Mental Health-Related Risk Factors and Interventions in Patients with Heart Failure.

A Position Paper endorsed by the European Association of Preventive Cardiology (EAPC).

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Abstract

The prevalence and public health burden of chronic heart failure (CHF) in Europe is steadily increasing mainly caused by the ageing population and prolonged survival of CHF patients. Frequent hospitalizations, high morbidity and mortality rates, and enormous healthcare costs contribute to the health related burden. However, multidisciplinary frameworks that emphasize effective long-term management and the psychological needs of the patients are sparse. The present position paper endorsed by the European Association of Preventive Cardiology (EAPC) provides a comprehensive overview on the scientific evidence of psychosocial aspects of heart failure (HF). In order to synthesize newly available information and reinforce best medical practice, information was gathered via literature reviews and consultations of experts. It covers the evidence for aetiological and prospective psychosocial risk factors and major underlying psycho-biological mechanisms. The paper elucidates the need to include psycho social aspects in self-care concepts and critically resumes the current shortcomings of psychotherapeutic and psycho-pharmacological interventions. It also highlights the need for involvement of psychological support in device therapy for HF patients and finally calls for more, earlier and better palliative interventions in the final stage of HF progression.

Introduction

Heart Failure (HF) is a major public health challenge worldwide. The European Society of Cardiology defines HF as a clinical syndrome characterized by symptoms (e.g., breathlessness, ankle swelling, tiredness, and fatigue) and/or signs (e.g. elevated jugular venous pressure, hepatojugular reflux, and a third heart sound) caused by a structural and/or functional cardiac pathology, leading to reduced cardiac output[1]. The diverse clinical presentations of HF can be described in terms of three broad dimensions: the role of left ventricular function, the timing of HF symptoms and functional limitations related to HF. The main terminology used to describe HF subtypes is related to the measurement of left ventricular ejection fraction (LVEF). Patients with signs and/or symptoms of HF are grouped into those with 1) HF with preserved LVEF (≥50%, HFpEF), 2) HF with mid-range reduced LVEF (40-49%, HFmrEF), and HF with reduced LVEF (< 40%, HFrEF)[1]. Another frequently used terminology related to HF refers to the time course of heart failure. Patients who suffer from HF for already longer periods are often classified to have "chronic HF (CHF)". Chronic stable HF may worsen/decompensate acutely resulting in aggravation of symptoms/signs, often leading to hospital admission. De novo HF may also present acutely (e.g., in the setting of acute myocardial infarction) or in an incremental fashion, (e.g., patients with dilated cardiomyopathy (DCM)[1]. A third broadly implemented terminology relates to the severity of symptoms and functional limitations usually described by the New York Heart Association (NYHA) functional classification[2]. It is important to emphasize that these three dimensions of CHF do not necessarily overlap (e.g., left ventricular function measures in HF correlate poorly with symptom severity[1]. These differences in the dimensions of HF are attributable to compensation mechanisms in cardiac structure and function and patients also adjust their daily behaviours to manage their symptoms or under-report the severity of their symptoms, resulting in poor correspondence between HF-related measures such as measures of left ventricular function, chronicity of HF and functional limitations.

HF is caused by various aetiologies which can be grouped into underlying pathologies that lead to: 1) diseased myocardium causing systolic and/or diastolic ventricular dysfunction (e.g., ischemic heart disease), 2) abnormal loading conditions (e.g., hypertensive cardiomyopathy, abnormalities of the valves, pericardium, and endocardium), and 3) arrhythmias (e.g. atrial tachyarrhythmias)[1].

The prevalence and public health burden of chronic HF in Europe is steadily increasing. A recent analysis of health records of 4 million individuals from the UK Clinical Practice Research Datalink evidenced an increase in the absolute number of prevalent HF cases of 23% from 2002 to 2014 mainly caused by the ageing population and prolonged survival of patients with HF, despite a decrease of HF incidence by 7%[3]. Socioeconomically deprived individuals were more likely to develop HF and did so earlier in life[3]. The high individual and societal burden of HF are associated with frequent hospitalizations, high morbidity and mortality rates, and enormous healthcare costs [4]. However, many patients with CHF are not receiving optimal care with a multidisciplinary approach that emphasizes effective long-term management and the psychological needs[5 6 7].

Although substantial progress has been made in recent years particularly within cardiac rehabilitation [7], psychosocial risk factors and mental health-related issues in HF remain often under-diagnosed and hence undertreated[1]. To address this issue, the European Association of Preventive Cardiology (EAPC) convened a task force with the remit to comprehensively review the published evidence on the role of psychosocial and psychobiological risk factors for incident HF and HF progression, and identify areas in which these factors could be used to optimize treatment in patients with chronic HF. This paper provides expert recommendation resulting from the EAPC Task Force discussion on how to improve self-care and other health behaviours and outline interventions that

target the psychosocial correlates of chronic HF, including the importance of palliative care and advanced care planning.

1. Psychosocial risk factors for incident CHF and clinical outcomes in patients with CHF

1.1 Psychosocial risk factors for incident CHF

Large-scale epidemiological studies on the association of psychosocial factors with incident HF have primarily focused on depression, anxiety, anger/hostility, and social isolation/loneliness. As displayed in Table 1, evidence is strongest for the predictive value of major depression. Inconsistencies in the literature probably reflect the multifactorial aetiology and the long-time intervals between the psychological assessment and incident CHF. However, findings are strong enough to encourage clinicians to assess depressed mood, and possibly also anger proneness and social isolation in patients at high risk of CHF during clinical evaluation.

1.2. Association of psychosocial risk factors for clinical outcomes and mortality in patients with CHF

Extensive research has addressed the predictive value of psychosocial factors on the clinical prognosis in patients with established CHF. Table 2 summarizes the most recent meta-analyses suggesting that depression and social isolation/loneliness are independent contributors to an adverse long-term course of patients with CHF (hospitalisation, mortality), thus emphasizing the urgent need to consider these conditions in treating CHF patients in everyday life. Patients with CHF may be more susceptible to social isolation as they tend to be older and may suffer from CHF-induced physical and mobility limitations[8] but also from disrupted social relationships due to life course factors (e.g. being widowed). The role of anxiety and anger/hostility has less been investigated.

Figure 1

Although poor LV function does not play a primary causal role for depression in CHF[9], functional limitations, biological correlates [10] and psychological reactions to having a life-threatening disease are primary factors driving depression in patients with CHF. As illustrated in Figure 1, disease progression is likely to facilitate restrictions in daily activities and increased awareness of limited life expectancy, resulting in transient episodes of despair and hopelessness, which may induce reduced adherence with effective treatment ending up in refractory depression.

Box 1: Position on psychosocial risk factors for incident CHF and CHF progression

1. **State-of-the-science**:

- Evidence from population based studies indicate that depression and social isolation/loneliness are associated with increased risk for incident (new-onset) HF. For other psychosocial risk factors (e.g. anxiety, anger/hostility), current evidence is insufficient.
- For patients with CHF, there is strong evidence that depression is associated with increased risk of HF progression and mortality; the predictive value of other psychosocial factors requires further research.

