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Review

Role of depression in heart failure — Choosing the right antidepressive treatment

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ABSTRACT

Major depression is a common feature of heart failure patients and possibly stems from their common biochemical background. Depression and heart failure co-morbidity has several clinical implications on the prognosis of these patients. Furthermore antidepressive drugs have known cardiovascular side effects, while their safety and efficacy in heart failure has not been fully elucidated yet. The right choice of antidepressive treatment in heart failure constitutes an issue of high importance as it can affect the clinical outcome of these patients. In this article we highlight the role of major depression in heart failure and demonstrate their common biochemical background. Moreover we review the acquired so far knowledge on the use of the various categories of antidepressants in heart failure by reference to the existing clinical studies on antidepressants efficacy and safety in heart failure. Even though certain conclusions cannot be drawn yet, evidence suggests that the use of selective serotonin reuptake inhibitors may have a beneficial effect on clinical outcome of heart failure patients.

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1. Introduction

Heart failure (HF) constitutes a major cause of hospitalization and morbidity in the elderly. Despite advances in HF treatment with a combination of drugs, cardiac muscle dysfunction is usually progressive and irreversible, negatively affecting patients' quality of life [1]. Prevalence of major depression in the general population has risen in the U.S over the last decade and is estimated about 7% [2]. Nevertheless major depression prevalence can reach up to 33–45% in patients post myocardial infarction (MI). Moreover, in end stage HF prevalence of major depression is dramatically high (~40%) [3]. Evidence suggests that the co-existence of psychiatric disorders in HF patients can affect the clinical outcome, morbidity and cost of treatment [4,5].

Reduced exercise capacity of HF patients has a negative impact on psychological condition and can theoretically promote depressive symptoms. However this explanation oversimplifies a complex situation. Studies show that the close relation between major depression and HF is caused by the common neuro-endocrine background of the two diseases. HF patients with major depression are at increased cardiovascular mortality risk compared to non-depressed patients [6]. Furthermore, evidence suggests that antidepressants have various cardiovascular side effects and may also negatively affect clinical outcome of HF [7,8].

In the present review article we sought to highlight the common biochemical background that links HF with major depression and to examine the clinical impact of major depression in HF patients. We summarize the known cardiovascular complications of the several types of antidepressants and stress the important implications of antidepressive treatment in the clinical outcome of HF.

2. Depression in heart failure

2.1. Prevalence of major depression in heart failure patients

The close association of major depression with HF has been demonstrated in many studies. Especially in hospitalized HF patients the prevalence of major depression is strongly associated with the severity of cardiac disease and has a great impact on the quality of life [3,9]. Freedland et al. [3] in a large cohort of 682 HF patients observed that the prevalence of major depression is increased compared to the general population but differs significantly between groups. Age, gender, employment status, daily activities, past history of major depression are all independent predictors of major depression development in HF patients, while functional HF severity has also a striking effect on depression prevalence. Prevalence of major depression among NYHA I class HF patients, was as low as 8% while among NYHA IV class patients it reached even the level of 40% [3]. However, the prevalence of major depression differed significantly between strata defined by the functional severity of HF, age, gender, employment status, dependence in activities of daily living, and past history of major depression. Importantly, major depression was even more frequent among NYHA IV class patients under 60 years old [3]. The Myocardial INfarction and Depression–Intervention Trial (MIND–IT) also demonstrated that the severity of left ventricular dysfunction post-MI is positively associated with higher rates of depression [10].

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However, it has been argued that the association of major depression with HF severity is overestimated due to the fact that depression modifies patient (and clinician) perceptions of disease severity [11]. Notably, Gottlieb et al. in the HF-ACTION study [11] demonstrated that depression is minimally related to objective assessments of HF severity, like peak O_2 consumption, brain natriuretic peptide levels or ejection fraction. However, depression significantly affects subjective measurements of HF severity like NYHA classification or 6-minute walk test, indices largely dependent on patient' perception of disease severity and motivational status respectively [11]. The authors elegantly demonstrated that depression influences the perception of severity of disease and quality of life to a greater extent than severe HF caused depression, partly toppling the traditional view of depression development due to reduced functional capacity [11].

