on the increase. Hospital readmissions are still high among patients with HF at a rate of about 25% within 30 days after discharge [4]. This high readmission rate among patients with HF in the United States is also accompanied by a very high cost burden which is over 20 billion dollars [5]. Several factors have been attributed to both high readmission and mortality rates some of which include poor adherence with therapy, inability to keep up with clinic appointments and even failure to recognize early symptoms of HF deterioration which may be a result of cognitive impairment (CGI) [6, 7].

CGI is prevalent among patients with HF and about 30% to 80% of patients with HF have varying degree of CGI [6-9]. CGI in its broadest definition ranges from mild CGI at one end of the spectrum to dementia at the other end [10]. Interest in understanding the associations between heart disease and cognitive performance started several decades ago after a report in the Lancet which described "cardiogenic dementia" and the findings of Wanless *et al.* that reported variabilities in cardiac output having a direct impact on cerebral blood flow (CBF) [11, 12].

This review seeks to compile the most recent relevant information about the link between HF and dementia or CGI. We also aim to assess the prognostic consequences of CGI complicating HF, therapeutic and preventative strategies among patients with HF and CGI as well as provide focus on future areas of research that would reduce the prevalence of CGI, reduce its severity and also ameliorate the effect of CGI coexisting with HF.

2. SEARCH METHODS

The search strategy for this review article was carried out using PubMed, Science Direct, Web of Science, Scopus, Cochrane Library databases and Google Scholar. The reference lists of relevant articles were searched for additional studies related to heart failure and cognitive impairment.

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All articles were reviewed in detail and only the most relevant articles were referenced.

Several search terms were used such as; "cognitive impairment and heart failure" "dementia and heart failure among elderly patients" "pathophysiology of cognitive dysfunction among elderly patients with heart failure" "prognosis of heart failure with cognitive impairment" "therapeutic considerations among patients heart failure and cognitive impairment".

3. COGNITIVE IMPAIRMENT

CGI in its most severe form can have untoward effects on how people function on a daily basis and its effects are even more deleterious in patients with co-morbidities such as HF [13]. Mild degrees of CGI may still alter an individual unfavorably especially if it is a sequel to a disease state such as HF with an underlying dismal prognosis [14]. As stated earlier, CGI is a spectrum with mild CGI at one end and dementia at the other end [10, 14]. Mild CGI has been described by some researchers as an intermediary stage between normal aging and dementia. Mild CGI describes a state characterized by objective reduction in cognitive function with preserved daily functioning with or without loss of memory which can progress to dementia [14].

Dementia on the other hand, is a chronic progressive cognitive disorder which usually primarily affects memory and is also associated with aphasia, apraxia, agnosia and disturbances of executive functioning [15]. The most common form of dementia is Alzheimer's disease (AD), and one of the major risk factors for its development is increasing age [16]. AD is characterized by accumulation of amyloid-beta and neurofibrillary tangles in the absence of a cerebrovascular insult. However, it has been noted that 20-40 % of dementia cases in elderly patients are mixed AD and vascular dementia (combination of ischemic lesions and AD pathology) [17, 18]. There are some reports that AD is preceded by cardiovascular disease [17, 19]. There are also reports that suggest cardiovascular disease trigger AD-specific pathology [17, 19]. HF has been singled out among the cardiovascular diseases to be the most common contributor to the development of AD [20]. Some evidence also suggests that HF is an independent risk factor for AD [20].

4. PATHOPHYSIOLOGY OF COGNITIVE IMPAIRMENT AMONG PATIENTS WITH HEART FAILURE

Distorted autoregulation with regards to cerebral blood flow (CBF) has been implicated in the occurrence of CGI among elderly patients as well as individuals with severe HF [21, 22]. CBF declines with increasing age and such gradual disruptions in cerebral hemodynamics appear to play a critical role in the pathogenesis of CGI [17, 19]. HF is another notable factor that may cause brain perfusion to drop below a critical threshold increasing the risk of CGI especially in elderly patients who as stated above also have intrinsically reduced CBF [17]. This line of thinking has been corroborated by some data indicating cognitive performance in patients with HF is closely related to the measurements of cerebral perfusion because decreased cardiac output was shown to be associated with lower brain volumes and the rate information is processed [7, 23]. In addition, some re-

gions of the brain including the frontal cortex and parahippocampal gyrus, which are implicated in cognition, appear to be more vulnerable in patients with HF [7, 24]. Imaging studies with magnetic resonance imaging (MRI) have revealed [7, 25] that patients with HF have increased frequencies of focal brain abnormalities ranging from multiple cortical or subcortical infarcts to small vessel disease with white-matter lesions and lacunar infarcts with cerebral embolism and hypo-perfusion being the most plausible pathophysiologic process [7, 26].

The domain of specific CGI is determined by the location of the lesions in each individual with HF and these differences among patients with HF may account for the inconsistencies between the studies regarding the impairment of specific cognitive domains [7]. In addition to location, severity of the lesion and the consequent cortical atrophy are also important determinants of CGI. Imaging techniques that integrate lesion location and severity of the lesion would be a valuable tool to fully evaluate patients with both HF and CGI [7].

