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Individualized Nutritional Support for Hospitalized Patients with Chronic Heart Failure

Brief title: Individualized Nutritional Support for Chronic Heart Failure

[1,9]Lara Hersberger, MD*, [1,9]Anna Dietz*, [1,9]Helene Bürgler, [1,9]Annika Bargetzi, MD, [1,9]Laura Bargetzi, MD, [1]Nina Kägi-Braun, MD, [2]Pascal Tribolet, RD, [1,13]Filomena Gomes, PhD, [3]Claus Hoess, MD, [3]Vojtech Pavlicek, MD, [4]Stefan Bilz, MD, [4]Sarah Sigrist, MD, [4]Michael Brändle, Prof., [5]Christoph Henzen, Prof., [6]Robert Thomann, MD, [7]Jonas Rutishauser, Prof., [8]Drahomir Aujesky, Prof., [8,11]Nicolas Rodondi, Prof., [8,12]Jacques Donzé, Prof., [10]Zeno Stanga, Prof., [1,9]Beat Mueller, Prof., [1,9]Philipp Schuetz, Prof.

Equally contributing first authors
1 Medical University Department, Division of General Internal and Emergency Medicine, Kantonsspital Aarau, Aarau, Switzerland;
2 Internal Medicine, Spital Lachen, Switzerland;
3 Internal Medicine, Kantonsspital Muensterlingen, Switzerland;
4 Internal Medicine & Endocrinology/Diabetes, Kantonsspital St. Gallen, Switzerland;
5 Internal Medicine, Kantonsspital Luzern, Switzerland;
6 Department of Internal Medicine, Buergerspital Solothurn, Switzerland;
7 Internal Medicine, Kantonsspital Baden, Switzerland;
8 Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland;
9 Medical Faculty of the University of Basel, Switzerland;
10 Division of Diabetology, Endocrinology, Nutritional Medicine & Metabolism, Inselspital, Bern University Hospital, University of Bern, Switzerland;
11Institute of Primary Health Care (BIHAM), University of Bern, Switzerland;
12Division of General Internal Medicine, Brigham and Women's Hospital, Boston, MA, USA;
13The New York Academy of Sciences, New York City, NY, USA

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Correspondence and reprint requests:
Prof. Dr. med. Philipp Schuetz, MD, MPH
University Department of Medicine
Kantonsspital Aarau
Tellstrasse
CH-5001 Aarau, Switzerland
Tel: +41 62 838 4141
Fax: +41 62 838 4100
E-mail: schuetzph@gmail.com
Twitter: @ksaarau

Abstract
Background: Deterioration of nutritional status during hospitalization in patients with chronic heart failure increases mortality. Whether nutritional support during hospitalization reduces these risks, or on the contrary, may be harmful due to an increase in salt and fluid intake, remains unclear.
Objectives: to study effect of nutritional support on mortality in hospitalized chronic heart failure patients at nutritional risk.
Methods: We included 645 patients with chronic heart failure (36% [n=234] with acute decompensation) participating in the investigator-initiated, open-label EFFORT trial. Patients were randomised to protocol-guided individualized nutritional support to reach protein and energy goals (intervention group) or standard hospital food (control group). The primary endpoint was all-cause mortality at 30 days.
Results: Mortality over 180 days increased with higher severity of malnutrition (odds ratio per 1 point increase in NRS: 1.65, 95%CI 1.21 to 2.24) p=0.001). By 30 days, 27 of 321 intervention group patients (8.4%) died, compared to 48 of 324 (14.8%) control group patients (odds ratio 0.44, 95%CI 0.26 to 0.75, p=0.002). Patients at high nutritional risk showed most benefit from nutritional support. Mortality effects remained significant in 180-day follow-up. Intervention group patients also had a lower risk for MACE (17.4% vs. 26.9%, odds ratio 0.50 (95%CI 0.34 to 0.75) p=0.001).
Conclusion: Among hospitalised chronic heart failure patients at high nutritional risk, individualised nutritional support reduced the risk for mortality and MACE as compared to standard hospital food. These data support malnutrition screening upon hospital admission followed by an individualised nutritional support strategy in this vulnerable patient population.

Condensed Abstract
Deterioration of nutritional status during hospitalization in patients with chronic heart failure is associated with increased mortality and morbidity. Within this pre-planned secondary analysis of the randomised multicentre EFFORT trial, we found significantly lower morality rates at 30- and 180-days, and lower risk for MACE in patients receiving individualized nutritional support group as compared to standard hospital food. Our data support malnutrition screening upon hospital admission followed by individualised nutritional support to reach protein and energy goals in this vulnerable patient population.

