Should patients perception of health status be integrated in the prognostic assessment of heart failure patients? A prospective study.

TITLE

Should patients perception of health status be integrated in the prognostic assessment of heart failure patients? A prospective study.

Author. Network of Nurses of GISSI-HF

Corresponding author

Paola Di Giulio

Mario Negri Institute and Turin University

Via La Masa 19, 20156 Milano

+39 02 39014457; +39 02 33200049

digiulio@marionegri.it

ABSTRACT (words 250)

Purpose. Health status measures are widely recognized as providing substantial information on heart failure (HF) patients conditions and prognosis, but they are not included in the data routinely collected.

The aim of the study was to assess in a prospective cohort of HF patients, the independent prognostic value of health status measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ) on mortality and hospital admissions over a period of 3.3 years.

Method. Eighty-three Italian cardiology centres included all their patients randomised in the GISSI-HF trial in an observational outcome study where the KCCQ was administered at baseline by nursing personnel. A total of 1465 outpatients with chronic HF, NYHA class II-III, with coronary and non -coronary etiology were included and followed-up for mortality and admissions.

Results. The effect of baseline perception of health status on mortality and all causes hospitalizations was explored with Cox proportional hazard regression models progressively adjusted for several variables. When stratified according to pre-defined criteria, lower values of KCCQ scores (<25) as compared with best scores (>75) were predictive of mortality (1.85; IC95% 1.16-2.95) but not of hospital admissions risk (p for trend significant for mortality with decreasing scores). Lower KCCQ scores discriminated the risk also within the NYHA II and III classes.

Conclusions. KCCQ scores provide a clinically important and statistically robust independent prognostic information on hard outcome end-points of HF patients on the top of the clinical scores. It is suggested that KCCQ should become a routine component of the patients care and of prognostic profiles.

Key words. Health Status, Heart Failure, Prognosis, Mortality

Introduction

Health status is a very broad concept encompassing and describing several dimensions: patients' perception of their health, symptoms, functional limitations, and quality of life [1-2]. The inclusion of these "important to patient" measures in trials' designs, as well as in clinical decision-making processes, has been suggested[3-4] mainly for patients with chronic complex conditions such as heart failure (HF), *where a worst perceived Health Status has been associated with more events* [5-11]. Recommendations to incorporate these findings in evidence-based guidelines have however failed so far: *lack of easy to administer validated questionnaires, difficult transferability of mean scores of health status perceptions into concrete management implications for individual patients[12], and scarce motivation of doctors and nurses [13] have been suggested as the most relevant obstacles*.

In the broader framework of the GISSI-HF trial[14], health status perception of HF patients was measured in an independent study, run autonomously by the nursing personnel to explore:

a) whether the health status perception, measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ) [15] (previously tested in research settings as a predictor of clinical outcome*[5-11]*), can be applied in routine conditions of care, with a specific prognostic yield on the *hard* end-points of mortality and hospital admissions;

b) whether results obtained in a large population, *and over a follow-up comparable to that accepted for the validation of clinical, instrumental and biochemical scores, could provide* sufficient evidence to formally recommend the adoption of patient-based measures in the overall prognostic profiles.

Methods

The GISSI-HF design and population have been described in detail elsewhere. [14] A cohort of 6975 outpatients with chronic HF, NYHA class II-III, with ischemic and not-ischemic etiology, and already treated for heart failure with optimal recommended therapies were randomly assigned to n-3 PUFA and placebo and to rosuvastatin and placebo and closely followed up (at 3, 6, 12 months and then every 6 months until the end of the trial) for a mean of 3.9 years. Clinical, instrumental and biochemical measures allowing prognostic assessment on the outcomes of mortality and hospitalization were collected. The nursing personnel of 83 of the participating centers *agreed to activate an independent protocol (approved by the competent ethical Committees)* and administered the KCCQ to all patients randomized in their centres from February 2003 to February 2005. The resulting cohort comprised 1465 patients (22% of the GISSI-HF population) *whose clinical characteristics are closely comparable to those of the main cohort, was followed-up for 3.3 years.*

Health status assessment. We adopted the validated Italian version of the KCCQ[15], one of the most recent instruments for measuring health status[16,17]. It is a specific 23-item questionnaire that encompasses several domains including physical limitations, symptoms (frequency, severity and recent changes) self-efficacy, social interference and quality of life. The summary score ranges from 0 to 100, higher scores denoting better health status. In a recent systematic review that compared the main instruments to assess HRQoL in HF patient, the KCCQ showed good Chrombach's alpha coefficients for the main dimensions for internal consistency (Physical 0.90-0.91; Quality of life 0.78-0.84; Social limitations 0.86-0.90; Symptoms 0.86-0.88; Self efficacy 0.62-0.66) and reproducibility, with the exception of self efficacy (Physical 0.79; Quality of life 0.67; Social limitations 0.73; Symptoms 0.78; and Self efficacy 0.41) [13]. The KCCQ was compared to MLHF (Minnesota Living With Heart Failure Questionnaire) showing a better

sensitivity in identifying more compromised patients [15, 16] and a better association with long-term event-free survival[12, 15].

