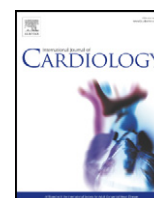


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# Effect of training general practitioners in drug treatment of newly detected heart failure patients with reduced or preserved ejection fraction: A cluster randomized trial



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## ABSTRACT

**Objective:** To assess the effect of training general practitioners (GPs) in the optimization of drug treatment for newly detected heart failure (HF).

**Design:** Cluster randomized trial comparing the training programme to care as usual.

**Participants:** Community-dwelling older persons with a new HF diagnosis after diagnostic work-up.

**Methods:** Thirty GPs were randomized to care as usual or the training. Sixteen GPs of the latter group received a half-day training on optimizing HF medication in HF patients with a reduced (HFrEF), or with a preserved ejection fraction (HFpEF). At baseline and after six months of follow-up, the 46 HF patients in the intervention group and the 46 cases in the care as usual group were assessed on medication use, functionality, health status, and health care visits.

**Results:** After 6 months, uptake of HF medication and health status were similar in the two groups. Interestingly, patients in the intervention group had a longer walking distance with the six-minute walk test than those in the care as usual group (mean difference in all-type HF 28.0 (95% CI 2.9 to 53.1) meters; HFpEF patients 28.2 (95% CI 8.8 to 47.5) meters and HFrEF patients 55.9 (95% CI – 16.3 to 128.1) meters). They also had more HF-related GP visits (RR 1.8, 95% CI 1.3 to 2.5) and fewer visits to the cardiologist (RR 0.6, 95% CI 0.3 to 1.1).

**Conclusions:** Training GPs in optimization of drug treatment of newly detected HFrEF and HFpEF did not clearly increase HF medication, but resulted in improvement in walking distance.

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## 1. Introduction

Heart failure (HF) is a progressive chronic syndrome causing symptoms such as shortness of breath, fatigue and fluid retention. It is a common encountered health problem in older people in the population at

**Abbreviations:** HF, Heart failure; HFpEF, Heart failure with preserved ejection fraction; HFrEF, Heart failure with reduced ejection fraction; ESC, European Society of Cardiology; ACE, Angiotensin converting enzyme; MRA, mineralocorticoid receptor antagonists; GP, General practitioner; 6MWT, six-minute walk test; ECG, Electrocardiogram; NTproBNP, Amino-terminal pro-B-type natriuretic peptide; EQ-5D, EuroQol-5 Dimensions questionnaire; SF-36, Medical Outcomes Study 36-item Short Form Health Survey; PCS, physical component summary; MCS, mental component summary; MLHF, Minnesota Living with Heart Failure questionnaire; ICC, intra-cluster coefficient; GEE, generalized estimating equations; CI, confidence interval; RR, relative risk (for dichotomous outcomes) or rate ratio (for count outcomes); ARB, Angiotensin receptor blocker; NYHA, New York Heart Association.

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large, with a prevalence rising from 0.8% in the group of 55–64 year olds to 20% among the age group of 85 years and older [1].

Heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) are the major phenotypes within the HF spectrum. Both are disabling conditions with high morbidity and mortality, and a substantial loss in functional capacity and health status [2]. The impact on health status is in general larger than for other chronic diseases such as osteo-arthritis, chronic obstructive pulmonary disease (COPD), and depression [3]. Reduced physical functioning seems to be a main driving force behind this.

Management of HF is complex. The European Society of Cardiology (ESC) provides guidance on patient counselling, including advices on lifestyle, how to optimize HF medication, monitor the individual clinical course of the disease and patient specific comorbidities, and when to consider devices [4]. For HFrEF the recommendations on initiation of drug treatment are clear: loop diuretics in case of volume overload, and mortality-reducing treatment with beta-blockers and angiotensin-converting enzyme inhibitors (ACE-inhibitors) (or when intolerated angiotensin receptor blockers (ARBs)), followed by mineralocorticoid

receptor antagonists (MRAs) if symptoms persist. ACE-inhibitors or ARBs and beta-blockers need to be up-titrated, 'starting low, going slow', targeting for recommended doses. For HFpEF the guidance on drug treatment is less clear, because clear evidence-based mortality-reducing treatment is lacking. Diuretics are useful for symptom relief in case of sodium and water retention in HFpEF patients, while blood pressure and comorbidities should be adequately managed [4].

The majority of patients with HF is primarily diagnosed and treated by their general practitioner (GP) [5], but treatment in the primary care setting seems suboptimal [6–8]. Physician-related barriers to guideline adherence include deficits in knowledge, skills, and lack of confidence to up-titrate medication [9–11]. Hence, education seems indicated to increase GPs' knowledge and competence on initiating HF drug therapy, and this could improve their patients' health status.

The aim of the present study was to evaluate whether a single half-day training of GPs in the practical application of a scheme to optimize HF drug treatment in newly detected patients with HFrEF and HFpEF results in improvements in uptake of HF medication, functional capacity, health status, and influences the number of health care visits.

## 2. Methods

### 2.1. Trial design

This cluster randomized trial was the second part of a combined diagnostic-therapeutic study conducted between December 2010 and December 2012 with the aim to improve both the diagnosis and treatment of HF in primary care. The diagnostic part included selective screening for HF of older persons who visited their GP with shortness of breath within the last 12 months. Among these patients, those with newly detected HF were eligible for this cluster randomized therapeutic study.

Random allocation to one of the treatment groups was executed at the level of the GP. As a result, patients with HF of one GP (a cluster) were all managed according to the same arm, hereby reducing the risk of contamination between patient groups. After a six month follow-up period outcomes were compared between groups, taking clustering into account. The study protocol was published previously [12].

