Review

Melatonin and Heart Failure: More Questions Than Answers

Esther Zelenovskiy, OMS-II[1], Thomas Evans, OMS-II[1], Brian W. Skinner, PharmD[1]

[1]Marian University Tom and Julie Wood College of Osteopathic Medicine, Indianapolis, IN

Introduction

Public discussions about medical issues often begin and end with a headline. Headlines are designed to capture attention rather than convey nuance, they often blur vital details and can frame preliminary findings as definitive. Recent media coverage suggesting melatonin may contribute to heart failure illustrates this issue. Major outlets that ran headlines of "Is melatonin bad for your heart? Here's what to know.",[1] "What to know about melatonin use and heart failure",[2] and "Melatonin linked with higher heart failure rate in preliminary study",[3] reached large audiences despite the preliminary data they referenced.

When a topic reaches national news, many readers engage only with the headline, not the underlying data. The phrase "heart failure" has a way of stopping people in their tracks, and the way it is presented can make a tenuous association sound like something firmly established. Clinicians are tasked with deciphering what the evidence supports and what remains unsubstantiated. Despite best efforts, many patients may make decisions based on their limited research before they ever consult their physician. The tendency to react to the headline, rather than understand the components of the study, can create a gap between public perception and clinical evidence. It is within this gap that misinterpretations and preemptive conclusions can begin to form.

Clinicians find themselves addressing both the science and the misconceptions that formed long before research was examined in context. In that light, this review examines the recently reported association between melatonin and heart failure to explore the foundational aspects of the study and determine what questions are answered and what questions remain.

At the 2025 American Heart Association (AHA) Scientific Sessions in November, a poster was presented with a non-peer-reviewed abstract linking melatonin use to heart failure. Conference abstracts are not peer-reviewed and frequently change before final publication, so their findings should be interpreted with caution until published in a peer-reviewed journal. The abstract concluded that, after an analysis of more than 130,000 adults with chronic insomnia, long-term melatonin users were approximately 90% more likely to develop heart failure over a 5-year period compared with matched non-users. In a secondary analysis, the abstract highlighted that melatonin users were also 3.5 times more likely to be hospitalized for heart failure than non-users.[4,5] Given melatonin's popularity and heart failure mortality, the abstract was widely disseminated via different news outlets.

CLINICAL ANALYSIS

Difference Between Causation and Association

To better understand the implications of these findings, it is important to examine how the study was conducted and what limitations may

influence its interpretation. When analyzing the results of research, causation and association have vastly different meanings. Causation means that A causes B, like the way smoking causes lung cancer. Association implies that A and B happen together, though it is not clear if the two have a causal relationship. For example, in the summer months, the incidence of sunburn and ice cream sales rises. Neither causes the other, but a confounding variable, sunshine and warm weather, causes both. While some associations are spurious or coincidental, others represent a genuine underlying relationship. Given that this is a retrospective cohort study, it can identify potential associations but cannot establish causation, and it is particularly vulnerable to confounding variables and reverse causation.

Strengths of the Study and What it Adds

Despite the questions that may arise from this abstract, the study should not be disregarded completely. This study raises an important hypothesis that warrants testing through prospective, controlled research to potentially find a causal link between melatonin use and heart failure. Given the widespread use of melatonin, any observed clinical association should be recognized, investigated, and communicated properly. The current findings of this study emphasize the need for additional caution when determining if there is a need for additional supplementation and if the benefits outweigh perceived risks.[4,5]

The large sample size of (n=130,828 adults) and 5-year follow-up period provide sufficient statistical power to detect associations. Additionally, multiple distinct endpoints for analysis were used throughout the study, including incident heart failure, heart failure–related hospitalization, and all-cause mortality, each analyzed as a separate clinical outcome over the follow-up period. This approach provides clinically meaningful evidence by allowing the investigators to evaluate whether the observed association between melatonin use and heart failure was consistent across several related but distinct outcomes, rather than relying on a single endpoint alone.[4,5] Although there may be more questions raised than answers provided, credit should be given to the work and foundation this abstract has laid for further research.