Patients gave their consent to participate in the study, following individual briefing on its aims, and were informed that the nurses were available for any further information and clarification, but with no interference in the self completion of the KCCQ. The nurses were given a brief training on how to administer the KCCQ at study entry, and then at 1, 2 and 3 years' follow-up.

Endpoints. Mortality and hospital first admission (any reason and cardiovascular) where collected for the trial and adjudicated blindly by an ad hoc committee [18].

Criteria for analyses. Overall baseline scores were divided into four categories with pre-set cut-off points found in previous studies[8, 10] to be associated with a progressive increase in the risk of mortality and hospital readmissions for patients with decreasing scores: 0 to <24 (worst); 25 to 49 (poor); 50 to 74 (fair); and 75 to 100 (good).

Statistical analysis. Patients' characteristics are presented as frequencies and percentages for categorical variables and as median and interquartile range for continuous variables. Trends across categories were analyzed using Cochran-Armitage trend tests for categorical variables and Spearman's Rank Correlation for continuous variables. Cox proportional hazard regression models to assess the effect of baseline perception of health status on mortality and all-causes hospital readmissions (Model 1, unadjusted), progressively included the following variables: KCCQ categories, age and sex (model 2); cardiovascular signs, symptoms and markers (NYHA class, myocardial infarction (MI), left ventricular ejection fraction (EF) quintiles, endsystolic volume (quintiles), hepatomegaly, pulmonary rales, heart rate (quintiles) (model 3); cardiovascular risk factors: smoking, diabetes (history or blood glucose >126 mg/dl or Hb1Ac >7.0%), total cholesterol (quintiles) (model 4); comorbidities [chronic obstructive pulmonary disease (COPD), estimated

glomerular filtration rate (GFR) (quintiles); hemoglobin (HB) (quintiles), liver dysfunction (ALT >80 or AST >70 IU/L)](model 5); education (model 6); drugs (model 7).

Each model was reduced with multiple regression analysis using the backward method; the covariates with p value > 0.15 were removed. A final model (Model 8) sequentially added the different sets of variables. For parsimony in model construction, we excluded from the final model some covariates (education, drugs and trial treatment) that were neither independently associated with outcomes nor materially altered the relation between the KCCQ score and outcomes. Tests for trend for relative risk were calculated using the median for each category as a continuous variable; a $P \leq 0.05$ and indicates the linear relationship between increasing age and worsening of health status.

A formal test of statistical interaction between KCCQ score and the NYHA class was performed [19]. A significance level of 0.05 was used and all p-values are two-sides. Cox-proportional hazards event-free survival curves adjusted for covariates were plotted using the corrected group prognosis method[20]. All analyses were done using the SAS statistical package (SAS Institute, Inc., Cary, North Carolina).

Results

The KCCQ could be validly administered to the greatest majority of patients (1465/1542, 97.7%). Only 14 refused consent. In the other cases the questionnaire was not delivered for organizational reasons. The baseline clinical characteristics of the 1465 patients are reported in Table 1.

Almost two thirds of the patients (64.3%) were older than 65 years and 11.1% were over 80. Patients were well treated at baseline: 70.9% were prescribed ACE inhibitors, 19% angiotensin receptor blockers, 69.2% beta blockers and 52.7% antiplatelet agents. Overall, patients with less than good health status were, as expected, older, more frequently in NYHA class III, less educated, with more comorbidities and had been admitted to hospital more often in the previous year. The proportion of women with poor/worst health status was higher than men (men 166/1144, 14.5%; women 94/321, 29.2%). No differences were seen for EF. More than half the population (56.1%) reported good KCCQ scores ($\geq$75). Worst scores (<25) were found only in a small proportion of the NYHA class II (12, 1.2%) and class III patients (33, 7.0%).