It is also important to note that the reduction in CBF following HF may be further compounded by the ill effects of comorbid states such as hypertension, diabetes, sleep apnea, and depression [17]. In fact, concomitant increase in sympathetic tone associated with HF can cause chronic vasoconstriction in general and as well as in the cerebral circulation in response to physical and mental stress. These in turn can result in cerebrovascular damage and subsequent CGI.

Therefore, imbalance in hemodynamics can result in glucose and oxygen deprivation, which are critical for normal brain cell function. Disturbance of glucose and oxygen can in turn lead to a cascade of biochemical alterations that eventually lead to metabolic and tissue damage, including alterations to critical brain regions such as the hippocampus—a region highly sensitive to hypoxic episodes [24-32]. These biochemical changes can trigger neurodegeneration and cognitive decline.

5. ROLE OF EJECTION FRACTION IN DEVELOPMENT OF COGNITIVE IMPAIRMENT

The correlations between different cardiac variables with CGI have been previously reported, although, with conflicting findings. In 1997, Zuccalà, *et al.* [33] suggested a positive correlation between left ventricular ejection fraction (LVEF) and cognition using the minimental state examination (MMSE) global score. The authors described a poorer cognitive performance in older adults with LVEF lower than 30% in a non-linear positive correlation. However, the degree of memory and CGI in presence of a reduced LVEF seems to be variable with age according with a study published by Festa *et al.* [34] which included younger adults with HF. This study showed that memory abilities in subjects younger than 63 years remained unchanged regardless of the level of LVEF while patients older than 63 years had a significant reduction in memory functions when LVEF was below 30% (P < 0.02). Furthermore, Bhattacharya *et al.* [35] reported how the volume of cerebral grey matter, measured with *in-vivo* brain MRI segmentation study, was inversely proportional to the LVEF levels, although, with a modest correlation (r=0.51, p=0.06).

However, the results of the findings by Jefferson *et al.* [36] was somewhat interesting. Their findings suggest a U-shaped association, rather than a linear relationship, between LVEF and markers of abnormal brain aging. Their findings also corroborated the fact that lower level of LVEF is related to abnormal brain aging but also noted an unexpected observation that participants with the highest (top quintile) LVEF values also had poorer cognitive performances [36]. The mechanism for their observation is unknown but they surmised that very high LVEF values may correspond to subtle cognitive impairment and that the U-shaped association between LVEF and cognitive aging requires further study [36].

LVEF at rest (*i.e.* without physical or mental stress) may be unrelated to severity of HF as reported by Franciosa *et al.* [37]. They noted that symptoms of HF occur most commonly during exertion, but cardiac evaluation is usually quantitated at rest. Franciosa *et al.* [37] also noted that the measures of left ventricular performance obtained at rest do not accurately reflect exercise tolerance and symptomatic status of patients with HF. Therefore, the potential relationship between LVEF and cognition probably has no physiopathological basis.

In spite of the unclear relationship between LVEF and cognitive dysfunction, it is still interesting to note that a significant improvement of cognitive function following heart transplantation was observed by some researchers [38]. Dixit *et al.* [39] also reported improvement in cognitive function after cardiac resynchronization suggesting that when hemodynamic compensation is achieved, the improvement in blood perfusion and specifically CBF leads to the recovery of cognition.

6. ROLE OF HYPERTENSION IN DEVELOPMENT OF COGNITIVE IMPAIRMENT

About 65% of individuals aged 65 years and over have hypertension [14, 40, 41]. Hypertension is a major risk factor for vascular dementia but it may also be involved in Alzheimer's dementia which is also associated with some vascular abnormalities [19, 42]. As a result, mixed vascular and neurodegenerative dementia is the leading cause of age-related cognitive impairment [43].

Interestingly, diastolic blood pressure rather than systolic blood pressure has been reported to be predictive of cognitive impairment [44]. The association between blood pressure and poor cognitive performance has also been reported to be related by U-shaped curves such that both low and high blood pressures can result in CGI [45-47].

Systemic hypertension over an extended period induces hemodynamic stress on the cerebral blood vessels with resultant damage to the endothelium and consequent increase in vascular tone [48]. The role of hypertension and other factors in the pathophysiology of CGI among patients with HF is displayed in Fig. (**1**).

