

# Is depression a problem in patients with chronic heart failure?

Bożena Szygula-Jurkiewicz<sup>1</sup>, Agata Duszańska<sup>2</sup>, Lech Poloński<sup>1</sup>

<sup>1</sup> III Department of Cardiology, Medical University of Silesia, Katowice, Poland

<sup>2</sup> I Department of Cardiology, Medical University of Silesia, Katowice, Poland

**Abstract:** Depression is a common psychiatric disorder, characterized by a persistent lowering of mood, loss of interest in routine activities and diminished ability to experience pleasure. There are several depression classification systems and diagnostic tools based on clinical symptoms, i.e. the International Classification of Diseases (ICD-10), the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the Hamilton Depression Rating Scale, the Montgomery-Asberg Scale and Beck's Depression Inventory. Depression frequently occurs in patients with heart failure, as similar pathophysiological mechanisms of neurohormonal activation, arrhythmia, inflammation and hypercoagulation are present in both these diseases. Prognosis in patients with depression is also affected by insufficient cooperation between a patient and his doctor as regards the lifestyle and medication intake of a patient. Depression is usually accompanied by remission and relapse periods which might be related to the current heart failure status of a patient and despite intensive medical treatment they may recur. Depression is often difficult to diagnose or even left undiagnosed and thus untreated, because its symptoms: fatigue, apathy and decreased exercise tolerance, are common in the general population. Furthermore, safety and efficacy of antidepressant therapy in patients with cardiovascular diseases are not well established. Evidence from clinical trials evaluating the influence of depression behavioral and pharmacological treatment on morbidity and mortality in patients with heart failure is also limited. Taking into account that depression affects prognosis in patients with variety of disorders and common pathological mechanisms present both in depression and heart failure, screening tests for depression should be considered not only in patients with diagnosed heart failure but also those at risk of heart failure development.

**Key words:** depression, heart failure

Depression is a common psychiatric disorder, characterized by a persistent lowering of mood, loss of interest in usual activities and diminished ability to experience pleasure. Diagnosis of depression is difficult as the difference between decreased mood and depressive syndrome is not always obvious. There are two main classification systems of depression based on clinical symptoms: ICD-10 (International Classification of Diseases and Deaths) such a and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) [1].

According to ICD-10 the fundamental symptoms of depression are as follows:

- 1) persistent lowering of mood for at least two weeks resistant to external stimuli

- 2) loss of interest in usual activities and diminished ability to experience pleasure
- 3) loss of vigour or increased fatigue.

There are additional signs of depression such as reduction of self-trust or self-respect, feeling remorse or guilt without reason, recurrent thoughts regarding death or suicide, decreased ability to think/analyze or concentrate, hesitation, changes in psychomotor behaviour (activation or inhibition), sleep and eating disorders with significant changes of body mass.

The other well-known and commonly used in practice system of depressive disorder classification is American DSM-IV [1]. To diagnose depression according to DSM-IV it is necessary to recognize at least 2-week persistence of mood lowering or loss of interest in usual activities/experience pleasure as the key-symptom together with four of the following signs: almost daily mood lowering confirmed by subjective complaints or other people's observations, noticeable decrease in interest in usual activities and ability to experience pleasure, significant reduction or increase of weight not related to diet, insomnia or somnolence, excitation or psychomotor retardation, fatigue or loss of energy, excessive or inadequate feeling of guilt, de-

#### Correspondence to:

Bożena Szygula-Jurkiewicz, MD, PhD, III Katedra i Oddział Kliniczny Kardiologii, Śląski Uniwersytet Medyczny, Śląskie Centrum Chorób Serca, ul. Szpitalna 2, 41-800 Zabrze, Poland, phone: +48-32-373-36-19, 604-102-999, fax: +48-32-273-23-16, e-mail: b.szygula@scs.pl

Received: October 10, 2007. Accepted in final form: December 20, 2007.

Conflict of interest: none declared.

Pol Arch Med Wewn. 2008; 118 (1-2): 52-56

Translated by Agata Duszańska, MD

Copyright by Medycyna Praktyczna, Kraków 2007

creased efficacy of thinking process, inability to concentrate or make decisions, recurrent thoughts of death or suicide.

