BACHURSKA, Dominika, MAREK, Jakub, GRYGORCZUK, Oliwia and CZACH, Zuzanna. The Treatment of Depression in Patients with Heart Failure. Journal of Education, Health and Sport. 2024;66:50064. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.66.003
https://apcz.umk.pl/JEHS/article/view/50064
https://zenodo.org/records/10993547

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 17.03.2024. Revised: 10.04.2024. Accepted: 15.04.2024. Published: 18.04.2024.

The Treatment of Depression in Patients with Heart Failure

BACHURSKA Dominika[1]*, MAREK Jakub[2], GRYGORCZUK Oliwia[3], CZACH Zuzanna[4]

1. Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
2. 2nd Department of Clinical Radiology, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
3. Faculty of Medicine, Medical University of Lodz, al. Tadeusza Kościuszki 4, 90-419 Łódź, Poland
4. Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

*Correspondence: dominika.bachurska@gmail.com

Abstract

This narrative review critically examines the utilization of Selective Serotonin Reuptake Inhibitors (SSRIs) in managing coexisting depression and heart failure (HF), integrating findings from various studies, clinical trials, and observational data. SSRIs, pivotal in treating mood and anxiety disorders by elevating synaptic serotonin levels, have been observed to potentially impact cardiovascular health. Specifically, SSRIs like sertraline show promise in enhancing endothelial function and exerting anti-inflammatory effects, which are beneficial in conditions like HF with preserved ejection fraction (HFpEF). Furthermore, SSRIs

demonstrate favorable outcomes in reducing platelet aggregation and modulating the renin-angiotensin-aldosterone

system (RAAS), suggesting a multifaceted role in HF management. However, their safety profile, particularly concerning bleeding risks, QTc prolongation, and drug interactions, necessitates careful consideration. Despite theoretical and molecular evidence supporting SSRIs' beneficial effects in HF, clinical data remain inconclusive, highlighting the need for further research. This review aims to provide a comprehensive understanding of SSRIs' effectiveness, safety, and potential benefits in treating depression and HF, offering insights for evidence-based decision-making and future research directions.

Keywords: Selective Serotonin Reuptake Inhibitors; Heart Failure; Depression; Endothelial Dysfunction; Drug Interactions

Introduction

Selective Serotonin Reuptake Inhibitors (SSRIs) represent a prominent class of pharmacological agents widely utilized in the field of psychiatry for the management of various mood and anxiety disorders [1]. These agents work by selectively inhibiting serotonin reuptake, a neurotransmitter pivotal in the regulation of mood, emotions, and cognitive functions. By impeding the serotonin transporter, SSRIs elevate synaptic serotonin levels, thereby augmenting signaling and potentially alleviating symptoms associated with mood disorders [2].

As the primary intervention for Major Depressive Disorder (MDD), SSRIs heighten serotonin levels in the brain, thus reducing persistent sadness and associated symptoms. What is more, SSRIs play a crucial role in addressing other various disorders, including Generalized Anxiety Disorder, Obsessive-Compulsive Disorder, Panic Disorder, Social Anxiety Disorder, Post-Traumatic Stress Disorder, and Premenstrual Dysphoric Disorder [3].

The frequency of depression in individuals with heart failure (HF) occurs on average in 20-40% of cases. Its prevalence is higher in individuals experiencing more prominent symptoms of HF [4]. HF initiates changes in the cardiovascular system, leading to reduced cardiac output and compromised blood flow [5]. This, in turn, affects the brain, which heavily relies on adequate blood supply. The diminished perfusion can impact neurotransmitter

function, including serotonin, a pivotal factor in mood regulation. Additionally, the release of inflammatory markers in HF may contribute to neurophysiological changes associated with depression [6]. The enduring nature of HF places a significant chronic illness burden on individuals. The ongoing challenges of HF and the potential for exacerbations can lead to feelings of hopelessness and helplessness, which are key signs of depression. Symptoms linked to HF, such as fatigue, dyspnea, and reduced exercise tolerance, can profoundly disrupt daily life. Engaging in previously enjoyed activities becomes challenging, diminishing the overall quality of life. Moreover, certain medications commonly prescribed for HF may cause mood-altering side effects [7]. For instance, beta-blockers and specific diuretics may contribute to fatigue and lethargy, symptoms aligning with depression [8].

Many of these patients, who suffer concurrently from both depression and HF, take the previously mentioned SSRIs. It has been proven that they are effective in treating depression, but their impact is not neutral on HF.