Despite these observations, as many studies have consistently demonstrated, depression prevalence in HF patients is considerably high, disproportional to that of the general population, even though its exact rate is dependent on the diagnostic criteria used. Besides, such a close association does not seem to be valid for depression and other organic diseases, like cancer for example [3].

2.2. Impact on clinical outcome

Development of major depressive disorder is an additive burden for the national health system economics but existing data implicate that major depression may have also adverse effects on the clinical course and prognosis of HF patients. In multiple studies the association of major depression with poor clinical outcome of HF patients has been consistently highlighted [9,12–14]. Close psychological surveillance of HF patients over the last years has spotlighted the pivotal role of depression in HF. Depressive symptoms are closely associated with reduced functional capacity of HF patients as evaluated by the 6-minute walk test [15–17]. While simple stress disorders have no impact on the clinical course of HF, we and others have demonstrated that major depression is independently associated with increased mortality risk in HF patients [7,18]. In a cohort of end-stage HF patients, all at NYHA IV class, that we followed up prospectively for 18 months, non-depressed patients had significantly reduced risk for cardiovascular death compared to depressed patients; indeed this association remained significant even after adjustment for age, gender, atherosclerosis risk factors, type of HF, medication and BNP, hazard ratio = 0.709 (95% confidence interval, 0.519–0.969, $P = 0.031$) [7]. In addition in the landmark study of Sherwood et al. [18] 204 HF outpatients were assessed for HF severity and depressive symptoms using the Beck Depression Inventory (BDI). After a median follow up of 3 years, clinically significant symptoms of depression as defined by BDI score ≥10 were associated with a hazard ratio of 1.56 (95% confidence interval, 1.07–2.29) for the combined end point of death or cardiovascular hospitalization [18]. Therefore major depression seems to constitute an independent predictive factor for the clinical outcome of HF patients equally important to other well established risk factors like left ventricular dysfunction, smoking or history of MI.

2.3. Assessing depressive symptoms in heart failure patients

Notably major depression diagnosis in HF patients has some major pitfalls, as depressive symptoms are often downplayed by clinicians and attributed to the reduced functional capacity of these patients. However the high rate of major depression in HF warrants clinicians' vigilance, given its postulated association with an adverse impact on the prognosis of these patients. Clinicians should be able to diagnose possible presence of major depression in HF patients based on the major depression criteria as have been put forth in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [19] and through standardized structured clinical interview for depression (SCID-I) [20] (Table 1). Some easily administered inventories are the Zung Self-rating Depression Scale (SDS) [21] or the Hospital Anxiety and Depression Scale (HADS) [22] that evaluate presence of major depression with adequate validity and sensitivity in the clinical setting. Besides the presence and/or severity of depression can be assessed with other structured and standardized questionnaires, like the 17-item or 24-item Hamilton Rating Scale for Depression (HAM-D) [23,24], Depression Severity Score (DSS), BDI and the Montgomery Asberg Depression Scale (MADRS) [25]. Finally, the use of functional questionnaires, like the Kansas City Cardiomyopathy Questionnaire (KCCQ) or the Duke Activity Status Index (DASI) can provide valuable information about functional capacity of HF patients which is, as already mentioned, closely associated with depressive symptoms.

3. Heart failure and major depression: common background

The association between depression and HF or chronic pulmonary disease is indeed very interesting. Both patients with cardiac and pulmonary disease exhibit similarities regarding the limitation of physical activity and gravity of depressive symptoms, however they differ in rates of mortality and morbidity [26]. This fact possibly demonstrates the special character of HF and depression co-morbidity in terms of etiology and treatment requirements. Major depression is closely related to the gravity of cardiac dysfunction, demonstrating that a common biochemical background is implicated in the pathogenesis of both diseases (Table 2).

