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Pharmacy-based interdisciplinary intervention for patients with chronic heart failure: results of the PHARM-CHF randomized controlled trial

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Aims	Medication non-adherence is frequent and is associated with high morbidity and mortality in patients with chronic heart failure (CHF). We investigated whether an interdisciplinary intervention improves adherence in elderly CHF patients.
Methods and results	The study population (mean age 74 years, 62% male, mean left ventricular ejection fraction 47%, 52% in New York Heart Association class III) consisted of 110 patients randomized into the pharmacy care and 127 into the usual care group. The median follow-up was 2.0 years (interquartile range 1.2–2.7). The pharmacy care group received a medication review followed by regular dose dispensing and counselling. Control patients received usual care. The primary endpoint was medication adherence as proportion of days covered (PDC) within 365 days for three classes of heart failure medications (beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and mineralocorticoid receptor antagonists). The main secondary outcome was the proportion of adherent patients (PDC $\geq$ 80%). The primary safety endpoint was days lost due to unplanned cardiovascular hospitalizations (blindly adjudicated) or death. Pharmacy care compared with usual care resulted in an absolute increase in mean adherence to three heart failure medications for 365 days [adjusted difference 5.7%, 95% confidence interval (CI) 1.6–9.8, $P = 0.007$]. The proportion of patients classified as adherent increased (odds ratio 2.9, 95% CI 1.4–5.9, $P = 0.005$). Pharmacy care improved quality of life after 2 years (adjusted difference in Minnesota Living with Heart Failure Questionnaire scores -7.8 points (-14.5 to -1.1; $P = 0.02$), compared to usual care. Pharmacy care did not affect the safety endpoints of hospitalizations or deaths.
Conclusion	Pharmacy care safely improved adherence to heart failure medications and quality of life.
Keywords	Chronic heart failure • Medication adherence • Community pharmacy services • Interdisciplinary care • Randomized controlled trial • Pharmacy care

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Introduction

Heart failure (HF) is an increasingly prevalent condition, limiting functional capacity associated with impaired quality of life and mortality imposing a high burden on health care systems.[1] Guideline-directed pharmacotherapy decreases morbidity and mortality in patients with HF with reduced ejection fraction. Guidelines recommend the use of diuretics for symptom relief and appropriate management of co-morbidities in patients with HF with preserved or mid-range ejection fraction.[2] Non-adherence to pharmacotherapy, however, affects 20−50% of all patients, and affects morbidity and mortality in patients with chronic HF (CHF).[3−5] Patients with CHF often receive additional drugs for co-morbidities leading to polypharmacy with an increased risk of drug-related problems (DRPs).[6,7] DRPs are potentially preventable by interdisciplinary advise involving physicians and pharmacists. These efforts appear to be successful when the pharmacist acts as part of a multidisciplinary team.[8] However, there are no pharmacy-based randomized controlled trials (RCT) aiming to improve medication adherence in elderly CHF patients by structured, regular and long-term patient contacts. HF is associated with impaired quality of life (QoL), but few RCTs have provided evidence with regard to interventions improving QoL.[9] PHARM-CHF investigated whether an interdisciplinary intervention consisting of regular contacts with the local pharmacy and weekly dosing aids improves medication adherence and QoL in elderly patients with CHF, and whether it affects hospitalizations and mortality.

Methods

Study design and participants

PHARM-CHF was an investigator-initiated, prospective multicentre, randomized controlled study. The study design has been published previously.[10] In brief, patients aged 60 years and older with CHF defined by HF symptoms, currently treated with a diuretic, and a hospitalization for HF within the last 12 months or increased B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide concentrations, were recruited by study physicians. After choosing the attending community pharmacy, patients were randomized via a secure web interface tool (www.pharm-chf.de) in a 1:1 ratio to the intervention (pharmacy care) or control group (usual care). The PHARM-CHF trial was conducted according to the principles stated in the current version of the Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practice (GCP), and to local and national regulations. Documented approvals from independent ethics committees were obtained for all participating centres and written informed consent from all patients. The study is registered with ClinicalTrials.gov, identifier: NCT 01692119.

Study protocol

Details on study visits, data collection, intervention, and standardization were previously described.[10] In brief, the intervention consisted of the following components: first, medication review (Type 2a according to the Pharmaceutical Care Network Europe (PCNE) classification[11])

in the community pharmacy at baseline with the aim of generating a consolidated medication plan. This included the following:

- compilation of the patient's entire medication (based on the physician's medication list, documented drug dispensing in the pharmacy, and patient interview in the pharmacy),
- check for DRPs such as drug interactions and double medications using a standardized check-list, and
- contact with the physician to discuss problems and risks if necessary.

Based on the subsequently consolidated medication plan, the patient received a weekly dosing aid together with a printout of the medication plan. The type of the dosing aid (dosette, pill-box) was at the discretion of the pharmacist and in agreement with the patient. Pharmacy care continued by (bi-)weekly visits to the local pharmacy including:

- updating the medication plan if necessary,
- receiving the supply of medicines in dosing aids filled by the pharmacist for 1 or 2 weeks,
- counselling regarding medication, adherence, potential side effects, signs and symptoms of decompensation,
- measurement of blood pressure and pulse rate,
- in case of newly detected DRP and/or significant changes in vital signs, contact with the physician.

Patients in the usual care group continued to visit pharmacies of their choice to fill prescriptions without further intervention. Usual care mainly consisted of dispensing prescribed medication, including counselling by the pharmacist or pharmacy technician on the safe and appropriate use of the drug. Medication review, measuring blood pressure and pulse rate or providing medication in a weekly dosing aid are neither part of usual care nor reimbursed.

Study endpoints

The primary efficacy endpoint was medication adherence, defined as a significant difference between the pharmacy care and usual care groups using pharmacy claims data during the 365 days following randomization for three HF medication classes [beta-blockers, angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists (MRA)] prescribed at baseline. Adherence was calculated using the proportion of days covered (PDC), which is the ratio of number of days in the period covered by a medicine (numerator) to the total number of days in the observation period (denominator).

The main secondary efficacy endpoint was the proportion of patients classified as adherent (mean PDC $\geq$ 80%). We further analysed the PDC for each drug class (beta-blockers, ACEi/ARB, MRA), and the percentages of patients with a PDC $\geq$ 80% for each drug class for the periods of 365 as well as 730 days post-randomization.