Aim

This narrative review aims to critically assess and synthesize existing literature to comprehensively explore the utilization of SSRIs in individuals with coexisting depression and HF. Through an in-depth analysis of relevant studies, clinical trials, and observational data, this review aims to provide a nuanced understanding of the effectiveness, safety, and potential benefits of SSRIs in managing both depressive symptoms and HF. The resulting synthesis of evidence is anticipated to provide valuable insights for clinicians, researchers, and healthcare providers, informing evidence-based decision-making and guiding future research endeavors in the holistic management of depression and HF.

Material and methods

Databases such as Pubmed, Medline, Google Scholar, and Europe PMC were used for the literature review with the keywords: Selective Serotonin Reuptake Inhibitors; Antidepressants; Depression; Heart Failure; Endothelial Dysfunction; Major Depressive Disorder; Inflammation; Oxidative Stress; Nitrosative Stress; Endothelial Function; Remodeling; Renin–angiotensin–aldosterone System; Cardiovascular Risk

Forty-six articles considered for inclusion were those published between 2000 and 2023, ensuring relevance to contemporary understanding and practices. Studies with weak-quality research, outdated information, or those not directly related to the topic were excluded.

The Impact on Endothelial Function

Endothelial dysfunction, triggered by oxidative stress, plays a notable role in the progression of HF. Changes in endothelial function and the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) pathway contribute to the pathophysiology of heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF)[9].

SSRIs, especially sertraline, can enhance endothelial function, as evidenced by changes in selected biomarkers related to endothelial dysfunction and inflammatory status such as flow-mediated dilation [10]. Alterations in FMD over the short term may result in long-term enhancement of endothelial function, providing a protective effect against atherosclerosis (Thijssen et al., 2019) [11].

Furthermore, it was found that sertraline promotes endothelial stabilization [12]. Consequently, sertraline could be particularly advantageous for individuals diagnosed with HFpEF, where endothelial dysfunction plays pivotal roles in the pathophysiological processes leading to the progression of HF [13]. In another study, it was observed that sertraline shows a noticeable vasodilatory effect [14].

Additionally, after 16 weeks of sertraline administration, a reduction in the activation of both the endothelium and blood platelets was noted. This was confirmed by a decrease in the levels of markers such as PECAM-1 (a marker of blood platelet activation) and VCAM-1 (a marker of endothelial activation) [12].

The Impact on Inflammation

The role of inflammation in individuals with HF has been scrutinized in numerous clinical trials exposing that it inevitably leads to myocardial damage [PMID: 22223210]. Inflammatory agents contribute to the worsening and progression of HF. It appears that antidepressant medications, such as selective serotonin reuptake inhibitors (SSRI) when administered to patients with HF and depression, result in a reduction of inflammatory cytokines such as TNF-α and CRP [15].

Interestingly, it was observed that patients treated with Serotonin and norepinephrine reuptake inhibitors (SNRI) or Tricyclic antidepressants (TCA) presented lower levels of these cytokines than those treated with SSRI [16].

Another study shows that the use of sertraline in patients with HFpEF appears promising due to its anti-inflammatory properties, including the reduction and regulation of pro-inflammatory cytokine levels [17,18]. Several other observations also have been gathered, indicating a potent anti-inflammatory impact of sertraline [19]. This impact manifests through the reduction of CRP and IL-6 [20].

The Impact on Nitrosative/oxidative stress

It was found that in the population of individuals with HFpEF, nitrosative/oxidative stress is significantly intensified compared to healthy individuals and HFrEF [21]. Serotonin has been linked to the reduction of lipid peroxide generation and improved antioxidant status [22]. There is a significant increase in superoxide dismutase (SOD) activity in patients with major depression as compared to healthy subjects, and this trend can be reversed by SSRI treatment [23].

The Impact on Remodeling

One of the primary issues in HF is adverse cardiac remodeling, which worsens cardiac muscle function, leading to clinical manifestations [24]. Numerous studies are underway to develop pharmacological therapy aimed solely at preventing potential adverse remodeling of the left ventricle in individuals after a myocardial infarction (MI). Data indicates that G protein-coupled receptor (GPCR) kinase 2 (GRK2), which is up-regulated in individuals with HF, is pivotal in HF progression by fostering dysfunctional adrenergic signaling and myocyte death [25]. Furthermore, paroxetine inhibits GRK2 and thus improves cardiac function after MI, preventing or potentially reversing cardiac damage in a mouse model. In comparison to the ongoing decline in function observed in the control and fluoxetine groups, paroxetine exhibited substantial improvement in left ventricular function [26]. In another study by Fratucci de Gobbi et al., augmentation of central serotonin neurotransmission by paroxetine had a beneficial effect on cardiovascular remodeling caused by volume overload. However, the mechanisms underlying this effect are unknown [27].

