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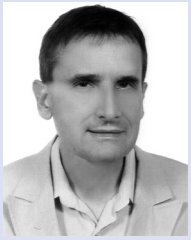
ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Depression and anxiety in cardiovascular disease

Krzysztof Małyszczak[1], Joanna Rymaszewska[2]

[1]Department of Psychiatry, Division of Psychotherapy and Psychosomatic Medicine, Wroclaw Medical University, Wroclaw, Poland
[2]Department of Psychiatry, Division of Consultation Psychiatry and Neuroscience, Wroclaw Medical University, Wroclaw, Poland



Associate Professor **Krzysztof Małyszczak** is a head of the Division of Psychotherapy and Psychosomatic Medicine at the Department of Psychiatry, Wroclaw Medical University. He is a psychiatrist and a psychotherapy supervisor, the organiser and chief specialist in a ward for the treatment of neuroses and personality disorders. His projects are focused on mood, anxiety, and personality disorders, especially in cases coexistence of somatic diseases. He participated in a study of factors affecting depression in cancer and hepatitis C virus infection and the relationship between personality traits and hypertension.

Professor **Joanna Rymaszewska**, MD, PhD, Dean of Medical Faculty of Postgraduate Training, Wroclaw Medical University (2012–2016), Professor of Medicine, Department of Psychiatry, Wroclaw Medical University, Head of Division of Consultation Psychiatry and Neuroscience, Senior psychiatrist in outpatient university clinic, consultant in Wroclaw University Hospital and Silesian Oncology Centre. Her research interests include: old age psychiatry, consultation-liaison psychiatry (psychiatry in somatic medicine), social psychiatry, and neuroscience.

INTRODUCTION

Cardiovascular disease (CVD) and mental disorders often coexist. Almost all mental disorders result in behavioural changes, leading to reduced physical activity, an inadequate diet, smoking, alcohol addiction, psychoactive substance abuse, and an increased reaction to stress. Cardiovascular disease may also promote depression and anxiety, which are caused by disease-related stress as well as hormonal and biochemical abnormalities.

In the study by Kessler et al. [1] carried out in the United States, the 12-month prevalence of mental disorders in the general population between 2001 and 2003 was 26.2%. 18.1% of those disorders were anxiety disorders, 9.5% were mood disorders, 8.9% were impulse control disorders, and 3.8% included substance abuse. Together, anxiety and mood disorders comprise 4/5 of all mental disorders. In Spain, the 12-month prevalence of anxiety disorders was 9.7%, the prevalence of mood disorders was 6.6%, and the overall prevalence was 16.3% [2]. The proportion of the prevalence of anxiety and mood disorders was similar in both studies.

In cardiology, mood and anxiety disorders are important factors that influence the treatment of CVD. Mood and anxiety disorders are common in patients treated by general practitioners, where the prevalence of those disorders may be two times higher than in the general population (35%). Moreover, the prevalence rises up to 40% in patients suffering from CVD [3, 4].

THE INFLUENCE OF ANXIETY AND DEPRESSION ON THE FORMATION OF CVD

Anxiety disorders often accompany CVD and may also imitate them in the form of cardiac functional syndromes. Depression causes behavioural and physiological changes, which contribute to the development of CVD and may accelerate their progression [5, 6]. Depression may prompt smoking and alcohol abuse, reduced physical activity, an inadequate diet, and noncompliance with medical advice. Physiological factors, such as the activation of the autonomous nervous system, hormonal disorders, metabolic disorders, inflammation, hypercoagulation, increased platelet aggregation, and

Address for correspondence:
Krzysztof M. Małyszczak, MD, PhD, Department of Psychiatry, Division of Psychotherapy and Psychosomatic Medicine, Wroclaw Medical University, Wybrzeże Ludwika Pasteura 10, 50–367 Wrocław, Poland, e-mail: krzysztof.malyszczak@umed.wroc.pl
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endothelial dysfunction, may act as an intermediary between psychosocial factors and CVD.