The Cox regression analyses presented in Table 2 report the independent association of KCCQ scores on mortality and hospital admissions. The risk of mortality remained significant across all levels of adjustment for possible confounders and in the fully adjusted model for patients with worst health status, with a clear increase with the worsening of health status (fair 1.22, 95%CI 0.96-1.55; poor HR 1.31, 95% CI 0.96-1.78; worst HR 1.85, 95%CI 1.16-2.95; p for trend 0.007). When the analyses were repeated for mortality and admissions using the KCCQ scores as a continuous variable, the scores were significant for each 10-point decline for mortality (Final model HR 1.07, 95%CI 1.02-1.12) and admissions (Final model HR1.07, 95% CI 1.03-1.10, p<0.001). As shown in Figure 1, patients with poor and worst KCCQ scores had higher mortality rates, and differences between subgroups were statistically significant at each one-year interval. The differences between subgroups were even larger by the end of the study (mean observation time 3.3 years). For all-

cause admissions the risk was significant in the fully adjusted model only for patients with poor health status perception (HR 1.64; 95%CI 1.33-2.03).

AS THE NYHA RECOGNISED AS THE STANDARD CLINICAL PRACTICE THE SPECIFICITY OF THE ROLE WAS ESXPORED WITHIN THE SAME TWO NYGHA CLASSES The specificity of the role of KCCQ scores was explored also within the same NYHA class recognized as the standard clinical score (Table 3). The lowest KCCQ scores (poor and worst are considered together because of the small numbers) coincided with a significant worse prognostic difference for overall mortality, both at one and three years of follow-up, for NYHA II patients, the *implications are clear: NYHA II class patients* with health status scores <50 (poor/worst) had a comparable 1 year mortality as patients in NYHA class III with good health status (10.2% vs 12.4%).

A similar pattern although not all the differences are statistically significant can be observed for all cause and cardiovascular *first hospital* admissions.

Discussion

The main take home message of this prospective MULTICENTRE outcome e study conducted by a network of nursing personnel is original and clear-cut.

IN A POPULATION OF HF PATIENTS OD ANY ERIOLOGY THE PERCEPTION OF The patients perception of their health status provides robust prognostic information on the medium term mortality, *of HF patients of any etiology*, on the top and independently of the full package of the other clinical and instrumental measures. *Other studies investigated the prognostic role* of KCCQ in HF patients OF ISCHAEMIC ETIOLOGY on the combined endpoint of mortality and *hospital* admissions, [6, 8-9, 11, 21] where the less reliable variable of hospital admissions could have a greater weigh, and on patients with HF of ischemic etiology[8, 21].

Because of the IMPORTANTl clinical implications for the routine prognostic DEFINITION ANA management of more severe HF patients, these findings deserve a careful and critical ATTENTION. The POPULATION OF THE STUDY WITH ALMOST IS LARGER THAN OTHER SIMILAR STUDIES findings of the study are produced on a population of almost 1500 patients, larger than other similar studies[8-9] and, differently from Kosiborod et al., [21] on patients with coronary and non-coronary etiology of HFTOGLIERE. The patients were followed up for more than three years (vs 1 year[8], or a mean of 14 months[21]). The outcome events were fully AND BLINDLY validated by an independent Committee, according to the protocol of the GISSI-HF trial[18]. The mean age of the study population is higher than that in other similar studies (mean age 67.9 vs 63.5[22], with 11.1% of patients over 80 years), AND SOMEHOW CLOESER the mean age most frequently seen in routine care of HF patients. INTERESTIUNGLY the prognostic strength of the KCCQ score was consistent irrespective of age (data not shown).

The stepwise analyses presented in Table 2 show the consistency of the predictive power of KCCQ scores over all models of adjustment for clinical (including main comorbidities) and demographic

variables. The analyses document how patients' own perception of their health status captures information different from clinical tests, but with quantitatively similar additive prognostic value. The results over the 3.3 years, as *illustrated by the adjusted survival curves, that show that the differences in mortality steadily increase along the observation time*, appear even more robust, because confirmed both in the score based and continuous analyses, and obtained in a population already managed according to the best recommended diagnostic and therapeutic criteria.

A further point of interest for its clinical implications can be seen in the discriminatory power of KCCQ within the same NYHA class (Table 3): a poor-worst KCCQ makes NYHA II class patients much closer prognostically to those in NYHA III with a good KCCQ score. Although the limitations of the NYHA classification, strongly influenced by the physician's perception[22], are known, it is however used in clinical practice as a comprehensive indicator of the clinical status and prognosis of individual patients.

