Rationale and design of a randomised, controlled, multicenter trial investigating the effects of selective serotonin re-uptake inhibition on morbidity, mortality and mood in depressed heart failure patients (MOOD-HF)

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on behalf of the MOOD-HF Investigators

Abstract

Background: Depression and chronic heart failure (CHF) are common conditions, both of which are clinically and economically highly relevant. Major depression affects 20–40% of CHF patients and predicts adverse outcomes in terms of quality of life, morbidity and mortality as well as health care expenditure, independent of other factors of prognostic relevance.

Aims: The purpose of the MOOD-HF trial is to clarify whether antidepressant pharmacotherapy improves outcome in CHF patients, and if so by which mechanism(s).

Methods: MOOD-HF is a prospective, randomised, double-blind, placebo-controlled, 2-armed, parallel-group multicenter trial investigating the effects of the serotonin re-uptake inhibitor (SSRI) escitalopram on morbidity and mortality (primary endpoint), severity of depression, anxiety, cognitive function, quality of life and health care expenditure in 700 patients with symptomatic systolic CHF and major depression diagnosed by structured clinical interview. All patients will receive optimised pharmacotherapy for CHF. Duration of follow-up, including close safety monitoring, is 12–24 months from randomisation.

Perspective: MOOD-HF is the first prospective randomised controlled trial to assess the effects of antidepressant pharmacotherapy on hard somatic endpoints, the mechanism(s) of action of SSRI treatment, as well as safety in New York Heart Association functional class II-IV CHF patients. The results are expected to promote the development of evidence-based recommendations for managing depression in the context of CHF.

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Keywords: Depression; Chronic heart failure; Selective serotonin re-uptake inhibition; Prognosis; Quality of life; Cost effectiveness

1. Introduction

Major depression affects 20–40% of patients with chronic heart failure (CHF) [1–4] and is 4–5 times more common in CHF than in the general population [5]. Recently published...
baseline data from the MIND-IT trial indicate that after myocardial infarction, the prevalence and severity of depression are interrelated with the degree of cardiac dysfunction and CHF development [6]. In patients with CHF, depression was associated with higher short and long-term morbidity and mortality rates [7–9] and also worse outcome in terms of health-related quality of life and health care expenditure [2,10].

1.1. Pathophysiological implications of depression in cardiovascular disease

The adverse effects of depression in cardiovascular disease (CVD) may be mediated by shared pathophysiological mechanisms. We have previously demonstrated in an experimental model that in CHF natriuretic peptides may be specifically altered in brain areas regulating blood pressure and fluid control [11]. Drugs commonly used in CHF may reverse these changes [12]. Central natriuretic peptides represent an antagonistic principle against pressure and fluid retention neurotransmitters [13], but have also been shown to be associated with mental and emotional changes in CHF patients [14]. Depression may contribute to dysregulation of the autonomic nervous control in CHF, resulting in reduced parasympathetic and increased sympathetic tone, which is known to increase resting heart rate, decrease heart rate variability, and lower the threshold for myocardial ischaemia and adverse cardiac events in patients with CVD [15–17]. Augmented sympathetic tone is also associated with increased levels of plasma cortisol [15], serotonin, renin, aldosterone, angiotensin and free radicals [5]. Elevated levels of circulating catecholamines may induce a pro-coagulant state by enhancing platelet activation through direct agonist effects [18,19], and may inhibit vascular synthesis of protective eicosanoids by increasing haemodynamic stress on the vascular wall [20]. Further, diminished inhibition of macrophage activation via cholinergic anti-inflammatory pathways may contribute to an elevation of pro-inflammatory markers such as C-reactive protein (CRP) and cytokines such as IL-1β, IL-6, and TNF-α in depression. Administration of tumour necrosis factor (TNF)-α to healthy volunteers not only resulted in elevated extracellular serotonin levels [21], but also in depressed mood, sleep disorders and general malaise. From experimental research, there is strong evidence for an important modulating role of the immune system in the interrelationship between depression and CVD, acting via the hypothalamic–pituitary–adrenal axis and the autonomic nervous system (reviewed in [22]).

However, firm clinical evidence corroborating these suggestive experimental findings is lacking. Most clinical studies were case-controlled or cross-sectional and did not control for behavioural mediators such as poor treatment adherence. Although multiple interrelations between emotions and cardiovascular pathophysiology have been demonstrated, to date, a causal relationship has not been established in humans.

