Long-term follow-up in optimally treated and stable heart failure patients: primary care vs. heart failure clinic. Results of the COACH-2 study

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Long term follow-up in optimally treated and stable Heart Failure patients;
Primary Care versus Heart Failure Clinic.
Results of the COACH-2 study

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Abstract

Aim

It has been suggested that home-based Heart Failure (HF) management in primary care may be an alternative to clinic-based management in HF patients. However, little is known about adherence to HF guidelines and adherence with the medication regimen in these home-based programmes. The aim of the current study was to determine whether long-term follow-up and treatment in primary care is equally effective as follow-up at a specialized HF clinic in terms of guideline adherence and patient adherence, in HF patients initially managed and up-titrated to optimal treatment at a specialized HF clinic.

Method and Results

We conducted a multi-centre, randomized, controlled study in 189 HF patients (62% male, age 72 ± 11 yrs), who were assigned to either follow-up in primary care (n=97) or in a HF clinic (n=92). After 12 months, no differences between guideline adherence, as estimated by the Guideline Adherence Indicator (GAI-3), and patient adherence, in terms of the medication possession ratio (MPR), were found between treatment groups. There was no difference in the number of deaths (n=12 in primary care, and n=8 in the HF clinic; $p=0.48$), and hospital readmissions for cardiovascular (CV) reasons were also ~~comparable~~similar. The total number of unplanned non-CV hospital readmissions, however, tended to be higher in the primary care group (n=22) than in the HF clinic group (n=10; $p=0.05$).

Conclusion

Patients discharged after initial management in a specialized HF clinic can be discharged to primary care for long-term follow-up with regard to maintaining guideline adherence and patient adherence. However, the complexity of the HF syndrome and its associated co morbidities, requires continuous monitoring. Close collaboration between health care providers ~~in the different echelons~~ will be crucial in order to provide HF with optimal,

integrated care.

Introduction

Although treatment of heart failure (HF) has improved in the past decades with the development of multiple medications and devices, mortality and morbidity are still considerable.^{1,2} In addition to optimal medical management, the HF guidelines³ recommend to enrol HF patients in a multidisciplinary-care management including follow-up after discharge (by visits, telephone support or remote monitoring). An important issue is whether long-term management of HF patients must remain under the care of a HF clinic (in a hospital), or whether patients can be referred back to the general practitioner (GP) to be further managed in the primary care setting. There is little documentation and limited evidence suggesting that follow-up in primary care assures successful continuation of evidence-based therapy. Moreover, the study of Ojeda and colleagues⁴ showed that after ending an intervention program, the results of the initial optimization and education decreased within the next year⁴ Clearly, if such a home-based programme in primary care would be similarly effective, this would have large clinical, practical and economic advantages. However, the optimal model for the delivery of long term multidisciplinary-care management is still unknown.^{5,6}

Recent large-scale studies show that not all models are equally successful to improve outcomes and they indicate that a tailored approach to HF management is needed.^{7,8} The WHICH? trial which was conducted in Australia indicated that a home-based HF management programme was equally effective in terms of outcome, and associated with lower healthcare costs as to an equivalent clinic-based programme.⁹ In the much larger Danish NorthStar study, it was shown that stable HF patients on optimal therapy did not benefit from long-term follow-up in a specialized HF clinic, and indeed, they could be referred back safely to their GP.¹⁰

Although these studies reported baseline medication, they did not examine whether guideline recommended HF medication was continued throughout the study. This is important since it has been shown that guideline adherence in HF patients primarily treated by their GP is lower than in patients treated by cardiologists, which may, at least be partly attributable to the fact that GPs usually deal with older patients with more co-morbidity.¹¹⁻¹³ GPs seem to experience barriers in the initiation and optimization of pharmacological treatment.¹⁴ Little is known about the long term adherence to HF guidelines, after initial optimization of medication. Patient compliance, nowadays known as patient adherence, is an important predictor of outcome in HF^{15,16} and patients often have difficulty to remain compliant to treatment in the long run.⁴ The role of patient adherence to guideline therapy in home-based management programmes has not been studied yet.