Data collection, use of information and calculating the PDC were the same in both groups and for all time-periods analysed. Health insurance companies and data processing centres provided claims data of prescribed drugs, dispensed at community pharmacies. These data included information on the active ingredient(s), the dosage per unit (strength), the package size, and the dispensing date. For all patients, the information on the daily dose documented by the study physician in the electronic case report form was used. Medication

Figure 1 Trial flowchart. mITT, modified intention to treat population.
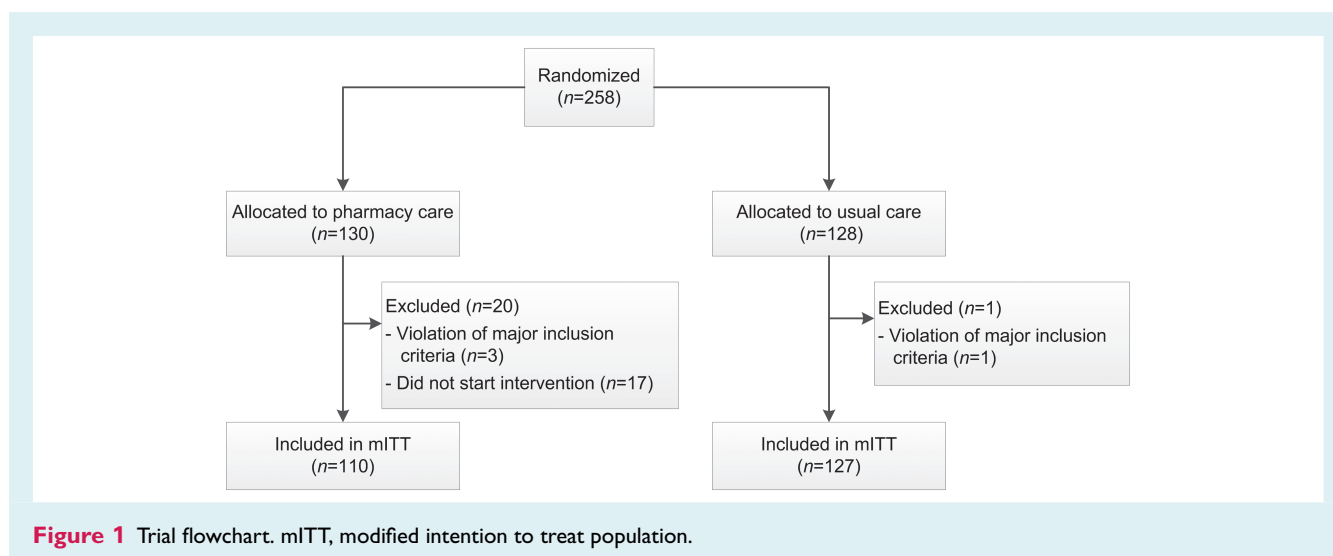
switches, stockpiling, hospital stays, medication fills prior to randomization, and death were considered. To measure baseline adherence, the PDC for the period 183 days before randomization was analysed. In case of inpatient days, the proportion was adjusted by excluding days from both the numerator and denominator assuming that patients did not deplete their medication on their medication supply on those excluded days. If a patient switched medications within a class (including ACEi/ARB), the patient's medication supply was replaced with the new medication supply. If a patient died, all days following the death were censored. Existing medication at randomization and medication dispensed during 14 days after randomization were considered if at least one additional dispensing occurred during the 365-day follow-up. Existing medication at randomization was captured, but only the days during the 365-day follow-up contributed to the final proportion.

Other secondary efficacy endpoints included QoL, depression, and Patient Global Assessment (PGA). QoL was measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) at baseline, and after 12 and 24 months. Depression was assessed using the 9-item Patient Health Questionnaire (PHQ-9).[12] Patients were characterized (dichotomized) as non-depressed (< 10 points) and as suspected to currently have depression (≥ 10 points).

The primary composite safety endpoint was days lost due to unplanned cardiovascular hospitalizations (blindly adjudicated) or all-cause death. Secondary safety endpoints were percentage of days lost due to unplanned cardiovascular hospitalizations or death of any cause, all-cause mortality or unplanned cardiovascular hospitalizations as recurrent event, unplanned cardiovascular hospitalizations, unplanned hospitalizations for HF, days lost due to hospitalizations of any cause or death, unplanned all-cause hospitalizations, and all-cause mortality.[10]

Sensitivity analyses

Pre-specified subgroup analyses were performed for age, sex, New York Heart Association class, level of illness burden, diabetes, depression, heart rate, HF medication, time between last HF hospitalization and randomization, and QoL as previously defined.[10]

Statistical analyses

Assuming a mean PDC before randomization of approximately 70%, a sample size of 176 patients (88 per group) was calculated to detect a 10% [standard deviation (SD) 22%] improvement of the mean PDC between the intervention and the usual care group with a power of 85% and an alpha of 5%.[10]

The primary and secondary efficacy and safety analyses were performed as described. Baseline characteristics are summarized as number of patients (%) for categorical variables and as mean (SD) or median [interquartile range (IQR)] for continuous variables. For continuous variables such as the PDC or the MLHFQ score, changes in means of both study groups at 12 and 24 months were compared by ANCOVA models adjusted for the baseline value. Odds ratios (OR) for a PDC ≥ 80% between groups were calculated via logistic regression, adjusting for the baseline PDC. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). PDC calculations were performed using Microsoft SQL 2016.