2. Knowledge gaps:

- Further research is needed to determine high-risk subgroups based on psychological and social factors, in combination with biological processes and health behaviours relevant to HF progression.
- Research on the bi-directional relationship between depression and the clinical sequelae of CHF (e.g., symptoms and functional limitations) is still in its infancy. More research is needed whether interventions targeting one “pathway” of these bi-directional processes will also positively influence the related pathways relevant to HF progression.
- The contributions of contextual socio-economic variables require critical consideration (e.g., loss of work or social engagement).
- Knowledge gaps exist for the importance of follow-up periods and age-, sex-, and ethnicity-related issues in comorbid mental health disparities.

Table 1. Psychosocial factors and incident HF: Findings from observational prospective population based studies.

Authors (year)	Study type (Acronym)	Psychosocial Factors	Sample size Total N	Risk of incident HR (95%CI) *)	Comments
Cené et al. (2012) [11]	Prospective cohort study (ARIC)	Social isolation	12,976	1.18 (1.06-1.32)	Adjusted for age, sex, race/study community, and education. Effect-mediation by (vital) exhaustion
Gustad et al. (2014) [12]	Prospective population-based study (HUNT)	Depression	62,567	1.41 (1.07-1.87) 1.07 (0.87-1.30)	Risk for severe and moderate depressive symptoms
		Anxiety		1.00 (0.70-1.43)	
Garfield et al. (2014) [13]	Retrospective cohort study baseline age 50-80 yrs (VA-Database)	Depression	236,079	1.56 (1.45-1.67)	Major depressive disorder (comorbid anxiety excluded)
		Anxiety		1.46 (1.35-1.58)	For high levels of anxiety (composite of GAD, PTSD and Anxiety Disorder Un-specified (comorbid Depression excluded
		Depression +		1.74 (1.61-1.88)	Comorbid Depression and Anxiety
Ogilvie et al. (2016) [14]	Prospective cohort study (MESA)	Depression	6,782	1.06 (0.91-1.22)	Comparison per inter-quartile. Comparisons of highest vs. lowest quartile also presented.
		Anxiety		0.91 (0.74-1.13)	Overall effects stronger for individuals with poor physical health
		Anger		1.00 (0.83-1.20)	
		Hostility		1.16 (0.96-1.40)	
		Chronic stress		1.25 (1.00-1.57)	
Kucharska-. Newton et al. (2014) [15]	Prospective cohort study mean age 56.9 yrs (ARIC)	Anger (trait)	13,171	1.44 (1.23-1.69)	Age-adjusted (Model 2) Effects stronger for men Association was atten-uated when adjusting for vital exhaustion

HF – heart failure; *) Hazard rates (HR) > 1.0 indicate significantly increased risks with regard to the special endpoint under consideration, CI – confidence interval; yrs – years

Table 2. Association of psychosocial risk factors with clinical outcomes and mortality in patients with chronic heart failure

Study	Study type	Psychosocial	Number of Risk factors	Follow up studies (k) in meta-analysis (total sample size: N), duration	HR (95%CI)	Outcome and comments
Meta-analyses						
Rutledge et al. 2006 [16]	prospective cohort studies	Depression	8 (1,862)	6 months->4 yrs	2.1 (1.7-2.6)	Mortality and major clinical events
Fan et al. 2014 [17]	Prospective cohort studies	Depression	9 (4,012)	>1 yr Risk of minor depression was not significant (HR=1.04; CI=0.75-1.45)	1.98 (1.23-3.29)	Mortality (all-cause)
Sokoreli et al. 2016 [18]	Prospective cohort studies	Depression	26 (80,627)	> 6 months Unadjusted HR=1.57; 95%C= 1.30-1.89	1.40 (1.22-1.60)	Mortality (all cause)
		Anxiety	6 (17,,214)	> 6 months	1.02 (1.00-1.04)	Mortality (all cause) Not conclusive because of < number of studies
Gathright et al. 2017 [19]	Prospective cohort studies	Depression	18, (5,629)	756 days -12 yrs	1.20 (1.10-1.31) unadjusted HR=1.75, 95%CI=1.33-2.30	Mortality (all-cause) Effects stronger for patients ≥ 65 years
Machado et al.	Review of	Depression	22	>5 yrs	1.46 (1.30-1.65)	Mortality (all-cause)

2018 [20]	systematic reviews and meta-analyses			Multiple conditions examined (k=246). Of studies with HF (k=22) 3418 had depression and 4345 died during follow-up The N of HF is not reported total N = 3,825,380. Includes the 3 meta-analyses reported above		
Kewcharoen et al. 2020 [21]	Prospective cohort studies	Depression	10 (53,165)	> 1 week	1.54 (1.22-1.94)	Re-hospitalization 6,194 had depression Risks for short ≤90 days and > 90 were similar
Heidari Gorji et al. 2019 [22]	Prospective cohort studies	Social isolation	13 (6,468)	> 1 week	1.55 (1.39-1.73) Odds ratios are reported	Re-hospitalization
Individual studies published after the meta analysis						
Adelborg et al. 2016 [23]	Registry-based study	Depression History of depression, not post HF depression	204,523	>1 year	1.03 (1.01-1.06)	Mortality (all-cause)
Freedland et al. 2016 [24]	Prospective cohort study	Depression	662	20 yrs	1,64 (1.27-2.11)	Mortality (all-cause)
Saito et al. 2019 [8]	Prospective cohort study	Social isolation	148	90 days	1.85 No 95%CI reported, log rank test for Kaplan-Meier p=0.036; regression analyses provided (LASO)	Re-hospitalization
Sokoreli et al.	Prospective	Depression	242	360 days	3.0 (1.3-7.0)	Mortality (all-cause)

2016 [25]	cohort study (OPERA-HF)					Patients hospitalized for HF progression Moderate-to-severe depression This study overlaps with 2018 report on larger sample.
Sokoreli et al. 2018 [26]	Prospective cohort study (OPERA-HF)	Depression Anxiety Cognitive dysfunction Living alone	779	> discharge > 1 yr: N=641	1.74 (1.24-2.44) 1.67 (1.21-2.30) 1.43 (0.90-2.28) HRs for first event 1.04 (0.85-1.27) adjusted for covariates	Psychosocial assessments (HADS and other) complete for > 4 in 54% of pts 41 death and N=518 had readmission.
Vinggaard et al. 2020 [27]	Registry-based cohort study	Loneliness Social isolation	987	1 year Data for combined cardiac cardiac patients/N=13.443	2.92 (1.55-5.49) 2.14 (1.43-3.22)	Mortality (all-cause)
individual studies not included into the meta-analyses being cited						
Endrighi et al. 2016 [28]	Prospective cohort study	Perceived stress	144	9 months	1.10 (1.04-1.17) Odds ratios reported	Mortality and re-hospitalisation
Rafanelli et al. 2016 [29]	Prospective cohort study	Hostility	60	4 yrs	2.38 (1.04-5.45)	Mortality and re-hospitalisation No associations for DSM-based depression and well-being with end-points

