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DISSERTATION

Patient-reported outcomes in heart failure

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Summary

Abstrakt (Deutsch)

Einleitung

Herzinsuffizienz ist eine globale Herausforderung an die Gesundheitssysteme und geht einher mit hoher Mortalität, Morbidität und reduzierter selbst-eingeschätzter Gesundheit sowie Lebensqualität. In einem ganzheitlichen Versorgungskonzept der Patienten spielen die vom Patienten berichteten Eindrücke und Bewertungen über sein Wohlbefinden, seine Therapie und seine Teilnahme an der Versorgung eine wesentliche Rolle. Diese „Patient-reported Outcomes" wurden bislang aber bei der Herzinsuffizienz wenig eingesetzt und sind nicht ausreichend untersucht.

Ziele

Ziel dieser Arbeit war es, Patient-reported Outcomes bei Patienten mit Herzinsuffizienz in Hinsicht auf potenzielle Verbesserungen bei der Versorgung und für die Risikoprädiktion zu untersuchen. Hierfür sollten die folgenden Fragen beantwortet werden:

- Wie ist der Zusammenhang von der durch den Patienten selbst-eingeschätzten Gesundheit und dem Auftreten von unerwünschten Ereignissen während einer Einstellung auf Betablocker bei herzinsuffizienten Patienten?

- Wie und in welchem Umfang wird die Lebensqualität durch klinische und psychologische Faktoren während der Betablocker Behandlung beeinflusst?

- Wie gut wenden herzinsuffiziente Patienten in verschiedenen Ländern spezielle Selbstpflege-Maßnahmen an, und was sind nationale Unterschiede?

- Welchen Vorhersagewert haben zwei aufeinander folgende Messungen der selbst-eingeschätzten Gesundheit hinsichtlich des Sterberisikos bei herzinsuffizienten Patienten?

Methoden

Selbst-eingeschätzte Gesundheit, Lebensqualität und Depression wurden in der Investigator-initiierten, multizentrischen, doppelblinden Studie „Cardiac insufficiency bisoprolol study in elderly" (CIBIS-ELD) untersucht. Herzinsuffizienz Selbstpflege-Verhalten und Sterblichkeit wurden in einer Langzeitnachbeobachtung nach 2-4 Jahren untersucht. Statistische Methoden bestanden aus beschreibender Statistik, Student T-Test, Chi-Quadrat Test, Kendalls Korrelationsanalyse, Cox-Regression, logistischer Regression, multipler lineare Regression und Kaplan-Meier Analyse. Ein p-Wert ≤ 0.05 wurde als statistisch signifikant erachtet.

Ergebnisse

Die vom Patienten selbst-eingeschätzte Gesundheit sagte unabhängig unerwünschte Ereignisse und Verzögerungen bei der Einstellung auf Betablocker voraus. Außerdem war eine mehrfach als „schlecht" selbst-eingeschätzte Gesundheit mit schlechter Prognose bei herzinsuffizienten Patienten in der Langzeitbeobachtung assoziiert. Veränderungen der Lebensqualität während der Medikamenteneinstellung hingen mehr vom Vorhandensein und der Ausprägung einer Depression ab, als von Veränderungen des klinischen Schweregrades der Herzinsuffizienz. Aus globaler Perspektive variierte das Selbstpflege-Verhalten erheblich zwischen den untersuchten Ländern und sollte weltweit verbessert werden.

Schlussfolgerungen

Diese Arbeit trägt zum Verständnis von Patient-reported Outcomes bei herzinsuffizienten Patienten bei. Pflegende und Ärzte sollten beim Umgang mit herzinsuffizienten Patienten die selbst-eingeschätzte Gesundheit, die Lebensqualität, Depression und das Selbstpflege-Verhalten erheben und beurteilen. Patient-reported Outcomes sind unabdingbar bei der patientenzentrierten Behandlung, die Wert legt auf Mitbestimmung bei der Behandlung und der weiteren Versorgung.