Tully et al. [7] carried out a meta-analysis based on 43 studies selected from a database of more than 4000 research articles about anxiety in ischaemic heart disease. The authors evaluated the relationship between anxiety disorders and serious cardiovascular events. They did not find a statistically significant effect of panic disorders, agoraphobia, social anxiety disorder, or obsessive-compulsive disorders on serious cardiovascular events. General anxiety disorder was significantly associated with an increased probability of major adverse cardiac events in ambulatory patients. The authors described this as a result of the long-term influence of unrest and psychological stress that accompany general anxiety, on the increased stress response. The authors also found that an increase in the concentration of C-reactive protein, an increase in systolic blood pressure, and disturbances in the function of the autonomic nervous system caused a reduction in heart rate variability.

Most studies assessing the effect of various factors on the incidence and course of CVD are based on a hazard ratio (HR), which indicates the extent to which there is a risk of the occurrence of a disease or complications in a group exposed to the risk factor in comparison to a group not exposed. In a large retrospective study, Scherrer et al. [8] demonstrated that the diagnosis of an anxiety disorder (HR = 1.34; 95% confidence interval [CI]: 1.21–1.47), a panic disorder (HR = 1.43; 95% CI: 1.11–1.83), a posttraumatic stress disorder (HR = 1.25; 95% CI: 1.16–1.36), and depression (HR = 1.39; 95% CI: 1.34–1.45) statistically significantly increased the risk of myocardial infarction (MI) [8]. Garfield et al. [9] obtained similar results in a retrospective study conducted on 236,000 patients. They found that anxiety disorders, depression, or both disorders combined increased the risk of heart failure (HF) (HR = 1.19; 95% CI: 1.10–1.28; HR = 1.21; 95% CI: 1.13–1.28; HR = 1.24; 95% CI: 1.17–1.32, respectively).

Van Dijk et al. [10] examined the effect of anxiety and depression on the all-cause mortality in patients undergoing percutaneous coronary angioplasty. The prevalence of depression and anxiety was 24.8% and 27.7%, respectively. Depression was a predictor of all-cause mortality (HR = 1.77; 95% CI: 1.36–2.29). Anxiety was associated with an increased risk for all-cause mortality (HR = 1.50; 95% CI: 1.14–1.98). A sub-analysis showed that cumulative survival rates did not differ for depressed, anxious patients versus depressed, non-anxious patients. They concluded that depression was associated with an increased risk of 77% for all-cause mortality, independently of anxiety. Although anxiety was associated with all-cause mortality, it had no additional value in the case of concurrent depression. Connery et al. [11] also found that depression had a significant effect on mortality of patients with coronary artery bypass grafting (CABG), where a statistically significant HR value of 1.8 was obtained. Burg et al. [12] obtained similar results in a group of 89 patients.

Roest et al. [13] carried out a meta-analysis on the effect of anxiety on mortality after MI based on 20 research articles using data collected from 5750 patients. Patients suffering from anxiety had worse clinical outcomes than patients without anxiety (odds ratio [OR] = 1.36; 95% CI: 1.18–1.56; $p < 0.001$). Anxiety was also associated with the all-cause mortality (OR = 1.47; 95% CI: 1.02–2.13; $p = 0.04$), cardiovascular mortality (OR = 1.23; 95% CI: 1.03–1.47; $p = 0.02$), and new cardiac events (OR = 1.71; 95% CI: 1.31–2.23; $p < 0.001$).

Meijer et al. [14] carried out a meta-analysis on depression based on 29 studies including a total of 16,889 patients. They found that depression was associated with an increased risk of death from various causes (OR = 0.25; 95% CI: 1.73–2.93; $p < 0.001$), increased cardiovascular mortality (OR = 2.71; 95% CI: 1.68–4.36; $p < 0.001$), and a greater risk of cardiovascular events (OR = 1.59; 95% CI: 1.37–1.85; $p < 0.001$).

There are also studies reporting contradictory results, showing no effect of anxiety and depression on mortality following MI. Lane et al. [15] carried out a study on 288 patients and showed that depression and anxiety were not a predictor of all-cause mortality or cardiac-related mortality during a 12-month follow-up. Similarly, Dickens et al. [16] did not find a correlation between depression, all-cause mortality, and cardiac-related mortality in 588 patients following MI during a 12-month observation period (HR = 0.81; 95% CI: 0.44–1.47). Kornerup et al. [17] assessed 536 patients admitted to hospital due to CVD and did not find a correlation between anxiety, depression, and mortality. However, they found that those symptoms correlated with a higher incidence of stroke (HR = 2.25; 95% CI: 1.05–4.82 and HR = 2.34; 95% CI: 0.99–5.50, respectively).