We therefore designed the (Comparative study On guideline Adherence and patient Compliance in Heart failure patients (COACH-2) study¹⁷ COACH-2 study aimed to determine whether long-term follow-up in primary care can be equally effective as compared to follow-up in a specialized HF clinic in terms of guideline adherence to the guideline recommended HF medication and patient adherence with medication with these recommendations.

Methods

Study design

The COACH-2 study was a multi-centre, non-inferiority, randomized, controlled trial and a detailed description of its rationale and design has been published previously.¹⁷ COACH-2 trial was approved by the Central Ethics Committee of the University Hospital Groningen and performed according to The Helsinki Declaration. The study is listed in the Netherlands Trial Register (NTR1729).

Study patients

Patients were recruited from 4 outpatient HF clinics in the Netherlands. HF clinics were all settled in hospitals delivering specialized consultative health care, in a facility with personnel and facilities for advanced medical investigation and treatment. All visiting patients were screened for their eligibility to participate in the study. Patients were eligible if they: 1) had documented symptoms of HF (either currently or at time of diagnosis), 2) HF with evidence for structural underlying ventricular dysfunction (LVEF < 45% at time of diagnosis), 3) were up-titrated to optimal pharmacological treatment; Angiotensin-Converting-Enzyme Inhibitor (ACE-I) / Angiotensin Receptor Blockers (ARB), beta-blockers and mineralocorticoid (aldosterone) receptor antagonists (MRAs) for NYHA III patients according the ESC guidelines of 2008¹⁸, 4) clinically stable for at least 1 month, i.e. no hospital admission in the previous month, no visits to the emergency unit for decompensated HF in the previous month and no unplanned medication changes in the previous month, 5) optimally educated and informed about HF and required lifestyle changes and 6) 18 years or older.

Exclusion criteria included 1) management by a cardiologist planned for diagnostics or if additional treatment was needed according to the cardiologist or GP, 2) the GP had substantial arguments against patient participation in the study, 3) the patient was unable to fill in data collection materials, 4) the patient had a life expectancy <6 months, 5) the patient was living in a nursing home or 6) the patient had a current psychiatric disorder.

Study procedure

Patients and their caregivers were informed about the study when visiting the outpatient HF clinic in one of the participating centres. Thereafter, patients were titrated to optimal, guideline recommended HF medication and were educated about HF, its treatment and

lifestyle changes. After being titrated to optimal HF medication and confirmed stable for at least 4 weeks, patients were approached to participate in the study and to give their informed consent. Patients were then randomly allocated to follow-up by their GP (PC group) or follow-up by the HF clinic (HF clinic group). GPs were randomly selected following the randomization of patients and were not specifically trained for this study. Contacts and visits in both groups were assumed to take place according to the European Guidelines for treatment of acute and chronic heart failure¹⁸ and according to the Dutch Multidisciplinary Guideline on Chronic Heart Failure.¹⁹ Within the HF clinic group, contact with the GP was possible following the ‘care as usual’ principle. Within the PC group no visits at the HF clinic were scheduled, however consultation of the HF clinic by the GP was possible. At the end of the follow-up period (12 months), all patients from both treatment groups were invited to an end of study visit at the HF clinic.

Study outcomes

This study had two primary outcomes, guideline adherence and patient adherence. It was hypothesized that long-term follow-up under the described conditions, would be equally effective in both groups in terms of guideline adherence and patient compliance at 1 year follow-up. Guideline adherence was measured by means of the Guideline Adherence Indicator (GAI)²⁰, including guideline recommended prescription of ACE-I (or ARB) and Beta-blocker for all patients and spironolactone in patients with NYHA $\geq$ III. Guideline adherence for the primary end point was defined as a GAI of 100 %. The other primary endpoint was patient adherence with medication in terms of the medication possession ratio (MPR) calculated from digital pharmacy records over 12 months of follow-up. The MPR reflects the number of days that prescribed medication was available for patients based on their drug refill behaviour following the prescribed medications.²¹

Medication that started after randomization was not included, unless it was a switch between drugs within the same therapeutic class. Patients who died during follow up (n=20) and patients that had their drugs weekly delivered automatically by a multi-dose medication dispense system (n=31) were excluded from the analyses. For 17 patients, pharmacy data were missing or incomplete. Secondary outcomes included mortality and readmission rates. The researchers adjudicated hospital readmissions based on the medical records and blinded for group assignment.

