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RESEARCH ARTICLE

Telemonitoring in patients with chronic heart failure and moderate depressed symptoms: results of the Telemedical Interventional Monitoring in Heart Failure (TIM-HF) study

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Aims Depression is a frequent comorbidity in patients with chronic heart failure (CHF). Telemonitoring has emerged as a novel option in CHF care. However, patients with depression have been excluded in most telemedicine studies. This pre-specified subgroup analysis of the Telemedical Interventional Monitoring in Heart Failure (TIM-HF) trial investigates the effect of telemonitoring on depressive symptoms over a period of 12 months.

Methods and results The TIM-HF study randomly assigned 710 patients with CHF to either usual care (UC) or a telemedical intervention (TM) using non-invasive devices for daily monitoring electrocardiogram, blood pressure and body weight. Depression was evaluated by the 9-item Patient Health Questionnaire (PHQ-9) with scores ≥10 defining clinically relevant depressive symptoms. Mixed model repeated measures were performed to calculate changes in PHQ-9 score. Quality of life was measured by the Short Form-36. At baseline, 156 patients had a PHQ-9 score ≥10 points (TM: 79, UC: 77) with a mean of 13.2 points indicating moderate depressiveness. Patients randomized to telemedicine showed an improvement of their PHQ-9 scores, whereas UC patients remained constant ($P = 0.004$). Quality of life parameters were improved in the TM group compared to UC. Adjustment was performed for follow-up, New York Heart Association class, medication, age, current living status, number of hospitalizations within the last 12 months and serum creatinine. In the study population without depression, the PHQ-9 score was similar at baseline and follow-up.

Conclusion Telemedical care improved depressive symptoms and had a positive influence on quality of life in patients with CHF and moderate depression.

Keywords Heart failure • Depression • Telemedicine • Quality of life

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Introduction

Depression is common and affects ~20% of patients with chronic heart failure (CHF).[1] Depression in CHF is associated with higher mortality, higher risk for hospitalizations and an increased utilization of healthcare. CHF events such as hospitalizations worsen depressive symptoms.[2] Therefore, the guidelines of the European Society of Cardiology recommend screening and — if positive for major depression — a combination of psychosocial interventions and pharmacological treatment, as well as cognitive behavioural therapy.[3] However, evidence-based treatment options are very limited.[4–6] Indeed, an association between the prescription of anti-depressants and higher cardiovascular mortality has been discussed.[7] Additional therapeutic options such as collaborative care management, physical training and internet-based cognitive behavioural therapy on depressive symptoms appear to be promising but are inconclusive in terms of effectiveness on clinical outcomes. Furthermore, quality of life is reduced in patients with CHF.[8–11]

Remote patient management using telemedicine has emerged as a tool to optimize therapy, improve compliance, and enable detection of signs and symptoms of cardiac decompensation in CHF.[12,13] However, there are very limited data available on the effects of a telemedicine programme on depressive symptoms and quality of life. The complex intervention interferes with patients' daily life and thus could potentially exert positive effects but also may induce or increase both depressiveness and quality of life.

The Telemedical Interventional Monitoring in Heart Failure (TIM-HF) trial was a randomized, multicentre, controlled intervention study designed to investigate the effects of telemonitoring in patients with stable CHF in New York Heart Association (NYHA) functional class II and III and with a left ventricular ejection fraction (LVEF) ≤25% measured at least twice within the past 6 months or a LVEF ≤35% and at least one cardiac decompensation with hospitalization due to CHF or therapy with intravenous diuretics within 24 months prior enrolment. Depressive symptoms were prospectively assessed in TIM-HF using the well-established Patient Health Questionnaire (PHQ-9) at baseline as well as after 3, 6, 9, 12, 18 and 24 months.[14] Overall, TIM-HF did not show a positive effect in the primary endpoint of all-cause mortality.[15]

The impact of the telemedical intervention used in the TIM-HF trial on depressive symptoms and quality of life were pre-specified endpoints of the TIM-HF trial. Therefore, the aim of this analysis was to characterize the time course of depressive symptoms in patients with CHF receiving telemedical intervention compared to usual care in the TIM-HF study.

Methods

Study design/the TIM-HF study

TIM-HF was a randomized, prospective multicentre clinical trial investigating the impact of telemonitoring on mortality in ambulatory patients with CHF (NCT00543881).[15] Between January 2008 and June 2009, 710 patients were enrolled by 165 cardiology, internal medicine or general medicine practices in Germany. To fulfil the inclusion criteria, CHF symptoms had to be stable and patients had to receive optimal medical treatment according to the current guidelines. Furthermore, all patients had to meet NYHA class II or III criteria and to be diagnosed with a LVEF ≤25% measured at least twice within the past 6 months or a LVEF ≤35% and at least one cardiac decompensation with hospitalization due to CHF or therapy with intravenous diuretics within 24 months prior enrolment.