Various biological systems have been postulated as etiologic factors in the development of depression. These include the monoaminergic neurons of brain [27], the renin–angiotensin–aldosterone (RAAS) axis [28], the hypothalamus–hypophysis (HH) axis and the corticotropin releasing factor (CRF) [29]. Recently the theory of the immune system participation in the pathogenesis of depression, via macrophages action and pro-inflammatory cytokines, has been also developed [30]. Indeed circulating levels of aldosterone [28] and glucocorticoids [29] are increased in depressed patients due to the activation of the RAAS and HH axis. Existing data also demonstrates that in major depression a low grade inflammation exists, as reflected on the raised circulating levels of pro-inflammatory cytokines, and a prothrombotic state due to platelets activation [31]. As we recently showed, depressed HF patients had significantly higher circulating levels of vascular cell adhesion molecule-1 and interleukin-6 (IL-6) compared to non-depressed HF patients [7].

Table 1
Diagnostic criteria for major depressive disorder as put forth by DSM-IV (Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition).

Major depressive disorder DSM-IV diagnostic criteria
• Major criteria
1. Depressed mood most of the day, nearly every day, as indicated either by subjective report (e.g. feels sad or empty) or observation made by others
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day, as indicated either by subjective account or observation made by others. Do not include symptoms that are clearly due to general medical condition or mood-incongruent delusions or hallucinations
• Minor criteria (at least 2)
1. Significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day
2. Insomnia or hypersomnia nearly every day
3. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
4. Fatigue or loss of energy nearly every day
5. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
6. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
7. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

On the other hand HF syndrome is characterized by the inability of cardiac muscle to maintain sufficient blood supply to peripheral tissues in order to satisfy metabolic demands. As a result of tissue hypoperfusion and fluid retention neuro-endrocrine mechanisms are activated. Sympathetic autonomous neural system, RAAS axis and hormones like aldosterone, catecholamines and glucocorticoids all have a key role in the pathophysiology of HF. Additionally raised circulating levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-6 and interleukin-1β (IL-1β) [32] have a negative impact on myocardial cells function. More importantly, the levels of these pro-inflammatory mediators can be considered predictive factors for HF development [33].

Several theories have tried to explain the causative relationship between HF and major depression. It is well established that depression and HF share a common biochemical background that includes the main hormones – mediators of stress. In addition their common background is highlighted further by the observation that both depressed and HF patients exhibit some common features, like immune alterations, inducing proinflammatory cytokines production, creating a subclinical proinflammatory and prothrombotic state. The neuro-endocrine dysregulation involves autonomic and cardiovascular dysregulation including increased sympathetic drive, withdrawal of parasympathetic tone, cardiac rate and rhythm disturbances, and altered baroreceptor reflex function. This dysregulation can be assessed by heart rate variability (HRV), an index with prognostic value, which is indeed decreased both in patients with depression [34] and HF [35]. This has been demonstrated also in animal models where depression is associated with higher basic heart rate and sympathetic activity [36] as well as with increased arrhythmogenicity [37], common features in HF. In addition animal models of HF are prone to the development of depressive symptoms. Experimentally induced HF in rats results in behavioral modification and exhibition of depressive symptoms [38]. Cell studies further support the hypothesis of the common neuro-humoral background of HF and major depression. In a recent study it was demonstrated that there is an increased expression of serotonin receptors 5-HT(4) in rat myocardium in HF [39]; this observation provides a rational connective mechanism for the co-morbidity of depression and HF [39]. Despite the fact that the exact biochemical mechanisms remain largely unknown, all these accumulating evidence demonstrate that HF and depression share a common neuro-endocrine background that can partly explain their increased co-morbidity. Overall, increased sympathetic activity, neuro-hormonal pathways activation and a proinflammatory and prothrombotic state seem to be common features of both HF and depression.

4. Safety of antidepressants in cardiovascular disease

Antidepressants adverse effects on cardiovascular system have long been recognized. Indeed many studies have linked antidepressants use in HF with increased mortality. Both the safety of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) has been questioned [40].

Table 2
Etiologic factors for the development of major depression in heart failure.