The general clinical relevance of the findings can also be seen in the fact that a single baseline measure of KCCQ (apparently a limiting factor) is solidly informative on the medium long term clinical evolution of HF. *Although the patients' clinical conditions may vary over time, the study adopted the criteria of analysis and interpretation of results applied in clinical trials, where the end points are confronted with the baseline characteristics of the populations.*

The high acceptability of KCCQ by the patients, as in other studies[10, 21] with populations of comparable age, confirms that the KCCQ can be considered a component of care, not only of research. Further, our data suggest that the cut-off points, created mainly to optimize the statistical power for the prognostic differences between extremes of health status (good vs worst), could be usefully collapsed only to two categories (< or >50), to make it even easier to include and use KCCQ results in overall prognostic scores.

The information provided is consistent with the growing awareness on the role of the patients perception in the assessment of the effects of therapy and care[3-4]. However, this “evidence” is not easily amenable to explanations fitting the mainly biological and functional frameworks of the culture and organization of (not only) cardiological care. The variables which document the “importance to patient” outcomes are hardly retained as component of trial outcomes and even less in guidelines[23-25].

Although the evidence now available on the performance of the KCCQ is robust, to date, it is not immediately evident how a poor-worst KCCQ score could be used in routine care and translated into the adoption of additional well tailored interventions. Besides possibly increasing alertness or sympathy for the severity of the patients overall condition, it is difficult to identify a range of effective interventions, *that should be tailored also considering social and financial status*. The literature is supportive of the long-term effectiveness of care strategies on the top of clinical treatments[26-28], but is far less informative on whether and how scores such as the KCCQ (which include heterogeneous dimensions) could be used to target treatments.

Far from being reasons for not including KCCQ in the prognostic assessment of patients, the adoption of patient-based measures, should be an opportunity for promoting research to improve our capacity for better understanding the role and management of health status dimensions, whose measures are confirmed to provide valuable prognostic information even on the hardest end-point of mortality.

Aknowledgements

The QDF is a companion study of the GISSI-HF trial, promoted and coordinated by ANMCO (Associazione Nazionale Medici Cardiologi Ospedalieri), Mario Negri Institute and Mario Negri Sud Consortium, S. Maria Imbaro (CH).

Steering Committee: Luigi Tavazzi (Chairman), Gianni Tognoni (Co-Chairman), Maria Grazia Franzosi, Roberto Latini, Aldo P. Maggioni, Roberto Marchioli, Gian Luigi Nicolosi, Maurizio Porcu.

We are grateful to Judith Baggott for language assistance.

The corresponding author affirms that everyone who contributed significantly to the work was listed in the Acknowledgments

Funding

A fraction (130.000 € over 4 years) of the funds of GISSI-HF was allocated to this project to cover the costs for meetings and data analysis. The funding source had no role in the trial design, conduct, data collection, analyses, data interpretation, or writing of the report. The corresponding author had full access to all the data. Data were stored and analysed at the Consorzio Mario Negri Sud (S. Maria Imbaro CH).

All members of the steering and writing committees had full access to the database and had final responsibility for the decision to submit for publication.

Conflict of interests. All Authors declare they have no competing interests.

References

1. Rumsfeld, J.S. (2002). Health status and clinical practice: when will they meet? Circulation, 106(1), 5-7.
2. Spertus, J.A. (2008). Evolving applications for patient-centered health status measures. Circulation, 118(20), 2103-2110.
3. Garratt, A. (2009). Patient reported outcome measures in trials. British Medical Journal, 338 a2597.doi:1136/bmja2597.
4. Greenhalgh, J. (2009). The application of PROs in clinical practice. What are they, do they work and why? Quality of Life Research, 18(1),115-123.
5. Konstam, V., Salem, D., Pouleur, H., Kostis, J., Gorkin, L., Shumaker, S., et al. (1996). Baseline quality of life as a predictor of mortality and hospitalization in 5.025 patients with congestive heart failure. SOLVD Investigations. Studies of Left Ventricular Dysfunction Investigators. American Journal of Cardiology, 78(8), 890-895.
6. Soto, G.E., Jones, P., Weintraub, W.S., Krumholz, H.M., Spertus, J.A. (2004). Prognostic value of health status in patients with heart failure after acute myocardial infarction. Circulation, 110(5), 546-551.
7. Rodríguez-Artalejo, F., Guallar-Castillón, P., Pascual, C.R., Otero, C.M., Montes, A.O., Garcia, A.N., et al. (2005). Health-related quality of life as a predictor of hospital readmission and death among patients with heart failure. Archives of Internal Medicine, 165(11), 1274-1279.
8. Heidenreich, P.A., Spertus, J.A., Jones, P.G., Weintraub, W.S., Rumsfeld, J.S., Rathore, S.S., et al. (2006). Health status identifies heart failure patients at risk for hospitalization or death. Journal of American College of Cardiology, 47(4), 752-756.

