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Do Self-Management Interventions Work in Patients With Heart Failure? An Individual Patient Data Meta-Analysis

Running title: *Jonkman et al.; Self-management interventions for heart failure*

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Abstract

***Background*—**Self-management interventions are widely implemented in care for patients with heart failure (HF). Trials however show inconsistent results and whether specific patient groups respond differently is unknown. This individual patient data meta-analysis assessed the effectiveness of self-management interventions in HF patients and whether subgroups of patients respond differently.

***Methods and Results*—**Systematic literature search identified randomized trials of self-management interventions. Data of twenty studies, representing 5624 patients, were included and analyzed using mixed effects models and Cox proportional-hazard models including interaction terms. Self-management interventions reduced risk of time to the combined endpoint HF-related hospitalization or all-cause death (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.71-0.89), time to HF-related hospitalization (HR, 0.80; 95%CI, 0.69-0.92), and improved 12-month HF-related quality of life (standardized mean difference 0.15; 95%CI, 0.00-0.30). Subgroup analysis revealed a protective effect of self-management on number of HF-related hospital days in patients <65 years (mean number of days 0.70 days vs. 5.35 days; interaction p=0.03). Patients without depression did not show an effect of self-management on survival (HR for all-cause mortality, 0.86; 95%CI, 0.69-1.06), while in patients with moderate/severe depression self-management reduced survival (HR, 1.39; 95%CI, 1.06-1.83, interaction p=0.01).

***Conclusions*—**This study shows that self-management interventions had a beneficial effect on time to HF-related hospitalization or all-cause death, HF-related hospitalization alone, and elicited a small increase in HF-related quality of life. The findings do not endorse limiting self-management interventions to subgroups of HF patients, but increased mortality in depressed patients warrants caution in applying self-management strategies in these patients.

Key words: heart failure; self-management; meta-analysis; individual patient data meta-analysis; subgroup analysis

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Heart failure (HF) is one of the most prevalent chronic conditions[1] and despite advances in medical treatment, patients diagnosed with HF face an increased risk of hospitalization and mortality.[2] The impact of HF on patients' lives is substantial, as they are expected to adhere daily to drug treatment, lifestyle changes and monitoring of signs and symptoms to prevent decompensation.[3] Self-management interventions, which aim at improving patients' knowledge and skills to perform those behaviors and manage their condition, have received increasing attention in care for patients with HF.

A meta-analysis on the effects of self-management interventions in patients with HF showed significant reductions of all-cause and HF-related hospitalization in patients receiving the self-management intervention, although there were no effects on mortality and quality of life (QoL).[4] A more recent systematic review, however, emphasized the heterogeneous findings across studies.[5] Several recently conducted large randomized controlled trials (RCTs) were unable to show beneficial effects of self-management interventions on mortality or hospitalization rates,[6-9] further illustrating heterogeneity in observed effects.

Part of this heterogeneity may be attributable to varying trial designs, intervention components, follow-up periods, or outcome assessments. Since individual RCTs included different groups of patients, variations in patient characteristics are another likely source of heterogeneity. Specific subgroups of patients might benefit more, or even might not benefit, from self-management interventions. Such knowledge will contribute to targeting self-management interventions to those groups anticipated to benefit most, which may become indispensable in times of decreasing resources.

Sample sizes in individual trials are generally too small to identify factors modifying the success of self-management interventions. By combining data from multiple trials, individual

patient data (IPD) meta-analysis allows a reliable identification of patient subgroups with a differential treatment response. Furthermore, IPD meta-analysis enables a uniform definition of subgroups across studies, uniform imputation of missing data and statistical analysis, and analysis of unreported endpoints.[10] Additionally, the main effects of included self-management interventions can be pooled and analyzed in a uniform manner.

This IPD meta-analysis aimed to evaluate effectiveness of self-management interventions regarding HF-related or generic quality of life, HF-related or all-cause hospitalization, and all-cause mortality and to identify subgroups of patients with HF that respond differently to such interventions.

Methods

Data Sources and Study Selection

The electronic databases of PubMed, EMBASE, CENTRAL, PsycINFO and CINAHL were searched from January 1985 through June 2013, as well as reference lists of systematic reviews.

Studies were included if they (1) met the definition of self-management intervention, (2) had a RCT design, (3) included patients with an established diagnosis of HF, (4) compared the self-management intervention to usual care or another self-management intervention, (5) reported data on one or more of the selected outcomes, (6) followed patients for at least six months, and (7) were reported in English, Dutch, French, German, Italian, Portuguese, or Spanish. Self-management interventions were defined as interventions providing information to patients and minimally two of the following components: (1) stimulation of sign/symptom monitoring, (2) education in problem solving skills, and enhancement of (3) medical treatment adherence, (4) physical activity, (5) dietary intake, or (6) smoking cessation. Studies were

independently assessed by two researchers (NHJ and HW) on risk of bias (low/unclear/high) using three criteria based on the 'Risk of bias' tool from the Cochrane Collaboration[11]: (1) random concealed allocation to treatment, (2) intention-to-treat analysis, and (3) other deviances (e.g., high drop-out, imbalances between groups). Any discrepancies were solved through consensus with a third researcher (JCAT). Studies scoring a high risk of bias on one or more criteria used from the 'Risk of bias' tool[11] were defined as 'high risk of bias'. Those studies were included in the analysis, but the impact of studies of lower methodological quality was assessed in a sensitivity analysis by excluding these studies.

Data collection

The principal investigators of selected studies were invited to participate in this IPD meta-analysis and share their de-individualized raw trial data. For details on the search syntax, collaboration with principal investigators, and a list of all requested variables, we refer to the study protocol.[12] Data from each trial were checked on range, extreme values, internal consistency, missing values, and consistency with published reports. When recoding of categorical variables was needed to create uniform categories, principal investigators were consulted to ensure correct interpretation of variables. This IPD meta-analysis is exempt from formal approval by the Medical Research Ethics Committee of University Medical Center Utrecht, since it re-analyzes de-identified data from trials in which informed consent has been obtained by principal investigators.

Outcomes

This study focused in the analysis on 8 main outcomes, divided into HF-related outcomes and general outcomes. HF-related outcomes were time to the combined endpoint of HF-related hospitalization or all-cause death, time to first HF-related hospitalization, total days of HF-

related hospital stay at 12 months, and HF-related quality of life (HF-QoL) at 12 months (measured with Heart Failure Symptom Scale,[13] Kansas City Cardiomyopathy Questionnaire,[14] MacNew Heart Disease Health-related Quality of Life Instrument,[15] or Minnesota Living With Heart Failure Questionnaire[16]). General outcomes were generic QoL at 12 months (measured with Short Form Health Survey 12[17] or 36[18]), time to all-cause death, time to first all-cause hospitalization, and total days of all-cause hospital stay at 12 months. In addition, outcomes at 6 months and binary outcomes for mortality and hospitalization at 6 and 12 months were collected and analyzed, but are presented in **Supplemental Tables 1 and 2** as subordinate outcomes.

Patient-specific effect modifiers

Clinically relevant potential effect modifiers (i.e., variables, such as sex or age, that modify the effect of self-management interventions) were selected based on the self-management literature in HF patients[19] and availability of comparable data across trials. The selected patient characteristics are presented along with the baseline data in **Table 1**[20]. We assumed that these characteristics could modify the effect of interventions; e.g., self-management interventions might be more effective in patients with only primary education compared to higher educated patients.

Statistical analyses

Principal investigators were involved in designing a detailed plan for the statistical analysis and agreed upon this prior to data analysis (see Supplemental Methods for detailed statistical plan). Data from individual studies were merged to create one database. Using multiple imputation by chained equations (25 imputations),[21] missing values for baseline variables and outcomes were imputed within studies. The imputed datasets were analyzed using a one-stage approach (i.e., simultaneously analyzing all observations while accounting for clustering of observations within

studies).[22] Results of imputed datasets were pooled using Rubin's rules and presented as the primary results.[23]

All analyses were performed according to the intention-to-treat principle. For time-to-event endpoints, effects of self-management were quantified by estimating hazard ratios (HR) using Cox proportional-hazard models, including a frailty term to account for clustering within studies. The continuous outcomes (HF-QoL and generic QoL) were quantified by standardized mean differences (SMD) between intervention arms and analyzed using linear mixed effects models. To correctly model the presence of overdispersion in count data of total days of hospital stay, negative binomial mixed effects models were used to estimate relative length of stay. Binary outcome data (all-cause mortality, all-cause, and HF-related hospitalization) were analyzed with log-binomial mixed effects models, which estimated risk ratios (RR). In case of non-convergence of a model, odds ratios (OR) were estimated using a logistic mixed effects model, which is an addition to the published protocol.[12] All mixed effects models included a random intercept and random slope for the treatment effect to take clustering within studies into account.

To assess whether the effect of self-management was modified by patient characteristics, the aforementioned models were extended with interaction terms for categorical patient characteristics included in **Table 1**. This was performed for each characteristic separately. If there were two or more effect modifiers with $p<0.10$ for the interaction (likelihood ratio test), the interaction terms were included in a multivariable model to estimate the effect of self-management within subgroups independent of other relevant effect modifiers. Effect modification was considered significant if the interaction term showed $p<0.05$ in the final model.

As a sensitivity analysis, we investigated potential retrieval bias (i.e., selective inclusion

of studies in the IPD meta-analysis). Published main effects of studies for which we could not obtain the original data (and thus were not included in the IPD meta-analysis) were pooled in a random effects meta-analysis, together with the main effects of included studies. We repeated the main effects analysis by excluding the studies with enhanced usual care. To assess the impact of studies of lower methodological quality, a sensitivity analysis was performed excluding studies with a high risk of bias. Three additional sensitivity analyses assessed the robustness of the effect modifier analysis: (1) complete-case analysis to assess the effect of imputing data, (2) analyses restricted to newer studies (recruitment since 2000), and (3) excluding studies one-by-one to assess if the observed subgroup effects are attributable to a specific study. All analyses were done in R for Windows version 3.1.1 (R Development Core Team, Vienna).

Results

Thirty-two studies (n=8737) met the inclusion criteria and principal investigators were approached to participate in this IPD meta-analysis. The investigators of five studies could not be contacted, IPD of three studies were no longer available, and investigators of four studies were not willing to participate. This resulted in inclusion of data of 20 RCTs, representing 5624 patients in total.

