

# Effect of atrial fibrillation on cognitive function in heart failure patients

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As the population ages, conditions like heart failure (HF), atrial fibrillation (AF) and cognitive impairment (CI) demonstrate higher prevalence. HF is a very common clinical syndrome affecting many people worldwide. It is estimated that in the developed countries approximately 1%–2% of the adult population suffers from HF, whereas in adults > 70 years old the incidence rises to ≥ 10%.<sup>[1]</sup> Additionally, it has been reported that the lifetime risk for developing HF for men and women at the age of 55 is 33% and 28%, respectively. HF seems to be the cause of high mortality and morbidity rates globally,<sup>[2]</sup> impaired quality of life,<sup>[3]</sup> emergency department admissions and hospitalizations,<sup>[4]</sup> adding a major burden to the health-care system. It is also associated with a very heavy burden to the economy of the states, with an estimated annual cost of approximately 99 billion euro.<sup>[5]</sup>

One of the most common type of arrhythmia in clinical practice is AF,<sup>[6]</sup> with a prevalence of millions of adults worldwide.<sup>[7]</sup> Similar to HF, AF is a major cause of high mortality and morbidity rates and its incidence is approximately 2%–4% in the general population.<sup>[8]</sup> Moreover, the lifetime risk of AF at the age of 55 is 33% and it has been pointed out that the early AF diagnosis is beneficial to the patients and the healthcare systems, reducing its burden and preventing future adverse complications.

## COGNITIVE IMPAIRMENT

Cognition refers generally to the human behavior

and cerebral function. It describes all the processes conducted by the human brain in daily activities, including memories, decision making, motivation, thought process, etc.<sup>[9]</sup> CI is an increasing issue, especially for older adults, due to its high prevalence in this population. It has been linked with high mortality rates,<sup>[10,11]</sup> impaired self-care<sup>[12]</sup> and quality of life,<sup>[13]</sup> affecting negatively the life of those individuals.

According to previous studies, there has been an association of HF with the progressive decline in cognitive function,<sup>[13–19]</sup> the development of Alzheimer's disease and vascular dementia.<sup>[20,21]</sup> Furthermore, AF has also been associated with declined cognitive function.<sup>[22–26]</sup> Finally, some scientists suggest that AF may accelerate the progression of HF and vice versa.<sup>[27]</sup> Although they have been linked individually to CI and depending on the fact that AF is the most common arrhythmia in patients with HF, it has yet to be clarified if there is an association between AF and CI in HF patients. The aim of this study is to review the data from the literature and evaluate whether or not atrial fibrillation affects cognitive function in heart failure patients.

## AVAILABLE DATA ON THE EFFECTS OF AF IN COGNITIVE FUNCTION IN HF PATIENTS

Our team reviewed the literature in detail twice. We used the Medline (PubMed) database from their inception up to October 28, 2020. The initial PubMed

search was conducted in March 2020 and was updated in October 2020. The terms we used in PubMed search were the following: (atrial fibrillation) AND (cognitive decline OR cognition OR cognitive impairment OR cognitive function) AND (heart failure OR congestive heart failure). Animal studies and studies published in languages other than English were excluded. On the other hand, all types of articles were included and the references of selected articles, also, reviewed for any omitted studies.

The initial PubMed search revealed 178 articles. The authors excluded 150 of them using only the title and the abstract of each article. Out of the 28 remaining articles one was excluded because it was letter to the editor, two because they were author's reply and 19 because they were partially relevant to the subject. Finally, five studies and one systematic review and meta-analysis were fully eligible for our subject and were reviewed in detail (Table 1).

Overall, the available data on the concomitant existence of these three conditions were very limited. In 2007, Debette, *et al.*<sup>[28]</sup> studied 83 patients with chronic HF during a 3-month period and assessed any CI based on their medical history, their neurologic examination and the Mini-Mental State Examination (MMSE). The study evaluated as well all the main characteristics and co morbidities of the patients, such as age, arterial hypertension, diabetes mellitus, atrial fibrillation, hypercholesterolemia, etc. According to the results, two-thirds of the patients admitted in the hospital for chronic heart fail-

ure (CHF) decompensation were presented with some degree of CI, the MMSE score was < 24 in one-third of the patients. Cerebrovascular events were not necessarily the cause of CI, while MMSE score < 24 was more likely to occur in patients with low educational level with AF or atrial flutter and severe CHF. This study came to the conclusion that patients with CI may be led to worse cardiac outcomes due to impaired compliance ability and therefore the inclusion of cognitive assessment in CHF diagnostic process as well as the effect of CHF treatment in cognitive function should be considered.<sup>[28]</sup>

Later, in 2015, Alosco, *et al.*<sup>[29]</sup> included 187 patients with HF in their study with no previous medical history of neurological or psychiatric disorder and divided them into two groups, individuals with and without AF. The patient's characteristics assessed were cognitive function based on their medical history and some neuropsychological tests (global cognitive function, attention/executive function, memory, language) and the cerebral blood flow measured by transcranial doppler ultrasonography targeting on the determination of AF impact. The results of the study reported that AF contributes to CI in older adults with HF by reducing cerebral blood flow. AF was also presented to be associated with brain abnormalities and dementia, leading to the suggestion that further research should investigate the effect of intervention (pharmacological control, ablation, exercise programs) in the prevention of CI in

