Neth Heart J (2012) 20:307–312
DOI 10.1007/s12471-012-0284-8

ORIGINAL ARTICLE

Design and methodology of the COACH-2 (Comparative study on guideline adherence and patient compliance in heart failure patients) study: HF clinics versus primary care in stable patients on optimal therapy

M. L. A. Luttik · M. Brons · T. Jaarsma · H. L. Hillege · A. Hoes · R. de Jong · G. Linssen · D. J. Lok · M. Berger · D. J. van Veldhuisen

Published online: 24 April 2012

Abstract
Background Since the number of heart failure (HF) patients is still growing and long-term treatment of HF patients is necessary, it is important to initiate effective ways for structural involvement of primary care services in HF management programs. However, evidence on whether and when patients can be referred back to be managed in primary care is lacking.
Aim To determine whether long-term patient management in primary care, after initial optimisation of pharmacological and non-pharmacological treatment in a specialised HF clinic, is equally effective as long-term management in a specialised HF clinic in terms of guideline adherence and patient compliance.
Method The study is designed as a randomised, controlled, non-inferiority trial. Two-hundred patients will be randomly assigned to be managed and followed in primary care or in a HFclinic. Patients are eligible to participate if they are (1) clinically stable, (2) optimally up-titrated on medication (according to ESC guidelines) and, (3) have received optimal education and counselling on pre-specified issues regarding HF and its treatment. Furthermore, close cooperation between secondary and primary care in terms of back referral to or consultation of the HF clinic will be provided.The primary outcome will be prescriber adherence and patient compliance with medication after 12 months. Secondary outcomes measures will be readmission rate, mortality, quality of life and patient compliance with other lifestyle changes.
Expected results The results of the study will add to the understanding of the role of primary care and HF clinics in the long-term follow-up of HF patients.

M. L. A. Luttik (✉) · M. Brons · D. J. van Veldhuisen
Department of Cardiology, University Medical Center Groningen, University of Groningen,
PO BOX 30.001, 9700 RB Groningen, the Netherlands
e-mail: m.l.a.luttik@thorax.umcg.nl

T. Jaarsma
ISV, Department of Social and Welfare Studies, Faculty of Health Sciences,
Linköping, Sweden

H. L. Hillege
Department of Epidemiology, Trial Coordination Center, University Medical Center Groningen/University of Groningen,
Groningen, the Netherlands

A. Hoes
Department of Cardiology, University Medical Center Amsterdam,
Amsterdam, the Netherlands

R. de Jong
Department of Cardiology, Wilhelmina Ziekenhuis Assen,
Assen, the Netherlands

G. Linssen
Department of Cardiology, Ziekenhuisgroep Twente,
Almelo, the Netherlands

D. J. Lok
Department of Cardiology, Stichting Deventer Ziekenhuizen,
Deventer, the Netherlands

M. Berger
Department of General Practice Medicine, University Medical Center Groningen, University of Groningen,
Groningen, the Netherlands

Keywords Heart failure · Primary care · Follow-up · Guideline adherence · Patient compliance · Quality of life

Background

Chronic heart failure (HF) represents an emerging epidemic in Western societies [1]. Although treatment of HF has certainly improved in the past decades with the development of multiple medications and devices, mortality and morbidity are still considerable. There is no doubt that adherence to evidence-based drug therapy and lifestyle advice is crucial in optimising prognosis in HF patients [1, 2]. To achieve this, a multidisciplinary approach is advocated including counselling to enhance patient compliance.

Although the COACH study [3] has shown that the optimal model of HF disease management is not known yet, other studies have revealed that multidisciplinary HF disease management programs can be effective in terms of improving patient adherence, decreasing hospital readmission and mortality [4–6] and are now generally accepted as standard care [7–9]. Most of these studies evaluated *hospital based* (outpatient) disease management. Only a few studies included primary care, and within these studies the intervention was mainly nurse driven. Furthermore, structural involvement of primary care by the general practitioner (GP) is limited in most European countries, with the exception of some of the Western European countries, such as Scotland. In the Netherlands, GPs play a crucial role in 30 % of the HF management programs [8].

With the growing number of HF patients needing treatment and long-term follow-up, it becomes more and more important to look critically at the effective use or different healthcare resources and different models of care. Terminating follow-up does not seem to be a favourable option since studies have shown that after a short intervention or after ending an intervention program the results of the initial optimisation and education will decrease within the next year [10, 11]. The structural involvement of primary care services in HF management programs needs to be initiated moreover, since GPs are able to see patients in their home environment, it may be preferable to incorporate additional follow-up within the primary healthcare system.