Abstract (English)

Background

Heart failure is a global health care challenge that is associated with high morbidity and mortality, as well as reduced self-rated health and quality of life. In a holistic approach to patient care, assessment of the patient's perspective on their wellbeing, treatment, and participation in care can be captured by patient-reported outcomes. Utilisation of patient-reported outcomes in heart failure in clinical practice and research remains limited.

Aims

The aim of this work was the integration of patient-reported outcomes in heart failure research to improve our understanding of their potential benefit in patient care and risk prediction. Specifically, the aim of this work was to answer the following questions:

- What is the relationship between self-rated health and occurrence of adverse events during up-titration of beta-blocker therapy in patients with heart failure?

- How, and to what extent, are changes in quality of life influenced by clinical and psychological factors during up-titration of beta-blockers in patients with heart failure?

- How well do patients with heart failure perform specific self-care behaviours across the world and what are the differences and/or similarities between countries?

- What is the predictive value of two consecutive self-rated health assessments with regard to mortality in patients with heart failure?

Methods

Self-rated health, quality of life and depression were assessed in the investigator-initiated, multicentre, double blind cardiac insufficiency bisoprolol study in elderly (CIBIS-ELD). Heart failure self-care and mortality were assessed in an observational long-term follow-up survey after 2-4 years. Statistical analyses included descriptive methods, Student's t-tests and chi-squared tests, Kendall's correlation coefficient analysis, Cox proportional hazard regressions, logistic regressions, multiple linear regressions, and Kaplan-Meier analysis, as appropriate. For all tests, a p-value of ≤ 0.05 was considered statistically significant.

Results

Patients' self-rated health independently predicted adverse events and titration failure during up-titration of beta-blockers. Further, when assessed consecutively, poor self-rated health predicted long-term mortality in elderly patients with chronic heart failure. Changes in health-related quality of life over the course of medication up-titration were determined more strongly by changes in depression than changes in cardiac severity markers. From a global perspective, heart

failure self-care skills vary significantly in different countries and need to be improved worldwide.

Conclusions

This work makes a significant contribution to our understanding of patient-reported outcomes in chronic heart failure. Clinicians are recommended to include the assessment of self-rated health, quality of life, depression and self-care behaviour in their interactions with patients with heart failure. The inclusion of patient-reported assessments is encouraged in the patient centred, shared decision-making process about further support, treatment, and follow-up.

Background

Heart failure is a clinical syndrome caused by functional or structural abnormalities of the heart, resulting in its inability to meet fully the body's oxygen demands [1]. Heart failure-associated morbidity and mortality are high, and patients are frequently hospitalised with decompensation resulting in considerable healthcare system cost [2]. Heart failure patients are burdened by symptoms of fatigue, breathlessness, and recurring signs of fluid retention such as oedema. Hence, quality of life and ability for social participation are reduced [3]. Depression, fear and anxiety are common experiences for patients with chronic heart failure [3].

Heart failure is also a global healthcare challenge: approximately 2% of the world's population are affected, and the prevalence particularly of heart failure with preserved ejection fraction (HFpEF) is rising [4]. In Western Europe, 1-3% of total health care expenditure is attributable to heart failure [2]. There is a need for international collaboration to combine knowledge and understanding in a concerted effort to reduce the burden of heart failure worldwide [5].

Risk for hospitalisation and adverse outcomes can be evaluated by combining clinical (e.g. New York Heart Association (NYHA) class, heart rate), laboratory (e.g. N-terminal pro b-type natriuretic peptide (NTproBNP)), and psychological factors (e.g. depression) [1]. In line with a holistic approach to clinical nursing and medical decision-making, patient-reported outcomes (PROs) can reflect a person's perspective and experience of their health, illness, health care system factors and treatment [6]. A PRO is defined as "… a report that comes directly from the patient … without amendment or interpretation of the patient's response by a clinician or anyone else." [7]. PROs can contain a variety of information relating to quality of life, functional status, symptoms, treatment adherence, or overall self-rated health [8]. Self-rated health is a measure of a person's subjective perception of his or her health as the person defines it, and is an independent predictor of mortality in the general population [9,10]. Data on the value of self-rated health in predicting outcome in heart failure are limited.