### 2.2. Participants

General practices in the Zeist region in the center of the Netherlands, were invited to participate in this study. A total of thirty practices were recruited.

Persons aged 65 years or over who in the previous 12 months presented themselves to the GP with shortness of breath on exertion were selected from the electronic medical files of the participating GPs by a single physician (EvR). The selection was irrespective of whether persons were suspected of HF by the GP or not, or any prior non-HF diagnosis; thus, patients known with a pulmonary disease were also eligible. Those already known with an established diagnosis of HF, confirmed with echocardiography by the cardiologist, were excluded, as were patients with a life expectancy shorter than six months, and those unable to give informed consent. Informed consent was obtained from all participants and the study was performed according to the principles of the current version of the declaration of Helsinki.

Participants underwent a standardised diagnostic work-up conducted at the outpatient clinic of the Julius Center in Utrecht, or were visited at home if they were unable to travel to the study center. Diagnostic investigations included history taking, physical examination, electrocardiography (ECG), and a blood test for N-terminal pro B-type natriuretic peptide (NTproBNP) levels. Only participants with an abnormal ECG or NTproBNP levels above 125 pg/ml (15 pmol/l) underwent additional echocardiography, in accordance with the ESC HF guidelines [4], in the outpatient clinic of the Diaconessenhuis Hospital Zeist.

An expert panel consisting of two cardiologists (AL and ML) and a GP with special expertise in HF (FR) established or excluded HF following

the latest criteria on HF of the ESC [4]. HF was further classified in HFrEF (defined as an ejection fraction  $\leq 45\%$ ), HFpEF (defined as an ejection fraction  $>45\%$  in combination with structural or functional abnormalities compatible with diastolic dysfunction) and 'isolated' right-sided HF. The study population of the trial consisted of the participants with newly detected HF according to the expert panel, except for those having a potentially treatable cause of their HF, who were directly referred to a cardiologist.

### 2.3. Interventions

The intervention consisted of a single half-day educational session. The GPs in this arm received training in the optimization of HF drug treatment for both HFrEF and HFpEF. They received detailed instructions on how and when to initiate diuretics and initiate and up-titrate ACE-inhibitors (or ARBs in case of intolerance to ACE-inhibitors), beta-blockers and possibly MRAs, in patients with HFrEF. For those with HFpEF, individualised titration of diuretic therapy was explained, and also the importance of optimal blood pressure control, and in those with atrial fibrillation, heart rate control [4]. See Fig. 1 for a simplified version of the initiation- and up-titration scheme, and the Additional file for the full content of the scheme. The protocol was designed to guide the GPs through the optimization steps to be fulfilled within three months after the new diagnosis of HF.

During the training session, special attention was given to potential barriers in HF drug treatment, such as fear of adverse effects and worries about ACE-inhibitors and beta-blockers in patients with comorbidities or polypharmacy [10].

The GPs randomly allocated to the care as usual group managed their newly detected cases of HF as they were used to, and did not receive the training. Both groups had access to the Dutch GPs' HF guideline ('NHG-standaard Hartfalen 2010') [13], a Dutch equivalent of the ESC Guideline on HF [4]. Referral to a cardiologist was possible at any stage in this pragmatic trial.

### 2.4. Outcomes

#### 2.4.1. HF medication uptake

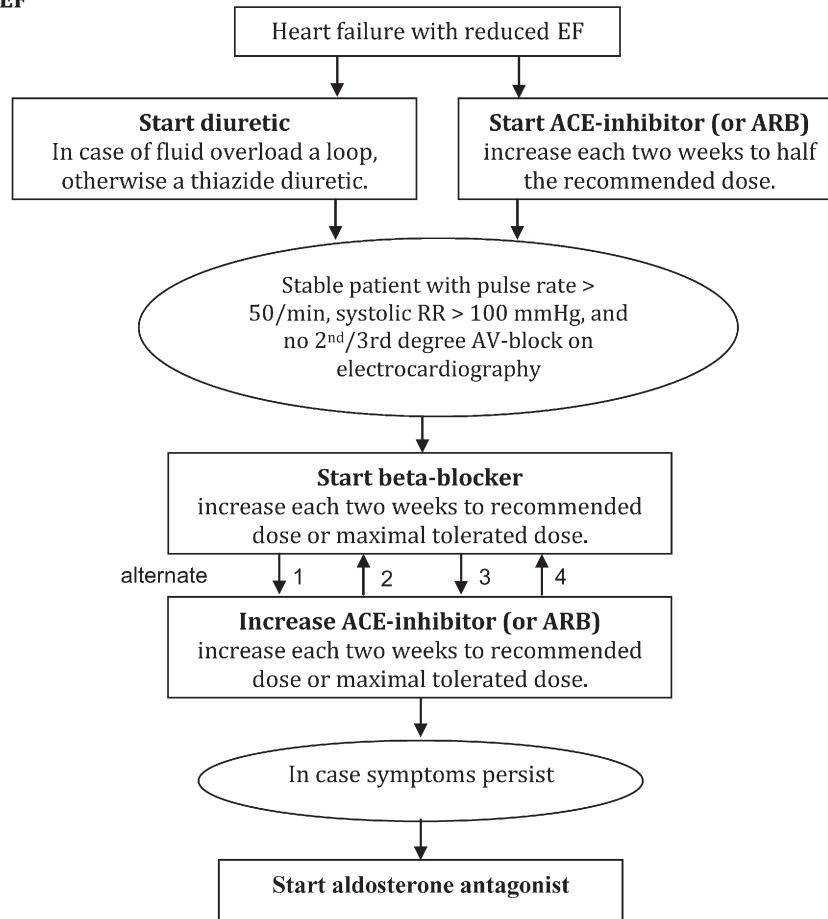
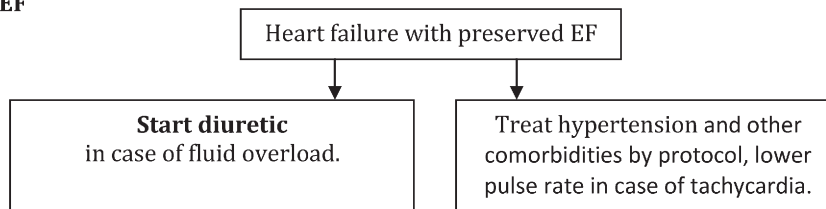
During the diagnostic work-up at baseline, patients were asked about their current drug use. In a preparatory letter, they were asked to bring their medication containers or a list of prescribed medication. Six months after the diagnosis of HF, the electronic medical files of GPs were scrutinized for medication changes. Changes within groups and differences between the two groups regarding use of diuretics, ACE-inhibitors or ARBs and beta-blockers after six months of follow-up were assessed.