Exclusion criteria were age <18 years, diagnosis of any disease reducing life expectancy to less than one year, insufficient compliance and planned revascularization or cardiac resynchronization therapy. Further exclusion criteria were unstable angina pectoris, congenital heart defect, primary heart valve disease, hypertrophic or restrictive cardiomyopathy and chronic kidney disease.

Intervention and follow-up

Patients were randomized (1:1) to receive usual care (UC group) or a telemedical intervention (TM group). In both groups the main responsibility for patients' therapy was taken by their primary care physicians.

Patients of the TM group had a telemonitoring system installed at home to perform daily measurements of a 3-lead electrocardiogram, blood pressure and their weight by themselves additionally to usual care. The devices were connected by secure Bluetooth™ to a personal digital assistant which transferred the data via an integrated cell phone module to the telemedical centre (TMC). The data were accessible to the primary care physicians.

A home emergency call system provided the possibility to contact the TMC where physicians ensured medical support for 24 h a day, 7 days a week. Patients were regularly contacted by a member of the TMC on a monthly basis and in case of requests by the patient or in case adaptations were necessary.

The first patient was randomized on 10 January 2008. The follow-up period of the study stopped at a fixed stopping date (30 April 2010). Therefore, every patient had an individual follow-up period with a minimum of 12 months and a maximum of 28 months. The impact of the intervention on depressive symptoms and quality of life was investigated for the first 12 months since the number of missing values increased after 12 months (*Figure 1* and online supplementary *Table S2*).

Outpatient visits were scheduled every 3 months during the first year and every 6 months during the second year. During visits a blood sampling and physical examination was performed as well as the assessment of symptoms of depression and quality of life.

Assessment of depressive symptoms and quality of life

Depressive symptoms were prospectively evaluated by the 9-item Patient Health Questionnaire (PHQ-9) in self-administration at baseline and on every follow-up visit (months 3, 6, 9, 12, 18, 24). The PHQ-9 represents the 9-item depression module of the PHQ, a questionnaire used to screen for the five most common mental health disorders in primary care. Every item corresponds to one of the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for depression.[16] The PHQ-9 scale ranges from 0 to 27. A score ≥10 has a sensitivity of 88% and a specificity of 88% for the diagnosis of major depression.[14] Therefore, this cut-off was prospectively defined in the statistical analysis plan.[17] Referring to this scale, 5–9 points reflect 'mild depression', 10–14 points 'moderate depression', 15–19 points 'moderately severe' and 20–27 points 'severe depression'.[14] The PHQ-9 has been validated for detection of depressive symptoms in patients with