**Table 1 Summary in chronological order of the studies associating AF with CI in HF patients.**

Author, year	Number of Patients	Results	Supporting references
Debette, <i>et al.</i> , 2007	83	CHF is frequently associated with CIAF seems to be associated with CI in CHF patients	[28]
Alosco, <i>et al.</i> , 2015	187	AF may induce CI via reduced cerebral blood flow in HF patients AF is related with brain abnormalities and dementia	[29]
Coma, <i>et al.</i> , 2016	881	HF patients with persistent AF are independently associated with CI, with no significant difference observed in HFpEF or HFrEF groups	[30]
Pulignano, <i>et al.</i> , 2016	331	AF is independently associated with CI, gait speed and disability in HF patients No clear association between CI and OACs has been proved	[31]
Yang, <i>et al.</i> , 2016	188	Independent association of onset AF with CI, after adjusting for demographic, medical and psychological characteristics Independent association of AF with poorer cognitive function in patients diagnosed with HF and AF	[32]
Myserlis, <i>et al.</i> , 2016	1670	Patients with HF and AF had almost 2 times the odds of developing CI, compared with non-AF patients	[33]

AF: atrial fibrillation; CI: cognitive impairment; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction.



HF and AF patients.<sup>[29]</sup>

In 2016, Coma, *et al.*<sup>[30]</sup> conducted a study with 881 patients with stable HF, including an assessment of their cognitive function and age/educational level. The patients were divided into two groups, those with and without permanent AF and their characteristics were documented (e.g., age, arterial hypertension, diabetes mellitus). The target of the study was the evaluation of the suggestion that the presence of AF is associated with CI. The results of the study revealed an independent association between persistent AF and CI in patients with HF. There was no significant difference between the HF with preserved and reduced ejection fraction (HFpEF, HFrEF) subpopulation groups. No other factors [e.g., previous history of stroke, oral anticoagulant therapy (OAC), or CHA2DS2-VASc risk assessment score] affected the association of AF with CI in HF population.<sup>[30]</sup>

In the same year, Pulignano, *et al.*<sup>[31]</sup> conducted a 1-year prospective study with 331 individuals with advanced age, chronic HF and AF and assessed the relation between AF and CI, disability and frailty in these patients. The findings of the study supported that patients with concomitant HF and AF were associated with higher prevalence of frailty, CI and disability. The study did not come to a conclusion concerning the association between the administration of OACs and CI, while the existing data on this subject are also controversial. The inclusion of screening for these variables in clinical practice may improve the intervention strategies in high-risk subpopulations.<sup>[31]</sup>

Later in 2016, Yang, *et al.*,<sup>[32]</sup> enrolled 188 patients with HF and examined whether or not AF was an independent predictor of CI after adjustments for demographic, medical and psychological characteristics. The study reported that AF was independently associated with CI after correction for the previously mentioned characteristics as well as with poorer cognitive function in patients diagnosed with HF and AF.<sup>[32]</sup>

Finally, in 2016 Myserlis, *et al.*<sup>[33]</sup> performed a systematic review and meta-analysis included five studies with a total of 1 670 patients with HF in an attempt to assess the association between AF and impaired cognitive function in those patients. Concomitant AF and HF was demonstrated to poten-

tially exacerbate the cognitive dysfunction. AF was significantly associated with the development of CI in HF patients (odds ratio = 1.94; 95% confidence interval: 1.30–2.87), with significant heterogeneity ( $I^2 = 39%$ ). Due to many limitations of the studies and significant heterogeneity, the pathophysiological role of AF in CI of heart failure patients should be evaluated in future studies, including an analysis of different cognitive domains and the effect of interventions in the attenuation of CI in these patients.<sup>[33]</sup>

## DISCUSSION

HF and AF have been independently associated with impaired cognitive function in previous studies.<sup>[34–38]</sup> HF is a well-known risk factor for dementia and Alzheimer's disease<sup>[20]</sup> and when complicated with AF, it can further result in vascular dementia due to the increased incidence of strokes (silent or not).<sup>[39,40]</sup> AF is, also, a well-known risk factor for impaired cognitive function even without the presence of cardioembolic or other types of strokes.<sup>[41]</sup> However, since these two conditions coexist very often in older patients, the review of the literature provided evidence on whether or not AF affects the cognitive function in HF patients.