#### 2.4.2. Functional capacity

Especially for older persons exercise tolerance is of major clinical importance. Of the several modalities available, the six-minute walk test (6MWT) was used for the objective evaluation of functional capacity because the exercise level is consistent with daily physical activities [14]. The 6MWT is considered a valid, well-tolerated, and inexpensive test for functional capacity, that measures the distance that a patient can walk on a flat, hard surface during 6 min [15]. The test was executed according to the guidelines of the American Thoracic Society, at baseline (at the time of diagnosis) and after six months follow-up [14]. In general, an increase of 50 m in walking distance is considered a 'substantial improvement', and an increase of 20 m a 'small meaningful change' [16,17].

#### 2.4.3. Health status

The EuroQol-5 Dimensions (EQ-5D) and the Short Form-36 (SF-36) were chosen as instruments to measure general health status. Both questionnaires have been extensively validated and are widely used [18–21].

**a. HFrEF****b. HFpEF**

HFrEF, heart failure with reduced ejection fraction; EF, ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; min, minute; RR, blood pressure; AV-block, atrioventricular block; HFpEF, heart failure with preserved ejection fraction.

**Fig. 1.** Simplified version of the treatment scheme for heart failure.

The EQ-5D consists of a 5-item health state assessment, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. A single index score can be produced using data from the five dimensions; a score of 1.0 represents perfect health and 0 represents death.

The SF-36 provides an eight-dimension health profile with the following subscales; physical functioning, role limitation due to physical problems, bodily pain, general health, vitality, social functioning, role limitation due to emotional problems, and mental health, and two summary scores for the physical and mental components (PCS and MCS). Scores range from 0–100 with higher scores indicating a better health status.

The Minnesota Living with Heart Failure (MLHF) questionnaire was added as a condition-specific measurement of health status [22]. The

MLHF has 21 items and scores range from 0 to 105 with a low score reflecting a better health status.

Minimal clinically important differences were estimated as follows; 0.074 for the EQ-5D [23], 10–15 points for PCS of the SF-36 [24], and 5 points for the MLHF questionnaire [25].

Baseline EQ-5D and SF-36 questionnaires were filled out by participants during the diagnostic visit to our center. The baseline MLHF questionnaire was disseminated through the general practitioners at the time of diagnosis. This latter strategy resulted in a large number of missings for the MLHF questionnaire, and therefore we decided to change this strategy for the follow-up measurement. The project manager (EvR) administered all three questionnaires after six months follow-up.

#### 2.4.4. Health care visits

Information on the number of HF-related appointments with the GP during six months of follow-up, and the number of (HF-related) referrals to the cardiologist and HF-related hospitalizations during six and twelve months following the new HF diagnosis were extracted from the electronic medical files at the GP's office, and differences in the number of visits between groups were determined.

#### 2.5. Sample size

We assumed that in a standard general practice with 2400 patients, at least 50 patients aged 65 years or over experience shortness of breath during a one-year period. The prevalence of newly detected HF in such patients was expected to be around 14% [26]. With a participation rate of 50%, a mean number of 3.5 patients with newly detected HF (k) was expected per GP.

Because of the relevance of functional capacity for patients with HF, the sample size calculation for this study was based on the difference in mean distance walked during the 6MWT at baseline and after 6 months between the two groups.

We used the two-sample t-test power analysis to examine how many HF patients were needed per group to demonstrate an effect on the 6MWT. We anticipated an increase in walking distance in the intervention group from 350 m (standard deviation 85 m) to 400 m. With an alpha of 0.05 and beta of 0.2, group sample sizes of two times 45 patients per arm would be sufficient, that is, without taking clustering into account.

We used an intra-cluster correlation coefficient (ICC) of 0.05 to allow for taking clustering into account [27]. The sample size from conventional planning ( $n = 90$ ) was inflated by a factor  $1 + (k - 1) * ICC = 1.13$  [28], resulting in 104 participants; 52 per arm. Hence, we needed to include  $104/3.5 = 30$  GP practices.

#### 2.6. Randomization and blinding

Random allocation of the participating GPs to the intervention or care as usual was undertaken by the project manager in a blinded fashion.

Since it was not deemed feasible to keep the GPs in the care as usual arm unaware of the existence of an intervention arm, blinding of the participants was considered necessary to minimize bias in assessing the outcome parameters. The researcher who performed the 6MWT was blinded to the patient's allocation arm. The risk of observer bias for the other endpoints was minimized, because the health status questionnaires were filled out at home by the participants themselves, and retrieving information on health care visits and HF medication from the electronic medical files was not subject to interpretation.

#### 2.7. Data analysis

Baseline characteristics of patients across the intervention and care as usual group are presented as means or proportions. Data with a skewed distribution are summarized as medians with an interquartile range.

