General discussion and future perspectives

Patient-reported outcomes in patients with heart failure
Discussion and future perspectives

One of the key challenges in heart failure care is to improve patient outcomes. Heart failure research generally uses traditional outcomes such as hospitalization and mortality to evaluate the efficacy and safety of new interventions. The question is, however, whether these traditional outcomes hold priority over other outcomes that patients might find equally or even important.

Another major challenge in heart failure care is to find ways to help patients live an optimal life within the limits imposed by their disease. Therefore in-depth knowledge about treatment goals from the patient’s perspective is vital. Such knowledge can be used to identify the most appropriate patient-reported outcome for clinical trials, to optimize heart failure care on a population level, and to personalize care on a patient level. This thesis aimed to investigate the use of patient-reported outcomes in patients with heart failure and to the perception of these outcomes by the patients themselves.

Most important findings of this thesis

- Patients attach more weight to quality of life than to longevity. Disease severity and dyspnoea during exertion were associated with the preference of quality of life over longevity. (Chapter 1)
- Patients with heart failure consider ‘not getting worse’ as the treatment goal that matters. (Chapter 2)
- The most prevalent impairments caused by heart failure are not by definition the impairments that patients themselves perceive as severely harsh with the exception of the impairments tiredness and having difficulties working around the house/yard. (Chapter 3)
- There is an association between optimism and health-related quality of life in outpatients with heart failure. (Chapter 4)
- There is an association between health-related quality of life and (severe) anemia in hospitalized patients with heart failure. (Chapter 5)
- The measurement of patient satisfaction with non-invasive telemedicine in patients with heart failure is under-researched despite the fact that this measurement is
recommended by the FDA and is increasingly seen as an important component of the quality of health care. (Chapter 6)

- ICT-guided disease management in combination with telemonitoring, as implemented in the IN TOUCH study, neither affected the primary (composite) endpoint of mortality, heart failure readmission and health-related quality of life, nor the separate individual outcomes of this composite endpoint. However, the IN TOUCH study demonstrated that the use of telemonitoring is safe and can reduce heart failure related visits to the outpatient clinic. (Chapter 7)

**Quality of life versus longevity in heart failure patients: discussion and future perspectives**

Knowledge of the preferences of patients with heart failure is vital for delivering optimal healthcare. Over the past 15 years, however, only a limited number of studies on patient preferences regarding quality of life and longevity have been performed in patients with heart failure. These studies reported contradictory results on the willingness to trade time for quality of life and the utility score.\(^1\)\(^-\)\(^4\) Furthermore, the representativeness of the included patients in the studies was not always optimal. For instance, 2 studies were not performed during routine care and were part of randomized controlled multicenter trials. Patients participating in these trials are not always representative of patients treated in daily clinical practice,\(^5\) as they often include younger patients with fewer comorbidities. Only 2 non-European studies on utilities in patients included patients from daily clinical practice; however, the patients participating in these studies had a mean age that was substantially lower than the age of the average patient in daily practice.\(^1\)\(^,\)\(^3\)

The study described in Chapter 1 showed that 61% of the included patients attached more weight to quality of life than to longevity. This finding supports the assumption that patients are willing to trade time for an improvement in health status\(^1\)\(^-\)\(^3\),\(^6\) and contradicts the recent European findings from a randomized controlled trial that reported that most of the patients are not willing to trade time for an improvement in health status.\(^4\) One recent study assessed the resuscitation preferences of patients with heart failure in a clinic in the US and how these preferences change over time.\(^7\) Seventy-three percent of patients had as the resuscitation preference ‘all efforts’; 15% preferred ‘do not resuscitate’ and 11% had no documentation of preferences at the start of the study. The strongest predictors of the preference ‘do not resuscitate’ were found to be older age, COPD, history of malignancy, and
General discussion and future perspectives

Reduced mobility. When these results are compared with the patient preference study – use of a different method notwithstanding, having COPD or a history of malignancy was not related to more willingness to trade time. In the patient preference study, patients were more willing to trade time and attached more weight to quality of life when they experienced dyspnea during exertion, had a higher level of NT-pro-BNP, or had a lower score on the EQ VAS. Like Dunlay et al. we also found that a heart failure specific indicator such as NYHA classification was not related to preference for quality of life or longevity. Dunlay et al. suggested that end-of-life decisions are not disease-specific but rather driven by frailty and decline in clinical status. This is in accordance with the findings regarding the preference of quality of life over longevity.