Keith et al. 2017 [30]	Prospective cohort study	Anger / Hostility	146	3 yrs	no risk ratios reported	Re-hospitalisation Outward anger expression showed significant Regression coefficients with outcome measure

Data are presented for meta-analyses, individual studies that were published after the meta=analyses, and individual studies on psychosocial factors that have not yet been reviewed in meta-analyses

CI – confidence interval
ES – effect size
HF – heart failure
HR – hazard ratio
MDD – major depressive disorder
NS – not significant in multivariable analyses
OR – odds ratio
pts - patients
yrs – years

2. Autonomic nervous system dysregulation, neuro-humoral processes, and inflammation as mediators

A compensatory neuro-hormonal overdrive, as a consequence of an increasing decline of the contraction and relaxation capacity of the heart, is one major pathway to decompensated heart failure. In early stages of the disease process, the activation of the sympathetic branch of the autonomic nervous system (ANS) and the endocrine renin-angiotensin-aldosterone system (RAAS) contribute to the maintenance of an adequate intravascular volume [31]. Sustained neuro-hormonal activation, however, drives systemic vascular resistance and increased LV afterload which in turn increases myocardial demand and LV end-diastolic pressure and promotes inflammatory pathways[32] (usually framed as "*inflammatory reflex*").

Severe sustained psychological distress results in autonomic, neuroendocrine and inflammatory responses in order to support the organism to cope with high-demand conditions[10]. They substantially overlap with the compensatory neuro-hormonal overdrive associated with CHF and therefore likely result in a synergism between the neurobiological correlates of CHF and psychosocial distress - further reinforcing their deleterious effects on the progression of CHF (Figure2) best framed within the allostatic load model according to which an initially adaptive compensatory mechanism can develop into maladaptive processes. Although the concept is intriguing, the empirical evidence is still in its infancy.

Figure 2

Autonomic nervous system dysregulation: Sympathetic overdrive and parasympathetic withdrawal are clinically common features of sustained adverse psychosocial conditions which can be indexed with heart rate variability (HRV) measures and impedance cardiogram analysis[33]. However, to date no studies have investigated an additive impact of psychosocial distress and autonomic dysregulation on CHF progression. Clinical studies that have addressed HRV response patterns in CHF patients revealed rather blunted than exaggerated reactions[34]. A prospective follow-up study of patients with systolic CHF demonstrated an excess mortality risk among those who exhibited lowest cardiovascular reactivity to mental stress most likely reflecting a suboptimal pressure responses as a prognostic relevant factor in CHF progression[35].

Neuroendocrine processes: Impairments of the hypothalamic-pituitary-adrenal (HPA) axis as reflected by increased serum cortisol levels were found in CHF patients[36] and, more importantly, contribute substantially to disease progression[37,38]. Thus, sustained stress-induced hypercortisolemic states further amplify the critical neuroendocrine activation in patients with CHF. In contrast to these findings, a recent investigation revealed heightened evening salivary cortisol levels[39] as an independent predictor of decompensated chronic CHF which points to a disturbed or even blunted circadian rhythm of cortisol secretion. Of note, a synergistic evaluation of cortisol levels in CHF patients with and without comorbid mental health disparities has not been undertaken to date. Cortisol may also activate mineralocorticoid receptors in CHF. The mineralocorticoid aldosterone has gained limited attention as stress hormone in human stress biology so far. Yet, findings from a large population-based study showing that the combined presence of depression and social isolation was associated with a substantial increase in aldosterone levels, particularly in men, point to considerable psychosocial involvement in the activation of the renin-angiotensin-aldosterone (RAAS) system[40].

Inflammation: Evidence of the role of inflammation in the association between depression and CHF progression is based on several cross-sectional and prospective clinical investigations involving sTNFR1[41], IL-6 and CRP[42,43] and more extended patterns of inflammation markers[44]. All but one study[45]

confirmed a positive relationship between increased sustained inflammation and depression – a combination which may contribute to an excess mortality risk in patients with CHF and depression[46].

Box 2: Position on the mechanistic involvement of psycho-neuro-biological pathways on CHF disease progression

State of the science:

- Sustained stress-induced activation of the autonomic, neuroendocrine and inflammatory pathways - superimposed on well-established compensatory neuro-hormonal overdrive in CHF progression - increase the risk of fatal disease outcomes.
- In advanced stages of CHF, blunted rather than exaggerated response patterns may be observed.
- In addition to the potential synergy between biological correlates of psychosocial stress and CHF, there is a bidirectional association between functional limitations associated with CHF (e.g., reduced physical activity and CHF-related psychological challenges) and psychosocial factors such as depression.

Knowledge gaps:

- Larger, statistically well-powered epidemiological and clinical intervention studies are needed to determine the (difference in) effect sizes of biological processes that mediate the association between psychosocial factors and CHF progression.
- Novel data-analytic models are needed to clarify the synergistic roles of psychosocial factors, biological processes, and CHF-related features.

3. Association of psychological factors with poor self-care and other health behaviors

Self-care involves practices that patients engage in maintaining their own health[47]. Key elements of CHF-related self-care refer to adherence to medication, detecting, monitoring and managing signs and symptoms of disease progression and reducing water and sodium intake. Less specific CHF features include favourable health behaviours with increasing physical activity, quitting smoking and reducing alcohol consumption. Insufficient self-care affect more than half of the patients with CHF and are leading causes for poor outcomes including increased CHF exacerbations, higher risk for hospital admission and death[47]. A systematic review on the efficacy of adherence-promoting interventions[48], including 24 trials with 15,016 CHF patients, found only modest improvements.

Table 3: Goals of CHF patients' adherence to self-care

Interventions to improve CHF-related self-care should be components of structured cardiac rehabilitation[49]. Specific eHealth interventions to enhance disease management of patients with CHF are an attractive option for the future. A Cochrane Review[50] indicates that structured telephone support and non-invasive home tele-monitoring for CHF patients reduced the risk of all-cause mortality, heart failure-related hospitalization and QoL by improvements in HF knowledge and self-care behaviours. Psychological interventions tend to improve self-care in CHF patients without clinical depression and cognitive impairments[51]. Yet, improvements disappeared as the length of time from the intervention increased. There were no statistically significant intervention effects on anxiety.

Among psychological techniques promoting self-care, motivational interviewing (MI) is receiving increasing attention. A Cochrane review[52] based on 8 studies (with 758 patients, age range 58-79 years) reported a positive impact of MI over advice-giving, implicating that MI improves the long-term CHF outcomes through better general self-care behaviours, especially when delivered over a longer duration. The quantitative pooling of effect sizes of MI on enhancing self-care behaviours

among patients with CHF in a meta-analysis of nine randomized controlled trials[53] yielded moderate effects on enhancing self-care confidence and self-care management and large effects on improving self-care maintenance (i.e., adherence to treatment and symptom monitoring) (Hedge's g = 0.873; 95%CI = 0.430-1.317; P < 0.001). Of note, no effects were found for directly assessed physical functioning using the 6-min walking test.