Chamberlain et al. [18] carried out a detailed analysis of the effect of anxiety and depression on the mortality of patients with CVD. Their study included 799 patients with post MI and HF, where the mean observation period was 6.2 years. The use of the Minnesota Multiphasic Personality Inventory (MMPI) was a unique feature of the study. Aggravation of depression and anxiety was observed in 282 (35%) and 210 (26%) of the patients, respectively. Depression (HR = 1.28; 95% CI: 1.08–1.51) and anxiety (HR = 1.26; 95% CI: 1.03–1.53) were associated with an increased risk of hospitalisation. Depression also led to an increase in the all-cause mortality (HR = 1.23; 95% CI: 1.00–1.51). The HR for anxiety was not statistically significantly greater than 1 (HR = 1.15; 95% CI: 0.91–1.45). The co-occurrence of depression and anxiety increased the risk of hospitalisation (HR = 1.35; 95% CI: 1.08–1.71) but did not increase the risk of mortality (HR = 1.21; 95% CI: 0.91–1.61).

Seldenrijk et al. [19] carried out a cohort study on 2510 people without CVD during a six-year observation period, in which 106 (4.2%) individuals developed CVD.

The co-occurrence of depression and anxiety (HR = 2.86; 95% CI: 1.49–5.49) or only depression (HR = 2.30; 95% CI: 1.10–4.80) were significantly associated with an increased risk of developing CVD. Anxiety alone (HR = 1.48; 95% CI: 0.74–2.96) and diseases in remission (HR = 1.48; 95% CI: 0.80–2.75) were not associated with CVD. An exacerbation of the symptoms increased the incidence of CVD (HR = 1.51; 95% CI: 1.25–1.83). The use of benzodiazepines also increased the risk of developing CVD (HR = 1.95; 95% CI: 1.16–3.31).

Observational studies revealed that depression not only caused increased incidence of CVD, but also increased the risk of incidents that led to cardiac-related death in patients with a history of CVD. A meta-analysis of 11 cohort studies found that depression was associated with a 64% increased risk of a fatal MI, non-fatal MI, and the development of ischaemic heart disease. In the subgroup of patients with depression, the incidence of coronary heart disease (CHD) was almost three-fold higher than in patients without clinical depression [20]. The risk of death and other adverse cardiovascular events is two times higher in individuals suffering from depression within two years of MI, CABG, percutaneous angioplasty, or coronary angiography [21, 22].

Suzuki et al. [23] studied the effect of combined depression and anxiety on the mortality and readmissions in patients with HF. They included 221 patients with HF and based their study on an observation that depression and anxiety often coexist and may be a common factor impacting heart disease. Patients with depression and those with coexisting depression and anxiety were at an increased risk of hospital readmission or death (HR = 2.24; 95% CI: 1.17–4.28; p = 0.01 and HR = 2.75; 95% CI: 1.51–4.99; p = 0.01, respectively) compared to patients without any symptoms. The multivariate analysis took into account the influence of the age, gender, functional class according to the New York Heart Association, the B-type natriuretic peptide, the presence of an implantable device, renal dysfunction, and an abnormal left ventricular function. Coexisting depression and anxiety (but not depression or anxiety alone) was an independent predictor of a cardiac event (HR = 1.96; 95% CI: 1.00–3.27; p = 0.04).

Damen et al. [24] studied the effect of the symptoms of anxiety on the course of HF. The prospective 12-month cohort study revealed that anxiety symptoms were not significantly associated with the number of hospitalisations in the univariate (OR = 1.13; 95% CI: 0.59–2.17; p = 0.72) or multivariate (OR = 0.94; 95% CI: 0.38–2.31; p = 0.89) analysis.

THE EFFECT OF ANTIDEPRESSANT AND ANXIOLYTIC TREATMENT ON CVD

Depressive episodes are associated with an increased number of cardiovascular events and increased mortality. Numerous studies evaluated the effectiveness of antidepressant treatment on CVD. Thombs et al. [25] found six research articles describing randomised studies assessing the effect of antidepressant treatment on the course of CVD. The number of incidents was the dependent variable, including cardiac-related hospitalisation and death. Four studies also described the effect of antidepressant treatment using fluoxetine, sertraline, mirtazapine and citalopram, cognitive-behavioural therapy, and complex treatment led by a psychiatrist using a number of antidepressant drugs. Two studies showed a limited effect of the antidepressant treatment on reducing depression. None of the studies found a statistically significant effect of the treatment on CVD.