Results

The study was performed at 31 sites (general practitioners, internal medicine specialists, and both office- and hospital-based cardiologists) and 69 community pharmacies in nine different Federal States of Germany.[10] In total, 258 patients were recruited between October 2012 and January 2016, and 130 were randomized to the pharmacy care group and 128 into the usual care group. In this interdisciplinary study, randomization was performed by the physician without involvement of a pharmacist but the intervention was delivered by the pharmacy. Three patients in the pharmacy care and one patient in the usual care group were excluded because of major protocol violations (i.e. patients were not prescribed a diuretic as required).[10] Furthermore, due to the nature of the pharmacy care intervention, we defined the intention to treat (ITT) analyses as those who completed randomization by attending their pharmacy – a modified ITT (mITT). For various reasons, 17 patients randomized into the pharmacy care group by their physician did not present to a participating pharmacy. According to the pre-specified

Table 1 Baseline characteristics of the participants in the PHARM-CHF study

Characteristic	Pharmacy care (n = 110)	Usual care (n = 127)
Demographics		
Age, years, mean ± SD	74.1 ± 6.8	74.1 ± 7.2
Female sex, n (%)	42 (38)	49 (39)
Physical examination, mean ± SD		
BMI, kg/m^2	29.0 ± 5.2	29.2 ± 4.9
Systolic blood pressure, mmHg	127.1 ± 17.0	129.4 ± 15.5
Diastolic blood pressure, mmHg	76.0 ± 10.9	77.3 ± 9.9
Heart rate, b.p.m.	73.5 ± 13.2	75.8 ± 13.8
Heart failure characteristics		
Heart failure aetiology, n (%)		
Ischaemic	65 (59)	61 (48)
Non-ischaemic	36 (33)	49 (39)
Other	9 (8)	17 (13)
LVEF[a], %, mean ± SD (n = 91/104)	47.1 ± 15.1	46.4 ± 14.1
LVEF < 40%, n (%)	27 (25)	31 (24)
LVEF 40–49%, n (%)	40 (36)	49 (39)
LVEF ≥ 50%, n (%)	43 (39)	47 (37)
NYHA class, n (%)		
I	7 (6)	6 (5)
II	38 (35)	46 (36)
III	58 (53)	65 (51)
IV	7 (6)	10 (8)
Medical history		
Different co-morbidities, mean ± SD	7.4 ± 2.5	6.9 ± 2.2
Hypertension, n (%)	107 (97)	124 (98)
CAD, n (%)	80 (73)	85 (67)
Hyperlipidaemia, n (%)	90 (82)	95 (75)
Cardiomyopathy, n (%)	40 (36)	51 (40)
Valvular disease, n (%)	51 (46)	58 (46)
Atrial fibrillation, n (%)	63 (57)	81 (64)
Chronic renal disease, n (%)	50 (45)	45 (35)
Diabetes mellitus, n (%)	58 (53)	67 (53)
Myocardial infarction, n (%)	32 (29)	33 (26)
Stroke/TIA, n (%)	22 (20)	18 (14)
Sleep apnoea, n (%)	15 (14)	11 (9)
Depression, n (%)	18 (16)	19 (15)
COPD, n (%)	32 (29)	33 (26)
Treatments, n (%)		
ICD or CRT[*]	44 (40)	31 (24)
Medication, n (%)		
ACEi/ARB	86 (78)	106 (83)
Beta-blocker	100 (91)	121 (95)
MRA	49 (45)	52 (41)
Diuretic[b]	110 (100)	127 (100)
Loop diuretic	87 (79)	106 (83)
Cardiac glycoside	17 (15)	16 (13)
Lipid-modifying agent	74 (67)	80 (63)
Antithrombotic agent	98 (89)	115 (91)
Antidepressant	6 (5)	14 (11)

Table 1 Continued

Characteristic	Pharmacy care (n = 110)	Usual care (n = 127)
Oral antidiabetic/insulin	35 (32)	39 (31)
No. drug packages, mean ± SD	8.8 ± 3.0	8.9 ± 3.2
No. single doses per day, mean ± SD	10.7 ± 3.8	11.0 ± 4.3
No. drug intakes per day, median (IQR)	3.0 (2−3)	3.0 (2−3)
Laboratory measurements, mean ± SD		
Serum creatinine, mg/dL	1.37 ± 0.51	1.34 ± 0.77
eGFR, mL/min	59.6 ± 25.6	62.9 ± 24.7
LDL-cholesterol, mg/dL	107.3 ± 35.8	110.4 ± 42.3
Blood urea nitrogen[**], mg/dL	60.6 ± 29.5	52.0 ± 23.6
Quality of life (MLHFQ[c]), mean ± SD	39.9 ± 19.9	42.5 ± 22.3
Depression (PHQ-9[d]), mean ± SD	6.2 ± 4.9	7.4 ± 5.6
PHQ-9 score ≥ 10, n (%)	25 (23)	35 (28)
Medication adherence (mean PDC[e]) mean ± SD (n = 88/109)	68.1 ± 29.7	68.5 ± 27.6
Patients with mean PDC ≥ 80%[e], n (%)	39 (44)	46 (42)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (Cockcroft−Gault formula); ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; PDC, proportion of days covered; PHQ-9, 9-item Patient Health Questionnaire; QoL, quality of life; SD, standard deviation; TIA, transient ischaemic attack.
[*]$P = 0.01$.
[**]$P = 0.02$.
[a] According to available chart data.
[b] MRAs were considered as diuretics.
[c] MLHFQ total score: 0 = best QoL, 105 = worst QoL.
[d] Patients with a score ≥ 10 are suspected to currently have depression.
[e] Mean PDC for beta-blockers, ACEi/ARB, and MRAs for the 183 days before randomization.

analytical plan in the study protocol,[10] these individuals were not included in the analyses. A comprehensive statistical comparison showed no relevant differences between these individuals compared to the 110 patients included in the pharmacy care cohort of the mITT population (*Figure 1*). Patients in the mITT population had a mean (±SD) age of 74.1 ± 7.0 years (median 75.0, range 60−88) and 62% were male. The median number of drugs used was nine and the mean baseline PDC for three HF medication classes was 68%. Both groups had similar baseline characteristics (*Table 1*). The median follow-up was 2.0 years (IQR 1.2−2.7). Median adherence to the intervention during this time was 96% (IQR 84−100), considering the weeks where medication was dispensed. Patients visited the pharmacies with a median interval of 8.4 days (IQR 8.0−10.3).