Factors known to compromise readiness and maintenance of CHF self-care include depression[54], but also factors like illness perception, physical functioning, social support, and more general health-related attitudes such as self-efficacy[47]. Anxiety has no particular detrimental impact on CHF self-care[55]. Surprisingly, the level of evidence linking social support with better adherence to medical recommendations is modest[56]. Reasons for why depressed patients with CHF often are non-adherent to their treatment regime are related to the specific phenotype of depression (e.g. reduced energy to carry out activities)[57] but also interfere with reductions in cognitive functioning that may affect memory[58]. Both depressed mood and impaired cognitive functioning probably affect self-care behaviours indirectly: a study of 628 Italian patients with CHF showed that self-efficacy (or task-specific confidence) mediated the relationship between cognitive functioning and poor CHF self-care [59].

Box 3: Position on the importance of self-care management and consideration of psychological barriers

State of the science:

- CHF self-care interventions are recommended for detecting CHF exacerbations, improving symptom management and preventing hospitalizations.
- Insufficient CHF self-care conditions (e.g. lack of adherence to medication) affect more than half of the patients with CHF and is one of the leading causes of poor outcomes
- The efficacy of CHF self-care interventions usually applied in clinical practice is modest, most likely because the majority of concepts do not consider the impact of impaired cognition, depressed mood and other psychological barriers.
- Efforts aimed at promoting self-care are the cornerstone of CHF disease management and should be components of structured cardiac rehabilitation.

Knowledge gaps:

- Health psychology research on how to motivate patients in an early stage of CHF to engage in exercise training on a regular basis is missing.
- Among brief psychological techniques promoting self-care, MI is receiving increasing attention. Given the many opportunities of nursing staff to interact with patients, it is recommended that specialized nurses should be trained to incorporate this psychological technique to maximize intervention effectiveness.
- eHealth interventions specific to CHF (telephone support and home tele-monitoring) to enhance disease management programs are a clear option for the future. More knowledge is needed to optimally tailor these interventions to individual patient and provider needs and to incorporate mental health outcomes.

4. Psychotherapy, psycho-pharmacotherapy, and other health psychological interventions

4.1. Psychotherapy in CHF

Psychotherapy involves psychological and behavioural methods grounded in a defined psychological theory and based on interactions with a formally trained mental health professional to

help a person change cognitions, attitudes and behaviour, so to overcome emotional and other psychological problems.

Cognitive Behavioural Therapy (CBT) – A few mainly small psychotherapy studies have used CBT to treat depressive symptoms in patients with CHF (e.g.[60], summarized by two meta-analyses[61,62]). The first meta-analysis included 5 RCTs and one observational study (total n=320) and found that CBT for depression had small but significant positive effects on depressive symptoms and QoL[51]. A more recent meta-analysis (k=8; N=480) patients) confirmed the beneficial effect on depressive symptoms (SMD=-0.27) but found only a marginal effect on QoL (SMD=0.21) and no effect on self-care or physical functioning (6-minute walk test)[60,61,63]. Insufficient evidence that treatment for depression improves physical capacity is not limited to CBT[63]. However, benefits of CBT can possibly be enhanced by complementing CBT with structured exercise programs[64,65]. The effectiveness of psychological interventions such as psycho-dynamically oriented interventions have not been systematically investigated in a large enough number of patients with CHF.

Other psychotherapeutic interventions – At advanced stages of CHF, issues related to end-of-life questions, fear of dying and existential topics require different approaches than CBT[66,67]. (see also section 6 addressing palliative care). Here, alternative psychotherapeutic approaches (e.g. family dynamics) may be better suited to meet the needs of CHF patients[68].

(Blended) collaborative care and disease management – Several RCTs have used supervised nurses to continuously support CHF patients in disease coping and health behaviours. While a German RCT found beneficial effects on all-cause mortality and physical but not mental QoL[69], two American trials[70,71] found no intervention effects on overall QoL but a beneficial effect on depressive symptoms, especially in the depressed subgroup. No RCT has so far published results on blended collaborative care specifically targeting mental comorbidity in CHF[72]. However, simultaneous integrated care for CHF health behaviour and mental distress[72] may be most appropriate for improving not only mental well-being and QoL but also prognosis, although this still needs to be demonstrated [63].

4.2. Psycho-pharmacological Interventions in patients with CHF

Adequate treatment of depressive disorders typically includes pharmacological treatment, especially for moderate and severe depression. As a consequence of interactions with somatic CHF symptoms and concomitant cardiac medications, more adverse reactions may occur in response to pharmacological therapy in CHF patients. Several large scale health registries[73,74] have examined frequency and adverse effects of antidepressants in the general population and evidenced a significant increase in prescriptions of antidepressants over the long term clinical course and an increased all-cause and cardiovascular mortality risk (even independent from depression). An overflowing use of antidepressants in CHF patients was recently confirmed in an US data set[75].

A systematic review revealed that specifically for patients with CHF and depression, the use of selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) are significantly associated with increased all-cause mortality (SSRIs RR = 1.26; SNRIs RR = 1.17; TCAs RR = 1.30), although not CVD-related mortality[76]. It is therefore important to weigh the improvements in QoL against a potentially increased mortality risk associated with depression and antidepressant medications. This risk estimation should include the cardiac risk of untreated depression in comparison to the risk due to adverse cardiac events of the psychopharmacological treatment. Therefore, individualized medication treatment plans are needed to optimally treat these patients with a focus on tolerability and effectiveness. Of note, a recent systematic review concluded that more RCTs are needed to obtain valid information on whether antidepressants are safe and effective[77].

Currently, two large scale RCTs of antidepressants for patients with CHF are available: the MOOD-CHF RCT which failed to show reduced mortality or even antidepressant efficacy[78] and the prior SAD HEART-HF study[79] which demonstrated no significant effects for sertraline on depression or cardiovascular outcomes. In consequence, recommendations to prescribe SSRIs in these patients were withdrawn[80]. Nevertheless, secondary analyses indicate that remission from depression may improve cardiovascular outcome of patients with CHF[81] mainly due to a mean reduction in heart rate[82]. Among SSRI treated patients, heart disease related risks seem to be the highest with (es)citalopram[83], medium with sertraline and fluoxetine in patients with specific risk factors[84] and low in patients treated with paroxetine[83] although paroxetine has been linked to the induction of orthostatic hypotension due to its anticholinergic properties[85].

SNRI (selective serotonin and noradrenaline reuptake inhibitors) – Given the spectrum of potential adverse side effects of SNRIs likely to provoke worsening and exacerbation of CHF[86], SNRIs should be avoided or at least cautiously used with regular monitoring[86]. The same holds true for TCA, their use has been associated with an increased risk of myocardial infarction[87], orthostatic hypotension, conduction delays and increased heart rates, all increasing the risk of cardiac morbidity and mortality[88]. Therefore, TCAs should be avoided in CHF patients[89].