1.2. Treatment trials in depressed patients with cardiovascular disease

Three major randomised outcome trials of antidepressant therapy in patients with CVD have been published. The SADHART trial proved safety and efficacy of the selective serotonin re-uptake inhibitor (SSRI) sertraline in depressed patients after myocardial infarction, but was underpowered to detect a survival benefit [23]. In a similar patient population, the ENRICHD trial showed that cognitive behavioural therapy plus optional SSRI treatment improved depression but not survival [24]. A recent post-hoc analysis of ENRICHD revealed, however, that the risk of reaching a hard cardiovascular endpoint was significantly lower in patients receiving SSRI compared with those on placebo [25]. Both SSRI and structured psychotherapy were effective in relieving major depression symptoms in patients without comorbid CVD [26]. The MIND-IT trial evaluated the prevalence of depression in patients with a recent myocardial infarction, and also compared antidepressant pharmacotherapy with care as usual. The first-choice treatment was double-blind placebo-controlled administration of the selective noradrenaline re-uptake inhibitor mirtazapine. In case of refusal or insufficient treatment response after eight weeks, open treatment with the SSRI citalopram was offered. Over an 18 month observation period, antidepressants did not alter long-term depression and also did not improve cardiac prognosis [27]. A post-hoc analysis of the MIND-IT trial comparing responders to antidepressant medication with either non-responders or untreated control subjects provided preliminary evidence that non-response to treatment and thus persistence of post-myocardial infarction depression may be associated with an even increased cardiac event rate [28]. The recent CREATE trial documented safety and antidepressant efficacy of citalopram, which, in contrast to interpersonal psychotherapy, had a significantly better response rate than placebo in patients with chronic CVD [29]. The duration of this trial was too short, however, to elucidate effects on cardiovascular event rates. The only published evidence in depressed patients with CHF originates from a recent small randomised study with a 12 week observation period comparing the SSRI paroxetine (controlled-release) with placebo in 28 patients with NYHA II or III CHF. In this study, a higher recovery rate from depression CHF was observed in the intervention arm [30]. To the best of our knowledge, no larger randomised outcome trials to evaluate either treatment efficacy with regard to depression or long-term effects on somatic endpoints of antidepressant medication have been carried out or are under way in patients with symptomatic CHF comprising also advanced CHF stages. The ongoing SADHART Congestive Heart Failure study, which compares treatment with either sertraline or placebo, is including only CHF patients in NYHA functional class II.

Accordingly, we have designed a large randomised placebo-controlled trial to investigate MOrbidity, mOdalitry and mood in Depressed Heart Failure patients (MOOD-HF), testing the hypothesis that the SSRI escitalopram would
improve outcome in depressed patients with NYHA II to IV CHF and impaired LV systolic function.

2. Design of the MOOD-HF trial

MOOD-HF is an investigator-initiated prospective, randomised, double-blind, placebo-controlled, 2-armed, parallel-group, multicenter, phase IV clinical trial, using an approved drug, escitalopram, for an indication covered by the approval. Although approval of escitalopram is backed by consistent data showing efficacy, safety and tolerability in otherwise healthy subjects with depression, data in patients with physical comorbidities such as CHF are less clear. The aim of the MOOD-HF study is to test the safety and efficacy of escitalopram with respect to mortality, morbidity, severity of depression, anxiety, cognitive function, quality of life, and health care expenditure, as well as to surmount known or presumed to possess clinical and/or prognostic relevance in CHF. The anticipated duration of the entire trial is 36 months with a projected minimum/maximum intervention period per patient of 12/24 months, respectively, followed by a one month down-titration phase.

2.1. Patient selection criteria

Table 1 lists the study inclusion and exclusion criteria. Patients with symptoms of CHF (≥NYHA II) of any aetiology, a left ventricular ejection fraction (LVEF) <45% and a Diagnostic & Statistical Manual-IV diagnosis of a current episode of major depression based on the structured clinical interview for depression (SCID) [31], will be included. The study aims to recruit a representative sample of the ‘real world’ adult CHF population characterised by a high prevalence of suspected major depression according to the Patient Health Questionnaire (PHQ-9 [32]), multiple comorbidities and high mortality and morbidity. Therefore, exclusion criteria have been kept to a minimum.

2.2. Study flow: screening, randomisation, treatment and follow-up

Fig. 1 shows details of the study flow. Eligible patients enter step 1 of the screening process for depression, by answering the PHQ-9 [32]. Patients with a PHQ-9 sum score of >11 are suspected to suffer from a current episode of major depression. These patients qualify for step 2 of the screening process and will undergo a Structured Clinical Interview (SCID [31]). The SCID will be performed by a certified expert at least 14 days after the PHQ-9 testing, to confirm major depression according to the Diagnostic & Statistical Manual of Mental Disorders [31]. If current major depression is verified, all other inclusion and exclusion criteria will be reviewed and the patient will be familiarised with the concept of the MOOD-HF trial. Informed consent will be obtained the next day. No patient will undergo any study-related procedures before his/her written informed consent has been given. Randomisation will take place at visit 1.