Specific treatment strategies of heart failure include pharmacological therapy, interventional and device therapy, and non-pharmacological therapy [1]. These strategies are aimed at reducing mortality and morbidity, reducing symptom burden, and improving quality of life [1]. Quality of life has been conceptualised as "the degree to which a person enjoys the important possibilities of his or her life" and has three domains: being, belonging, and becoming [11]. Quality of life is

therefore an essential PRO in chronic illness. Little is known about the specific biomedical and psychosocial factors associated with improvement of quality of life in heart failure.

Pharmacological treatment of heart failure includes initiation and up-titration of beta-blockers. However, international surveys demonstrate that many patients are on less than guideline-recommended doses [12]. A possible reason for this is clinically, 'objectively' assessed intolerability to increasing doses in a typically older population with multiple other co-morbidities. Patients also describe subjectively perceived intolerability, such as worsening fatigue in the initial stages of treatment. There is limited information on self-rated health and quality of life during medication titration.

Cornerstones of non-pharmacological therapy are education and the support and empowerment of heart failure patients to engage proactively in care, namely to self-care [1]. Self-care behaviours in the context of heart failure include healthy lifestyle and exercise, monitoring and evaluating symptoms such as breathlessness or fatigue, signs of fluid retention such as peripheral oedema, and managing these symptoms, for example, using flexible diuretic regimens [13]. Successful heart failure self-care has been shown to improve quality of life, reduce symptom load, and decrease the number of fatal readmissions, length of stay, and health care cost [14]. Hence, the support of self-care skills is recommended in guidelines for long-term heart failure management worldwide [1,15,16]. It is unclear whether self-care behaviours as reported by the patient are performed equally well and consistently across the world.

Aims

The aim of this work was to answer the following questions:

- What is the relationship between self-rated health and occurrence of adverse events during up-titration of beta-blocker therapy in patients with heart failure?

- How, and to what extent, are changes in quality of life influenced by clinical and psychological factors during up-titration of beta-blockers in patients with heart failure?

- How well do patients with heart failure perform specific self-care behaviours across the world and what are the differences and/or similarities between countries?

- What is the predictive value of two consecutive self-rated health assessments with regard to mortality in patients with heart failure?

Methods

To gain a better understanding of the value of PROs during medication titration and in predicting outcome in heart failure, self-rated health, quality of life and depression were assessed in the investigator-initiated, double-blind cardiac insufficiency bisoprolol study in elderly (CIBIS-ELD) [17,18]. Heart failure self-care and mortality were assessed in an observational long-term follow-up survey after 2-4 years [19,20].

Details of the design and main outcomes of CIBIS-ELD have been described previously [17,18]. CIBIS-ELD was a multinational study conducted in 41 study centres in Germany, Serbia, Slovenia and Montenegro. In brief, between April 2005 and April 2008, stable chronic heart failure patients over 65 years (n=883, mean age 73 years, 38% women, left ventricular ejection fraction (LVEF) 42% ± 14%) were randomised to bisoprolol or carvedilol, and the respective beta-blockers were up-titrated at fortnightly intervals. Primary endpoint of CIBIS-ELD was tolerability of target doses after 10-12 weeks (follow-up). Self-rated health, quality of life and depression were measured twice, at baseline, and at follow-up.

Self-rated health was measured by asking patients "In general, would you say your health is…?", with response options of excellent, very good, good, fair, poor on a 5-point Likert scale. Validity and reliability of this single-item PRO have been established [21]. Outcome and adverse events, including death, hospitalisations, cardiovascular symptoms, and pulmonary symptoms, were recorded at the titration visits and at the end of titration [17,18].

Health-related quality of life was measured using the Medical Outcomes Study Short Form-36 Questionnaire (SF-36) [22]. This instrument comprises eight sub-domains of quality of life: physical function, role physical, pain, general health, vitality, social function, role emotional, and mental health [22]. The questionnaire also allows for computation of two global health domains: physical and psychosocial health. On the SF-36, scores range from 0-100 with higher scores reflecting better quality of life. In the current analyses, both specific dimensions and the two component scores were used [23].

