

Medizinische Klinik mit Schwerpunkt Kardiologie am Campus Virchow-Klinikum  
Medizinische Fakultät Charité - Universitätsmedizin Berlin

**DISSERTATION**

Physical well-being in patients with chronic heart failure – Investigation of a  
new aspect of quality of life and comparison with the physical and mental  
component of quality of life

zur Erlangung des akademischen Grades  
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## Abstrakt (Deutsch)

**Hintergrund:** Herzinsuffizienz (HI) ist eine schwerwiegende Erkrankung mit hoher Sterblichkeit und hohen Hospitalisierungsraten. Therapieoptimierung, wie Betablocker-Titration, ist oft mit unerwünschten Ereignissen (AEs) vergesellschaftet. Neben der Verbesserung der Sterblichkeit und Reduktion der Rehospitalisierungen, wurde die Steigerung der selbsteingeschätzten Gesundheit (SRH) und der Lebensqualität als wichtige Therapieziele erkannt. Dennoch ist bislang wenig bekannt über den Zusammenhang zwischen SRH und AEs und über die Determinanten einer Veränderung der Lebensqualität. Körperliches Wohlbefinden wird als eine Komponente der Lebensqualität angesehen und kann mit dem innovativen FEW-16-Fragebogen erhoben werden. Jedoch wurde dieser noch nicht bei Herzinsuffizienz validiert.

### Ziele:

1. Wie ist der Zusammenhang zwischen SRH und AEs bei Patienten mit Herzinsuffizienz während einer Betablocker-Titration?
2. Was sind die Determinanten einer Veränderung der Lebensqualität?
3. Kann der FEW-16-Fragebogen bei Patienten mit Herzinsuffizienz validiert werden?

**Methoden:** Dies sind vordefinierte Analysen der CIBIS-ELD-Studie über ältere Herzinsuffizienzpatienten ( $\geq 65$  Jahre), randomisiert zu Bisoprolol oder Carvedilol. Die Patienten wurden bei Einschluss, nach 12 Wochen und nach 2-4 Jahren mit dem Short-Form-Health-Survey (SF-36), dem Fragebogen für die Erhebung des körperlichen Wohlbefindens (FEW 16) und dem Patient-Health-Questionnaire for Depression (PHQ-D) untersucht.

**Ergebnisse:** Mehr Patienten berichteten mäßige/schlechte SRH bei Einschluss (36% vs. 30%,  $p=0.012$ ); nach 12 Wochen verbesserte sich SRH bei 34% und verschlechterte sich bei 8% ( $p=0.001$ ). Bei 64% der Patienten traten AEs auf. SRH war neben dem Alter, der 6-Minuten-Gehtest-Distanz und der Ejektionsfraktion ein unabhängiger Prädiktor für das Auftreten von AEs. Während der Behandlung verbesserte sich die mittlere psychosoziale und physische Komponente der Lebensqualität. Die Lebensqualität und Depression bei Einschluss sowie Veränderung der Depression waren die stärksten Determinanten einer Veränderung der Lebensqualität. Klinische Parameter waren schwächere Prädiktoren. Bei Einschluss, nach 3 Monaten und nach 2-4 Jahren war der mittlere FEW-Score  $3.04 \pm 1.04$ ;  $3.19 \pm 0.94$ ; und  $2.77 \pm 0.94$ . Cronbachs Alpha war für die Subskala "Belastbarkeit" 0.84; "Genussfähigkeit" 0.80; "Vitalität" 0.88; "Innerer Frieden" 0.87; Gesamtscore 0.95. Der Intraclass Korrelationskoeffizient war 0.87 (95% CI 0.84–0.89, ICC (1.4). Die Korrelation nach Pearson vom FEW16 mit SF36 und PHQ-D waren signifikant. Der absolute FEW-Score korrelierte mit der 6-Minuten-Gehtest-Distanz und der Herzfrequenz.

**Schlussfolgerung:** Die selbsteingeschätzte Gesundheit ist ein unabhängiger Prädiktor für das Auftreten von AEs während Betablocker-Titration. Depression war die Hauptdeterminante von Veränderungen der Lebensqualität. Klinische Parameter hingegen spielten eine untergeordnete Rolle. Der FEW16-Fragebogen zeigte eine gute Reliabilität, interne Konsistenz

und intraclass Korrelation. Die FEW16-Scores korrelierten gut mit physischen und psychischen SF36-Scores der Lebensqualität und klinischen Parametern der Belastbarkeit.

## Abstract (English)

**Background:** Heart failure (HF) is a severe condition with high mortality and hospitalization rates. Therapy optimization, like beta-blocker titration, is often accompanied by adverse events (AEs). Besides improvement of survival and reduction of re-hospitalizations, enhancement of self-rated health (SRH) and quality of life (QoL) have been recognized as important therapy targets. However, little is known about the relationship between SRH and AEs; and about the determinants of change in QoL. Physical well-being is thought to be one component of QoL and can be assessed with the innovative questionnaire FEW16. Yet, it hasn't been validated in HF.

### Aim:

1. What is the relation between SRH and AEs in HF patients undergoing beta-blocker titration?
2. What are the determinants of change in QoL during beta-blocker titration in HF?
3. Can the FEW16 questionnaire be validated for its use in HF?