Table 1

<table>
<thead>
<tr>
<th>Key inclusion and exclusion criteria for patients in the MOOD-HF trial</th>
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<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
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<tr>
<td>Age &gt;18 years.</td>
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<tr>
<td>Systolic CHF of any aetiology (≥NYHA II and LVEF &lt;45%).</td>
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<tr>
<td>Diagnostic and Statistical Manual-IV diagnosis of current episode of major depression based on the SCID.</td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td>Recent history of acute myocardial infarction (&lt;3 months) or acute cardiac decompensation.</td>
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<tr>
<td>Significantly reduced life expectancy due to other co-morbidity (e.g. malignancy).</td>
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<tr>
<td>Use of any antidepressants including SSRI, lithium, or anticonvulsants for mood disorder.</td>
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<tr>
<td>Currently undergoing any form of psychotherapy.</td>
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<td>History of early termination (&lt;8 weeks) of escitalopram treatment because of adverse event or adverse reaction.</td>
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<tr>
<td>SCID documented bipolar disorder, major depression with psychotic features; evidence of substance abuse or dependency during the previous 12 months.</td>
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<tr>
<td>Serious suicide risk based on clinical judgement.</td>
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<tr>
<td>Investigators judgment that patient is unable/unwilling to comply with the study protocol (e.g. co-morbidity, inability to speak German, lack of access to telephone).</td>
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The study intervention consists of optimal cardiological care, according to current treatment guidelines [33] for all patients, plus either escitalopram 10–20 mg or placebo 10–20 mg p.o. once daily. Study medication will be up-titrated and CHF therapy optimised over 3 months. During this time patients will be seen at 0.75, 1.5 and 3 months (±2 days, visits 2–4; Fig. 1). Telephone monitoring of depression and cardiac state will be performed weekly during up-titration and bimonthly thereafter. Maintenance therapy will first be evaluated after 6 months (visit 5). Thereafter, visits will take place at 6-month intervals (visits 6–8). Patients will attend for at least 6 visits, resulting in a minimum follow-up time of 12 months. Subjects recruited early in the trial will be followed-up for longer (up to 24 months). Prior to down-titration, patients will be re-evaluated once more by MADRS [34]. The decision to recommend open post-study antidepressant therapy will be based on these MADRS results. The timing of patient assessments during the study is shown in the trial flow diagram (Fig. 1). Scheduled safety and secondary efficacy measures are described in more detail in Table 2.
2.3. Patient safety

The MOOD-HF study has reliable safeguards built-in to assure patients’ safety in both trial arms. The study drug will be given on top of evidence-based, guideline-adjusted CHF therapy. The study protocol specifies careful up-titration of CHF medication and regular monitoring of drug compliance with cardiovascular medications besides supervision of the study drug. Repeat determination of safety markers including natriuretic peptides during patients’ visits to the study centres will facilitate reliable CHF surveillance. Weekly telephone calls during up-titration and bimonthly thereafter will (together with repeat cardiac and depression assessment during the trial) ensure timely recognition of worsening of the patients’ mental and physical state, and will facilitate close supervision of patients particularly during the early treatment phase, thus accounting for a possibly increased risk of suicide in the first weeks of treatment with an SSRI [30]. Suspected suicidal tendencies or significant worsening of depression will immediately initiate pre-specified supportive strategies, such as psychiatric assessment and open pharmacological treatment according to the patients’ individual needs. The need for premature study termination will be a joint cardiological and psychiatric decision.

2.4. Sub-studies

There are four predefined sub-studies of MOOD-HF, which are described briefly below.

SCREEN-MOOD: The objectives are to determine the prevalence and positive predictive value of a PHQ-9 sum score $>11$ in a large cohort of patients with symptomatic systolic CHF and to describe the correlation of the PHQ-9 sum score and its positive predictive value with patients’ sex, age and NYHA class. All subjects entering screening step 1 will participate in this sub-study.

THROMBO-MOOD: The objective is to investigate the effect of escitalopram on platelet activation in depressed patients with CHF. Consecutive subjects ($n=60$) recruited at the coordinating centre in Würzburg will be included. Markers of platelet activation comprising platelet surface expression of P-selectin and soluble CD40 ligand, binding of fibrinogen to activated glycoprotein IIb/IIIa on the platelet surface, and measurement of circulating platelet/leucocyte and platelet/monocyte aggregates will be analyzed at baseline and after 6 months. In addition, soluble P-selectin, soluble CD40 ligand and thromboglobulin will be determined in plasma.

VASO-MOOD: The objective is to assess vasoreactivity of the dominant brachial artery and to relate baseline measurements and changes in vasoreactivity to the primary endpoint and inflammation markers. Consecutive subjects ($n=100$) recruited at the coordinating centre in Würzburg will be included. The effects of escitalopram on endothelium-dependent (flow-mediated) and -independent (nitroglycerin-induced) vasoreactivity and concurrent changes in inflammation markers and CHF severity will be determined at baseline and after 6 months.