Due to the cluster design, patients within a practice were more likely to be similar to one another than to patients in other practices regarding characteristics such as age, ethnicity, and socioeconomic status, and they were subject to the same physician's behaviour. Generalized estimating equations (GEE) were used to account for clustering of patients within practices. Robust variance estimates were used.

Comparison of the continuous outcomes (6MWT, health status) between the two study arms was done using a generalized linear model, expressed as difference in means with 95% confidence intervals (CIs). Comparison of the count outcomes (health care visits) between the two groups was done with a binary logistic model, and expressed as adjusted rate ratios (RRs) with 95% CIs. Analyses were also performed

separately for HFrEF and HFpEF. Patients with right-sided HF were categorized as HFpEF.

GEE analysis of continuous outcomes was performed in three steps; 1) without correction for baseline characteristics, 2) with adjustment for baseline scores on the outcome (6MWT distance and health status), and 3) as 2, but with the addition of baseline characteristics (age and gender alone, and in combination with history of ischemic heart disease, atrial fibrillation and depression) as covariates in the models.

To prevent biased results due to incomplete data and selective loss to follow-up, multiple imputation of missing values on health status questionnaires and 6MWT was performed before GEE analyses [29, 30]. With regression methods, five imputation sets were created and pooled estimates were obtained. For the three patients (3.3%) who died during follow-up a score of zero was imputed as follow-up score for EQ-5D and SF-36. Data were analysed using SPSS software (version 20.0 for Windows SPSS Inc. Chicago, IL, USA).

### 3. Results

Thirty GPs participated and 16 were randomized to the intervention group and 14 to the care as usual group. Of 1527 eligible patients, 585 gave written informed consent and were included in the diagnostic part of the study. In 92 (15.7%, 95% CI 12.9 to 19.0) patients a new diagnosis of HF was established; 17 (2.9%, 95% CI 1.8 to 4.7) with HFrEF, 70 (12.0%, 95% CI 9.5 to 14.9) with HFpEF, and five (0.9%, 95% CI 0.3 to 2.1) with isolated right-sided HF.

Five (0.9%) participants were referred directly to the cardiologist after the diagnostic assessment; one with brady-arrhythmia, one with an ascending aorta aneurysm, one with grade III mitral valve insufficiency, one with a large, old myocardial infarction, and finally one with contradictory parameters on the echocardiogram.

All patients with newly detected HF proceeded to the cluster randomized trial, in which 46 were treated by a GP in the intervention group and 46 by a GP in the care as usual group (see Fig. 2 for the flow-chart of the study).

The median age of the trial participants was 78.0 (interquartile range 74.0–82.0) years, and 52.2% were female (Table 1). Patients in the intervention group were younger (median 76.0 vs. 79.5 years) and slightly more often female (54.3% vs. 50.0%) than those in the care as usual group. Ischaemic heart disease (26.1% vs. 39.1%), hypertension (65.2% vs. 80.4%) and atrial fibrillation (13.0% vs. 23.9%) were less common in the intervention group. Baseline scores on the 6MWT and health status questionnaires differed only slightly between the two groups.

#### 3.1. HF medication uptake

At the end of the follow-up, 57% of HFrEF patients in the intervention group were prescribed a diuretic, 72% an ACE-inhibitor or ARB, 57% a beta-blocker and none MRAs. These percentages were comparable to HFrEF patients with care as usual: 60% were prescribed a diuretic, 70% an ACE-inhibitor or ARB, 50% a beta-blocker and also none MRAs. The majority in both groups already used these drugs at baseline, in only a few cases new medication was started (Table 2). Also for HFpEF, the percentage of patients in which medication was initiated or up-titrated was similar in both groups.

#### 3.2. Functional capacity

Of patients invited for the 6MWT, 74% participated at baseline and 71% at the follow-up. After correction for baseline scores of the 6MWT, the patients in the intervention group walked on average 28.0 m (95% CI 2.9 to 53.1) farther than the patients in the care as usual group at follow-up (Table 3). The corresponding numbers for HFrEF and HFpEF were 55.9 m (95% CI – 16.3 to 128.1) and 28.2 m (95% CI 8.8 to 47.5), respectively. The absolute mean distances walked by patients with HFrEF were longer than those with HFpEF in both groups.