• Underlying biological mechanisms
Increased activity of the rennin–angiotensin–aldosterone axis
Increased activity of the hypothalamus–hypophysis axis
Alterations in autonomous nervous system activity
Low grade systemic inflammation
Increased serotonin levels
Increased catecholamine levels
• Psychosocial factors
Reduced ability for exercise and self-service
Poor psychological and social support

The arrhythmiogenic effect and QT interval prolongation of drugs such as phenothiazines and TCAs, which have type IA antiarrhytmic properties, is well established [41]. TCA overdose may trigger AV block, bundle branch block or ventricular arrhythmias. The Cardiac Arrhythmia Suppression Trial (CAST) [42] suggested that TCAs should be avoided in patients with cardiovascular disease (CVD) due to the risk of life-threatening arrhythmias especially when co-prescribed with other drugs prolonging QT interval [43]. On the other hand SSRIs have lower risk of adverse anti-cholinergic and anti-histaminergic side effects [43]. Several clinical trials have also demonstrated a negative impact of TCAs on blood pressure. Orthostatic hypotension seems to be a common side-effect after imipramine or bupropion administration in HF patients [44,45], even though bupropion might be a safer alternative solution [45]. Trimipramine is also relatively safe and effective, as it was associated with a low rate of complications when administered in HF patients and depressive symptoms were improved [46]. Nevertheless the adverse effects of TCAs on cardiac conduction and rhythm may adversely affect cardiovascular outcome. Cohen et al. [47] in a cohort of 2247 patients with depression that were followed-up for up to 4.5 years, demonstrated that TCAs use increases MI risk, an adverse effect alien to SSRIs.

Monoaminoxidase (MAO) inhibitors have known adverse effects on blood pressure (including orthostatic hypotension and risk of hypertensive crisis) and therefore have not been evaluated in HF patients [48]. Nevertheless a myocyte-rescue effect of MAO-inhibitors has been suggested in animal models with beneficial effects on myocardial redox state and cardiac function [49].

On the other hand studies on SSRIs have shown that this class of antidepressants combines efficacy and safety, as SSRIs are associated with lower rate of adverse cardiovascular effects [47]. Goettlieb et al. [50] showed that SSRIs, particularly paroxetine, are effective drugs for depression treatment in patients with CVD. Paroxetine seems to have a lower rate of adverse cardiovascular effects compared to nortriptyline (a TCA) when administered to patients with ischemic heart disease [51]. In the large multicentre SADHART study (Sertraline Treatment of Major Depression in Patients with Acute MI or Unstable Angina) [52], the relative efficacy and safety of SSRIs was demonstrated compared to placebo, even in high cardiovascular risk patients as those with recent MI or unstable angina. Sertraline did not carry the risk of any life-threatening medical conditions [52]. Furthermore in depressed patients post recent MI sertraline is well tolerated [53] and accelerates the restoration of HRV, a well identified predictor of clinical outcome [54]. Another SSRI, fluoxetine, seems to be safe in patients with cardiac disease. No adverse effect on heart rate, blood pressure or ejection fraction has been observed with the use of fluoxetine in depressed patients with cardiac disease [55] or MI [56]. Additionally it seems that fluoxetine has a positive effect on cardiac function [57]. The recent CREATE trial (Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy) [58] provided an additional confirmation of SSRIs (citalopram) safety and efficacy in depression treatment in CVD patients. Furthermore a subsequent sub-analysis of CREATE implicated that SSRIs might have beneficial effects on endothelial function and nitric oxide bioavailability [59]. Nevertheless it should be noted that SSRIs might have also some adverse effects, mainly increased bleeding risk due to their suppressive effects on platelets [60].

The majority of studies conducted demonstrate the comparative advantage of SSRIs in terms of cardiovascular safety. Even in longer follow-up periods SSRIs use has been associated with a low rate of adverse side-effects or life-threatening drug–drug interactions.

5. Depression treatment and heart failure clinical outcome

Despite the close association of depression with adverse clinical outcomes in HF patients [12,13,16,18], it is still obscure whether depression treatment can alter HF prognosis [40].

Non-pharmacologic treatment of depression is known to improve exercise capacity and emotional status of patients with HF [61]. Furthermore cognitive behavioral therapy is thought to be superior in preventing relapsing depression than pharmacotherapy [62]. However CREATE trial [58] suggested that interpersonal psychotherapy had no added value over clinical management for depression treatment. Despite the possible benefits of non-pharmacologic treatment on top of optimal drug therapy or separately in improving depressive symptoms, its capacity in conferring any benefits on clinical outcome of HF is debatable. Antidepressants have several cardiovascular effects apart from anti-depressive effects that might modulate HF clinical outcome. However it should be noted that the recently published SEARCH study (Support, Education, and Research in Chronic Heart Failure) [63] demonstrated an improvement in HF symptoms at 12 months after an 8-week mindfulness-based psychoeducational intervention in depressed HF patients.