Those authors carried out another review in 2013 and compared the results of eight randomised studies carried out on patients with CHD. The same set of drugs as well as cognitive-behavioural therapy, interpersonal therapy, and "active treatment" using various drugs chosen by attending psychiatrist were studied. Similar findings were made, and no effect of antidepressant therapy on the number of serious cardiac events was found. The authors concluded that screening for depression may be of value because it may allow the identification of undiagnosed patients with depression. Furthermore, they concluded that the treatment may be effective in reducing the severity of depression and mental suffering in patients, and that it does not have an effect on the course of CHD. There is still no evidence that this potentially costly strategy would be beneficial for all patients.

A meta-analysis carried out by Mazza et al. [26] presents detailed results of five randomised studies that assessed the effect of antidepressant treatment on the course of heart disease after acute coronary syndromes. Sertraline, fluoxetine, and citalopram were evaluated. In four studies these drugs were effective in reducing the severity of depression. Three studies comprehensively evaluated serious cardiac events. One study revealed a decrease in the number of such incidents, while two found no statistically significant difference in the number of those events related to antidepressant treatment. A decrease in the number of readmissions in the course of the treatment was observed in three studies. However, no statistically significant difference in overall mortality between treated and untreated patients was found. Three studies assessed the incidence of recurrent MI, where one study showed a reduction in the incidence and two studies reported no change in the incidence (as in the case of hospital readmission) among patients. A study showing a decrease in the severity of the disease during treatment with antidepressants was carried out in India on a group of 50 patients. The remaining studies were carried out in the United States, Canada, and Holland [27–30].

Those three meta-analyses indicate that antidepressant treatment does not have an effect on the underlying disease in patients with CVD and concomitant depression. Out of 19 studies carried out in different countries by different researchers using different methodologies, one study revealed an effect of antidepressant treatment on the course of heart

disease. Some of the studies showed mitigation of the severity of depression.

Despite the strong association between depression and the incidence of CVD as well as death caused by CVD, the results of clinical trials showed that pharmacological and cognitive-behavioural therapy in patients with depression and CVD slightly decreased the severity of depression and did not reduce the incidence of cardiovascular events and mortality [25]. Those contradictory findings complicate the interpretation of the available study results. In order to operationalise the paradigm of depression in CVD, an analysis of the psychosocial factors is necessary. Those factors combined with depression may have a negative effect on the treatment of patients with CVD. Firstly, psychological factors, such as personality and processual aspects, were omitted in the studies. Depression and anxiety are usually treated as separate, independent entities with or without an effect on CVD. This is not true, since depression and anxiety disorders result from personality vulnerabilities and psychosocial stress. Those factors may exert various effects on physiological and dysfunctional behaviour, leading to the development of CVD. A study by Faller et al. [31] attempted to clarify this issue. The authors studied the prognostic properties of depression in patients with CVD, and took into consideration the functional state of the patients, defined as the basic performance of patients in everyday duties. A total of 863 patients with CVD were included in the study. Symptoms of depression increased the risk of death (HR = 1.07; 95% CI: 1.04–1.09; $p < 0.001$), even when the severity of the HF and other comorbidities were taken into account (HR = 1.04; 95% CI: 1.01–1.07; $p = 0.017$). However, they were not a significant predictor of mortality (HR = 1.01; 95% CI: 0.98–1.05; $p = 0.46$) when the functional status, which was a separate predictor of the risk of death, was taken into account (HR = 0.90; 95% CI: 0.82–0.99; $p = 0.025$) [31]. Hence, depression in patients in that study was associated with reduced physical activity, which in turn resulted from CVD. The severity of depression could be directly associated with the severity of the underlying cardiac disease. That tautology explains the lack of effect of the antidepressant treatment in patients with CVD, considering that the primary factor causing depression is constantly present (the patient is constantly reminded of the risk of death).

Dempster et al. [32] carried out a meta-analysis of the impact of the perception of the disorder on the somatic state of the patient. They concluded that emotional representations of an illness were consistently the illness perceptions with the strongest relationship with the outcomes, so "further longitudinal work is needed if we are to apply this information to the design of interventions for the improvement of psychological health among people with physical health". The diagnosis of the disease changes the mental attitude and perception of the condition by the patient, which may potentially instigate depression and anxiety.