GENE-MOOD: Using polymerase chain reaction (PCR) and matrix-assisted laser desorption/ionisation–time of flight mass spectrometry (MALDI-TOF) techniques this sub-study aims to investigate candidate gene polymorphisms that predispose to depression in CHF, as well as polymorphisms that determine the therapeutic response to escitalopram. Objectives are a) to determine whether selected polymorphisms in candidate genes are associated with an increased risk for depression in CHF. Emphasis will be placed on candidate genes which have already been linked to depression and CHF (e.g., ACE or NOS3); b) to investigate whether polymorphisms in candidate genes affect plasma levels of escitalopram (pharmacogenomics, -kinetics); c) to test whether polymorphisms in
candidate genes impact on the therapeutic response towards escitalopram (pharmacogenomics, -dynamics). The panel of candidate genes will focus on functional polymorphisms in the serotonergic system (e.g., the serotonin transporter 5HTT, 5HT2a, and p11) (overview in [35]).

2.5. Outcome and efficacy measures

The primary efficacy endpoint of MOOD-HF is time to the first event of either all-cause death or unplanned hospitalisation. Domains, instruments, characteristics and targets of secondary efficacy variables are listed in Table 2. Outcome variables will be assessed at inclusion, and at all or some of the following time points as appropriate: 0.75, 1.5, 3, 6, 12, 18 and 24 months. These time points represent up-titration of cardiac medication and of escitalopram with evaluation of safety and antidepressant efficacy (visits 1–3) and follow-up visits (visits 4–8) with assessment of cardiac and psychological well-being. Physical and mental well-being will also be ascertained by telephone-monitoring at weekly or bimonthly intervals depending on the study phase using the PHQ-2 [36] and selected questions regarding CHF signs and symptoms. All endpoints will also be analysed according to sex and age.

Table 2
Secondary efficacy measures of the MOOD-HF trial: domains, instruments, characteristics and targets

<table>
<thead>
<tr>
<th>Domain</th>
<th>Instrument</th>
<th>Characteristics</th>
<th>Target</th>
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<tr>
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<td>Health related quality of life</td>
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<td></td>
<td>KCCQ</td>
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<td></td>
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<td></td>
<td>PHQ-GAD-7</td>
<td>SQ*, 7 items</td>
<td>Generalised anxiety symptoms</td>
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<td></td>
<td>MMSE</td>
<td>Therapist administered; 5 items</td>
<td>Cognitive function</td>
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<td></td>
<td>MADRS</td>
<td>Therapist administered, 10 items</td>
<td>Severity of depression</td>
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<td></td>
<td>SCID</td>
<td>Standardised interview</td>
<td>DSM-IV diagnosis of depression</td>
</tr>
<tr>
<td>Health economy</td>
<td>EuroQoL with SF-36</td>
<td>SQ*; 5 items &amp; SQ*, 36 items</td>
<td>Health care utilisation</td>
</tr>
<tr>
<td>Somatic variables</td>
<td>Clinical examination</td>
<td>Blood pressure, BMI, waist–hip ratio, glucose, electrolytes</td>
<td>Heart failure severity</td>
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<td></td>
<td>6-minute walk test</td>
<td>Walking distance</td>
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<td></td>
<td>Echocardiography</td>
<td>Left ventricular dimensions &amp; function</td>
<td>Heart failure aetiology &amp; severity</td>
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<td></td>
<td>ECG &amp; 24 h ECG</td>
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<td>Autonomic dysfunction</td>
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<td></td>
<td>Blood sample</td>
<td>Total-, LDL-, HDL-cholesterol, triglycerides</td>
<td>Classical risk factors</td>
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<td>Natriuretic peptides, Troponins</td>
<td>Heart failure severity</td>
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<td>Liver and renal profile,</td>
<td>Study drug parameters</td>
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<td>albumin/creatinine ratio</td>
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<td></td>
<td>Urine sample</td>
<td>Albumin/creatinine ratio</td>
<td>Classical risk factors</td>
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<td>24 h urine sample</td>
<td>Norepinephrine excretion</td>
<td>Neuroendocrinological function</td>
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<td>Saliva sample</td>
<td>Cortisol</td>
<td>Neuroendocrinological function</td>
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<td></td>
<td>Blood sample</td>
<td>Cortisol &amp; aldosterone</td>
<td>Neuroendocrinological function</td>
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<tr>
<td>Clinical events</td>
<td>CRF based questions</td>
<td>–</td>
<td>Clinical events, rehospitalisation</td>
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<tr>
<td>Study drug safety</td>
<td>SUSAR reporting</td>
<td>–</td>
<td>Study drug safety</td>
</tr>
<tr>
<td>Inflammatory/endothelial markers</td>
<td>Blood sample</td>
<td>CRP, uric acid, fibrinogen, TNF-α, IL-6, IL-10, CD 40 L, sICAM</td>
<td>Psycho-immunological reactivity</td>
</tr>
<tr>
<td>Study drug compliance</td>
<td>Blood sample</td>
<td>Escitalopram plasma levels</td>
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<tr>
<td>Heart failure medication</td>
<td>CRF based questions</td>
<td>Compliance assessment</td>
<td>Optimisation of heart failure pharmacotherapy</td>
</tr>
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<td></td>
<td>Blood sample</td>
<td>Platelet surface: expression of P-selectin and CD40 ligand, binding of fibrinogen to activated GP Iib/IIIa; circulating platelet/leucocyte &amp; platelet/monocyte aggregates</td>
<td>Platelet function</td>
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<td></td>
<td>Blood sample</td>
<td>Brachial artery vasoreactivity</td>
<td>Arterial endothelial function</td>
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<td></td>
<td>Blood sample with subsequent DNA extraction</td>
<td>PCR and MALDI-TOF</td>
<td>Determination of candidate gene polymorphisms for disease and drug response</td>
</tr>
</tbody>
</table>