Keywords: malnutrition, heart failure, cardiology, cardiovascular, nutritional support, clinical outcomes, Nutritional Risk Screening

Abbreviations

NRS 2002	Nutritional risk screening 2002
HF	Heart Failure
ESC	European Society of Cardiology
AHA	American Heart Association
EFFORT	Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of malnourished medical inpatients
MACE	Major cardiovascular events
LOS	Length of stay
EF	Ejection fraction

Introduction

Malnutrition is a well-recognized risk factor for poor patient outcome generally in the medical inpatient population (1), and more specifically in patients with chronic heart failure (2-4). The clinical presentation of malnutrition may vary from loss of appetite and/or weight, to loss of muscle mass with sarcopenia, to severe cardiac cachexia (5,6). While cardiac cachexia is strongly related to malnutrition, its definition also includes the presence of inflammation and a non-intentional weight loss of at least 6% over 6-12 months (7,8). Up to 40% of patients with chronic heart failure meet these criteria (8), which may be explained by different risk factors including old age, high burden of comorbidities, intestinal oedema leading to malabsorption, elevated cytokines and inflammation causing loss of appetite and anorexia, and fatigue and dyspnoea leading to impairment in activities of daily living (9,10). In addition, once admitted to the hospital, patients with chronic heart failure are at high risk for further deterioration of the nutritional status (11).

To prevent such adverse outcomes associated with malnutrition, current clinical practice guidelines recommend initiating nutritional support during the hospital stay in medical patients at risk of malnutrition (12,13). However, there is little evidence regarding the population of heart failure patients (2,14,15). A recent systematic review, found five trials involving heart failure patients with only one reporting mortality data(16). This trial from Spain with 120 included patients reported strong mortality reduction of >50% over a time period of 6 months (3). Still, despite these promising results, there is currently insufficient evidence regarding the clinical benefit of in-hospital nutritional support for heart failure patients. Importantly, there is potential harm from increasing salt and fluid intake associated with nutritional support for patients with heart failure.

Currently, the several international cardiology guidelines recommend a multidisciplinary approach to prevent malnutrition, including regular monitoring of body

weight as well as avoidance of excessive fluid and/or salt intake (17-19). Yet, due to the lack of strong trial data, there is no specific recommendation regarding nutritional support of hospitalised patients with chronic heart failure (17-19). Herein, we performed a pre-planned secondary analysis of a randomised multicentre trial in Switzerland (20,21), investigating the effect of nutritional support during the hospital stay compared to usual care hospital food on mortality and other clinical outcomes in patients with chronic heart failure.

Methods and materials

Study design

This secondary analysis included all patients with chronic heart failure included in the EFFORT (Effect of early nutritional support on Frailty, Functional Outcomes and Recovery of malnourished medical inpatients) trial (20,21). EFFORT was a prospective, non-commercial, multicentre, randomised controlled trial investigating the effect of early individual nutritional support on medical outcomes in patients at risk of malnutrition. The trial protocol and the main results were previously published elsewhere. The Ethics committee of Northwestern Switzerland (EKNZ; 2014_001) approved the trial, which was registered at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02517476). A total of eight secondary and tertiary care hospitals in Switzerland participated in this study.

Patient population

For the initial trial, we screened all medical patients upon hospital admission for risk of malnutrition using the Nutritional Risk Screening 2002 (NRS) (22). The NRS is a malnutrition screening tool based on patient self-report that includes items for the assessment of current nutritional status and disease severity.

For the trial, we included adult patients with a NRS total score ≥3 points, an expected length of stay (LOS) >4 days and written informed consent. We excluded patients treated in the intensive care or surgical units, unable to have oral intake, receiving long-term nutritional

support on admission, terminal illness, gastric bypass surgery, anorexia nervosa, acute pancreatitis, acute liver failure, cystic fibrosis, stem cell transplantation, and patients previously included in the trial. All patients eligible for this secondary analysis had a documented diagnosis of chronic heart failure on hospital admission, which was confirmed and validated by a complete chart review after hospital discharge. The reporting of heart failure thus differs from the original trial where diagnosis was based on admission data only. In line with the ESC guidelines, we stratified patients according to their ejection fraction into three groups: (1) reduced ejection fraction (HFrEF; EF <40%), (2) mid-range ejection fraction (HFmrEF; EF 40-49%), and (3) preserved ejection fraction (HFpEF EF ≥50%).

