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An Insidious Comorbidity: Depression and Chronic Heart Failure

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Abstract: *Depression and heart failure (HF) are in a close two-way relationship: the appearance of one is potentiated by the other entity and the effects on the outcome are amplified within this "dangerous liaison". Depression is present in about one in five HF patients and is severe in almost half of them. The risk factors for depression in HF are female gender, elderly, the severity of HF symptoms, a history of isolated systolic hypertension or coronary heart disease (CHD), previous hospitalization and previous depressive episodes. Depression in HF patients increases medication non-adherence, is associated with poor outcomes after heart transplantation and is predictive of events and mortality in cardiac resynchronization therapy (CRT). The current assumptions related to the physiopathological mechanisms include a common genetic polymorphism, inflammation, generalized immune system disturbance, disturbances of platelet function, increased catecholamine levels, deamination of monoamines linked with monoamine oxidase activity, a dysregulation of the autonomic nervous system, increased serotonin levels, ischemia, life-style and medication non-compliance, a poor familial support and social isolation. Assessment of cognitive functioning should be part of routine clinical examination in HF, the diagnosis of depression is based on questionnaires (e.g. Patient Health Questionnaire-2 - PHQ-2) and on clinical interview. There is still no consensus on the best therapy for HF patients with depression (non-pharmacological and pharmacological therapies) but, for sure, depression in HF is harder to treat.*

Keywords: *heart failure, depression, comorbidity, cognitive-behavioral.*

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The list of comorbidities associated with heart failure (HF) is long and depression is part of it. Thus, a severe condition as HF with a limited survival (50% of HF patients dying within five years of diagnosis)(McDonagh et al, 2021) is aggravated by another through insidious mechanisms which causes depression, making the short distance measured between the heart and the brain of 18 inches (almost 46 cm) to be easily overcome. The biunivocal relationship between these two entities also rise the question to what extent depression has an etiological relationship with the appearance and development of the HF (Lam et al., 2023) in the conditions in which "depression seems to increase the risk for HF, while HF increases the risk of depression" (Sbolii et al., 2020).

The statistical analysis highlights the following aspects:

- HF is affecting more than 5.7 million adults in the United States and 26 million adults worldwide (Ishak et al., 2020). On the other side, in the United States, depression has an almost three times higher prevalence than HF, affecting 17.2 millions of adults (Sbolii et al., 2020) and roughly 350 million people worldwide (Ishak et al., 2020).
- Depression is present in about one in five HF patients and is severe in almost half of them (McDonagh et al., 2021). A meta-analysis of 28 studies found a 46% increase in the risk of developing cardiovascular disease in depressed patients compared to healthy subjects (Van der Kooy et al., 2007; Anghel et al., 2022). The incidence of clinical depression in HF patients ranges from 19.3% to 33.6% based upon diagnostic interview versus questionnaires, and from 11% in New York Heart Association class I patients to 42% in class IV patients (Rutledge et al., 2006 & Moradi et al., 2022).
- The prevalence of major depression in chronic HF is about 20-40%, which is 4-5% higher than in the normal population (Mbakwem et al., 2016). Two large meta-analyses found that the estimated overall prevalence of depression in HF is approximately 20% to 30% (Rutledge et al., 2006; Sokoreli et al., 2016). The aggregated prevalence for women is higher than for men, with 32.7% (range 11–67%) of women being depressed compared with 26.1% (7–63%) of men. The prevalence of depression is similar in HF with reduced and preserved ejection fraction, and across different HF etiologies (Sbolii et al., 2020, Anghel et al., 2022). The prevalence of depression was higher in the EMRO (Eastern Mediterranean) region (70.1%) and lower economic status countries (56.7%) (Moradi et al., 2022).
- The risk factors for depression in HF are female gender, age, the severity of HF symptoms, a history of isolated systolic hypertension or

coronary heart disease (CHD), previous hospitalization and previous depressive episodes. In patients with type 2 diabetes mellitus (T2DM), depression at baseline or during follow-up period were associated with a higher risk of HF and this finding indicates that it is important to identify depression in patients with T2DM because they are at higher risk of developing HF (Chen et al., 2023, Chirita et al., 2012).