The ENRICHD trial [64] was a landmark attempt to elucidate the associations between antidepressive treatment and HF prognosis. In this large trial 2481 MI patients were recruited and followed prospectively in order to examine the effects of antidepressive behavioral treatment supplemented with an SSRI whenever necessary on clinical outcome. After a mean follow-up of 29 months it was demonstrated that depression treatment (cognitive behavioral treatment ± SSRI) did not modify in any way the patients' prognosis [64]. Despite the fact that ENRICHD was not specifically focused on HF patients, it did provide some key points of interest regarding the relation of depression treatment with CVD prognosis. Another important randomized controlled trial the MIND-IT [65] demonstrated that antidepressant treatment (mirtazapine ± citalopram ± psychotherapy) did not improve prognosis in patients with depression post-MI. Nevertheless a post-hoc analysis of MIND-IT [66] suggested that nonresponse to treatment of post-MI depression may be associated with cardiac events.

Notably the effects of depression treatment on HF clinical outcome may be dependent on antidepressants class. Beta blockers are considered essential in HF treatment since it is well confirmed that they improve clinical outcome of these patients. Nevertheless since all antidepressants interfere in adrenergic signaling they may possibly affect response of HF patients to β-blockers therapy. Indeed in a recent observational study on a cohort of 154 end-stage, NYHA IV, HF patients under antidepressant medication, we observed that combination of β-blockers with TCA or SNRIs had an adverse effect on clinical outcome of these patients [7]; on the other hand when b-blockers were combined with SSRIs a striking beneficial effect on survival was noted, (HR [95%CI] 2.201 [1.255–3.860], $p = 0.006$ for those under SSRIs without b-blockers vs those under SSRIs + β-blockers) [7].

Admittedly these findings are not easy to be extrapolated and should be confirmed by other prospective studies also. However a rational mechanistic effect seems to exist. HF is characterized by increased expression of 5-HT_4 receptors on failing myocardium. Stimulation of 5-HT_{2A} receptors has been demonstrated to lead to improved cardiac contractility without intracellular Ca^{2+} overload, while serotonergic receptors have been also linked to a myocyte-rescue effect [39,67]. The suggested improvement in endothelial function through raised nitric oxide bioavailability might be also important [59]. These serotonin-induced actions therefore may account for the improved HF patients' survival in cases of combined SSRI and β-blockade treatment (Fig. 1a). On the other hand TCA/SNRIs lead to increased circulating levels of catecholamines. Even in the presence of β-blockade, this may lead to overstimulation of α_1 myocardial adrenergic receptors by catecholamines, causing raised myocardial oxygen demands and Ca^{2+} overload. Additionally this class of antidepressants can lead to severe hypotension via stimulation of α_2 adrenergic receptors in CNS, especially in presence of concomitant β-blockade. All these adverse myocardial effects of TCAs together with QT-prolongation and increased arrhythmogeneicity may unfavorably affect clinical outcome of HF patients (Fig. 1b).

An additional issue that remains also to be clarified is the effect of SSRIs on platelets and thrombosis. Data support that SSRIs decrease the serotonin-induced activation of platelets [43], but we do not know yet the clinical implication of this effect. Ziegelstein et al. [60] demonstrated that patients with ACS, under SSRI treatment on top of conventional antiplatelet therapy, had a lower risk of myocardial ischemia, rise of cardiac enzymes and development of HF during hospitalization compared to those not receiving SSRIs, at the expense however of increased bleeding risk [60].