Table 2 Adherence to heart failure medications between the pharmacy care and usual care groups

Variable	Days post-randomization	Pharmacy care (n = 90)	Usual care (n = 112)	Intervention effect[a] (95% CI)	Odds ratio[b] (95% CI)	NNT	P-value
Mean PDC (PEP), mean ± SD[c]	365	91.2 ± 11.9	85.5 ± 16.6	5.7 (1.6–9.8)	NA	NA	**0.007**
	730	87.2 ± 15.4	83.5 ± 17.7	3.4 (−1.2–8.1)	NA	NA	0.15
Mean PDC ≥ 80%, n (%)[c]	365	77 (86)	76 (68)	NA	2.9 (1.4–5.9)	5.6	**0.005**
	730	67 (74)	73 (65)	NA	1.5 (0.8–2.8)	11.1	0.22
Beta-blocker (n = 185)							
PDC, mean ± SD	365	92.3 ± 13.7	83.6 ± 21.6	8.4 (3.0–13.8)	NA	NA	**0.003**
	730	88.5 ± 17.9	82.1 ± 22.8	6.1 (0.1–12.2)	NA	NA	**<0.05**
PDC ≥ 80%, n (%)	365	71 (86)	70 (69)	NA	2.7 (1.3–5.7)	5.9	**<0.01**
	730	68 (82)	69 (68)	NA	2.2 (1.1–4.6)	7.1	**<0.05**
ACEi/ARB (n = 153)							
PDC, mean ± SD	365	90.9 ± 17.4	87.6 ± 18.1	4.7 (−0.8–10.2)	NA	NA	0.09
	730	86.7 ± 20.6	85.0 ± 20.9	2.7 (−3.7–9.0)	NA	NA	0.41
PDC ≥ 80%, n (%)	365	59 (87)	64 (75)	NA	2.9 (1.1–7.5)	8.3	**<0.05**
	730	52 (76)	59 (69)	NA	1.6 (0.7–3.5)	14.3	0.22
MRA (n = 73)							
PDC, mean ± SD	365	88.6 ± 16.7	87.1 ± 19.9	−0.04 (−9.2–9.1)	NA	NA	0.99
	730	82.4 ± 21.5	84.5 ± 22.2	−4.1 (−14.8–6.7)	NA	NA	0.45
PDC ≥ 80%, n (%)	365	26 (72)	28 (76)	NA	0.6 (0.2–1.9)	–	0.37
	730	22 (61)	27 (73)	NA	0.5 (0.2–1.4)	–	0.16

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; NA, not applicable; NNT, number needed to treat; PDC, proportion of days covered; PEP, primary efficacy endpoint; SD, standard deviation.
[a]ANCOVA adjusted for baseline adherence (PDC).
[b]Logistic regression adjusted for PDC at baseline.
[c]Based on the three groups of heart failure medication classes of interest: beta-blockers, ACEi/ARB, and MRAs; patients with a PDC ≥ 80% are classified as adherent.

For 35 patients [20 (18%) of the pharmacy care and 15 (12%) of the usual care group] we were unable to calculate a PDC. Reasons included criteria to calculate a PDC not fulfilled, withdrawal of informed consent (n = 11), or claims data not provided (n = 4). Compared to the 202 patients for whom a PDC was calculated, these individuals showed no relevant differences (online supplementary *Table S1*).

Main efficacy outcomes

The data show a significant improvement for the primary endpoint, adherence to three HF medication classes within 365 days, in the pharmacy care compared to the usual care group (mean difference 5.7 [95% confidence interval (CI) 1.6–9.8]; P = 0.007) (*Table 2* and *Figure 2*A). The proportion of patients with a mean PDC ≥ 80% increased from 44% to 86% in the pharmacy care and from 42% to 68% in the usual care group, resulting in a 18% points difference [OR 2.9, 95% CI 1.4–5.9, P = 0.005; number needed to treat (NNT) 5.6] (*Table 2* and *Figure 2*B).

Secondary efficacy outcomes

Adherence to three CHF medications within 730 days post-randomization remained higher in the pharmacy care compared to the usual care group, but this difference was not statistically significant (mean difference 3.4%, 95% CI −1.2 to 8.1; P = 0.15) (*Table 2* and *Figure 2*A).

Baseline adjusted adherence to beta-blockers was significantly improved in the pharmacy care compared to the usual care group, both within 365 and 730 days (difference 365 days: 8.4%, 95% CI 3.0–13.8, P = 0.003; difference 730 days: 6.1%, 95% CI 0.1–12.2, P < 0.05) (online supplementary *Figure S1*). Within 365 days, the proportion of patients with a PDC ≥ 80% were 86% vs. 69%, a difference between the cohorts of 17% points (OR 2.7, 95% CI 1.3–5.7, P < 0.01; NNT 5.9). Within 730 days, the frequencies were 82% vs. 68%, a difference of 14% points (OR 2.2, 95% CI 1.1–4.6, P < 0.05; NNT 7.1) (*Table 2* and *Figure 2*B).

For ACEi/ARB there was a non-significantly higher adherence within 365 and 730 days (adjusted difference at 365 days: 4.7%, 95% CI −0.8 to 10.2, P = 0.09). The proportion of patients with a PDC ≥ 80% within 365 days was significantly higher in the pharmacy care group (OR 2.9, 95% CI 1.1–7.5], P < 0.05; NNT 8.3) compared to usual care (*Table 2* and *Figure 2*B). Changes in medication adherence for MRA were not significant (*Table 2*).

