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Design and Methodology of the COACH-2 study. Comparative study On guideline Adherence and patient Compliance in Heart failure patients; HF clinics versus primary care in stable patients on optimal therapy

Authors:

Marie Louise A.Luttik, RN, PhD¹

Maaïke Brons, RN, MSc ¹

Tiny Jaarsma, RN, PhD²

Hans L. Hillege, MD PhD³

Arno Hoes, MD PhD⁴

Richard de Jong, MD PhD⁵

Gerard Linssen, MD⁶

Dirk J. Lok, MD⁷

Marjolein Berger, MD PhD⁸

Dirk J. van Veldhuisen, MD PhD¹

¹ Department of Cardiology, University Medical Center Groningen/University of Groningen, the Netherlands

² ISV, Department of Social and Welfare Studies, Faculty of Health Sciences, Linköping, Sweden

³ Department of Epidemiology, Trial Coordination Center, University Medical Center Groningen/University of Groningen, the Netherlands

⁴ Department of Cardiology, University Medical Center Amsterdam, the Netherlands

⁵ Department of Cardiology, Wilhelmina Ziekenhuis Assen, the Netherlands

⁶ Department of Cardiology, Ziekenhuisgroep Twente, Almelo, the Netherlands

⁷ Department of Cardiology, Stichting Deventer Ziekenhuizen, Deventer, the Netherlands

⁸ Department of General Practice Medicine, University Medical Center Groningen, University of Groningen, The Netherlands

Corresponding Author

Dr. M.L.A. Luttik

Department of Cardiology

University Medical Center Groningen, University of Groningen

PO BOX 30.001

9700 RB Groningen

The Netherlands

Tel. 31 50 3611594 Fax. 31 50 3614391

E-mail: m.l.a.luttik@thorax.umcg.nl

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Abstract

Since the number of Heart Failure patients (HF) is still growing and longterm 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 optimization of pharmacological and non-pharmacological treatment in a specialized HF clinic, is equally effective as long term management in a specialized HF clinic in terms of guideline adherence and patient compliance.

Method

The study is designed as a randomized controlled non-inferiority trial. Two-hundred patients will be randomly assigned to be managed and followed in primary care or in a HF clinic. 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.

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 life style changes.

Expected results

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.

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 life style advice is crucial in optimizing 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 shown 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, in 30% of the HF management programs GPs play a crucial role [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 of different health care resources and different models of care. Terminating follow-up does not seem a favourable option since studies have shown that after a short intervention or after ending an intervention program the results of the initial optimization 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 GP's are able to see patients in their home

environment, it may be preferable to incorporate additional follow up within the primary health care 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 strong primary care-based health care 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 GP's 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 both patient populations (age, gender and co-morbidity), 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 optimization 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, 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 clinical stable, educated, and medical optimized patients (with NT-proBNP levels < 1000pg/ml) can safely be 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 Failure¹ and on the Dutch Multidisciplinary Guideline on Chronic Heart Failure [25], (3) patients have received optimal education and counselling on pre-specified 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.