SF-36, Short Form Health Survey -36; PHQ, Patient Health Questionnaire; MADRS, Montgomery Asberg Depression Scale; PHQ-GAD, Patient Health Questionnaire on General Anxiety Disorder; KCCQ, Kansas City Cardiomyopathy Questionnaire; SCID, Structured Clinical Interview for Depression; SQ, standardised questionnaire; MMSE, mini mental state examination; DSM, Diagnostic & Statistical Manual of Mental Disorders; QoL, Quality of Life; ECG, electrocardiogram; NYHA, New York Heart Association; LDL, low density lipoprotein; HDL, high density lipoprotein; CRF, case report form; SUSAR, suspected unexpected severe adverse reaction; TNF, tumour necrosis factor; IL, interleukin; sICAM, soluble intercellular adhesion molecule; sCD40L, soluble CD40 ligand; DNA, deoxyribonucleic acid; PCR, polymerase chain reaction; MALDI-TOF, matrix-assisted laser desorption/ionisation–time of flight mass spectrometry.
2.6. Sample size considerations and power analysis

According to the literature and our own data, a 45% annual event rate for the composite endpoint of morbidity and mortality is assumed during the natural course in our target population. We anticipate a 20% relative reduction of the event rate by study participation per se (due to superior CHF therapy and monitoring). Thus, the expected event rate in the placebo group is 36%. Since a more than 2-fold event rate has been observed in depressed compared with non-depressed CHF patients [3], 18% of the events may be attributable to depression. We assume that in the intervention group the annual excess event rate due to depression is reduced to one half or 27% by escitalopram. Observation of the first and last patient will last 24 and 12 months, respectively. A 15% annual drop-out rate is anticipated. Setting the type I error level at 5% and the power to detect a difference in event rates (36 vs. 27%) at 80%, 700 patients need to be randomised.

2.7. Primary efficacy analysis

For the primary efficacy analysis the log-rank test for Kaplan–Meier estimates for event-free survival will be used. This analysis includes all randomised patients according to the intention-to-treat principle. Ambiguous cases will be decided on by the Cardiovascular Endpoint Committee, which will also advise regarding sensitivity analyses when an informative drop-out (i.e., related to a foreseeable event) is suspected and is blinded to group assignment. Secondary analyses of the primary endpoint include Cox regression to identify and adjust for covariates of the primary endpoint (e.g. sex, age, severity of depression and CHF).

2.8. Safety analysis

Analyses will include: group comparison by Fisher’s exact test for frequency of particular adverse events; analysis of variance for severity of adverse events and left ventricular ejection fraction; Fisher’s exact test for frequencies of, and (if there are enough events) logistic regression to predict drop-out, reduced compliance with CHF medication, and the need for additional psychiatric intervention. A logistic regression using interaction terms will be employed to test for sex related differences in adverse reactions.

2.9. Secondary endpoints

Kaplan–Meier analysis for time to cardiovascular death or hospitalisation, extended multiple-state Kaplan–Meier analysis [37] for combined death and multiple hospitalisations, and time alive out of hospital will be applied. Analysis of covariates will be used to assess changes in depression and quality of life, and for biological variables and pill count, as well as correlation coefficients for the description of the relation between drug plasma levels and biological variables. Multi-level graph-based regression models will be employed to describe multivariate dependencies. Economic evaluation will examine whether the costs of antidepressant therapy are outweighed by savings resulting from a treatment-related reduction of clinical events as well as by improved quality of life.

3. Discussion

Depression is a frequent co-morbidity and has an adverse prognosis in CHF [3,7], but it remains recognised and untreated in most cases. Cardiologists are aware of the pathogenetic impact of various lifestyle behaviours and often attempt to manage problems such as overeating, physical inactivity and smoking, but they rarely assess and treat psychosocial risk factors. This may be partly a result of limited awareness, but is probably also due to the lack of convincing evidence for the efficacy of antidepressant treatment strategies in CHF patients regarding hard clinical endpoints. If depression is diagnosed, the choice of therapy will largely depend on clinicians’ preference and experience with pharmacological or non-pharmacological treatment options. Neither current German nor European [33] guidelines for CHF management provide specific handling directives for patients with CHF and depression.