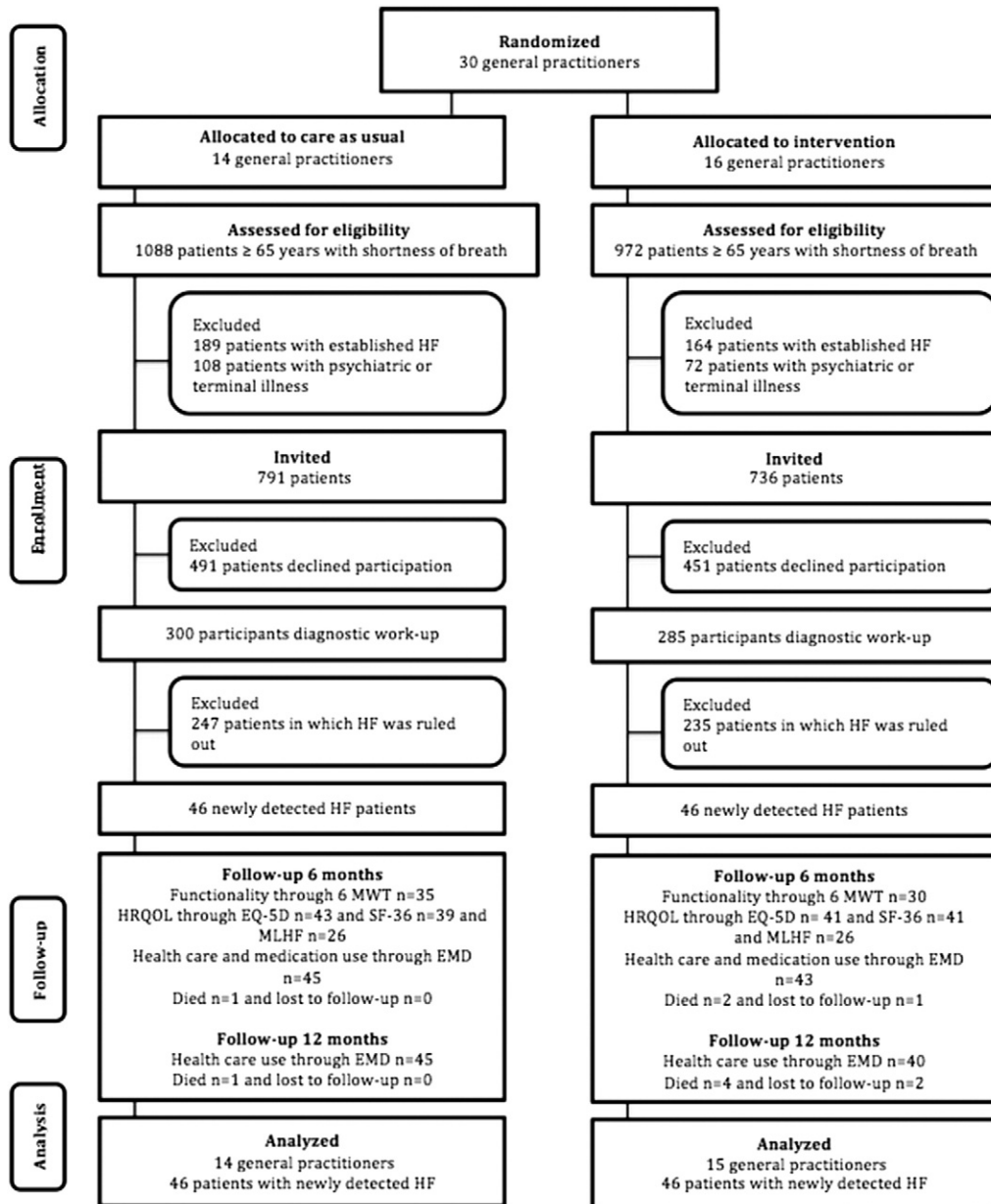


Fig. 2. Study flowchart

Additional adjustments for age and gender slightly reduced the mean differences in the number of meters walked, but the difference remained statistically significant for patients with HFpEF (mean difference 21.8 m, 95% CI 0.2 to 43.4).

### 3.3. Health status

All participants (100%) filled out the EQ-5D and SF-36 at baseline, and nearly 90% completed these questionnaires at follow-up. For the reasons outlined above, the MLHF questionnaire was completed by only 20% at baseline, but by 80% at follow-up. Most scores on health status remained the same or declined slightly in both the intervention and care as usual group during follow-up and none of the scores differed between the groups (Table 3). HFREF patients rated their quality of life higher than HFpEF patients in both groups. The difference in EQ-5D scores between HFREF patients in the intervention and care as usual group at follow-up exceeded the minimal clinically important

difference, but was not statistically significant (corrected mean difference 0.12, 95% CI – 0.03 to 0.26).

### 3.4. Health care visits

After six and twelve months of follow-up information on the number of health care visits and medication prescription was collected for all but one patient, whose data were untraceable after changing of GP.

Patients in the intervention group had on average one HF-related GP visit extra compared to those in the care as usual group during six months of follow-up (total number of visits 134 versus 80; mean number of visits 2.9 versus 1.7; RR 1.8; 95% CI 1.3 to 2.5). The intervention group less often consulted a cardiologist for any reason (total number of visits 22 versus 42; RR 0.6, 95% CI 0.3 to 1.1), and for HF (total number of visits 6 versus 13; RR 0.5, 95% CI 0.1 to 1.5) during twelve months of follow-up. The majority of referrals occurred in the first six months following the new HF diagnosis (Table 4).