Sensitivity analyses

In all subgroups examined,[10] the treatment effect for the primary efficacy endpoint was preserved. A consistent improvement in 365-day medication adherence in patients receiving pharmacy care
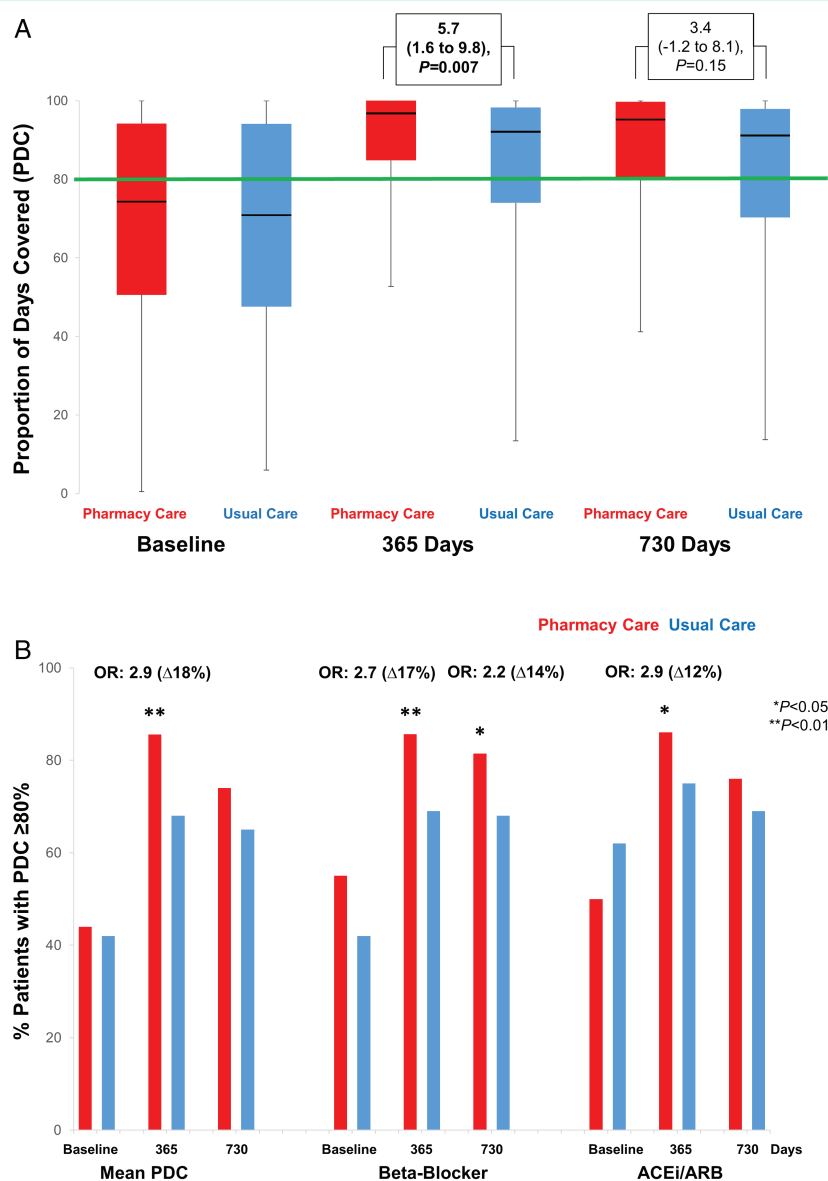
Figure 2 (A) Boxplots of adherence to three heart failure medication classes within 365 days (primary endpoint) and 730 days compared to baseline (183 days prior to randomization). The treatment effects are shown with the 95% confidence intervals. The green horizontal line represents the cut-off for classifying a patient adherent [proportion of days covered (PDC) ≥ 80%]. (B) Proportion of adherent patients (PDC ≥ 80%) for three heart failure medication classes (mean PDC), and separately for beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB) within 365 and 730 days compared to baseline (183 days prior to randomization). Shown are the odds ratios (OR) and the absolute percentage differences (Δ) between both groups for the significant effects.

when compared with usual care was demonstrated. For all subgroups, there was no significant interaction (*Figure 3*).

Quality of life, depression, Patient Global Assessment

Improvement in QoL was more pronounced in the pharmacy care group after 1 year and was significantly better after 2 years [difference in MLHFQ scores −7.8 points (−14.5 to −1.1), *P* = 0.02], compared to the usual care group (*Figure 4*).

Changes in PHQ-9 and PGA scores were not statistically different between groups at 12 and 24 months compared to baseline.