These findings reveal the potential of paroxetine to serve as an additional treatment for HF.

The Impact on Antiplatelet Protection

SSRIs have demonstrated favorable effects on platelet activity, particularly in individuals with HF concurrently utilizing aspirin [27]. Serotonin plays a significant role in the process of

platelet aggregation, which is crucial in both hemostasis and thrombosis. Through the inhibition of serotonin reuptake, SSRIs reduce the availability of serotonin for platelet binding, hence leading to a reduction in platelet aggregation [28]. Therefore antiplatelet therapy is essential in diminishing the risk of MI, which is a leading factor contributing to the development of HFrEF.

Further study is needed to identify patients at higher risk of bleeding and those who stand to benefit from antithrombotic effects through the administration of SSRIs [28,29].

The Impact on RAAS

The compensatory activation of neurohormones, including the sympathetic nervous system (SNS), the renin–angiotensin–aldosterone system (RAAS), and the release of inflammatory mediators, induces cardiac remodeling and increases arterial stiffness peripherally [30]. These factors contribute to the progression of HF.

Several studies have indicated potential interactions between SSRIs and the RAAS, suggesting that SSRIs might have modulatory effects on components of the RAAS [31]. It has been documented that citalopram and sertraline elevate the levels of both renin and aldosterone [32].

Further investigation is required to establish the potential interactions between SSRIs and the RAAS.

Clinical implications

The severity of depression symptoms has been associated with a higher risk of mortality [33]. Depressive symptoms negatively impact the quality of life (QoL) and significantly worsen the prognosis for patients with HF [34]. Additionally in individuals with HF, depression has been linked to higher short-term and long-term morbidity, as well as poorer outcomes in terms of health-related quality of life and healthcare expenditure [35].

The use of SSRI in individuals with depression following acute coronary syndrome (ACS), a major cause of HF, was linked to a 44% decrease in the relative risk of experiencing subsequent MI [36]. Furthermore, a retrospective analysis involving patients with ACS receiving SSRI treatment demonstrated a notable decrease in recurrent MI, HF, and asymptomatic enzyme elevation [4].

Additionally, studies have shown that individuals after MI with treated depression experienced a 1-year mortality rate comparable to those observed in individuals without

depression. In contrast, those with untreated depression faced a 70% to 90% elevated risk compared to individuals without depression or those with treated depression [37].

The impact of SSRI on depressive symptom severity, Health-Related Quality of Life, and morbidity/mortality was analyzed in a systematic review by Hedrick et al. - while escitalopram showed no significant impact on quality of life, paroxetine demonstrated notable improvements. The use of fluoxetine revealed potential benefits in mortality among patients achieving remission of depressive symptoms [38].

The association between the use of antidepressants and cardiovascular mortality in HF patients is a subject of ongoing discourse. According to a systematic review and meta-analysis by He et al., the use of SSRIs, TCAs, and SNRIs, irrespective of the presence of depression, is associated with a higher risk of all-cause mortality, though not specifically cardiovascular mortality [39].

A clinical study shows that among individuals with HFrEF and depression, an 18-month course of escitalopram treatment when compared to a placebo, did not result in a significant decrease in overall mortality or hospitalization. Additionally, no significant improvement in depression was noted [40].

On the other hand, a study by Lepola et al. shows that escitalopram is beneficial for depression. Escitalopram exhibited a statistically significant therapeutic advantage of 2.9 points, indicating its consistent effectiveness as an antidepressant and its excellent tolerability in primary care patients with MDD [41].

The Safety of SSRI

In terms of safety, SSRIs demonstrate a limited incidence of adverse cardiac side effects. They induce slight elevations in norepinephrine levels and exhibit minimal binding affinity for adrenergic receptors, reducing the risk of orthostatic hypotension or tachycardia [42].

As outlined in the review article by Chittaranjan et al, SSRIs decreased heart rate and systolic blood pressure within particular patient subgroups. Additionally, attenuates the cardiovascular stress response, boosting the ejection fraction and enhancing various cardiovascular indicators in heart failure, all without causing adverse effects on electrocardiographic parameters [43]. The clinical evidence suggests that, in general, SSRIs are safe in patients with ischemic heart disease and may exert a cardioprotective effect. The clinical data is less clear in patients with HF, and the evidence for the benefits of SSRIs remains weak.