Low blood pressure and orthostatic hypotension have been linked to CGI among elderly patients [48]. Orthostatic hypotension is especially common in elderly patients taking antihypertensive medications [48, 49].
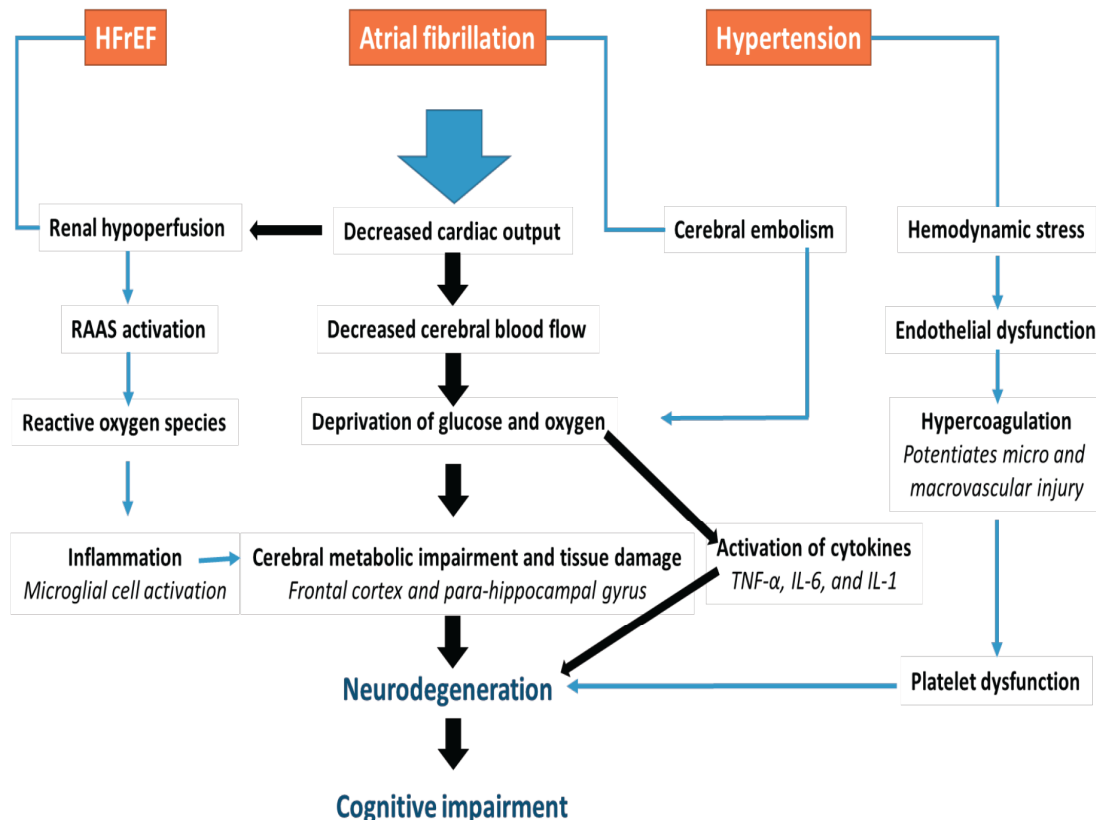
Fig. (1). Pathophysiology of cognitive impairment in heart failure.
Abbreviations: TNF-α (tumor necrosis factor alpha), IL-6 (interleukin 6), IL-1(interleukin-1), RAAS (renin angiotensin aldosterone system).

Some reports indicate that the cerebrovascular system compensates for transient hypertension more efficiently as compared with hypotension [50, 51]. This was somewhat corroborated by a report that showed that the blood flow velocity in the middle cerebral artery was less affected by hypertension than by hypotension [52]. It therefore follows that, with the brain possibly being unable to compensate efficiently, low systemic blood pressure may result in a reduced cerebral blood flow, making the brain tissue susceptible to ischemic events [53].

Blood pressure abnormalities are common in patients with HF. Hypotension is particularly common in patients with a reduced ejection fraction [54]. Patients with a preserved ejection fraction on the other hand frequently exhibit elevated blood pressure [55, 56]. Therefore, patients with HF irrespective of the ejection fraction are predisposed to cerebrovascular damage and CGI because of blood pressure fluctuations.

7. ROLE OF CORONARY ARTERY DISEASE IN DEVELOPMENT OF COGNITIVE IMPAIRMENT

Patients with coronary artery disease (CAD) and CGI share many similar risk factors especially cardiovascular risk factors. The exact connection between CAD and CGI is still poorly understood. There are however some possible pathophysiologic mechanisms one of which is higher platelet activation among patients who have CAD and CGI in comparison with patients who have CAD without CGI [57]. Increased platelet activity may hasten the progression of CGI by increasing the adhesion of platelets on endothelial cells at the sites of vascular lesions by mechanisms involving Platelet-bound glycoprotein IIb–IIIa and P-selectin which could trigger perivascular inflammation in the brain [58]. Platelet activation is also associated with progression of carotid artery diseases and cerebral vasoconstriction which can further perpetuate cognitive decline [59].

8. ROLE OF ATRIAL FIBRILLATION IN DEVELOPMENT OF COGNITIVE IMPAIRMENT

The prevalence of new atrial fibrillation (AF) is high in patients with HF and, ranges from 13 to 27% with increased prevalence as HF becomes more symptomatic [60-62]. Several mechanisms have been proposed for the association between AF and CGI. Ischemic brain lesions secondary to micro-embolism may be one of the mechanisms [63]. Zito *et al.* [64] also noted that elderly patients with non-valvular chronic AF, who used anticoagulants infrequently, had an inverse relationship between the number of lacunar lesions and MMSE value.