**Methods:** These are prespecified analyses of CIBIS-ELD trial in elderly HF patients ( $\geq 65$  yrs), randomized to bisoprolol or carvedilol. Patients were examined at baseline, 12 weeks, and 2-4 years with the Short Form Health Survey (SF-36), Fragebogen für die Erhebung des körperlichen Wohlbefindens (FEW 16) and Patient Health Questionnaire for Depression (PHQ-D).

**Results:** More patients reported fair/poor SRH at baseline (36% vs. 30%,  $p=0.012$ ); after 12 weeks, SRH improved in 34% and worsened in 8% ( $p=0.001$ ). In 64 % AEs were reported. SRH predicted AEs in a multivariate model along with age, 6-min. walk test distance and ejection fraction. During the treatment mean psychosocial and physical QoL improved. Baseline QoL and depression, and change in depression were main determinants of changes in QoL, cardiac severity markers were weaker predictors. At baseline, after 3 months and after 2-4 years mean FEW16 scores were  $3.04 \pm 1.04$ ;  $3.19 \pm 0.94$ ; and  $2.77 \pm 0.94$ . Cronbach's alpha for subscales resilience: 0.84; ability to enjoy: 0.80; vitality: 0.88; inner peace: 0.87; total score: 0.95. Intraclass correlation coefficient (ICC) was 0.87 (95% CI 0.84–0.89, ICC (1.4). Pearson's correlations of FEW16 with SF36 and PHQ-D were significant. FEW16 total score correlated with six minutes walking distance and heart rate.

**Conclusion:** SRH seems to be an independent predictor of AEs during titration of beta-blockers. Depression was the main determinant of change of QoL, whereas clinical parameters were less associated. FEW16 questionnaire showed high validity through its reliability, internal consistency, and intraclass correlation. The FEW-16-scores correlated well with SF36-scores (physical and mental) and clinical markers of exercise tolerance.

## Background

Heart failure (HF) is known to be a global health problem that affects millions of patients worldwide. In Europe only, around 15 million people are living with HF [1]. These patients experience impaired functional status, diminished quality of life (QoL) and poor survival [2]. HF studies have been mainly focused on cardiovascular events, hospitalization and mortality, but recently patient reported outcomes have drawn new interest and are considered now by researchers and regulators as a relevant therapy target [3].

Self-rating of health is one of the most frequently assessed health perceptions in the research of QoL. Self-rated health (SRH) refers to a single question (“in general, would you say your health is excellent, very good, good, fair, or poor?”). QoL is a construct related to SRH. It assesses how a person feels about his/her health status and other non-medical aspects of life [4]. It is known that SRH is in HF patients generally worse than in other populations and diseases [5]. Additionally, HF therapy is generally challenging and therapy optimization, like beta-blocker titration, is often accompanied by side effects and adverse events. Nevertheless, the relation between SRH and adverse events in this group of patients still has not been discussed.

There are a number of questionnaires available for the measurement of QoL. A commonly used one (which was used within this work as well) is the Short Form (36) Health Survey (SF-36) questionnaire. Also, recently, many specific QoL questionnaires have been developed and they are more and more used as outcome measures in trials, but in practice as well [6]. Still, not much is known about what can lead to QoL improvement in this group of patients and about the exact determinants of change in QoL.

FEW16 questionnaire (Fragebogen zur Erhebung des körperlichen Wohlbefindens) is a 16-item questionnaire for assessing physical well-being [7]. There is no consensus on a single definition on well-being, but there is a general agreement that it includes the presence of positive emotions and moods, the absence of negative emotions, satisfaction with life, fulfillment and positive functioning [8]. Besides physical component of well-being, according to researchers from different fields, other components include the following: economic well-being, social well-being, emotional well-being, psychological well-being. The FEW16 questionnaire has been previously validated, but in healthy student population and population from rehabilitation centers. It has not yet been validated in HF patients. This research examines for the first time physical well-being in a larger multicenter cohort of elderly patients with chronic heart failure on beta blocker treatment. Although beta-blockers are part of an evidence-based therapy, its acceptance is limited due to various adverse effects. Evidence of rising physical well-being could improve this aspect of their use.

## Aim

The presented work aimed at answering the following questions:

1. What is the relation between SRH and adverse events in HF patients undergoing beta-blocker titration?
2. What are the determinants of change in health-related QoL during beta-blocker up-titration in HF patients?
3. Can the FEW16 questionnaire be validated for its use in patients with HF? Is there a relationship between changes in FEW16 values and clinical parameters and QoL?

## Methods

The Cardiac Insufficiency Bisoprolol Study in ELDerly (CIBIS-ELD) was an investigator-initiated, multi-centre, randomized, parallel, double-blind group phase III trial in elderly patients with chronic HF (controlled-trials.com, number ISRCTN34827306). The overall aim of the study was to compare the tolerability of bisoprolol and carvedilol in these patients [REF Rationale and Design Paper of CIBIS]. The trial was performed in 55 centres in four countries (21 in Germany, 15 in Serbia, 1 in Montenegro and 4 in Slovenia). Eligible patients were 65 years or older with symptomatic chronic heart failure consistent with New York Heart Association (NYHA) functional class  $\geq$  II at time of enrolment or with an LVEF  $\leq$  45%. At baseline, participants had to be beta-blocker naïve or on 1/4 of the guideline-recommended target or equivalent dose. Patients were 1:1 randomized to receive bisoprolol or carvedilol (bisoprolol with a 10 mg/day target dose and carvedilol with a target dose of 25 mg b.i.d) . More on rationale and design has been published previously [9].