9. Sullivan, M.D., Wayne, W.C., Russo, J.E., Crane, B., Spertus, J.A. (2007). Summary health status measures in advanced heart failure: relationship to clinical variables and outcome. Journal of Cardiac Failure, 13(7), 560-568.
10. Chan, P.S., Soto, G., Jones, P.G., Brahmajee, K., Nallamothu, K, Zhang, Z., et al. (2009). Patient health status and costs in heart failure. Insights from the Eplenorone post-acute myocardial infarction Heart Failure Efficacy and Survival Study (EPHESUS). Circulation, 119(3), 398-407.
11. Mommersteeg, P.M.C., Denollet, J., Spertus, J., Pedersen, S.S. (2009). Health status as a risk factor in cardiovascular disease: a systematic review of current evidences. American Heart Journal,157(2), 201-218.
12. Parissis, J.T., Nikolau, M., Farmakis, D., Paraskevaidis IA, Bistola V, Venetsanou K, et al. (2009). Self assessment of health status is associated with inflammatory activation and predicts long term outcomes in chronic heart failure. Heart Failure Reviews;11(4), 163-169.
13. Garin, O., Ferrer, M., Pont, A., Rué, M., Kotzeva, A., Wiklund, I., et al. (2009). Disease specific health-related quality of life questionnaires for heart failure: a systematic review and meta-analyses. Quality of Life Research,18(1), 71-85.
14. GISSI-HF Investigators, Tavazzi, L., Maggioni, A.P., Marchioli, R., Barlera, S., Franzosi, M.G.,et al. (2008). Effect of n-3 polynsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. The Lancet, 372(9645), 1223-1230.
15. Miani, D., Rozbowsky, P., Gregori, D., Pilotto, L., Albanese, M.C., Fresco, C., et al. (2003). The Kansas City Cardiomiopathy Questionnaire: Italian translation and validation. Italian Heart Journal, 4(9), 620-626.

16. Green, C.P., Porter, C.B., Bresnahan, D.R., Spertus JA. (2000). Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. Journal of the American College of Cardiology, 35(5), 1245-1255.
17. Spertus, J., Peterson, E., Conard, M.W., Heidenreich, P.A., Krumholz, H.M., Jones, P., et al. (2005). Monitoring clinical changes in patients with heart failure: a comparison of methods. American Heart Journal, 150(4), 707-715.
18. Tavazzi,L., Tognoni, G., Franzosi, M.G., Latini, R., Maggioni, A.P.M., Marchioli, R., et al. on behalf of the GISSI-HF investigators. (2004). Rationale and design of the GISSI heart failure trial: a large trial to assess the effects of n-3 polyunsaturated fatty acids and rosuvastatin in symptomatic congestive heart failure. The European Journal of Heart Failure, 6(5), 635– 641.
19. Hosmer DW & Lemeshow S. (1989). Applied logistic regression. New York, NY: John Wiley & Sons.
20. Ghali, W.A,. Quan, H., Brant, R.,van Melle, G., Norris, C.M., Faris, P.D., et al. for the APPROACH Investigators. (2001). Comparison of 2 methods for calculating adjusted survival curves from proportional hazard models. Journal of the American Medical Association, 286(12),1494-1497
21. Kosiborod, M., Soto, G.E., Jones, P.G., Krumholz, H.M., Weintraub, W.S., Deedwania, P., et al. (2007). Identifying heart failure patients at high risk for near term cardiovascular events with serial health status assessments. Circulation, 115(15), 1975-1981.
22. Raphael, C., Briscoe, C., Davies, J., Ian Whinnett, Z., Mainsty, C., Sutton, R., et al. (2007). Limitations of the New York Heart Association functional classification system and self reported walking distances in chronic heart failure. Heart, 93(4), 476-482.
23. Tengs TO, Wallace A. (2000). One thousands health related quality of life estimates. Medical Care, 38(6) 583-637.