Nonetheless, SSRIs can contribute to some notable side effects in patients with heart failure and other cardiovascular conditions. Firstly, by inhibiting platelet aggregation/activation and increasing gastric acid secretion, SSRIs can elevate the risk of bleeding, especially in patients taking antiplatelet or anticoagulant medications [12,44]. Additionally, SSRIs may lead to QTc prolongation, elevating the risk of life-threatening ventricular arrhythmias [45], which can lead to sudden cardiac death [46]. However, this risk is notably lower in comparison to other antidepressants [45]. Ultimately, particular SSRIs may induce alterations in cardiovascular and antidepressant medication levels by interacting with other cardiovascular agents (such as warfarin, and antiarrhythmics) potentially resulting in side effects [35]. Among the group of SSRIs escitalopram, citalopram, and sertraline demonstrated a reduced likelihood of interactions, whereas fluoxetine, fluvoxamine, and paroxetine were associated with greater risk [35].

Conclusions

SSRIs exhibit significant potential in managing mood disorders and may offer additional benefits in addressing HF symptoms. While SSRIs show promise in enhancing endothelial function, reducing inflammation, and mitigating oxidative stress in HF, clinical data remain inconclusive regarding the positive impact of this treatment.

Declarations

Funding: This Research received no external funding.

Author contributions:

Conceptualization, Methodology, Formal analysis, Investigation, Writing: [DB]

Conflicts of interest: The authors declare no conflict of interest.

Data availability: Not applicable.

Ethics approval: Not applicable.

References

1. Vaswani M, Linda FK, Ramesh S. Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. *Prog Neuropsychopharmacol Biol Psychiatry*. Feb 2003;27(1):85-102. doi:10.1016/s0278-5846(02)00338-x

2. Harmer CJ, Cowen PJ. 'It's the way that you look at it'--a cognitive neuropsychological account of SSRI action in depression. *Philos Trans R Soc Lond B Biol Sci*. 2013;368(1615):20120407. doi:10.1098/rstb.2012.0407

3. Hamon M, Blier P. Monoamine neurocircuitry in depression and strategies for new treatments. *Prog Neuropsychopharmacol Biol Psychiatry*. Aug 1 2013;45:54-63. doi:10.1016/j.pnpbp.2013.04.009

4. Angermann CE, Gelbrich G, Stork S, et al. Rationale and design of a randomised, controlled, multicenter trial investigating the effects of selective serotonin re-uptake inhibition on morbidity, mortality and mood in depressed heart failure patients (MOOD-HF). *Eur J Heart Fail*. Dec 2007;9(12):1212-22. doi:10.1016/j.ejheart.2007.10.005

5. Strait JB, Lakatta EG. Aging-associated cardiovascular changes and their relationship to heart failure. *Heart Fail Clin*. Jan 2012;8(1):143-64. doi:10.1016/j.hfc.2011.08.011

6. Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. *Neurosci Biobehav Rev*. Dec 2002;26(8):941-62. doi:10.1016/s0149-7634(03)00003-4

7. Casagrande Tango R. Psychiatric side effects of medications prescribed in internal medicine. *Dialogues Clin Neurosci*. Jun 2003;5(2):155-65. doi:10.31887/DCNS.2003.5.2/rcasagrandetango

8. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. Oct 15 2013;128(16):1810-52. doi:10.1161/CIR.0b013e31829e8807

9. Zuchi C, Tritto I, Carluccio E, Mattei C, Cattadori G, Ambrosio G. Role of endothelial dysfunction in heart failure. *Heart Fail Rev*. Jan 2020;25(1):21-30. doi:10.1007/s10741-019-09881-3

10. Delialis D, Mavraganis G, Dimoula A, et al. A systematic review and meta-analysis on the effect of selective serotonin reuptake inhibitors on endothelial function. *J Affect Disord*. Nov 1 2022;316:71-75. doi:10.1016/j.jad.2022.08.007

11. Thijssen DHJ, Bruno RM, van Mil A, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. *Eur Heart J*. Aug 7 2019;40(30):2534-2547. doi:10.1093/eurheartj/ehz350

12. Serebruany VL, Glassman AH, Malinin AI, et al. Platelet/endothelial biomarkers in depressed patients treated with the selective serotonin reuptake inhibitor sertraline after acute coronary events: the Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy. *Circulation*. Aug 26 2003;108(8):939-44. doi:10.1161/01.CIR.0000085163.21752.0A

13. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. Jul 23 2013;62(4):263-71. doi:10.1016/j.jacc.2013.02.092

14. van Melle JP, Buikema H, van den Berg MP, et al. Sertraline causes strong coronary vasodilation: possible relevance for cardioprotection by selective serotonin reuptake inhibitors. *Cardiovasc Drugs Ther*. Nov 2004;18(6):441-7. doi:10.1007/s10557-004-6221-3

15. Marchant DJ, Boyd JH, Lin DC, Granville DJ, Garmaroudi FS, McManus BM. Inflammation in myocardial diseases. *Circ Res*. Jan 6 2012;110(1):126-44. doi:10.1161/CIRCRESAHA.111.243170

16. Oikonomou E, Tousoulis D, Siasos G, Zaromitidou M, Papavassiliou AG, Stefanadis C. The role of inflammation in heart failure: new therapeutic approaches. *Hellenic J Cardiol*. Jan-Feb 2011;52(1):30-40.

17. Tynan RJ, Weidenhofer J, Hinwood M, Cairns MJ, Day TA, Walker FR. A comparative examination of the anti-inflammatory effects of SSRI and SNRI antidepressants on LPS stimulated microglia. *Brain Behav Immun*. Mar 2012;26(3):469-79. doi:10.1016/j.bbi.2011.12.011

18. Lu Y, Xu X, Jiang T, et al. Sertraline ameliorates inflammation in CUMS mice and inhibits TNF-alpha-induced inflammation in microglia cells. *Int Immunopharmacol*. Feb 2019;67:119-128. doi:10.1016/j.intimp.2018.12.011

19. Taler M, Gil-Ad I, Korob I, Weizman A. The immunomodulatory effect of the antidepressant sertraline in an experimental autoimmune encephalomyelitis mouse model of multiple sclerosis. *Neuroimmunomodulation*. 2011;18(2):117-22. doi:10.1159/000321634

20. Tavakoli Ardakani M, Mehrpooya M, Mehdizadeh M, Beiraghi N, Hajifathali A, Kazemi MH. Sertraline treatment decreased the serum levels of interleukin-6 and high-sensitivity C-reactive protein in hematopoietic stem cell transplantation patients with depression; a randomized double-blind, placebo-controlled clinical trial. *Bone Marrow Transplant*. Apr 2020;55(4):830-832. doi:10.1038/s41409-019-0623-0

21. Momot K, Krauz K, Czarzasta K, Zarebinski M, Puchalska L, Wojciechowska M. Evaluation of Nitrosative/Oxidative Stress and Inflammation in Heart Failure with Preserved and Reduced Ejection Fraction. *Int J Mol Sci*. Nov 3 2023;24(21)doi:10.3390/ijms242115944

22. Munoz-Castaneda JR, Montilla P, Padillo FJ, et al. Role of serotonin in cerebral oxidative stress in rats. *Acta Neurobiol Exp (Wars)*. 2006;66(1):1-6. doi:10.55782/ane-2006-1581

23. Khanzode SD, Dakhale GN, Khanzode SS, Saoji A, Palasodkar R. Oxidative damage and major depression: the potential antioxidant action of selective serotonin re-uptake inhibitors. *Redox Rep*. 2003;8(6):365-70. doi:10.1179/135100003225003393

24. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol*. Mar 1 2000;35(3):569-82. doi:10.1016/s0735-1097(99)00630-0

25. Hullmann J, Traynham CJ, Coleman RC, Koch WJ. The expanding GRK interactome: Implications in cardiovascular disease and potential for therapeutic development. *Pharmacol Res*. Aug 2016;110:52-64. doi:10.1016/j.phrs.2016.05.008

26. Schumacher SM, Gao E, Zhu W, et al. Paroxetine-mediated GRK2 inhibition reverses cardiac dysfunction and remodeling after myocardial infarction. *Sci Transl Med*. Mar 4 2015;7(277):277ra31. doi:10.1126/scitranslmed.aaa0154

27. De Gobbi JI, Omoto AC, Siqueira TF, Matsubara LS, Roscani MG, Matsubara BB. Antidepressant treatment decreases daily salt intake and prevents heart dysfunction following subchronic aortic regurgitation in rats. *Physiol Behav*. May 15 2015;144:124-8. doi:10.1016/j.physbeh.2015.02.037

28. de Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: mechanisms, clinical outcomes and implications for use in elderly patients. *Drugs Aging*. May 1 2011;28(5):345-67. doi:10.2165/11589340-000000000-00000