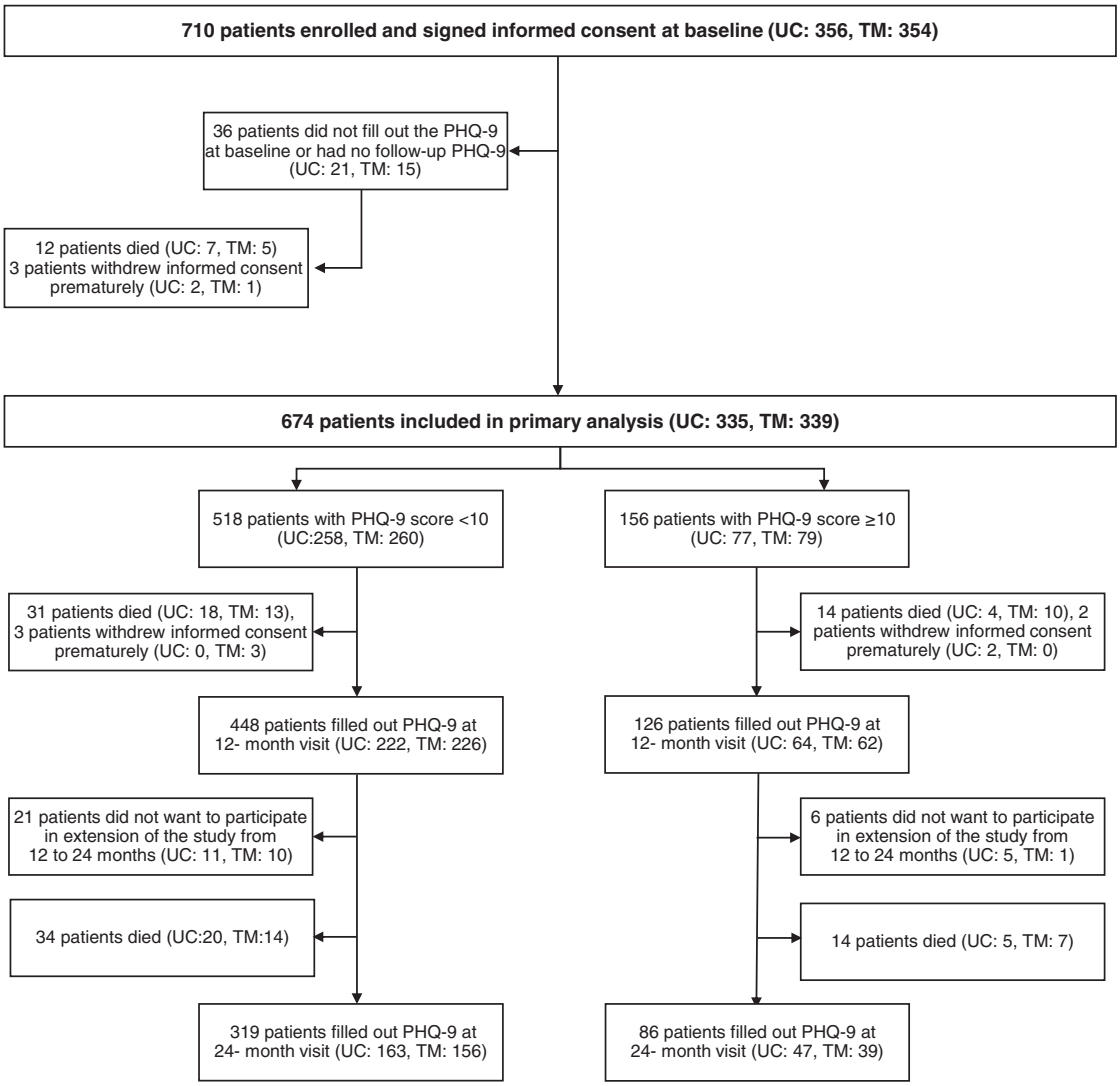

Figure 1 Study design. Non-depressed patients: PHQ-9 <10; clinically relevant depressive symptoms: PHQ-9 ≥10. TM, telemedical group; PHQ-9, 9-item Patient Health Questionnaire; UC, usual care group.

CHF.[18] According to the rules of the manual of PHQ-9, scores with a maximum of two missing items were augmented by the average of the completed items. All others were set missing, and sum scores were replaced by imputed values by multiple imputation.

Additionally health-related quality of life was measured by the 36-item Short Form health survey of the Medical Outcome Study (SF-36) in self-administration at every visit. The SF-36 represents an internationally well-established instrument and contains eight different scales including limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities because of physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities because of emotional problems, vitality (energy and fatigue) and general health perceptions. These domains can be summarized in physical (PCS) and mental component scores (MCS). The scale ranges between 0 and 100 points, whereas lower scores reflect higher impairment.[19]

Statistical analysis

All analyses were conducted using IBM SPSS Statistics (version 25) and StataCorp. 2019 (Stata Statistical Software: Release 16; StataCorp LLC, College Station, TX, USA). Patients without complete PHQ-9 at baseline or without any follow-up PHQ-9 were excluded from analysis ($n = 36$, 5.1%). Included were all patients who completed the questionnaire at baseline and on at least one further visit regardless if the last visit was missed.

Categorical baseline characteristics were described by frequencies and percentages and compared using χ^2 test. Continuous variables were reported as means with standard deviation using independent samples *t*-test. Missing values were imputed using chained equations (MICE) with 50 imputations. The imputation model includes the following variables (at all described time points): PHQ (baseline up to 24 months), SF-36 components (baseline up to 24 months), NYHA class (baseline, 3 months, 6 months), dyspnoea on exertion (baseline

and 3 months); furthermore sex, age, body mass index, living alone, number of hospitalizations within the last 12 months, alcohol consumption, baseline creatinine serum level and N-terminal pro-brain natriuretic peptide (NT-proBNP), LVEF, diabetes, right ventricular and biventricular pacemaker, implantable cardioverter defibrillator, peripheral artery disease, history of myocardial infarction, dyspnoea at rest, medication with statins, antidepressants or sedatives at baseline. Imputation was performed stratified by treatment. PHQ and SF-36 components as well as alcohol consumption and NT-proBNP were imputed by predictive mean matching with the 10 nearest neighbours; for all other variables, we used a parametric approach depending on the measurement level of the variable.[20] Mixed model repeated measures were used to compare mean changes in the PHQ-9 score. Study group and depressive symptoms at baseline were modelled as fixed effects as well as their two-way interaction and their three-way interaction with the effect over time. For adjustment, baseline characteristics were added to the model that were prospectively expected to potentially affect depressiveness. Age, NYHA class, depression level at baseline, dyspnoea on exertion, hospitalizations within the last 12 months, current living situation, baseline creatinine serum level and medication with statins, antidepressants or sedatives were included in the statistical model. Two-sided *P*-values below $\alpha = 0.05$ were considered significant.