Perception of treatment goals by patients with heart failure: discussion and future perspectives

Gaining insights into the perspectives of patients regarding their most important treatment goal is necessary to be able to provide personalized patient-centered care. To our knowledge, this is the first study to use a focus group discussion to learn more about how patients with heart failure perceive their treatment goals. The patients in the focus group considered ‘not getting worse’ as the treatment goal that matters. The reflections of the patients demonstrated that their perception of important treatment goals is not in accordance with the standard endpoints for the evaluation of a treatment in clinical trials.

The clinical composite score, proposed by Packer, includes the term ‘not getting worse’, which was also referred to by patients in the focus group. Using the clinical composite score, each patient can be classified as ‘improved’, ‘unchanged’ or ‘worse.’ The aforementioned treatment goal of the patients in the focus group was met when the majority of patients scored ‘improved’ and ‘unchanged.’ A ‘worse’ score meant the treatment goal of the patients was not met. The clinical composite score combines two types of end points: mortality and re-hospitalization. In this focus group, however, none of the patients mentioned improving survival as a treatment goal. They did mention the importance of preventing a readmission, and this was seen in relation to the goal of ‘not getting worse’ and the fact that the patients experienced an acute readmission - via ambulance or sometimes helicopter- as very distressing. Patients were unable to assign a weight to the different
categories. More research is needed to develop endpoints, that are both consistent with the perception of patients and measurable.

**Perception of impairments by patients with heart failure: discussion and future perspectives**

Detailed insight into how patients perceive impairments related to their disease is important for delivering optimal patient-centered care. Recent studies have demonstrated beneficial effects of patient-centered care. These includes improved clinical status, improved quality of life and self-care, less symptom burden, more effective discharge processes and shorter hospital stays. These beneficial effects confirm that it is important to assess functional impairments in clinical trials and to research how patients perceive those impairments.

To date, very little research has explored the perception of impairments by patients with heart failure. A recent study assessed the physical and cognitive impairments in patients with heart failure. How the patients perceived those impairments was not investigated. Another study reported that having functional impairments was associated with an increased risk of 30-day all-cause readmission in community-dwelling seniors admitted for heart failure, myocardial infarction or pneumonia.

Until now no other studies investigated the perception of impairments in patients with heart failure. The term perceived harshness as defined by Rhodes et al. was adopted to render this end. This study showed that impairments that were perceived as severely harsh were not by definition the most prevalent impairments. Furthermore, some of the most prevalent impairments did not contribute to the sum-score of the original MLHFQ and thus had no effect on health-related quality of life. This indicates that it is important for healthcare providers to offer patient-centered care and to identify those impairments that are less prevalent, for those were often perceived by the patients as causing severe discomfort. Therefore, those impairments should be discussed with the patients together with the more classical health-related quality of life items. Furthermore, the impairment ‘stay in a hospital’ was not very prevalent in this study population and was by definition not perceived as severely harsh. Although the impairment ‘stay in a hospital’ was almost equally distributed over the categories ‘no perceived harshness,’ ‘moderate degree of perceived harshness,’ and ‘severe degree of perceived harshness,’ it did contribute relevantly to the sum-score of the original MLHFQ. This is in accordance with the results of the focus group session.
Association between optimism and health-related quality of life in outpatients: discussion and future perspectives