Statistical analysis

The trial was powered for a non-inferiority comparison for guideline adherence. Non-inferiority for guideline adherence was considered proven if the lower limit of the 1-sided 95% CI of the difference between adherence during the GP follow-up and the HF clinic follow-up did not exceed a margin of 20%. In total 75 patients randomized to receive standard care and 75 patients to receive primary care are needed to demonstrate non-inferiority assuming a standard care guideline adherence rate of 60% and a power of 80%. Categorical variables, including the primary endpoint, were compared with the chi-square test or Fisher's exact test, where appropriate. Continuous data were presented as a mean $\pm$ SD or median plus interquartile range (IQR), depending on the distribution of the data. Mann-Whitney *U* tests were used for comparison of non-normally distributed continuous data and Student *t* test for normally distributed continuous data. The analysis of the secondary primary endpoint, patient adherence, was performed by using the Mann Whitney *U* test for non-normally distributed percentages or medication possession ratio's. Incidence rates and incidence rate differences per year were determined for death and readmissions per treatment group. A *p*-value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS, Chicago version 12.0 and STATA,

College Station, Texas, version 12.1 on an intention to treat basis.

Results

Patients

A total of 419 patients met the inclusion criteria (Figure 1). Of these, 230 were not willing to participate for various reasons such as ‘not willing to be referred to their GP’ (n=160), ‘not willing to visit the HF clinic’ (n=12), ‘participation too stressful’ (n=34), ‘refusal to participate in research studies’ (n=21), and other reasons (n=3). The remaining 189 patients were the present study population, and they were randomized to either follow-up in primary care (n=97) or follow-up at the HF clinic (n=92).

The mean age of the patients was 72 ± 11 years, and they were predominantly male (62%) and were mainly classified as NYHA II or III at baseline. Co-morbidities such as diabetes, COPD and atrial fibrillation were common and there were no significant differences in baseline characteristics between the groups (Table 1).

Primary endpoints

Guideline Adherence

Since titration to optimal, guideline recommended medication was an inclusion criterion, guideline adherence at baseline was high with 90 % and 87% in the PC and HF clinic group respectively. Guideline recommended medication rates were high with 90 % and 92% of patients having an ACE-I or ARB prescribed in the PC and HF clinic group respectively.

Primary care, as compared with follow-up at the HF clinic, resulted in similar rates of guideline adherence at 12 months follow-up (81% and 80%, respectively; difference, 1.0 % ; 95% CI, -10 % to 12 %; *P* for non-inferiority <.001). In total 94% and 90% of patients had a

beta-blocker prescribed in the PC and HF clinic group respectively and 43% and 53% of patients had an MRA prescribed in the PC and HF clinic group respectively. Prescription rates at 12 months follow-up were comparable-similar with baseline rates (Table 2)

Guideline adherence, as estimated by the Guideline Adherence Indicator (GAI-3), did not show significant differences between both treatment groups at baseline nor at 12 months follow-up (Table 2 and 3).