MOOD-HF will investigate a vulnerable cohort requiring a dedicated interdisciplinary approach. The trial was initiated by cardiologists with a study design tailored to the specific medical needs of patients with CHF irrespective of commercial interests. Close cooperation with psychiatrists and/or psychosomatic specialists will ensure expert guidance on and evaluation of SSRI treatment and facilitate successful testing of the study hypotheses. MOOD-HF will, for the first time, address hard somatic endpoints in patients with CHF NYHA II-IV rather than only psychometric variables measuring improvement of depression, anxiety or cognitive function.

3.1. Rationale of the MOOD-HF trial

In patients with CHF, no efficacy data regarding hard clinical endpoints are available for any treatment modality of depression. Considering i) the very large population at risk qualifying for treatment in case of a positive study outcome, ii) the physical incapacity of most elderly individuals with advanced CHF precluding repeat visits to specialists, and iii) the frequency of cognitive impairment in CHF [38,39], we propose to evaluate antidepressant pharmacotherapy rather than psychotherapy vs. placebo on top of optimal CHF care according to current guidelines [33] for all patients. Careful frequent monitoring of the effects of CHF therapy, study medication and of treatment safety will be complemented by optional expert psychiatric support. Published evidence suggests that SSRI are safe in patients with coronary artery disease [4,23,29,40] and may favourably influence the mortality risk by improving health behaviour and/or via direct modulation of biological pathways. While some markers reflecting these biological systems seem to vary with the severity of depression, others may independently impact on prognosis. For example, a
platelet sub-study of the SADHART trial demonstrated that **sertraline** treatment in patients with coronary artery disease was associated with diminished platelet/endothelial activation despite co-administration of antiplatelet regimens including **aspirin** and **clopidogrel** [41]. In addition, a large retrospective study in patients with an acute coronary syndrome treated with an SSRI showed a significant reduction in recurrent myocardial ischaemia, heart failure or asymptomatic enzyme elevation at the expense of a significantly higher bleeding rate [42]. Correspondingly, the THROMBO-MOOD sub-study will prospectively address the effects of **escitalopram** on platelet function and determinants of plasmatic coagulation in patients with CHF and thus at increased thromboembolic risk.

### 3.1.1. Rationale for the use of escitalopram

**Escitalopram oxalate** is the S-enantiomer of the racemic bicyclic phthaline derivative **citalopram** and is approved in Germany for treatment of major depression and anxiety. The mechanism of its antidepressant action is presumed to be linked to enhanced serotoninergic activity in the central nervous system, resulting from inhibition of neuronal re-uptake of serotonin. **Escitalopram** has very little effect on other receptors, rendering it the most selective SSRI so far. **Escitalopram** is >100 times more potent than the R-enantiomer; its plasma concentration is approximately 1/3 of the total **citalopram** concentration indicating that the other 2/3 are biologically inactive [43]. **Escitalopram** was chosen in MOOD-HF for its superior efficacy, as demonstrated in a meta-analysis of >2000 patients treated with different antidepressants [40], in conjunction with a more rapid onset of action, more favourable side-effect profile compared with other compounds (e.g. tricyclic antidepressants), and a relative lack of toxicity in overdose. Also, its low potential for drug–drug interactions renders **escitalopram** attractive in patients with CHF who are usually taking multiple concomitant medications. Although **escitalopram** is safe if contraindications are respected, safety issues are reflected in the design of MOOD-HF by i) stepwise up-titration of study medication, and ii) telephone-monitoring of patient psychological and somatic well-being at short intervals during the up-titration period.

### 3.1.2. Rationale for the use of placebo

We consider it ethically justified to withhold **escitalopram** from a control population of depressed CHF patients. Currently, there is no established reference treatment for patients with CVD in general and CHF in particular who suffer from depression as co-morbidity. It remains to be demonstrated whether the efficacy and tolerability of **escitalopram** are superior to treatment with a **pill-placebo** in these patients, who are usually elderly and multimorbid, show some degree of renal failure, may suffer from diabetes, and take numerous other medications. In contrast, optimised CHF care as offered to all study participants is associated with a proven survival benefit [33]. This constitutes an additional ethical justification for the trial. In order to ensure the maximum safety for study participants, the study schedule includes pre-specified supportive and therapeutic strategies including individualised psychiatric management. The need for premature study termination will be a joint cardiological and psychiatric decision.

### 3.2. Hypotheses of the MOOD-HF trial

The major hypothesis of the MOOD-HF trial is that long-term therapy with **escitalopram** in patients with symptomatic systolic CHF is safe and improves outcome defined as a prolongation of the time to a first clinical event (death or unplanned hospitalisation). We further hypothesise that treatment with **escitalopram** improves depression as assessed by serial PHQ-9- and MADRS-testing, anxiety as assessed by the PHQ-GAD-7, cognitive function as assessed by the mini-mental state examination (MMSE) [38], generic quality of life as assessed by the SF-36, and disease-related quality of life as assessed by the KCCQ, the German version of which has been validated by our group [44]. Further, we will test the hypothesis that **escitalopram** increases the number of patient days spent alive outside the hospital and reduces cardiovascular mortality and morbidity. By prospectively measuring a variety of clinical and biological factors related to adverse prognosis in patients with CVD and depression, we should be able to generate and support new hypotheses for the biological mechanism(s) by which **escitalopram** may improve outcome in depressed CHF patients.