Clinical presentation and intensity of depressive syndromes is best described by Hamilton Depression Rating Scale, Montgomery-Asberg Scale and Beck's Depression Inventory [1].

Although DSM-IV and ICD-10 classification systems are very useful in diagnosing depression, they do not evaluate its etiology, which is essential in order to differentiate endogenous from psychogenic depression. Analysis of depression etiology shows the influence of psychological, genetic as well as biological factors on its development. In every clinical presentation of depression it is possible to recognize "biological" elements such as vegetative symptoms, sleep and eating disorders, motor activity, and psychological factors with impairment of interpersonal relations, feeling of guilt, disorders of thinking process. Therefore when treating depression it is necessary to combine both psychotherapy, applied mainly in endogenous syndromes, and pharmacotherapy used as a first-line treatment of psychogenic disorders. Diagnosis of depression is often complicated by its atypical presentation with domination of symptoms such as sleep disorders, headache, fear or obsession. Patients with atypical depression usually seek help with a variety of specialists but seldom psychiatrists. They are usually treated with anxiolytics, sedatives and analgetics instead of antidepressants in adequate doses [1].

Diagnosis and treatment of depressive disorders becomes even more complex if depression coexists with a chronic somatic disease such as heart failure (HF) that can mask symptoms of depression.

Heart failure occurs when the heart fails to maintain sufficient circulation to provide adequate tissue oxygenation. Heart failure diagnosis is difficult as typical symptoms such as dyspnea or fatigue or signs such as peripheral oedema are not specific just for HF. The variety of HF symptoms are not strictly related to myocardial pathology but to the skeletal muscle, kidney, endocrinal or immunological system dysfunction. Impaired tissue perfusion and neurohormonal activation result in tissue and organ dysfunction. Increased activity of sympathetic and decreased activity of parasympathetic system, elevated plasma noradrenaline (NA), reduced NA storage and  $\beta$ -adrenergic receptors concentration in myocardium as well as activation of renin-angiotensin-aldosterone system are also observed [2].

According to its definition HF can be diagnosed if HF symptoms at rest or on exertion coexist with objective signs, preferably echocardiographic, of systolic or diastolic myocardial dysfunction at rest. Positive response to HF treatment may solve bias against HF diagnosis [2].

Heart failure is recognized not only as a medical but also economic and social problem. It is essential to eliminate any factors that may affect prognosis in HF patients. Depression is associated with increased mortality [3-5], impaired quality of life [6] and activity in HF patients despite somatic parameters [6]. Sullivan et al. [7] have reported increased costs of HF treatment in patients with HF and depression.

The presence of depression in HF patients is much more common than in the general population [4,8-10]. Depression

affects 5–10% of people in the general population, 11–25% of ambulatory and 35–70% of in-hospital patients with chronic HF [11].

Jiang et al. have shown that presence of depression in HF patients increases the risk of death at least twofold as compared to HF patients without depression. Depression is also identified as a risk factor of one-year re-admission into hospital due to HF progression [4].

Several studies have proved that the influence of depression on mortality in HF patients is related to the duration of depression [12]. Koenig et al. [9] have reported that depression in a 12-month observation does not affect the patient survival. Juenger et al. evaluated prognosis in HF patients followed by 24.8 months. They discovered that the negative influence of depression on HF patients survival began after 1 year of observation [13]. Vaccarino and Murberg found a linear relation between the degree of depression and HF patients' mortality in a 2-year follow-up. They noted a 4-fold increase in mortality of patients with HF and depression compared to HF patients without depression. [3,5].

Abramson et al. [14] identified depression as an independent risk factor for HF development in patients with isolated hypertension in 4.5 years of follow-up. Fredman et al. [15] reported a significant correlation between depression and mortality in older women. The influence of depression on mortality was related to duration of depression and was found much stronger after 6 years compared to a 2-year observation.

Thomas et al. [16] analyzed the results of 8 studies on depression in HF patients. They discovered that recognition of depression was dependent on the type of diagnostic test. The lowest rate of depression diagnosis was found in the Depression Interview Schedule. In Friedman's report depression was diagnosed in 30% and in Jiang's in 13.9% of the study population [4,6]. The same analysis according to Beck's Depression Inventory showed the rate of depression twice as high as in Jiang's study [4].