### Data collection and instruments

For purposes of these prespecified analyses, QoL of CIBIS-ELD patients was measured using different questionnaires. The data was collected at baseline, after 3 months and after 2-4 years (follow-up). Questionnaires were completed by the patients themselves [10,11,12].

For answering the aim presented in this work, SRH has been assessed at baseline and after 12 weeks, using a question from the SF-36 “In general, would you say your health is...?” Patients had the following options: excellent, very good, good, fair and poor. Baseline SRH was available for 777 patients, of whom 628 reported SRH at baseline and at follow-up [10].

Health-related QoL (related to second aim within this work) was measured using 36-item QoL questionnaire, widely used in heart failure patients. The eight dimensions are scaled 0–100 with 0 reflecting worst and 100 reflecting best QoL. For physical and psychosocial component scores, raw values are rescaled based on established population norms with a score of 50 assigned to the population average and a difference in 10 points reflecting one standard deviation of the distribution observed in the reference population. Higher scores on each of the two components reflect better QoL.

The 9-item Patient Health Questionnaire is a questionnaire for the assessment of depression. Within this questionnaire, higher scores reflect more depressive symptoms. It is commonly used in clinical trials and it was used for answering the second aim presented in this work.

For answering the third question presented within aim, we used the FEW16 questionnaire, SF-36 questionnaire and the PHQ-D questionnaire. The FEW16 measures the subjective habitual physical well-being through the last 3 weeks by concentrating on the psychological well-being in the sense of affective experiencing and abilities. The FEW16 consists of four subscales: Resilience, Ability to Enjoy, Vitality, and Inner Peace, each of which contains four items. The items are to be answered on a 6-point Likert scale with answer options ranging from 'fully applies' (5 points) to 'does not apply at all' (0 points). Higher scores indicate better physical well-being.

The PHQ-D questionnaire originally developed as 'PRIME MD Patient Health Questionnaire (PHQ)', but later on designed for the recognition of the main psychological symptoms. For assessing these questions, we used the authorized German version of the questionnaire's short version for depression (PHQ-D). This short version consists of 9 questions which are used to assess depressive symptoms (scale ranging from '0' ('not at all') to '3' ('almost every day')). The points from all questions are summed up, and if the score is <5 it indicates healthy individuals/no depression, 6–9 indicates mild depression, 10 – 14 major depression with the distinction of medium, 15 – 19 pronounced, 20 – 27 severe.

### Statistics

Changes in the relationships between SRH and adverse events as well as clinical variables were assessed using Student's t-test and chi-squared test. Simple and multivariable logistic regression analyses were used to identify determinants of fair/poor baseline SRH. Regression model included the following variables: age, sex, PHQ-9 score ( $\geq 12$  points), beta-blocker pre-treatment, heart rate, NYHA class III/IV, distance on 6MWT, NT-proBNP tertiles, anaemia, and treatment with loop diuretics. Models that are presented later on in this work included and excluded SRH. A  $p \leq 0.05$  (two-sided) was considered statistically significant.

For assessing the change in health-related QoL during beta-blocker titration and in order to identify the factors that predicted the change of physical and psychosocial QoL (from BL to FU), multiple linear regression analyses were used.

For the validation of the FEW16 questionnaire in a HF population we calculated intraclass correlations (type 3), Cronbach's alpha coefficient and Guttman's lambda, for internal consistency. On the other hand, for a cross-validation with the SF36 questionnaire and the PHD-Q, we calculated Spearman rank correlations. For the analysis of a relationship between changes in FEW16 values and clinical parameters Spearman rank correlations for quantitative values and Kruskal-Wallis rank sum test for categorical data were calculated.

The software package SPSS 18.0 (SPSS Inc., 2009, USA) and R program were used for calculations in the presented work.

## Results

1. What is the relation between SRH and adverse events in HF patients undergoing beta-blocker titration?

During the CIBIS-ELD study, 883 patients were randomized. On average, they were 73 years old ( $\pm 6$  years), mainly male (62%) and with mean LVEF  $42\% \pm 14\%$ . Baseline SRH was available in 777 patients and both baseline and follow-up in 628 patients. SRH was rated good at baseline and follow-up, but it was noticed that at baseline, more patients reported fair/poor SRH (36% vs 30%,  $p=0.012$ ). Further analysis showed that women, beta-blocker-naïve patients, patients in NYHA class III/IV and those with PHQ-9 score  $\geq 12$  reported in a greater number fair/poor baseline SRH ( $p < 0.001$  for all). During follow-up, SRH improved in 34% of patients and worsened in 8% ( $p=0.001$ ). In 64% of patients adverse events were reported, 38% of them reported more than one adverse event or serious adverse event. The prevalence of adverse events was higher in patients with lower SRH categories. It was also shown that SRH, age, 6-minute-walk-test distance and  $> LVEF 45\%$  predicted adverse events ( $p=0.05$  for all) in a multivariate analysis (Figure 1). This analysis suggests that SRH is an independent predictor of adverse events during beta-blocker titration.