Newer generation antidepressant drugs – The newer generation antidepressants such as the NARI (selective noradrenaline/norepinephrine reuptake inhibitor) reboxetine[90], the DNRI (selective dopamine and norepinephrine reuptake inhibitor) bupropion[91], the NaSSA (specific noradrenergic and specific serotonergic antidepressant) α_2-blocker mirtazapine[91] and also the melatonin MT_1/MT_2 agonist and $5HT_{2c}$ antagonist agomelatine may all exert (with the exception of agomelatine) negative cardiac effects due to their noradrenergic properties and the potential to prolong the QTc interval (with the lowest risk for bupropion[92] and their negative influence on heart rate variability (e.g. mirtazapine)[93]. Close monitoring (particularly ECG monitoring during initiation of treatment) for these drugs is mandatory[94].

Table 4: The role of selected psycho-pharmacological treatment options and their potential risks in CHF-patients with depression

Treatment resistant depression: A substantial proportion of CHF patients with comorbid depression suffers from a protracted, often treatment-resistant clinical course forcing cardiologists to achieve a *competence in delegation* by rapidly involving psychiatric specialists for further anti-depressive treatment. Here, psychiatrists have several third line treatment options at hand, among them the irreversible monoamine oxidase (MAO) inhibitor tranylcypromine for which a protective effect in CHF is currently discussed[95]. Caution is warranted for lithium[96] and also for atypical newer generation antipsychotics which may cause serious cardiovascular side-effects including QT interval prolongation[97]. ECG monitoring[98] and detailed individual risk estimation when using these medications is mandatory. The cardiac safety profile of intranasal administration of esketamine (a NMDA receptor antagonist) seems to be acceptable [99].

Benzodiazepines and Non-Benzodiazepine hypnotics (Z-substances) - Benzodiazepine derivatives are frequently used in case of acute suicidality, agitation, and anxiety and considered as relatively safe medications with low risk of cardiac safety-related problems apart from increases in nocturnal blood pressure in the elderly[100]. For non-benzodiazepine hypnotics (e.g. zolpidem), no specific cardiac risks have been published[101] but the body of evidence is relatively weak.

4.3. Other intervention options to improve psychosocial risk factors in patients with CHF

Herbal antidepressants - The herbal antidepressant hyperforin, a major constituent of St. John's Wort preparations (Hypericum perforatum) represents a treatment alternative for CHF patients. It seems to have anti-inflammatory properties[102]. Safety and tolerability are better than that of SSRIs[103]. Nevertheless, the risk of a substantial interaction potential with concomitant cardiac medications has to be taken into consideration.

Polyunsaturated Omega-3 fatty acids (n-3 PUFA) - Advantages of n-3 PUFA in CHF are supported by intervention studies[104] beneficial effects for CHF are suggested predominantly by preclinical studies, but also by an epidemiologic study[105]. Several reviews and meta-analyses confirmed the efficacy of n-3 PUFA in the treatment of depression[106]. Many depressed patients have a deficiency of these nutritional factors[107] and n-3 PUFA prescription may therefore be beneficial for both, the treatment and for the secondary prophylaxis of cardiac disorders[108]. Sufficient dosage is needed to induce a satisfactory reduction in depressive symptoms[108].

Exercise-based interventions – Exercise training programmes are a crucial part of CHF rehabilitation and have benefits for physical and mental health (including QoL) even in CHF patients with severely reduced systolic LV-function (49). Nevertheless, they still are poorly implemented in European countries, mainly because of the lack of resources or national guidelines[109]. Research on the effects of exercise training on depression in CHF is summarized in a meta-analysis (k = 16, N = 3226) evidencing a reduction in depressive symptoms (SMD = -0.38] (109), particularly in patients >65 years and in those with poor systolic function. Centre-based interventions (vs. home setting) have stronger effects on depression[110]. Another meta-analysis of randomized controlled trials (k = 12 studies, 516 patients) indicates that combined aerobic and resistance training improves exercise capacity, muscle strength, and 6-minute walk distance as well as QoL in patients with CHF. Here, no effects were found for depression and sleep[111]. However, a meta-analysis of 21 studies (k = 21; total N = 4563) comparing different treatment approaches on reducing depression in CHF patients, evidenced the strongest improvements in depression following physical exercise training (effect size SMD) = -0.38 (SMD -0.16)[65]. Individually adapted supervised exercise training - although not always associated with improved clinical prognosis in terms of mortality - goes along not only with an increased exercise capacity but also with enhanced QoL. Against this background, an important recommendation is to establish ambulatory "heart failure groups" not only providing a "CHF-specialized" supervised exercise training but also contributing to improvement of QoL by maintaining the individual exercise capacity and by supporting continuous social contacts of these patients. Adverse events are rare if the programme is gradually incremental in volume/intensity. Key point here is that patients need interventions to be weened off supervised sessions and encouraged how to integrate physical activity into their daily lives. Complementing structured exercise programs with CBT possibly further enhances their favourable effects[65,66]. In the future, digital health technologies may also help to promote sustained physical activity behaviour changes[112].

Box 4: Position on psychotherapy, pharmacotherapy, and other Health Psychological approaches for the treatment of co-morbid mental diseases in patients with CHD

State-of-Science

- Multiple (psycho) therapeutic options are available for treating CHF patients with mental impairments. However, currently, no single approach is completely convincing.
- Complementing exercise programs can possibly enhance benefits of psychological interventions.

- CBT seems to be moderately effective in improving depressive symptoms and possibly other mental comorbidities in CHF resulting in small improvements in QoL but without clear benefit in terms of somatic disease outcomes.
- Multiple psychopharmacological interventions are available for patients with CHF but may all increase all-cause mortality risk. Caution is warranted.
- Monitoring the continuous disease progression with increasing suffering from disabling symptoms during psychotherapy and psychopharmacological interventions is mandatory.
- Treatment possibilities for mental health conditions (including use of psychotherapy) should be discussed openly with all potential (dis)advantages in patients with CHF, applying a shared decision-making process.
- Initiating ambulatory "heart failure groups" which provide a "CHF-specialized" supervised exercise training may contribute to improvement of QoL by maintaining the individual exercise capacity and by supporting continuous social contacts of these patients.

Knowledge gaps:

- More research is needed to support conclusive evidence for other forms of psychotherapy than CBT in CHF and which patients will benefit most.
- Because of the scarcity of clinical trials, there is still little evidence that antidepressants are effective for depression in patients with heart failure CHF.
- The complex crosstalk of psychopharmacology on decompensated heart muscle cells (among others by influencing norepinephrine-related pathways) is only poorly understood, so careful monitoring for negative cardiovascular side effects of antidepressants is required.
- Health psychology research on how to motivate patients in the early stages of HF to engage in regular exercise training is lacking.