**Table 1**  
Baseline characteristics of 92 participants with newly detected heart failure divided by study arm.

Characteristics	All (n = 92)	Intervention (n = 46)	Care as usual (n = 46)
Age in years, median (IQR)	78.0 (74.0–82.0)	76.0 (73.0–81.0)	79.5 (74.8–83.0)
Female gender	48 (52.2)	25 (54.3)	23 (50.0)
Living situation			
Independent, alone	34 (37.0)	18 (39.1)	16 (34.8)
Independent, with others	43 (46.7)	23 (50.0)	20 (43.5)
Dependent of care	15 (16.3)	5 (13.1)	10 (18.5)
Level of education			
Primary	14 (15.2)	7 (15.2)	7 (15.2)
Secondary	52 (56.5)	25 (54.3)	27 (58.7)
Tertiary	26 (28.3)	14 (30.4)	12 (26.0)
MRC score $\geq 3^a$	52 (56.5)	27 (58.7)	25 (54.3)
BMI in kg/m <sup>2</sup> , mean (SD)	29.9 (4.6)	30.1 (5.5)	29.6 (3.5)
NT-proBNP in pg/ml <sup>b</sup> , median (IQR)	390 (203–754)	322 (195–623)	470 (242–964)
Abnormal ECG <sup>c</sup>	60 (65.9)	26 (57.8)	34 (73.9)
<i>Comorbidities<sup>d</sup></i>			
Ischemic heart disease <sup>e</sup>	30 (32.6)	12 (26.1)	18 (39.1)
Atrial fibrillation	17 (18.5)	6 (13.0)	11 (23.9)
Hypertension	67 (72.8)	30 (65.2)	37 (80.4)
Diabetes mellitus	21 (22.8)	11 (23.9)	10 (21.7)
Stroke or TIA	15 (16.3)	7 (15.2)	8 (17.4)
Asthma/COPD	44 (47.8)	22 (47.8)	22 (47.8)
Depressive symptoms	11 (12.0)	8 (17.4)	3 (6.5)
<i>Medication</i>			
Loop diuretics	25 (27.2)	9 (19.6)	16 (34.8)
Thiazide diuretics	24 (26.1)	10 (21.7)	14 (30.4)
ACE-inhibitors/ARBs	59 (64.1)	27 (58.7)	32 (69.6)
$\beta$ -Blockers	39 (42.4)	17 (37.0)	22 (47.8)
MRAs	4 (4.3)	1 (2.2)	3 (6.5)
Statins	37 (40.2)	14 (30.4)	23 (50.0)
Calcium channel-blockers	23 (25.0)	6 (13.0)	17 (37.0)
<i>Type of heart failure</i>			
HF reduced ejection fraction	17 (18.5)	7 (15.2)	10 (21.7)
HF preserved ejection fraction	70 (76.1)	37 (80.4)	33 (71.7)
'Isolated' right-sided HF	5 (5.4)	2 (4.3)	3 (6.5)
<i>Baseline scores on functional capacity and health status, mean (SD)</i>			
6MWT distance in meters	283.4 (72.1)	282.0 (79.5)	284.8 (70.4)
EQ-5D	0.67 (0.21)	0.67 (0.23)	0.68 (0.18)
PCS	41.2 (9.0)	42.7 (9.0)	39.8 (8.7)
MCS	50.8 (8.9)	50.5 (9.9)	51.1 (7.8)
MLHF	28.5 (6.8)	27.6 (6.7)	29.5 (7.6)

Values are numbers (percentage) unless stated otherwise.

IQR, interquartile range; MRC, Medical Research Council; BMI, body mass index; SD, standard deviation; NTproBNP, N-terminal pro B-type natriuretic peptide; ECG, electrocardiogram; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ACE-inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; 6MWT, six-minute walk test; EQ-5D, EuroQol-5 Dimensions questionnaire; PCS, physical component summary; MCS, mental component summary; MLHF, Minnesota Living with Heart Failure questionnaire.

<sup>a</sup> MRC score  $\geq 3$  means that patients report walking slower than contemporaries on level ground because of breathlessness or need to stop for breath when walking at his/her own pace, or shortness of breath at even lower exercise.

<sup>b</sup> The conversion factor for NT-proBNP is 1 pg/ml = 0.118 pmol/L.

<sup>c</sup> The ECG was considered abnormal when one of the following was present: atrial fibrillation, sinus or other tachycardia (heart rate > 100 beats/min), left and right bundle branch block (complete and incomplete), left anterior and posterior block, left ventricular hypertrophy, pathological Q-waves suspected for previous myocardial infarction, P-wave abnormalities compatible with left atrial enlargement, any ST and T-wave abnormalities, or second- or third-degree atrioventricular block.

<sup>d</sup> Comorbidities as mentioned by the patient with history taking.

<sup>e</sup> Previous myocardial infarction, angina pectoris, percutaneous coronary intervention or coronary artery bypass grafting.

#### 4. Discussion

A single training of GPs in optimizing HF drug treatment did not result in increased HF medication uptake in patients with newly detected HFrEF and HFpEF. There was also no significant effect on health status between the intervention group and the care as usual group after six months of follow-up. However, patients in the intervention group showed an improvement in functional capacity as measured with the 6MWT (mean difference 28 m, 95% CI 3 to 53), more often visited the GP (RR 1.8; 95% CI 1.3 to 2.5) and less often consulted a cardiologist (RR 0.6; 95% CI 0.3 to 1.1).

Our single half-day training of GP's did not clearly result in better HF medication uptake in patients with newly detected HFrEF and HFpEF. Some changes in prescription occurred, but these did not result in clear differences between the intervention and care as usual group. Numbers were too small to explore changes in dosage during the follow-up. For HFpEF cases the lack of effect in drug uptake is quite understandable; it is difficult to catch fine-tuning of blood pressure and subtle diuretic treatment adjustments during periods of fluid overload. For HFrEF we had hoped on higher prescribed percentages of the three types of medication that are the mainstay of HFrEF therapy, i.e. diuretics, ACE-inhibitors or ARBs, and beta-blockers.

**Table 2**  
Changes in drug treatment during six months follow-up in the care as usual and intervention group, separately for those with HFrEF and HFpEF\*

	HFrEF		HFpEF	
	Intervention (n = 7)	Care as usual (n = 10)	Intervention (n = 36)	Care as usual (n = 33)
<i>Loop/thiazide diuretics</i>				
No use at begin and end	3 (42.9)	4 (40.0)	15 (41.7)	8 (24.2)
Continued use	1 (14.3)	4 (40.0)	13 (36.2)	19 (57.5)
Up-titrated	1 (14.3)	2 (20.0)	2 (5.6)	1 (3.0)
Initiated	2 (28.6)	0	6 (16.7)	5 (15.2)
Stopped	0	0	0	0
<i>ACE-inhibitors/ARBs</i>				
No use at begin and end	2 (28.6)	3 (30.0)	10 (27.8)	6 (18.2)
Continued use	3 (42.9)	4 (40.0)	17 (47.2)	18 (54.5)
Up-titrated	2 (28.6)	1 (10.0)	3 (8.3)	5 (15.2)
Initiated	0	2 (20.0)	5 (13.9)	2 (6.1)
Stopped	0	0	1 (2.8)	2 (6.1)
<i>B-blockers</i>				
No use at begin and end	1 (14.3)	5 (50.0)	23 (63.9)	14 (42.4)
Continued use	3 (42.9)	4 (40.0)	10 (27.8)	13 (39.4)
Up-titrated	0	0	0	1 (3.0)
Initiated	1 (14.3)	1 (10.0)	3 (8.3)	4 (12.1)
Stopped	2 (28.6)	0	0	1 (3.0)
<i>MRAs</i>				
No use at begin and end	7	10	35 (97.2)	27 (81.8)
Continued use	0	0	0	3 (7.7)
Up-titrated	0	0	0	0
Initiated	0	0	0	3 (9.1)
Stopped	0	0	1 (2.8)	0

Values are numbers (percentage).