Randomization and study intervention

After trial inclusion, we randomized patients using an interactive web system 1:1 to the intervention group (receiving individualised nutritional support according to an implementation protocol [**Figure 1** adapted according to a previous consensus conference (23)]) or the control group (receiving usual hospital food). In the intervention group, nutritional support was initiated as soon as possible after randomization within 48 hours of hospital admission. Patients received individualized nutritional support to reach protein and energy goals, defined for each patient upon hospital admission by a trained registered dietician. Energy requirements were predicted using the weight-adjusted Harris-Benedict equation.(24) Daily protein intake was set at 1.2–1.5 g/kg body weight to adjust for higher protein breakdown during acute disease(25), with lower targets for patients with acute renal failure (0.8 g per kg of body weight). To reach these goals, an individual nutritional plan was developed by a trained registered dietician for each patient. This plan was initially based on oral nutrition provided by the hospital kitchen (including food adjustment according to patient preferences, food fortification [e.g., enrichment of hospital food by adding protein powder] and providing patients with between-meal snacks) and oral nutritional

supplements(26,27). A further increase in nutritional support to enteral tube feeding or parenteral feeding was recommended if at least 75% of energy and protein targets could not be reached through oral feeding within 5 days. Nutritional intake was reassessed every 24–48 h throughout the hospital stay by a trained registered dietician based on daily food records for each patient. Upon hospital discharge, patients received dietary counselling and, if indicated, a prescription for oral nutritional supplements in the outpatient setting. There was no planned follow-up regarding nutritional intake in the outpatient setting.

Control group patients received standard hospital food according to their ability and desire to eat, with no nutritional consultation and no recommendation for additional nutritional support. Swiss hospitals offer standard European/International food. There was no restriction in salt intake in participating hospitals and fluid restriction was ordered individually based on a patient's medical situation.

Outcomes

The primary endpoint of this analysis was all-cause mortality up to day 30 after inclusion in the trial. To verify outcome information, trained study nurses blinded to the intervention conducted structured telephone interviews with all patients. If the patient was unable to provide information, a family member or the family doctor confirmed their survival status. Secondary endpoints included (a) major cardiovascular events (MACE) including myocardial infarction, stroke and death within 30 days; (b) major complications including major cardiovascular events, acute renal failure, or infection needing antibiotic treatment within 30 days of inclusion; (c) length of the index hospital stay (LOS); (d) non-elective hospital readmission, and (e) need for admission to an intensive care unit. We also assessed functional outcomes, including quality of life, functional impairment, fractures and accidental falls. To assess the functional impairment in activities of daily living, we used the Barthel index and focused on a decline of at least 10% in functional performance. Quality of life was

assessed with the European Quality of Life 5 Dimensions Index (EQ-5D), ranging from 0 to 1 points, and with an increasing score indicative of better quality of life. Further, we used the combination of the EQ-5D and the visual analogue scale (EQ-5D VAS), with scores from 0 to 100 points, and higher scores again indicating better quality of life. As an additional secondary outcome, we also assessed mortality after a follow-up time of 6 month, where we had information from 1995 from 2028 patients (98%) included in the initial trial.(28)

Statistical analyses

We used a similar statistical approach as in the original trial(20,21). We tested the hypothesis that individualised nutritional support is superior to usual hospital food with regard to mortality and other secondary endpoints. We performed all analyses in the intention-to-treat population, which included all patients with chronic heart failure who had undergone randomisation unless they withdrew consent. For the primary outcome, we compared frequencies using a chi-square test. To investigate the effect of nutritional support on outcomes, we fitted a logistic regression model adjusted for predefined prognostic factors (Barthel's index and NRS scores at baseline) and study centre. We report adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI's). We used Student's T test and linear regression models for continuous outcomes and Kaplan–Meier method to graphically display time to event analyses. We performed all statistical analyses with STATA 15.1 (Stata Corp., College Station, TX, USA). A *P* value <0.05 (for a 2-sided test) was considered statistically significant.

Results

This analysis included 645 patients with a documented diagnosis of chronic heart failure (321 intervention group patients and 324 control group patients). The median age was 78.8 years, 52% were male and all patients were at risk of malnutrition according to their NRS score (NRS total score ≥3 points). Patients had a high burden of comorbidities,

including 181 patients (28%) with diabetes, 450 (70%) with hypertension and 119 (18%) with obesity. A total of 36% of patients were hospitalized for acute heart failure and 64% had chronic heart failure and other acute medical illnesses requiring hospitalisation. Randomisation arms were well balanced regarding baseline characteristics (**Table 1)**.

Association of nutritional risk with clinical outcomes

First, we investigated associations between nutritional risk based on the NRS total score and clinical outcomes (**Table 2**). Compared to patients with moderate nutritional risk scores (NRS total score of 3 or 4 points), patients with a high nutritional risk (NRS total score >4 points) had a 65% increase in risk of mortality over 180 days (24.7% vs. 38.4%, adjusted HR 1.65, 95%CI 1.21 to 2.24, p= 0.001). These results were also confirmed in Kaplan-Meier survival estimates showing a shorter time to death in patients with higher nutritional risk (**Central Figure and Appendix Figures 2 & 3**).

Additionally, we investigated the associations of the different individual components of NRS 2002 (i.e., BMI, unintentional weight loss, reduced food intake, loss of appetite and severity of illness) and mortality to understand which part drives the increased mortality risk (**Table 3**). Low food intake of normal requirement in the preceding week had the strongest association with mortality.

