Novel markers in chronic heart failure

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Added value of a physician-and-nurse-directed heart failure clinic. Results from the Deventer-Alkmaar heart failure study (DEAL-HF).

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■ Abstract

Aim: To determine whether an intensive intervention at a heart failure (HF) clinic by a combination of a clinician and a cardiovascular nurse, both trained in HF, reduces the incidence of hospitalisation for worsening HF and/or all cause mortality (primary endpoint) and improves functional status (including left ventricular ejection fraction, NYHA class and quality of life) in patients with New York Heart Association (NYHA) class III or IV.
Setting: Two regional teaching hospitals in The Netherlands.
Methods: 240 patients were randomly allocated to the 1-year intervention (n=118) or usual care (n=122). The intervention consisted of nine scheduled patient contacts - at day 3 by telephone, and at week 1, 3, 5, 7 and month 3, 6, 9 and 12 by a visit- to a combined, intensive physician-and-nurse-directed HF outpatient clinic, starting within a week after hospital discharge or referral from the outpatient clinic. Verbal and written comprehensive education, optimisation of treatment, easy access to the clinic, recommendations for exercise and rest, and advice for symptom monitoring and self care were provided. Usual care included outpatient visits initialised by individual cardiologists in the cardiology departments involved and applying the guidelines of the European Society of Cardiology.
Results: During the 12 months study period the number of admissions for worsening HF and/or all-cause deaths in the intervention group was lower than in the control group (23 vs 47; relative risk (RR) 0.49; 95% confidence interval (CI) 0.30, 0.81; p= 0.001). There was an improvement in left ventricular ejection fraction (LVEF) in the intervention group (plus 2.6%) compared to the usual care group (minus 3.1%; p= 0.004). Patients in the intervention group were hospitalised for a total of 359 days compared with 644 days for those in the usual care group. Beneficial effects were also observed on NYHA classification, prescription of spironolactone, maximally reached dose of beta-blockers, quality of life, self-care behaviour and health care costs.

Conclusion: A heart failure clinic involving an intensive intervention by both a clinician and a cardiovascular nurse, substantially reduces hospitalisations for worsening HF and/or all cause mortality and improves functional status, while decreasing health care costs, even in a country with a primary care-based healthcare system.

■ Introduction

Despite survival benefit due to new medical strategies, the prognosis of patients with heart failure (HF) remains poor. Studies consistently show 5-year survival rates between 35% and 60%[1-4]. A prospective study of patients hospitalised for HF showed that about 50% of early re-admissions were preventable, with factors such as poor compliance with medication or diet, suboptimal discharge planning and follow-up and inadequate self management by patients in case of worsening symptoms of HF being the most important determinants of deterioration[5].

HF management programmes could be the answer for this. Many randomised studies of HF management programmes have been performed in the United States, Australia and Europe[6,7]. Methodological limitations of these studies include the short follow-up periods and relatively small sample sizes, whereas heterogeneity in setting and intervention programmes[8] hamper the applicability of results. Of the 21 randomised trials mentioned in a recent review[8] five showed a reduction in the combined end point of all-cause readmissions and/or mortality[9-13], two studies reported a statistically significant reduction in the combined end point of readmission rates for HF and/or death[14,15] and only 1 reported a statistically significant reduction in total mortality[13].
A study on discharge education published later showed a reduction in the total number of deaths and days in hospital[16]. A study on telephonic disease management showed a statistically significant survival benefit[17]. Overall, multidisciplinary HF management programmes seem to be effective, but they have to be validated for various settings.

In several articles[6,18,19] it has been suggested that greater benefit could be expected from a HF management programme if a clinician trained in HF is more directly involved. One trial demonstrated a beneficial effect with an intervention based on a physician-directed HF clinic assisted by nurses and the patient's primary care physician[20]. A HF clinic with an intensive standardized intervention by a combination of a clinician and a cardiovascular nurse has not been studied yet. This was one of the justifications for our prospective, randomized parallel group trial aimed at estimating the effects of an intensive physician-and-nurse-directed intervention on hospitalisation for worsening HF and/or all cause mortality and on functional status. In addition, we wondered whether such a HF clinic would be beneficial in countries such as The Netherlands and the UK, where general practitioners act as gatekeepers for secondary care, with high quality guidelines for many chronic diseases, including HF.