Another possible mechanism is related to consequent chronic hypoxic injury, secondary to reduced cardiac output among patients with AF and HF [48]. Cerebral hypoperfusion may result from elevated ventricular rate, reduced cardiac filling time and consequent reduced cardiac output [48, 65]. Therefore, patients with AF in the presence of HF have a reduced cardiac output which subsequently contributes to reductions in CBF to a critical point of causing neurocognitive dysfunction [66].

9. ROLE OF INFLAMMATION IN DEVELOPMENT OF COGNITIVE IMPAIRMENT

Systemic inflammation is an established accompaniment of HF [67-70]. Peripheral tissue hypoxia is one of the factors that activate cytokines such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and IL-1 in patients with HF [67-70]. These cytokines have also been implicated in the neuronal inflammatory state associated with cognitive decline [67-70]. It is postulated that inflammatory mediators influence cognitive performance *via* various cytokine-mediated interactions between neurons and glial cells [69, 70]. Some in vitro and animal models appear to be in keeping with the hypothesis of a link between inflammation and cognitive decline [69].

The inflammatory state associated with HF is further potentiated by renal impairment as a complication of severe HF. Renal hypoperfusion is an important trigger for the activation of the renin aldosterone angiotensin system (RAAS), which then results in activation of the sympathetic nervous system and consequent release of reactive oxygen species (ROS) [71, 72]. ROS then escalate oxidative stress and result in a self-perpetuating inflammatory state characterized by constant release of cytokines and progressive cognitive decline [71, 72].

10. ROLE OF HYPERCOAGULABLE STATE IN DEVELOPMENT OF COGNITIVE IMPAIRMENT

Patients with HF have an increased risk of developing a thrombus because the hemodynamic alterations lead to impaired blood flow and lower flow velocities. This in turn leads to stasis of blood and subsequent formation of thrombi in the left ventricle [73].

This state of hypercoagulability among patients with HF may also be potentiated by neuro-hormonal activation from HF related endothelial injury characterized by a cascade of platelet activation, platelet hyperreactivity, systemic inflammation, elevated levels of procoagulants and impaired fibrinolysis. All these act in concert to mediate hypercoagulability in patients with HF [73].

Hypercoagulability has been noted to be a feature of both HF and CGI resulting in the hypothesis that this may be an important pathophysiologic process linking HF and CGI [73, 74]. In line with this hypothesis, some studies have explored the effect of antithrombotic medication on cognitive decline and suggested a protective effect but some other studies could not demonstrate a very clear benefit [74, 75]. Therefore, further research may still be needed to corroborate the efficacy of antithrombotic therapy in reducing the risk of cognitive dysfunction.

11. DIAGNOSIS OF COGNITIVE IMPAIRMENT

There are many screening tools used in the assessment of cognitive function. One of the most commonly used screening measure for cognitive assessment in clinical practice is the MMSE [76]. Other screening tools are the Montreal Cognitive Assessment (MoCA) and European Consortium Criteria (ECC). The ECC has been stated to be the gold standard but its application into clinical practice outside of specialized clinics may be somewhat cumbersome. Some re-

searchers therefore opined that the use of the MoCA may be more universally applicable as it balances sensitivity and complexity issues [76-78].

Some comparative studies also revealed that MMSE was not a sensitive instrument in diagnosing mild CGI and that MoCA and ECC have far better sensitivity in diagnosing CGI [76-78]. They also pointed out appropriate use of screening tools with excellent sensitivities would increase the success rate in identifying patients at risk for developing dementia and also help with preventive strategies [76-78]. Interestingly, some researchers have used even easier tools such as the mini cog test to screen for mild cognitive impairment [79, 80]. The mini cog test combines a three-item memory test with a clock-drawing test.

Irrespective of what screen tool a physician decides to employ, the most important fact is that cognitive dysfunction among patients with HF should be screened because it may have far reaching consequences as discussed below.

12. CLINICAL AND PROGNOSTIC IMPLICATIONS OF HEART FAILURE CO-EXISTING WITH COGNITIVE IMPAIRMENT

Cognitive dysfunction is infrequently assessed among hospitalized patients [81, 82]. Cognitive dysfunction can impede management of HF as patients are likely to be oblivious of having a deficit in cognition [83]. CGI may result in non-adherence to dietary and medication management as well as follow-up clinic visits [76].

Agarwal *et al*. [79] reported that individuals with HF and CGI were readmitted at twice the rate of individuals who had HF without CGI and individuals with neither HF nor CGI. This result suggests that the relationship between CGI and hospital readmission may be different depending on the presence of comorbid conditions as well as other factors.

Mild CGI has also been noted to be related to higher cost of care as the direct cost of medical care was 44% higher for patients with mild CGI when compared to those without CGI [84].

Since CGI has been noted to be a marker for increased risk of readmission in HF, it may be useful to screen for CGI before discharge and follow up with modalities to ameliorate this condition [85-90].