Currently, there are no studies assessing whether and when patients can be referred back to the GP to be managed further in primary care. Referral to the GP is more likely to be a viable option in European countries with a strong primary care-based healthcare system with GPs working with high quality primary care guidelines for many chronic diseases [4]. The guideline of the Dutch College of General Practitioners [12] suggests that HF patients can and should be treated and monitored by GPs (in collaboration with primary care nurses) in the primary care setting. On the other hand, treatment and monitoring of HF patients by GPs is described as not optimal [13]. For example, guideline adherence in HF patients primarily treated by their GP was shown to be lower than in those treated by cardiologists [13–17]. These differences can be partly explained by differences in the characteristics of the two patient populations (age, gender and comorbidity), but more importantly, differences may also be attributable to the GPs attitude towards the uptake of treatment. GPs often experience barriers in implementing the prevailing guidelines especially regarding the optimisation of the drug regimen [18, 19]. There are a limited number of studies that have evaluated improvement of treatment skills of general practitioners [20–23]. These studies show that with specific training interventions or with specific specialist recommendations, improvement is possible. Studies that actually compare the long-term treatment and follow-up in the HF clinic with long-term treatment and follow-up in primary care after initial treatment at the HF clinic are not (yet) available. In the NorthStar study [24], Danish researchers test the hypothesis that clinically stable, educated, and medically optimised patients (with NT-proBNP levels < 1000 pg/ml) can be safely managed by the GP.

Within the current study patients will be referred back to the GP in primary care under the following conditions; (1) patients are in a stable condition (no hospital admissions in the previous month, no visits at the emergency unit for decompensation in the previous month, no unplanned medication changes in the previous month), (2) patients are optimally up-titrated on medication according to the current European Guideline on the Diagnosis and Treatment of Chronic Heart Failure [1] and on the Dutch Multidisciplinary Guideline on Chronic Heart Failure [25], (3) patients have received optimal education and counselling on prespecified issues [26, 27]. Furthermore, close cooperation between secondary and primary care in terms of back referral to or consultation of the HF clinic will be provided as it is an important condition to facilitate optimal follow-up.

The aim of the current study is to determine whether long-term follow-up in primary care, under the above-described conditions, is equally effective as follow-up at a specialised HF clinic in terms of guideline adherence, patient compliance and readmission rates in patients with heart failure.

Methods

Design

A multicentre, non-inferiority, randomised, controlled trial will be performed. The study complies with the Declaration of Helsinki and is approved by the Central Ethics Committee of the University Medical Hospital Groningen. HF

patients visiting the HF clinics of the participating centres will be (pre)screened for their eligibility for the study. Within a period of 3–4 months patients will be up-titrated to optimal medication and educated on HF, its treatment and lifestyle changes. When a stable condition is reached for at least 4 weeks and for a maximum of 2 years (for definition: see below), patients will be randomly allocated to one of two treatment arms: follow-up care by the GP or follow-up care by the specialised HF clinic. Patients will be followed for 12 months (Fig. 1). This trial is listed at www.ntr.nl (NTR1729).

Study population

Patients are recruited from 4 outpatient HF clinics in the Netherlands: Groningen (UMCG), Ziekenhuis Groep Twente (Almelo and Hengelo), the Deventer Hospital and the Wilhelmina Hospital (Assen).

Inclusion criteria

Patients will be screened and are eligible when they have:

- Documented symptoms of HF (either currently or at time of diagnosis);
- HF with evidence for structural underlying ventricular dysfunction (left ventricular ejection fraction (LVEF) <45 % at time of diagnosis);

and when they:

- Are up-titrated to optimal pharmacological treatment (notably use of adequate dosages of ACE inhibitors/angiotensin receptor blockers(ARBs) and β-blockers);
- Have been in a clinically stable condition for at least 1 month and for a maximum of 2 years: no hospital admissions in the previous month, no visits to the emergency unit for decompensation in the previous month, no unplanned medication changes in the previous month;
- Are optimally educated and informed on heart failure and the required lifestyle changes following a pre-specified protocol;
- Aged above 18 years.