■ Methods

Patients
We performed a parallel group, randomised controlled trial, with measurements at baseline, after 3 months and at the end of the study at 12 months. The local ethics committees of the participating Deventer and Alkmaar hospitals approved the study.

Patients either hospitalised or visiting the cardiology out patient clinic, with New York Heart Association (NYHA) class III or IV HF, who gave written informed consent, were eligible for the study. A diagnosis of HF was established by typical clinical signs and symptoms of HF in conjunction with echocardiographic or radionuclide ventriculographic findings of a reduced left ventricular systolic function left ventricular ejection fraction (LVEF) ≤45% or of a diastolic dysfunction with preserved left ventricular systolic function, according to the 2001 guidelines for the diagnosis of HF of the European Society of Cardiology[21]. The exclusion criteria were having dementia or psychiatric illness, having been discharged to or staying in a nursing home, having any disease other than HF with an expected survival of undergoing ≤ 1 year, participation in another randomised trial, being under on-going or planned hospitalisation and undergoing kidney function replacement therapy. After screening, eligible patients were randomised by computer-generated allocation to either the intervention group or the control group.

■ Intervention

The intervention, performed in addition to usual care, consisted of an intensive follow-up of the patients during one year at a HF outpatient clinic led by a HF physician and a cardiovascular nurse. The actual intervention commenced within a week after hospital discharge or referral from the outpatient clinic with a telephone call. At the first visit (at week 1) and second visit (at week 3) to the HF clinic, verbal and written comprehensive education was imparted about the disease and the aetiology, medication, compliance and possible adverse events. Patients were advised about individualised diet with salt- and fluid restriction, weight control, early recognition of worsening HF, when to call a healthcare provider and about physical exercise and rest. A patient diary was given. Easy access to the clinic was offered during working hours. An appointment with a dietician was made. The nurse asked the patient about his or her social and medical circumstances, and performed a short physical examination. The physician assessed, after a short review given by the nurse, the clinical condition of the patient, the laboratory results and ECG, performed a physical examination and,

Table 1. Baseline characteristics of the study patients.

Characteristics	Intervention Group (N=118)	Control Group N=122)
Demography		
Mean age (years)	70±10	71±10
Male	78(66%)	96(79%)
Living alone	23(20%)	21(17%)
CHF		
Aetiology CHF: Ischemia	60%	65%
Prior admissions for CHF	48%	51%
Mean LVEF*	31%	31%
Systolic dysfunction	98%	98%
Diastolic dysfunction	34%	30%
NYHA III†	98%	95%
NYHA IV	2%	5%
Co-Morbidity ‡		
Ischemic heart disease	60%	55%
Myocardial infarction	53%	56%
Current angina	15%	16%
Prior stroke	11%	9%
PTCA‖/CABG¶	14%/20%	16/27%
Atrial fibrillation	25%	28%
Pacemaker	10%	7%
Hypertension	39%	43%
COPD**	29%	28%
Current smoker/ ex-smoker	12 % /54%	14% /52%
Diabetes mellitus	31%	28%
Anaemia	21%	12%
Hypercholesterolemia	54%	43%
Laboratory values		
NT proBNP (pmol/l) and (pg/ml) ††,‡‡	262/2216	244/2064
Erythropoietin (mU/ml)	24	26
Haemoglobin (mmol/l)	8.4	8.4
hs-CRP (mg/L)	11.5	13.7
Potassium (mmol/l)	4.4	4.4
Creatinine (µmol/l)	123	130
Microalbumin./creatinine ratio (mg/mmol)	23	20
Blood urea nitrogen (mmol/l)	11	11
Mean systolic blood pressure (mmHg)	123	125
Mean diastolic blood pressure (mmHg)	73	76
Mean heart rate (bpm)	79	78
Medication at entry		
Diuretics	97%	96%
ACE inhibitor	84%	88%
Angiotensin receptor blocker	14%	8%
Beta-blocker	60%	69%
Spironolactone	36%	30%
Long acting nitrate	19%	17%
Digoxin	23%	27%
Anticoagulant agents	62%	67%
Acetyl salicylic acid	31%	23%
Statins	44%	33%
NSAID's §	3%	5%

