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Connecting the Dots: Heart Failure and Insomnia

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ABSTRACT

Introduction and aim. This study investigates the relationship between heart failure (HF) and insomnia, focusing on this two-way association's clinical significance, epidemiology, and management.

Material and methods. Literature available in November 2023 was searched using Pubmed, Medline, Google Scholar, and Europe PMC with keywords associated with Heart Failure, Insomnia, and related pharmaceuticals. 69 articles were included.

Analysis of the literature. Insomnia is associated with higher mortality and a potential risk of sudden cardiac death, particularly in individuals with HF. Treatment is challenging and side effects can worsen the symptoms of HF. The use of benzodiazepines in HF patients raises concerns about cardiovascular risks, prompting the exploration of other medications like nonbenzodiazepines, antidepressants with sedative effects, and histamine receptor antagonists. On the other hand, HF is also a condition that affects sleep quality. Drugs including ACE-I, beta-blockers, MRA, and SGLT2i are essential for its treatment. Some of them may have an impact on the intensity of insomnia.

Conclusion. Considering the impact of insomnia medications on heart failure outcomes and vice versa is necessary. It is important to consider all aspects when treating these two conditions simultaneously.

Keywords. Cardiovascular Disease; Dyssomnia; Heart Failure; Life Quality; Public Health; Sleep;

Introduction

This study examines the relationship between heart failure (HF) and insomnia, focusing on the clinical significance, epidemiology, and management of this two-way association. Some research reveals the connection between insomnia and HF ¹; however, it is worth noting that this topic still needs to be researched despite the potential interplay between these critical conditions.

A significant dissatisfaction with sleep quantity or quality characterizes insomnia. The occurrence of insomnia in the general population varies from 12% to 20% ². It involves experiencing difficulty in falling asleep and staying asleep, often resulting in frequent awakenings or challenges in returning to sleep after waking up for at least three months ³. Additionally, Insomnia and sleep disorders are related to decreased quality of life (QoL) ⁴ and higher mortality ⁵. Sleep disorders can also be associated with sudden cardiac death, which may be linked to ventricular arrhythmias ⁶, whose prevalence is higher in individuals with both insomnia and HF ^{7,8}. It is established that the occurrence of insomnia is a modifiable risk factor for the development of HF ⁹, which is a complex clinical syndrome that imposes a substantial burden on individuals and leads to a diminished QoL ¹⁰. Also, patients with HF frequently develop symptoms related to decreased sleep quality, which is associated with a shortened period of cardiac events-free survival ¹¹. One of the types of HF is Heart Failure with Reduced Ejection Fraction (HFrEF), which has become a significant public health challenge worldwide. HFrEF has a substantially high prevalence among older adults, especially in more developed countries with improved survival rates for acute heart conditions like myocardial infarction ¹². It is worth noting that these patients also have insomnia more frequently ¹³. Conversely, insomnia can exacerbate HF symptoms, such as fatigue and low energy levels ¹⁴. Due to the interplay between HF and insomnia, it remains uncertain whether

treatments for insomnia will be equally effective in managing comorbid insomnia in individuals with HF.

More than one specific underlying cause contributes to HFrEF development, like ischaemic heart disease, hypertension, valvular and rheumatic heart disease, cardiomyopathies, or congenital heart disease ¹⁵. It has also been proven that insomnia increases the risk for these conditions, including metabolic syndrome ¹⁶, hypertension, and ischaemic heart disease ¹⁷. In multiple preclinical and clinical studies, HF is strongly implicated in the pathogenesis of oxidative stress ^{18,19} and inflammation ²⁰. These factors also play a role in insomnia ^{21,22}. Moreover, the neurohormonal compensatory mechanism in HF is hypothesized to play a role in insomnia pathogenesis ²³⁻²⁶.

Comprehensive treatment for both HF and insomnia is crucial because it can improve symptoms in both conditions simultaneously. Nevertheless, the focus is often put on treating just one disease rather than adopting a holistic approach. However, it is essential to acknowledge that treating one condition may sometimes lead to side effects that exacerbate symptoms of the second disease.

Aim

This narrative review provides a comprehensive view of the relationship between HF and insomnia, focusing on this two-way association's clinical significance, epidemiology, and management.