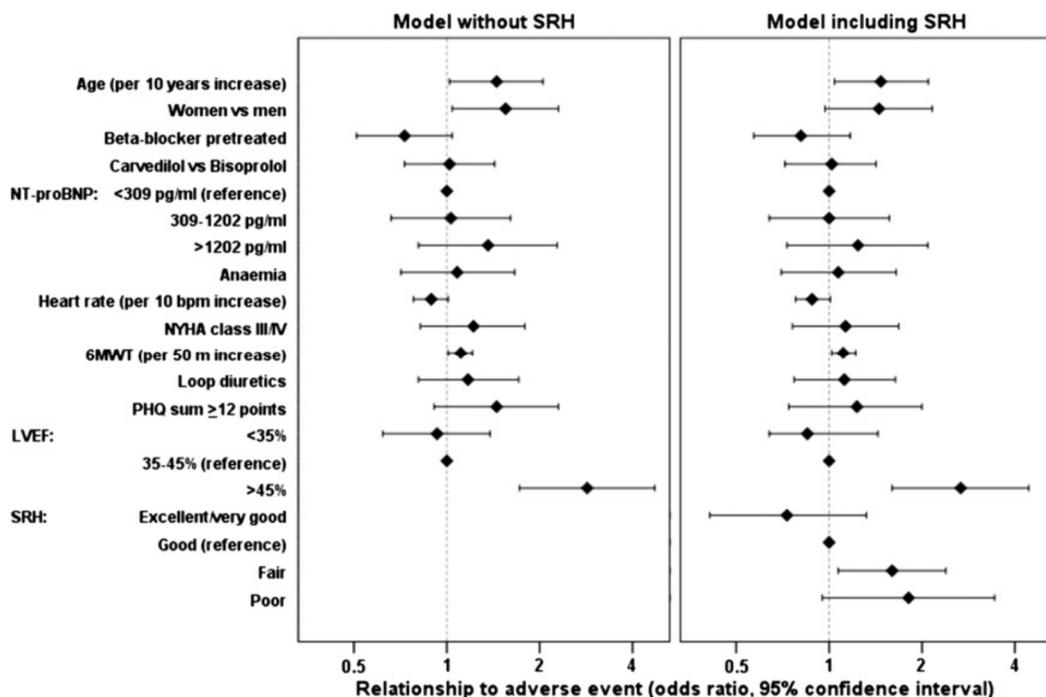


Figure 1. Predictors of adverse events; data are presented as odds ratio and 95% confidence interval (Lainscak et al.; 2011)

2. What are the determinants of change in health-related QoL during beta-blocker up-titration in HF patients?

In our second analysis, we analyzed psychosocial and biomedical factors determination change of QoL. Data for baseline and follow-up QoL from 589 patients were available. Out of these 589 patients, 292 were in the bisoprolol group and 297 in the carvedilol group. We showed that all dimensions of QoL improved from baseline to follow-up ( $p < 0.001$ ) Figure 2.

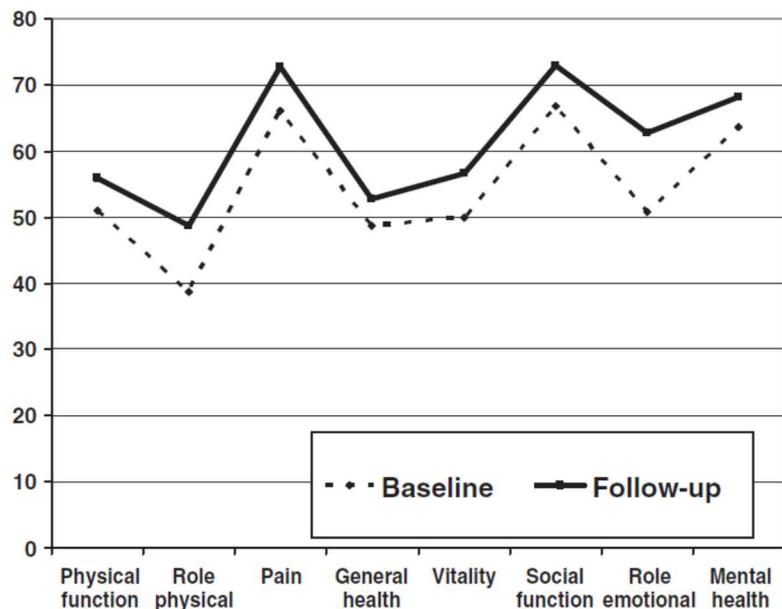


Figure 2. Dimensions of quality of life before and after beta-blocker up-titration (n=589; all changes significant at  $p < 0.001$ ; Scherer et al 2013).

Better improvement in physical QoL was predicted by younger age, longer 6-minute-walk-test distance and absence of COPD (minimally, change in model  $R^2 = 0.053$ ) in two separate hierarchical linear regression analyses (Table 1).