The observation that depression and anxiety may be caused by CVD complicates the treatment of depression, but may explain the lack of effect of treatment in patients. Piegza et al. [33] showed that cardiac arrest causes an increase in the severity of depression and increases the incidence of depression. A prolonged cardiac arrest was associated with more severe symptoms.

Wilkowska et al. [34] demonstrated that MI leads to an increase in the concentration of plasma inflammatory cytokines that persists for several days, or longer, as in the case of interleukin-6. Interleukin-6 is one of the factors that cause sickness behaviour — a behavioural syndrome that resembles depression, which is associated with decreased physical activity, psychomotor retardation, and cognitive impairment. Therefore, it can be assumed that an inflammatory reaction triggered by MI and myocardial necrosis, which occurred in 70% of the patients in the study of Wilkowska et al. [34], is an important cause of depression. A similar mechanism may be associated with the occurrence of depression following CABG [35].

In addition, behavioural factors do not directly arise from depression or anxiety, but are caused by an externalisation of internal psychological problems. Hence, alcohol abuse and smoking are not the result of depression, but of minor or serious personality disorders. Patients suffering from depression are able to internalise stress, which prevents abnormal behaviour that may impact CVD.

THE SAFETY OF ANTIDEPRESSANT TREATMENT IN CVD

Psychotropic drugs affect the cardiovascular system. This effect is less pronounced in recently developed drugs because consecutive generations of drugs have fewer side effects. The classic tricyclic antidepressants (TCA) and phenothiazine antipsychotics, which have a similar chemical structure, may affect the cardiovascular system by increasing or decreasing blood pressure and by causing orthostatic hypotension, tachycardia, palpitations, cardiac arrhythmias, and atrioventricular conduction abnormalities [36]. New antidepressant and antipsychotic drugs have fewer side effects, but continue to have effects on the cardiovascular system.

Brouwers et al. [37] carried out a retrospective study of 121,252 patients with HF. The subjects were divided into four groups depending on whether they were diagnosed with depression or not and whether they were treated with antidepressants. 84.4% (n = 101,904) of the patients did not receive antidepressant treatment. Of those patients, 99.2% (n = 101,095) did not suffer from clinical depression, while 0.8% (n = 809) of the patients were diagnosed with clinical depression. The remaining 15.6% of the patients (n = 19,348) received antidepressant treatment, of which 13.3% (n = 2568) were diagnosed with clinical depression and 86.7% (n = 16,780) did not suffer from depression.

Statistical analyses showed that patients who were not treated with antidepressants (HR = 1.23; 95% CI: 1.20–1.26; $p < 0.001$), patients who were treated with antidepressants who did not suffer from clinical depression (HR = 1.27; 95% CI: 1.40–1.42; $p < 0.001$), and patients treated with antidepressants suffering from depression (HR = 1.33; 95% CI: 1.26–1.42; $p < 0.001$) were at a greater risk of death than patients who did not take antidepressants and who did not suffer from clinical depression. After excluding untreated patients without depression, there were no statistically significant differences in cardiac-related death or all-cause death between the remaining groups. In other words, treatment using antidepressants did not decrease mortality in patients suffering from depression and could increase mortality in patients without depression.

Detailed analyses revealed various effects of different antidepressant drugs. The use of citalopram, venlafaxine, and mirtazapine at the beginning of the study was associated with increased mortality from any cause as well as cardiac-related death. The use of fluoxetine, sertraline, nortriptyline, amitriptyline, and duloxetine was associated with an increased risk of overall mortality. In contrast, the use of paroxetine, imipramine, and mianserin did not affect the mortality. The results were surprising since TCA appeared to pose the greatest risk to patients with CVD, while selective serotonin reuptake inhibitors (SSRI) and selective norepinephrine reuptake inhibitors (SNRI) were considered safe for those patients [38].

Most of the other studies did not find a significant influence of the use of SSRI on the overall mortality [14, 39–44], and some demonstrated that SSRIs significantly reduced the risk of death [45, 46].

Diez-Quevedo et al. [39] did not find an association between the use of antidepressants and increased mortality (HR = 0.89; 95% CI: 0.71–1.13). They found benzodiazepines to have a protective role (HR = 0.70; 95% CI: 0.57–0.87). The use of fluoxetine was associated with increased mortality (HR = 1.66; 95% CI: 1.13–2.44).