*LVEF= Left Ventricular Ejection Fraction; †NYHA= New York Heart Association classification
‡ More than one item possible; ‖ PTCA= Percutaneous Transluminal Coronary Angioplasty; ¶CABG= Coronary Artery Bypass Graft; **COPD= Chronic Obstructive Pulmonary Disease; †† Values are medians ‡‡To convert from pmol/l to pg/ml
multiply by 8.457; § NSAID's= Non-Steroid Anti-Inflammatory Drugs

together with the nurse, proposed a treatment regimen. At the regular follow-up visits at week 5 and 7, and at months 3, 6, 9 and 12, the nurse provided counseling, check-up and reinforcement of the education and performed a short physical examination. At six of the nine follow-up visits, the physician assessed the condition of the patient, optimised (medical) treatment and performed an overall assessment together with the nurse. The intervention was described in more detail elsewhere[8].

Control Group

The cardiologists of the Deventer and Alkmaar cardiology department are known for their special interest in HF. They treated the patients with HF by randomisation to routine care, according to their "usual care". Their routine care was no doubt largely according to the guideline of the European Society of Cardiology prevailing at that time (version 2001) with optimal application of medical therapy including target dose or high dose of HF medication (see baseline medication, table 1). As we aimed to compare the intervention with routine care, we decided not to develop a special protocol for the management of the control group of the Deventer-Alkmaar heart failure (DEAL-HF) study. All cardiologists saw patients from the control group at their outpatient clinic.

Data collection

At baseline, 3 and 12 months LVEF was measured, NYHA classification assessed and plasma samples for neurohormone tests (NT-proBNP) were taken. Ejection fraction was measured by technicians blinded to the patient's intervention, either with a Philips Sonos 5500 (Philips Medical Systems, Best, The Netherlands) or with a Philips NZE28 Sonos 7500- Live 3D echo machine (Philips Medical Systems) (biplane Simpson's method) or by radionuclide ventriculography.

In addition, the patient completed quality of life questionnaires at baseline and after 3 and 12 months. Health-related quality of life was evaluated using the Rand Short Form 36 quality of life questionnaire[22], whereas disease-specific quality of life was assessed by means of the Minnesota Living with Heart Failure questionnaire[23,24]. Self-care behaviour was measured by the European Heart Failure Self-Care Behaviour scale[25] .

Clinical history, physical examination, blood and urine biochemistry and ECG were also recorded at baseline and after 3 and 12 months. A chest X-ray was taken at baseline only. Clinical and demographic data were collected from the patient and from chart review.

Hospitalisations during the study period were tracked by means of chart review, hospital databases and patient recall/diary. The cardiologist on call of the emergency room always assessed the need for hospitalization. He was not aware of the group to which the patient was allocated. Deaths were verified by chart reviews, hospital databases, general practitioner records and family recall. There

was no loss to follow-up. An external clinical endpoint committee, consisting of three experienced cardiologists and blinded to the allocation status of the patient, judged all causes of hospitalisation and death.
The costs of intervention were based on prospective data collection. Hospitalisation costs were based on the mean daily cost at a specific level of care. Outpatient clinic costs included the nurse's, dietician's and doctor's salary.