Patient characteristics for which baseline data were available are presented in **Table 1**. A majority of patients was male (57.2%) and mean age was 69.7 years (SD 12.4). Mean left-ventricular ejection fraction (LVEF) was 39.2% (SD 18.2) and 26.0% of patients had a preserved ejection fraction (≥50%). Median time since diagnosis of HF was 1.6 years (IQR 0.1-5.4). Baseline characteristics of patients included in this IPD meta-analysis were similar to those of patients in eligible studies that did not provide original data, except for the percentage males and

current smokers (resp. 63.8% and 11.2% in non-participating studies).

Characteristics of included studies are presented in **Table 2**[24-41]. Sample size ranged from 42[31] to 1023 patients.[7] The majority of interventions were delivered by a specialized nurse, two interventions used a group approach,[29,39] and two interventions consisted of telephonic case management.[36,37] One trial included two intervention arms.[7] Duration of the interventions ranged from 0.5[25,30] to 18[7] months. Two studies provided "enhanced care" to the control patients,[6,29] consisting of some educational components. These components were judged marginal and in line with the education delivered to HF patients in usual care. Consequently, these two studies were included in the analysis.

Main effects of self-management interventions

Self-management interventions showed significant effects on several HF-related outcomes (**Table 3**). Interventions reduced risk of time to the combined endpoint of HF-related hospitalization or all-cause death (HR, 0.80; 95% confidence interval [CI], 0.71-0.89) and time to HF-related hospitalization alone (HR, 0.80; 95% CI, 0.69-0.92). There was a small improvement in HF-QoL at 12 months in patients receiving the intervention (SMD, 0.15; 95% CI, 0.00-0.30). No effects were found for total days in hospital due to HF readmissions or any of the general outcomes. **Figure 1** shows the effects across studies for HF-QoL, HF-related hospitalization, and all-cause mortality.

Effects in patient subgroups

In the HF-related outcomes, subgroup analysis revealed significant effect modification by age on days in hospital due to HF (**Table 3**). For younger patients (<65 years), mean number of days in hospital due to HF in the intervention group was 0.70 days, while this was 5.35days in the control group (relative length of stay, 0.09; 95% CI, 0.02-0.38). This difference was not found in

patients aged 65-80 years (3.30 days in intervention group vs. 3.84 days in control group, interaction p=0.03). For general outcomes (**Table 3**), there was significant effect modification by comorbid depression on time to all-cause death. While no significant effect of self-management was found in patients with no/mild depression on all-cause death (HR, 0.86; 95% CI, 0.69-1.06), there was a negative effect in patients with moderate/severe depression on all-cause death (HR, 1.39; 95% CI, 1.06-1.83, interaction *p*=0.01). In univariable analysis, level of education showed significant effect modification on time to first all-cause hospitalization with lower educated patients showing a positive effect of the self-management intervention (HR, 0.82; 95% CI, 0.71-0.96, **Supplemental Table 3**), while there was no effect in patients who had completed secondary education (HR, 0.98; 95% CI, 0.82-1.17), or higher education (HR, 1.26; 95% CI, 0.99-1.60; interaction *p*=0.02). After adjustment for potential effect modification by age, effect modification by level of education was no longer significant (interaction *p*=0.07). Additional analyses of outcomes measured at 6 months did not yield different insights (**Supplemental Tables 1 and 2**).

Sensitivity analyses

Including published effects of eligible studies for which original data could be obtained, did not change the primary findings (**Supplemental Table 4**), neither did the sensitivity analysis of excluding studies with enhanced usual care (**Supplemental Table 5**). The other sensitivity analyses also yielded similar effects. Only when subgroup analysis was repeated without the trial by Jaarsma and colleagues,[7] effect modification by depression on time to all-cause death was no longer statistically significant (interaction *p*=0.22) and the negative effect for patients with moderate/severe depression on all-cause death was no longer present (HR, 0.63, 95% CI, 0.29-1.34).

Discussion

To our knowledge, this study is the first IPD meta-analysis including sufficiently large numbers of HF patients to be able to identify subgroups of patients that respond differently to self-management interventions. We observed protective effects of self-management interventions on time to the combined endpoint of HF-related hospitalization or all-cause death, HF-related hospitalization alone and HF-QoL. Subgroup analyses showed that younger patients responded better to self-management in terms of reduced total days of HF-related hospitalization, and that HF patients with depression showed a reduced survival following the self-management intervention.

The beneficial effects found on time to the combined endpoint of HF-related hospitalization or all-cause death and on HF-related hospitalization alone have also been reported by previous (aggregate data) meta-analyses on similar interventions.[4,42] Earlier systematic reviews consistently stressed the large heterogeneity across studies regarding effects of self-management on health-related QoL.[5] Our study included several recent large neutral trials[6,7] and was the first to pool the results for HF-QoL and compute an overall effect. Although 95% confidence intervals were rather wide, we observed a small positive effect for HF-QoL at 12 months. In contrast to HF-related outcomes, we found no effects of self-management interventions on general outcomes (i.e., generic QoL, all-cause mortality, all-cause hospitalization). This is in line with previous meta-analyses.[4,42] Thus, it seems that self-management interventions are particularly effective in HF patients for improving outcomes directly related to their disease.

The subgroup analysis showed that younger patients (<65 years) benefited more from self-management interventions than older patients. Younger patients in intervention groups were

discharged sooner from hospitalization for HF during follow-up than their counterparts in control groups. There was no intervention effect in older patients. Older hospitalized patients have an increased risk of functional decline, cognitive dysfunction and generally suffer from more comorbid conditions, complicating their overall functioning and recovery time once hospitalized.[43] Especially older persons are at high risk in the period after hospitalization due to deprived sleep, poor nutrition, stress, symptoms, new treatments, and inactivity. Equipping patients with self-management skills might not be sufficient in such complex situations. Post-discharge instability may need new approaches not only targeting HF itself for a safer transition from hospital to home.[44] Still, the effect modification by age was not consistent across other health outcomes studied and the number of patients aged <65 included in the analysis was relatively small (n=139). The findings should therefore be considered hypothesis-generating.

Self-management interventions increased the risk of all-cause mortality in patients with moderate/severe depression. Sensitivity analyses indicated that this effect was driven by the largest study included in this IPD meta-analysis.[7] The authors of that study reported a similar trend of their intervention for patients with depressive symptoms in their subgroup analysis.[45] These findings question the suitability of generic self-management interventions in HF patients with depressive symptoms. Depression is often associated with reduced motivation, which might compromise adherence to medication regimen and lifestyle changes,[46] particularly if multiple comorbid conditions (and treatment) need to be self-managed. These patients may be burdened with self-managing their HF. Increased mortality following self-management interventions might therefore be caused by suboptimal (self-)management of their illnesses, including HF. Interestingly, the negative effect was limited to all-cause mortality. In the five studies that measured depression, self-management interventions showed an overall HR of 0.95 on time to

HF-related hospitalization (95% CI, 0.94-0.97) and subgroup analysis did not reveal a differential treatment effect between patients with and without depression (HR depression, 1.00; 95% CI, 0.74-1.35; HR without depression, 0.92; 95% CI, 0.71-1.18; interaction *p*=0.64). With no clear explanation for reduced survival in HF patients with depression, caution is warranted before applying self-management strategies in care for those patients. Patients with depressive symptoms might need additional psychological interventions or medication before initiating self-management interventions.[47] Screening HF patients on symptoms of depression might help to determine to what extent attention should be paid to self-management skills or additional psychological interventions in the treatment plan.

Previous subgroup analyses in three large RCTs have shown that self-management interventions might be more effective for patients with low socio-economic status. DeWalt and colleagues found that only patients with low literacy showed a positive effect on HF-related hospitalizations after self-management support.[6] A Dutch self-management trial found greatest improvements in health-related QoL in patients with lower education.[48] The third trial showed that patients with reduced income benefitted most from self-management.[8] The pattern across studies generates the hypothesis that patients with a lower socio-economic status may benefit most from self-management interventions. Similarly, our analyses indicate a protective effect of self-management on time to first all-cause hospitalization in patients with lower education. However, after adjusting for other potential effect modifiers, this effect did not reach statistical significance.

This IPD meta-analysis was one of the first attempts to pool individual patient data on self-management interventions for patients with HF. The study included sufficient patients (n=5624) to analyze treatment effects in patient subgroups and applied robust statistical

modelling according to a pre-specified plan. Reported effects were found across cultures and healthcare settings. Nevertheless, this study has several limitations that deserve further discussion. First, despite numerous efforts to reach all principal investigators, we were unable to include all 32 eligible trials. Inclusion of 62.5% (20/32) of eligible trials is relatively high compared to IPD meta-analyses on similar interventions.[49] Including published results of trials for which no IPD were available did not change main effects, but this could not be checked for the subgroup analysis due to limited published subgroup data. Second, included self-management interventions differed in terms of intensity, duration, mode, and content. Although reported effects were found for self-management interventions in any setting, specific types of interventions might work better for specific subgroups of patients. Addressing the question "what works for whom?" deserves attention in subsequent research. Third, this IPD meta-analysis was highly dependent on data previously collected in individual studies which limited choice of potential effect modifiers to be studied. Individual trials indicated that self-management interventions might be more effective in non-adherers to regimens[25] or in patients with better cognitive status.[48] We could not analyze those potential effect modifiers, since variables were not collected in all studies. If uniform standards for baseline variables were established, a meaningful comparison of patient subgroups across studies may provide further insight into patient characteristics modifying treatment effects. Finally, although all (subgroup) analyses were pre-planned and documented in our protocol,[12] their large number increases the risk of false-positive findings. Our subgroup analysis was exploratory in nature and not intended to demonstrate causal mechanisms. Causal mechanisms of subgroup effects need to be completely understood before any final conclusions can be drawn. Validation of our findings in large trial databases may confirm our subgroup findings.

Conclusion

We found that despite diversity in intensity, content, and personnel delivering the intervention, self-management interventions in patients with HF improve outcomes directly related to their disease. Although self-management interventions might be more effective in younger patients in reducing length of hospital stay, we did not observe consistent subgroup effects across different health outcomes. This study does not endorse limiting self-management interventions to specific subgroups of HF patients, but increased mortality in depressed patients warrants caution in applying self-management strategies in these patients.

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Clinical Perspective

Although self-management interventions are widely implemented in chronic care for patients with heart failure (HF), many clinicians question the actual impact of such interventions on patient outcomes. This study summarizes the evidence of randomized trials on self-management interventions. It revealed that, despite diverse content and intensity, self-management interventions elicit positive effects in HF patients on outcomes directly related to their disease (i.e., HF-related quality of life, HF-related hospitalization and the combined endpoint of HF-related hospitalization or all-cause death). There were no effects on general outcomes (i.e., all-cause hospitalization or all-cause mortality). Furthermore, we observed that particularly younger HF patients (<65 years) benefited from self-management interventions, as those patients showed a ten-fold decrease in length of hospital stay due to HF. On the other hand, there was a higher mortality rate in HF patients with comorbid depression who received the self-management intervention. Based on our findings, we recommend practicing clinicians to pay considerable attention to self-management skills in the treatment plans for their HF patients. However, the higher mortality in patients with comorbid depression cautions against application of self-management strategies in this patient group. Clinicians caring for HF patients may consider to screen HF patients for symptoms of depression and, if present, address the depression first, before initiating self-management interventions.