O'Connor et al. [40] showed that sertraline can be safely used in patients with advanced HF. However, the authors found that its use did not alleviate the severity of depression and did not improve the CVD in patients with HF and concomitant depression.

In a prospective study including almost 15,000 patients, Hamer et al. [41] demonstrated that the use of TCA was associated with an increased risk of developing CVD (HR = 1.35, 95% CI: 1.03–1.77). After taking into account a range of covariates, the association between the use of TCA and coronary events was not statistically significant (HR = 1.24; 95% CI: 0.87–1.75). The use of SSRI was not associated with the development of CVD. The use of TCA and SSRI was not associated with increased mortality. Hippisley-Cox et al. [43] studied 933 patients with CHD compared to a much larger control group. They found that the OR of developing CHD was higher in patients treated with TCA (OR = 1.56, 95% CI: 1.18–2.05). Patients treated with dosulepin (Dothiepin, unavailable in Poland) had significantly higher ORs of developing ischaemic heart disease, independently of the concomitant use of other antidepressants (OR = 1.67, 95% CI: 1.17–2.36). The ORs were not increased for amitriptyline, lofepramine (unavailable in Poland), and SSRI. Increasing the maximum dose of dosulepin increased the OR of ischaemic heart disease. Meijer et al. [14] retrospectively assessed 3319 post-myocardial patients treated by family doctors and a larger group of controls and found that the OR of CHD was 0.9 (95% CI: 0.5–1.8), 0.9 (95% Cl: 0.7–1.2), and 1.3 (95% Cl: 0.6–2.8), respectively, when using SSRI, TCA, and trazodone or other antidepressants compared to the untreated group.

The OR of the use of SSRIs compared to no pharmacological treatment (irrespective of other antidepressants) was 1.1 (95% CI: 0.7–1.6). Those authors concluded that exposure to SSRIs did not increase the risk of acute MI in patients without the risk factors for CHD [14].

Monster et al. [44] studied 8887 patients treated for MI and a larger control group. They found that the use of antidepressants may be associated with a decreased risk of hospitalisation for MI in patients with CVD, although it remains unclear whether there are differences between different classes of antidepressants. There was a tendency toward a lower risk of MI in patients treated with SSRI (OR = 0.85; 95% CI: 0.62–1.16), non-selective serotonin reuptake inhibitors (OR = 0.83; 95% CI: 0.50–1.38), and other antidepressants (OR = 0.55; 95% CI: 0.31–0.97). There was no such tendency in patients without a history of CVD. However, the OR of MI was statistically significantly lower than in the patients who received drugs other than SNRI [44].

Uniform conclusions concerning the safety of use of antidepressants in patients with CVD cannot be drawn based on the results of the above described studies. TCAs were not found to be significantly harmful and SSRIs were not found to be completely safe. The only harmful TCA is dosulepin, which has been withdrawn due to toxicity in a number of countries (including Poland). Amitriptyline and imipramine, the most commonly used TCAs, showed similar effects on CVD as SSRIs. SSRIs, in turn, were not always found to be safe. Most researchers questioned the safety of use of citalopram, escitalopram, and fluoxetine. The remaining SSRIs seemed safe to use. There have been few other studies focusing on other antidepressants. Based on the study of Brouwers et al. [37], venlafaxine and duloxetine (SNRI) as well as mirtazapine may be considered potentially dangerous to use. Mianserin proved to be safe.

CONCLUSIONS

There is an association between depression and increased risk of cardiac-related incidents and death in patients with CVD and HF. Anxiety seems to be an adequate predictor of those diseases only in conjunction with depression. Antide-

pressant treatment of patients with CVD was not associated with an improvement in the CVD prognosis. There is no current evidence that antidepressant treatment improves CVD. It may be effective in the reduction of depression and may improve patient quality of life [45–47], but does not reduce the risk of death or serious cardiac events [48]. Most antidepressants proved to be safe in patients with CVD and HF and, if necessary, may be used to treat depression (with some exceptions), to improve the symptoms of the patient, and reduce patient suffering. Dudek et al. [47] believe that the screening of patients with CVD and the implementation of treatment is beneficial and should be routinely applied. The exact effects of antidepressant treatment on CVD are still unclear and further studies to clarify this issue are required.

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