24. Rahimi, K., Malholtra, A., Banning AP & Jenkinson C. (2010). Outcome selection and role of patients reported outcomes in contemporary cardiovascular trials: systematic review. BMJ;314:c5750 doi:10.1136/bmj.c507.
25. Guyatt, G.H., Oxman, A.D., Kunz, R., Vist, J.E., Falk-Ytter Y., Schünemann, H.J. (2008).What is quality of evidence and why is it important to clinicians? British Medical Journal, 336(7650), 995-998.
26. McAlister, F.A., Stewart, S., Ferrua, S, McMurray, J.J. (2004). Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. Journal of the American College of Cardiology, 44(4), 810-819.
27. Gesica Investigators. (2005). Randomised trial of telephone intervention in chronic heart failure: DIAL trial. British Medical Journal, 331(7514), 425-429.
28. Ferrante, D., Varini, S., Macchia, A., Soifer, S., Badra, R., Nul, D., et al. (2010). Long-term results after a telephone interview intervention in chronic heart failure. Journal of the American College of Cardiology, 56(5), 372-378.

Table 1. Demographic and clinical characteristics of the general population and of subgroups with different Health Status scores

	All N=1465	Health status scores N (%)				
		GOOD (100-75) N=822 (56.1%)	FAIR (50-74) N=413 (28.2%)	POOR (25-49) N=185 (12.6%)	WORST (<25) N=45 (3.1%)	P for trend
Median age (IR)	69.1 (61.8-75.7)	67.7 (60.4-73.8)	69.5 (62.9-76.7)	73.1 (65.9-77.8)	72.2 (66.4-77.6)	<0.001
Males	1144 (78.1)	689 (83.8)	319 (77.2)	144 (61.6)	22 (48.9)	<0.001
Education (years) ≤5	834 (57.0)	429 (52.2)	253 (61.3)	120 (64.9)	32 (71.1)	
≤8	323 (22.1)	193 (23.5)	90 (21.8)	30 (16.2)	10 (3.1)	<0.001
>8	308 (21.0)	200 (24.3)	70 (17.0)	35 (18.9)	3 (6.7)	
Smoke	175 (12.0)	105 (12.8)	46 (11.1)	19 (10.3)	5 (11.1)	n.s.
NHYA class II	996 (68.0)	636 (77.4)	272 (65.9)	76 (41.1)	12 (26.7)	<0.001
III*	469 (32.0)	186 (22.7)	141 (34.1)	109 (58.9)	33 (73.3)	
Ejection fraction <35% (%)	779 (53.2)	442 (53.8)	223 (54.0)	93 (50.3)	21 (46.7)	n.s.
Admission for HF in previous year	736 (50.2)	377 (45.9)	213 (51.6)	115 (62.2)	31 (68.9)	<0.001
Comorbidities						
History of Hypertension	805 (55.0)	436 (53.0)	221 (53.5)	115 (62.2)	33 (73.3)	0.004
Diabetes †	536 (36.6)	267 (32.5)	161 (39.0)	85 (46.0)	23 (51.1)	<0.001
COPD	277 (18.9)	121 (14.7)	82 (19.9)	57 (30.8)	17 (37.8)	<0.001
Stroke	76 (5.2)	34 (4.1)	18 (4.4)	20 (10.8)	4 (8.9)	0.001
eGFR <60 (ml/min) ‡	658 (45.1)	351 (42.9)	187 (45.4)	97 (52.7)	23 (51.1)	0.017
Haemoglobin (g/dl)§ ≤13.0	495 (34.0)	237 (29.1)	162 (39.3)	70 (37.8)	26 (57.8)	
13.1-14.3	475 (32.6)	275 (33.7)	123 (29.9)	64 (34.6)	13 (28.9)	<0.001
>14.3	487 (33.4)	303 (37.2)	127 (30.8)	51 (27.6)	6 (13.3)	

Liver disease (ALT > 80 or AST >70)	27 (1.8)	13 (1.6)	8 (1.9)	5 (2.7)	1 (2.2)	0.333

For continuous variables values are median (Interquartile Range). For categorical variables: percentage values are given in parenthesis

*36 patients were in NYHA class IV

† Defined as history of diabetes or fasting blood glucose ≥ 126 (mg/dl) or HbA1C > 7.0 %

‡ eGFR = estimated Glomerular Filtration Rate available for 1459 patients;

§ Haemoglobin available for 1457 patients;

Table 2. Relation between health status, mortality and the risk of admissions for all causes after the adjustment for different variables during 3.3 years mean follow-up.