The relationship between depression and HF is not well understood. However, it is known that the same neurohormonal pathomechanisms play a role in the development of both depression and HF [17]. Activation of hypothalamo-pituitary-suprarenal feedback in response to stress results in hypercortisolaemia and increase in corticotropin realising factor as well as in enlargement of pituitary and suprarenal glands. Hyperactivation of hypothalamo-pituitary-suprarenal axis stimulates the central sympathetic system to produce catecholamines which thereby results in a decrease of heart rate variability, increase in heart rate and plasma norepinephrine concentration.

Sympathetic system activation affects prognosis in HF patients. Endothelial dysfunction may lead to vasospasm, reduction of coronary flow and in consequence LV systolic and diastolic abnormalities, electrical instability and arrhythmia [18-20]. In patients with depression increased plasma pro-inflammatory and decreased anti-inflammatory cytokines [21] as well as activation of platelets aggregation and coagulation

is a common finding [22,23]. Dysfunction of the parasympathetic system may lead to arrhythmia. [17,18,24].

Prognosis in patients with depression is also affected by insufficient co-operation between the patient and doctor with regard to the patient's lifestyle and medication intake [24,25]. Patients' disregard for diet regime or medical therapy result in 42–64% readmissions into hospital [24,25]. Chronically ill patients with concomitant depression neglect medical recommendations three times as often as compared to patients without depression [26]. Mental health in patients with chronic heart failure is recognized as a prognostic factor of adjustment to diet or a rehabilitation programme.

Diagnosis and adequate treatment of depression have an impact on prognosis in patients with chronic HF. High incidence of depression in HF patients corresponds with the fact that in the majority of the HF population accurate depression treatment is not applied. Sebastian and Jacob evaluated the frequency of psychotropes application in HF patients admitted into non-psychiatric wards [27]. According to their data just in 7.9% of patients antidepressants were administered and in 20.5% benzodiazepines. The main indications for this type of therapy were anxiety and insomnia but not depression. Depression is often difficult to diagnose or even left undiagnosed, and thus untreated, because symptoms such as fatigue, apathy and decreased exercise tolerance are common in the general population. Patients often associate dyspnoe, fatigue, lowering of mood with heart but not mental problems which they find embarrassing [28,29]. General clinical knowledge is usually not sufficient to diagnose and treat depression. Overuse of beta blockers may lead to increased depression incidence [30]. Although metaanalysis carried out by Ko et al. [31] showed no such relation, in clinical practice depression is often attributed to beta blockers administration. Furthermore, safety and efficacy of antidepressant therapy in patients with cardiovascular diseases are not well established. Evidence from clinical trials evaluating the influence of behavioral and pharmacological treatment of depression on morbidity and mortality in patients with heart failure is also limited.

Antidepressants are recognized as the fundamental line of depression treatment. They resolve or improve depression symptoms in 70% of cases. Depression displayed as anxiety or delusions is usually treated by neuroleptics with antidepressant components such as levopromazine or olanzapine, or combined therapy with antidepressants and antipsychotics. Mild to moderate depression treatment should be accompanied by psychotherapy [1]. There are several groups of antidepressants: tricyclic drugs (e.g. imipramine, desimipramine, amitriptyline, doxepin), tetracyclic drugs (maprotyline, mianserine, mirtazapine), selective serotonin/noradrenaline reuptake inhibitors (venlafaxine), selective serotonin reuptake inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), selective noradrenaline reuptake inhibitors (reboxetine), monoamine oxidase inhibitors (tranylcypromine, moclobemid) or others such as oxitriptan, viloxazine, tianeptine and trazodone [32].