On the other hand, less depression at baseline, better NYHA class and improvement in 6-minute-walk test predicted more improvement in physical QoL over time. When it comes to psychosocial QoL, it was only not predicted by baseline NYHA class and LVEF (change in model  $R^2 = 0.022$ ,  $p = \text{non-significant}$ ). Less depression at baseline was once again a strong predictor for change in psychosocial QoL. Changes in ejection fraction or heart rate did not predict change, neither in physical nor psychosocial QoL.

	Model I; dependent: Change in phys. QoL		Model II; dependent: Change in psych. QoL	
	Beta	p	Beta	p
<b>Block I</b>				
Age	-.071	.044	.059	.052
Sex	-.024	.541	.002	.946
Smoking status (baseline)	.005	.891	.024	.445
CHD	.045	.329	-.033	.409
History of MI	.019	.687	.057	.158
Baseline NYHA class	-.054	.195	-.097	.007
Baseline 6 min walking distance	.113	.006	-.020	.565
Baseline LVEF [%]	-.013	.764	-.097	.008
COPD	-.089	.012	.044	.155
Baseline antidepressant meds	-.044	.204	-.001	.979
<b>Block II</b>				
Baseline SF-36 component*	-.619	<.0005	-.703	<.0005
Baseline PHQ depression	-.240	<.0005	-.442	<.0005
<b>Block III</b>				
Change in 6 min walking distance	.135	<.0005	-.029	.362
Change in LVEF	.057	.131	-.002	.956
Change in NYHA class	-.117	.004	-.145	<.0005
Change in heart rate	-.031	.362	-.035	.244
Change in PHQ depression	-.291	<.0005	-.529	<.0005
Change in model R <sup>2</sup>				
Block I	.053	.001	.022	.267
Block II	.248	<.0005	.300	<.0005
Block III	.096	<.0005	.226	<.0005
Adjusted R <sup>2</sup> for full model	.377	<.0005	.533	<.0005

Significant coefficients printed in boldface.

Table 1: Prediction of change in SF36 quality of life components by baseline characteristics and changes in clinical variables during beta-blocker up-titration (multiple linear regression analyses; n=548; Scherer et al, 2013).

3. Can the FEW16 questionnaire be validated for its use in patients with HF? Is there a relationship between changes in FEW16 values and clinical parameters and QoL?

For the validation of the FEW16 questionnaire, German patients diagnosed with heart failure with reduced ejection fraction (LVEF ≤ 45%) were analyzed. The complete data set (FEW16, SF36 and PHQ-D) for baseline and 3 months follow-up was available for 118 patients and for the 4 year follow-up for 44 patients.

The scores of all questionnaires at baseline, follow up 1 and long term follow up 2 are displayed in figure 3. From baseline to follow-up after 3 months the FEW16 total score increased significantly ( $3.04 \pm 1.04$  to  $3.19 \pm 0.94$ ). When concentrating on the subscales, the scores for “Ability to Enjoy” and “Vitality” increased between baseline and first follow-up. Also, values for all subscales of the SF36 increased from baseline to follow-up at 3 months. Interestingly, at the follow-up after 4 years, we noticed that the total FEW16 score had slightly decreased to  $2.77 \pm 0.94$  (non-significant).