#### 3.2.1. Endpoint selection

Time to the first event of either death or unplanned hospitalisation was chosen as the primary efficacy endpoint of the MOOD-HF trial because it likely reflects the improvement of patient well-being with the greatest sensitivity in a population prone to hospitalisation or even CHF-related death. All-cause (not cardiovascular) events were chosen in order to avoid components of subjective assessment in the primary endpoint in this multimorbid patient population. Hospitalisation is an important component of the primary endpoint, because depression is associated with 26–29% excess costs for CHF hospitalisation in this patient population [10] thus representing a key issue also for health economy. We are aware that effects might be seen in only one component of the combined endpoint, leading to a non-significant result in the primary analysis. However, because little is known in this research area we regard MOOD-HF as explorative rather than confirmatory in this respect. ‘Days alive out of hospital’ is perhaps the most relevant endpoint from the patients’ perspective, but was still specified as a secondary efficacy measure because it may reflect not merely clinical but also administrative aspects of hospitalisation due to the disease-related groups policy in Germany. ‘Cardiovascular mortality’ and ‘cardiovascular morbidity’ were also categorised as secondary endpoints. These endpoints will be ascertained by the Cardiovascular Endpoint Committee.

Changes in the MADRS, PHQ-9, PHQ-GAD-7 and MMSE scores were selected as major secondary efficacy endpoints. The MADRS is a 10-item therapist-administered psychometric
tool measuring the direct effects of the intervention on depression. Its use is particularly advantageous in patients with somatic comorbidities, because it contains few somatic items and is, therefore, not very sensitive to drug side-effects or disease-related physical symptoms [45]. The self-administered PHQ-9 questionnaire represents a widely used validated instrument for depression diagnosis and serial monitoring with proven responsiveness to antidepressant medication with an SSRI [46]. The PHQ-GAD-7 has recently also been recommended for the self-assessment of CHF patients when anxiety was also recognised as important with regard to prognosis [47]. During telephone-monitoring, the PHQ-2 serves as a brief multipurpose measure adequate for detection, grading and monitoring of depression [29]. The MMSE is a neuropsychological test with proven capability to quantify cognitive impairment in patients with CHF and also assess reversibility [38]. Changes in depression, anxiety and cognitive function have been categorised as secondary, because the principal efficacy of SSRI in improving these endpoints has been established in other cohorts including patients with CVD [6,29]. The variable ‘change in depression’ is assumed to act as a mediator between the intervention and the primary endpoint.

Amongst the other secondary endpoints ‘quality of life’ is particularly relevant for the patients. The SF-36 is widely employed for quantitative assessment of generic quality of life facilitating the comparison with other cohorts, whereas the KCCQ facilitates assessment of disease-related quality of life. We expect that improvement of depression due to pharmacotherapy with escitalopram will also result in improved quality of life. Health economy assessment will allow assessment of the cost effectiveness of escitalopram treatment [2,10]. This information will be derived from demographic data, clinical and treatment information, SF-36 and EuroQol [48]. Adherence to study medication will be ascertained by pill counting. Adherence to CHF medication will be assessed from a detailed history of the type and dosage of cardiovascular drugs taken. This will allow us to clarify whether improvement in depression increases compliance with CHF pharmacotherapy, and/or conversely whether adverse reactions to escitalopram treatment would possibly reduce compliance. Determination of escitalopram plasma levels will not only ascertain compliance with the study medication but also facilitate correlation of escitalopram plasma concentrations with antidepressant efficacy, and investigation of the interrelationship between escitalopram plasma levels and changes in surrogate markers of the pathogenesis of CVD and CHF.

4. Perspective

Apart from a favourable individual risk–benefit ratio for patients participating in the MOOD-HF trial, a yield regarding future management strategies for the CHF population as a whole may be expected. MOOD-HF has the potential to impact significantly on CHF management practice guidelines by (i) proving the safety and antidepressant efficacy of the SSRI escitalopram in the entire symptomatic CHF population and (ii) by elucidating the pathophysiological links between depression and CVD thus potentially also promoting evidence-based management strategies for patients suffering from both conditions.

5. Role of the funding sources

The investigator-initiated MOOD-HF study receives public funding from the German Ministry for Education and Research (BMBF, Project number GFVT01024505). Lundbeck A/S, Denmark, provides study medication and additionally contributes to case payment. Neither sponsor interfered in any respect with the study design, or will influence data collection, analysis and publication or interfere with the investigators intellectual property rights.