Study end-points
All study end points were pre-specified in the protoco[18]. The primary end point was the composite of incidence of hospitalisation for worsening HF and/all cause mortality. Additional end points included the effect on LVEF, NYHA class, quality of life, NT-proBNP, and self-care behaviour. Furthermore, time to death, utilisation of HF medication and costs of care were assessed.

Statistical aspects
The sample size was based on an incidence of the composite primary end point in the usual care group of 30% and an expected 50% reduction in this incidence in the intervention group. With an α of 5%, and a discriminating power of 80%, the total number of patients required in each treatment arm was 118. Statistical analysis was conducted according to the intention to treat principle. The frequencies of the primary outcome measure "occurrence of hospitalisation for worsening HF and/or all cause mortality" were compared and relative risks (RR) with 95% confidence intervals (CI) and risk difference (RD) were calculated. To adjust for possible confounding arising out of unequal distribution of the baseline characteristics, logistic regression analysis was performed with the primary outcome measurements as the dependent variable. For the change in normally distributed continuous variables, the Student's t-test was used. The Mann-Whitney U test was used to test the difference in no normally distributed continuous variables. The differences in change in quality of life were compared by the Wilcoxon rank-sum test. Differences between the groups were tested by the log rank test. In subjects who died or about whom these data were not available because of hospitalisation for worsening HF, LVEF, NYHA class, quality of life and NT-proBNP measurements, were assessed with the worst rank assigned. Because NT-proBNP measurements showed high values and a skewed distribution, natural logarithmic transformation was applied.

■ Results

Baseline characteristics

We screened 797 patients over a period of 3 years from March 2000- April 2003 (Fig.1). Of these, 221 patients were not eligible according to the exclusion criteria (125 NYHA I-II; 37 terminal illness; 15 participation in other studies; 22 cognitive dysfunction; 22 planned hospitalization). Among the 979 patients, the reasons that 103 did not participate included the presence of a variety on non-cardac disorders, having sick relatives, and sometimes unknown. Of the 473 patients who were eligible, 81 refused to participate mainly because they felt participation in the study would be too tiring and/or the travel distance was too large and 152 refused because they did not want to participate in a randomised trial at all. Eventually 240 of the 473 eligible patients (51% (30% of the 797 screened patients)) gave written informed consent and were randomly allocated to the intervention group (n=118) or to the usual care group (n=122; fig.1).