- The spectrum of *Cognitive Impairment* (CI) in HF may range from delirium to isolated memory or non-memory-related deficits to dementia (Correale et al., 2020). The highest prevalence, up to 80%, is reported in patients hospitalized due to acute decompensation. Vascular CI is already present in the early stage of HF, even before LV systolic dysfunction (Alagiakrishnan et al., 2016).
- The combined outcome of mortality and cardiovascular events was twofold higher in HF patients with depression (Rutledge et al., 2006). Depression in HF patients is associated with poor outcomes after heart transplantation and is predictive of events and mortality in cardiac resynchronization therapy (Sbolii et al., 2020). Depression increases medication non-adherence (Paduraru et al., 2019).
- HF is associated with an increased risk of suicide (influenced by depressive symptoms), especially during the first 6 months and up to 2 years after HF diagnosis (Korkmaz et al., 2019).
- Depression and HF also influence quality of life (QOL) (Basile et al., 2023).

Physiopathological mechanisms

There are some assumptions related to the physiopathological mechanisms involved in the relationship between HF and depression (no only one but rather many factors), based on still fragmentary information and in the process of accumulation, their importance mainly consists in identifying some prophylactic or curative therapeutic solutions (Dimos et al., 2009). The current hypotheses are the following:

- a common genetic polymorphisms predisposition (e. q. a link between depression and hypertension has been demonstrated involving an allele of the angiotensin-converting enzyme gene) (Dimos et al., 2009);

- inflammation in the conditions of a disruption of of cytokine network and activation of apoptosis signaling molecules (high levels of C-reactive protein and of circulating proinflammatory cytokines IL-6, IL-1, TNFα, together with a significantly lower levels of IL-10 and of an soluble

apoptosis mediator). So far, only small studies have provided evidence pointing to this role of inflammation (Sbolii et al., 2020);

- generalized immune system disturbance (immunological stimulation and cellular immunity, a imbalance of the T1:T2 lymphocyte ratio);

- platelet function disorders (platelet activation generating hyperviscosity as a result of hypercoagulability). Nevertheless, in larger studies this platelet activation is not statistically significantly different in depressed vs non-depressed groups with stable coronary disease (Gehi et al., 2010);

- increased catecholamine levels, deamination of monoamines linked with monoamine oxidase activity (Corbineau et al., 2017), an imbalance in the activity of the autonomic nervous system (with sympathetic hyperactivity and parasympathetic hypoactivity) (Basile et al., 2023), increased serotonin levels. The mechanism underlying the pro-arrhythmic state in depressed HF patients is not yet well understood (Sbolii et al., 2020);

- ischemia due to stress (basal heart rate was higher with an impaired heart rate variability in patients with severe depressive symptoms) (Walter et al., 2019);

- dietary and medication non-compliance, smoking, sedentary lifestyle, a poor familial support (in terms of marital status, social isolation is associated with poor outcomes) (Christensen et al., 2020).

Diagnosis

In the case of patients with HF, an evaluation of their cognitive function should be part of the routine (McDonagh et al., 2021) (Figure 1). There is also a difference regarding the diagnostic arguments of each of the two entities: the diagnosis of HF requires the presence of specific symptoms and/or signs and objective evidence of cardiac dysfunction (biomarkers, mainly natriuretic peptides and echocardiography), while depression diagnosis is based on the information provided by questionnaires and interviews. Let's not forget that differentiating depression from a normal reaction determined by a chronic disease remains a real challenge, especially in the early post-hospitalization period (Sbolii et al., 2020). Furthermore, concentration impairment and fatigue, for example, as some cognitive or physical symptoms can be seen in both HF and depression.