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Table 1. Baseline characteristics of heart failure patients included in individual patient data meta-analysis.

	Control	Intervention	Total
Sample size, n	2674	2950	5624
Sex			
Male	1505 (56.2)	1711 (58.0)	3126 (57.2)
Female	1169 (43.7)	1239 (42.0)	2408 (42.8)
Age, y	69.9 ± 12.3	69.6 ± 12.4	69.7 ± 12.4
<65 years	796 (29.8)	917 (31.1)	1713 (30.5)
65-80 years	1358 (50.8)	1491 (50.5)	2849 (50.7)
>80 years	520 (19.4)	542 (18.4)	1062 (18.9)
Systolic dysfunction: LVEF	39.7 ± 18.4	38.7 ± 18.1	39.2 ± 18.2
>35% LVEF	805 (48.8)	903 (47.3)	1708 (48.0)
≤35% LVEF	846 (51.2)	1008 (52.7)	1854 (52.0)
NYHA class			
NYHA I & II	1141 (45.2)	1317 (47.0)	2458 (46.1)
NYHA III	899 (35.6)	1065 (38.0)	1964 (36.9)
NYHA IV	484 (19.2)	422 (15.0)	906 (17.0)
Comorbidity index*			
No comorbid conditions	401 (16.7)	556 (20.7)	957 (18.8)
Comorbid conditions in 1 cluster	925 (38.6)	991 (36.9)	1916 (37.7)
Comorbid conditions in >1 cluster	1070 (44.7)	1136 (42.3)	2206 (43.4)
Depression†			
No/mild depression	959 (73.9)	1169 (68.8)	2128 (71.0)
Moderate/severe depression	339 (26.1)	531 (31.2)	870 (29.0)
Level of education			
Primary education or below	807 (42.3)	910 (39.4)	1717 (40.7)
Secondary education	711 (37.3)	939 (40.6)	1650 (39.1)
Higher education	388 (20.4)	461 (20.0)	849 (20.1)
Years since diagnosis (median and interquartile range)	2.0 (0.1-6.0)	1.3 (0.1-5.2)	1.6 (0.1-5.4)
<1 year diagnosed	400 (41.3)	619 (46.2)	1019 (44.1)
1-2 years diagnosed	118 (12.2)	171 (12.8)	289 (12.5)
>2 years diagnosed	451 (46.5)	551 (41.1)	1002 (43.4)
Living status			
Living with others	1064 (75.2)	1076 (73.2)	2140 (74.2)
Living alone	350 (24.8)	393 (26.8)	743 (25.8)
Body mass index	28.2 ± 6.9	27.9 ± 6.4	28.0 ± 6.6
<25	483 (34.2)	647 (36.1)	1130 (35.3)
25-29.99	508 (36.0)	611 (34.1)	1119 (35.0)
≥30	420 (29.8)	532 (29.7)	952 (29.7)
Smoking status			
Current non-smoker	933 (79.9)	993 (82.1)	1926 (81.1)
Current smoker	234 (20.1)	216 (17.9)	450 (18.9)

LVEF indicates left ventricular ejection fraction; and NYHA, New York Heart Association.
Values are n(%), mean±SD or median(interquartile range).
*Categories in the present IPD meta-analysis are based on clusters of the Cumulative Illness Rating Scale.[20]
†Based on validated cut-off scores of instrument used in each specific study.

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Table 2. Description of trials on self-management in heart failure patients included in individual patient data meta-analysis (N=20).

Study	Country	Sample size	Setting	Intervention group	Control group	Duration (months)*
Agren, 2012[24]	Sweden	155	Clinic/hospital or home	3 individual sessions for patient and partner by nurse	Usual care	3
Aldamiz, 2007[25]	Spain	279	Clinic/hospital and home	4 home visits by nurse/physician	Usual care	0.5
Atienza, 2004[26]	Spain	338	Clinic/hospital	1 individual session before discharge by nurse, 1 visit to physician, 3-monthly follow-up visits, and tele-monitoring	Usual care	12
Blue, 2001[27]	United Kingdom	165	Clinic/hospital and home	Home visits by nurse, follow-up telephone calls with intensity based on patient's needs	Usual care	12
Bruggink, 2007[28]	Netherlands	240	Clinic/hospital	2 individual sessions by nurse/physician, 1 telephone call, follow-up 6 visits	Usual care	12
DeWalt, 2012[6]	United States	605	Clinic/hospital	1 individual session by health educator, follow-up multiple telephone calls	Usual care + 1 session on self-management and educational manual	12
Heisler, 2013[29]	United States	266	Clinic/hospital and home	1 group session by lay peer tutor, weekly telephone contact with matched peer, follow-up 3 optional group sessions	Usual care + 1 group session on self-management	6
Jaarsma, 1999[30]	Netherlands	179	Clinic/hospital and home	1 home visit and 1 telephone call after discharge by nurse	Usual care	0.5
Jaarsma, 2008[7]	Netherlands	1023	Clinic/hospital	1: 2 individual sessions by cardiologist, 9 visits to nurse, possibility to contact nurse 2: 2 individual sessions by cardiologist, 18 visits to nurse, 2 home visits, 2 multidisciplinary sessions, follow-up regular telephone contact by nurse	Usual care	18
Leventhal, 2011[31]	Switzerland	42	Clinic/hospital and home	1 home visit by nurse, educational booklet, follow-up 17 telephone calls	Usual care + booklet	12

Martensson, 2005[32]	Sweden	153	Home (recruitment general practice)	1 individual session by nurse, follow-up educational CD-ROM and telephone contact	Usual Care	12
Otsu, 2011[33]	Japan	102	Clinic/hospital	6 individual sessions by nurse	Usual care	6
Peters-Klimm, 2010[34]	Germany	197	Home (recruitment general practice)	1 individual session by nurse/physician, follow-up 3 home visits and telephone calls	Usual care	12
Rich, 1995[35]	United States	282	Clinic/hospital and home	Daily visits by multidisciplinary professionals during hospitalization, follow-up home visits and telephone calls by nurse at decreasing intensity	Usual care	3
Riegel, 2002[36]	United States	358	Telephonic case-management	Telephone calls by nurse at decreasing intensity	Usual care	6
Riegel, 2006[37]	United States	135	Telephonic case-management	Telephone calls by nurse at decreasing intensity	Usual care	6
Sisk, 2006[38]	United States	406	Clinic/hospital	1 individual session by nurse, follow-up telephone calls	Usual care	12
Smeulders, 2009[39]	Netherlands	317	Clinic/hospital	6 group sessions by lay peer tutor and nurse, handbook, follow-up telephone contact with co-participants	Usual care	1.5
Stromberg, 2003[40]	Sweden	106	Clinic/hospital and home	1 visit after discharge to nurse, follow-up based on patient's status and needs (face-to-face and/or telephone)	Usual care	12
Tsuyuki, 2004[41]	Canada	276	Clinic/hospital	1 individual session by pharmacist, follow-up 7 telephone calls by nurse	Usual care + general heart failure brochure	6

*Duration of the self-management intervention evaluated.

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Table 3. Effects of self-management interventions in patients with heart failure included in individual patient data meta-analysis.

Outcome	Effect size	N studies	n patients	Treatment effect (95% CI)	Subgroups Age	n patients	Treatment effect (95% CI)	p-value for interaction	Subgroups Depression	n patients	Treatment effect (95% CI)	p-value for interaction
Heart failure-related outcomes												
HF-related hospitalization/ mortality *time-to-event*	HR	10	3461	0.80 (0.71-0.89)	<65 years	1086	0.84 (0.66-1.07)	0.77	No/mild	1274	0.81 (0.66-0.99)	0.12
					65-80 years	1739	0.81 (0.69-0.95)		Moderate/ severe	696	1.05 (0.81-1.36)	
					>80 years	636	0.74 (0.58-0.95)					
HF-related QoL *12 months*	SMD	11	3356	0.15 (0.00-0.30)	<65 years	1208	0.20 (0.02-0.38)	0.65	No/mild	1832	0.16 (0.14-0.19)	0.41
					65-80 years	1607	0.12 (-0.04-0.29)		Moderate/ severe	772	0.25 (-0.01-0.50)	
					>80 years	541	0.09 (-0.12-0.30)					
HF-related hospitalization *time-to-event*	HR	10	3461	0.80 (0.69-0.92)	<65 years	1086	0.81 (0.62-1.07)	0.88	No/mild	1274	0.92 (0.71-1.18)	0.64
					65-80 years	1739	0.78 (0.64-0.94)		Moderate/ severe	696	1.00 (0.74-1.35)	
					>80 years	636	0.85 (0.63-1.15)					
Total days HF-related hospital stay *12 months*	RLOS	5	892	0.86 (0.44-1.67)	<65 years	139	0.09 (0.02-0.38)	**0.03**	No/mild	228	0.49 (0.13-1.84)	0.94
					65-80 years	521	0.95 (0.46-1.94)		Moderate/ severe	39	0.37 (0.01-9.70)	
					>80 years	232	0.96 (0.31-2.97)					
General outcomes												
Generic QoL-PCS 12 months	MD	8	1739	0.95 (-1.15-3.05)	<65 years	561	1.84 (-0.74-4.42)	0.63	No/mild	796	0.41 (0.09-0.73)	0.45
					65-80 years	882	0.41 (-1.80-2.61)		Moderate/ severe	191	-1.29 (-5.67-3.09)	
					>80 years	296	1.13 (-2.01-4.26)					

Generic QoL-MCS *12 months*	MD	8	1739	0.27 (-2.53-3.08)	<65 years	561	2.07 (-1.54-5.68)	0.37	No/mild	796	-0.88 (-1.36--0.39)	0.52
					65-80 years	882	-0.26 (-3.49-2.97)		Moderate/ severe	191	-2.91 (-9.36-3.54)	
					>80 years	296	-1.19 (-5.62-3.24)					
Mortality *time-to-event*	HR	14	4312	0.91 (0.79-1.04)	<65 years	1232	1.12 (0.80-1.56)	0.25	No/mild	1619	0.86 (0.69-1.06)	**0.01**
					65-80 years	2224	0.93 (0.78-1.11)		Moderate/sev re	814	1.39 (1.04-1.87)	
					>80 years	856	0.79 (0.62-1.00)					
All-cause hospitalization *time-to-event*	HR	12	3833	0.93 (0.85-1.03)	<65 years	1188	1.09 (0.91-1.31)	0.07	No/mild	1469	0.99 (0.84-1.15)	0.10
					65-80 years	1928	0.92 (0.81-1.05)		Moderate/ severe	767	1.22 (1.00-1.49)	
					>80 years	717	0.79 (0.64-0.97)					
Total days all-cause hospital stay *12 months*	RLOS	9	2304	0.97 (0.77-1.23)	<65 years	741	1.14 (0.80-1.63)	0.39	No/mild	1036	1.06 (0.72-1.56)	0.45
					65-80 years	1110	0.98 (0.74-1.31)		Moderate/ severe	359	0.90 (0.49-1.64)	
					>80 years	453	0.77 (0.49-1.20)					

CI indicates confidence interval; HF, heart failure; HR, hazard ratio; MCS, mental component scale; MD, mean difference; PCS, physical component scale; QoL, quality of life; RLOS, relative length of stay; and SMD, standardized mean difference.