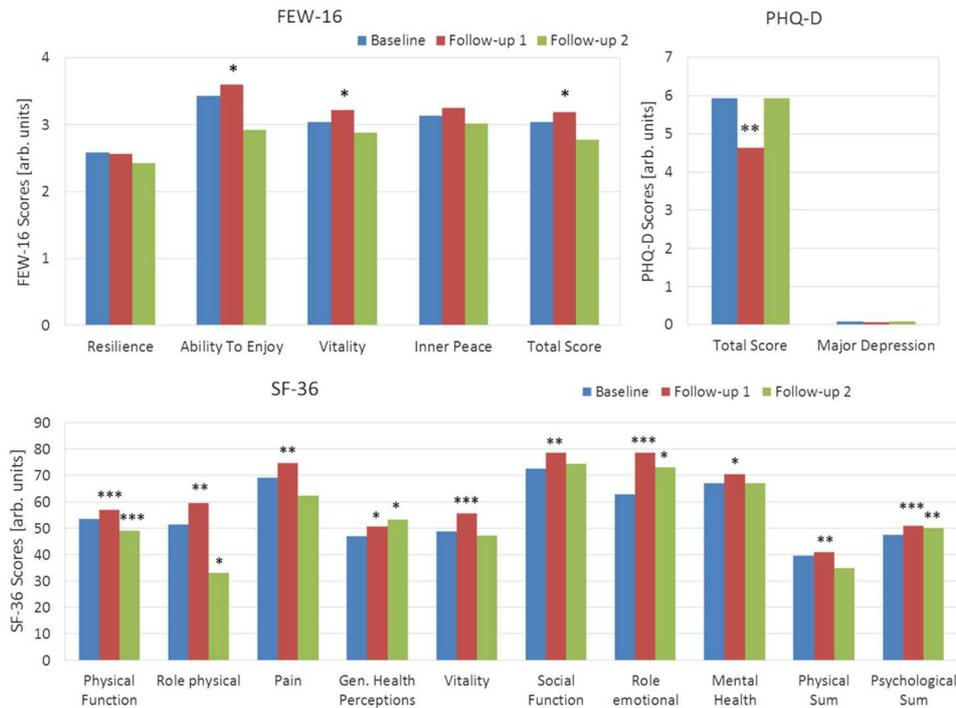


Figure 3: Mean scores of FEW16, 36-Item Short-Form Health Survey (SF36) and PRIME MD Patient Health Questionnaire German short version (PHQ-D) at all three time points with standard errors. Stars indicate significant difference to baseline. n = 127 at baseline, n = 118 at after 3 months (FU1), n = 44 at 2 to 4 years after baseline (FU2). Pairwise calculation of change significances. \*\*\* P<0.001, \*\* P<0.01, \* P<0.05 (Tahirovic et al 2015).

The scale values for the Cronbach’s alpha coefficient were between 0.84 and 0.91, and Guttman’s lambda6 values were 0.83 to 0.91; both results indicating good reliability and internal consistency in the subscales.

The FEW16 correlated significant (positively) with the total score and all subscales of the SF36 questionnaire and the highest correlations were shown with Vitality and Mental Health subscales (table 2). Noteworthy, the FEW16 total score showed a stronger correlation with the psychological component score than with the physical component score of the SF 36. The physical component scale correlated best with FEW16 Vitality. Further, the correlations of the FEW16 scores with PHQ-D scores were significant (negatively). The correlations of the FEW16 with the SF36 and PHQ-D subscales are presented in Table 2.

The 6-minute-walk-test (6MWT) showed significant correlation with the FEW16 total score (0.24), as well as with the FEW16 subscales Resilience (0.26), Inner Peace (0.21), and Ability to Enjoy (0.18). Heart rate showed significant negative correlations with the FEW16 total score (-0.22) and with the subscales Ability to Enjoy (-0.22) and Resilience (-0.20). For age, sex, NYHA class, LVEF and beta blocker therapy, there were no significant correlations with any FEW16 scale, although tendencies were noted for a correlation between sex and Vitality, Inner Peace and the total FEW16 score, and for NYHA class and Resilience. The medical history finding “Major depression” correlated with all subscales and with the total FEW16.

Variable		Resilience	Ability to Enjoy	Vitality	Inner Peace	FEW16
SF36	Vitality	0.666***	0.727***	0.713***	0.628***	0.801***
	Mental Health	0.504***	0.627***	0.532***	0.756***	0.703***
	Social Functioning	0.491***	0.471***	0.449***	0.534***	0.551***
	General Health Perceptions	0.514***	0.439***	0.443***	0.495***	0.543***
	Role—Physical	0.452***	0.454***	0.519***	0.342***	0.514***
	Physical Functioning	0.460***	0.467***	0.455***	0.384***	0.501***
	Pain	0.406***	0.403***	0.444***	0.433***	0.474***
	Role—Emotional	0.295**	0.311***	0.382***	0.325***	0.385***
	Physical, sum	0.435***	0.418***	0.476***	0.304***	0.469***
	Psychological, sum	0.466***	0.541***	0.540***	0.620***	0.634***
PHQ-D	Difficulties sleeping	-0.461***	-0.576***	-0.627***	-0.420***	-0.618***
	Feeling tired or having little energy	-0.501***	-0.567***	-0.549***	-0.412***	-0.600***
	Feeling down, depressed or hopeless	-0.458***	-0.517***	-0.449***	-0.556***	-0.573***
	Little interest or pleasure in doing things	-0.455***	-0.477***	-0.392***	-0.401***	-0.510***
	Thoughts of suicide	-0.390***	-0.437***	-0.413***	-0.529***	-0.496***
	Physical impairments	-0.397***	-0.434***	-0.383***	-0.487***	-0.469***
	Lack of self-confidence	-0.332***	-0.425***	-0.370***	-0.495***	-0.455***
	Difficulties concentrating on things	-0.298***	-0.435***	-0.323***	-0.459***	-0.438***
	Poor appetite or overeating	-0.238**	-0.410***	-0.270**	-0.342***	-0.365***

\*\*\* $P < 0.001$ , \*\* $P < 0.01$ .

SF36, 36-Item Short-Form Health Survey; PHQ-D, PRIME MD Patient Health Questionnaire German short version.

Table 2. Correlation coefficients of FEW16 subscales with the subscales of SF36 and the PRIME MD instruments at baseline (Tahirovic et al.; 2015)

We also examined the potential impact of gender on the relations between FEW16 scales and clinical measurements. A positive relationship was found between physical well-being (total score FEW16) and the 6MWT, in men only.

Changes from baseline to follow-up after 4 years measured by the FEW16 were compared to the changes measured by the SF36 and PHQ-D and those of clinical parameters. With changes in clinical parameters like 6MWT, LVEF, and heart rate, there was no correlation with the FEW16 total score changes, but these correlated with changes of the SF36 subscales General Health Perceptions, Vitality, Social Functioning, Physical Functioning, Mental Health, and the physical and the psychological component scores. When focused on gender and age, we have found that FEW16 is gender-independent and age-independent.