When there is a clinical suspicion of depression, screening using a validated questionnaire is always recommended. *Beck Depression Inventory II* (BDI-II) and *Cardiac Depression Scale* (CDS), mainly or *Geriatric Depression Scale* (GDS), *Hamilton Rating Scale for Depression* (HAM-D) and *Hospital Anxiety and*

Depression Scale (HADS) can be used (Sbolii et al, 2020 & Jha et al, 2019). For a simpler and more accurate screening can be used Patient Health Questionnaire-2 (PHQ-2), a six-item scale, much more versatile than PHQ-9, a comprehensive instrument that assesses several domains depressed, but on a scale of 27 points (Piepenburg et al., 2015).

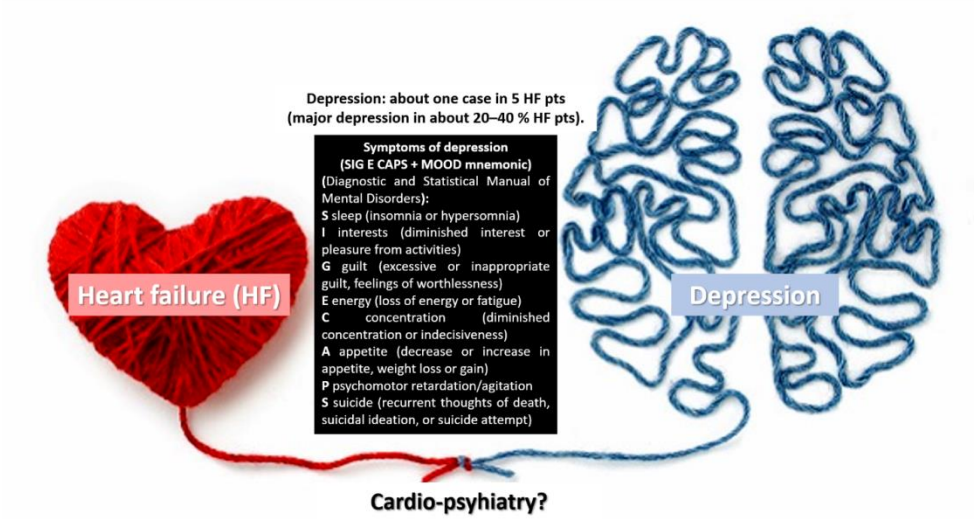

Figure 1. Awareness of the two-way relationship between heart failure and depression with the check-list of symptoms (SIG E CAPS mnemonic) and the suggestion of need to develop a better connected cardio-psychiatry interface (HF heart failure; pts patients).

An important predictor in of CI in ambulatory patients with HFrEF is six-minute walk distance, but not left ventricular ejection fraction (LVEF) or NYHA functional class (Graham et al., 2014). For mild CI the *Montreal Cognitive Assessment* appears to be a more useful diagnosis tool than *Mini-Mental Status Exam* (Alagiakrishnan et al., 2017). The most accurate method of diagnosing depression appears to be the clinical interview (American Psychiatric Association, 2013) using the Diagnostic and Statistical Manual of Mental Disorders V (DSM-5) (Sbolii et al., 2020).

There is now an opportunity to improve screening and diagnosis of depression through the use of wearable devices with mobile applications and the interconnectivity of social networks to enable early detection of signs of depression in HF patients and thus enable initiation of treatments appropriate as soon as possible (Sbolii et al., 2020).

Treatment

There are several therapeutic resources for the patient who has associated HF with depression without being able to firmly support which is the best option (McDonagh et al., 2021) and, for sure, depression in HF is harder to treat. A non-pharmacological and pharmacological therapies have been initiated for the treatment of depression (Sbolli et al., 2020). Data from a network meta-analysis (21 randomized trials, n=4563) showed that training and cognitive behavioral therapy (CBT) causes improvement of symptoms, and antidepressant drugs also reduced the clinical manifestation, but without their effect reaching a level of statistical significance (Das et al., 2019).