Patient adherence

Medication Possession Ratio (MPR) was calculated per therapeutic class (ACE-I/ARB, beta-blocker and MRA) using a fixed 1-year period (365 days) following date of randomisation. Analyses of patient adherence data is based on 120 patients (Table 4). Patients who died during follow up (n=20) and patients that had their drugs weekly delivered automatically by a multi-dose medication dispense system (n=31) were excluded from these analyses. For 18 patients, pharmacy data were missing or incomplete. During follow-up, no significant differences between patients in the PC group and patients in the HF clinic group were found for any of the medication classes nor for the average total score. Patient adherence in terms of MPR was high for both ACE-I/ARB (93.5% and 95.2% in the PC group and HF clinic group respectively) and beta-blockers (93.5% and 94.9% in the PC group and HF clinic group respectively). Patient adherence for MRA was 87.1% in the PC group and 93.3% in HF clinic group.

Secondary outcomes

During the 12 months follow-up period 20 patients died, 12 (12%) in the PC group and 8 (9%) in the HF clinic group (p=0.48). In total 42 patients had an unplanned rehospitalisation within 12 months, 25 patients in the PC group and 17 patients in the HF clinic, resulting in a

total of 58 unplanned hospital readmissions, with 13 patients being hospitalized more than once (Table 5). Readmissions for HF and other cardiovascular reasons were ~~comparable~~ similar in both treatment groups (8 vs 7 for HF and 5 vs 6 CV reasons in the PC group versus the HF clinic group respectively).

The number of unplanned non-CV hospital readmissions tended to be higher in the PC group with 22 versus 10 readmissions in the HF clinic group ($p=0.05$). Some patients had more than one non-CV readmission, and the difference in number of patients readmitted between both groups was not significant ($p=0.09$). Reasons for these non-CV hospital readmissions in both treatment groups are presented in table 6.

Discussion

The COACH-2 study compared guideline adherence and patient adherence in two different HF care delivery models, i.e. home-based management by the general practitioner in primary care versus hospital-based management in a HF clinic, in patients initially managed and up-titrated to optimal treatment at the specialized HF clinic. The main finding of the study is, that after initial uptake and optimization of HF treatment in a specialized HF clinic, long-term follow-up by general practitioners in primary care is ~~comparable~~ similar, i.e. non-inferior in terms of guideline adherence and adherence with medication in patients. During follow-up, the number of deaths as well as the number of hospitalizations for CV were ~~comparable~~ similar between groups, while the number of non-CV hospitalizations tended to be higher ($p=0.05$) in the primary care group.

The present findings are in line with the results of the NorthStar study¹⁰, which showed that clinically stable HF patients, on optimal medical therapy can be safely referred back to follow-up in primary care in terms of mortality and HF readmissions. The current

study provides additional evidence in that long term follow-up at a HF clinic does not lead to a benefit in terms of guideline adherence and patient adherence in clinically stable patients with mild to moderate HF.

Despite optimal treatment and presumed clinical stability, 20 out of 189 patients died within a year and 58 unplanned hospital admissions occurred. More than half (55%) of these hospitalizations were for non-CV reasons which is in line with the results of the first COACH study.⁷ Importantly, we observed more non-CV hospital admissions in the primary care group compared to the HF clinic group, although this was of borderline statistical significance. This relatively high number of non-CV hospitalizations confirm the complexity of the HF syndrome, which is associated with a large number of co morbidities, particularly in the elderly.^{22,23} Although non-significant, baseline differences between both treatment groups e.g. the prevalence of diabetes may have influenced the difference in non CV hospitalisations. Along with these multiple co morbidities, the clinical course of HF patients is often unpredictable with clinically stable phases interspersed with periods of exacerbation and deterioration finally ending in a terminal phase.²⁴ Over time, patients' needs, treatment and care may become more complex, often requiring regular adjustments. Continuous monitoring of the patients' condition is therefore needed and intensive collaboration between primary care and specialized HF care will be crucial in these phases to determine how and where best treatment and care can be provided according to the patient's needs. The ultimate goal, as described by the ESC Heart Failure Association²², can be described as 'to provide a "seamless" system of care across primary care and hospital care so that management of every patient is optimal, no matter where they begin or continue their health care journey'.