Material and methods

Databases such as Pubmed, Medline, Google Scholar, and Europe PMC were used for the literature review with the keywords: “Heart Failure”, “Insomnia”, “Dyssomnia”, “Sleep”, “Cardiovascular”, “Benzodiazepines”, “Non-benzodiazepines”, “Sedative antidepressants”, “Histamine receptor antagonists”, “Angiotensin-converting enzyme inhibitor”, “Angiotensin Receptor Blocker”, “Beta-blocker”, “Mineralocorticoid receptor antagonist”, “Sodium-

glucose cotransporter-2 inhibitor". 248 Articles were found from the period of December 1945 until October 2023. Finally, 69 titles that described together association between heart failure and insomnia were selected from May 1985 until October 2023, but mostly from the last five years.

Analysis of the literature

Insomnia

Insomnia is a common issue in HF patients, and they are often prescribed medication to reduce the described symptoms. Regular use of hypnotics is observed in approximately 9.5% to 30% of patients with HF ²⁷. However, cognitive behavioral therapy is the preferred form of treatment for insomnia in adults, and it is a first-line therapy in guidelines ²⁸. In addition, cognitive behavioral therapy alleviates symptoms of insomnia in the group of patients with HF ²⁹. Medications used for the management of insomnia disorder in Poland can be classified into distinct categories based on their mechanisms of action: Benzodiazepine receptor agonists, including benzodiazepines (BZD) and non-benzodiazepines (non-BZD); sedative antidepressants and histamine receptor antagonists ²⁸. There are other drugs approved in the USA or Europe to treat insomnia, such as Ramelteon or Daridorexant. However, these drugs are not available in Poland.

Benzodiazepine receptor agonists

The BZD is linked to a higher overall risk of cardiovascular death and HF hospitalization ^{30,31}. Both insomnia and BZD in the treatment of insomnia have a negative impact on the course of HF - a phenomenon of a dead-end road. The Non-BZD group seems to exhibit fewer side effects and enhance sleep quality in older adults with HF ^{27,32}. These drugs are linked to reduced prevalence of side effects, including less tolerance and dependence and increased overall sleep duration, improved sleep efficiency, and do not raise the occurrence of apnea and hypopnea events compared to BZD ^{27,33}. Additionally, they decrease low saturation levels

without impacting the central respiratory effects ^{27,32}. However, some authors maintain that there remains a risk of adverse respiratory events, dependence, and abuse in patients with HF³³.

In clinical practice, when there is a need for prolonged use of a medication for insomnia, alternatives to BZD and non-BZD are used, including antidepressants with sedative effects and histamine receptor antagonists.

Sedative antidepressants

Trazodone is an antidepressant drug whose ability to enhance sleep is due to inhibiting serotonin 5-HT₂ receptors, which increases the depth of sleep ^{34,35}. Trazodone may occasionally be linked to orthostatic hypotension, QT interval prolongation, and cardiac arrhythmias ³⁶. These effects could be particularly detrimental in patients with HF. Doxepin, a tricyclic antidepressant used for insomnia treatment, is an antagonist of the histamine H₁ and H₂ receptors ³⁷. Despite the absence of evidence indicating a deterioration in ventricular function ^{38,39}, doxepin carries cardiotoxic side effects, manifesting as QTc prolongation, conduction delay, AV junction, and bundle branch blocks, potentially resulting in life-threatening arrhythmias ⁴⁰, which makes the use of doxepin less valuable in HF patients, who have significantly higher prevalence of ventricular arrhythmias ⁴¹.

Mianserin, functioning as a norepinephrine–serotonin modulator, typically reduces systolic and diastolic blood pressure by lowering total vascular resistance. This effect also may lead to orthostatic hypotension and falls ⁴², a frequent phenomenon in HF ⁴³. Mirtazapine is one of the antidepressants which can be used in the treatment of insomnia. Mirtazapine acts as an antagonist to specific adrenergic and serotonin receptors ⁴⁴. Mirtazapine is a medication associated with QT prolongation ⁴⁵. Mirtazapine can also lead to orthostatic hypotension and falls, but more rarely than mianserin ^{38,42,46}. However, literature also shows that mirtazapine

does not affect blood pressure ⁴⁷ but can increase the heart rate ⁴⁶. Recently, it has been regarded as a safe medication for individuals with cardiovascular conditions ⁴⁸.