Non-pharmacological therapies, such as exercise training (investigated in HF-ACTION trial), psychosocial intervention (Berkman et al., 2003) with self-care focus and cognitive-behavioral therapy (CBT) has been proven to have beneficial effects on depressive symptoms. There are data that emphasize that an improvement in CI in patients with HF can be achieved with CRT-D and exercise (Druncker et al., 2015).

However, the CBT use in HF patients with depression produces only a modest reduction in depressive symptoms and a small increase in quality of life (Jeyanantham et al., 2017).

The PAL-HF trial a palliative care strategy including a physician, a palliative care nurse, and a psychiatrist resulted in reduced depressive symptomatology in patients with advanced HF compared with standard care (Rogers et al., 2017). It is important to take into account the fact that support from relatives may decrease anxiety and depression. No improvement in QOL compared to usual care in *Patient-Centered Disease Treatment* trial, a multi-component collaborative care intervention for patients with depression and HF (Freedland et al., 2015).

Pharmacological therapy of depression in patients with HF has not been shown to significantly alter outcomes. Selective serotonin reuptake inhibitors (SSRIs) are stil now the the main antidepressant medication. They seem to be well tolerated in patients with HF but, in short- and long-term randomized clinical trials, have not shown superiority over placebo. In SADHART-CHF, patients who received antidepressants (mainly SSRIs) had conflicting results showing an increased risk of hospitalization or death from a CV cause (O'Connor et al., 2010). This randomized, double-blind trial investigated the use for 12 weeks, in HF patients received supportive care from nurses, of sertraline 50 to 200 mg per day vs placebo. Although

sertraline appears to be safe for use in the HF population, no difference was found in reduction of depressive symptoms or adverse CV effects. Interestingly, many patients also improved in the placebo arm, showing the importance of providing better care to these patients. Both studies (SADHART-CHF and MOOD-HF Study) showed the safety of sertraline and escitalopram, respectively (O'Connor et al., 2010; Angermann et al., 2016).

Caution: tricyclic antidepressants should be avoided for the treatment of depression in patients with HF, as they may cause hypotension, worsening of HF and arrhythmias (Sbolii et al., 2020; Jha et al., 2019). By the way, the most frequent side effects of antidepressant drugs on the cardiovascular system are hypotension or hypertensive crisis, QT interval prolongation, brady- or tachyarrhythmias, increase/decrease in prothrombin time and myocardial contractility disorders (Dimos et al., 2009).

There are some new treatments under investigation that seem to be effective to treat depression, like N-methyl-D-aspartate (NMDA) receptor antagonists (e.g. the intranasal S-enantiomer of ketamine, esketamine), with pleiotropic targets (neuronal plasticity, inflammation, monoamine oxidase inhibitors, and opioid), omega-3 supplementation and the repetitive transcranial magnetic stimulation. Vitamin D and omega-3 fatty acid supplements (e. g. OCEAN trial) (Jiang et al., 2018) intended to reduce cardiac events in patients with moderate to severe depressive symptoms. Transcranial magnetic stimulation (TMS) is effective as an antidepressant monotherapy, but various implantable cardiac devices appear to be a limitation for the use of this treatment in this HF population.

Ever since 1993, the *Depression Guidelines Panel* proposed, in a very pragmatic manner, the following therapeutic strategy:

- *cognitive-behavioral therapy (CBT)* is preferable when depression 1) is not severe; 2) it is not chronic; 3) does not have the characteristic features of psychosis; 4) showed a positive response to CBT during a previous transient depressive episode; 5) does not benefit from available CBT services; 6) associate a contraindication for antidepressant drugs; 7) did not respond effectively to drug treatment alone; and 8) associate psychosocial factors that complicate the current situation.