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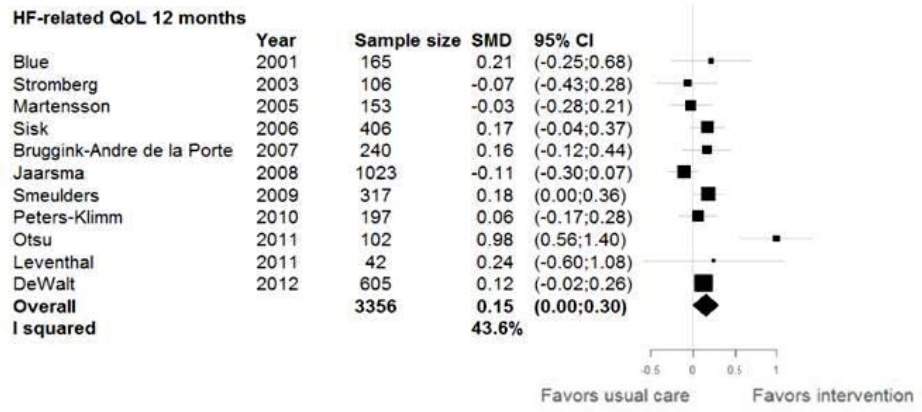
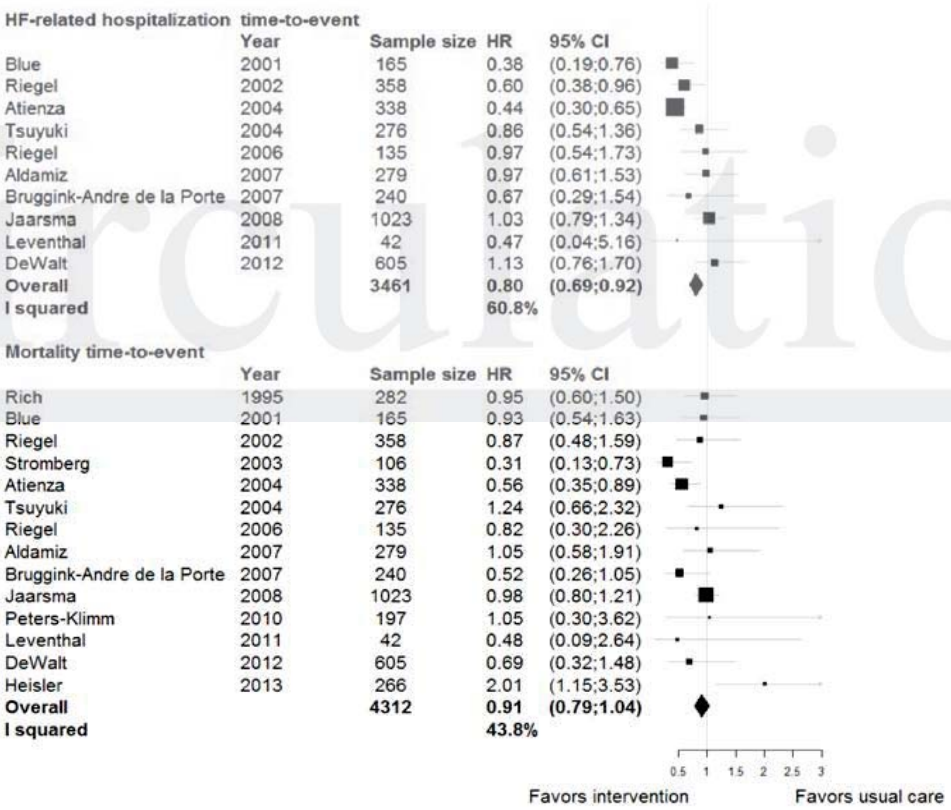
Figure Legend:

Figure 1. Forest plot of effects of self-management interventions on heart failure-related quality of life, heart failure-related hospitalization, and all-cause mortality. CI indicates confidence interval; HR, hazard ratio; and SMD, standardized mean difference.





Do Self-Management Interventions Work in Patients With Heart Failure? An Individual Patient Data Meta-Analysis

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SUPPLEMENTAL MATERIAL

Do self-management interventions work in patients with heart failure work?
An individual patient data meta-analysis

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7	**Supplemental Table 2:** Effects of self-management interventions on subordinate outcomes in subgroups of patients with heart failure included in the individual patient data meta-analysis.
8	**Supplemental Table 3:** Effects of self-management interventions on main outcomes in subgroups of patients with heart failure included in the individual patient data meta-analysis.
9	**Supplemental Table 4:** Sensitivity analysis on main outcomes by including published main effects of eligible studies without available individual patient data.
10	**Supplemental Table 5:** Sensitivity analysis on main outcomes by excluding trials with enhanced usual care in the comparison group.
11	**Supplemental References**

Supplemental Methods: Statistical analysis plan

This document contains the plan for the statistical analysis for the individual patient data (IPD) meta-analysis in heart failure (HF) patients. Input from the conference calls on March 20th, 2014 and March 31st, 2014 and email contact has been processed in the statistical plan presented in this document.

A schematic overview of the statistical analysis is present in Figure 1. Each step will be explained in more detail in the subsequent paragraphs. For all statistical analyses, the software R for Windows version 3.1.1 (R Development Core Team. Released 2013. Vienna, Austria: R Foundation for Statistical Computing) will be used.

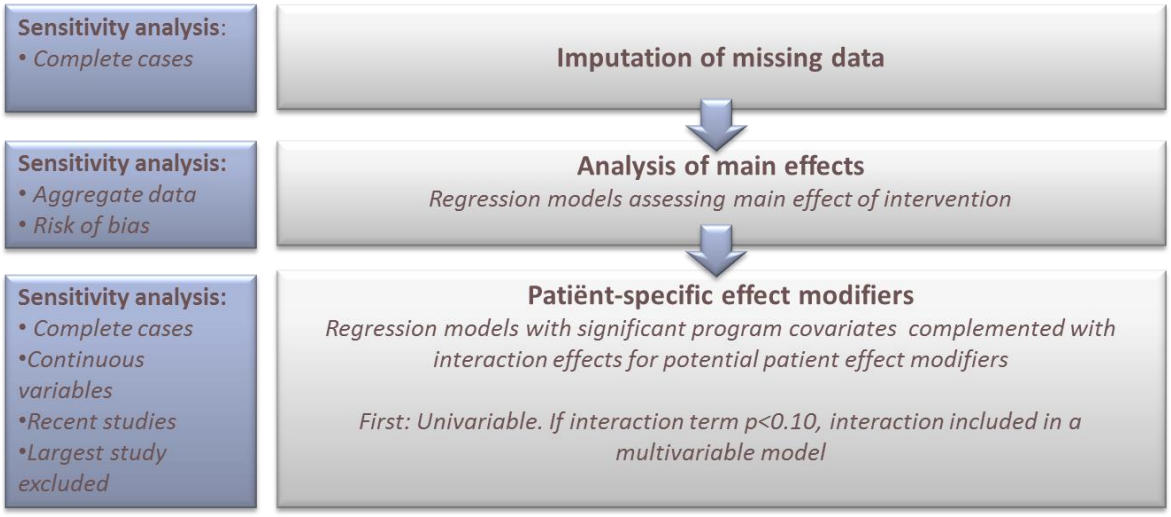

Figure 1: Steps of the statistical analysis of patient-specific determinants of self-management interventions.

1. Imputation of missing data

To address bias due to missing data, we will impute missing data using multiple imputation by chained equations (MICE).[1] The MICE algorithm accounts for the order in which the values of separate variables are predicted through chained equations. To address the uncertainty of just one single imputation, MICE creates multiple imputations, resulting in multiple imputed datasets.

The imputation will be performed according to the following principles:

- Missing values will only be imputed *within* studies: this implies that only the correlation between variables available within one study will be used to estimate the missing values in that particular study
- All available variables (except patient identifiers) will be used to estimate missing values
- Multiple imputation will be used to estimate missing values for patient characteristics and outcomes
- Multiple imputation will be performed 25 times, resulting in 25 imputed datasets
- As a result, all analyses will be carried out 25 times. Results will be pooled using Rubin's rule for the final results.[2]

A complete-case analysis, using only the available patient data, will be performed as a sensitivity analysis to assess the impact of imputing data (see '4. Sensitivity analyses').

2. Analysis of main effects

All data will be analyzed according to the intention-to-treat principle. A so-called one-stage approach will be used, where all patients are analyzed simultaneously in one model while clustering of observations within studies is taken into account.[3]

The present study will analyze the following main outcome measures:

- Composite of time to first disease-related hospital admission or all-cause death;
- Change in health-related quality of life (HRQoL) at 12 months, compared to baseline;
    - A distinction will be made between disease-specific and generic HRQoL to address the different instruments used by original studies
- Time to first disease-related hospital admission;
- Total number of days spent in hospital for HF at 12 months.
- Time to all-cause death;
- Time to first all-cause hospital admission;
- Total number of days spent in hospital for any cause at 12 months.

Additionally, the following subordinate outcomes measures will be analyzed:

- Change in health-related quality of life (HRQoL) at 6 months, compared to baseline;
    - A distinction will be made between disease-specific and generic HRQoL
- Total number of days spent in hospital for HF at 6 months and at 12 months;
- Hospitalized for HF at 6 months;
- All-cause mortality at 6 months and at 12 months;
- Hospitalized for any cause at 6 months and at 12 months;
- Total number of days spent in hospital for any cause at 6 months.