Cardiovascular side-effects of tricyclic antidepressants include decreased myocardial contractility, arrhythmia and postural hypotension [32]. A combination of selective serotonin reuptake inhibitors (SSRI) with behavioral therapy seems to be the best solution in HF patients. Depression and anxiety activate the sympathetic system and may lead to progression of the disease. Accordingly, SSRI application could be beneficial in this group of patients. Clinical data show that SSRI intake in patients with cardiovascular problems is safe [33,34] due to minimal anticholinergic, antihistamine and noradrenergic effect and inhibition of platelets aggregation. Apart from occasional mild bradycardia they do not cause any other significant ECG changes. As they inhibit platelet aggregation they may prolong bleeding time. They can also interact with other cardiovascular drugs inhibiting cytochrome P450 enzymes such as beta blockers, calcium blockers, antiarrhythmic class Ic drugs, angiotensin converting enzyme inhibitors or warfarin derivatives [34,35]. Selective serotonin reuptake inhibitors may increase plasma concentration of the drugs mentioned above. Therefore application of those drugs together with SSRI requires special caution and prothrombin time monitoring especially during warfarin administration. Since SSRI join together with plasma proteins they dislodge other medications bound to plasma proteins which may cause their increased biological activity. Tianeptine is also considered a relatively safe drug which acts as an serotonin reuptake activator [32].

In summary it should be emphasized that depression frequently accompanies chronic heart failure as a result of common pathophysiological mechanisms such as neurohormonal activation, arrhythmia, inflammation and hypercoagulation. Depression has been also identified as an independent risk factor of unfavourable prognosis in patients with chronic HF. Prognosis in patients with depression is also affected by insufficient co-operation between the patient and his doctor with regard to the patient's lifestyle and medication intake. Unfortunately the evidence from medical studies evaluating the influence of behavioral and pharmacological treatment of depression on prognosis in HF patients is not sufficient yet. Taking into account that depression affects prognosis in patients with variety of disorders and common pathomechanisms present both in depression and HF, screening tests for depression should be considered not only in patients with diagnosed heart failure but also in those at risk of heart failure development.

## REFERENCES

1. Bilikiewicz A. *Psychiatria. Podręcznik dla studentów medycyny*. Wyd. 3, Warszawa, WL PZWL, 2006.
2. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). The task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology. *Eur Heart J*. 2005; 26: 1115-1140.
3. Vaccarino V, Kasl SV, Abramson J, et al. Depressive symptoms and risk of functional decline and death in patients with heart failure *J Am Coll Cardiol*. 2001; 38: 199-205.
4. Jiang W, Alexander J, Christopher E, et al. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Arch Intern Med*. 2001; 161: 1849-1856.