- *administration of antidepressant drugs* should be considered when depression: 1) is severe; 2) is chronic or repeated; 3) associates the characteristic features of psychosis; 4) presented a previous positive response to medication; 5) it is a hereditary form; 6) makes the patient unable to participate in psychotherapy (Dimos et al, 2009).

The largest CBT trial for patients with HF was the *Depression and Self-Care of HF trial*, were the efficacy of CBT intervention was tested in patients diagnosed with major depression and HF (Freedland et al., 2015). Clinically significant improvements can be achieved in depressed patients with inadequate self-care with an individually tailored self-care intervention (Freedland et al., 2022), using CBT alone or combined with antidepressant medication may be more effective than using only SSRI therapy for these patients (Freedland et al., 2023).

The impact of depression on the fate of the patient with heart failure (this comorbid condition are under-recognized and under-treated despite the fact that is recognized in current European and North American HF guidelines) poses additional problems in current medical practice in a particular cardio-psychiatric context that brings back into discussion the opinion of Steve Maraboli "happiness is not the absence of problems, it's the ability to deal with them".

References

Anghel, L., Baroiu, L., Popazu, C. R., Pătraş, D., Fotea, S., Nechifor, A., ... & Ciubara, A. B. (2022). Benefits and adverse events of melatonin use in the elderly. *Experimental and Therapeutic Medicine*, *23*(3), 1-8.

Anghel, L., Ursu, D., Caramfil, S. M., Stefanescu, C., Moisa, S. M., Ciubara, A., & Baroiu, L. (2022) The link between lipidic profile, depression and cardiovascular disease. *Archiv Euromedica, 12*, Special Issue, DOI 10.35630/2022/12/psy.ro.17.American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Washington, DC: American Psychiatry Association

Angermann, C. E., Gelbrich, G., Störk, S., Gunold, H., Edelmann, F., Wachter, R., ... & Ertl, G. (2016). MOOD-HF Study Investigators and Committee Members. Effect of escitalopram on all-cause mortality and hospitalization in patients with heart failure and depression: the MOOD-HF randomized clinical trial. *JAMA*, *315*(24), 2683-93.

Alagiakrishnan, K., Mah, D., Ahmed, A., & Ezekowitz, J. (2016). Cognitive decline in heart failure. *Heart Fail Rev., 21*(6), 661 – 73

Alagiakrishnan, K., Mah, D., Dyck, J. R., Senthilselvan, A., Ezekowitz, J. (2017). Comparison of two commonly used clinical cognitive screening tests to diagnose mild cognitive impairment in heart failure with the golden standard European Consortium Criteria. Int J Cardiol, 228, 558 - 62

Basile, C., Parlati, A. L. M., Paolillo, S., Marzano, F., Nardi, E., Chirico, A., ... & Montisci, R. (2023). Depression in heart failure with reduced ejection

fraction, an undervalued comorbidity: An up-to-date review. *Medicina*, *59*(5), 948.

Berkman, L. F., Blumenthal, J., Burg, M., Carney, R. M., Catellier, D., Cowan, M.J. (2003). Enhancing recovery in coronary heart disease patients investigators. (2003). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial. *JAMA, 289*, 3106 - 3116

Chen, Y., Long, C., & Xing, Z. (2023) Depression is associated with heart failure in patients with type 2 diabetes mellitus. *Front Public Health 11*, 1181336. doi: 10.3389/fpubh.2023.1181336

Chirita, R., Sacuiu, I., Burlea, A., & Chirita, V. (2012). The role of nitric oxide inhibitors in treatment on symptom severity and cognitive deficits in schizophrenia. *International Journal of neuropsychopharmacology, 15*, 113-113

Christensen, A. V., Juel, K., Ekholm, O., Thrysøe, L., Thorup, C. B., Borregaard, B., Mols, R. E., Rasmussen, T. B., & Berg, S.K. (2020). Significantly increased risk of all-cause mortality among cardiac patients feeling lonely. *Heart 106*, 140 - 146