Depression was assessed using the Patient Health Questionnaire, PHQ-9 [24], which is widely used for assessing depression in primary care. Reliability and validity of this instrument are well documented [25,26]. On a scale of 0-27, higher scores indicate more depressive symptoms [24].

At baseline, data on patient socio-demographic characteristics, medical history, and medication were recorded. Echocardiography and electrocardiogram were performed at the baseline visit or retrieved from clinical records if less than 3 months old [17,18]. At both baseline and follow-up, patients underwent full clinical examination including blood pressure, heart rate, body weight and height, and NYHA class assessment. Effort tolerance was assessed using a six-minute walk test, which was performed using the guidelines from the American Thoracic Society [27]. Body mass index (BMI) was calculated from body weight and height (kg/m2) [28]. Laboratory testing included NTproBNP, renal function, and full blood count. Anaemia was defined in line with the World Health Organisation recommendations of haemoglobin <120 g/l for women and <130 g/l for men [29].

Information on long-term mortality (vital status: alive or dead) was obtained during an observational longitudinal follow-up of CIBIS-ELD patients after 2-4 years between 2010-2012. Vital status data were gathered from patients, general practitioners, hospital records, or State registries [20].

Self-care behaviour was assessed in patients attending the long-term observational follow-up survey in Germany (n=135, mean age 77 years, 57% female) and Serbia (n=106, mean age 76 years, 32% female), using the Self-care of Heart Failure Index (SCHFI) [19]. The SCHFI is an instrument assessing self-care maintenance, management, and confidence, and is openly available worldwide for use within clinical practice and research. Validity and reliability have been verified [30]. On a scale of 0-100, higher scores indicate better self-care. A cut-off of 70 has been determined as reflecting adequate self-care, with changes of +/- 10 deemed as clinically relevant [30]. For the international analysis, the data on self-care and basic clinical characteristics of the two samples were added to a pool of samples of heart failure patients from across the world (n=5964, mean age 69 years, 38% female), and analysed together [19].

Statistical calculations were performed using SPSS statistical software. Analyses included descriptive statistics, Student's t-tests and chi-squared tests, Kendall's correlation coefficient analysis, Cox proportional hazard regressions, logistic regressions, multiple linear regressions, and Kaplan-Meier analysis, as appropriate. For all tests, a p-value of ≤0.05 was considered statistically significant.

Ethical and institutional approval was gained for both the CIBIS-ELD study as well as the observational follow-up survey in all study centres. Patients provided written informed consent prior to inclusion in the studies.

Results

Question 1: What is the relationship between self-rated health and occurrence of adverse events during up-titration of beta-blocker therapy in patients with heart failure?

From baseline to follow-up, self-rated health remained the same in 364 (58%) patients, but improved in more patients than it worsened: 211 (34%) vs. 53 (8%), p < 0.001. At baseline, women, beta-blocker-naïve patients, patients in NYHA class III/IV, and those with PHQ-9 scores ≥12 were more likely to report fair/poor self-rated health (p < 0.001 for all). Improvement of self-rated health did not differ by sex (men 33% vs. women 35%, p = 0.798), and was associated with higher rates of improved NYHA class (42% vs. 26%, p < 0.001), greater decrease of heart rate (-9 vs. -6 bpm, p = 0.003) and greater gain in 6-minute walk test distance (+27 m vs. +12 m, p = 0.004), regardless of the beta-blocker dose achieved at follow-up (p = 0.56) [31].

From baseline to follow-up, 496 (64%) patients experienced at least one adverse event. Of these, 295 (38%) experienced two or more events, or at least one serious event. The proportion of patients with adverse events and the average number of adverse events per patient increased in relation to worsening of baseline self-rated health and were highest for poor self-rated health. Fair/poor self-rated health at baseline was related to higher rates of adverse events during beta-blocker titration (70% vs. 56%, p < 0.001), particularly temporary worsening of heart failure (28% vs. 14%, p < 0.001), dizziness, drowsiness or fatigue (14% vs. 9%, p = 0.02), pulmonary side effects (7% vs. 3%, p = 0.02), and hospitalisation (5% vs. 1%, p = 0.008). The proportion of patients reaching the target dose differed significantly in relation to baseline self-rated health: 43% for excellent/ very good, 54% for good, 53% for fair, and 44% for poor (p = 0.007) [31].