For time-to-event data, effects of self-management will be quantified by estimating hazard ratios (HR) and 95% confidence interval (CI). Cox proportional-hazard models will be used to analyze the data, including a cluster statement to allow inter study variability. For binary outcome data (mortality, all-cause and disease-related hospital admissions), risk ratios (RR) and 95% CI will be estimated using log-binomial mixed effects models. Effects on continuous outcomes (HRQoL) will be quantified by mean differences and 95% CI and will be estimated using linear mixed effects models. Effects on total length of hospital stay will be analyzed with negative binomial mixed effects models to model overdispersion in the data. In the (generalized) linear mixed effects models, random intercepts and random slopes will be included to take clustering within studies into account.

3. Patient-specific effect modifiers

The aforementioned models will be extended to study effect modification by patient characteristics. Effect modification implies that the effect of the intervention on an outcome differs depending on the value of a third variable, the effect modifier. As such, we will be able to identify subgroups of patients in which self-management interventions work best. Interaction terms will be included in the final model resulting from the previous step, which includes the significant program determinants.

We have selected clinically relevant patient characteristics as potential effect modifiers, these are presented in Table 1. Numbers of patients differ per variable due to the fact that some baseline variables have not been collected in one (or more) studies. We would like to categorize the variables to create relevant subgroups for the interpretation of findings. This has been discussed extensively during the conference calls, and the proposed categories are a result of the discussions.

Like the analysis of program characteristics, patient characteristics with $p<0.10$ in the separate analyses will be fitted together in a multivariable model. Effect modifiers will be presented with 95% confidence intervals. Results will be interpreted with great caution to decrease the risk of type I error (i.e. descriptive analysis, consistency with expectations, other findings).

After consulting the investigators during the conference calls we have decided to exclude baseline ***self-efficacy level*** of patients from the analysis. This variable has only been collected in 4 studies (n=1321), each using a different instrument.

Table 1: Patient characteristics to be analyzed as potential effect modifiers.

Determinant	Data in database	Proposed categories for analysis	Statistics in database
Sex (n=5624)	1. Male 2. Female	1. Male 2. Female	57.2% 42.8%
Age (n=5624)	Years	 1. <65 years 2. 65-80 years 3. >80 years	Mean(SD)=69.7(12.4) 30.5% 50.7% 18.9%
Disease severity (n=3562)	% LVEF	 1. ≤35% LVEF (REF) 2. >35% LVEF (based on ESC Guidelines 2012)	Mean(SD)=39.2(18.2) 52.0% 48.0%
Symptom severity (n=5328)	NYHA class (I-IV)	1. NYHA I & II 2. NYHA III 3. NYHA IV	46.1% 36.9% 17.0%
Comorbidity index (n=5079)	# of clusters of comorbid conditions	1. No comorbid conditions 2. Comorbid conditions in 1 cluster 3. Comorbid conditions in ≥2 clusters	*Categories still to be calculated for each individual study*
Depression (n=2998)	Score on instrument	1. No/mild depression 2. Moderate/severe depression (based on validated cut-offs of each instrument)	*Cut-offs still to be calculated for each individual study*
Level of education (n=4216)	1. Primary or below 2. Secondary 3. Higher	1. Primary or below 2. Secondary 3. Higher	40.7% 39.1% 20.1%
Years since diagnosis (n=2310)	Months/Years/Categories	 1. <1 year diagnosed 2. 1 -<2 years diagnosed 3. ≥2 years diagnosed	Median(IQR)=1.6(0.1-5.4) 44.1% 12.5% 43.4%
Living status (n=2883)	1. Living alone 2. Not living alone	1. Living alone 2. Not living alone	25.8% 74.2%
Body Mass Index (n=3201)	BMI score	 1. BMI <25 (underweight/normal) 2. BMI 25 - 29.99 (overweight) 3. BMI ≥30 (obese)	Mean(SD)=28.0(6.6) 35.3% 35.0% 29.7%
Smoking status (n=2376)	1. Current smoker 2. Former smoker 3. Never smoker	1. Current smoker 2. Current non-smoker	18.9% 81.1%

BMI indicates Body Mass Index;; LVEF, Left Ventricular Ejection Fraction; NYHA, New York Heart Association; and REF, Reduced Ejection Fraction.

Explanation of scoring comorbidity index

We would like to study the effect of comorbid conditions on effectiveness of self-management, since we expect patients with a higher comorbid burden to benefit less from self-management interventions. Yet, comorbidity has been collected very differently across the different studies. If we simply score the number of comorbidities as all comorbidities collected in a study, patients in studies collecting more diagnoses have a higher risk of having a higher comorbidity score (which biases the results).

We propose a recoding of comorbid diagnoses collected in each study into the following clusters:

1. Cardiovascular conditions
2. Endocrine conditions (incl. diabetes)
3. Neurological/psychiatric conditions
4. Respiratory conditions
5. Renal/hepatic/gastrointestinal conditions
6. Cancer
7. Musculoskeletal conditions

Patients will be scored on presence of a comorbid condition within each cluster. Clusters of comorbid conditions are based on the Cumulative Illness Rating Scale.[4]

We aim to score the comorbid burden of patients by categorizing patients in:

- No comorbid conditions
- Comorbid conditions in 1 cluster
- Comorbid conditions in ≥2 clusters

Data will be analyzed more in-depth in a descriptive manner to cautiously interpret any findings with regard to this comorbidity index.

4. Sensitivity analyses

Several sensitivity analyses will be performed to assess the robustness of the findings:

1. *Inclusion of aggregate data of studies for which IPD are unavailable:*
   To assess if IPD included are representative of all studies invited for this project, an aggregate data meta-analysis will be performed to assess the impact of missing studies on the main effect for each endpoint.
2. *Inclusion of only studies with a low risk of bias:*
   To assess whether methodological quality of studies has an impact on findings, the studies scoring a 'high risk of bias' on attrition bias on tool from the Cochrane Collaboration[5] will be left out of the analysis to assess the impact on the main effect for each endpoint.
3. *Inclusion of only complete cases:*
   To assess the effect of imputing missing data, all analyses will be repeated with a dataset containing only the patients for whom data are available. This will be performed for the analyses for main effects as well as patient-specific effect modifiers.
4. *Inclusion of continuous patient characteristics instead of categorized scores:*
   To assess the loss of information by categorizing continuous patient characteristics for the subgroup analysis, a sensitivity analysis is performed using the continuous data instead of categorized data for those patient characteristics. This applies to the effect modification of the variables age, % LVEF, years since diagnosis, and BMI.
5. *Inclusion of only newer studies (recruitment since 2000):*
   To assess of observed effects are robust over time, the sensitivity analysis will be repeated by only including more recently conducted studies (recruitment since 2000).
6. *Excluding the largest trial:**
   To assess if subgroup effects are attributable to a specific study (particularly the largest trial) or whether they can be generalized across studies, the subgroup analysis will be repeated without the largest trial.

**N.B: this sensitivity analysis was extended post hoc, by excluding each study one-by-one and repeating the subgroup analysis without that study (i.e., a leave-one-out analysis) to assess the impact of each study.*

Supplemental Table 1: Effects of self-management interventions on subordinate outcomes in patients with heart failure included in the individual patient data meta-analysis.

Outcome	N studies	n patients	Effect measure	Treatment effect (95% CI)
Heart failure-related outcomes				
HF-related QoL – 6 months	10	3419	SMD	0.13 (0.00-0.26)
HF-related hospitalization – 6 months	12	3742	RR	0.81 (0.66-0.99)
HF-related hospitalization – 12 months	11	3503	RR	0.82 (0.64-1.05)
Total days HF-related hospital stay – 6 months	8	1734	RLOS	0.67 (0.46-0.99)
General outcomes				
Generic QoL – PCS – 6 months	3	888	MD	1.13 (-2.25-4.52)
Generic QoL – MCS – 6 months	3	888	MD	1.89 (-2.90-6.68)
Mortality – 6 months	17	4999	RR	0.83 (0.66-1.05)
Mortality – 12 months	14	4204	RR	0.86 (0.72-1.03)
All-cause hospitalization – 6 months	14	4329	RR	0.92 (0.83-1.01)
All-cause hospitalization – 12 months	13	4266	RR	0.95 (0.87-1.04)
Total days all-cause hospital stay – 6 months	10	2820	RLOS	0.96 (0.74-1.25)

CI indicates confidence interval; HF, heart failure; MCS, mental component scale Short Form Health Survey; MD, mean difference; PCS, physical component scale Short Form Health Survey; QoL, quality of life; RLOS, relative length of stay; RR, risk ratio; and SMD, standardized mean difference.

Supplemental Table 2: Effects of self-management interventions on subordinate outcomes in subgroups of patients with heart failure included in the individual patient data meta-analysis.

Outcome	n patients	Effect measure	UNIVARIABLE ANALYSIS		MULTIVARIABLE ANALYSIS	
			Treatment effect (95% CI)	p-value for interaction	Treatment effect (95% CI)	p-value for interaction
Heart failure-related outcomes						
Subgroup						
HF-related QoL – 6 months						
No subgroup effects.						
HF-related hospitalization – 6 months						
No subgroup effects.						
HF-related hospitalization – 12 months						
NYHA I-II	1770	OR	0.81 (0.56-1.18)	0.06	*	
NYHA III	1323		0.90 (0.62-1.28)			
NYHA IV	410		0.44 (0.26-0.75)			
Total days HF-related hospital stay – 6 months						
<65 years	339	RLOS	0.24 (0.10-0.61)	0.06	*	
65-80 years	985		0.82 (0.45-1.48)			
>80 years	410		0.91 (0.39-2.12)			
General outcomes						
Subgroup						
Generic QoL – PCS – 6 months						
No subgroup effects.						
Generic QoL – MCS – 6 months						
No subgroup effects.						
Mortality – 6 months						
<65 years	1538	RR	1.32 (0.85-2.06)	0.02	1.32 (0.70-2.48)	0.07
65-80 years	2537		0.80 (0.61-1.06)		0.82 (0.47-1.43)	
>80 years	934		0.63 (0.45-0.89)		0.64 (0.36-1.16)	
No comorbidities	835	RR	0.87 (0.56-1.35)	0.02	1.32 (0.70-2.48)	0.02
Comorbidities in 1 cluster	1632		0.59 (0.44-0.79)		0.86 (0.50-1.48)	
Comorbidities in >1 cluster	1885		0.99 (0.77-1.27)		1.56 (0.92-2.66)	
Mortality – 12 months						
No subgroup effects.						
All-cause hospitalization – 6 months						
No subgroup effects.						
All-cause hospitalization – 12 months						
Not living alone	1555	RR	0.88 (0.78-0.99)	0.08	*	
Living alone	571		1.05 (0.87-1.27)			
Total days all-cause hospital stay – 6 months						
No subgroup effects.						