Effect of nutritional support on clinical outcomes

Most patients in the intervention group received oral nutritional support including oral nutritional supplements only (level I nutrition, **Figure 1**) with only 2 patients (0.7%) requiring enteral tube feeding and 5 patients (1.7%) requiring parenteral nutrition. Compared to patients in the control group, intervention group patients had a significantly higher mean (±SD) daily energy (1419 ±589 vs. 1190 ±517 kcal adjusted difference of 257 kcal per day [95%CI 172 to 343), p<0.001]) and protein intake (53.4±22.9 g vs. 46.7±21.1 g/day, adjusted difference 8.2 g protein per day [95%CI 4.7 to 11.7, p<0.001]). At hospital discharge 25.2%

of intervention group patients received oral nutritional support in the outpatient setting compared to only 0.9% of control group patients.

By 30 days, 27 of 321 intervention group patients (8.4%) receiving nutritional support had died compared to 48 of 324 (14.8%) control group patients (adjusted OR 0.44 (95%CI 0.26 to 0.75) p=0.002) (**Table 4)**. These results were also found in Kaplan Meier estimates, with a significantly shorter time to reach the primary endpoint in control group patients (**Figure 2).** When stratified by nutritional risk, patients with high nutritional risk (NRS >4 points) showed most benefit from nutritional support compared to patients with moderate nutritional risk **(Central Figure)**. Effects on 30-day mortality were similar to the overall effect reported in the initial EFFORT trial (OR 0.65, 95%CI 0.47 to 0.91, p=0.011; p for interaction=0.083). Results were also confirmed in a chi square test with results showing a significant difference for all-cause mortality within 30 days (Pearson chi^2= 6.146; p=0.013).

The effect on mortality was still significant in the long-term follow-up after 180 days, where 102 (31.5%) control group patients vs. 85 intervention group (26.5%) patients had died (adjusted HR 0.74, 95%CI 0.55 to 0.996, p=0.047) **(see Kaplan Meier plot in the Appendix Figure 4)**.

Other secondary endpoints

We investigated several other secondary endpoints **(Table 4).** Intervention group patients also had a significantly lower risk for MACE within 30 days (17.4% vs 26.9%, adjusted OR 0.50, 95%CI 0.34 to 0.75, p=0.001). There was no difference between groups with regard to ICU admission or LOS. When compared to the control group, intervention group patients had significant improvements in their quality of life measured by the EQ-5D index (0.74 (±0.31) vs. 0.66 (±0.38) points, adjusted difference 0.09 points, 95%CI 0.04 to 0.15, p=0.001) and by the visual analogue scale (58 (±27) vs. 51 (±30), adjusted difference 8.91 points, 95%CI 4.14 to 13.67, p=0.001).

Subgroup analysis

We also performed several pre-planned subgroup analyses to investigate whether effects of nutritional support were similar among patients with different sociodemographic characteristics, different severities and etiologies of heart failure, and different comorbidities. Overall, we found no evidence for a relevant subgroup effect among all groups investigated for mortality (p for interaction >0.05) **(Figure 3a).** Similarly, for the endpoint MACE, the results were consistent except that patients with valvular heart failure showed a stronger benefit from the nutritional intervention (adjusted OR 0.30, 95% CI 0.15 to 0.61, p interaction 0.048) (**Figure 3b**).

Discussion

The principal findings of this secondary analysis of a large-scale, randomised-controlled nutritional trial focusing on patients with chronic heart failure are twofold. First, nutritional risk was strongly associated with both short-term and long-term mortality, corroborating previous reports in this patient population. Second, compared to a control group of patients receiving standard hospital food, the use of individualised nutritional support to reach nutritional goals resulted in a significant improvement in mortality at short and long-term, and other clinical outcomes. This effect was consistent among different subgroups.

Several points of this secondary analysis are worth discussing.

First, our data demonstrate that nutritional risk identified by the NRS 2002 score puts patients with chronic heart failure at excessive risk of mortality, with an increase of 30-50% in patients with higher malnutrition risk scores. These findings are in line with previous research on cardiac cachexia, and previous cross-sectional studies demonstrating that the prognostic implications of nutritional risk in predicting complications and LOS were independent of oedema in patients with chronic heart failure(29). Importantly, patients in the

high nutritional risk group had an almost 40% mortality risk over 6 months. Interestingly, when looking at the different components of NRS (i.e., BMI, unintentional weight loss, reduced food intake, loss of appetite and severity of illness), we found that all of these were associated with higher risks.