In multivariate logistic regression analysis without self-rated health, factors that predicted adverse events between baseline and follow-up were age, female sex, distance on 6-minute walk test, and LVEF > 45%. When adding baseline self-rated health to the multivariate model, patient sex lost its predictive power, but self-rated health was an independent predictor of adverse events [31].

Question 2: How and to what extent are changes in quality of life influenced by clinical and psychological factors during up-titration of beta-blockers in patients with heart failure?

All dimensions as well as the component scores of quality of life improved from baseline to follow-up (p < 0.001). In hierarchical linear regression analyses, younger age, better baseline performance on the 6-minute walking test and absence of chronic obstructive pulmonary disease (COPD) minimally predicted better improvement in physical quality of life (change in model R^2 = 0.053). Poor baseline quality of life and less depression predicted more improvement over time, and these effects were much stronger (change in model R^2 = 0.248). Of note, improvement in depression (baseline 6.6 ± 5.0; change -1.0 ± 5.3) was a significantly stronger predictor of physical quality of life (beta = -0.29; 95% CI -0.37 to -0.21) than change in either 6-minute walk test distance (beta = 0.14; 95% CI 0.06 to 0.20) or NYHA class (beta = -0.12; 95% CI -0.20 to -0.04) [23].

Change in psychosocial quality of life was minimally predicted by baseline NYHA class and LVEF (change in model R^2 = 0.022; p = n.s.). Again, poor baseline psychosocial quality of life and lower depression scores predicted better improvement in psychosocial quality of life (change in model R^2 = 0.300). Larger changes in psychosocial quality of life were independently related to improvements in NYHA class and depression (change in model R^2 = 0.226). Depression was once more a significantly stronger predictor (beta = − 0.53; 95% CI − 0.59 to − 0.46) than change in NYHA class (beta = − 0.14; 95% CI − 0.21 to − 0.08). Changes in other cardiac parameters did not contribute to the model [23].

Question 3: How well do patients with heart failure perform specific self-care behaviours across the world and what are the differences and/or similarities between countries?
The pooled data from 21 international samples were analysed with a focus on five specific self-care behaviours: medication adherence, exercise, weight monitoring, flu vaccination, and salt restriction. Results indicated that overall, self-care behaviours could be improved. There was considerable variability between countries [19].

Most patients reported high medication adherence. The median value of patients not taking their medications as prescribed was 7%. Israel reported the highest number of patients who stated not taking their medication on a regular basis. Patients in most countries reported low exercise levels. In 16 of the 21 samples, more than 50% of the patients reported low exercise levels (median 54%). Low rates ranged from 36% in one of the samples from Germany to 90% in one of the Italian samples, and 89% in the sample from Brazil. In 16 samples, less than half of the patients weighed themselves regularly, with large differences between the countries. The lowest

number of people not weighing themselves regularly was reported in one of the Australian samples (24%) and the highest percentages of not weighing were found in the samples in Hong Kong (95%) and Brazil (89%) [19].

There were considerable variations in the samples with regard to patients opting to receive an annual flu vaccination. Overall, 16–75% of patients reported not getting annual flu vaccinations (median 38%). Hong Kong, Israel, Brazil, Taiwan and Japan reported the highest percentages of patients not receiving a flu vaccination. Adhering to a sodium-restricted diet varied more across countries than any other self-care behaviour: between 18% and 91% (median 40%) of patients reported not adhering to a low salt diet. Countries with the highest percentage of patients reporting to follow a sodium-restricted diet were the Netherlands (18%), Vietnam (22%) and Australia (23%). Countries with the highest percentage of patients not restricting their sodium intake were Taiwan (91%) and Hong Kong (63%) [19].

Question 4: What is the predictive value of two consecutive self-rated health assessments with regard to mortality in patients with heart failure?