Exclusion criteria

Patients will be excluded from the study when:

- Patient management by a cardiologist planned for diagnostics or treatment is needed;
- The general practitioner has substantial arguments against patient participation in the study;
- The patient has restrictions that render him/her unable to fill in data collection material (inadequate mastering of the Dutch language);
- The patient has a life expectancy shorter than 6 months;
- The patient is living in a nursing home;
- The patient has a current psychiatric disorder as documented in the medical record.

Sample size calculation

The study is designed as a non-inferiority trial. Non-inferiority for guideline adherence will be declared if the lower limit of the one-sided 95 % CI of the difference does not exceed a delta of 20 % from the guideline adherence rate in standard care. Seventy-five patients randomised to receive standard care and 75 patients to receive primary care are needed to demonstrate non-inferiority for guideline adherence assuming a standard care guideline adherence rate of 60 % and a power of 80 %. From earlier research it is known that guideline adherence in primary care is substantially lower (20 % conform the IMPROVEMENT study [13] and Rutten's study [15] compared with treatment by a cardiologist (60 % conform the MAHLER

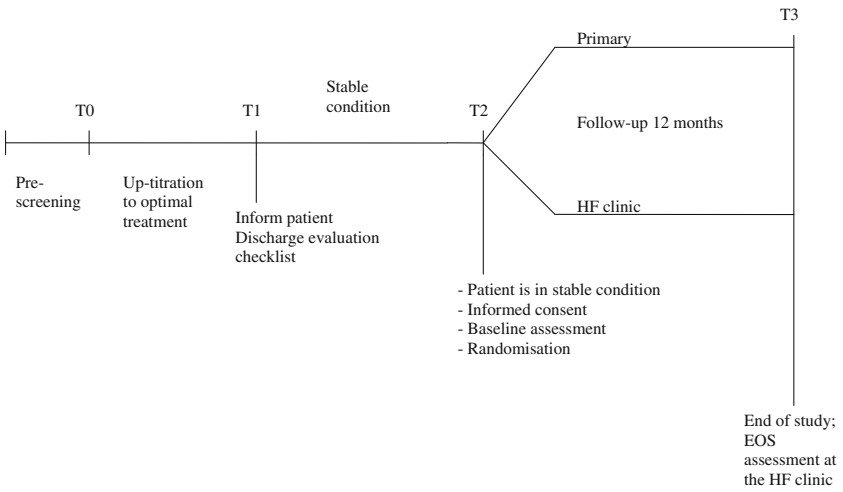

Fig. 1 Study Design

Table 1 Guideline adherence indicator-3

	ACE-I/ ARB	Beta blocker	Aldosterone antagonist	GAI-3 (%)
NYHA II	Yes	Yes	-	50+50
NYHA III/ IV	Yes	Yes	Yes	33.3+33.3+33.3

ACE-I ACE inhibitors, *ARB* angiotensin receptor blockers, *GAI* Guideline Adherence Indicator, *NYHA* New York Heart Association

study [2]. The lower acceptable margin of 40 % has been chosen to provide assurance that the standard care arm of this study has a clinically relevant superiority over historical data. In our point of view this rather wide non-inferiority margin could be justified because the primary care arm has subjective advantages in a number of other aspects when compared with standard care. To ensure the appropriate patient number at the end of the study 2×100 patients will be included.

Primary outcome

The primary outcome of the study is guideline adherence defined as the prescription of guideline recommended HF medication (β-blocker and ACE inhibitor/ARB and spironolactone). The global Guideline Adherence Indicator (GAI-3), from the MAHLER study [2], will be used to assess overall guideline adherence. This is a score addressing the relevant groups of medication for heart failure correcting for New York Heart Association (NYHA) class and is quantified for each patient as the proportion of evidence-based recommendations followed by the HF clinic or GP out of the total number of recommendations that applied for that particular patient (Table 1).

The secondary primary outcome is patient compliance with medication: patient compliance with medication is calculated from digital pharmacy records in terms of the medication possession ratio, e.g. the number of days for which the prescribed medication was available between the last refill in the observation year and the last refill in the foregoing year divided by the number of days between these refills, expressed in a percentage [28].

Secondary endpoints

Secondary endpoints of the study will be guideline adherence regarding medication (optimal dose and adjusted for comorbidity), readmission rate, mortality, (N-terminal) pro-brain natriuretic peptide ((NT-pro)BNP), patient compliance with lifestyle changes and quality of life (Table 2).