Despite the fact that the majority of data comes from small, observational studies, a relative advantage of SSRIs compared to TCAs in depression treatment in HF patients. Up to present SSRIs have been correlated with a clearly lower rate of adverse cardiovascular effects, while it seems that they constitute efficient drugs for depression treatment in the context of HF. However positive data exists also in favor of TCAs/serotonin norepinephrine reuptake inhibitors (SNRIs). In a recent study we conducted in HF patients [8], circulating levels of proinflammatory molecules were decreased in those HF patients under TCA/SNRI treatment compared to those under SSRIs or without

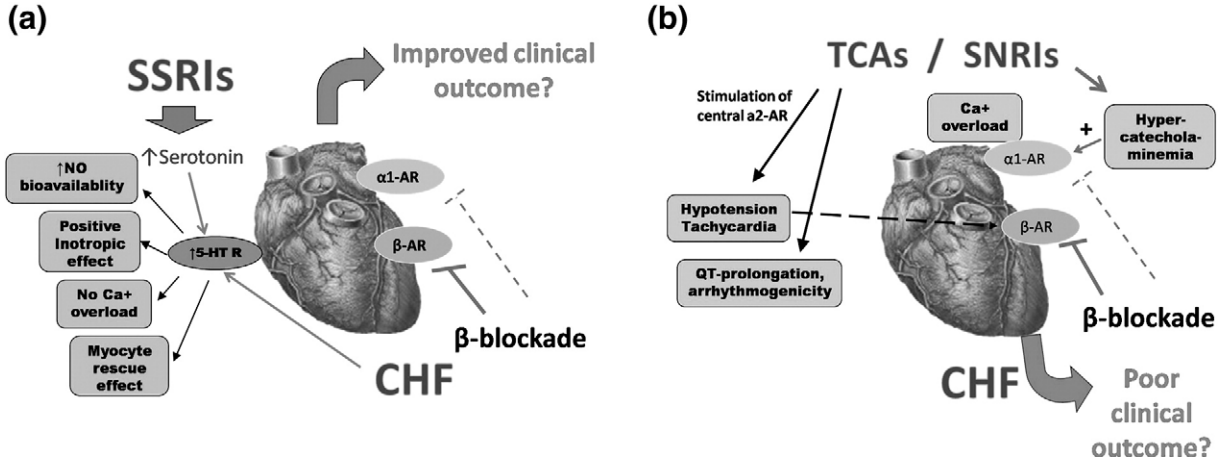

Fig. 1. Antidepressants and Heart Failure outcome – proposed mechanisms and interactions with β-blockers. (a) The possible beneficial effect of selective serotonin reuptake inhibitors (SSRIs) on clinical outcome in congestive heart failure (HF) patients may be associated with an improvement in cardiac contractility without leading to Ca^{2+} overload. Furthermore it has been suggested that stimulation of cardiac 5-HT receptors induces a myocyte-rescue effect, while a beneficial effect on nitric oxide (NO) bioavailability and endothelial function has also been suggested. (b) Raised catecholamines levels by tricyclic antidepressants (TCA) or serotonin norepinephrine reuptake inhibitors (SNRIs) administration may lead to overstimulation of α1 myocardial adrenergic receptors (AR), even in presence of beta blockade, raising myocardial oxygen demands and intracellular Ca^{2+}. Other well-known adverse cardiovascular side effects, like hypotension, tachycardia, QT prolongation and increased risk of cardiac arrhythmias may also be associated with a poorer clinical outcome in heart failure patients.

depression. TCA/SNRIs significantly reduced plasma levels of proinflammatory cytokines, like IL-6 and TNF-a, as also of acute phase reactants like CRP and fibrinogen, all molecules with a predictive value in HF [8].

Due to the lack of large randomized clinical trials in HF patients a certain conclusion cannot be drawn. However it seems that the cardiovascular effects of antidepressants rather than their antidepressive effects per se can confer possible benefits on HF prognosis. Pharmacological treatment affects not only depressive symptoms but is positively or negatively implicated in cardiac function. The choice of antidepressive treatment seems also to have a significant impact on the underlying inflammatory mechanisms and potentially also affect

Table 3
Efficacy and safety of depression treatment in patients with cardiovascular disease.