Model	KCCQ overall scores						P for Trend
	Fair 50-74 Event/ N (%) 126/413 (30.5)		Poor 25-49 Event/N (%) 68/185 (36.8)		Worst 0-24 Event/N (%) 24/45 (53.3)		
All cause mortality	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	
M1 Unadjusted	1.50 (1.19-1.89)	0.001	2.05 (1.55-2.71)	<0.001	3.04 (1.98-4.65)	<0.001	<.001
M2 Age and Sex-adjusted	1.40 (1.11-1.76)	0.004	1.97 (1.48-2.62)	<0.001	3.01 (1.94-4.66)	<0.001	<.001
M3 M2+ Cardiac Disease	1.32 (1.04-1.66)	0.021	1.45 (1.08-1.96)	0.014	1.98 (1.26-3.12)	0.003	<.001
M4 M2+ CVRF	1.36 (1.08-1.71)	0.010	1.85 (1.38-2.46)	<0.001	2.90 (1.87-4.51)	<0.001	<.001
M5 M2+ Co-morbidity	1.31 (1.03-1.65)	0.025	1.74 (1.30-2.33)	<0.001	2.65 (1.69-4.13)	<0.001	<.001
M6 M2+ Education	1.40 (1.11-1.76)	0.004	1.97 (1.48-2.62)	<0.001	3.01 (1.94-4.67)	<0.001	<.001
M7 M2+ Drugs	1.39 (1.10-1.74)	0.006	1.73 (1.29-2.32)	<0.001	2.54 (1.63-3.96)	<0.001	<.001
M8 M2 +M3+M4+M5	1.22 (0.96-1.55)	0.100	1.31 (0.96-1.78)	0.084	1.85 (1.16-2.95)	0.010	0.007
All cause admissions	Event/N (%) 251/413 (60.8)		Event/N (%) 134/185 (72.4)		Event/N (%) 30/45 (66.7)		
M1 Unadjusted	1.24 (1.06-1.44)	0.007	1.93 (1.59-2.34)	<0.001	1.49 (1.03-2.15)	0.036	<.001
M2 Age and sex-adjusted	1.20 (1.03-1.40)	0.022	1.87 (1.53-2.27)	<0.001	1.43 (0.98-2.08)	0.061	<.001
M3 M2+ cardiac Disease	1.16 (1.00-1.36)	0.058	1.70 (1.38-2.09)	<0.001	1.23 (0.84-1.81)	0.290	<.001
M4 M2+ CVRF	1.18 (1.01-1.37)	0.043	1.81 (1.48-2.22)	<0.001	1.37 (0.94-2.00)	0.100	<.001
M5 M2+ Co-morbidity	1.18 (1.01-1.38)	0.041	1.84 (1.50-2.24)	<0.001	1.38 (0.94-2.01)	0.102	<.001
M6 M2+ Education	1.20 (1.03-1.40)	0.020	1.86 (1.53-2.27)	<0.001	1.44 (0.99-2.10)	0.055	<.001
M7 M2+ Drugs	1.19 (1.02-1.39)	0.031	1.78 (1.45-2.18)	<0.001	1.33 (0.91-1.95)	0.139	<.001
M8 M2+M3+M4+M5	1.13 (0.97-1.33)	0.124	1.64 (1.33-2.03)	<0.001	1.18 (0.80-1.75)	0.414	0.003