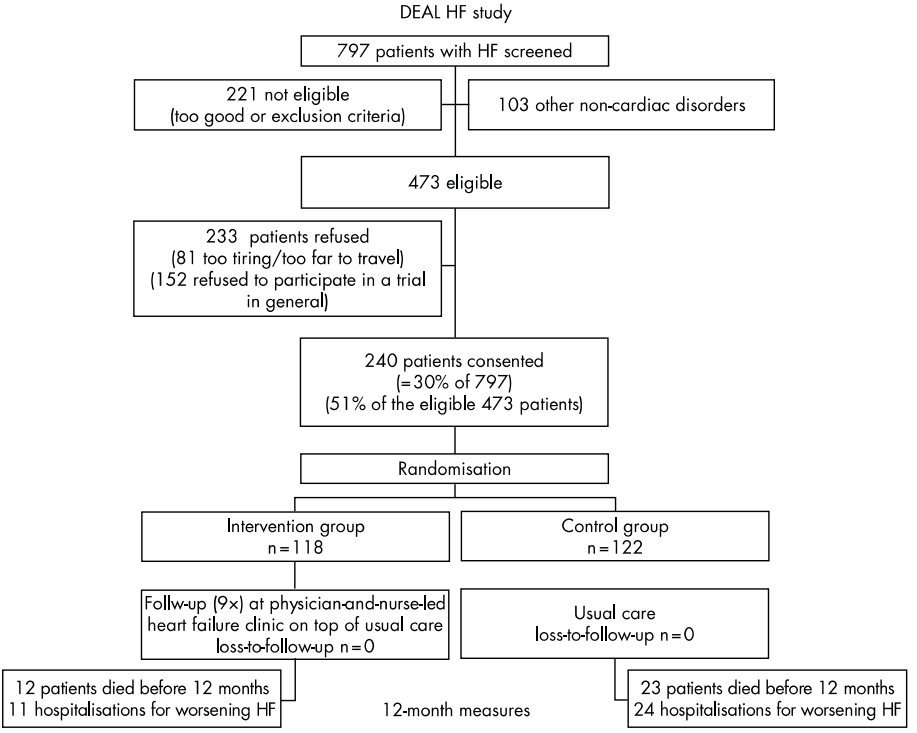

Figure 1. Flow chart of the trial

Of these, 31% were hospitalised due to HF at time of recruitment and 69% was referred from the cardiology outpatient clinic. The mean age of the patients in the included group was 71 years (male 70.5 years, women 72 years); that for the total group was 72 years and that for the not-included group 74.0 years (male 72.6 years, women 76.4 years). The percentage of male patients in the included group was 72%, in the total group 71% and in the not-included group 70%. In all, 96% were in NYHA functional class III (table 1). The mean ejection fraction was 31%. The two groups were well balanced with respect to baseline characteristics except for sex.

Effect on hospitalisation for worsening HF and/or all cause mortality.
The incidence rate of this composite end point was 20.7 per 100 patient years in the intervention group and 42.2 per 100 patient years in the usual care group: rate ratio 0.49 (95% CI 0.30 to 0.81; p=0.001) and rate difference 21.5 (95% CI 0.07 to 0.36) per 100 patient years (table 2). Twelve patients in the intervention group died during the intervention period and there were 11 hospitalisations for worsening HF in this group, compared with 23 deaths and 24 hospitalisations for HF in the usual care group. Of the 12 deaths in the intervention group 7 were sudden deaths, 2 were non-cardiovascular deaths and 3 were terminal HF deaths. In the usual care group, there were 12 sudden deaths, 8 non-cardiovascular deaths and 3 terminal HF deaths.

Table 2. Effect of a nurse- and- physician -directed HF clinic on hospitalization, death and days in hospital

Variable	Intervention group	Usual care group N=122	Rate Ratio (95% Confidence Interval)	Rate Difference (95% Confidence Interval) Numbers needed to treat (NNT)
Hospitalisation for CHF and/or death	23 (Incidence rate: 20.7 per 100 patient years)	47 (Incidence rate: 42.2 per 100 patient years)	0.49 (0.30, 0.81)	0.215 (0.07,0.36) NNT 5
Death (all cause)	12 (Incidence Rate: 10.8 per 100 patient years)	23 (Incidence Rate: 20.6 per 100 patient years)	0.52 (0.26, 1.05)	RD 0.098 NNT 10
Days in Hospital	359 (Incidence rate: 324 per 100 patient years)	644 (Incidence Rate: 578 per 100 patient years)	0.56 (0.49, 0.64)	RD 2.54 NNT 0.4

Ventricular function and NYHA classification

After 3 months there was no difference (p= 0.22) in LVEF between the intervention and the usual care group. At 12 months, however, the LVEF had improved in the intervention group, whereas that in the usual care group decreased (p= 0.004; table 3). After 3 months and 12 months the NYHA class had significantly improved in the intervention group compared with the usual care group (p<0.001 for the difference at 3 and 12 months; table 3).

Table 3. Effect of a nurse-and-physician-directed HF clinic on LVEF, NYHA class, NT proBNP, Quality of life and Self-Care Behaviour.