Patients with heart failure have a seriously reduced health-related quality of life compared with both a normative population in the community, and with patients suffering from other chronic diseases. Despite improvements in medical treatment, resulting in prolonged survival and a reduction in hospitalizations, patients with heart failure still have an impaired health-related quality of life. Previous research has focused mainly on medical and physical factors related to health-related quality of life. However, emotional factors such as depressive symptoms are also highly prevalent in patients with heart failure and are related to health-related quality of life. Patients with heart failure with a comorbid depressive disorder, for example, have a lower health-related quality of life than patients without a comorbid depressive disorder. There is a paucity of literature specifically pertaining to optimism and heart failure. This study is the first to examine the relation between dispositional optimism and health-related quality of life in outpatients with heart failure. An association between optimism and health-related quality of life was found. The variable optimism can be used as a possible mechanism for improving health-related quality of life. The literature suggests that optimism is a modifiable condition; therefore improving optimism may be a promising way to improve the health-related quality of life in patients with heart failure. Although optimism seems to have an insignificant impact on global quality of life at the end of life, recent findings suggested that optimism may help to maintain a positive psychological perspective when facing an age-related decline. In addition it helps to maintain a higher quality of life then pessimists in a setting that the time to live is short. Furthermore, it is suggested that psychological interventions may be useful for improving the quality of life in heart transplant recipients and that personal resources, including optimism, can be improved and strengthened through cognitive behavioral therapy.

Although the cross-sectional design of this study precludes conclusions about causality, the findings suggest that improving optimism may lead to improved health-related quality of life in patients with heart failure. More research is needed to assess new interventions that can help to improve the health-related quality of life by improving optimism. Furthermore, the type of patient that will benefit most from improving optimism also needs to be identified.
Association between (severe) anemia and health-related quality of life in hospitalized patients:
discussion and future perspectives

Patients with heart failure are known to have a poor health status which affects their health-related quality of life dramatically.\textsuperscript{13,14} This means the search for new interventions needs to take other variables that may influence the health-related quality of life in patients with heart failure into account. This is the first study to investigate the association between anemia and health-related quality of life in hospitalized patients with heart failure. Health-related quality of life was found to be independently associated with anemia in hospitalized patients in terms of global well-being, general health, physical functioning, and limitations due to physical functioning. Health-related quality of life was found to be particularly compromised in patients with severe to moderate anemia. The association between health-related quality of life and (severe) anemia could serve as a possible mechanism for improving health-related quality of life in anemic patients with heart failure.\textsuperscript{27} Patients with anemia are caught in a downward spiral characterized by a reduced exercise tolerance, which in turn leads to relative immobility, muscle wasting, increased risk of falling and a diminished cardiovascular fitness. As a result, exercise tolerance is even further reduced. Subsequently, patients become frail, are prone to dependency and depression,\textsuperscript{27} and experience lower health-related quality of life. The ESC heart failure guidelines recommend treatment of anemia because it is linked to more symptoms, worse functional status, greater risk of readmission for worsening heart failure, and reduced survival.\textsuperscript{28} It is, however, still unclear which treatment method for anemia has the most effect on health-related quality of life.\textsuperscript{29}

The cross-sectional design of this study precludes conclusions about causality. However, the findings suggest treatment of anemia should be considered because effective treatment may improve health-related quality of life in these patients. More research is needed to assess whether new interventions can improve health-related quality of life by correcting the degree of anemia. Furthermore, the type of patient that will benefit most from correcting the degree of anemia also needs to be researched.

Measurement of patient satisfaction in telemonitoring studies in heart failure patients:
discussion and future perspectives

This study found that measurement of patient satisfaction with non-invasive telemedicine in patients with heart failure is under-researched and that validated instruments to measure
patient satisfaction are hardly available. Although, previous studies have measured patient satisfaction with non-invasive telemonitoring in patients with heart failure, only one study used patient satisfaction as the primary outcome.

Furthermore, only one recent study used a well-designed but adapted validated questionnaire to measure patient satisfaction. This means the recommendation of the FDA to use validated questionnaires to measure patient satisfaction is still not observed. This is an underwhelming result given that patient satisfaction is considered to be an important indicator of quality of healthcare. Furthermore, satisfied patients will have fewer complaints, fewer second opinions and fewer repeated investigations, leading to lower healthcare costs. In addition, it is suggested that patient satisfaction, which is related to patients’ adherence to medical treatment regimens, is very important for a successful treatment. The measurement and understanding of patient satisfaction is therefore a prerequisite for the successful treatment of heart failure, and future studies should address this.