Results

Clinical characteristics

Out of 710 patients, 674 patients completed at least seven out of nine items of the PHQ-9 at baseline and at least one additional PHQ-9 questionnaire during follow-up. The median follow-up was 25.0 months (mean 21.5). The mean age was 67.0 ± 10.8 years and 81.3% of the patients were male.

Figure 1 depicts the numbers of TIM-HF patients divided into two groups with and without a depression score of at least 10 points at baseline. In 156 patients, the PHQ-9 score was 10 points or above (TM: 79, UC: 77). The mean PHQ-9 score in those 156 patients was 13.2 ± 3.2 points (median 12.0 points TM 12.9 ± 3.0, median 12.0 points vs. UC 13.4 ± 3.3, median 12.0 $P = 0.360$), presenting moderate but clinically relevant depressive symptoms at baseline. Patients in the non-depressed groups presented mean PHQ-9 scores of 4.5 ± 2.5 points in the TM group vs. 4.6 ± 2.6 points in the UC group ($P = 0.560$, median 4.0 vs. 4.0). Overall, 124 TM patients and 122 UC patients were mildly depressed (mean 6.7 ± 1.3 vs. 6.9 ± 1.4), 59 TM patients and 57 UC patients were moderately depressed (mean 11.4 ± 1.3 vs. 11.7 ± 1.4), 17 TM patients and 16 UC patients were moderately severely depressed (mean 16.5 ± 1.3 vs. 17.1 ± 1.4) and 3 TM patients and 4 UC patients were severely depressed (mean 21.7 ± 0.6 vs. 22.0 ± 2.2).

There was no significant difference at baseline in PCS between groups (TM 36.6 ± 10.2 vs. UC 36.7 ± 10.7, $P = 0.848$) and MCS (TM 48.5 ± 11.0 vs. UC 48.9 ± 10.7, $P = 0.707$).

Patients in the TM group reporting depressive symptoms at baseline were characterized by older age (68.3 ± 9.1 years vs. UC 64.3 ± 11.4 years, $P = 0.017$), higher prevalence of NYHA class III (74.7% vs. UC 55.8%, $P = 0.013$), higher serum creatinine levels (117.0 ± 47.3 vs. UC 103.0 ± 34.6 µmol/L, $P = 0.037$), mid-regional pro-adrenomedullin levels (1.2 ± 0.6 vs. UC 1.0 ± 0.5 nmol/L, $P = 0.013$) and more frequent prescription of cardiac glycosides (39.2% vs. UC 23.4%, $P = 0.033$; online supplementary *Table S1*). In 518 patients without depressive symptoms, there were no significant differences in baseline characteristics between both study arms except hyperlipidaemia, baseline serum sodium and haemoglobin levels at baseline.

Depressive symptoms

The questionnaire was completed by 574 patients (85%) after 12 months, 78.5% of the TM patients vs. 83.1% of the UC patients with depressive symptoms at baseline (*Figure 2B* and online supplementary *Table S2*). After 12-month follow-up, 10 patients (12.7%) in the TM group and 4 patients (5.2%) in the UC group of these patients have died (*Figure 1*). Mortality was significantly higher in patients with comorbid depression at baseline in the TM group compared to UC ($P = 0.004$), but this effect did not persist after adjustment for NYHA class, age and serum creatinine levels ($P = 0.147$). Patients who died during follow-up were included in the analysis of PHQ-9 and quality of life.

The data show a significant interaction of randomization and depression level at baseline on changes in PHQ-9 scores during follow-up. The effects persisted with $P = 0.004$ after adjustment for baseline NYHA class, dyspnoea on exertion, medication of statins, sedatives, antidepressants, current living situation, age, number of hospitalizations within the last 12 months and serum creatinine.

Patients with depressive symptoms at baseline in the TM group showed an improvement of mean change [−1.6 points, 95% confidence interval (CI) −2.4 to −0.7, $P < 0.001$], whereas PHQ-9 score in the UC group showed no significant change (−0.2 points, 95% CI −1.05 to 0.74) (*Table 2* and *Figure 2A*). Thirty-three patients (11.5%) in the TM group and 32 patients (11.2%) in the UC group of the depressed patients at baseline reported an improvement of depression status measured by PHQ-9 <10 points after 12 months.