While the negative prognostic implications of deteriorating nutritional status in chronic heart failure patients have previously been demonstrated, conclusive evidence regarding clinical effects of nutritional support in this population is currently lacking(30,31). Importantly, clinicians may be reluctant to provide nutritional support to patients with heart failure to reduce salt and fluid intake. Herein, our data provide evidence that patients show strong benefit from nutritional support, with a more than 50% reduction in the risk of mortality. Patients in our trial received nutritional support according to a previously published nutritional support protocol (**Figure1**) with individual definition of each patient's energy, protein and micronutrient goals and individualized nutritional support to reach those goals(23). Unlike other trials investigating the effect of specific nutritional formulas(32), we used a variety of nutritional support strategies with the support of trained dieticians to reach nutritional goals. Our trial does thus not provide evidence for effects of single nutritional components, but rather suggests that the overall strategy of providing nutritional support to reach different nutritional goals during a hospital stay for an acute illness is beneficial for patients with chronic heart failure. Because nutritional support after discharge was not standardized, and not part of the main protocol focusing on inhospital nutrition, the impact of continuing nutrition in the outpatient setting remains undefined from our data. Clearly, there is need for additional trials validating our findings in the population of chronic heart failure patients including also continued outpatient treatment.

Interestingly, we also found benefits of nutritional support regarding functionality of patients, which in turn may influence survival of patients (33,34). Indeed, a Spanish trial with

>9,000 acute heart failure patients recently reported that patients with impairments in activities of daily living had a two-fold increase in mortality.(35). Thus, the improvements in mortality observed in our study may be partly explained by improvements in functionality associated with nutritional support.

There are important differences regarding the malnutrition in the heart failure patient compared to the general medical patients (8,36,37). Two main mechanisms leading to malnutrition in heart failure patients include oedema of the intestinal wall resulting in malabsorption and negative effects on appetite, and low grade inflammation leading to central appetite loss and fatigue(8). Causative mechanisms and treatment effects may also depend on type and severity of heart failure. Herein, results of our subgroup analysis did not suggest that treatment effects strongly differed according to type and severity of heart failure and comorbidities. Still, the most pronounced effects were observed in patients with HFrEF, which may be due to different energy metabolism for HFrEF and HFpEF (37). Whether different types of heart failure also need different nutritional goals regarding quality and quantity of proteins and micronutrients warrants further research.

Historically, dietary recommendations for heart failure management focused on sodium and fluid restrictions (19). More recently, some studies reported associations of these recommendations with higher readmission rates and increased mortality(19,38,39), but the usefulness of salt restriction in heart failure management remains debated (40). Still, these restrictions may have interfered with patients' normal eating habits, resulting in weight loss and anorexia(41). The GOURMET-HF randomized trial observed higher quality of life and a lower readmission rate in heart failure patients receiving home-delivered, sodium-restricted Dietary Approaches to Stop Hypertension meals (DASH) when compared to a control group(15). Still, there are several shortcomings in this trial including a small sample size, the unblinded setting possibly influencing the behavior of the comparator group, and possible

performance and detection bias(42). While the GOURMET-HF trial included geriatric outpatients with heart failure, our secondary analysis focuses on the nutritional support of inpatients. In fact, our protocol did not specify to continue nutritional support after hospital discharge resulting in only about 25% of intervention group patients receiving nutritional support in the long term. Clearly, trials focusing on the post-discharge management of heart failure patients at nutritional risk is warranted.

We are aware of several limitations of this trial. First, this was a pre-planned, secondary analysis limited to the subgroup of heart failure patients and thus not powered for mortality. We also had only limited information regarding underlying conditions for heart failure (based on the availability from routine care) and did not perform additional tests in patients to confirm heart failure. Still, we validated the diagnosis of heart failure in all patients by complete chart review. We did not look at cost-effectiveness of nutritional support in this analysis, but found the nutritional support strategy to be cost efficient in the original EFFORT trial(43). We were not able to better characterise cardiac cachexia and distinguish it from malnutrition. In addition, we did not collect detailed data on sodium consumption and fluid intake. Also, the unblinded nature of the trial may have caused performance and detection bias and intervention group patients may have received better care through the attention of dieticians. Finally, we included a mixed population of heart failure patients with about one third presenting with acute decompensation and the rest with stable heart failure and another main illness requiring hospitalization. Despite the absence of differences in our subgroup analysis (**Figure 3a and 3b**), there are not sufficient numbers of patients to draw strong conclusions whether the effects of nutritional support would apply equally to both groups. Clearly, a prospective validation of our findings is mandatory.

In conclusion, our data suggest that among hospitalised patients with chronic heart failure, malnutrition as assessed by the NRS 2002 is an important risk factor for short- and

long-term mortality and other clinical outcomes. The use of individualised nutritional support, as compared to standard hospital food, was effective in reducing these risks, particularly in the group of patients at high nutritional risk. These data thus support malnutrition screening upon hospital admission followed by an individualised nutritional support strategy in this vulnerable patient population.

Clinical Perspectives

Competency in Patient Care: In hospitalized patients with chronic heart failure, individualized nutritional support reduces adverse cardiovascular events and mortality.

Translational Outlook: Future studies should focus specifically on interventions to correct malnutrition and prevent cardiac cachexia in patients with heart failure.