5. Devices in patients with CHF: Implantable Defibrillators and Left Ventricular Assist Devices

5.1 Implantable cardioverter defibrillators (ICD):

ICDs continuously monitor cardiac rhythm and provide overdrive pacing in case of ventricular tachycardia and an electric shock in case of a life-threatening arrhythmia such as ventricular fibrillation. Specific device settings are tailored to the patient's clinical characteristics. Having an ICD may be associated with substantially elevated psychological burden and often results in anxiety related to experiencing an (appropriate or inappropriate) ICD discharge which can be very painful. Current state of knowledge on the prevalence of depression and anxiety in ICD patients is not convincing: a meta-analyses covering over 5,000 ICD patients from 45 studies disclosed a wide range of 11% to 28% of patients suffering from depression and 11-26% who had an anxiety disorder[113].

Phobic anxiety may be up to be 10-fold higher in ICD patients compared to the general population and data from a prospective 7-years follow-up clinical study indicated a progressive increase in phobia incidence (31% vs. 24%, p=0.048)[112]. Depression is an independent risk factor for experiencing adequate ICD discharges[114], and is also associated with (total) mortality[115]. Among ICD patients, posttraumatic stress disorder (PTSD) should also be taken into consideration as it may impact survival independent of depression and major concurrent somatic risk factors[116].

Surprisingly, studies do not find substantially different levels of QoL in patients with an ICD compared to non-ICD controls but shocks appear to adversely affect QoL[117]. Few studies have been conducted on psychological interventions in patients with ICD, with some meta-analytic evidence supporting the effectiveness of CBT for depression and anxiety[118] and that individual tailoring of

interventions will be essential[119]. Because most patients with ICDs have relatively minor CHF symptoms (NYHA class I/II), psychological problems in ICD patients are in most cases related to experiencing shocks from the device.

5.2. Left ventricular assist devices (LVAD):

Mechanical circulatory support systems (LVADs) were originally conceived as temporary treatment for heart transplant candidates ("*Bridge-To-Transplant*" BTT) as strategy to rescue patients with end-stage heart failure[120]. However, given the growing prevalence of end-stage CHF and the limited availability of organs for transplantation, utilizing LVAD solely as BTT is subject to current debate and is increasingly in use as a permanent therapy ("*Destination Therapy*" DT)[121] further stimulated by the advent of smaller continuous flow (CF) pumps. Conservative estimates count a total of 500,000 eligible CHF patients in the EU and an annual implantation rate of >2,000 LVADs[122].

Accompanying measures how to cope psychologically with an LVAD are urgently needed[123]. Living with an LVAD is very challenging for both the patients and their caregivers. During the pre-implantation phase, patients with advanced CHF experience severe and frightening symptoms. They face an excess risk of dying (>90%) within one year. Comorbid depression and anxiety (including fear of death) in this stage is omnipresent. Patients often employ denial to cope with such an almost unbearable situation. In one study, physicians regarded 69% of CHF patients to be at high risk for transplant, LVAD, or death, whereas only 14% patients felt they were at high risk[124].

Patients undergoing LVAD implantation must strictly adhere to medical therapies. Substance abuse contraindicates LVAD placement[122]. Implantation of an LVAD requires open-heart surgery often accompanied by cognitive decline and delirium in the immediate aftermath and the risk of serious adjustment disorders[125]. Nevertheless, in the post-acute implantation phase, most CHF patients with DT experience a relief reaction with the strongest improvements in patients' QoL in the first month after LVAD placement[126]. Data from RCTs consistently demonstrate that ≈80% of patients achieve a NYHA functional class I/II symptom level at 24 months post-implantation contributing to an immediate improvement in QoL[127] (whereas it tends to decrease while patients wait for a transplant)[128].

Nonetheless, major restriction in daily life caused by technical features of the extracorporeal support system (e.g. a percutaneous driveline connected to an external controller and energy source requiring replacement every 4–12 h) often compromise the patient's relief reaction. The CF pumps inhibits the perception of heart beats/peripheral pulses thus further contributing to a continuous adverse awareness of being dependent on the functioning of a technical device. Notably, patients experience high rates of LVAD-related adverse events (e.g. 65% to 80% one year-rehospitalisation rates)[129]. Gradually, levels of psychological distress, depression, and poor QoL[130] may increase again. Of note, depression in this stage is associated with increased risk of readmission[131].

Remarkably, despite all these obstacles, the majority of patients achieve a satisfactory mental health status quo. Social network and marital status are important factors for good outcomes with LVAD therapy[132]. LVAD patients who are ambulatory stable may even safely return to driving without an increased risk of motor vehicle accidents[133]. Caregiver engagement plays an important role in the care of patients with an LVAD. Pursuing an LVAD is a major "preference-sensitive decision"[134] that requires high-level caregiver engagement and specific knowledge. Currently, feasible strategies on how to involve caregivers or how to apply shared decision are lacking[134]. Most caregiver distress occurs prior to LVAD placement and in the first month after LVAD placement[126]. A better understanding of the role of patients' caregivers when considering LVAD placement and during post-LVAD follow-up is needed.

Box 5: Impact of implanted devices in CHF treatment

State-of-Science

- The number of CHF patients eligible for treatment with an ICD or LVAD is increasing rapidly.
- Subjective health technology assessments regarding its technical impact on psychological conditions to minimize unnecessary interventions and to prevent psychological and ethical conflicts are sparse.
- Concepts of how to cope psychologically with living with these medical devices are missing.

Knowledge gaps:

- Systematic psychological counselling of patients and their caregivers should be an integral part of the ICD and LVAD treatment management. Tools and concepts are missing.
- Development of critical incidence management tools are urgently required.

6. Palliative Care in End stage CHF

In their final few months, CHF patients are often faced with burdensome and debilitating symptoms, with increasing cognitive impairments and loss of independence, often overshadowed by the increasing awareness of dying soon[135]. Up to 40% of patients will die within 12 months of first CHF hospitalisation[135], and many physical symptoms (e.g. pain and severe shortness of breath[136]) are often under-treated and emotional symptoms (e.g. depression) are under-recognised[137]. Therefore, the need for palliative care in CHF patients is increasingly acknowledged[138]. In this paper, we maintain a neutral attitude towards assisted suicide or euthanasia, which has been recently legalized in some but not all European countries.

Palliative care focuses on maximising QoL and reducing suffering for patients and families at the (anticipated) last stages in their life cycle, where the aims clearly differ from standard medical care. However, because of the unpredictable trajectory of CHF, palliative care should not be viewed as an intervention of last-resort[139]. An interdisciplinary palliative care approach can improve QoL for patients and their families at various stages of the disease[140]. Of note, the ESC 2020 position paper[138] emphasizes the need to steadily revisit earlier decisions on therapy, recalibrating goals of care because of the inexorable nature of end-stage CHF progression. Palliative care providers need to acknowledge that previously expected outcomes may have become unrealistic and may now represent false hopes.