29. Maurer-Spurej E, Pittendreigh C, Solomons K. The influence of selective serotonin reuptake inhibitors on human platelet serotonin. *Thromb Haemost*. Jan 2004;91(1):119-28. doi:10.1160/TH03-05-0330

30. Grosman-Rimon L, Billia F, Wright E, et al. Neurohormones, inflammatory mediators, and cardiovascular injury in the setting of heart failure. *Heart Fail Rev*. Sep 2020;25(5):685-701. doi:10.1007/s10741-019-09860-8

31. Vian J, Pereira C, Chavarria V, et al. The renin-angiotensin system: a possible new target for depression. *BMC Med*. Aug 1 2017;15(1):144. doi:10.1186/s12916-017-0916-3

32. Murck H, Schussler P, Steiger A. Renin-angiotensin-aldosterone system: the forgotten stress hormone system: relationship to depression and sleep. *Pharmacopsychiatry*. May 2012;45(3):83-95. doi:10.1055/s-0031-1291346

33. Jiang W, Kuchibhatla M, Cuffe MS, et al. Prognostic value of anxiety and depression in patients with chronic heart failure. *Circulation*. Nov 30 2004;110(22):3452-6. doi:10.1161/01.CIR.0000148138.25157.F9

34. Drohomirecka A, Jankowska EA, Banasiak W, Ponikowski P. [Depression in patients with chronic heart failure]. *Kardiol Pol*. Dec 2008;66(12):1325-32. Depresja u chorych z niewydolnoscia serca.

35. Celano CM, Villegas AC, Albanese AM, Gaggin HK, Huffman JC. Depression and Anxiety in Heart Failure: A Review. *Harv Rev Psychiatry*. Jul/Aug 2018;26(4):175-184. doi:10.1097/HRP.0000000000000162

36. Fernandes N, Prada L, Rosa MM, et al. The impact of SSRIs on mortality and cardiovascular events in patients with coronary artery disease and depression: systematic review and meta-analysis. *Clin Res Cardiol*. Feb 2021;110(2):183-193. doi:10.1007/s00392-020-01697-8

37. Smolderen KG, Buchanan DM, Gosch K, et al. Depression Treatment and 1-Year Mortality After Acute Myocardial Infarction: Insights From the TRIUMPH Registry (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status). *Circulation*. May 2 2017;135(18):1681-1689. doi:10.1161/CIRCULATIONAHA.116.025140

38. Hedrick R, Korouri S, Tadros E, et al. The impact of antidepressants on depressive symptom severity, quality of life, morbidity, and mortality in heart failure: a systematic review. *Drugs Context*. 2020;9doi:10.7573/dic.2020-5-4

39. He W, Zhou Y, Ma J, Wei B, Fu Y. Effect of antidepressants on death in patients with heart failure: a systematic review and meta-analysis. *Heart Fail Rev*. Nov 2020;25(6):919-926. doi:10.1007/s10741-019-09850-w

40. Angermann CE, Gelbrich G, Stork S, et al. Effect of Escitalopram on All-Cause Mortality and Hospitalization in Patients With Heart Failure and Depression: The MOOD-HF Randomized Clinical Trial. *JAMA*. Jun 28 2016;315(24):2683-93. doi:10.1001/jama.2016.7635

41. Lepola UM, Loft H, Reines EH. Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol*. Jul 2003;18(4):211-7. doi:10.1097/00004850-200307000-00003

42. Alvarez W, Jr., Pickworth KK. Safety of antidepressant drugs in the patient with cardiac disease: a review of the literature. *Pharmacotherapy*. Jun 2003;23(6):754-71. doi:10.1592/phco.23.6.754.32185

43. Andrade C, Kumar CB, Surya S. Cardiovascular mechanisms of SSRI drugs and their benefits and risks in ischemic heart disease and heart failure. *Int Clin Psychopharmacol*. May 2013;28(3):145-55. doi:10.1097/YIC.0b013e32835d735d

44. Serebruany VL. Selective serotonin reuptake inhibitors and increased bleeding risk: are we missing something? *Am J Med*. Feb 2006;119(2):113-6. doi:10.1016/j.amjmed.2005.03.044

45. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry*. May 2014;75(5):e441-9. doi:10.4088/JCP.13r08672

46. Sulej L, Momot K, Zarębiński M, Wojciechowska M. Reperfusion arrhythmias – Underestimated cause of sudden cardiac death? *Medical Hypotheses*. 2023;174. doi:10.1016/j.mehy.2023.111060