In both study groups without depression at baseline, depression levels remained constant over time (change from baseline: TM −0.3, 95% CI −0.7 to 0.1, $P = 0.170$ vs. UC −0.02, 95% CI −0.41 to 0.38, $P = 0.930$). However, the differences between groups did not reach statistical significance ($P = 0.312$) (*Table 2* and *Figure 2A*).

The estimated marginal means in *Figure 2B* show a constant benefit of the telemedicine intervention over time in patients with depressive symptoms. Trends were not significantly different.

Quality of life

There is a significant difference in mean change of the physical and mental component summary in favour of the TM group regardless of the level of depression at baseline (PCS 1.34 points, 95% CI 0.30 to 2.38, $P = 0.011$ and MCS 1.29 points, 95% CI 0.17 to 2.41, $P = 0.024$; *Table 3* and *Figure 2B*).

Discussion

In patients with CHF, the specific telemedical intervention used in TIM-HF improved pre-existing depressive symptoms. This positive effect was observed as early as 3 months after starting the

Table 1 Baseline demographic data and clinical characteristics

	PHQ-9 <10 (n = 518)		PHQ-9 ≥10 (n = 156)	
	Usual care (n = 258)	Telemedicine (n = 260)	Usual care (n = 77)	Telemedicine (n = 79)
Demographics and history				
Sex				
Male	220 (85.3)	211 (81.2)	56 (72.7)	61 (77.2)
Female	38 (14.7)	49 (18.8)	21 (27.3)	18 (22.8)
Age, years	67.64 ± 10.31	66.77 ± 11.41	64.34 ± 11.35	68.30 ± 9.13*
Living alone	45 (17.4)	53 (20.4)	23 (29.9)	17 (21.5)
NYHA class				
II	139 (53.9)	149 (57.3)	34 (44.2)	20 (25.4)
III	119 (46.1)	111 (42.7)	43 (55.8)	59 (74.7)*
Left ventricular ejection fraction, %	26.93 ± 5.78	27.02 ± 5.74	27.16 ± 6.28	26.68 ± 5.37
Duration of heart failure, years	6.83 ± 6.29	6.61 ± 6.82	7.00 ± 7.19	6.86 ± 5.80
Body mass index, kg/m^2	28.00 ± 4.87	28.31 ± 5.31	29.35 ± 6.56	28.65 ± 5.73
Blood pressure, mmHg				
Systolic	123.00 ± 17.15	120.80 ± 16.44	116.86 ± 15.54	119.57 ± 15.98
Diastolic	74.76 ± 9.42	74.46 ± 10.12	73.09 ± 10.87	73.77 ± 9.92
History of myocardial infarction	129 (51.8)	129 (50.6)	39 (51.3)	39 (50.0)
History of PCI	109 (42.2)	110 (42.3)	30 (39.0)	30 (38.0)
Implantable cardioverter defibrillator	111 (43.0)	121 (46.5)	38 (49.4)	35 (44.3)
History of CABG	67 (26.0)	74 (28.5)	23 (29.9)	23 (29.1)
Alcohol, drinks per week	3.07 ± 6.20	2.34 ± 3.91	2.41 ± 4.97	1.98 ± 3.88
Current smoker	31 (12.0)	38 (14.6)	11 (14.3)	5 (6.3)
Comorbidities				
Diabetes mellitus	97 (37.6)	97 (37.5)	33 (42.9)	36 (45.6)
Hyperlipidaemia	190 (73.6)	182 (70.0)*	56 (72.7)	56 (70.9)
History of depression	10 (4.0)	5 (2.0)	12 (16.9)	15 (20.3)
Laboratory values at baseline				
Haemoglobin, mmol/L	8.6 ± 1.5	8.3 ± 1.8*	8.2 ± 1.5	8.4 ± 1.6
Serum creatinine, μmol/L	108.28 ± 33.53	108.77 ± 40.94	103.02 ± 34.63	117.00 ± 47.25*
Uric acid, μmol/L	432.56 ± 125.54	429.59 ± 146.97	412.93 ± 141.02	436.13 ± 157.08
Serum sodium, mmol/L	139.14 ± 3.27	139.73 ± 3.00*	139.44 ± 3.76	138.97 ± 3.21
Potassium, mmol/L	4.62 ± 0.60	4.62 ± 0.62	4.54 ± 0.53	4.57 ± 0.53
Total cholesterol, mmol/L	4.69 ± 1.53	4.66 ± 1.52	4.89 ± 1.54	4.61 ± 1.57
Haematocrit, %	42.20 ± 3.86	41.40 ± 4.68*	40.95 ± 4.21	41.43 ± 4.80
C-reactive protein, mg/L	4.76 ± 6.13	5.21 ± 6.70	5.46 ± 7.76	8.95 ± 15.56
Thyroid-stimulating hormone, mU/L	1.50 ± 1.28	1.61 ± 1.50	2.23 ± 2.68	1.76 ± 1.86
NT-proBNP, pg/mL	2107.36 ± 3381.85	2279.01 ± 3028.66	2676.26 ± 4557.62	3086.79 ± 3915.92
MR-proADM, nmol/L	0.93 ± 0.45	0.93 ± 0.43	0.97 ± 0.49	1.18 ± 0.56*