CI indicates confidence interval; HF, heart failure; MCS, mental component scale Short Form Health Survey; NYHA, New York Heart Association; OR, odds ratio; PCS, physical component scale Short Form Health Survey; QoL, quality of life; RLOS, relative length of stay; and RR, risk ratio.

Results of the subgroup analyses are only presented if a potential effect modifier showed an effect with $p<0.10$ in the univariable analysis.

*To adjust for other relevant effect modifiers, multivariable analysis was only performed if there were two or more potential effect modifiers in the univariable analysis.

Supplemental Table 3: Effects of self-management interventions on main outcomes in subgroups of patients with heart failure included in the individual patient data meta-analysis.

Outcome Subgroup	n patients	Effect measure	UNIVARIABLE ANALYSIS		MULTIVARIABLE ANALYSIS	
			Treatment effect (95% CI)	p-value for interaction	Treatment effect (95% CI)	p-value for interaction
Heart failure-related outcomes *Subgroup*						
HF-related hospitalization/ mortality – time to event						
No subgroup effects.						
HF-related QoL – 12 months						
No subgroup effects.						
HF-related hospitalization – time to event						
NYHA I-II	1579	HR	0.87 (0.70-1.08)	0.06	*	
NYHA III	1399		0.83 (0.68-1.03)			
NYHA IV	483		0.53 (0.37-0.77)			
Total days HF-related hospital stay – 12 months						
<65 years	139	RLOS	0.09 (0.02-0.38)	**0.03**	*	
65-80 years	521		0.95 (0.46-1.94)			
>80 years	232		0.96 (0.31-2.97)			
General outcomes *Subgroup*						
Generic QoL - PCS – 12 months						
No subgroup effects.						
Generic QoL - MCS – 12 months						
Current non-smokers	796	MD	-0.19 (-3.34-2.97)	0.09	*	
Current smokers	113		4.91 (-1.07-10.89)			
Mortality – time to event						
No/mild depression	1619	HR	0.86 (0.69-1.06)	**0.01**	*	
Moderate/severe depression	814		1.39 (1.06-1.83)			
All-cause hospitalization – time to event						
<65 years	1188	HR	1.09 (0.88-1.36)	0.07	0.93 (0.73-1.18)	0.35
65-80 years	1928		0.92 (0.75-1.15)		0.82 (0.69-0.98)	
>80 years	717		0.79 (0.60-1.04)		0.73 (0.57-0.95)	
Primary education	1283	HR	0.82 (0.71-0.96)	**0.02**	0.93 (0.73-1.18)	0.07
Secondary education	1110		0.98 (0.82-1.17)		1.09 (0.86-1.38)	
Higher education	653		1.26 (0.99-1.60)		1.33 (1.01-1.76)	
<1 year diagnosed	822	HR	1.13 (0.91-1.41)	0.08	†	
1-2 years diagnosed	168		1.61 (1.00-2.58)			
>2 years diagnosed	549		0.91 (0.72-1.14)			
Total days all-cause hospital stay – 12 months						
No subgroup effects.						

CI indicates confidence interval; HF, heart failure; HR, hazard ratio; MCS, mental component scale Short Form Health Survey; MD, mean difference; NYHA, New York Heart Association; PCS, physical component scale Short Form Health Survey; QoL, quality of life; and RLOS, relative length of stay.

*To adjust for other relevant effect modifiers, multivariable analysis was only performed if two or more potential effect modifiers in the univariable analysis were $p<0.10$.

†Years diagnosed not included as covariate in multivariable analysis since only N=1 study contained data on all covariates.

Supplemental Table 4: Sensitivity analysis on main outcomes by including published main effects of eligible studies without available individual patient data.

		Primary analysis (individual patient data only)			Pooled analysis of individual patient data and published effects		
	Effect	**Studies**	**Patients**	**Effect size (95% CI)**	**Studies**	**Patients**	**Effect size (95% CI)**
Heart failure-related outcomes							
HF-related hospitalization/ mortality - time to event	HR	10	3461	0.80 (0.71-0.89)	Published data could not be pooled		
HF-related QoL 12 months	SMD	11	3356	0.15 (0.00-0.30)	17	4370	0.14 (0.03-0.26)
HF-related hospitalization time to event	HR	10	3461	0.80 (0.69-0.92)	12	4327	0.79 (0.69-0.90)
Total days HF-related hospital stay - 12 months	RLOS	5	892	0.86 (0.44-1.67)	Published data could not be pooled		
General outcomes							
Generic QoL - PCS 12 months	MD	8	1739	0.95 (-1.15-3.05)	Published data could not be pooled		
Generic QoL - MCS 12 months	MD	8	1739	0.27 (-2.53-3.08)	Published data could not be pooled		
Mortality time to event	HR	14	4312	0.91 (0.79-1.04)	17	5326	0.89 (0.78-1.01)
All-cause hospitalization time to event	HR	12	3833	0.93 (0.85-1.03)	14	4699	0.93 (0.85-1.00)
Total days all-cause hospital stay - 12 months	RLOS	9	2304	0.97 (0.77-1.23)	Published data could not be pooled		

CI indicates confidence interval; MCS, mental component scale Short Form Health Survey; MD, mean difference; PCS, physical component scale Short Form Health Survey; QoL, quality of life; RLOS, relative length of stay; RR, risk ratio; and SMD, standardized mean difference.

Supplemental Table 5: Sensitivity analysis on main outcomes by excluding trials with enhanced usual care in the comparison group.

		Primary analysis (all studies included)				Analysis without DeWalt, 2012[6] & Heisler, 2013[7]			
	Effect	**Stu-dies**	**Pa-tient**	**Effect size (95% CI)**	I^2	**Stu-dies**	**Pa-tient**	**Effect size (95% CI)**	I^2
Heart failure-related outcomes									
HF-related hospitalization/ mortality - time to event	HR	10	3461	0.80 (0.71-0.89)	51.6%	9	2856	0.78 (0.69-0.88)	53.2%
HF-related QoL 12 months	SMD	11	3356	0.15 (0.00-0.30)	43.6%	10	2751	0.16 (-0.02-0.34)	48.7%
HF-related hospitalization time to event	HR	10	3461	0.80 (0.69-0.92)	60.8%	9	2856	0.76 (0.66-0.89)	59.7%
Total days HF-related hospital stay - 12 months	RLOS	5	892	0.86 (0.44-1.67)	0.0%	No outcomes reported by DeWalt/Heisler			
General outcomes									
Generic QoL - PCS 12 months	MD	8	1739	0.95 (-1.15-3.05)	0.0%	No outcomes reported by DeWalt/Heisler			
Generic QoL - MCS 12 months	MD	8	1739	0.27 (-2.53-3.08)	0.0%	No outcomes reported by DeWalt/Heisler			
Mortality time to event	HR	14	4312	0.91 (0.79-1.04)	43.8%	12	3441	0.87 (0.76-1.00)	24.4%
All-cause hospitalization time to event	HR	12	3833	0.93 (0.85-1.03)	53.1%	10	2962	0.89 (0.80-0.99)	49.6%
Total days all-cause hospital stay - 12 months	RLOS	9	2304	0.97 (0.77-1.23)	82.2%	7	1443	0.90 (0.68-1.20)	86.3%

CI indicates confidence interval; MCS, mental component scale Short Form Health Survey; MD, mean difference; PCS, physical component scale Short Form Health Survey; QoL, quality of life; RLOS, relative length of stay; RR, risk ratio; and SMD, standardized mean difference.

Supplemental References

1. Groothuis-Oudshoorn K, van Buuren S. MICE: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software.* 2011;45.
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SUPPLEMENTAL MATERIAL

Do self-management interventions work in patients with heart failure work?
An individual patient data meta-analysis

Page	Content
2	**Supplemental Methods:** Statistical analysis plan
6	**Supplemental Table 1:** Effects of self-management interventions on subordinate outcomes in patients with heart failure included in the individual patient data meta-analysis.
7	**Supplemental Table 2:** Effects of self-management interventions on subordinate outcomes in subgroups of patients with heart failure included in the individual patient data meta-analysis.
8	**Supplemental Table 3:** Effects of self-management interventions on main outcomes in subgroups of patients with heart failure included in the individual patient data meta-analysis.
9	**Supplemental Table 4:** Sensitivity analysis on main outcomes by including published main effects of eligible studies without available individual patient data.
10	**Supplemental Table 5:** Sensitivity analysis on main outcomes by excluding trials with enhanced usual care in the comparison group.
11	**Supplemental References**

Supplemental Methods: Statistical analysis plan

This document contains the plan for the statistical analysis for the individual patient data (IPD) meta-analysis in heart failure (HF) patients. Input from the conference calls on March 20th, 2014 and March 31st, 2014 and email contact has been processed in the statistical plan presented in this document.

A schematic overview of the statistical analysis is present in Figure 1. Each step will be explained in more detail in the subsequent paragraphs. For all statistical analyses, the software R for Windows version 3.1.1 (R Development Core Team. Released 2013. Vienna, Austria: R Foundation for Statistical Computing) will be used.

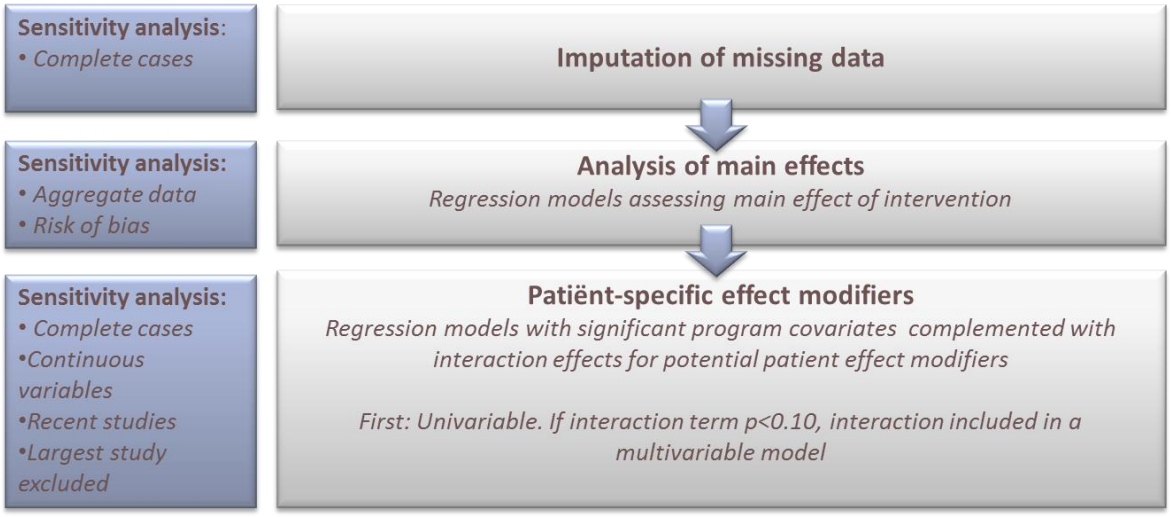

Figure 1: Steps of the statistical analysis of patient-specific determinants of self-management interventions.