During the study, data will be collected on demographics, clinical variables (medical history, time since HF diagnosis, previous admissions, comorbidity, heart rate, ECG, LVEF, NYHA class, RR, laboratory findings) and patient and partner satisfaction with care.

Assessment, randomisation and intervention protocol

Randomisation and assessments

Following confirmation of the patient's eligibility and after informed consent has been obtained, baseline characteristics

Table 2 Variables and measurements

Variable	Data collection method
Prescribed medication	Chart review/Pharmacy records
Patient compliance	Pharmacy records
Readmission rate	Chart review
Mortality	Chart review
(NT-pro)BNP	Blood sample
Patient compliance with lifestyle changes	Questionnaires; European Self-Care Behaviour Scale [29] Revised Heart Failure Compliance Questionnaire [30] Medication Adherence Report Scale [31] Weight diary
Heart failure knowledge	Dutch Heart Failure Knowledge Questionnaire [32]
Quality of life (QoL)	Questionnaires: SF 36 [33] Kansas City Cardiomyopathy Questionnaire [34] EuroQol5D [23, 35, 36]
Demographics	Chart review
Medical history	Chart review
Comorbid diseases	Chart review
NYHA	Chart review
LVEF	Chart review
Laboratory	Chart review
Patient/partner depression	Questionnaires (CES-D [37])
Patient/partner perceived control	Questionnaires (CAS-4 [38])
Patient and partner/family satisfaction	Questionnaires (SF 36 [33], EuroQol5D [23, 36]
Caregiver QoL	Questionnaires (Caregiver Reaction Assessment [39]
Caregiver tasks and burden	Dutch Objective Burden Inventory [40]

LVEF left ventricular ejection fraction, *NYHA* New York Heart Association

of the patient will be assessed from the medical chart and patient questionnaires. After baseline assessment, patients will be randomly allocated in each participating centre to either long-term follow-up in primary care (study group 1) or at the HF clinic (study group 2). Follow-up assessment will be done at the end of study after 12 months. Data will be collected through patient questionnaires and medical charts at the HF clinic or at the GP's office.

'Intervention' protocol

Patients in study group 1 will be followed in primary care. Contacts and visits will take place according to the European Guideline [1] and the recently published Dutch Multidisciplinary Guideline on Chronic Heart Failure [25]. Routine visits to the cardiologist or HF nurse are not scheduled; however, referral back to or consultation of the HF clinic is possible. Patients randomised into study group 2 will be followed at the hospital-based heart failure clinic (cardiologist and HF nurse). Contacts and visits will take place according to the Dutch Multidisciplinary Guideline on Chronic Heart Failure [25]. Contact with the GP will be following the care as usual principal.

Data analysis

The primary analysis will compare differences in guideline adherence at 1 year between the two study groups (relative risk and risk difference with 95 % confidence intervals). For continuous secondary endpoints, comparisons between the two study groups will be made with ANCOVA, adjusted for differences in baseline values, when appropriate. For categorical variables, adequate statistical techniques will be used, with adjustment for baseline values, when appropriate.

Study organisation

Study centres

In order to include 200 patients, 4 hospitals in the Netherlands will participate in the study.

The *Steering Committee* consists of: M.L. Luttik, RN, PhD, chair and project leader; Prof. T. Jaarsma, RN, PhD; Prof. H.L. Hillege, MD, PhD; Prof. A.W. Hoes MD, PhD; Prof K. van der Meer, MD, PhD; Prof. A.A Voors, MD, PhD; Prof D.J. van Veldhuisen, MD, PhD (principal investigator); G. Linssen, MD; D. Lok, MD; and R.M. de Jong, MD, PhD.

Support and monitoring

The study will be supported by the Trial Coordination Centre (University Medical Center, Groningen, the Netherlands), a contract research organisation for clinical trials. Both the quality of the data and of the intervention will be monitored closely.

Conclusion

The results of the COACH-2 study will add to the understanding of the role of primary care in the long-term follow-up of HF patients. This study is the first to provide data on the effectiveness of long-term treatment of clinically stable HF patients who are on optimal treatment by the GP in the primary care setting. This insight is needed in order to create and assure optimal long-term care for HF patients. Accordingly, this strategy may imply an increased participation of primary care in evidence-base HF management.

Funding The Netherlands Heart Foundation (NHF) financially supports the study as one of their research programs (2008B083).

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