Data are presented as mean ± standard deviation.
CABG, coronary artery bypass grafting; MR-proADM, mid-regional pro-adrenomedullin; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PHQ-9, 9-item Patient Health Questionnaire.
*Statistically significant differences between study groups at $P < 0.05$.

intervention and persisted to the end of the follow-up. Secondly, in CHF patients without depressive symptoms at baseline, telemedical monitoring did not cause depressive symptoms. In addition, patients randomized to telemedicine show better quality of life compared to patients receiving usual care regardless the level of depression (*Table 3* and *Figure 3*).

In the study population in TIM-HF, 22% of the CHF patients (n = 156) exhibited clinically relevant depressive symptoms at baseline, which is consistent with other HF studies.[1] During follow-up none of the patients underwent psychological treatment. The pre-defined subgroup of the TIM-HF patients with PHQ-9 scores ≥10 at baseline suffered from higher rates in mortality and hospitalizations.[17] TIM-HF confirmed the negative impact of comorbid depression on clinical outcomes.[1,2]

There are many studies investigating the effect of conventional psychiatric therapy strategies for patients suffering from depression in the subgroup of depressive patients with CHF but the results of these trials are inconsistent. For example, the benefit of selective serotonin reuptake inhibitors (SSRI) on depressive symptoms in CHF is uncertain. Both escitalopram[4] and sertraline[5] did not provide greater reduction of depressive symptoms than placebo. The use of tricyclic antidepressants is not recommended since they

Table 2 Estimated adjusted mean changes in 9-item Patient Health Questionnaire and between-group differences

Level of depression at baseline	Change from baseline			Between-group differences		
	Adjusted mean (95% CI)	SE	*P*-value	Adjusted mean (95% CI)	SE	*P*-value
Non-depressed (PHQ-9 <10)						
Telemedicine	−0.28 (−0.68 to 0.12)	0.21	0.170	0.26 (−0.25 to 0.77)	0.26	0.312
Usual care	−0.02 (−0.41 to 0.38)	0.20	0.930			
Depressed (PHQ-9 ≥10)						
Telemedicine	−1.57 (−2.44 to −0.70)	0.44	<0.001	1.42 (0.46 to 2.37)	0.49	0.004
Usual care	−0.15 (−1.05 to 0.74)	0.46	0.741			

Mixed model repeated measures, autoregressive model, dependent variables: mean change of PHQ-9, adjusted for follow-up, New York Heart Association class, dyspnoea on exertion, medication of statins, sedatives, antidepressants, current living situation, age, number of hospitalizations within the last 12 months and serum creatinine. Missing values were imputed using the multiple imputation method.
CI, confidence interval; PHQ-9, 9-item Patient Health Questionnaire; SE, standard error.

Table 3 Estimated adjusted mean changes in Short Form-36 and between-group differences

SF-36	Change from baseline			Between-group differences		
	Adjusted mean (95% CI)	SE	*P*-value	Adjusted mean (95% CI)	SE	*P*-value
Physical component summary						
Telemedicine	1.713 (0.980 to 2.447)	0.374	<0.001	1.34 (0.30 to 2.38)	0.53	0.011
Usual care	0.372 (−0.384 to 1.128)	0.386	0.335			
Mental component summary						
Telemedicine	1.286 (0.462 to 2.110)	0.420	0.002	1.29 (0.17 to 2.41)	0.57	0.024
Usual care	−0.005 (−0.806 to 0.797)	0.409	0.991			

Mixed model repeated measures, dependent variables: mean change in SF-36 physical component summary and mental component summary, adjusted for follow-up, New York Heart Association class, dyspnoea on exertion, medication of statins, sedatives, antidepressants, current living situation, age, number of hospitalizations within the last 12 months and serum creatinine. Missing values were imputed using the multiple imputation method.
CI, confidence interval; SE, standard error; SF-36, Short Form-36.