Study	Design–population	Depression assessment	End-points	Conclusions
Depression post MI				
ENRICHD [64]	CBT for 6 months ± group therapy ± SSRI in 2481 depressed patients (1084 women, 1397 men) enrolled within 28 days after MI (RCT)	DSM-IV criteria HAM-D(17) scale	Composite primary: death or recurrent MI; secondary: change in HAM-D(17) or ESSI scores (for LPSS) at 6 months.	CBT ± SSRI did not increase event-free survival. Depression and LPSS were improved although less than expected.
SADHART [52]	Sertraline (50 to 200 mg/d) or placebo for 24 weeks in 369 hospitalized MI or UA patients with MDD (RCT)	DSM-IV criteria HAM-D(17) scale CGI-I scale	Primary: change in LVEF, surrogate cardiac measures (heart rate, blood pressure, PR interval, QRS duration, QTc interval and SDNN) Secondary: cardiovascular adverse events, change in HAM-D(17) or CGI-I scales	Sertraline is safe and effective recurrent depression treatment in patients with recent MI or UA
MIND-IT [65]	Intervention (mirtazapine ± citalopram ± psychotherapy, $n=209$) or care as usual ($n=122$) in 331 depressed post-MI patients, follow-up for 18 months (RCT)	BDI, CIDI, HAM-D(17)	Primary: cardiac events (cardiac death or non-fatal MI, myocardial ischaemia, coronary revascularization, HF or ventricular tachycardia) Secondary: depression improvement, QoL	Antidepressant treatment did not alter long-term depression status post-MI or improve cardiac prognosis
Honig et al. [71]	Mirtazapine or placebo in 91 post-MI patients with minor or MDD for 24 weeks (RCT)	DSM-IV criteria HAM-D(17) scale BDI, SCL-90, CGI	Primary: reduction in HAM-D(17) scale Secondary: change in BDI, dSCL-90, CGI	Mirtazapine is effective and safe in the treatment of post-MI depression.
Strik et al. [57]	Fluoxetine or placebo for 9 weeks in 54 depressed MI-patients (RCT)	HAM-D(17) SCL-90	Primary: (efficacy) change in HAM-D(17) or SCL-90; Secondary: (safety) ECG, echocardiography	A trend towards depression improvement with fluoxetine, no adverse cardiac effects
McFarlane et al. [54]	Sertraline (50 mg/d) or placebo for 6 months in 38 post-MI depressed patients plus 11 control MI patients (RCT)	IDD	HRV recovery post MI	Sertraline facilitates SDNN-HRV recovery post MI
SADHAT [53]	Sertraline in 26 depressed post-MI patients (open label)	DSM-IV	Efficacy – cardiovascular safety (heart rate, blood pressure, cardiac conduction, EF%)	Sertraline was associated with depression improvement and was well tolerated
Depression in stable CAD patients				
CREATE [58]	12 weeks of IPT plus CM ($n=142$) or CM only ($n=142$); 12 weeks of 20–40 mg/d citalopram, ($n=n=142$) or placebo ($n=n=142$) in 284 CAD patients (RCT, 2×2 design)	DSM-IV criteria HAM-D(24) scale BDI–II	Primary: change in HAM-D(24) scale Secondary: change in BDI–II	Citalopram is effective for depression treatment in CAD patients. IPT has no additional value over CM
Depression in HF patients				
Gottlieb et al. [50]	Paroxetine CR or placebo for 12 weeks in 28 HF patients (RCT)	IDS-C BDI	Efficacy: changes in BDI score, QoL: changes in MLWHFQ and SF-36	Paroxetine CR significantly improved depression and psychological aspect is of QoL in HF patients
Glassman et al. [44]	Single dose of imipramine in 15 depressed patients with LVD (open label)	–	Primary: changes in EF% Secondary: cardiovascular safety	Imipramine does not modify EF% but may be induce severe hypotension (7/15 patients)
Roose et al. [72]	Imipramine or bupropione in 10 patients with LVD (RCT, cross-over design)	–	Cardiovascular safety (EF%, blood pressure)	Imipramine caused severe orthostatic hypotension; bupropione is a safer antidepressant in HF patients
Roose et al. [45]	Bupropione (442 ± 47 mg/d) for 3 weeks in 36 depressed HF patients with ventricular arrhythmias and/or conduction delays (open label)	DSM-III	Cardiovascular safety (pulse, blood pressure, 24 h-ECG, EF%)	Bupropion is relatively safe in HF patients. However in 14% of patients bupropion deteriorated arterial hypertension
Roose et al. [55]	Fluoxetine (60 mg/d) for 7 weeks in 27 depressed patients with HF, conduction disease and/or ventricular arrhythmias (open label)	DSM-IV	Cardiovascular safety (heart rate, 24 h-ECG, EF%, conduction intervals, blood pressure)	Fluoxetine treatment was not associated with the cardiovascular side-effects
Cohn et al. [46]	Trimipramine (50–200 mg/d) for 28 days in 22 depressed HF patients (NYHA I–III) (open label)	HAM-D	Primary: (efficacy) HAM-D Secondary: cardiovascular safety (24 h-ECG, blood pressure, conduction intervals)	Trimipramine is efficient and relatively safe antidepressant in HF patients. A slight prolongation of QRS was observed.
Patients with depression				
Cohen et al. [47]	2247 patients under antidepressants and 52,750 controls followed-up for up to 4.5 years (observational)	–	Primary: hospitalization or death due to MI	TCAs, but not SSRIs, were associated with an increased risk of MI compared to controls