**IN TOUCH study: discussion and future perspectives**

ICT-guided disease management in combination with telemonitoring, as used in the IN TOUCH study, did not affect the (composite) primary endpoint of mortality, heart failure readmission, and health-related quality of life or its separate individual components. An explanation for this could be that the study population was relatively healthy compared with other studies. A recent large study also showed no significant effects of the use of telemonitoring on all-cause readmission after hospitalization for heart failure. Another explanation could be that the effect of the intervention was too small to be able to discriminate. The scoring system of the primary composite endpoint was adapted from the A-HeFT study. This endpoint has been used in several other studies and is also recommended in a recent statement by the Heart Failure Association. However, the development of this composite endpoint was not based on the opinion of patients, but on the opinion of clinicians and scientists. It is a known fact that the opinion of clinicians and scientists sometimes differs from the opinion of patients. Further research is necessary for the development of an endpoint that reflects the treatment preferences of patients. This type of endpoint will make it easier to provide patient-centered care. As mentioned before, the use of a composite endpoint is recommended in a recent statement by the European Society of Cardiology Heart Failure Association.
General discussion and future perspectives

A composite endpoint makes it possible to include the opinion of the patients, the impact of on patients’ lives, and the effect on costs (mortality and hospitalization, respectively).

Furthermore, the telemonitoring intervention used in the IN TOUCH study proved to be safe to use and can reduce heart failure-related visits to the outpatient clinic, which will keep heart failure care accessible. Patient satisfaction was not measured in the IN TOUCH study, but the adherence of the patients using telemonitoring was very high. This indicates that the telemonitoring intervention in combination with daily measurements was well accepted by patients.

Limitations

The studies described in this thesis have certain limitations regarding study sample, generalizability, and validity and reliability of the questionnaires that were used.

Study sample and generalizability

The studies described in Chapters 1, 2, 3, and 4 were performed using the same study population. Patients were recruited from a heart failure clinic at a university medical center in the Netherlands, and the sample size was relatively small. Nevertheless, the results are generalizable because the demographic and clinical parameters of the patients in the study sample are comparable with those of the general heart failure outpatient population. The study in Chapter 2 was performed in a small and selected study sample. Only one focus group session was held. A second focus group session might have yielded other results or might have confirmed the findings. More non-interventional research is needed on routine care in a broader patient population to strengthen the results of future studies.

The studies described in Chapters 5 and 7 were performed in other heart failure clinics in the Netherlands. Data from clinical trials are known to present difficulties in terms of generalizability. However, it is reasonable to assume that both study samples are a reasonable representation of the heart failure patient population at large because of the mean age of 71 years and the distribution of male patients in the study population. The study sample in Chapter 7 was smaller than anticipated initially. It was not possible to include the intended number of patients, despite an extended inclusion period and an adjustment of the study protocol. This could have influenced the outcome in terms of lack of power. However, no
numerical differences were found between both groups, indicating that a larger population would probably not have made a difference in outcomes.

**Methods**

The studies described in Chapters 1, 3, 4, 5, and 7 were quantitative and had a cross-sectional study design. A cross-sectional design precludes conclusions about causality; therefore, more prospective research is needed to confirm the findings. A qualitative design was used in Chapter 2. The study described in Chapter 6 was a systematic literature review.