1. Imputation of missing data

To address bias due to missing data, we will impute missing data using multiple imputation by chained equations (MICE).[1] The MICE algorithm accounts for the order in which the values of separate variables are predicted through chained equations. To address the uncertainty of just one single imputation, MICE creates multiple imputations, resulting in multiple imputed datasets.

The imputation will be performed according to the following principles:

- Missing values will only be imputed *within* studies: this implies that only the correlation between variables available within one study will be used to estimate the missing values in that particular study
- All available variables (except patient identifiers) will be used to estimate missing values
- Multiple imputation will be used to estimate missing values for patient characteristics and outcomes
- Multiple imputation will be performed 25 times, resulting in 25 imputed datasets
- As a result, all analyses will be carried out 25 times. Results will be pooled using Rubin's rule for the final results.[2]

A complete-case analysis, using only the available patient data, will be performed as a sensitivity analysis to assess the impact of imputing data (see '4. Sensitivity analyses').

2. Analysis of main effects

All data will be analyzed according to the intention-to-treat principle. A so-called one-stage approach will be used, where all patients are analyzed simultaneously in one model while clustering of observations within studies is taken into account.[3]

The present study will analyze the following main outcome measures:

- Composite of time to first disease-related hospital admission or all-cause death;
- Change in health-related quality of life (HRQoL) at 12 months, compared to baseline;
    - A distinction will be made between disease-specific and generic HRQoL to address the different instruments used by original studies
- Time to first disease-related hospital admission;
- Total number of days spent in hospital for HF at 12 months.
- Time to all-cause death;
- Time to first all-cause hospital admission;
- Total number of days spent in hospital for any cause at 12 months.

Additionally, the following subordinate outcomes measures will be analyzed:

- Change in health-related quality of life (HRQoL) at 6 months, compared to baseline;
    - A distinction will be made between disease-specific and generic HRQoL
- Total number of days spent in hospital for HF at 6 months and at 12 months;
- Hospitalized for HF at 6 months;
- All-cause mortality at 6 months and at 12 months;
- Hospitalized for any cause at 6 months and at 12 months;
- Total number of days spent in hospital for any cause at 6 months.

For time-to-event data, effects of self-management will be quantified by estimating hazard ratios (HR) and 95% confidence interval (CI). Cox proportional-hazard models will be used to analyze the data, including a cluster statement to allow inter study variability. For binary outcome data (mortality, all-cause and disease-related hospital admissions), risk ratios (RR) and 95% CI will be estimated using log-binomial mixed effects models. Effects on continuous outcomes (HRQoL) will be quantified by mean differences and 95% CI and will be estimated using linear mixed effects models. Effects on total length of hospital stay will be analyzed with negative binomial mixed effects models to model overdispersion in the data. In the (generalized) linear mixed effects models, random intercepts and random slopes will be included to take clustering within studies into account.

3. Patient-specific effect modifiers

The aforementioned models will be extended to study effect modification by patient characteristics. Effect modification implies that the effect of the intervention on an outcome differs depending on the value of a third variable, the effect modifier. As such, we will be able to identify subgroups of patients in which self-management interventions work best. Interaction terms will be included in the final model resulting from the previous step, which includes the significant program determinants.

We have selected clinically relevant patient characteristics as potential effect modifiers, these are presented in Table 1. Numbers of patients differ per variable due to the fact that some baseline variables have not been collected in one (or more) studies. We would like to categorize the variables to create relevant subgroups for the interpretation of findings. This has been discussed extensively during the conference calls, and the proposed categories are a result of the discussions.

Like the analysis of program characteristics, patient characteristics with $p<0.10$ in the separate analyses will be fitted together in a multivariable model. Effect modifiers will be presented with 95% confidence intervals. Results will be interpreted with great caution to decrease the risk of type I error (i.e. descriptive analysis, consistency with expectations, other findings).

After consulting the investigators during the conference calls we have decided to exclude baseline ***self-efficacy level*** of patients from the analysis. This variable has only been collected in 4 studies (n=1321), each using a different instrument.

Table 1: Patient characteristics to be analyzed as potential effect modifiers.

Determinant	Data in database	Proposed categories for analysis	Statistics in database
Sex (n=5624)	1. Male 2. Female	1. Male 2. Female	57.2% 42.8%
Age (n=5624)	Years	 1. <65 years 2. 65-80 years 3. >80 years	Mean(SD)=69.7(12.4) 30.5% 50.7% 18.9%
Disease severity (n=3562)	% LVEF	 1. ≤35% LVEF (REF) 2. >35% LVEF (based on ESC Guidelines 2012)	Mean(SD)=39.2(18.2) 52.0% 48.0%
Symptom severity (n=5328)	NYHA class (I-IV)	1. NYHA I & II 2. NYHA III 3. NYHA IV	46.1% 36.9% 17.0%
Comorbidity index (n=5079)	# of clusters of comorbid conditions	1. No comorbid conditions 2. Comorbid conditions in 1 cluster 3. Comorbid conditions in ≥2 clusters	*Categories still to be calculated for each individual study*
Depression (n=2998)	Score on instrument	1. No/mild depression 2. Moderate/severe depression (based on validated cut-offs of each instrument)	*Cut-offs still to be calculated for each individual study*
Level of education (n=4216)	1. Primary or below 2. Secondary 3. Higher	1. Primary or below 2. Secondary 3. Higher	40.7% 39.1% 20.1%
Years since diagnosis (n=2310)	Months/Years/Categories	 1. <1 year diagnosed 2. 1 -<2 years diagnosed 3. ≥2 years diagnosed	Median(IQR)=1.6(0.1-5.4) 44.1% 12.5% 43.4%
Living status (n=2883)	1. Living alone 2. Not living alone	1. Living alone 2. Not living alone	25.8% 74.2%
Body Mass Index (n=3201)	BMI score	 1. BMI <25 (underweight/normal) 2. BMI 25 - 29.99 (overweight) 3. BMI ≥30 (obese)	Mean(SD)=28.0(6.6) 35.3% 35.0% 29.7%
Smoking status (n=2376)	1. Current smoker 2. Former smoker 3. Never smoker	1. Current smoker 2. Current non-smoker	18.9% 81.1%

BMI indicates Body Mass Index;; LVEF, Left Ventricular Ejection Fraction; NYHA, New York Heart Association; and REF, Reduced Ejection Fraction.

Explanation of scoring comorbidity index

We would like to study the effect of comorbid conditions on effectiveness of self-management, since we expect patients with a higher comorbid burden to benefit less from self-management interventions. Yet, comorbidity has been collected very differently across the different studies. If we simply score the number of comorbidities as all comorbidities collected in a study, patients in studies collecting more diagnoses have a higher risk of having a higher comorbidity score (which biases the results).

We propose a recoding of comorbid diagnoses collected in each study into the following clusters:

1. Cardiovascular conditions
2. Endocrine conditions (incl. diabetes)
3. Neurological/psychiatric conditions
4. Respiratory conditions
5. Renal/hepatic/gastrointestinal conditions
6. Cancer
7. Musculoskeletal conditions

Patients will be scored on presence of a comorbid condition within each cluster. Clusters of comorbid conditions are based on the Cumulative Illness Rating Scale.[4]

We aim to score the comorbid burden of patients by categorizing patients in:

- No comorbid conditions
- Comorbid conditions in 1 cluster
- Comorbid conditions in ≥2 clusters

Data will be analyzed more in-depth in a descriptive manner to cautiously interpret any findings with regard to this comorbidity index.

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Several sensitivity analyses will be performed to assess the robustness of the findings:

1. *Inclusion of aggregate data of studies for which IPD are unavailable:*
   To assess if IPD included are representative of all studies invited for this project, an aggregate data meta-analysis will be performed to assess the impact of missing studies on the main effect for each endpoint.
2. *Inclusion of only studies with a low risk of bias:*
   To assess whether methodological quality of studies has an impact on findings, the studies scoring a 'high risk of bias' on attrition bias on tool from the Cochrane Collaboration[5] will be left out of the analysis to assess the impact on the main effect for each endpoint.
3. *Inclusion of only complete cases:*
   To assess the effect of imputing missing data, all analyses will be repeated with a dataset containing only the patients for whom data are available. This will be performed for the analyses for main effects as well as patient-specific effect modifiers.
4. *Inclusion of continuous patient characteristics instead of categorized scores:*
   To assess the loss of information by categorizing continuous patient characteristics for the subgroup analysis, a sensitivity analysis is performed using the continuous data instead of categorized data for those patient characteristics. This applies to the effect modification of the variables age, % LVEF, years since diagnosis, and BMI.
5. *Inclusion of only newer studies (recruitment since 2000):*
   To assess of observed effects are robust over time, the sensitivity analysis will be repeated by only including more recently conducted studies (recruitment since 2000).
6. *Excluding the largest trial:**
   To assess if subgroup effects are attributable to a specific study (particularly the largest trial) or whether they can be generalized across studies, the subgroup analysis will be repeated without the largest trial.

**N.B: this sensitivity analysis was extended post hoc, by excluding each study one-by-one and repeating the subgroup analysis without that study (i.e., a leave-one-out analysis) to assess the impact of each study.*

Supplemental Table 1: Effects of self-management interventions on subordinate outcomes in patients with heart failure included in the individual patient data meta-analysis.