In addition to increasing the risk of readmission, CGI has been shown to also increase the risk of death. Lan *et al*. [91] conducted a three-year follow up retrospective cohort study where CGI was shown to be an independent risk factor for mortality. The severity of CGI was noted to be a very important factor. When a comparison was made between patients with severe CGI and patients without CGI a worse outcome [hazard ratio (HR) of 2.710, (p=0.011)] was found among patients with HF and severe CGI [91]. These findings were similar to those reported by Byrne *et al*. [92].

The underlying mechanism for increased mortality found among patients with HF and CGI compared to their cognitively intact peers is still nebulous. Some plausible theories are that CGI results in increased readmission due to poor self-care, nonadherence with therapy and diet. Some authors have also noted that readmission for HF is on its own a po-

tent risk factor for HF associated mortality [93] implying that the CGI may have an indirect role in causing death among patients with HF.

An interesting study done in Australia revealed that patients with HF who were enrolled in special management programs after hospitalization for HF had a reduced likelihood of post-hospital adverse outcomes as compared to patients with HF who had regular care post discharge [94]. This also parallels findings in another study where patients with HF and CGI were noted to have better adherence with medications if they were discharged to a long term care facility as opposed to being discharged home [95]. It suffices to state that a comprehensive and integrated plan prior to discharge among patients with HF and CGI may improve outcomes.

13. THERAPEUTIC CONSIDERATIONS AMONG PATIENTS HEART FAILURE AND COGNITIVE IMPAIRMENT: NON-PHARMACOLOGIC APPROACH

The benefits of aerobic physical activity among healthy individuals on cognitive function are well established in the literature [96, 97]. Evidence shows that when aerobic physical activity is performed consistently over a long period of time, it has the potential to promote beneficial effects on cardiovascular health, mediated by increased vagal tone and decreased sympathetic activity in the sinus node [96, 97]. This consequently leads to improved vascular function, cardiac remodeling, and improved renal-adrenal functions [96, 97]. Regular aerobic physical activity also has an important role in the modulation of some regions of the brain related to cognitive functioning, through the increase of cerebral blood flow in the prefrontal cortex [98, 99] increased volume in the hippocampus [100], increased concentrations of vascular endothelial growth factors (VEGF) and brain-derived neurotrophic factor (BDNF) (strengthening of synaptic connections) [101], as well as angiogenesis in lobofrontal regions [102].

In the work of Tanne *et al*. [103], exercise improved the cognitive functions of selective attention and psychomotor speed among patients who had HF with New York Heart Association (NYHA) functional class III and ejection fraction $\leq 35\%$. It was an 18 week intervention (twice a week) of physical exercises performed as alternating between treadmill, cycle ergometer and stair simulator.

Some authors have also demonstrated a direct correlation between the six-minute walk test and the MMSE score indicating that the lower the functional cardiovascular capacity of the patient, the lower their cognitive function [104].

It therefore follows that supervised exercise training may be useful as it improves mental health, helps to prevent depression, and promotes or maintains positive self-esteem [97].

It is a known fact that adherence to guideline directed medical therapy (GDMT) for HF improves symptoms, reduces re-hospitalizations and mortality [105, 106]. However therapy for HF is only effective if patients take their medications regularly. Sadly, adherence to pharmacotherapy among patients with HF is appallingly low at only 50% and may

even decline overtime among individuals who were initially adherent [105-108].

Therefore, cognitive training should be norm among patients with HF as some observational and experimental studies have shown that this improves memory and cognitive performance which in turn may be beneficial in improving medication adherence [105, 109-111].

14. PHARMACOLOGIC CONSIDERATIONS

It is concerning to note that prescription rates are relatively low for GDMT among patients with HF because of the contra-indications these medications may be fraught with [112-117]. More worrisome is the fact that, these medications even when administered fail to reach target dosages that are associated with improved clinical outcomes less than 50% of the time [112-117]. CGI has been implicated as one of the multiple factors contributing to low prescription rates of GDMT among patients with HF [112-117].

The role of RAAS in the pathophysiology of CGI among patients with HF has been described above. Some authors looked into the efficacy of RAAS modulation in altering the prevalence of cognitive dysfunction among patients with HF. Goh *et al.* [118] conducted an analysis of patients with HF treated with angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme inhibitors (ACEIs) and followed up at the end of one year to identify the number of new diagnoses of dementia [118]. There was weak evidence of a decreased risk of dementia with exposure to angiotensin receptor blockers with a smaller reduction in dementia risk in comparison to ACEIs [118].

On the other hand, the relationship between ACEIs and cognition is equivocal. Hoth *et al.* [119] documented that patients with HF who were taking ACEIs did not perform differently than patients not taking ACEIs. Surprisingly, they noted that patients taking ACEIs performed significantly worse on a measure of attention than patients not taking ACEIs [119]. The lack of a significant correlation between ACEIs and cognitive function may be related to dosing as well as the ability to cross the blood brain barrier. This line of thinking is corroborated by two studies. The first is one by Sink *et al.* [120] who reported that ACEIs as a class do not appear to be independently associated with risk of dementia or cognitive decline in older hypertensive adults. However, centrally active ACEIs were noted to be associated with 65% less decline in three MMSE scores per year of exposure (p= 0.01) and non-centrally active ACEIs were associated with greater risk of incident dementia (adjusted HR 1.20 (1.00-1.43) per year of exposure) and greater odds of independent activities of daily living disability (adjusted odds ratio (OR) 1.16 (1.03-1.30) per year of exposure) compared to other antihypertensive drugs [120]. This was also corroborated in another study where centrally acting ACEIs (captopril and perindopril) were compared to those that do not (enalapril and imidapril) cross the brain barrier [121].