Multidisciplinary palliative care approaches are highlighted in systematic reviews of randomised trials[141] evidencing that such approaches lead to decline in symptom burden and depression, to better QoL and functional status, patient and caregiver satisfaction.. Basic levels of palliative care should therefore be provided by both primary care clinicians and cardiologists and should address CHF patients' and their families' needs. In some European countries, community support care models but also practitioners who specialize in palliative care are now available. However, to date, only a minority of end stage CHF patients receive help in designated palliative care units in the EU[138]. Systemic and organisational factors, insufficient staff training and attitudes, along with the unpredictability of the HF trajectory and missing agreement regarding referral criteria, contribute to this lack of care. Also, a multitude of ethical, legal, family and psychosocial issues can act as barriers to palliative care provision.

Box 6: Position on the need to integrate palliative care in end-stage CHF patient support

State-of-Science

1. An interdisciplinary palliative care approach and advanced care planning appear to increase QoL in patients with CHF and their families.

2. Because of the unpredictable trajectory of CHF, palliative care should not be viewed as an intervention of last-resort. We support earlier integration of advanced care planning into CHF management.

Knowledge gaps:

3. Further research is required to enhance confidence in this evidence, to determine which individuals will benefit, and the optimal settings for such care. The psychological impact on care providers should also be investigated. Currently, such research and funding is insufficiently prioritised.
4. There is an urgent need to develop training curricula for all health care providers dealing with CHF patients to increase professional competence in order to assist patients and their family members in all issues surrounding the inexorable progressing terminal phase of life.

7. General conclusions

Recent years have witnessed an increasing interest of implementing psychosocial aspects into every day cardiology practice throughout Europe. In support of this paradigm shift, the present position paper argues for the inclusion of these issues in the diagnosis and treatment of CHF patients by systematically outlining the scientific evidence relevant for this achievement and by providing practical recommendations.

a. Evidence from large-scale prospective population-based and long-term clinical studies confirm the effect size of psychosocial risk factors for incident CHF and as prognostic covariates in the long term course of the disease where they are associated with poor QoL, an unfavourable prognosis and increased mortality rates. Particularly for depression and social isolation/ loneliness, findings are strong enough to encourage clinicians to assess these conditions in patients at high risk of CHF and during clinical evaluation.
b. Disease progression is likely to facilitate increased awareness of limited life expectancy, resulting in transient episodes of despair and hopelessness, which may compromise effective treatment and end up in refractory depression.
c. CHF progression associated with mental health impairments is mediated in part by biological processes (autonomic dysregulation, neuro-endocrine processes and inflammation), all likely contributing to a dysregulated compensatory neuro-hormonal overdrive in CHF progression.
d. Physicians should be aware that mental health impairments often facilitate denial of illness reality and cause reduced adherence to effective therapeutic interventions and life style changes. Moreover, they are often associated with self-damaging behaviour (such as medication non-adherence, physical inactivity, poor dietary control, insufficient self-care) which yield an independent impact on CHF disease progression.
e. Multiple treatment options exist for depression in CHF, with the strongest evidence for exercise and cognitive behavioural therapy. However, such interventions are likely to miss essential psychological processes that are important to CHF patients, particularly those related to end-of-life issues, dealing with frightening physical symptoms and limitations.
f. This position paper provides an in-depth overview about anti-depressive medication strategies which are however of questionable use for alleviating depressive symptoms and improving QoL in CHF patients. It clearly states antidepressants whose use may come at a price for increased mortality. For treatment resistant depression, it argues for a competence in delegation and proposes to refer these patients to specialized psychiatrists.

g. Engagement of CHF patients with the goal to maintain their own health is of utmost importance. Among brief psychological techniques promoting self-care, motivational interviewing is receiving increasing attention. Interventions to improve self-care should be components of structured cardiac rehabilitation.

h. It is expected that novel blended collaborative care and remote monitoring techniques will be useful in helping patients and the families deal with CHF because they enable easy access, reduce hospital-based assessments, and create flexibility in methods and patient-tailoring of interventions. In addition to family-related issues, ethnic and cultural factors are important factors to consider in integrative CHF care.

i. E-health strategies are likely to become a major treatment option in the future. However, these technical strategies should not replace direct personal support. A careful balance needs to be found between these e-health interventions and personal provider-patient interactions that facilitates in-depth discussions of personally relevant issues.

j. A substantial proportion of CHF patients require device therapy (ICDs or LVADs) at some time of the disease progression. Resourcing of psychological counselling of these patients and their caregivers urgently needs to become an integrative part of device treatment.

k. The unpredictable clinical disease progression of CHF is a major challenge for patients and their families. We support earlier integration of palliative care and advanced care planning at an early stage of CHF into CHF management. When possible, caregivers should be involved in decision making with regard to complicated care and end-of-life decisions.

l. There is an urgent need to develop training curricula for all health care providers dealing with CHF patients to increase professional competence in order to assist patients and their family members in all issues surrounding the inexorable progressing terminal phase of life.

Heart failure is a multifactorial syndrome and, consequently, a multi-approach strategy is needed to reduce risk and cope with the disease. There is a substantial mismatch between “objective” disease indicators such as LVEF and blood-based biomarkers associated with CHF, and patients’ symptoms and functional abilities. The evidence reviewed here indicates that psychosocial factors are strongly interrelated with biological and functional aspects of CHF by interfering the patients’ QoL and CHF-related health care decisions. The scientific evaluation of patient-centred approaches that address psychosocial and biomedical processes and related interventions require different methodologies than standard randomized controlled trials; there is a need for new research methodologies in this area. Future collaborations with other European clinical and research societies that focus on the management of heart failure are needed to optimally integrate the present suggestions with clinical practice.

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Tables and Figures

Table 1. Psychosocial factors and incident HF: Findings from observational prospective population based studies

Table 2. Association of psychosocial risk factors with clinical outcomes and mortality in patients with chronic heart failure

Table 3: Goals of CHF patients' adherence to self-care

Table 4: The role of selected psycho-pharmacological treatment options and their potential risks in CHF-patients with depression

Figure 1: BI-directionality between depression and the clinical sequelae of CHF

Figure 2. Flow-chart demonstrating the impact of (psychosocial) stress induced autonomic, endocrine and inflammatory pathways on compensatory neuro-humoral processes aggravating the progression to end stage heart failure.