To begin with, all the reviewed studies suggest that there is a link between AF and cognition in HF population. HF patients with AF had higher prevalence of CI compared to patients without AF. First of all, Debette, *et al.*<sup>[28]</sup> showed that although most patients admitted in emergency department with HF decompensation had some degree of declined cognitive function, AF seemed to be associated with further decline, in those patients. One interesting suggested hypothesis is that it should be clarified, whether the cognitive impairment is primary to HF and AF or secondary to metabolic and hemodynamic changes. Later, Alosco, *et al.*<sup>[29]</sup> reported that patients with HF and AF were more likely to be older in age, have progressed HF and receive anticoagulant compared to patients without AF. Additionally, AF patients observed to have worse global cognitive function (assessed with modified MMSE) and memory. The presence of AF was accompanied by reduced cerebral blood flow velocity in the major brain arteries, adding a possible new pathogenetic mechanism. Among patients with HF and AF, re-



duced cerebral blood flow velocity was linked to worsened attention/executive function, memory capacity and language usage. Conclusively, AF seems to exacerbate cognitive function through reduced cerebral blood flow.

Coma, *et al.*<sup>[30]</sup> tried to examine whether or not AF worsens CI in two groups of HF patients, HFpEF and HFrEF. Of the entire population (irrespective of the presence of AF), 1/3 had CI, equally observed in reduced and preserved ejection fraction HF patients. Additionally, HF patients with permanent AF were observed to have an independent association with CI, without being affected by the OAC therapy, or the ejection fraction. These patients were also reported to have orientation issues. Finally, they demonstrated that systolic blood pressure affects the CI in HF, enriching the suggested pathophysiology theories with new data.

Pulignano, *et al.*<sup>[31]</sup> identified an independent correlation between AF, age, depressive symptoms and severe chronic kidney disease with CI in HF patients. They also revealed impaired gait speed and increased disability in these patients. It is interesting that this association was even observed in patients without medical history of any cardiovascular accident. Moreover, Yang, *et al.*<sup>[32]</sup> showed in their study that HF patients with AF scored lower in the neuropsychological tests than the patients without AF. Additionally, among patients with AF and HF, those with incident AF scored lower in these tests than those with preexisting AF. Furthermore, an independent association of AF onset with CI was demonstrated in relation to the HF diagnosis, after adjusting for demographic, medical and psychological characteristics. Finally, after assessing these five studies together, Myserlis, *et al.*<sup>[33]</sup> in their systematic review and meta-analysis showed that patients with AF had almost two times the risk of developing CI, compared with non-AF patients.

After reviewing the previous studies, it was proved that there is a link between AF and cognition in HF patients. However, since the pathogenetic mechanisms are not fully understood, there have been some suggestions for possible underlying mechanisms. The proposed pathophysiology behind this condition may be either of the following: (1) via silent cardiovascular events associated with the thrombogenic state of HF (such as silent mi-

croemboli, clinical and subclinical stroke);<sup>[40,42,43]</sup> (2) through reduced cerebral blood flow, leading to cerebral hypoperfusion, as examined by Alosco, *et al.*,<sup>[29]</sup> (3) via some neurodegenerative processes not very well understood (such as the proinflammatory state that AF may cause); (4) as a result of adverse effects of some cardiovascular medications, which may cause cerebral microbleeds, associated with the increasing use of OAC medications; and (5) through reduced cardiac output combined with hypotension that ultimately result in cerebral hypoperfusion,<sup>[44]</sup> suggested, also, by Debette, *et al.*<sup>[28]</sup>

Other characteristics, such as age, gender, arterial hypertension, diabetes mellitus, etc., which are well known cardiovascular risk factors, were also taken under consideration in the studies. Coma, *et al.*<sup>[30]</sup> showed that female gender and age are major risk factors for CI in HF patients with AF. They all agree that all the modifiable conditions should be optimally treated in order to prevent further complications. Additionally, when assessing medications used for AF, Pulignano, *et al.*<sup>[31]</sup> showed that prescribed OACs to the patients had no association with CI. However, there are no reliable data on the effect of OACs or other medications in CI in those patients and further evidence is necessary for the establishment of such a suggestion.<sup>[45,46]</sup> Interestingly, ventricular rate response in patients with AF and preexisting CI has been found to increase the risk for developing dementia,<sup>[47]</sup> while altered hemodynamic conditions seem to worsen cognitive function.<sup>[13,48]</sup>

Another very important issue that the studies raised as a concern is the pharmacological compliance of the patients. It is very well understood that non-compliance results in complications leading to CI, while, at the same time, CI itself causes the patients not to be compliant with their medication.<sup>[49]</sup> This may lead to high risk of complication development in these patients, including HF decompensation, stroke, increased fall risk and potential need of operations, etc.

In conclusion, after reviewing the previous studies, it is shown that AF causes a decline in cognitive function in patients with HF. It is very important to raise awareness for clinicians when treating HF patients to early diagnose and treat AF in order to prevent cognitive decline.<sup>[50]</sup> Cognitive assessment



should be considered in all HF patients and especially in those with concomitant AF. Additionally, the clinicians need to individualize the treatment options for each patient, increasing patients' compliance with their prescribed medications. Thus, complications associated with those situations may be avoided, which will ultimately be beneficial to the healthcare systems and the social life of the patients. Finally, further studies should be performed to fully understand the pathogenesis of impaired cognitive function in HF patients with AF and to declare whether other risk factors such as arterial hypertension, diabetes mellitus etc. affect this pathogenetic mechanism, as well.

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