There are plausible reasons for why centrally active ACEIs may be useful in reducing the risk of cognitive decline. Firstly, in addition to the anti-inflammatory actions of ACEIs is its role in modulation of the increased concentration of angiotensin converting enzymes, angiotensin II, and

angiotensin I (AT1) receptors in the cerebral cortex of patients with Alzheimer's disease [121, 122]. Animal studies have also shown that angiotensin II inhibits acetylcholine release [123]. Therefore, centrally active ACE inhibitor could decrease angiotensin II levels, potentially reducing the inhibitory action on acetylcholine release and thereby increase acetylcholine concentration [121-123]. Indirect increase in cerebral blood flow by centrally active ACEIs by decreasing vasoconstriction may be another plausible mechanism [121-123].

The above stated mechanism was also extended to centrally acting ARBs such as losartan which was shown to improve cognitive function in patients with hypertension, including in those who were elderly (up to 73 years of age) [124].

In the study by Zuccala *et al.* [125] the beneficial effect of ACEIs was more or less a dose-response relationship. They studied over 1,200 hospitalized patients with HF and found that patients who were started on ACEIs experienced improved scores on measures of global cognitive function during their hospital stay. They also found that higher doses and longer duration of ACEIs were associated with greater improvement of cognition across hospitalization even after controlling for multiple confounders in linear regression models [112, 125].

Few studies have looked at the relationship between newer therapies such as the sacubitril/valsartan combination in relation to cognitive decline. There is a theoretical risk of increased incidence of Alzheimer type dementia because neprilsyn inhibition also reduces the breakdown of amyloid-β peptides in the central nervous system [126-128]. This same association with regards to amyloid-β peptides has also been noted with ACEIs as angiotensin converting enzyme has been noted to be important in converting amyloid--β 1-42 into Aβ1-40 and that ACEIs block this process and increase Aβ1-42 deposition in the brain of mice [120, 129].

This association was explored by Cannon *et al.* [126] in their study were the incidence of dementia-related adverse effects in patients treated with sacubitril/valsartan was similar to that in patients treated with enalapril in the **P**rospective Comparison of **AR**NI with **ACEI** to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure (PARA-DIGM-HF) trial and in patients enrolled in other heart trials [126]. De Vecchis *et al.* [130] did a retrospective cohort study comparing patients with HF on sacubitril/valsartan vs patients with HF not on sacubitril/valsartan. They concluded that patients taking sacubitril/valsartan for at least 3 months had similar mean MMSE scores to control subjects [130].

More research may need to be done to ascertain in more definite terms the effect of the new HF medication sacubitril/valsartan on cognitive function.

15. ATRIAL FIBRILLATION THERAPY AND COGNITIVE IMPAIRMENT

AF is the most common type of cardiac arrhythmia. Age is the single greatest risk factor for AF and the prevalence of AF also increases as people get older [131-134]. AF is also a major risk factor for ischemic stroke, thromboembolism, HF, myocardial infarction, death as well as cognitive decline

independent of ischemic stroke [131-134]. Therefore, therapeutic strategies that target important dementia pathophysiologic processes associated with AF may be useful. These accompaniments of AF include the coagulation pathway, inflammation, cholesterol metabolism as well as tachycardia associated complications. These would be discussed in the sub-sections below.

16. ANTICOAGULATION THERAPY

Several studies have assessed the impact of different anticoagulation strategies for AF treatment on dementia [131, 135]. The efficacy of warfarin in preventing worsening of cognitive decline was assessed by Bunch *et al.* [136] after review of medical records of 10537 patients on warfarin therapy for varying indications. They found out that the presence of AF significantly increased the risk of dementia, when compared with matched patients receiving warfarin anticoagulation for other reasons [136]. Some other authors have reported that the incidence of dementia among patients with AF who are on warfarin is higher among those who were for prolonged periods in the sub-therapeutic range for the international normalized ratio (INR) [137, 138]. Chronic cerebral injury from silent cerebral ischemia has been implicated for the possible pathophysiology for the association between sub-therapeutic INR and dementia [137-139]. A corollary to this hypothesis, is that the rate of incident dementia has been noted to be significantly higher among patients with poor adherence to anticoagulation therapy compared to those with the excellent adherence to anticoagulation therapy [131, 135, 136].

Conversely, supratherapeutic INR also appears to increase the risk of dementia among patients with AF who are on anticoagulation with warfarin as reported by Jacob *et al.* [140]. Jacobs *et al.* [140] reported that these findings may be in part, related to the presence of microbleeds in patients with frequent supratherapeutic INR levels. It therefore suffices to say that the quality of anticoagulation may play an important role in preventing dementia among patients with AF. Do these findings favour other forms of anticoagulation as keeping the INR within the therapeutic range with warfarin may be an arduous task.