Corbineau, S., Breton, M., Mialet-Perez, J. & Costemale-Lacoste, J. F. (2017). Major depression and heart failure: Interest of monoamine oxidase inhibitors. *International Journal of Cardiology, 247*,1 - 6

Correale, M., Paolillo, S., Mercurio, V., Limongelli, G., Barilla, F., Ruocco, G., ... & Nodari, S. (2020). Comorbidities in chronic heart failure: an update from Italian Society of Cardiology (SIC) Working Group on Heart Failure. *European journal of internal medicine*, *71*, 23-31 https://doi.org/10.1016/j.ejim.2019.10.008

Das, A., Roy, B., Schwarzer, G., Silverman, M. G., Ziegler, O., Bandyopadhyay, D., ... & Das, S. (2019). Comparison of treatment options for depression in heart failure: a network meta-analysis. *Journal of psychiatric research*, *108*, 7-23

Depression Guidelines Panel. In: Depression in Primary Care: Detection and Diagnosis: US Department of Health and Human Services. Public Health Service. 1993: AHCPR publication no. 93-0550

Dimos, A. K., Stougiannos, P. N., Kakkavas, A. T., & Trikas, A. G. (2009) Depression and heart failure. *Hellenic Journal of Cardiology, 50*(5): 410 – 7

Duncker, D., Friedel, K., König, T., Schreyer, H., Lüsebrink, U., Duncker, M., ... & Gardiwal, A. (2015). Cardiac resynchronization therapy improves psycho-cognitive performance in patients with heart failure. *EP Europace*, *17*(9), 1415-1421

Freedland, K. E., Carney, R. M., Rich, M. W., Steinmeyer, B. C., & Rubin, E. H. (2015). Cognitive behavior therapy for depression and self-care in heart

failure patients: a randomized clinical trial. *JAMA International Medicine*, 1 - 10.

Freedland, K. E., Skala, J. A., Carney, R. M., Steinmeyer, B. C., Rubin, E. H., & Rich, M. W. (2022) Sequential interventions for major depression and heart failure self-care: a randomized clinical trial. *Circulation: Heart Failure, 15,* https://doi.org/10.1161/ CIRCHEARTFAILURE.121.009422

Freedland, K. E, Skala, J. A., Carney, R. M., Steinmeyer, B. C. & Rich, M. W. (2023). Treatment of depression and inadequate self-care in patients with heart failure: One-year outcomes of a randomized controlled trial. *General hospital Psyhiatry, 84*, 82 – 88

Gehi, A., Musselman, D., Otte, C., Bruce Royster, E., Ali, S., & Whooley, M. A. (2010). Depression and platelet activation in outpatients with stable coronary heart disease: findings from the Heart and Soul Study. *Psychiatry Research, 175*, 200 – 204

Graham, S., Ye, S., Qian, M., Sanford, A. R., Di Tullio, M. R., Sacco, R. L., ... & WARCEF investigators. (2014). Cognitive function in ambulatory patients with systolic heart failure: insights from the warfarin versus aspirin in reduced cardiac ejection fraction (WARCEF) trial. *PloS one*, *9*(11), e113447 https://doi.org/10.1371/journal.pone.0113447

Ishak, W. W., Edwards, G., Herrera, N., Lin, T., Hren, K., Peterson, M., ... & Hamilton, M. (2020). Depression in heart failure: a systematic review. *Innovations in clinical neuroscience*, *17*(4-6), 27.

Jeyanantham, K., Kotecha, D., Thanki, D., Dekker, R.,Lane, D.A. (2017). Effects of cognitive behavioural therapy for depression in heart failure patients: A systematic review and meta-analysis. *Heart Fail Review, 22*, 731 -741

Jha, M. K., Qamar, A., Vaduganathan, M., Charney, D. S., & Murrough, J. W. (2019). Screening and management of depression in patients with cardiovascular disease: JACC state-of-the-art review. *Journal of the American College of Cardiology*, *73*(14), 1827-1845.