Variable	Intervention Group N=118	Control Group N=122	P-value
LVEF (with worst rank)			
- At baseline	30.6%	31.3%	p= 0.554
- At 3 months	30.6%	30.0%	p= 0.220
- At 12 months	33.2%	28.2%	p= 0.004
NYHA classification (with worst rank)			
- At baseline NYHA III; IV	98%; 2%	95%; 5%	p= 0.387
- At 3 months NYHA I;II;III;IV	3.4%;43.6%;42.7%;10.3%	0.9%;12.8%;73.5%;12.8%	p< 0.001
- At 12 months NYHA I;II;III;IV	10.2%;50%;22.9%;16.9%	0%;18.9%;54.1%;27%	p< 0.001
NT-proBNP (pmol/l) and (pg/ml)‡† (with worst rank)			
- At baseline	244/ 2064 IQR 101-540	262/ 2216 IQR 123-520	p= 0.677
- At 3 months	198/ 1666 IQR 86- 643	226/ 1911 IQR 100-599	p= 0.397
- At 12 months	182/ 1539 IQR 68- 802	277/ 2343 IQR 96-2242	p= 0.089
Rand SF36			
Total score at baseline	45.12	46.77	p= 0.506
Total score at 3 months	49.63	46.41	p= 0.131
Total score at 12 months	49.23	41.92	p= 0.021
Minnesota Living with HF questionnaire			
Total score at baseline	42.5	42.6	p=0.958
Total score at 3 months	28.8	36.3	p=0.001
Total score at 12 months	30.2	34.5	p=0.038
European HF Self-Care Behaviour Scale			
Total score at baseline	23.6	25.5	p= 0.092
Total score at 3 months	20.8	26.3	p< 0.001
Total score at 12 months	23.8	30.2	p< 0.001
Creatinine levels			
At baseline	123 µmol/l	130µmol/l	p= 0.144
At 3 months	124 µmol/l	132µmol/l	p= 0.08
At 12 months	121 µmol/l	138 µmol/l	p= 0.002

‡Values are medians; †to convert from pmol/l to pg/ml multiply by 8.457

Quality of life

Improvement in Minnesota Living With Heart Failure Questionnaire (MLWHFQ) scores at 3 months was greater in the intervention group than in the usual care group (p=0.001) and this difference persisted during the remaining 9 months (table 3). At 3 months, there was no statistically significant difference in the total score of the Rand Short Form 36 (p=0.131). At 12 months, the change from baseline in the intervention group compared whith that in the usual care was more pronounced (p=0.021).

Other outcome variables

The differences in median values of the NT-proBNP measurements at baseline, 3 and 12 months between the intervention group and the usual care group were not statistically significant. (Mann-Whitney tests at baseline (U=6795; Z=20.416; p=0.677), 3 months (U=6019; Z20.848; p=0.397) and 12 months (U=5604; Z=21.699; p=0.089; table3)). The values of the natural logarithm of NT-proBNP in the intervention group vs. the usual care group at 3 and 12 months were 5.43 vs. 5.58 (p=0.131) and 5.37 vs. 5.71 (p=0.070) respectively.

The mean time to death was 343 days in the intervention group and 333 days in the usual care group (p=0.06).

The scores of the European Heart Failure Self-Care Behaviour Scale (EurHFSCBSc) were significantly better in the intervention group than in the usual care group, both after 3 and 12 months of follow-up (table 3).

Table 4. Utilisation of medication

	% Receiving drug Baseline			% Receiving drug 12 months			Maximally reached dose during study		
	Usual care (n=122)	Intervention group (n=118)	p	Usual care (n= 99)	Intervention group (n=106)	p	Usual care	Intervention group	p
ACE inhibitors	88%	84%	NS	91%	83%	0.067	14.2mg	14.3 mg	NS
ARB's	8%	14%	NS	12%	25%	0.008	139mg	154 mg	NS
ACE's and/or ARB's	94%	96.6%	NS	102.5%	107.7%	NS			
Beta-blockers	69%	60%	NS	79%	78%	NS	106mg	135 mg	0.005
Spirono-lactone	30%	36%	NS	41%	60%	0.003	27 mg	25 mg	NS

For the ACE inhibitors: the dosages were converted to enalapril-equivalent dose for comparison; for the angiotensin receptor blockers (ARB's) to valsartan-equivalent dose; for the beta-blockers to metoprolol succinate-equivalent dose for comparison.