\* For this analysis we considered it not opportune to add the five patients to those with HFpEF, because of differences in drug therapy.

HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

**Table 3**  
Mean baseline and follow-up scores on functional capacity as measured in distance with the 6 min walk test and health status measured with the EQ-5D, SF-36, and MLHF in the intervention and care as usual group with differences between groups at the end of follow-up, with and without correction for the baseline score.

	Baseline		After 6 months follow-up		Difference (95% CI) between groups in outcome at 6 months	
	Interv	CAU	Interv	CAU	Without correction	Corrected for baseline distance or score
	7 HFrEF 39 HFpEF <sup>^</sup>	10 HFrEF 36 HFpEF <sup>^</sup>	7 HFrEF 39 HFpEF <sup>^</sup>	10 HFrEF 36 HFpEF <sup>^</sup>		
6MWT	282.0	284.8	314.9	287.7	27.2 <sup>#</sup> (−6.6 to 61.1)	28.0 (2.9 to 53.1)
HFrEF	313.6	319.6	411.0	357.9	52.4 (−29.3 to 134.1)	55.9 (−16.3 to 128.1)
HFpEF	276.4	275.1	297.7	268.3	29.4 (−2.3 to 61.0)	28.2 (8.8 to 47.5)
EQ-5D	0.67	0.68	0.67	0.67	−0.01 (−0.11 to 0.10)	−0.003 (−0.10 to 0.11)
HFrEF	0.83	0.77	0.86	0.71	0.16 (−0.03 to 0.35)	0.12 (−0.03 to 0.26)
HFpEF	0.64	0.66	0.64	0.66	−0.03 (−0.14 to 0.08)	−0.02 (−0.13 to 0.09)
SF-36*						
PCS	42.7	39.8	41.2	37.9	3.2 (−1.9 to 8.4)	1.0 (−3.1 to 5.0)
MCS	50.5	51.1	48.3	48.9	−0.6 (−4.9 to 3.6)	−0.3 (−4.5 to 3.9)
PF	48.5	41.5	47.5	40.2	7.3 (0.6 to 13.9)	2.0 (−3.9 to 8.0)
RP	48.5	50.2	56.1	44.0	12.3 (−0.4 to 25.0)	12.2 (−1.3 to 23.1)
BP	64.5	62.8	67.9	63.7	4.4 (−3.6 to 12.4)	3.2 (−2.9 to 9.4)
GH	49.9	47.1	50.7	47.0	3.7 (−1.3 to 8.8)	2.2 (−2.1 to 6.4)
VT	58.3	55.7	58.5	52.8	5.7 (−0.0 to 11.5)	4.4 (−0.4 to 9.2)
SF	73.9	68.1	71.1	68.4	2.7 (−6.2 to 11.7)	0.1 (−7.3 to 7.5)
RE	78.5	71.8	73.9	72.5	1.1 (−14.0 to 16.3)	−1.5 (−17.4 to 14.5)
MH	72.1	76.3	75.8	73.1	2.7 (−3.1 to 8.6)	5.1 (0.0 to 10.2)
MLHF	27.6	29.5	23.7	25.5	−1.8 (−6.1 to 2.5)	−0.5 (−5.3 to 4.3)
HFrEF	24.1	28.2	14.0	19.6	−5.8 (−15.2 to 3.6)	−4.0 (−13.5 to 5.4)
HFpEF	28.3	29.8	25.5	27.1	−1.7 (−6.5 to 3.2)	−0.6 (−6.1 to 4.9)

<sup>^</sup> Patients with right-sided heart failure were categorized as HFpEF for this analysis.

<sup>#</sup> The difference in the walking distance of all patients with HF is less than in both subgroups (HFrEF and HFpEF) separately, because HFrEF and HFpEF patients were not equally distributed over the intervention and control group, and HFrEF patients walked on average farther than those with HFpEF or right-sided HF.

\* SF-36 scores subdivided in those with HFrEF and HFpEF are not mentioned because differences in outcomes were marginal. Data are available on request.

95% CI, 95% confidence interval; interv, intervention group; CAU, care as usual group; 6MWT, six-minute walk test; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; EQ-5D, EuroQol-5 Dimensions questionnaire; SF-36 Short Form-36; PCS, physical component summary; MCS, mental component summary; PF, physical functioning; RP, role limitation due to physical problems; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role limitation due to emotional problems; MH, mental health; MLHF, Minnesota Living with Heart Failure questionnaire.

**Table 4**  
Health care use in the care as usual and intervention group during follow-up.

	Intervention (n = 46)	Care as usual (n = 46)	RR (95% CI)
<i>6 months follow-up</i>			
Total number of HF-related patient contacts with the GP	134	80	1.8 (1.3 to 2.5)
<i>12 months follow-up</i>			
Total number of patient contacts with the cardiologist of which HF-related	22	42	0.6 (0.3 to 1.1)
	6	13	0.5 (0.1 to 1.5)

RR, rate ratio; 95% CI, 95% confidence interval; HF, heart failure; GP, general practitioner.