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Figure Legends

Figure 1. Nutritional algorithm used during the trial

The protocol for nutritional support was adapted according to a previous consensus conference(23) and included first screening, followed by definition of individualized energy, protein and micronutrient goals and finally development of individual nutritional plan to achieve these nutritional goals with use of oral, enteral and parenteral nutrition.

Figure 2. Kaplan Meier estimate of 30-day mortality stratified by randomisation group

Time to death shown for patients receiving nutritional support (intervention group) and control group patients ($p \leq 0.00115$)

Figure 3A. Forrest Plot showing effects of nutritional support on 30-day mortality within different subgroups

The overall effect is listed as reference. Odds ratios are shown for point estimations. EF= ejection fraction. Heart failure = patients with an EF <40%, a previously diagnosed heart failure, acute decompensation or cardiac shock. Acute coronary syndrome = angina pectoris, NSTEMI, STEMI or cardiac arrest. The subgroup effect for patients with HFrEF and high nutritional risk" was not possible due lack of events in the intervention group

Figure 3B. Forrest Plot showing effects of nutritional support on MACE within different subgroups

Subgroup analysis for different cardiologic patient populations. The overall effect is listed as reference.

Central Figure. Kaplan Meier estimate of 30-day mortality (A) for patients with moderate nutritional risk and (B) with high nutritional risk.

Moderate nutritional risk was defined as NRS ≤4 points and high nutritional risk was defined as NRS > 4 points.

Table 1. Baseline patient characteristics

Parameters	Control group (n=324)	Intervention group (n=321)
Sociodemographic characteristics		
Male gender	175 (61.0%)	156 (55.7%)
Mean age (years)	79.0 (10.2)	78.7 (9.4)
Age group (years)		
<65	17 (5.2%)	11 (3.4%)
65-75	78 (24.1%)	96 (29.9%)
>75	229 (70.7%)	214 (66.7%)
Nutritional assessment		
Mean body-mass index (kg/m2)	25.3 (5.1)	25.5 (5.6)
Mean body weight (kg)	72.0 (15.1)	72.7 (17.6)
NRS total score (points)		
3 points	104 (32.1%)	94 (29.3%)
4 points	129 (39.8%)	115 (35.8%)
5 points	73 (22.5%)	94 (29.3%)
>5 points	18 (5.6%)	18 (5.6%)
Information regarding congestive heart failure		
Acute heart failure	117 (36.1%)	117 (36.4%)
Chronic stable heart failure	207 (63.9%)	204 (63.6%)
Ejection fraction (%)	n=134	n=167
<40%	29 (18.8%)	37 (22.0%)
40-49%	65 (42.2%)	70 (41.7%)
≥50%	60 (39.0%)	61 (36.3%)
Aetiology of heart failure		
Hypertensive	168 (51.9%)	172 (53.6%)
Coronary	185 (57.1%)	182 (56.7%)
Valvular	127 (39.2%)	108 (33.6%)
Other	25 (7.7%)	25 (7.8%)
Coronary artery disease		
Evidence of CAD	211 (65.1%)	226 (70.4%)
No acute ischemia present	160 (55.7%)	174 (62.1%)
Acute ischemia	17 (5.2%)	14 (4.4%)
Cardiovascular risk factors		
Diabetes	93 (28.7%)	88 (27.4%)
Dyslipidemia	109 (33.6%)	115 (35.8%)
Hypertension	211 (65.1%)	208 (64.8%)
Obesity	58 (17.9%)	65 (20.2%)
Family History of CAD	29 (9.0%)	32 (10.0%)
Active nicotine use	108 (33.3%)	102 (31.8%)
Other comorbidities		
History of stroke/transient ischemic attack	42 (13.0%)	30 (9.3%)
PAD	50 (15.4%)	41 (12.8%)
Admission laboratory values, mean		
LDL (mmol/l) N=291	1.8 (0.9)	1.8 (0.9)
HDL (mmol/l) N=294	1.0 (0.4)	1.1 (0.4)
Triglyceride (mmol/l) N=309	1.4 (0.8)	1.4 (0.7)
HbA1c (%) N=140	7.2 (1.7)	7.2 (1.6)
CK (U/l) N=420	157 (285)	253 (1269)
CK-MB (ug/l) N=223	38 (30)	41 (29)
Troponin T high sensitive (ng/l) N=105	79 (114)	230 (1060)
Troponin I high sensitive (ng/l) N=183	1148 (4521)	807 (3161)
GFR (ml/min/1.73m2) N=402	37.2 (16.0)	33.2 (16.0)
NTproBNP (ng/l), N=294		
<1300 ng/l	39 (25.2%)	35 (25.2%)
1301-4261 ng/l	39 (25.2%)	34 (24.5%)
4262-12,284 ng/l	42 (27.1%)	32 (23.0%)
>12,284 ng/l	35 (22.6%)	38 (27.3%)
Coexisting illnesses on admission (based on routine coding)		
Infection	88 (27.2%)	91 (28.3%)

Frailty	38 (11.7%)	32 (10.0%)
Malignant disease	33 (10.2%)	16 (5.0%)
Pulmonary disease	20 (6.2%)	26 (8.1%)
Other	54 (16.7%)	74 (23.1%)

Continuous values are presented as mean and SD, categorical/binary values as absolute number and percentage.
NRS = Nutritional Risk Screening 2002, PAD = peripheral artery disease, CAD = coronary artery disease, heart failure = CHF and/or EF <40% and/or acute heart failure. GFR= glomerular filtration rate.