Jacobs *et al.* [141] reported that there was significantly lower rates of incident dementia associated with use of direct oral anticoagulant (55.3% of participants were on rivaroxaban, 22.5% on apixaban, and 22.2% on dabigatran) for AF when compared to warfarin use for AF (0.3% with direct oral anticoagulants vs. 0.7% with warfarin, p=0.03) during a median follow-up of 243 days. However, some patients may have contra-indications to taking the direct oral anticoagulants and it may suffice to state that whatever anticoagulation modality is employed if used effectively may be associated with a lower risk of incident dementia.

17. STATIN THERAPY

On large-scale cohort study involving patients with AF older than 60 years of age receiving statin therapy compared with age- and sex-matched control participants with AF and no statin therapy revealed that statins were associated with a lower risk of nonvascular dementia (1.89% per year *vs.* 2.20% per year; P < 0.001) [135, 142]. This may be related

to the pleotropic role of statins as well as its effect on the cholesterol metabolism which has been implicated in the pathophysiology of dementia. Further studies would be needed to corroborate these findings.

18. CATHETER ABLATION

There are conflicting reports on the effect of rhythm or rate control treatment strategy for AF on neurocognitive decline. It is however an established fact that catheter ablation is a well-established option for symptomatic AF that is resistant to drug therapy [143-145]. The recent report from the CASTLE-AF (Catheter Ablation versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) trial indicates that patients with HF and AF who undergo catheter ablation have better outcomes [144-146].

The long term effect of catheter ablation for AF in preventing cognitive decline remains unclear. One prospective study compared 4212 consecutive patients who underwent AF ablation with 16,848 control participants with AF (matched for age and sex) [147]. The risk of dementia was significantly lower in patients with AF ablation compared with control participants (P < 0.0001).

The report of the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST), is still being awaited. They aim to randomize a total of 2745 patients with AF to early rhythm control therapy (antiarrhythmic drugs and AF ablation) or usual care [148, 149]. Cognitive function is a secondary end point that will be assessed after 24 months of follow-up. It would be exciting to see what the results are but preliminary results as mentioned above from one study appear to show a favorable response of early rhythm control therapy in preventing cognitive decline among patients with HF and AF.

19. CARDIAC RESYNCHRONIZATION THERAPY AND COGNITIVE FUNCTION IN PATIENTS WITH HEART FAILURE

For patients with HF who meet the criteria for cardiac resynchronization therapy (CRT) improvement in survival, quality of life, and reduction in HF symptoms have been reported [150-152]. Duncker *et al.* [153] carried out a prospective study of patients with HF assigned to CRT in combination with an implantable cardioverter defibrillator (ICD) compared with ICD therapy alone. Cognitive functioning, concentration ability besides reduction in depressive symptoms and quality of life were noted to be significantly better after CRT-ICD compared with ICD alone in patients with HF. The exact reason is not fully understood but may be related to the fact that the benefit may result from secondary effects of both device therapies combined in reducing morbidity and quality of life.

One study looked specifically at the direct effect of CRT on cognitive dysfunction [39]. This study demonstrated that cognitive functioning associated with chronic HF significantly improved in patients responding to CRT, specifically in the domains of attention, working memory, and speed of processing [39]. This improvement may be related to the improvement of left ventricular ejection, reversal of cardiac

remodeling, reduction of mitral regurgitation which ultimately results in less stretch of the myocardium and secondary reduction in incidence of malignant arrhythmias [154-157].

Large scale studies are still required to fully explore these potential secondary beneficial effects of CRT. However, since few of the preliminary studies in this regard have only proven these beneficial effects on cognition among CRT responders, more work needs to be done on increasing the response rate among patients with HF who are on CRT.

20. IMPLANTABLE CARDIOVERTER DEFIBRILLATOR AND COGNITIVE FUNCTION IN PATIENTS WITH HEART FAILURE

The ICDs though noted to be pivotal to improving survival among patients with severe HF has been noted to also have some complex trade-offs [152, 158]. ICDs come with a host of potential adverse events including a lower quality of life if shocked, increased number of hospitalizations and possible suffering at the end of life if they are not properly deactivated [158-160]. It would be interesting to note the effect of ICDs in improving cognitive function among patients with HF as well as to identify the effect of dementia on the efficacy of ICDs among patients with HF.

In line with the above, Green *et al.* [161] reported that more than 10% of patients receiving primary prevention ICDs are frail or have dementia. Frailty and dementia were also reported to be more strongly associated with mortality within the first year after ICD implantation than are traditional comorbidities [161]. Apparently patients with HF who have dementia do not appear to have long term benefits of ICDs in improving survival which has made some researchers to opine that it behooves on physicians to screen patients with HF for dementia before placing ICDs [161, 162]. Another study looked at a head to head comparison among patients with HF and CGI who had ICDs compared to a cohort of patients with HF and ICDs without cognitive dysfunction [163]. They found out that the 5-year survival of patients with CGI or dementia with pacemaker or ICD insertion was significantly lower than that of matched controls without cognitive impairment or dementia [163].