Safety outcomes

During 365 days post-randomization, eight patients in each group died (7% and 6%, respectively). Until the end of the study, 20 (18%) and 27 (21%) patients died in the pharmacy care and usual care groups, respectively. There was no significant difference between the pharmacy care and usual care groups in the days lost due
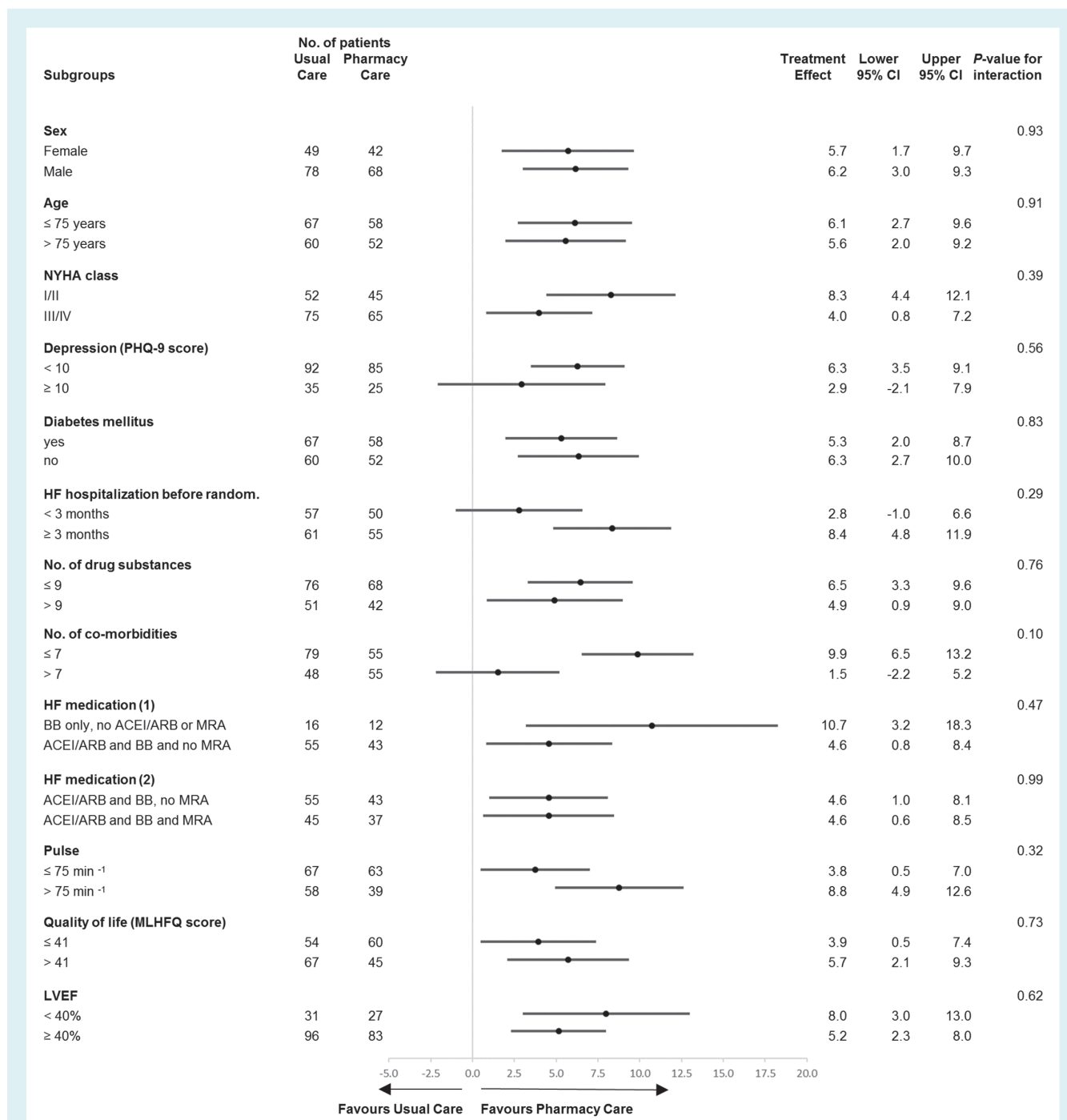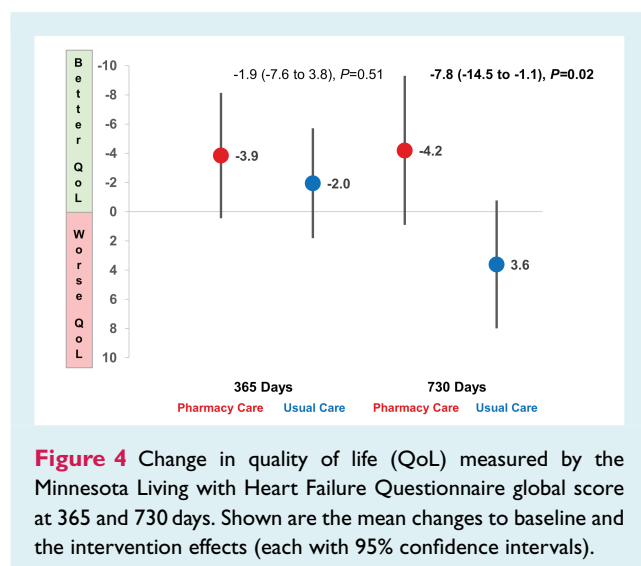
Subgroups	No. of patients Usual Care	Pharmacy Care		Treatment Effect	Lower 95% CI	Upper 95% CI	P-value for interaction
Sex							0.93
Female	49	42		5.7	1.7	9.7	
Male	78	68		6.2	3.0	9.3	
Age							0.91
≤ 75 years	67	58		6.1	2.7	9.6	
> 75 years	60	52		5.6	2.0	9.2	
NYHA class							0.39
I/II	52	45		8.3	4.4	12.1	
III/IV	75	65		4.0	0.8	7.2	
Depression (PHQ-9 score)							0.56
< 10	92	85		6.3	3.5	9.1	
≥ 10	35	25		2.9	-2.1	7.9	
Diabetes mellitus							0.83
yes	67	58		5.3	2.0	8.7	
no	60	52		6.3	2.7	10.0	
HF hospitalization before random.							0.29
< 3 months	57	50		2.8	-1.0	6.6	
≥ 3 months	61	55		8.4	4.8	11.9	
No. of drug substances							0.76
≤ 9	76	68		6.5	3.3	9.6	
> 9	51	42		4.9	0.9	9.0	
No. of co-morbidities							0.10
≤ 7	79	55		9.9	6.5	13.2	
> 7	48	55		1.5	-2.2	5.2	
HF medication (1)							0.47
BB only, no ACEI/ARB or MRA	16	12		10.7	3.2	18.3	
ACEI/ARB and BB and no MRA	55	43		4.6	0.8	8.4	
HF medication (2)							0.99
ACEI/ARB and BB, no MRA	55	43		4.6	1.0	8.1	
ACEI/ARB and BB and MRA	45	37		4.6	0.6	8.5	
Pulse							0.32
≤ 75 min $^{-1}$	67	63		3.8	0.5	7.0	
> 75 min $^{-1}$	58	39		8.8	4.9	12.6	
Quality of life (MLHFQ score)							0.73
≤ 41	54	60		3.9	0.5	7.4	
> 41	67	45		5.7	2.1	9.3	
LVEF							0.62
< 40%	31	27		8.0	3.0	13.0	
≥ 40%	96	83		5.2	2.3	8.0	

-5.0 -2.5 0.0 2.5 5.0 7.5 10.0 12.5 15.0 17.5 20.0

← Favours Usual Care   Favours Pharmacy Care →

Figure 3 Forest plot of sensitivity analyses for the primary efficacy endpoint. Shown are data of baseline-adjusted changes of the mean proportion of days covered for three heart failure (HF) medication classes, using ANCOVA analyses with each subgroup as a covariate, and treatment and the interaction between treatment and subgroup as covariates. The point estimate and the 95% confidence intervals (CI) are stated for each subgroup. The P-values of the interaction term (treatment and subgroups) are presented. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PHQ-9, 9-item Patient Health Questionnaire.

Figure 4 Change in quality of life (QoL) measured by the Minnesota Living with Heart Failure Questionnaire global score at 365 and 730 days. Shown are the mean changes to baseline and the intervention effects (each with 95% confidence intervals).

to unplanned cardiovascular hospitalizations or death of any cause in the 365 days following randomization or any other of the morbidity or mortality endpoints. During follow-up until the end of the study, there was a numerically higher number of deaths in the usual care group (*Table 3*). The Nelson−Aalen plot of time to first event (all-cause death or unplanned cardiovascular hospitalization) during 365 days post-randomization is shown in *Figure 5*.

Discussion

Poor medication adherence represents a major problem but provides a major opportunity to improve outcomes in patients with HF at the same time. Convincing evidence for effective interventions to improve adherence from prospective, randomized studies is lacking. The PHARM-CHF intervention improved mean adherence to three HF medications combined and the proportion of adherent patients (PDC ≥ 80%). The intervention led to a clinically meaningful improvement in QoL and was safe with regard

to unplanned cardiovascular hospitalizations or death of any causes. The analysis of all events that occurred until the end of the study showed a slight numerically higher number of deaths in the usual care group.

To our knowledge, PHARM-CHF is the first pharmacy-based RCT in ambulatory care of elderly HF patients investigating the impact of a multifaceted, interdisciplinary intervention. Although the overall intervention effect on the mean PDC across three HF medication classes was less than the assumed 10% for the sample size calculation, patients in the pharmacy care group had a three-fold higher likelihood to achieve a PDC ≥ 80%, which is a broadly accepted threshold for being classified as adherent, compared to the usual care group. The effects were most pronounced for beta-blockers and to a lesser extent for ACEi/ARB. The number of patients receiving MRAs was too small to show a significant difference.