Table 2. Association between NRS and clinical outcomes

Parameters	NRS ≤ 4 points N=442	NRS >4points N=203	p-value	Hazard ratio (HR) Odds ratio (OR), Coefficient	Regression analysis (unadjusted) (95% CI and p-value)	Regression analysis (adjusted) (95% CI and p-value)
Primary outcome						
All-cause mortality Day 30	45 (10.2%)	30 (14.8%)	0.091	HR	1.50 (0.945 to 2.38) p=0.085	1.53 (0.95 to 2.47) p= 0.078
All-cause mortality Day 180	109 (24.7%)	78 (38.4%)	<0.001	HR	1.73 (1.29 to 2.31) p<0.001	1.65 (1.21 to 2.244) p=0.001
Main cardiovascular outcome						
MACE	89 (20.1%)	54 (26.6%)	0.066	OR	1.43 (0.97 to 2.12) p=0.067	1.53 (0.86 to 2.73) p= 0.146
Other hospital outcomes						
Admission to the intensive care	16 (3.6%)	4 (2.0%)	0.26	OR	0.53 (0.17 to 1.62) p=0.269	0.76 (0.14 to 1.52) p= 0.205
Non-elective hospital readmission	41 (9.3%)	15 (7.4%)	0.43	OR	0.78 (0.43 to 1.41) p=0.424	0.76 (0.52 to 1.10) p= 0.146
Non-elective hospital readmission within 180 days	129 (29.2%)	47 (23.2%)	0.11	OR	0.91 (0.65 to 1.27) p=0.573	0.94 (0.66 to 1.35) p= 0.763
Mean length of stay (days)	10.1 (6.7)	10.1 (6.7)	0.93	Coefficient	0.05 (-1.05 to 1.16) p=0.926	0.47 (-0.71 to 1.64) p=0.435

Data are number of events (%), unless otherwise stated. Models were adjusted for gender, randomization, study center, admission diagnosis and comorbidities

Continuous values are expressed as mean and SD, categorical/binary values as absolute number and percentage. NRS = Nutritional risk screening, EQ-5D = Euroquol-5 Dimensions, VAS = visual analogue scale, MACE = major cardiovascular events containing myocardial infarction, stroke and all-cause mortality.

Table 3. Association of different component of the NRS with 30-day mortality

Parameters	Survivors	Non-survivors	Odds ratio (OR), Coefficient	Regression analysis (unadjusted) (95% CI and p-value)	Regression analysis (adjusted) (95% CI and p-value)
BMI					
>20.5 kg/m2	470 (82.2%)	59 (78.7%)	OR	1.0 (reference group)	1.0 (reference group)
18.5-20.5 kg/m2	59 (10.3%)	12 (16.0%)	OR	1.60 (0.86 to 2.98) p=0.136	1.48 (0.77 to 2.83) P= 0.234
<18.5 kg/m2	43 (7.5%)	4 (5.3%)	OR	0 .75 (0.27 to 2.07) p= 0.580	0 .83 (0 .77 to 2.83) p= 0.728
Severity of illness					
very mild	6 (1.0%)	1 (1.3%)	OR	1.0 (reference group)	1.0 (reference group)
mild	426 (74.0%)	49 (65.3%)	OR	0.71 (0.10 to 5.13) p= 0.734	0.79 (0.10 to 6.17) p= 0.825
moderate	137 (23.8%)	24 (32.0%)	OR	1.05 (0 .14 to 7.76) p=0.962	1.47 (0.18 to 12.14) p= 0.712
severe	7 (1.2%)	1 (1.3%)	OR	0.87 (0.05 to 13.94) p= 0.923	1.41 (0.07 to 27.17) p=0.818
Loss of apetite					
No	67 (11.6%)	4 (5.3%)	OR	1.0 (reference group)	1.0 (reference group)
Yes	509 (88.4%)	71 (94.7%)	OR	2.25 (0 .82 to 6.17) p= 0.113	2.25 (0.81 to 6.23) p=0.119
Weight loss (%)					
No Weight Loss	336 (58.3%)	38 (50.7%)	OR	1.0 (reference group)	1.0 (reference group)
Weight Loss >5% body weight in 3 months	73 (12.7%)	11 (14.7%)	OR	1.32 (0 .67 to 2.57) p=0.422	1.31 (0 .66 to 2.60) p= 0.439
Weight Loss >5% body weight in 2 months	73 (12.7%)	10 (13.3%)	OR	1.20 (0.60 to 2.41) p= 0.605	1.15 (0.57 to 2.34) p= 0.692
Weight Loss >5% body weight in 1 month	94 (16.3%)	16 (21.3%)	OR	1.46 (0.81 to 2.62) p= 0.202	1.59 (0 .87 to 2.93) p= 0.131
Food intake of normal requirement preceeding week - no. (%)					
≤25%	53 (9.2%)	1 (1.3%)	OR	1.0 (reference group)	1.0 (reference group)
50%	207 (35.9%)	27 (36.0%)	OR	6.48 (0.88 to 47.69) p= 0.066	6.12 (0.82 to 45.42) p= 0.077
75%	235 (40.8%)	34 (45.3%)	OR	7.16 (0.98 to 52.34) p= 0.052	7.59 (1.01 to 55.33) p=0.048
100%	81 (14.1%)	13 (17.3%)	OR	8.03 (1.05 to 61.36) p= 0.045	8.27 (1.06 to 63.93) p= 0.043