Appendix A. The MOOD-HF Trial Study Group

A.1. Organigram of the structural components of MOOD-HF

Fig. 2 illustrates the organisational and management components of the MOOD-HF trial. We have established an Independent Data Monitoring and Safety Committee (DMSC) and an Independent Advisory Board. An Independent Endpoint Committee serves to supervise in particular the endpoint ‘hospitalisation’ to guarantee careful and unbiased interpretation. Major decisions within the trial will be reached in close cooperation between the Coordinating Investigator, the Steering Committee, and the Advisory Board. Names and affiliations of all participants are given below.

Appendix B. Committees and offices

B.1. Study chair and co-chair

Christiane E. Angermann MD (Chair), Götz Gelbrich PhD (Co-chair).

B.2. Clinical and Biometrical Coordinating Centers

Medical Clinic I, Cardiovascular Center, Würzburg University, Stefan Siörk MD, PhD (Clinical Coordinator), Coordinating Center for Clinical Trials Leipzig University, Oana Brosteanu PhD, Götz Gelbrich PhD (Biometry, PI of SCREEN-MOOD-Substudy), Markus Löffler MD, PhD, Christiane Prettin PhD (Coordinator of Data and Quality Management).

B.3. Psychometric Core Laboratory and Training Center

Dept. of Psychiatry and Psychotherapy, Jürgen Deckert MD, Andreas J. Fallgatter MD, Andreas Reif MD (Coordinator of GENE-MOOD-Substudy); Institute for Psychotherapy and Medical Psychology Hermann Faller MD, PhD, Marion Schowalter PhD.
B.4. Core Laboratory Heart Rate Variability/Arrhythmia

Dept. of Cardiology, Humbold University Berlin, Charité
Mathias Rauchhaus MD, PhD.

B.5. Central Laboratory/Endocrinology/Escitalopram
Plasma Levels

Medical Clinic I, Cardiovascular Center, Würzburg University,
Bruno Allolio MD, Martin Eigenthaler MD, Ulrich Walter MD.

B.6. Steering Committee Members

Christiane E. Angermann MD, Georg Ertl MD, Jürgen
Deckert MD, Hermann Faller MD, PhD, Götz Gelbrich PhD,
Markus Löffler MD, PhD, Heribert Schunkert MD, Bernhard
Maisch MD, B. Pieske MD.

B.7. Data and Safety Monitoring Committee Members

Günter Breithardt MD, Martin Gottwik MD, Hans-Werner
Hense MD, PhD, Kurt Laederach MD, Bernd Löwe MD,
PhD.

B.8. Independent Advisory Board Members

Otto Hess MD, Uwe Siebert MD, PhD, Ulrich Hegerl MD.

B.9. Independent Endpoint Committee Members

Uta Hoppe MD, Siegfried Kropf PhD, Stefan Anker MD,
PhD.

Appendix C. Clinical Trial Centers

C.1. University of Würzburg

Medical Clinic I, Cardiovascular Center: Bruno Allolio MD (Core Laboratory Endocrinology), Christiane E. Angermann (Chair of MOOD-HF and local PI), Johann Bauersachs MD (PI of THROMBO-MOOD Sub-study), Georg Ertl MD, Stefan Störk MD, PhD (PI of VASO-MOOD Sub-study), Ulrich Walter MD (Central Core Laboratory).

Psychiatrist/Psychologist: Andreas J. Fallgatter MD, Hermann Faller MD, PhD, Marion Schowalter PhD, Andreas Reif MD (PI of GENE-MOOD sub Study)

C.2. University of Lübeck

Medical Clinic II: Heribert Schunkert MD, Joachim Weil MD (local PI).

Psychiatrist/Psychologist: Günter Jantschek.

C.3. University of Essen

Division of Cardiology, Essen Cardiac Center: Raimund Erbel MD, Till Neumann MD (local PI).

Psychiatrist/Psychologist: Irini Savidou MD.

C.4. Humbold University Berlin, Charité

Department of Cardiology: Rainer Dietz MD, Mathias Rauchhaus MD, PhD (local PI).

Psychiatrist/Psychologist: Martina Rauchfüβ MD.
C.5. Heart & Diabetes Center NRW, Bad Oeynhausen
Division of Cardiology: Dieter Horstkotte, MD, Barbara Lamp MD (local PI).
Psychiatrist/Psychologist: Susanne Krappel.

C.6. University of Marburg
Division of Cardiology: Bernhard Maisch MD, Sabine Pankuweit MD (local PI).
Psychiatrist/Psychologist: Beate Kolb-Niemann MD, Thomas Meyer MD.

C.7. University of Göttingen
Division of Cardiology & Pneumonology: Gerd Hasenfuss MD, Burkert Pieske MD (local PI).
Psychiatrist/Psychologist: Ullrich Buss MD, Christoph Herrmann-Lingen MD.

C.8. University of Heidelberg
Theresienkrankenhaus Mannheim, Medical Clinic: Markus Haass MD (local PI).
Psychiatrist/Psychologist: Florian Lederbogen MD.

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