Several systematic reviews have sought to identify the most effective interventions for improving medication adherence.[8,13] Despite differences in methodologies, the main findings have been consistent: only multifaceted and continuous interventions, combining several different elements, have the potential to improve adherence. However, a number of previous studies in cardiovascular patients failed to demonstrate a significant effect on medication adherence. The HeartStrong RCT tested whether a system of medication reminders using financial incentives and social support applied for 12 months delays subsequent vascular events in patients following acute myocardial infarction compared with usual care. Medication adherence (mean PDC for statins, beta-blockers, and antiplatelet agents) was low and did not differ between the control (42%) and intervention cohorts (46%).[14] The two-arm pragmatic cluster-randomized controlled STIC2IT trial enrolled patients with suboptimal hyperlipidaemia, hypertension, or diabetes disease control, who were non-adherent to prescribed medications for these conditions (mean baseline PDC from pharmacy claims data was 57%). A multicomponent intervention using telephone-delivered behavioural interviewing by trained clinical pharmacists, text messaging, pillboxes, and mailed progress reports was compared

Table 3 All-cause deaths and unplanned cardiovascular hospitalizations during 365-day follow-up and until end of the study

Events	Pharmacy care (*n* = 110)	Usual care (*n* = 127)	*P*-value
365-day follow-up			
All-cause deaths, *n* (%)	8 (7)	8 (6)	0.77
Unplanned CV hospitalizations, *n*	47	48	−
Days lost due to unplanned CV hospitalizations and death[a], mean (95% CI)	24.8 (10.6−38.9)	16.5 (6.1−26.8)	0.70
Percentage days lost due to unplanned CV hospitalizations and death, mean (95% CI)	6.78 (2.91−10.66)	4.51 (1.67−7.35)	0.70
Until end of the study			
All-cause deaths, *n* (%)	20 (18)	27 (21)	0.55
Unplanned CV hospitalizations, *n*	91	93	−
All events (hospitalizations of any cause and deaths), *n*	253	266	−

CI, confidence interval; CV, cardiovascular.
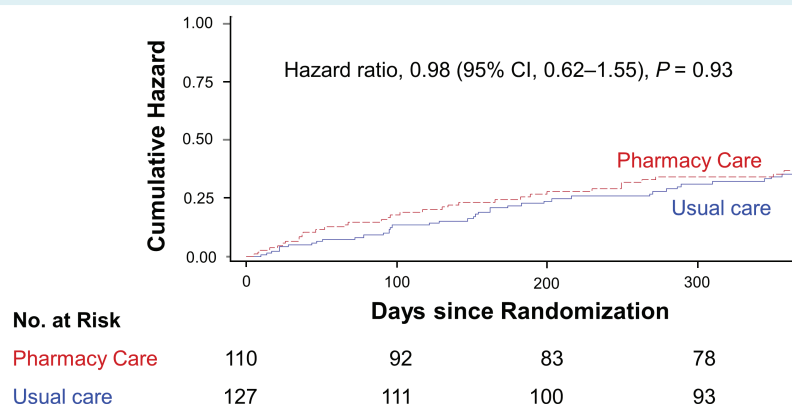[a]Primary safety endpoint.

Figure 5 Nelson−Aalen plot for time to first event (all-cause death or unplanned cardiovascular hospitalization) during 365-day follow-up. CI, confidence interval.

to usual care. The intervention was associated with a 10% increase in adherence, but did not change clinical outcomes.[15]

A pharmacist care programme combining education and counselling with the preparation of medicines in time-specific punch cards increased medication adherence to 97% measured by pill count. This improvement was associated with improved blood pressure and lipid values. However, 6 months after randomization, medication adherence decreased to 69% among those patients assigned again to usual care.[16] In accordance with this study, a multifaceted intervention comprising pharmacist interventions, education, interdisciplinary care, and voice messaging increased medication adherence in the year after an acute coronary syndrome with a 15% difference in the proportion of patients with a mean PDC $\geq$ 80%. Mean PDC was 7% higher in the intervention group.[17] Herein, a greater proportion of patients on intervention were adherent to clopidogrel, statins, and ACEi/ARB therapies, but not to beta-blockers. In the HF population included in PHARM-CHF, adherence to beta-blockers was markedly improved, suggesting that clinical trials addressing adherence in specific patient populations are needed.

A 9-month intervention provided by one pharmacist at a single study site improved medication adherence by 11% (measured by electronic monitoring) but was no longer significantly different during the 3 months post-study phase of the trial.[18] These data confirm that poor adherence cannot be persistently 'cured'; it decreases after stopping the interventions to improve adherence, indicating a need for a continuous strategy.

Heart failure patients are often symptomatic and have a poor QoL. Alleviating symptoms and improving well-being is important.[2] However, very few RCTs have provided evidence with regard to improvements in QoL. A recent systematic review on disease management interventions for HF concluded that clinic-based interventions may result in little or no difference in QoL.[19] In PHARM-CHF, QoL improved in both groups by 12 months with no significant group difference. QoL further improved in the second year in the pharmacy care group while deteriorating in the usual care group. Compared to the generally modest improvement of QoL by other interventions, including device therapy, the 7.8 points

change in the MLHFQ global score in favour of pharmacy care is of significant clinical importance.[20] This positive effect on QoL in the intervention group probably did not relate to medication adherence only as the control group was likewise adherent at 2 years (PDC $\geq$ 80%). We therefore assume an effect of constant support by study pharmacists and physicians, which may explain the increasing difference to the usual care group over time.

Limitations

The relevant improvement in medication adherence in the usual care group was unexpected and could have affected the difference to the effect of the intervention on the primary efficacy endpoint. By design, patients of the control arm were unknown to the pharmacies, minimizing contamination but at the same time limiting the availability of detailed information. We cannot therefore exclude the possibility of cross over with regard to general awareness, the use of dosing aids and/or physician interventions to optimizing pharmacotherapy in the usual care group. A certain degree of improved monitoring and care of patients during a RCT when compared to 'real-world' usual care is unavoidable. The effect of the intervention on the PDC as a continuous variable is quantitatively smaller than the effect on the proportion of patients with a PDC $\geq$ 80%. The 80% cut-point for PDC is widespread practice and was used because it is associated with improved clinical outcomes for several medications/diseases including HF.[5,21−23] Unfortunately, we were unable to calculate a PDC for 35 patients. However, these individuals did not differ in any relevant characteristic available and the power to detect a 10% difference in mean adherence was preserved by the remaining number of participants. Notably, this study was not powered to explore the effects on morbidity and mortality.