can worsen CHF due to causing hypotension and worsening of arrhythmias.[3,21] In fact, the prescription of antidepressants may be associated with higher cardiovascular mortality.[7] Similarly, the evidence for positive effects of psychotherapy on clinical outcomes in patients with CHF is inconclusive.[6] Physical training is able to improve depressive symptoms, but this approach is limited by the decreased exercise capacity in particular in patients with advanced CHF and represents a challenge to implement in routine care.[9,22] The inconsistent results using conventional psychiatric therapy in patients with CHF can be explained by the complex interactions between CHF and depression.[23] Therefore optimizing CHF therapy as well as addressing inactivity and the inability to engage in effortful behaviour could represent an approach to improve both CHF and depression as well as their interaction.[24] The telemedical care intervention used in TIM-HF aimed to reduce all-cause mortality and hospitalization rates. There was no specific antidepressant treatment intended. Nonetheless, the data showed significant differences in depression levels within the study period between the UC and TM groups in patients with depressive symptoms at baseline. Although the observed mean changes in the TM group did not reach the minimal clinically important difference in PHQ-9 scores of 5 points defined by Löwe *et al.*,[25] the data suggest that this kind of telemedical care does not worse depressive symptoms. Furthermore, the level of depressiveness in patients receiving usual care remained constant, while in comparison the TM group showed a consistent improvement. The range of change is consistent with other studies investigating therapy effects on depression, for example in the CASA trial,[10] which showed significant mean differences in PHQ-9 between intervention and control groups of not more than 1.6 points and is also considered a positive study on treating depression in CHF. Huffman *et al.*[8] reported significant improvements of a collaborative care management intervention in patients with CHF of 2.05 points in the MOSAIC trial.[8]

There are several aspects of the specific telemedical intervention used in TIM-HF that may explain the positive effect on depressive symptoms. First of all, patients were encouraged to perform daily measurements. When patients did not send the vital parameters, they were called the same day by a member of the TMC for further investigation. By this strategy high adherence to telemonitoring was achieved regardless of the level of depression.[26] In addition, another trial observed also higher adherence to medical therapy by using telemedicine.[27] Furthermore, this intervention includes a collaborative care management component, which has been shown to improve depressive symptoms in several previous studies.[8,10,28] A network between general practitioner, cardiologist, TMC and patient was established. Beyond the daily transfer of vital

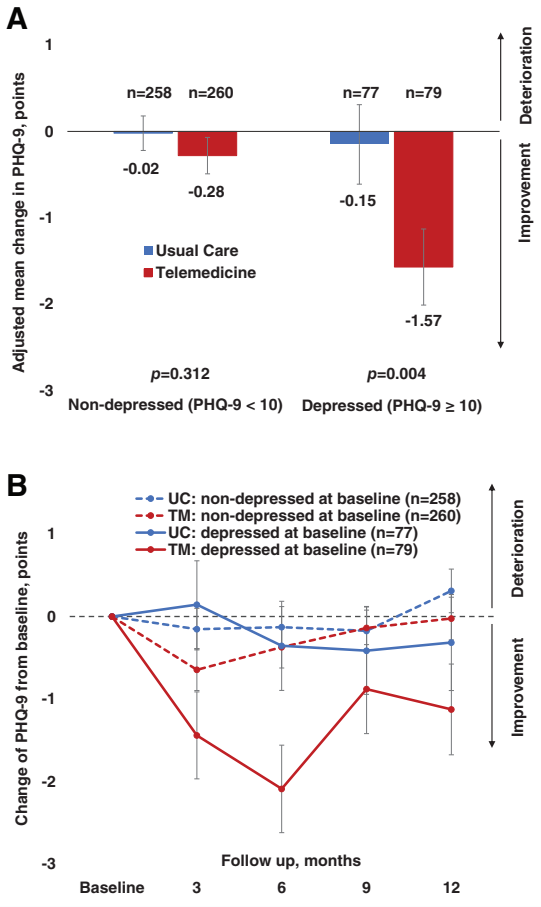

Figure 2 (*A*) Estimated adjusted mean changes in 9-item Patient Health Questionnaire (PHQ-9) scores from baseline. Mixed model repeated measures, dependent variable: mean change in PHQ-9, adjusted for follow-up, New York Heart Association class, dyspnoea on exertion, medication of statins, sedatives, antidepressants, current living situation, age, number of hospitalizations within the last 12 months and serum creatinine. Missing values were imputed using the multiple imputation method. (*B*) Mean changes in PHQ-9 score over time. Mixed model repeated measures, autoregressive model, dependent variable: mean change in PHQ-9, triple interaction 'follow-up, depression level at baseline and randomization'; adjusted for follow-up, New York Heart Association class, dyspnoea on exertion, medication of statins, sedatives, antidepressants, current living situation, age, number of hospitalizations within the last 12 months and serum creatinine. Missing values were imputed using the multiple imputation method. Trends were not significantly different.