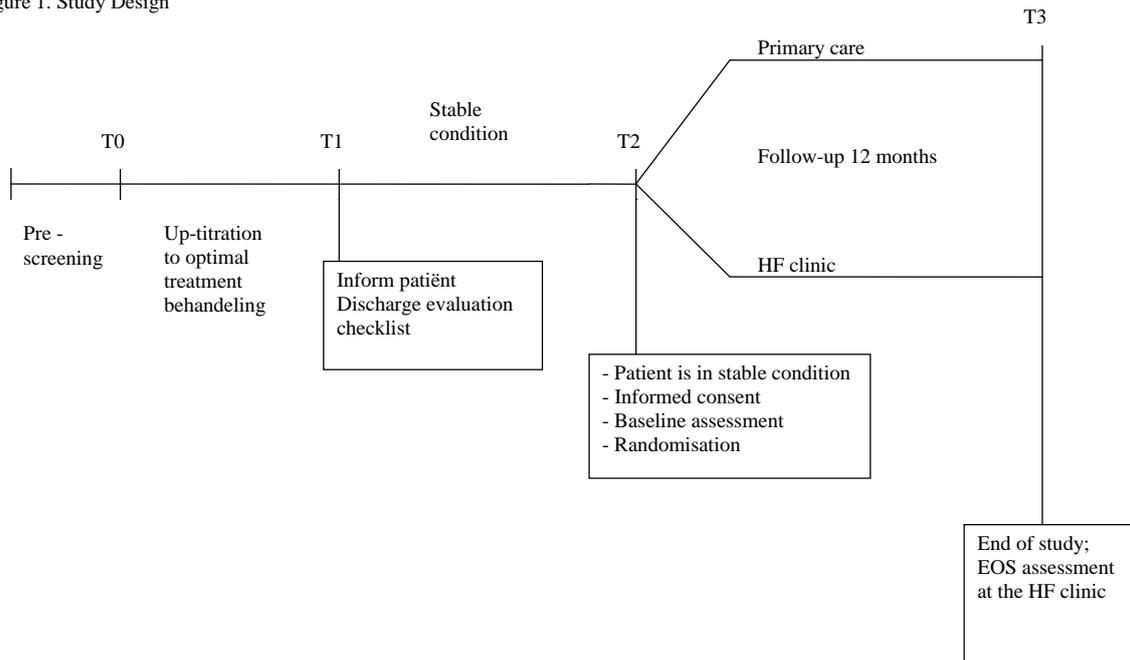
The aim of the current study is to determine whether long-term follow-up in primary care, under the above described conditions is equally effective as follow up at a specialized HF clinic in terms of guideline adherence, patient compliance and readmission rates in patients with heart failure.

METHODS

Design

A multicenter, non-inferiority, randomized 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 life style 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 specialized HF clinic. Patients will be followed for 12 months (Figure 1). This trial is listed at www.trials.nl (NTR1729)

Figure 1. Study Design



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 (LVEF<45% at time of diagnosis),

and when they are;

- up-titrated to optimal pharmacological treatment (notably use of adequate dosages of ACE-inhibitors/ARBs and beta blockers)
- in a clinically stable condition for at least one month and for a maximum of two years; 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.

- Optimally educated and informed on heart failure and the required life style 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 patients to fill in data collection materials (non-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 1-sided 95% CI of the difference will not exceed a delta of 20% from the guideline adherence rate in standard care. Seventy five patients randomized 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 the

study of Rutten [15] compared to treatment by a cardiologist (60% conform the MAHLER 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 appropriate patient number at the end of the study 2x 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 (B-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 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].

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

Secondary endpoints

Secondary endpoints of the study will be guideline-adherence regarding medication (optimal dose and adjusted for co-morbidity), readmission rate, mortality, (NT-pro)BNP, patient compliance with life style 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, co-morbidity, heart rate, ECG, LVEF, NYHA class, RR, Lab) and patient and partner satisfaction with care.

Assessment, randomization and intervention protocol

Randomization and assessments

Following confirmation of the patient's eligibility and after informed consent has been obtained, baseline characteristics of the patient will be assessed from the medical chart and patient questionnaires. After baseline assessment, patients will be randomly allocated in each participating center 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 on 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 randomized 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.

Table 2. Variables and measurements

Variable	Data collection method
Medication use	
Prescribed medication	Chart review/Pharmacy records
Patient compliance	Pharmacy records
Readmission rate	Chart review
Mortality	Chart review
(NTpro)BNP	Blood sample
Patient compliance with life style changes	Questionnaires; European Self-Care Behavior 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	Questionnaires; SF 36 [33] Kansas City Cardiomyopathy Questionnaire [34] EuroQoL5D [23, 36]
Additional assessments	
Demographics	Chart review
Medical history	Chart review
Co-morbid 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] and
Caregiver tasks and burden	Dutch Objective Burden Inventory [40]

DATA ANALYSIS

The primary analysis will compare differences in Guideline Adherence at one year between the two study groups (relative risk and risk difference with 95% confidence intervals). For continuous secondary end points, 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 ORGANIZATION

Study centers

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

The *Steeringcommittee* consists of: ML Luttik, RN, PhD, chair and projectleader,

Prof. T Jaarsma, RN, PhD, Prof. H.L. Hillege, MD, PhD, Prof. AW Hoes MD, PhD, Prof K

vd Meer, MD, PhD, Prof. A.A Voors, MD, PhD, Prof DJ 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 Center (University Medical Center, Groningen, the Netherlands), a contract research organization for clinical trials. Both the quality of the data and of the intervention will be monitored closely.

CONCLUSION

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 the 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.

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