The percentage of HFrEF patients in the intervention group on ACE-inhibitors or ARBs (72% vs. 70%) and beta-blockers (57% vs. 50%) was similar to care as usual, and the large majority already used these drugs at baseline, most likely for hypertension. This high baseline uptake of cardiovascular drugs also used in HF reduced the room for improvement. In previous studies that assessed prescription rates in primary care patients with HF similar prescription rates were found [7,8,31]. Prescription rates were higher in a study evaluating selectively patients with HFrEF, not HFpEF, in primary care; 80% were on ACE-inhibitors or ARBs, and 75% on beta-blockers. Also diuretics (60% vs. on average 84%) and MRAs (0% vs. on average 26%) were more often used in this study than in ours [32].

When interpreting our results, one has to realize that we evaluated newly screen-detected cases. The limited severity of symptoms in these early stages of HF may have hampered the motivation of both patient and GP to initiate or further up-titrate cardiovascular drugs. In our study, only one participant was hospitalized during the twelve months follow-up period and 13% visited the cardiology outpatient clinic for HF. These low numbers indicate that patients were detected very early in their disease trajectory.

Another possible explanation for the lack of improvement in prescription rates is the short duration of our training. We cannot tell whether our training increased knowledge and confidence of the GP while not affecting their actual evidence-based drug prescription. We did not assess the GPs' reasons for non-prescription. Also in other research fields, such as diabetes and asthma, educational interventions aimed at GPs often failed to improve prescription rates [33,34]. Systematic reviews have noted that passive disseminating approaches are generally ineffective and unlikely to result in behavior change. Multifaceted interventions targeting different barriers to change and reminders are more likely to be effective than single interventions [35,36].

Interestingly, we did find an improvement in functional capacity as measured by the 6MWT. While this finding could be the result of chance, we think the effect is likely true, especially for patients with HFpEF. Even after additional adjustment for baseline covariates (which in theory should not be necessary after randomization), the impact on walking distance remained significant in patients with HFpEF. Due to the small number of HFrEF patients, we cannot make definitive conclusions regarding results for these patients. The functional capacity of participants in our study was comparable to previous studies performed in patients with HF, with average 6MWT distance ranging from 125 to 499 m [37]. Mean distance in our study was 292 m, indicating a moderate functionality, known to be associated with increased mortality [16]. To our knowledge, we are the first to study the effect of training GPs in HFpEF management. It could well be that extra attention (reflected in the higher number of GP visits in the intervention group) for blood pressure control, fluid retention, adequate treatment of comorbidities and monitoring the disease trajectory in these patients results in optimization of functionality and increase in the walking distance. Since the number of included patients in our study was low, a larger trial should be performed to confirm our findings.

Such a future trial could be extended with a third arm, in which HFpEF patients receive the same drug treatment as HFrEF patients. It has been argued that standard medication therapy for HFrEF is likely to be beneficial also for HFpEF, despite the lack of a significant result on mortality [38,39]. This lack of effect is thought to be caused by exclusion, or inclusion of only the 'purest' forms, of HFpEF in the landmark clinical trials. A primary care trial would be ideally suited to establish or rule out an effect, since 'true' HFpEF patients (female, older, with comorbidities) are predominantly treated by their general practitioner and not in the hospital setting. Recent population-based opportunistic screening studies showed that up to even 80% of HF cases in the community are HFpEF, and only 20% HFrEF [40–42], hence recruitment should not be a problem.

The major strength of our study is thereby the pragmatic approach showing the results achievable in everyday general practice. Other strengths include the randomized design and the blinding of participants to the treatment assignment.

Some limitations of our study need to be addressed. Firstly, although we were able to recruit 30 GPs in our study, we included a somewhat lower number of patients (92) than the targeted 104 participants required to show an effect on the 6MWT. In the power calculation, we used a rather high value for the ICC (0.05), however, while previous studies indicated that ICCs of health outcomes are generally lower than 0.05 [43]. As it turned out, our study has enough power to show a difference in walking distance between the intervention arms, but the 95% confidence limits for subgroups of HF patients (and especially for HFrEF) were wide.

Secondly, functional capacity was not one of the original outcomes of our study. Uptake of HF medication was used for power calculations. However, a few months after the start of the study it became clear that we had an unexpected high prevalence of HFpEF among the participants with newly diagnosed HF (around 75% of all HF). Current medication does not clearly alter prognosis in these patients. We therefore decided to add functional capacity as a patient relevant outcome, and based our new power calculation on this outcome. These changes were done before any data analysis, and were approved by the Medical Ethics committee.

Thirdly, due to the delayed introduction of the 6MWT, one third of the patients (33%) missed the opportunity to take this test at baseline. At follow-up we had 29% missings on the 6MWT outcome. Almost half of those who did not participate declined because they did not feel physically well enough. The majority of the others just 'did not feel like it'. However, by state-of-the-art imputation techniques we could provide adequate predictions of the outcome.

Better results of a GP training program may be possible with a more intensified strategy, such as by addition of a clinical decision support system embedded within the electronic medical files, a medication feedback system, educational bulletins, or computer-based reminder systems. Adequate tackling barriers can also help to overcome organizational difficulties in primary care.

## 5. Conclusion

A single training session for GPs designed to improve outcomes for patients  $\geq 65$  years with newly detected HF did not result in an increase in HF medication uptake and health status, but improved walking distance.

## Registration and funding

This trial is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01202006), and was supported by a research grant from the Dutch Heart Foundation (2009B048).

## Conflicts of interest

All authors declare no conflicting interests.



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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ijcard.2016.04.171>.

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