There are very few reports on the effect of ICDs on cognitive function among patients with HF. One single-center observational study demonstrated that ICD implantation for primary prevention among patients with HF did not show a worsening in anxiety and depression of mood and demonstrated similar cognitive performance in comparison with HF patients without ICD implantation [164].

More studies are required to explore the complex interrelationship between cognitive function, ICD placement and HF prognosis.

21. DEMENTIA MEDICATIONS AND HEART FAILURE

It would be great know the potential outcome of patients with HF taking both GDMT for HF with medications for dementia.

Two main pharmacological treatments are available for treating dementia which are; cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and N-methyl-D-aspartate (NMDA) receptor antagonists (memantine). Both drug classes can lead to statistically significant but clinically marginal improvements in cognition and overall assessment of dementia [165, 166]

Cholinesterase inhibitors are however, the most commonly prescribed medications for dementia and have been noted by some authors to have some cardio-protective properties [5, 167, 168].

The mechanism of this beneficial effect may be due to the fact that cholinesterase inhibitors have a negative chronotropic effect on the heart and increase vagal tone by augmenting acetylcholine release [169, 170]. Cholinesterase inhibitors have also been noted to have anti-inflammatory properties which positively impact the inflammation underlying atherosclerosis [171].

Some other reports have opined that there may be some potential deleterious effects of cholinesterase inhibitors as excessive cholinergic stimulation, may cause arrhythmias, such as bradycardia, sick sinus syndrome and torsades de pointes [172].

Not much has been studied about memantine on the other hand. However, some authors reported that memantine may cause adverse cardiovascular events [173].

Fosbol *et al.* [165] conducted a comparative study between donepezil and memantine to assess their cardiovascular safety across populations in Denmark and the United States. They concluded that cardiovascular safety was similar for both medications but memantine was associated with higher rates of myocardial infarction and cardiac death in the Danish publication which was however attributed to the fact that they had sicker cohorts in their own population.

Very few studies have been done to fully establish the relationship above and would potentially be a good line of research to further explore.

CONCLUSION

CGI is prevalent among patients with HF and can have dire consequences in terms of mortality, readmissions, length of hospital stay as well as health care cost. Screening for cognitive dysfunction among patients with HF is not yet routine and even simplistic modes of assessment may be beneficial as early detection may help in curbing further deterioration and a vicious cycle of a poor outcome among patients with HF. Some of the therapeutic options for HF such as GDMT, device therapy as well as non-pharmacology therapy appear to be useful on the whole in preventing and halting the progression of cognitive dysfunction, however, more studies would be needed to fully substantiate this evidence.

FUTURE DIRECTION OF RESEARCH

Exploration of important markers and predictors of CGI among patients with HF which detects patients at risk of developing CGI would be very useful. Prospective cohort studies to assess the role of poor prognostic markers such as

hormone sensitive troponin T, brain natriuretic peptide, uric acid among others in predicting the occurrence of CGI among patients with HF would be useful. This is because some of these biomarkers are easy to measure and may help to easily stratify patients at high risk for developing CGI. Also, the effect of modifying other identified predictors and markers in reducing the prevalence and severity of CGI among patients with HF would be very beneficial.

The potential impact of lifestyle modification (*i.e.* physical training, cessation of cigarette smoking, diet *etc*.) should be explored as potential aids to improving cognition among patients with HF. Randomized control trials taking these into consideration may be beneficial.

LIST OF ABBREVIATIONS

ACEIs	=	Angiotensin-Converting Enzyme Inhibitors
AD	=	Alzheimer's Disease
AF	=	Atrial Fibrillation
ARBs	=	Angiotensin Receptor Blockers
AT1	=	Angiotensin I
BDNF	=	Brain-Derived Neurotrophic Factor
CAD	=	Coronary Artery Disease
CASTLE-AF	=	Catheter Ablation versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation
CBF	=	Cerebral Blood Flow
CGI	=	Cognitive Impairment
CRT	=	Cardiac Resynchronization Therapy
EAST	=	Early Treatment of Atrial Fibrillation for Stroke Prevention Trial
ECC	=	European Consortium Criteria
GDMT	=	Guideline Directed Medical Therapy
HF	=	Heart Failure
HR	=	Hazard Ratio
ICD	=	Implantable Cardioverter Defibrillator
IL-1	=	Interleukin-1
IL-6	=	Interleukin 6
INR	=	International Normalized Ratio
LVEF	=	Left Ventricular Ejection Fraction
MMSE	=	Mini-Mental State Examination
MoCA	=	Montreal Cognitive Assessment
MRI	=	Magnetic Resonance Imaging
NYHA	=	New York Heart Association
OR	=	Odds Ratio
PARADIGM-HF	=	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure
RAAS	=	Renin Angiotensin Aldosterone System
ROS	=	Reactive Oxygen Species
TNF-α	=	Tumor Necrosis Factor Alpha
VEGF	=	Vascular Endothelial Growth Factors

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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