## Discussion

During these analyses, we have shown that SRH correlates with the proportion and number of adverse events per patient, and hence titration failure. Comparing to previously reported SRH in different heart failure populations, our patients reported fair/poor baseline health in a lower percentage (36%). This may be explained with the more pronounced proportion of male in our cohort, better treatment and less patients with NYHA class III/IV [13,14,15]. Also, it is important to mention that our findings on SRH improvement during a well-established intervention for HF patients is not surprising when compared to the previously published works, such as Anker et al [16]. We have further shown that SRH independently has good predication of adverse events, during beta-blocker up-titration. This is important to note for clinical practice, since SRH is a parameter easy to assess and relevant for prediction of adverse events.

While answering the second question of the presented work, we showed that there was a general improvement of QoL, in all its dimensions and from baseline to follow-up, measured with the SF36. Depression was assessed by the PHQ-D. It was shown that low baseline depression is one of the strongest independent predictors of QoL improvement, in both psychosocial and physical QoL. NYHA class improvement was highly correlated with improvement of psychosocial and physical QoL. Increased 6-min walk test distance, on the other hand, only predicted improved physical QoL. In previous work, similar results to ours were noticed: Jünger et al. found comparable or slightly lower SF-36 dimension scores in 205 HF patients with reduced ejection fraction [17]. Holzapfel et al. [18] got comparable results in a sample of 320 patients. Slight differences could be explained by different proportions of NYHA I/II and NYHA III class patients in all of these studies.

The third aim of this presented work was the validation of the FEW16 as a disease-specific instrument for the assessment of physical well-being in HF patients. High values of Cronbach's alpha and Guttman's lambda 6 indeed proved good reliability and internal consistency of FEW16. These findings are similar to findings in other validations of this questionnaire [19,7]. Subscales of FEW16 and SF36 seem to correlate well. As expected, the Vitality scale of FEW16 strongly correlated with Vitality scale within SF36, what confirms Kolip's and Schmidt's finding in their first validation of the questionnaire [32]. The expected negative correlation of FEW16 with the PHQ-D was shown, due to the fact that this are two opposite questionnaires.

By comparing FEW16 with SF36, we confirmed the results of the second paper in this presented work [11]. This research, as above explained, showed that the mean physical and psychosocial QoL improved significantly during treatment. None of the HF parameters (as LVEF or NYHA) showed significance with the FEW16 scores, except a weak correlation between NYHA class and Resilience scale. It is interesting to make a comparison on this level: Müller-Tasch et al. reported that LVEF did not influenced QoL [20], whereas another study [21] found that NYHA class, as the indicator of the HF severity predicts QoL (specially, the physical dimension). Once again, these different results are most probably because of different NYHA classes of patients in question.

We have also found that FEW16 is gender-independent and age-independent. This differs from another study that proved higher FEW16 scores in men than in women [19]. Changes in clinical parameters from baseline and 4 years follow-up did not follow the changes in FEW16. On the other hand, changes in both QoL aspects between baseline and 4 years follow-up correlated well with changes in the FEW16.

Unexpectedly, the psychological scale of SF-36 correlated stronger with the total score of FEW16 than the physical SF36 scale. From all stated above, we can conclude that during the treatment and overall management of these patients, psychological and social situation are very well important for the patients' well-being.

## Limitations

The presented work has certain limitations that need to be mentioned. In the research that gave the answer to the first question, the follow-up period for identifying the changes in SRH was short. Also, certain determinants of SRH (socioeconomic circumstances and type of personality) were not followed [10]. When it comes to the second question, all findings apply to a 10 week (or 12 for patients > 85 kg) observational period, which was quite short [11].

## Conclusions

All these results show, that more factors impact on patient health than assessed through clinical measurement. We proved that SRH is an independent predictor of AEs during titration of beta-blockers and in that way might help with the disease management in individual cases. Depression was the main determinant of change of QoL, whereas clinical parameters were less associated. FEW16 questionnaire showed high validity through its reliability, internal consistency, and intraclass correlation. The scores obtained correlated well with SF36 scores (psychological and physical) and clinical markers of exercise tolerance.

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## Affidavit

I, Elvis Tahirovic, certify under penalty of perjury by my own signature that I have submitted the thesis on the topic “Physical well-being in patients with chronic heart failure – Investigation of a new aspect of quality of life and comparison with the physical and mental component of quality of life”. I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE [www.icmje.org](http://www.icmje.org)) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (s.o) and are answered by me. My contributions in the selected publications for this dissertation correspond to those that are specified in the joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author of correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Date

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Signature

## Declaration of publications

*Statement: All three publications listed below are pre-specified analyses of the CIBIS-ELD study, a multicenter and multinational trial, funded by German government (BMBF). Sponsor of the trial was Charite Universitätsmedizin Berlin, Principal Investigator PD Dr. Düngen. As a member of coordination team of the entire trial, I was responsible for the study coordination, including monitoring of 20 sites in Serbia, Slovenia and Montenegro. Also, I was responsible partially for data collection, query management and overall data quality.*

### Publication 1:

Lainscak M, Farkas J, Inkrot S, Gelbrich G, Neskovic AN, Rau T, **Tahirovic E**, Töpfer A, Apostolovic S, Haverkamp W, Herrmann-Lingen C, Anker SD, Düngen HD. Self-rated health predicts adverse events during  $\beta$ -blocker treatment: the CIBIS-ELD randomised trial analysis. *Int J Cardiol.* 2013 Feb 10;163(1):87-92. doi: 10.1016/j.ijcard.2011.05.037. Epub 2011 Jun 8.