There are potential limitations to the present findings. First, the number of patients enrolled is relatively small and was not powered to detect significant differences in terms of mortality nor the number of hospitalizations. Secondly, it is important to notice that the

generalizability of our study results is limited to the specific conditions that were applied within in the COACH-2 study. The study included clinically stable patients with systolic dysfunction who were optimally treated and educated at a specialized HF clinic, mainly classified as NYHA class II, who were followed for a period of 12 months. Whether our conclusion is also generalizable on a longer term and to more severe HF patients remains to be established. Furthermore, a substantial number of patients did not want to participate in the study, mainly because of their preference to receive follow-up care at the HF clinic. This finding may have biased our study population towards patients that are willing to be treated in primary care. Interestingly, this phenomenon was also reported by Stewart et al.⁹ in the WHICH? trial. Since it is acknowledged that patient preferences are vital in delivering optimal health care²⁵, patient's preferences for a specific delivery model of HF care may be an important dilemma in terms of delivering the patient's choice of care on the one hand versus cost effectiveness on the other hand. Finally, as far as the applicability of our findings to other countries is concerned, health care in the Netherlands is known as a primary care-based system where the GP acts as the gate-keeper for secondary care and where patients can consult their GP with only limited costs involved²⁶. This low threshold may generally be advantageous, but it cannot be excluded that some patients in the present study who were in the HF clinic group, also consulted their GPs when they felt that was necessary. General practitioners are well educated, working with high quality guidelines for many chronic diseases including HF.¹⁹ European practice guidelines are endorsed by the different echelons of health care professionals in the Netherlands. These conditions may be different in other countries with other health care systems; results may therefore not be generalized to countries with other health care- and educational systems.

Conclusion

Patients discharged after initial management, up-titration and education at a specialized HF clinic can be discharged to primary care for long-term follow-up with regard to maintaining guideline adherence and patient adherence. This study investigated the first step in optimizing the structural involvement of the GP in long-term HF management. The uptake of treatment and up-titration of medication by GPs in primary care could be a next step that needs further research. The complex clinical picture of HF and the high number of associated co morbidities needs continuous monitoring. Moreover, close collaboration between healthcare professionals will remain crucial to provide HF patients with integrated, optimal HF care that best fits patients in the different phases of their disease trajectory.

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Conflict of interest

None to declare

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Table 1. Baseline characteristics per treatment group (mean/sd or n/%)

	Primary Care (n=97)	HF clinic (n=92)
Demographics		
Age	73 (± 10)	72 (± 12)
Gender (female)	36 (37%)	36 (39%)
Medical History		
Myocardial Infarction (MI)	43 (44%)	35 (38%)
Diabetes (type I and II)	28 (29%)	15 (16%)
COPD	18 (19%)	17 (18%)
History of Atrial Fibrillation	45 (46%)	33 (36%)
Admission in past 6 months	10 (10%)	7 (8%)
Heart Failure/Clinical		
NYHA class		
NYHA I	12 (12%)	7 (8%)
NYHA II	75 (77%)	69 (75%)
NYHA III	10 (10%)	16 (17%)
NYHA IV	-	-
Blood pressure (mmHG)		
Systolic	119 (± 16)	120 (± 20)
Diastolic	69 (± 9)	71 (± 11)
Heart rate (bpm)	69(16/44-150)	71 (11/44-100)
LVEF (%/sd)		
At diagnosis	32 (± 9)	31 (± 9)
Most recent	40 (± 11)	37 (± 11)
Aetiology		
Ischemic	47 (48%)	43 (47%)
Duration of HF (days)	1134 (1312)	1095 (938)
≤ 2 years	51 (53%)	46 (50%)
> 2 years	46 (47%)	46 (50%)
Laboratory (median or mean/sd)		
NT proBNP (ng/L) (median/Q1-Q3)	1115 (410-1771) (n=77)	825 (360-2142) (n=69)
Sodium (mmol/L)	140 (± 2.7)	139 (± 5.7)
Potassium (mmol/L)	4.3 (± 0.5)	4.4 (± 0.4)
Creatinine (umol/L)	110 (± 32)	108 (± 37)
GFR (mL/min x 1.73m ²)	57 (± 18) (n=64)	58 (± 19) (n=63)
Medication Class Adherence		
ACE-I or ARB	88 (91%)	85 (92%)
Beta-blocker	91 (94%)	83 (90%)