Data are number of events (%), unless otherwise stated. Models were adjusted for gender, randomization, study center, admission diagnosis and comorbidities

Continuous values are expressed as mean and SD, categorical/binary values as absolute number and percentage.

Table 4. Primary and secondary clinical outcomes in control versus intervention groups

Parameters	Control group (N=324)	Intervention group (N=321)	p-value	Odds ratio (OR), Coefficient	Regression analysis (unadjusted) (95% CI and p-value)	Regression analysis (adjusted) (95% CI and p-value)
Primary outcome						
All-cause mortality within 30 days	48 (14.8%)	27 (8.4%)	0.013	OR	0.53 (0 .32 to 0.88) p= 0.014	0.44 (0.26 to 0.75) p= 0.002
All-cause mortality within 180 days	102 (31.5%)	85 (26.5%)	0.19	HR	0.81 (0.61 to 1.08) p= 0.149	0.74 (0.55 to 0.996) p=0.047
Secondary outcomes						
Main cardiovascular outcome						
MACE within 30 days	87 (26.9%)	56 (17.4%)	0.005	OR	0.58 (0.40 to 0.85) p= 0.006	0.50 (0.34 to 0.75) p=0.001
Other hospital outcomes						
Admission to the intensive care within 30 days	10 (3.1%)	10 (3.1%)	0.96	OR	1.02 (0 .42 to 2.49) p= 0.961	0.97 (0.39 to 2.40) p=0.943
Non-elective hospital readmission within 180 days	84 (25.9%)	92 (28.7%)	0.38	OR	1.16 (0.82 to 1.65) p= 0.383	1.23(0.86 to 1.76) p= 0.245
Non-elective hospital readmission within 30 days	27 (8.3%)	29 (9.0%)	0.72	OR	1.11 (0.64 to 1.91) p= 0.716	1.11 (0.64 to 1.94) p= 0.699
Mean length of stay (days)	9.8 (6.2)	10.4 (7.1)	0.24	Coefficient	0.61 (-0.41 to 1.63) p= 0.243	0.53 (-0.46 to 1.57) p=0.284
Functional outcome						
Decline in functional status of ≥10% within 30 days	60 (18.5%)	38 (11.8%)	0.022	OR	0.60 (0.387 to 0.93) p= 0.023	0.59 (0.38 to 0.93) p=0.023
Mean Barthel score (points) within 30 days	94.38 (9.98)	94.70 (9.05)	0.67	Coefficient	0.31 (-1.15 to 1.77) p= 0.674	0.43 (-0.99 to 1.86) p=0.551
Mean EQ-5D index (points) within 30 days †	0.66 (0.38)	0.74 (0.31)	0.43	Coefficient	0.08 (0.02 to 0.13) p= 0.005	0.09 (0.04 to 0.15) p=0.001
Mean EQ-5D VAS (points) within 30 days †	51 (30)	58 (27)	0.93	Coefficient	7.36 (2.50 to 12.22) p= 0.003	8.91 (4.14 to 13.67) p≤0.001
Decline in mean BARTHEL score (points) within 180 days	-20.9 (62.7)	-15.2 (69.7)	0.34	Coefficient	-17.75 (-22.94 to -12.55) p≤0.001	-20.90 (-75.94 to 34.13) p= 0.456

Data are number of events (%), unless stated otherwise. Models were adjusted for initial nutritional risk screening score and study centre. Continuous values are expressed as mean and SD, categorical/binary values as absolute number and percentage. EQ-5D = Euroquol-5 Dimensions, VAS = visual analogue scale, MACE = major cardiovascular events containing myocardial infarction, stroke and all-cause mortality.