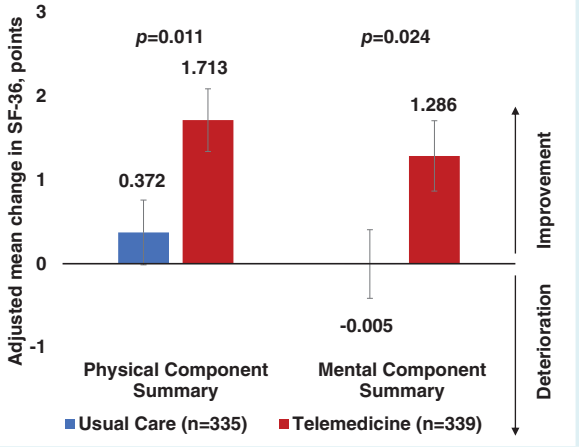

Figure 3 Estimated adjusted mean changes in Short Form-36 (SF-36). Mixed model repeated measures, dependent variables: mean change in SF-36 physical component summary and mental component summary, adjusted for follow-up, New York Heart Association class, dyspnoea on exertion, medication of statins, sedatives, antidepressants, current living situation, age, number of hospitalizations within the last 12 months and serum creatinine. Missing values imputed using the multiple imputation method.

parameters, there was a monthly structured telephone interview provided by the heart failure nurse of the TMC, which included also questions about the mood of the patient. A unique part of the telemedical intervention in TIM-HF was a 24/7 emergency service provided by physicians of the TMC. A specific consultation with regard to depressive symptoms was not included.

Despite these positive effects on depressive symptoms, patients in the intervention group with depression at baseline showed higher mortality and more days lost due to hospitalization and death compared to patients with depressive symptoms in the usual care group.[17] Our analysis explains this discrepancy of positive effects on depression and adverse clinical outcomes. PHQ-9 score was not part of the randomization process. Patients with depressed symptoms in the TM group were 4 years older, had higher serum creatinine levels and 74.7% were in NYHA class III, compared to 55.3% of the UC patients. After adjustment for these variables, differences between groups were not significant anymore.

Nevertheless, in the depressed TM group, the number of missing values was higher due to higher mortality compared to UC. To avoid a survivor bias, we included patients who died by imputation of missing values in the analysis of PHQ-9 and quality of life.

Besides the strengths of the study described above, several limitations should be considered. Regression towards the mean may have influenced the changes from baseline, although it seems unlikely if one considers the results of the UC sub-group in *Figure 2B*. For treatment group comparisons, regression towards the mean is anyway controlled by randomization. We cannot exclude a selection bias by the physicians neglecting the severe clinically depressed patients of participating in clinical studies. The analysis, despite being pre-defined, has also the caveats of a retrospective view. In the mixed model repeated measures procedure, data were assumed to be missing at random. A selection bias with regard to depression cannot be excluded with regard to missing questionnaires at different time points. We tried to address this problem by imputation of missing values by use of the multiple imputation method. Also the PHQ-9 itself — although validated for patients with CHF[18] — and especially its cut-off of 10 points

for clinical depression as a screening tool for CHF patients in telemedical studies can be discussed. For example, the PHQ-9 contains two items which are not only typical for depression but also symptoms in CHF: 'feeling tired or having little energy' and 'significant weight change or change in appetite'. In some studies investigators deleted these items to minimize bias. On the other hand, patients tend to misinterpret the item considering trouble staying asleep asking for nycturia. Therefore, patients may present higher levels of depressiveness in PHQ-9 compared to their actual clinical status. Thus, the cut-off of 10 points may need re-assessment when used to select patients profiting from a telemedical intervention. The SF-36 represents not a disease specific tool to evaluate quality of life. Therefore, it did not include questions on specific CHF symptoms. The minimal clinically important difference in SF-36 is described with five points.[29] In our analysis the estimated mean change difference between groups in PCS is 1.34 points ($P = 0.011$) and in MCS 1.29 points ($P = 0.024$). Though statistically significant, the clinical relevance is doubtful.

In summary, the study shows for the first time that telemedicine treatment has no negative impact on depressive symptoms in patients with CHF with or without depressive symptoms. The analysis provides evidence that in patients with CHF and clinically relevant depressiveness, telemedical care is able to improve depressive symptoms. Patients receiving telemedical care reported significantly better quality of life compared to the UC group, though of uncertain clinical relevance. As a consequence telemedical care can be offered to patients with CHF and moderate depression.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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