Jiang, W., Whellan, D. J., Adams, K. F., Babyak, M. A., Boyle, S. H., Wilson, J. L., ... & O'Connor, C. M. (2018). Long-chain omega-3 fatty acid supplements in depressed heart failure patients: results of the OCEAN trial. *JACC: Heart Failure*, *6*(10), 833-843.

Korkmaz, H., Korkmaz, S., Çakar, M. (2019). Suicide risk in chronic heart failure patients and its association with depression, hopelessness and self esteem. *Journal of Clinical Neuroscience, 68*, 51 - 54

Lam, M. I., Chen, P., Xie, X. M., Lok, G. K., Liu, Y. F., Si, T. L., ... & Xiang, Y. T. (2023). Heart failure and depression: A perspective from bibliometric analysis. *Frontiers in Psychiatry*, *14*, 1086638. doi: 10.3389/fpsyt.2023.1086638

McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., ... & Waltenberger, J. (2022). 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *European journal of heart failure*, *24*(1), 4-131

Mbakwem, A., Aina, F., & Amadi, C. (2016). Expert opinion-depression in patients with heart failure: is enough being done?. *Cardiac failure review*, *2*(2), 110.

Moradi, M., Doostkami, M., Behnamfar, N., Rafiemanesh, H., & Behzadmehr, R. (2022). Global prevalence of depression among heart failure patients: a systematic review and meta-analysis. *Current Problems in Cardiology, 47*(6), 100848

O'Connor, C. M., Jiang, W., Kuchibhatla, M., Silva, S. G., Cuffe, M. S., Callwood, D. D., ... & SADHART-CHF Investigators. (2010). Safety and efficacy of sertraline for depression in patients with heart failure: results of the SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial. *Journal of the American College of Cardiology*, *56*(9), 692-699.

Păduraru, I. M., Vollmer, J., Precupanu, D., Ciubara, A. B., Hozan, C. T., Firescu, D., & Ciubara, A. (2019). Anxiety and depression in patients with cancer. A case report. *BRAIN. Broad Research in Artificial Intelligence and Neuroscience*, *10*(3), 55-59.

Rogers, J. G., Patel, C. B., Mentz, R. J., Granger, B. B., Steinhauser, K. E., Fiuzat, M., ... & Tulsky, J. A. (2017). Palliative care in heart failure: the PAL-HF randomized, controlled clinical trial. *Journal of the American College of Cardiology*, *70*(3), 331-341

Rutledge, T., Reis, V. A., Linke, S. E., Greenberg, B. H., & Mills, P. J. (2006). Depression in heart failure: a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *Journal of the American college of Cardiology*, *48*(8), 1527-1537.

Sbolli, M., Fiuzat, M., Cani, D., & O'Connor, C. M. (2020). Depression and heart failure: the lonely comorbidity. *European journal of heart failure*, *22*(11), 2007-2017 https://doi.org/10.1002/ejhf.1865

Sokoreli, I., de Vries, J. J., Pauws, S. C., Steyerberg, E.W. (2016). Depression and anxiety as predictors of mortality among heart failure patients: systematic review and meta-analysis. *Heart Failure Review, 21*, 49 - 63

Van der Kooy, K., van Hout, H., Marwijk, H., Marten, H., Stehouwer, C., Beekman, A. (2007). Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *International Journal of Geriatric Psychiatry, 22*, 613 – 626

Walter, F. A., Gathright, E., Redle, J. D., Gunstad, J., & Hughes, J. W. (2019). Depressive symptoms are associated with heart rate variability independently of fitness: a cross-sectional study of patients with heart failure. *Annals of Behavioral Medicine*, *53*(11), 955-963