During the 2-4 years observation period, 144 patients died (20%). Lower self-rated health was associated with living alone, female sex, higher NYHA class, lower FEV1, presence of oedema, lower haemoglobin levels, and a history of diagnosed depression as well as higher self-reported depressive symptoms. Patients with fair/poor self-rated health were also more likely to be suffering from atrial fibrillation and chronic obstructive pulmonary disease, had higher NTproBNP levels, and had more hospitalisations in the past year. High educational level, better performance on the 6-minute walk test, and better overall self-reported physical as well as psychosocial and social function were associated with better self-rated health. Of note, there was no difference in self-rated health depending on whether patients were suffering from heart failure with reduced ejection fraction (HFrEF) versus HFpEF [20].

Worse self-rated health was associated with worse prognosis, independent of whether self-rated health assessment was made before or after beta-blocker titration. The worst of the two observations had the strongest ability to predict mortality (HR=1.42 per level worse, 95%CI 1.16-1.75, $p < 0.001$). Changes in self-rated health from baseline to follow-up were not predictive of mortality and the impact of self-rated health was the same in patients receiving bisoprolol vs carvedilol [20].

Using Kaplan Meier analysis, poor self-rated health predicted shorter survival than excellent/very good self-rated health ($p < 0.001$). In multivariate analysis using Cox regression, poor self-rated health remained independently significant after adjusting for NTproBNP and other known risk predictors such as NYHA class and heart rate (HR = 1.23, $p = 0.045$). One level worse self-rated health was as predictive for mortality as each of the following: age by 3.2 years older, heart rate higher by 16 bpm, haemoglobin lower by 1.4 g/dL, or a 1.9-fold increase in NTproBNP [20].

Discussion

This work makes a significant contribution to our understanding of PROs in patients with chronic heart failure. Specifically, patients' self-rated health independently predicted adverse events and hence titration failure during up-titration of beta-blockers. Further, when assessed consecutively, self-rated health predicted long-term outcome in elderly patients with chronic heart failure. It appears that repeated measurements of self-rated health might provide more accurate information about prognosis than a one-off assessment. Changes in health-related quality of life over the course of medication up-titration were determined more strongly by changes in depression than changes in cardiac severity markers. From a global perspective, heart failure self-care skills vary significantly in different countries and need to be improved worldwide.

This study is the first to report on self-rated health before and after beta-blocker titration. Interestingly, beta-blocker pre-treatment increased the likelihood of better baseline self-rated health, which confirms previous suggestions that even initiation of low beta-blocker doses are clinically relevant [32]. A number of randomised trials from the past two decades have failed to demonstrate a difference in outcome between intervention and placebo arms [33]. It appears that including the patient's perspective by way of assessing PROs might provide us with information relevant to outcome beyond 'objectively assessed' parameters such as ejection fraction, NYHA class or heart rate. The effect and experience of heart failure is unique for each patient, and this unique experience is possibly captured more accurately by PROs than clinician assessments alone. Of note, the NYHA class as an assessment of symptom severity, for example, has poor interrater reliability, and there are significant differences between patient and physician assessment [34].

Results of this work add important information on the trajectory of self-rated health and are the first to examine the relationship of two consecutive self-rated health assessments with regard to long-term mortality in patients with heart failure. Importantly, the findings provide insight to one of the central questions in self-rated health research: is it poor self-rated health that predicts mortality, or good self-rated health that predicts survival? [35]. In the present analyses, poor self-rated health at any one time independently predicted poor outcome, whereas good self-rated health indicated good prognosis reliably only when stated at repeated measurements. The

patient's perception of poor self-rated health at any one time might dominate the rest of the information [20].

Even though the value of PROs has been documented for decades and the integration of PROs into clinical practice and research is recommended by the World Health Organisation [36], their utilisation is still limited [6]. The underuse in clinical practice is partly due to limited information available with regard to their practical application and integration into clinical-decision making in everyday patient care. Up-titration of beta-blockers is part of routine clinical practice in patients with heart failure, as is evaluation of prognostic risk. By integrating the assessment of self-rated health as an essential PRO to a clinical trial of beta-blocker up-titration and documenting its value as predictor of titration success as well as long-term outcome, the results of this work provide clinicians with information for use in everyday practice.