Histamine receptor antagonists

Diphenhydramine is a first-generation antihistamine primarily used as a mild sleep aid ⁴⁹. In cases of toxicity, diphenhydramine can lead to adverse cardiovascular effects. This may manifest as observable ECG changes, including QRS-complex widening, QT interval prolongation, and T-wave flattening ⁵⁰⁻⁵². This leads to an elevated risk of developing potentially life-threatening arrhythmias, such as torsade de pointes ⁴⁹.

Heart Failure

Regardless of type, a diagnosis of HF significantly reduces both the QoF ⁵³. In contrast to the numerous established therapies for HFrEF, previous attempts at treatment have not shown improvement in outcomes for HFpEF, except for SGLT2i ⁵⁴. Thus, we explore medications that have been demonstrated to be effective in the context of HfrEF and their potential additional impact on insomnia. The treatment of HFrEF is multi-drug based, frequently relying on maximum doses of medications to dampen the neurohormonal response, which, as previously mentioned, can also be a cause of insomnia. Crucial drugs for the therapy of HFrEF include angiotensin-converting enzyme inhibitor (ACE-I) or Angiotensin Receptor Blocker (ARB), Beta-blocker, Mineralocorticoid receptor antagonist (MRA), and Sodium-glucose cotransporter-2 inhibitor (SGLT2i) ⁵⁵. The optimal treatment of HF reduces orthopnea and shortness of breath, which could be beneficial for falling asleep more easily and reducing nocturnal awakenings.

Renin-angiotensin–aldosterone system inhibitors

Reducing excessive sympathetic activity and enhancing parasympathetic activity due to ACE-I implementation has improved sleep quality in rats following a myocardial infarction. ACE-I

can help alleviate sympathetic hyperactivity after a myocardial infarction in a rat heart, improving sleep quality ⁵⁶. Moreover, the use of ACE-I therapy in humans does not show an association with the risk of developing insomnia ⁵⁷. ARBs are frequently prescribed for patients who do not tolerate ACE-I due to cough and edema. The AWAKE-HF study found no differences in sleep activity between patients with HFrEF treated with sacubitril/valsartan and those who received enalapril ⁵⁸. On the other hand, it was observed that patients taking losartan experienced a higher incidence of insomnia in comparison to the control group ^{59,60}. MRA can be associated with fewer nocturnal awakenings and less time in stage 1 sleep ⁵⁹. Nevertheless, most studies concentrate on MRAs concerning obstructive sleep apnea rather than explicitly addressing sleep quality and insomnia ⁶¹.

Beta-blockers

Sleep disruptions are frequent side effects of beta-blockers ⁶². Lipophilic beta-blockers can penetrate the blood-brain barrier and disrupt melatonin secretion ⁶³. Beta-blockers, by inhibiting the beta-1 receptors in the pineal gland and reducing melatonin secretion ^{64,65} can cause nightmares and hallucinations during sleep ⁶⁶. Melatonin administration can prevent these side effects of beta-blockers ⁶². Furthermore, for example, nadolol does not exhibit sleep-disrupting effects because of its low level of lipophilicity and lack of intrinsic sympathomimetic activity ⁶⁷.

Sodium-glucose cotransporter-2 inhibitors

SGLT2i notably reduces HbA1c levels, while no substantial alterations in sleep quality are detected. The investigators did not notice any decline in sleep quality, even as nocturia increased within the study group ⁶⁸. In a different study, empagliflozin had a beneficial impact on the sleep quality of patients with glycogen storage disease type Ib ⁶⁹.

Conclusion

This study highlights the dual relationship between HF and insomnia, emphasizing the need for careful consideration of insomnia medication effects on the heart, especially in HF patients. Particular attention should be paid to the use of BZD in treating insomnia in patients with HF. It appears that antidepressants with sedative effects and histamine receptor antagonists have a better safety profile, especially mirtazapine. When treating HF, particular consideration should be given to lipophilic beta-blockers, as they may penetrate the blood-brain barrier and potentially worsen sleep quality. In the context of sleep, nadolol appears to be a safe beta-blocker. Conflicting literature data exist regarding ACE-I, while other medications used in HF treatment may improve sleep quality or have no evident impact.

Declarations

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Author contributions

Conceptualization: M.K., K.M.; Methodology: A.Ž., M.S.; Formal analysis: M.K., M.M.; Investigation: J.P., G.N.; Writing - rough preparation: M.W., K.G.; Writing - review and editing: M.K., K.M.; Supervision: K.M., M.K.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Not applicable.

Ethics approval

Not applicable.

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