MRA	42 (43%)	49 (53%)
Other cardiac medication		
Diuretics	79 (81%)	79 (86%)
Thiazide	5 (5%)	3 (3%)
Digoxin	14 (14%)	14 (15%)
Statins/Lipid lowering agents	54 (56%)	50 (54%)
Nitrates	15 (15%)	17 (19%)
Anticoagulants	54 (56%)	54 (59%)

Table 2. Medication Class Adherence at baseline and 12 months

	Primary Care		HF clinic	
	Baseline (n=97)	Follow-up (n=85)	Baseline (n=92)	Follow-up (n=83)
ACE/ARB	88 (91%)	77 (91%)	85 (92%)	74 (90%)
Beta-blocker	91 (94%)	79 (93%)	83 (90%)	76 (93%)
MRA	42 (43%)	41 (48%)	49 (53%)	44 (54%)

Table 3. GAI-3 total scores at baseline and 12 months per treatment group

	Primary Care	HF clinic	<i>P</i>
	% (95% CI)	% (95% CI)	
GAI-3 total baseline*	95.0 (91.8-98.2)	94.6 (91.0-98.1)	0.85
GAI-3 total 12 months*	91.6 (87.7-95.4)	91.1 (86.9-95.3)	0.87
Difference	-3.4 (-5.6- -1.3)	-3.4 (-6.0- -.90)	0.99

* MRA corrected for NYHA class

Table 4. Patient compliance in medication possession ratio (MPR) per medication class at 12 months

	Primary Care	HF clinic	difference
ACE-I/ARB	93.5% (n=51)	95.2% (n=53)	0.67
Beta-blocker	93.5% (n=57)	94.9% (n=56)	0.42
MRA	87.1% (n=23)	93.3% (n=26)	0.28
Average total score	92.3% (n=61)	94.4% (n=59)	0.10

Table 5. Numbers and incidence rates of death and readmissions per treatment group

	Primary Care (n=97)	IR/yr	HF clinic (n=92)	IR/yr	IR dif (95%CI)
Total number of deaths	12	0.128	8	0.092	- .036 (-.133-0.061) P=0.481
Cause of death					
CVA	1		1		
Heart failure	2		2		
Other CV disorders	0		1		
Other non CV disorders	6		1		
Unknown	3		3		
Total number of readmissions for HF	8	0.082	7	0.076	-0.006 (-0.086-0.073) P=0.882
Total number of readmissions CV	5	0.052	6	0.065	-0.014 (-0.055-0.083) P=0.710
Total number of readmission non-CV	22	0.227	10	0.109	-0.118 (-0.234- -0.002) P= 0.05

Table 6. Non CV hospital readmissions in the Primary Care group and in the HF clinic group

Reason for readmission (MeDRA code)	Primary Care (n)	HF clinic(n)
Hypoglycaemia	1	-
Hyperglycaemia	1	-
Nausea and vomiting symptoms	3	1
Asthenic conditions	2	1
Electrolyte and fluid balance conditions	1	1
Melaena	3	1
Respiratory tract infections	5	-
Bronchospasm and obstruction (COPD)	1	-
Dyspnoea	1	-
Gastrointestinal therapeutic procedures	-	1
Abdominal and gastrointestinal infections	-	1
Skin lesion excisions	1	-
Ribfracture	-	1
Lower limb fractures and dislocations	1	
Bone related signs and symptoms	-	1
Infectious arthritis	-	1
Non-site specific procedural complications	1	-
Inguinal hernia	1	-
Poisoning and toxicity	-	1
Total	22	10

Figure 1 Flow diagram; screening, randomization, follow-up and analyses