Conclusion

A pharmacy-based interdisciplinary intervention improved mean adherence to three HF medication classes and the proportion of adherent patients, and led to clinically important improvements in QoL. For these important aims, pharmacy care represents

a valuable addition to the comprehensive care for HF patients. Morbidity and mortality effects need to be scrutinized in an adequately powered RCT.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Boxplots of adherence to beta-blockers within 365 days and 730 days compared to baseline (183 days prior to randomization). The treatment effects are shown with the 95% confidence intervals. The green horizontal line represents the cut-off for classifying a patient adherent (proportion of days covered ≥ 80%).

Table S1. Characteristics of participants with or without calculation of proportion of days covered.

Appendix

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Supplementary files

Schulz M et al.

Pharmacy-based interdisciplinary intervention for patients with chronic heart failure: results of the PHARM-CHF randomized controlled trial

Table S1   **Characteristics of participants with or without PDC calculation**

Figure S1   Boxplots of adherence to beta-blockers within 365 days and 730 days compared to baseline (183 days prior randomization). The treatment effects are shown with the 95% confidence intervals. The green horizontal line represents the cut-off for classifying a patient adherent (PDC ≥80%).

Table S1   Characteristics of participants with or without PDC calculation

Characteristic	With PDC (*n*=202)	Without PDC (*n*=35)	*P-v*alue
Demographics			
Age, mean ± SD, years	73.9 ± 7.0	75.5 ± 6.8	0.20
Female sex, n (%)	78 (39%)	13 (37%)	0.87
Physical examination, mean ± SD			
BMI, kg/m^2	29.2 ± 5.0	28.9 ± 5.1	0.75
Systolic blood pressure, mm Hg	128.6 ± 16.8	127.0 ± 12.2	0.52
Diastolic blood pressure, mm Hg	76.5 ± 10.0	77.7 ± 12.4	0.61
Heart rate, min^{-1}	74.7 ± 13.5	74.8 ± 13.8	0.97
Heart failure characteristics			
Heart failure aetiology, n (%)			0.72
Ischemic	107 (53%)	19 (54%)	
Non-ischemic	74 (37%)	11 (31%)	
Other	21 (10%)	5 (14%)	
LVEF, mean ± SD, %	46.9 ± 14.6	45.4 ± 14.4	0.62
LVEF <40%, n (%)	50 (25%)	8 (23%)	
LVEF 40–49%, n (%)	71 (35%)	18 (51%)	0.15
LVEF ≥50%, n (%)	81 (40%)	9 (26%)	
NYHA, functional class, n (%)			
I/II	82 (41%)	15 (43%)	0.80
III/IV	120 (59%)	20 (57%)	
Time since last hospitalization for heart failure, mean ± SD, years	0.36 ± 0.83	0.23 ± 0.51	0.21
Medical history			
Different co-morbidities, mean ± SD	7.0 ± 2.3	7.6 ± 2.5	0.16
Hypertension, n (%)	196 (97%)	35 (100%)	0.31
CAD, n (%)	139 (69%)	26 (74%)	0.52
Hyperlipidaemia, n (%)	160 (79%)	25 (71%)	0.31
Cardiomyopathy, n (%)	76 (38%)	15 (43%)	0.56
Valvular disease, n (%)	92 (46%)	17 (49%)	0.74
Atrial fibrillation, n (%)	119 (59%)	25 (71%)	0.16
Chronic renal disease, n (%)	77 (38%)	18 (51%)	0.14
Diabetes mellitus, n (%)	108 (53%)	17 (49%)	0.59
Myocardial infarction, n (%)	49 (24%)	16 (46%)	**0.009**
Stroke/TIA, n (%)	31 (15%)	9 (26%)	0.13

Sleep apnea, n (%)	22 (11%)	4 (11%)	0.93
Depression, n (%)	31 (15%)	6 (17%)	0.79
COPD, n (%)	54 (27%)	11 (31%)	0.57
Treatments			
ICD or CRT, n (%)	65 (32%)	10 (29%)	0.67
Medication, n (%)			
ACEi/ARB	168 (83%)	26 (74%)	0.21
Beta-blocker	194 (96%)	27 (77%)	**<0.0001**
MRA	88 (44%)	13 (37%)	0.48
Diuretic	202 (100%)	35 (100%)	
No. drug packages, mean ± SD	8.7 ± 3.0	9.5 ± 3.2	0.22
No. drug substances, mean ± SD	9.2 ± 3.2	9.8 ± 3.3	0.36
No. single doses/day, mean ± SD	10.9 ± 4.0	11.0 ± 4.5	0.86
No. drug intakes/day, mean ± SD	2.9 ± 0.7	2.8 ± 0.7	0.87
Laboratory measurements, mean ± SD			
Potassium, mmol/L	4.42 ± 0.68	4.41 ± 0.59	0.89
Serum creatinine, mg/dL	1.33 ± 0.65	1.44 ± 0.72	0.44
eGFR, mL/min	62.0 ± 24.8	57.3 ± 27.1	0.34
LDL-cholesterol, mg/dL	110.3 ± 39.8	100.5 ± 35.6	0.17
Blood urea nitrogen, mg/dL	55.8 ± 27.2	56.6 ± 23.9	0.86
Quality of life (MLHFQ score), mean ± SD	40.5 ± 21.0	46.0 ± 22.6	0.20
Depression (PHQ-9 score), mean ± SD	6.8 ± 5.2	7.6 ± 6.0	0.44

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association (functional class); PDC, percentage of days covered; PHQ-9, 9-Item Patient Health Questionnaire; SD, standard deviation; TIA, transient ischemic attack.

Figure S1 Boxplots of adherence to beta-blockers within 365 days and 730 days compared to baseline (183 days prior randomization). The treatment effects are shown with the 95% confidence intervals. The green horizontal line represents the cut-off for classifying a patient adherent (PDC ≥80%).