*Contribution: Additionally to the mentioned above, my contribution to this publication was participation in statistical analysis, discussion and interpretation of results obtained, review and personal input to the manuscript.*

### Publication 2:

Scherer M, Düngen HD, Inkrot S, **Tahirović E**, Lashki DJ, Apostolović S, Edelmann F, Wachter R, Loncar G, Haverkamp W, Neskovic A, Herrmann-Lingen C. Determinants of change in quality of life in the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD). *Eur J Intern Med.* 2013 Jun;24(4):333-8. doi: 10.1016/j.ejim.2013.01.003. Epub 2013 Feb 1.

*Contribution: Additionally to the mentioned above, my contribution to this publication was participation in statistical analysis, discussion and interpretation of results obtained, review and personal input to the manuscript.*

### Publication 3:

**E. Tahirović**, D. J. Lashki, T. D. Trippel, V. Tscholl, M. Fritschka, L. Musial-Bright, A. Busjahn, P. Kolip, S. Störk, M. Rauchfuß, S. Inkrot, M. Lainscak, S. Apostolović, J. Vesković, G. Lončar, W. Doehner, C. Zelenak and H. D. Düngen. Validation of the FEW16 questionnaire for the assessment of physical well-being in patients with heart failure with reduced ejection fraction: results from the CIBIS-ELD study. *ESC Heart Failure* (2015) Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ehf2.12045

*Contribution in detail: In this publication, I was the main responsible for the interpretation of results obtained and writing of the manuscript. As mentioned in the statement above, I was also responsible for the study coordination, data collection, query management and overall data quality.*

Signature, date and stamp of the  
supervising University teacher

Signature of the doctoral  
candidate

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## Publication 1: Self-rated health predicts AE during $\beta$ -blocker treatment

Lainscak M, Farkas J, Inkrot S, Gelbrich G, Neskovic AN, Rau T, **Tahirovic E**, Töpper A, Apostolovic S, Haverkamp W, Herrmann-Lingen C, Anker SD, Düngen HD. Self-rated health predicts adverse events during  $\beta$ -blocker treatment: the CIBIS-ELD randomised trial analysis. *Int J Cardiol.* 2013 Feb 10;163(1):87-92. doi: 10.1016/j.ijcard.2011.05.037. Epub 2011 Jun 8.

*Impact factor 2014: 4.036*

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## Publication 2: Determinants of change in QoL in the CIBIS-ELD

Scherer M, Düngen HD, Inkrot S, Tahirović E, Lashki DJ, Apostolović S, Edelmann F, Wachter R, Loncar G, Haverkamp W, Neskovic A, Herrmann-Lingen C. Determinants of change in quality of life in the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD). *Eur J Intern Med.* 2013 Jun;24(4):333-8.

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<http://dx.doi.org/10.1016/j.ejim.2013.01.003>

## Publication 3: Validation of the FEW16 questionnaire: results from the CIBIS-ELD

**E. Tahirović**, D. J. Lashki, T. D. Trippel, V. Tscholl, M. Fritschka, L. Musial-Bright, A. Busjahn, P. Kolip, S. Störk, M. Rauchfuß, S. Inkrot, M. Lainscak, S. Apostolović, J. Vesković, G. Lončar, W. Doehner, C. Zelenak and H. D. Düngen. Validation of the FEW16 questionnaire for the assessment of physical well-being in patients with heart failure with reduced ejection fraction: results from the CIBIS-ELD study. *ESC Heart Failure* (2015) Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ehf2.12045

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## Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

My CV will not be published in the electronic version of my thesis due to data privacy.



## Publication List

### 1. First Authorships

**E. Tahirović**, D. J. Lashki, T. D. Trippel, V. Tscholl, M. Fritschka, L. Musial-Bright, A. Busjahn, P. Kolip, S. Störk, M. Rauchfuß, S. Inkrot, M. Lainscak, S. Apostolović, J. Vesković, G. Lončar, W. Doehner, C. Zelenak and H. D. Düngen. Validation of the FEW16 questionnaire for the assessment of physical well-being in patients with heart failure with reduced ejection fraction: results from the CIBIS-ELD study. ESC Heart Failure (2015) Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ehf2.12045

### 2. Co – Authorships

1. Edelmann F, Musial-Bright L, Gelbrich G, Trippel T, Radenovic S, Wachter R, Inkrot S, Loncar G, **Tahirovic E**, Celic V, Veskovic J, Zdravkovic M, Lainscak M, Apostolović S, Neskovic AN, Pieske B, Düngen HD. Tolerability and Feasibility of Beta-Blocker Titration in HFpEF Versus HFrEF: Insights From the CIBIS-ELD Trial. JACC Heart Fail. 2016 Feb;4(2):140-9.

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