Confounding Variables and Reverse Causation

Several factors should be considered when exploring these results. One of the early symptoms of heart failure is orthopnea, in which patients experience shortness of breath while lying down.[6] As a result, patients with poor sleep due to orthopnea but still undiagnosed heart failure may turn to melatonin as a sleep aid. This represents a classic example of reverse causation, in which early manifestations of heart failure precipitate the use of melatonin. Shortly thereafter, patients could be diagnosed with heart failure, complicating the association between heart failure and melatonin use. Given this possible association, the results of the study are modest, only demonstrating a 1.9% increase in absolute risk of heart failure.[4,5]

Beyond reverse causation, to establish that melatonin is associated with heart failure, the study would need to rule out confounding variables. For example, insomnia, anxiety and depression, poor lifestyle habits, and obstructive sleep apnea can all lead to heart failure. Each of these variables is also associated with poor sleep, perhaps driving melatonin use. A study published in the European Heart Journal reports that an increase in the number of insomnia symptoms increased the hazard risk for heart failure for a demographic-matched cohort (n=12,761). While the study did not track melatonin use and its implications in heart failure, it did show that insomnia is independently associated with heart failure.[7] Consistent with this, a 2025 retrospective cohort study that identified patients who had sleep disorders prior to a heart failure diagnosis showed patients with insomnia, sleep apnea, any unspecified sleep disorder, or sleep disorders overall had a statistically significant increased risk of developing heart failure.[8] Sleep disordered breathing (SDB) is the most common

comorbidity of heart failure, but often remains untreated.

In this context, individuals with SDB may take melatonin to assist with sleep. These patients would be classified into the melatonin-taking cohort and be at higher risk for heart failure because of their SDB, not their melatonin use. The prevalence of SDB is especially high in overweight males and postmenopausal women, demographics also at higher risk for heart failure.[9,10] If these high-risk demographics were overrepresented in the melatonin cohort, the observed association would be substantially biased.

From a methodological standpoint, the methodology outlined in the abstract does not mention the cardiovascular risk factors the groups had and does not provide specifics on how each incidence of heart failure was determined. Without this, the study lacks a specific mechanism for matching control and experimental groups, all while ignoring the confounding variables of anxiety, depression, obesity, insomnia, unhealthy behavior, and stress on heart failure. The study also fails to address several other considerations, including whether the dose of melatonin had any impact on heart failure development. Moreover, the study identified melatonin users based on the presence of a prescription,[4,5] which is required in other countries such as the United Kingdom, it is possible that patients in the United States may have been classified into the non-melatonin-using group, regardless of their possible over-the-counter (OTC) melatonin use.

Due to OTC availability and classification as a supplement, melatonin can vary widely in purity and dosing, further confounding the results. Another important cardiovascular-specific confounder is the underlying etiology of heart failure itself. Ischemic cardiomyopathy (ICM) is strongly associated with lifestyle factors like dyslipidemia and diabetes, leading to ICM patients having a higher all-cause mortality rate and worse prognosis.[11] If the melatonin group had a higher burden of pre-existing diseases, which drove melatonin use, the underlying coronary artery disease (CAD) or heart attack induced heart failure, not melatonin. Properly comparing control and experimental groups for severity and control of chronic disease is exceedingly difficult, blurring the connection between heart failure and melatonin even more.

Biological Plausibility

Establishing biological plausibility is essential to evaluating proposed causal relationships, as it would be beneficial to derive a pathophysiological mechanism of how melatonin exerts its heart failure effects. Previous studies, however, have shown melatonin to be an antioxidant and potentially cardioprotective. Consider a longitudinal, double-blind, randomized, placebo-controlled trial of heart failure patients who take nightly melatonin (n=42) or a placebo (n=43). Nightly melatonin users enjoyed a significantly better quality of life, clinical outcome, and New York Heart Association (NYHA) class, validated by the Minnesota Living with Heart Failure Questionnaire and the Pittsburgh Sleep Quality Index.

Patients also demonstrated lower brain natriuretic peptide (BNP) levels (p=0.044) despite no reported improvement in sleep, indicating that melatonin may be intrinsically beneficial to heart failure patients.[12] The self-reporting approach to sleep limits the validity of the trial because patients may have experienced physiologically beneficial sleep that went unnoticed on their self-reporting questionnaire. Additionally, improvement in N-terminal pro-BNP analysis and NYHA class does not mean that melatonin is cardioprotective.