Outcome	N studies	n patients	Effect measure	Treatment effect (95% CI)
Heart failure-related outcomes				
HF-related QoL – 6 months	10	3419	SMD	0.13 (0.00-0.26)
HF-related hospitalization – 6 months	12	3742	RR	0.81 (0.66-0.99)
HF-related hospitalization – 12 months	11	3503	RR	0.82 (0.64-1.05)
Total days HF-related hospital stay – 6 months	8	1734	RLOS	0.67 (0.46-0.99)
General outcomes				
Generic QoL – PCS – 6 months	3	888	MD	1.13 (-2.25-4.52)
Generic QoL – MCS – 6 months	3	888	MD	1.89 (-2.90-6.68)
Mortality – 6 months	17	4999	RR	0.83 (0.66-1.05)
Mortality – 12 months	14	4204	RR	0.86 (0.72-1.03)
All-cause hospitalization – 6 months	14	4329	RR	0.92 (0.83-1.01)
All-cause hospitalization – 12 months	13	4266	RR	0.95 (0.87-1.04)
Total days all-cause hospital stay – 6 months	10	2820	RLOS	0.96 (0.74-1.25)

CI indicates confidence interval; HF, heart failure; MCS, mental component scale Short Form Health Survey; MD, mean difference; PCS, physical component scale Short Form Health Survey; QoL, quality of life; RLOS, relative length of stay; RR, risk ratio; and SMD, standardized mean difference.

Supplemental Table 2: Effects of self-management interventions on subordinate outcomes in subgroups of patients with heart failure included in the individual patient data meta-analysis.

Outcome	n patients	Effect measure	UNIVARIABLE ANALYSIS		MULTIVARIABLE ANALYSIS	
			Treatment effect (95% CI)	p-value for interaction	Treatment effect (95% CI)	p-value for interaction
Heart failure-related outcomes						
Subgroup						
HF-related QoL – 6 months						
No subgroup effects.						
HF-related hospitalization – 6 months						
No subgroup effects.						
HF-related hospitalization – 12 months						
NYHA I-II	1770	OR	0.81 (0.56-1.18)	0.06	*	
NYHA III	1323		0.90 (0.62-1.28)			
NYHA IV	410		0.44 (0.26-0.75)			
Total days HF-related hospital stay – 6 months						
<65 years	339	RLOS	0.24 (0.10-0.61)	0.06	*	
65-80 years	985		0.82 (0.45-1.48)			
>80 years	410		0.91 (0.39-2.12)			
General outcomes						
Subgroup						
Generic QoL – PCS – 6 months						
No subgroup effects.						
Generic QoL – MCS – 6 months						
No subgroup effects.						
Mortality – 6 months						
<65 years	1538	RR	1.32 (0.85-2.06)	0.02	1.32 (0.70-2.48)	0.07
65-80 years	2537		0.80 (0.61-1.06)		0.82 (0.47-1.43)	
>80 years	934		0.63 (0.45-0.89)		0.64 (0.36-1.16)	
No comorbidities	835	RR	0.87 (0.56-1.35)	0.02	1.32 (0.70-2.48)	0.02
Comorbidities in 1 cluster	1632		0.59 (0.44-0.79)		0.86 (0.50-1.48)	
Comorbidities in >1 cluster	1885		0.99 (0.77-1.27)		1.56 (0.92-2.66)	
Mortality – 12 months						
No subgroup effects.						
All-cause hospitalization – 6 months						
No subgroup effects.						
All-cause hospitalization – 12 months						
Not living alone	1555	RR	0.88 (0.78-0.99)	0.08	*	
Living alone	571		1.05 (0.87-1.27)			
Total days all-cause hospital stay – 6 months						
No subgroup effects.						

CI indicates confidence interval; HF, heart failure; MCS, mental component scale Short Form Health Survey; NYHA, New York Heart Association; OR, odds ratio; PCS, physical component scale Short Form Health Survey; QoL, quality of life; RLOS, relative length of stay; and RR, risk ratio.

Results of the subgroup analyses are only presented if a potential effect modifier showed an effect with $p<0.10$ in the univariable analysis.

*To adjust for other relevant effect modifiers, multivariable analysis was only performed if there were two or more potential effect modifiers in the univariable analysis.

Supplemental Table 3: Effects of self-management interventions on main outcomes in subgroups of patients with heart failure included in the individual patient data meta-analysis.

Outcome Subgroup	n patients	Effect measure	UNIVARIABLE ANALYSIS		MULTIVARIABLE ANALYSIS	
			Treatment effect (95% CI)	p-value for interaction	Treatment effect (95% CI)	p-value for interaction
Heart failure-related outcomes *Subgroup*						
HF-related hospitalization/ mortality – time to event						
No subgroup effects.						
HF-related QoL – 12 months						
No subgroup effects.						
HF-related hospitalization – time to event						
NYHA I-II	1579	HR	0.87 (0.70-1.08)	0.06	*	
NYHA III	1399		0.83 (0.68-1.03)			
NYHA IV	483		0.53 (0.37-0.77)			
Total days HF-related hospital stay – 12 months						
<65 years	139	RLOS	0.09 (0.02-0.38)	**0.03**	*	
65-80 years	521		0.95 (0.46-1.94)			
>80 years	232		0.96 (0.31-2.97)			
General outcomes *Subgroup*						
Generic QoL - PCS – 12 months						
No subgroup effects.						
Generic QoL - MCS – 12 months						
Current non-smokers	796	MD	-0.19 (-3.34-2.97)	0.09	*	
Current smokers	113		4.91 (-1.07-10.89)			
Mortality – time to event						
No/mild depression	1619	HR	0.86 (0.69-1.06)	**0.01**	*	
Moderate/severe depression	814		1.39 (1.06-1.83)			
All-cause hospitalization – time to event						
<65 years	1188	HR	1.09 (0.88-1.36)	0.07	0.93 (0.73-1.18)	0.35
65-80 years	1928		0.92 (0.75-1.15)		0.82 (0.69-0.98)	
>80 years	717		0.79 (0.60-1.04)		0.73 (0.57-0.95)	
Primary education	1283	HR	0.82 (0.71-0.96)	**0.02**	0.93 (0.73-1.18)	0.07
Secondary education	1110		0.98 (0.82-1.17)		1.09 (0.86-1.38)	
Higher education	653		1.26 (0.99-1.60)		1.33 (1.01-1.76)	
<1 year diagnosed	822	HR	1.13 (0.91-1.41)	0.08	†	
1-2 years diagnosed	168		1.61 (1.00-2.58)			
>2 years diagnosed	549		0.91 (0.72-1.14)			
Total days all-cause hospital stay – 12 months						
No subgroup effects.						

CI indicates confidence interval; HF, heart failure; HR, hazard ratio; MCS, mental component scale Short Form Health Survey; MD, mean difference; NYHA, New York Heart Association; PCS, physical component scale Short Form Health Survey; QoL, quality of life; and RLOS, relative length of stay.

*To adjust for other relevant effect modifiers, multivariable analysis was only performed if two or more potential effect modifiers in the univariable analysis were $p<0.10$.

†Years diagnosed not included as covariate in multivariable analysis since only N=1 study contained data on all covariates.

Supplemental Table 4: Sensitivity analysis on main outcomes by including published main effects of eligible studies without available individual patient data.

		Primary analysis (individual patient data only)			Pooled analysis of individual patient data and published effects		
	Effect	**Studies**	**Patients**	**Effect size (95% CI)**	**Studies**	**Patients**	**Effect size (95% CI)**
Heart failure-related outcomes							
HF-related hospitalization/ mortality - time to event	HR	10	3461	0.80 (0.71-0.89)	Published data could not be pooled		
HF-related QoL 12 months	SMD	11	3356	0.15 (0.00-0.30)	17	4370	0.14 (0.03-0.26)
HF-related hospitalization time to event	HR	10	3461	0.80 (0.69-0.92)	12	4327	0.79 (0.69-0.90)
Total days HF-related hospital stay - 12 months	RLOS	5	892	0.86 (0.44-1.67)	Published data could not be pooled		
General outcomes							
Generic QoL - PCS 12 months	MD	8	1739	0.95 (-1.15-3.05)	Published data could not be pooled		
Generic QoL - MCS 12 months	MD	8	1739	0.27 (-2.53-3.08)	Published data could not be pooled		
Mortality time to event	HR	14	4312	0.91 (0.79-1.04)	17	5326	0.89 (0.78-1.01)
All-cause hospitalization time to event	HR	12	3833	0.93 (0.85-1.03)	14	4699	0.93 (0.85-1.00)
Total days all-cause hospital stay - 12 months	RLOS	9	2304	0.97 (0.77-1.23)	Published data could not be pooled		

CI indicates confidence interval; MCS, mental component scale Short Form Health Survey; MD, mean difference; PCS, physical component scale Short Form Health Survey; QoL, quality of life; RLOS, relative length of stay; RR, risk ratio; and SMD, standardized mean difference.

Supplemental Table 5: Sensitivity analysis on main outcomes by excluding trials with enhanced usual care in the comparison group.

		Primary analysis (all studies included)				Analysis without DeWalt, 2012[6] & Heisler, 2013[7]			
	Effect	**Stu-dies**	**Pa-tient**	**Effect size (95% CI)**	I^2	**Stu-dies**	**Pa-tient**	**Effect size (95% CI)**	I^2
Heart failure-related outcomes									
HF-related hospitalization/ mortality - time to event	HR	10	3461	0.80 (0.71-0.89)	51.6%	9	2856	0.78 (0.69-0.88)	53.2%
HF-related QoL 12 months	SMD	11	3356	0.15 (0.00-0.30)	43.6%	10	2751	0.16 (-0.02-0.34)	48.7%
HF-related hospitalization time to event	HR	10	3461	0.80 (0.69-0.92)	60.8%	9	2856	0.76 (0.66-0.89)	59.7%
Total days HF-related hospital stay - 12 months	RLOS	5	892	0.86 (0.44-1.67)	0.0%	No outcomes reported by DeWalt/Heisler			
General outcomes									
Generic QoL - PCS 12 months	MD	8	1739	0.95 (-1.15-3.05)	0.0%	No outcomes reported by DeWalt/Heisler			
Generic QoL - MCS 12 months	MD	8	1739	0.27 (-2.53-3.08)	0.0%	No outcomes reported by DeWalt/Heisler			
Mortality time to event	HR	14	4312	0.91 (0.79-1.04)	43.8%	12	3441	0.87 (0.76-1.00)	24.4%
All-cause hospitalization time to event	HR	12	3833	0.93 (0.85-1.03)	53.1%	10	2962	0.89 (0.80-0.99)	49.6%
Total days all-cause hospital stay - 12 months	RLOS	9	2304	0.97 (0.77-1.23)	82.2%	7	1443	0.90 (0.68-1.20)	86.3%

CI indicates confidence interval; MCS, mental component scale Short Form Health Survey; MD, mean difference; PCS, physical component scale Short Form Health Survey; QoL, quality of life; RLOS, relative length of stay; RR, risk ratio; and SMD, standardized mean difference.

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