**Validity and reliability of the instruments**

*Health-related quality of life*

- The RAND 36-item Health Survey 1.0 was previously used in a Dutch population and was found to have good psychometric properties.\(^{45,46}\)
- Cantril’s Ladder of Life assesses a patient’s global well-being and has been used in heart failure research before.\(^{47,48}\)
- The Minnesota Living with Heart Failure Questionnaire (MLHFQ) is a widely used disease-specific questionnaire in heart failure research\(^{49,50}\) that has good psychometric properties.\(^{49}\)
- The EQ-5D is designed for use across a wide range of health interventions \(^{51}\) and is frequently used in cardiovascular trials. The scoring was based on the British tariff \(^{52}\)

*Patient preferences regarding quality of life or longevity*

- The Time Trade-off (TTO) approach developed by Torrance (1987) was used.\(^{53}\) The TTO approach is acknowledged as a gold standard for utility measurement\(^{54}\) and is specifically designed for use in health-care.\(^{53}\) A TTO assessment is limited by the hypothetical nature of its questions, which may be difficult for very old patients, for patients with multiple comorbidities, and for patients with long disease duration.\(^{55}\) However, in the study described in Chapter 1, these limitations were taken into account. The trained researchers described a situation in the past in which the patient did not suffer from constraints due to heart failure. Moreover, the protocol of York contains a test question to assess whether the patient is cognitively able to
understand the TTO approach. Three patients did not pass this test and were excluded from further analyses. A 5-years estimate of life-expectancy for the TTO was used because patients with heart failure have a mean prognosis of 5 year survival after their first readmission on a group level, and the aim was to generalize the utilities to the whole study population. However, this estimate of life-expectancy could be refined further using the NYHA score or a multivariable risk model and would be a suggestion for further research. In addition, a sensitivity analysis to reveal the validity of a hypothetical 5-year time horizon would be very interesting for future research as well.

**Life expectancy as estimated by the patient**

- Self-developed questionnaire; validity and reliability were not assessed.

**Social support**

- Questionnaire consisted of investigator-formulated questions; validity and reliability was not assessed were not assessed.

**Harshness of impairments**

- An alternative method based on the MLHFQ; validity and reliability were not assessed.
General discussion

This thesis provides more insights into preferences and opinions of patients with heart failure regarding their treatment and health status. The most important findings of this thesis is that patients with heart failure prefer health-related quality of life over longevity and expressed “not getting worse” as the treatment goal that matters.

Associations between optimism and health-related quality of life in outpatients with heart failure, and between health-related quality of life and (severe) anemia in hospitalized patients with heart failure were found. These relations may serve as possible mechanisms for improving health-related quality of life in these patients. However more research is needed regarding this.

The use of composite endpoints, such as those used in the IN TOUCH study, is recommended by the European Society of Cardiology Heart Failure Association. The clinical composite score proposed by Packer includes the term “not getting worse” which was also referred to by patients in the focus group. Next to “not getting worse”, other important treatment goals of patients included decreasing their symptoms, improving physical status, avoiding readmission, and being able to live a normal life. These goals are included in the concept of health-related quality of life and can be measured with various generic and disease-specific health-related quality of life instruments. It is recommended that the ideal composite end-score includes the results of a general health-related quality of life questionnaire and a disease-specific health-related quality of life questionnaire, as well as data on hospital readmissions. It is important to include all–cause readmissions, for patients see these as related to “not getting worse”. It would also be very interesting to know the opinions of the patients regarding the weights of the attributes in the composite end-score. Future studies should examine the possibility of developing a measurement system for attributes based on the opinions of patients. In addition, more research is necessary to develop endpoints that are consistent with the perception of patients and measurable. Such research will result in composite endpoints that are clinically more relevant.
General conclusion and future directions

Insights into the preferences of patients regarding treatment outcomes and care decisions and insights into the perception of impairments will guide the future development of patient-centered care. Moreover, these insights are important with respect to providing personalized care on a patient level and optimizing care on a population level.

The association between health-related quality of life and (severe) anemia in patients with heart failure and dispositional optimism may serve as possible mechanisms for improving health-related quality of life in patients with heart failure. This also emphasize the need to use patient-reported outcomes in the search for new interventions that can help patients live with their disease. These insights are important in finding the most appropriate patient-reported outcome in clinical trials.

A start has been made to get more insights into the preferences of patients with heart failure. More research is necessary to be able to use these insights in the development of more specific patient-reported outcomes in clinical trials, and to further optimize care on a population level and personalize care on a patient level. Future research should include the opinions of patients to make the composite endpoint clinically more relevant.
References