When assessing determinants of quality of life, the findings of this work indicate that the effect of depression is significantly stronger than effects of objective biomedical factors. This was true not only for psychosocial quality of life but also for physical quality of life. Previous studies have documented a complex interaction between cardiac disease and psychosocial morbidity: anxiety and depression are related to elevated TNF-alpha levels in heart failure [37]. The direction of a causal relationship remains unclear. In everyday practice, it should be kept in mind that depression has a significant impact on future quality of life, which may be larger than the effect of established biomedical severity indicators [23]. Preliminary results of the OPERA-HF study demonstrate that depression is associated with a 5-fold increased mortality risk in patients with heart failure [38]. The finding that quality of life increased during beta-blocker titration in this study, and that changes in quality of life are correlated more with baseline and changes in depression than with cardiac severity measures, highlights the importance of assessment of depression in heart failure. This information can further guide clinicians to address self-reported depressive symptoms as well as addressing the physiological effects of heart failure [23].

In a global approach to reducing the burden of heart failure and improving care, the findings of this work draw attention to a need for improving heart failure patients' self-care skills worldwide. Findings demonstrate that there is wide variability in heart failure self-care across the world, and that regardless of country, patients report suboptimal adherence to self-care behaviours. The provision of the current state of reported self-care behaviours in different

countries can help us to tailor specific support strategies to individual countries' and cultures' requirements.

Self-care behaviours are not only highly individual, but occur within contexts of different health care systems, different cultural norms and traditions that influence people's behaviours in general, as well as their response to recommendations from health care professionals [39]. It is also important to consider that recommendations change over time, as information emerges from new research relating to the potential benefit of specific behaviours. For example, one of the questions in heart failure self-care questionnaires is concerned with whether patients are adhering to a fluid restriction [40,41]. In the latest European guidelines on the management and treatment of heart failure, fluid restriction is no longer recommended for asymptomatic stable chronic heart failure [1]. It is therefore imperative to be mindful of this when assessing self-care using established questionnaires, and to continually update questionnaires in line with international guidelines.

PROs are valuable in the assessment and understanding of the patient perspective and can help us create shared-decision making opportunities in heart failure, a chronic illness with many therapeutic options and challenges [42]. The results of this work support the recent call for creating a holistic approach to treatment [6]. We encourage patient empowerment and participation by assessing the patient's perspective, and including this is in clinical decision-making to improve care.

Clinicians are recommended to include the assessment of self-rated health, quality of life, depression and patient-reported self-care behaviour in their interactions with patients with heart failure. Specific recommendations and considerations are outlined below.

- Nursing and medical clinicians are encouraged to routinely capture self-rated health, quality of life, depression, and self-care behaviour in patients with heart failure in a standardised form.
- Patients rating their health as only fair or poor may be at greater risk for adverse events during medication titration, and at higher risk of mortality, independent of 'objective' clinical measurements. Given this higher risk for adverse outcome, clinicians may wish to consider closer follow-up in this case.
- Patients reporting relevant depressive symptoms may not experience the same degree of improvement in quality of life over the course of pharmaceutical treatment as patients without

depressive symptoms. Therefore, clinicians should address the exploration and potential treatment of depressive symptoms as well as attending to the physiological effects of heart failure.

- Clinicians are encouraged to help patients dealing with the effects of their chronic illness by supporting them to learn about and utilise specific heart failure self-care skills.

Further research is needed to better understand determinants of self-rated health and to explore how self-rated health can be improved, for example, by designing studies that test the effect of different interventions on self-rated health in a randomised fashion. Additional research into the complex interplay between quality of life and depression is also needed, and this is most likely to be fruitful using qualitative study approaches. A recent study on the successful treatment of depression in patients with heart failure using a cognitive behaviour therapy approach could serve as a positive guide for clinical practice as to how to address depression when identified [43]. Finally, although we demonstrated that self-care skills could be improved worldwide, there is still limited information on which specific, practical interventions are most effective in improving them. A mixed-method approach might be most useful in exploring this.