5. Murberg TA, Bru E, Aarsland T, et al. Functional status and depression among men and women with congestive heart failure. *Int J Psychiatry Med.* 1998; 28: 273-291.
6. Friedman MM, Griffin JA. Relationship of physical symptoms and physical functioning to depression in patients with heart failure. *Heart Lung.* 2001; 30: 98-104.
7. Sullivan MD, Levy WC, Crane BA, et al. Usefulness of depression to predict time to combined end point of transplant or death for outpatients with advanced heart failure. *Am J Cardiol.* 2004; 94: 1577-1580.
8. Havranek EP, Ware M, Lowes BD. Prevalence of depression in patients with congestive heart failure. *Am J Cardiol.* 1999; 84: 348-350.
9. Koenig H. Depression in hospitalized older patients with congestive heart failure. *Gen Hosp Psychiatry.* 1998; 20: 29-43.
10. Skotzko C, Krichen C, Zietowski G, et al. Depression is common and precludes accurate assessment of functional status in elderly patients with congestive heart failure. *J Card Fail.* 2000; 6: 300-305.
11. Szygula-Jurkiewicz B, Wojnicz R, Lekston A. Wpływ stężenia bilirubiny na rokowanie odległe u pacjentów z przewlekłą skurczową niewydolnością serca w przebiegu choroby nadciśnieniowej. *Pol Arch Med Wewn.* 2007; 117: 227-233.
12. Joynt KE, Whellan DJ, O'Connor CM. Why is depression bad for the failing heart? A review of the mechanistic relationship between depression and heart failure. *J Card Fail.* 2004; 10: 258-271.
13. Juenger J, Schellberg D, Muller-Tasch T. Depression increasingly predicts mortality in the course of congestive heart failure. *Eur J Heart Fail.* 2005; 7: 261-267.
14. Abramson J, Berger AC, Krumholz HM, et al. Depression and risk of heart failure among older persons with isolated systolic hypertension. *Arch Intern Med.* 2001; 161: 1725-1730.
15. Fredman L, Magaziner J, Hebel JR, et al. Depressive symptoms and 6-year mortality among elderly community-dwelling women. *Epidemiology* 1999; 10: 54-59.
16. Thomas SA, Friedmann E, Khatta M. Depression in patients with heart failure. *AACN Clinical Issues.* 2003; 14: 3-12.
17. Parissi JT, Founoulaki K, Paraskevaidis J, et al. Depression in chronic heart failure: novel pathophysiological mechanisms and therapeutic approach. *Expert Opin Investig Drug.* 2005; 14: 567-577.
18. Stein PK, Carney RM, Freedland KE, et al. Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary artery disease. *J Psychosom Res.* 2000; 48: 493-500.
19. Krittayaphong R, Cascio WE, Light KC, et al. Heart rate variability in patients with coronary artery disease: differences in patients with higher and lower depression scores. *Psychosom Med.* 1997; 59: 231-235.
20. Lown B, Verrier RL, Rabinowitz SH. Neural and psychologic mechanisms and the problem of sudden cardiac death. *Am J Cardiol.* 1977; 39: 890-902.
21. Appes A, Bar F, Bar J, et al. Inflammation, depressive symptomatology, and coronary artery disease. *Psychosom Med.* 2000; 62: 601-605.
22. Musselman DL, Tomer A, Manatunga AK, et al. Exaggerated platelet reactivity in major depression. *Am J Psychiatry.* 1996; 153: 1313-1317.
23. Patterson SM, Krantz DS, Gottdiener JS, et al. Prothrombotic effects of environmental stress: changes in platelet function, hematocrit, and total plasma protein. *Psychosom Med.* 1995; 57: 592-599.
24. Michalsen A, Konig G, Thimme W. Preventable causative factors leading to hospital admission with decompensated heart failure. *Heart.* 1998; 80: 437-441.
25. Monane M, Bohn RL, Gurwitz JH, et al. Noncompliance with congestive heart failure therapy in the elderly. *Arch Intern Med.* 1994; 154: 433-437.
26. Moser DK. Psychosocial factors and their association with clinical outcomes in patients with heart failure: why clinicians do not seem to care. *Eur J Cardiovasc Nurs.* 2002; 1: 183-188.
27. Jacob S, Sebastian JC, Abraham G. Depression and congestive heart failure. Are antidepressants underutilized? *Eur J Heart Fail.* 2003; 5: 399-400.
28. Goldman LS, Nielsen NH, Champion HC. Awareness, diagnosis and treatment of depression. *J Gen Intern Med.* 1999; 14: 569-580.
29. Davidson JR, Meltzer-Brody SE. The underrecognition and undertreatment of depression: what is the breadth and depth of the problem? *J Clin Psychiatry.* 2002; 52: 164-174.
30. Thiessen BQ, Wallace SM, Blackburn JL, et al. Increased prescribing of antidepressants subsequent to beta blocker therapy. *Arch Intern Med.* 1990; 150: 2286-2290.
31. Ko DT, Hebert PR, Coffey CS, et al. Beta blocker therapy and symptoms of depression, fatigue and sexual dysfunction. *JAMA.* 2002; 288: 351-357.
32. Mutschler E, Geisslinger G, Kroemer HK, et al. In: Danysz A (eds.). *Farmakoterapia i toksykologia.* Wrocław, Urban i Partner, 2004; 177-180.
33. Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina: Sertraline Antidepressant Heart Attack Randomized Trial. *JAMA.* 2002; 288: 701-709.
34. Roose SP, Glassman AH, Attia E, et al. Cardiovascular effects of fluoxetine in depressed patients with heart disease. *Am J Psychiatry.* 1998; 155: 650-655.
35. Harvey AT, Preskorn SH. Cytochrome P450 enzymes: interpretation of their interactions with selective serotonin reuptake inhibitors. Part I. I. *J Clin Psychopharmacol.* 1996; 16: 273-285.