CVFR: Cardiovascular Risk Factors

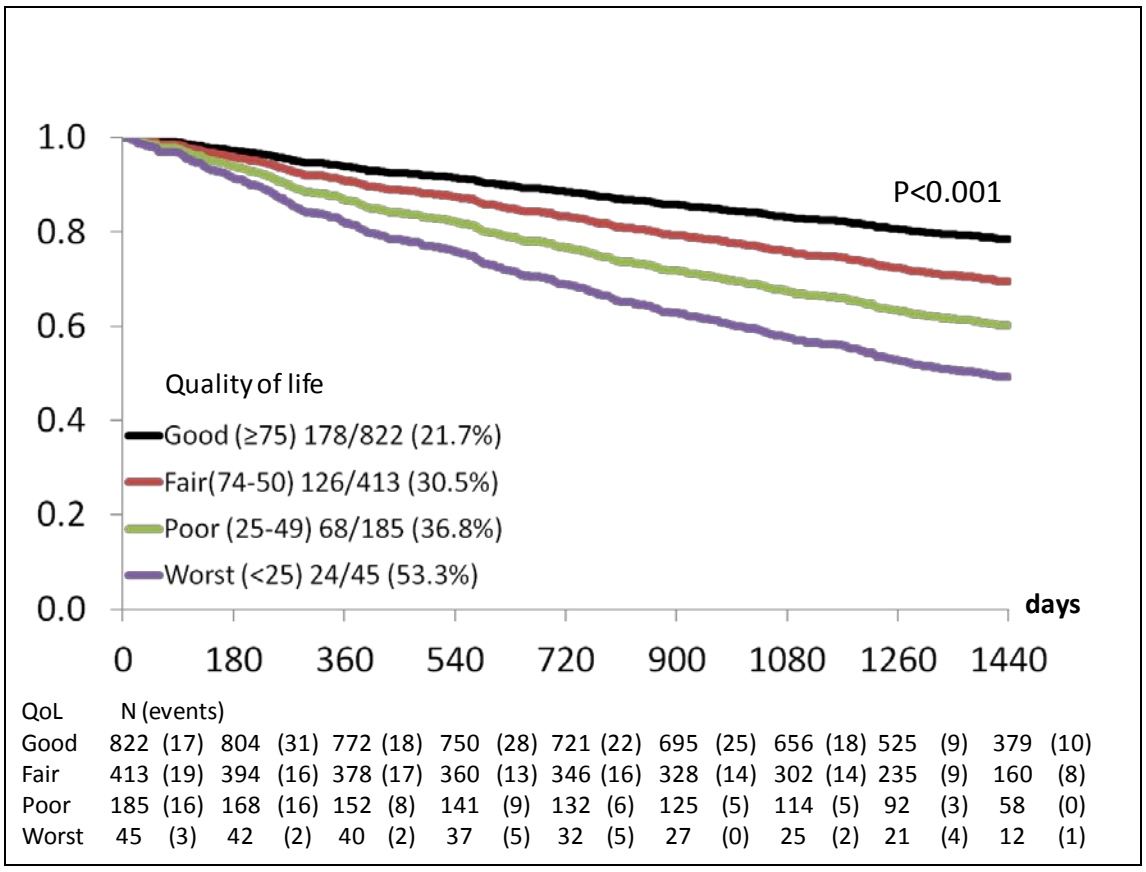
Reference category: patients with KCCQ scores 75-100 (N=822); deaths 178 (21.7%); readmissions 462 (56.2%)

Table 3. Mortality and all-causes hospital admissions by NYHA Class and KCCQ scores.

	NYHA II (N=996)			NYHA III (N=469)		
	Good (≥75) (N=636)	Fair (74-50) (N=272)	Poor/worst (<50) (N=88)	Good (≥75) (N=186)	Fair (74-50) (N=141)	Poor/worst (<50) (N=142)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Mortality						
1 year (§)	26 (4.1)	19 (7.0)	9 (10.2)	23 (12.4)	17 (12.1)	28 (19.7)
3.3 years (§) (*)	110 (17.3)	71 (26.1)	24 (27.3)	68 (36.6)	55 (39.0)	68 (47.9)
Cardiovascular Mortality						
1 year (§)	21 (3.3)	14 (5.2)	7 (8.0)	19 (10.2)	15 (10.6)	22 (15.5)
3.3 years	89 (14.0)	44 (16.2)	14 (15.9)	53 (28.5)	45 (31.9)	57 (37.3)
All cause admissions						
1 year (§) (*)	150 (23.6)	85 (31.3)	36 (40.9)	60 (32.3)	58 (41.1)	69 (48.6)
3.3 years(*)	347 (54.6)	150 (55.2)	57 (64.8)	115 (61.8)	101 (71.6)	107 (75.4)
Cardiovascular admissions						
1 year (§)(*)	115 (18.1)	62 (22.8)	28 (31.8)	51 (27.4)	49 (34.8)	54 (38.0)
3.3 years(*)	283 (44.5)	123 (45.2)	51 (58.0)	96 (51.6)	91 (64.5)	89 (62.7)

(§) $p<0.05$ for NYHA II patients

(*) $p<0.05$ for NYHA III patients



QoL	N (events)																	
Good	822	(17)	804	(31)	772	(18)	750	(28)	721	(22)	695	(25)	656	(18)	525	(9)	379	(10)
Fair	413	(19)	394	(16)	378	(17)	360	(13)	346	(16)	328	(14)	302	(14)	235	(9)	160	(8)
Poor	185	(16)	168	(16)	152	(8)	141	(9)	132	(6)	125	(5)	114	(5)	92	(3)	58	(0)
Worst	45	(3)	42	(2)	40	(2)	37	(5)	32	(5)	27	(0)	25	(2)	21	(4)	12	(1)

Adjusted for age, sex, cardiac diseases, cardiovascular risk factors and comorbidities

Table 1. Cox proportional hazards adjusted survival curves at 3.3 years