BDI: Beck's Depression Inventory, CAD: coronary artery disease, CBT: cognitive behavior therapy, CGI-I: Clinical Global Impression Improvement scale, CIDI: Composite International Diagnostic Interview, CM: clinical management, DSM-IV: Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, EF: ejection fraction, ESSI: ENRICHFD Social Support Instrument, HAM-D(17): 17-item Hamilton Rating Scale for Depression, HRV: heart rate variability, IDS-C: Inventory for Depressive Symptomatology–Clinician-Rated, IDD: Inventory to Diagnose Depression, IPT: interpersonal psychotherapy, LPSS: low perceived social support, LVD: left ventricular dysfunction, MDD: major depressive disorder, MI: myocardial infarction, MLWHFQ: Minnesota Living with Heart Failure Questionnaire, QoL: quality of life, SCL-90: Symptom Check List 90, SDNN: standard deviation of 24-hour N–N intervals, SF-36: Medical Outcomes Study 36-Item Short Form survey, SSRI: selective serotonin reuptake inhibitor, TCA: tricyclic antidepressants, UA: unstable angina,

clinical outcome [8]. However the existing data should be interpreted with caution since is originated mainly from observational studies. An important limitation is that the prospective studies conducted so far included only small population numbers and limited event rates. An overview of the studies on depression treatment in patients with CVD is given in Table 3.

In overall, SSRIs seem to be a safer and effective choice for the treatment of depressed HF patients, nevertheless their long-term effects on HF prognosis remains to be confirmed. Drug–drug interactions need to be evaluated and light should be shed on antidepressants effects on cardiac function, specifically on the failing myocardium. Clinical hard evidence from new large prospective studies regarding the effects of antidepressants on clinical outcome and survival of patients with HF is therefore needed. A large randomized double-blind, placebo-controlled clinical trial, the MOOD-HF (MOrbidity, mOrtality and mood in Depressed Heart Failure patients), is designed to prospectively investigate the effects of escitalopram on hard clinical end-points in NYHA II to IV HF patients [68]. Furthermore the congestive HF arm of SADHART (SADHART-CHF) [69] is intended to examine the comparative effects of sertraline over placebo on the prognosis of HF patients.

6. Conclusion

Conclusively, depression and heart failure share a common neurohumoral background which is possibly responsible for the high rates of their co-morbidity. Presence of depression negatively affects prognosis of heart failure patients. However up to present we do not know if depression treatment modifies clinical outcome of heart failure patients and due to lack of hard evidence, depression, as a modifiable risk factor, is frequently overlooked by clinicians. Data suggests that selective serotonin reuptake inhibitors are effective and safe drugs in the context of heart failure, while they may also confer beneficial cardiovascular effects. Despite the contradictory data, to which answers will be provided by large prospective studies being already conducted, choosing the right antidepressant in depressed heart failure patients might have important clinical implications. Evidence-based recommendations from randomized clinical trials are still needed for elucidating depression treatment in heart failure patients.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [70].

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