The cardioprotective effects of melatonin have been explored in meta-analyses and contradict the premise that melatonin would induce heart failure. Patients in a meta-analysis of randomized controlled trial studies displayed statistically significant higher left ventricular ejection fractions and lower troponin levels when treated with melatonin after cardiac reperfusion. Researchers suggest that its antioxidant properties create the cardioprotective effect.[13] Our searches found no studies that suggested a cardiotoxic effect.

The study refers to heart failure homogenously, failing to illuminate the differences in kinds of heart failure. Non-ischemic Cardiomyopathy (NICM) and ischemic cardiomyopathy (ICM) are two different forms of heart failure, each with

its own separate pathophysiology and etiologies. ICM refers to heart failure due to a lack of blood flow, often from myocardial infarction or coronary artery disease (CAD).[14] NICM is an impairment of the heart muscle itself, due to causes like myocarditis, autoimmune disease, genetic defects, or chronic hypertension.[15] Suppose the heart failure group was comprised predominantly of patients with ICM. In that case, the observed association may reflect underlying ischemic disease rather than a direct relationship with melatonin use.

ICD Coding

The International Classification of Diseases (ICD-10) is an organizational method used by healthcare professionals to assign known health condition with a specific code.[16] Many researchers use these codes to broadly identify diseases. In this study, the authors used ICD-10 code I50 to identify heart failure, and this code encompasses many kinds of heart failure because it is a diverse condition with many causes and presentations. For example, ICD-10 I50.0 refers to congestive heart failure, I50.9 refers to unspecified heart failure, I50.2 refers to systolic heart failure, and I50.3 refers to diastolic heart failure.[17] One cause of heart failure may be due to impaired systolic function, and another may be due to impaired diastolic function, yet both would be documented under the same ICD-10 I50 code based on the description of the methods. The underlying pathophysiology of these diagnoses is fundamentally different, which complicates the identification of a biologically plausible mechanism capable of producing competing effects. Consequently, this demonstrates how ICD codes are often insufficient to create a semantically reliable cohort or phenotype.

Conclusion

Although the current study is limited by confounding variables, reverse causation, misclassification, and its biological plausibility, it is already being interpreted by the public as clinically meaningful. We applaud the authors for their tempered language in presenting these findings, as they explicitly acknowledge that the results demonstrate an association rather than causation and appropriately underscore the need for additional trials to further explore this relationship. Further research on this association should include randomized, controlled trials, prospective cohort studies, increased clarification about the subtypes of heart failure, and a plausible biological mechanism of effect. Unfortunately, headlines often move faster than the science behind them, shaping people's assumptions long before clinicians can clarify what the data supports. The recent attention around melatonin and heart failure is a telling example. As clinicians, we have a responsibility to review and implement new research carefully. Further, we must help patients interpret these results and approach these discussions with shared decision-making in mind. Helping patients understand the difference between what is known and hypothesized is crucial in demonstrating that our medical decisions are based on evidence and not headlines.

References

1. Hopkins C. New York Times. 2025.
2. Rogers K. CNN. 2025.
3. Ziegler M. Fox News. 2025.
4. American Heart Association.
5. Nnadi E, et al. Circulation. 2025;152(suppl 3):Abstract 4371606.
6. Jurgens CY, et al. Res Nurs Health. 2009;32(5):551-560.
7. Mahmood A, et al. Eur Heart J. 2021;42(40):4169-4176.
8. Sedighi J, et al. Int J Cardiol Heart Vasc. 2025;57:101618.
9. Gueye-Ndiaye S, et al. Clin Chest Med. 2023;44(3):585-603.
10. Division of Sleep Medicine at Harvard Medical School.
11. Juricic S, et al. Int J Mol Sci. 2025;26(9):3924.
12. Hoseini SG, et al. Clin Cardiol. 2022;45(4):417-426.
13. Domínguez-Rodríguez A, et al. Front Cardiovasc Med. 2021;8:635083.
14. Pastena P, et al. Heart Fail Rev. 2024;29(1):287-299.
15. Heymans S, et al. Lancet. 2023;402(10406):998-1011.
16. Outland B, et al. Ann Intern Med. 2015;163(7):554-556.
17. Centers for Medicare & Medicaid Services.