Limitations

There are some limitations that need to be taken into consideration when interpreting results. In the first study, we did not control for some known determinants of self-rated health, such as socioeconomic circumstances, type of personality, and acute transient conditions (e.g. cold) that could affect self-rated health [31].

When investigating quality of life, it is important to remember that heart failure is an incurable chronic disease. In the current study on quality of life, a limited and defined period, i.e. the beta-blocker up-titration phase, was investigated. Findings of the up-titration period might not be applicable to the whole course of heart failure [23].

In the observational long-term follow-up addressing mortality, we captured all-cause mortality only, and are therefore unable to report details regarding cause-specific mortality or hospitalisations [20].

The pooled analysis of self-care behaviours across the world was a secondary analysis of studies that applied different inclusion and exclusion criteria and had different study designs. Further,

we did not have information on patients' previous knowledge of heart failure self-care; therefore the samples are heterogeneous with regard to the amount of time patients have had to practise behaviours prior to data collection [19].

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Declaration of any eventual publications

Simone Inkrot had the following share in the following publications:

Publication 1:
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 β-blocker treatment: the CIBIS-ELD randomised trial analysis. Int J Cardiol. 2013 Feb 10;163(1):87-92.
Contribution in detail: Study design and coordination, data collection, planning of data analysis, interpretation of data, co-writing of 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.
Contribution in detail: Study coordination, data collection, interpretation of data, co-writing of manuscript

Publication 3:
Jaarsma T, Strömberg A, Ben Gal T, Cameron J, Driscoll A, Duengen HD, **Inkrot S**, Huang TY, Huyen NN, Kato N, Köberich S, Lupón J, Moser DK, Pulignano G, Rabelo ER, Suwanno J, Thompson DR, Vellone E, Alvaro R, Yu D, Riegel B. Comparison of self-care behaviors of heart failure patients in 15 countries worldwide. Patient Educ Couns. 2013 Jul;92(1):114-20.
Contribution in detail: For samples provided to the pool of samples: Study design & study coordination, data collection, data clean-up, interpretation of data, critical revision of manuscript

Publication 4:
Inkrot S, Lainscak M, Edelmann F, Loncar G, Stankovic I, Celic V, Apostolovic A, Tahirovic E, Trippel T, Herrmann-Lingen C, Gelbrich G, Düngen HD. Poor self-rated health predicts long term mortality in patients with stable chronic heart failure. Eur J Cardiovasc Nurs 2015 Nov 3. pii: 1474515115615254. [Epub ahead of print]
Contribution in detail: Study design, study coordination, data collection, data analysis, interpretation of data, writing the manuscript

Signature, date and stamp of the   Signature of the doctoral
supervising University teacher   candidate

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Publication 1

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 β-blocker treatment: the CIBIS-ELD randomised trial analysis. Int J Cardiol. 2013 Feb 10;163(1):87-92.

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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.

Impact factor 2014: 2.891

Publication 3

Jaarsma T, Strömberg A, Ben Gal T, Cameron J, Driscoll A, Duengen HD, **Inkrot S**, Huang TY, Huyen NN, Kato N, Köberich S, Lupón J, Moser DK, Pulignano G, Rabelo ER, Suwanno J, Thompson DR, Vellone E, Alvaro R, Yu D, Riegel B. Comparison of self-care behaviors of heart failure patients in 15 countries worldwide. Patient Educ Couns. 2013 Jul;92(1):114-20.

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Publication 4

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Curriculum Vitae

My Curriculum Vitae will not be published in the electronic version of my work for reasons of data protection.

Complete list of publications

Inkrot S, Lainscak M, Edelmann F, Loncar G, Stankovic I, Celic V, Apostolovic A, Tahirovic E, Trippel T, Herrmann-Lingen C, Gelbrich G, Düngen HD. Poor self-rated health predicts long term mortality in patients with stable chronic heart failure. Eur J Cardiovasc Nurs 2015 Nov 3. pii: 1474515115615254. [Epub ahead of print]

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Affidavit

I, Simone Inkrot, certify under penalty of perjury by my own signature that I have submitted the thesis on the topic "Patient-reported outcomes in heart failure". 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) 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 (see above) 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   Signature

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