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Tables and Figures

Note: Table 1 and 2 are embedded into the textbody (chapter 1)

Tab. 3: Goals of CHF patients' adherence

- Symptom and weight control to detect fluid retention at an early stage
- Healthy low sodium diet and restricted fluid intake
- Promotion of healthy life style (e.g. moderate physical activity, quit smoking)
- Support for adherence to medication
- To pay attention to psychosocial barriers of own self care

Table 4: The role of selected psycho-pharmacological treatment options and their potential risks in CHF-patients with depression

class and indication	generic name	pharmaco-dynamic effects	typical cardiac side effects	cardiovascular risk estimation
antidepressants	agomelatine	$MT_{1/2}$ agonist	HRV ↓	o
	sertraline	SSRI		++
	fluoxetine	SSRI		++
	(es)citalopram	SSRI	QTc ↑	++
	vortioxetine*	SSRI		+
	paroxetine	SSRI	BP ↓	evidence weako
	duloxetine	SNRI	HR ↑	+++
	venlafaxine	SNRI	HRV ↓	+++
	milnacipran	SNRI	BP ↑	+++
	mirtazapine	NaSSA	HRV ↓	+
	reboxetine	NARI	BP ↑, QTc ↑	+
	bupropion	DNRI	BP ↑	+
	amitriptyline	TCA	BP ↓, MI ↑	++++
	doxepine	TCA	BP ↓, MI ↑	++++
	tranylcypromine	MAOI	BP ↓, BP ↑	++
augmentation strategies and concomitant treatment:				
mood stabilizer	lithium		QTc ↑	++++
atypical antipsychotics	aripiprazole	D_2-, $5HT_1$-partial agonist	QTc ↑, HR ↑	++
	quetiapine	D_2-, $5HT_2$-antagonist	QTc ↑, BP ↓	+++
	clozapine	D_2-, $5HT_2$-antagonist	QTc ↑, HRV ↓, HR ↑, BP ↓	++++
response accelerator	(es)ketamine	NMDA-antagonist	BP ↑, HR ↑	+o
hypnotics	lorazepam	GABA-modulator		evidence weak
	zopiclone	GABA-agonist		evidence weak

*vortioxetine is approved by the European Medicines Agency but not marketed in Germany

Cardiovaskular risk estimation:

o	+	++	+++	++++
very low	low	medium	high	highest (contra-indication)

Abbreviations: BP blood pressure; HR heart rate; HRV heart rate variability; MI risk for myocardial infarction

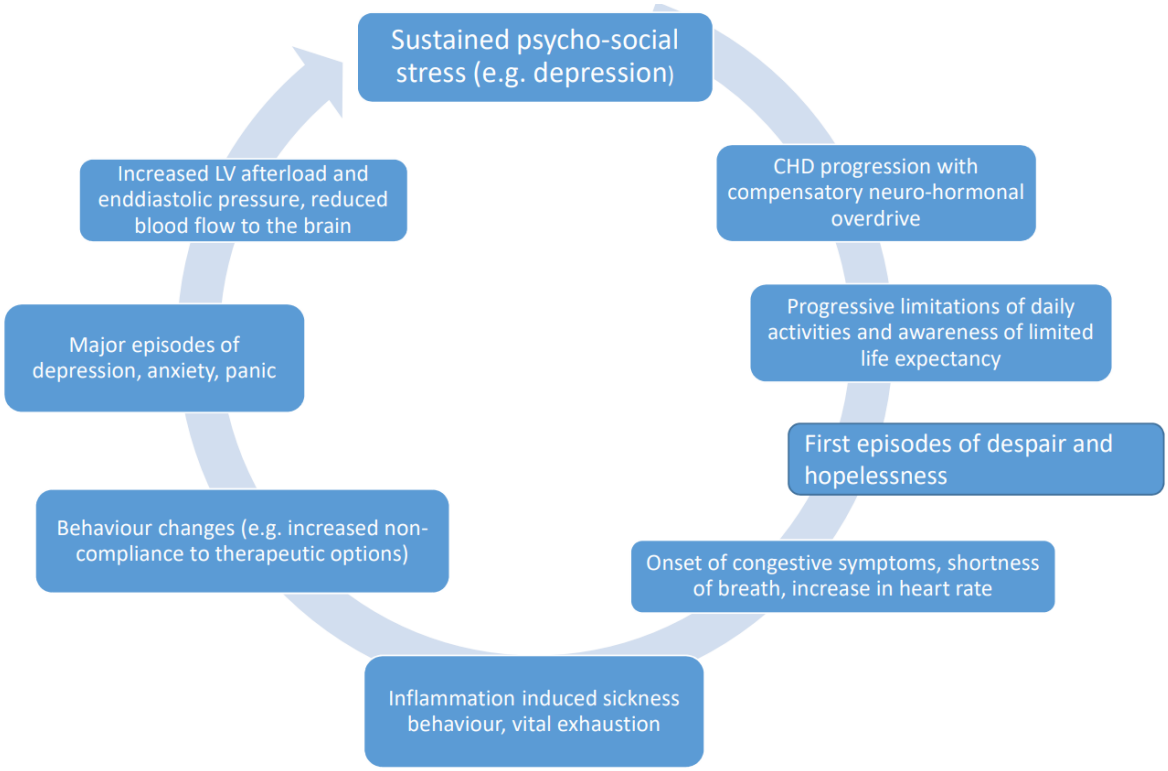

Figure 1: BI-directionality between depression and the clinical sequelae of CHF.

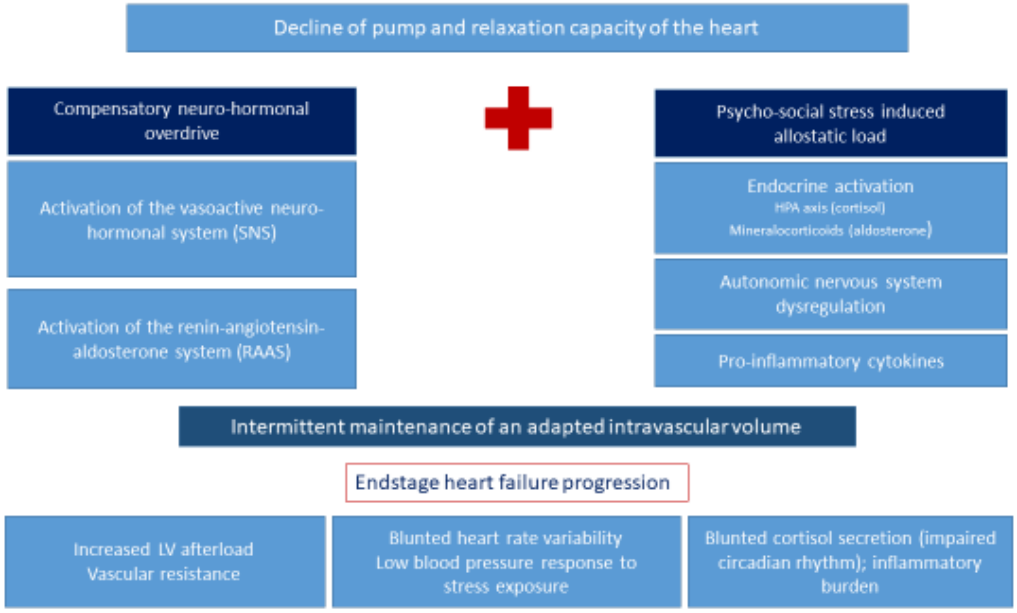

Figure 2. Flow-chart demonstrating the impact of (psychosocial) stress induced autonomic, endocrine and inflammatory pathways on compensatory neuro-humoral processes aggravating the progression to end stage heart failure.