There was a statistically significant difference in the prescription of spironolactone in the intervention group compared with the usual care group (60% vs 41%; p=0.003) after 12 months. No statistically significant differences were observed in the prescription or dose of ACE inhibitors and angiotensin receptor blockers (ARBs) and the prescription of β-blockers. Importantly, the maximally reached dose of β-blockers was significantly higher in the intervention group (table 4). Finally, creatinine levels were lower in the intervention group than in the usual care group at 3 months and 12 months (table 3). The mean number of visits of the patients to their cardiologist was 0.79 in the intervention and 1.43 in the usual care group (p< 0.001). The number of days in hospital constituted the major difference in costs between the two groups. Patients in the intervention group were hospitalised for a total of 359 days compared with 644 days for patients in the usual care group.
The difference between the costs of hospitalisation in the intervention group (€ 65,046 US$ 86 849 £ 44 103) and the usual care group (€ 202,728 US$ 270 648 £ 137 338) was € 137,682 (US$183 834 £93 279) . The total costs for the HF clinic programme (for the salary of the HF nurse, HF physician and the dietician, and for the extra lab and ECGs) were € 50,246.00 (US$ 67 093 £ 34 038). As a result, the positive balance for the intervention group was € 87,436 (US$ 116 764 £ 59 238) and the difference in the overall cost of care per patient was € 741 (US$ 989 £ 502).

■ Discussion

This 12 month intervention in an intensive, combined physician-and-nurse-directed HF clinic led to a 51% risk reduction of the primary end point - incidence of hospitalisation for worsening HF and/or all cause mortality - in comparison with usual care. Positive effects were also observed for LVEF, NYHA class, prescription of spironolactone, maximally reached dose of β-blockers, quality of life and health care costs.

Compared to most previous HF management studies[9,13,15,19,26-29], our patients were probably in a slightly worse condition, as 96% were in NYHA class III at randomisation and the mean LVEF was 31%.
As much as 69% of our included patients were not hospitalised but were referred by a cardiologist from the outpatient clinic. This is the first time that so many outpatients with NYHA III or IV were included in such a trial and it is relevant to know that this type of intervention can also be effective for this large target group. Although the content of the education included in our intervention was similar to those of earlier studies, our approach is rather unique in its intensive intervention by a combination of a clinician and a cardiovascular

nurse, both trained in HF. Several studies have reported collaboration with a cardiologist or a general physician as a consultant but not in such a standardised manner[11,13,19,26,27-30]. One study reported a physician directed HF clinic assisted by nurses and with a scheduled visit to the general practitioner[20]. In addition our 1-year intervention with 9 visits at the HF clinic and one telephone call is more intensive than those reported in most previous studies, except the home-based intervention of Naylor[31] and some studies with telemonitoring[9,15,26,32]. In a study by Doughty et al in New Zealand[19], regular clinical follow-up during 12 months was provided alternating between the general practitioner and the HF clinic, complemented by group education sessions, conducted by the nurse and a cardiologist. Several methodological aspects of this study were comparable to those of our study. The obvious differences with our study are the integrated involvement of primary care and the group education sessions in the New Zealand study and the structural involvement of a HF physician in our study. Interestingly, the study of Doughty did not show a statistically significant effect on the combined end point of hospitalisation or death.

Jaarsma et al[18] studied the effect of education and support by a nurse on self-care and resource utilization in patients with HF in the Netherlands. The education and support was provided during the hospital stay and at one home visit within a week of discharge. After 1 month, a statistically significant difference in self-care behaviour was observed in the intervention group compared with the usual care group. No statistically significant differences were found in the mean number of readmission days or with the number of readmissions between the two groups at the end of the 9-month study period. Jaarsma et al concluded that longer follow-up and the availability of a HF specialist would probably enhance the effects of education and support. This was applied successfully in our study.

In a recent study by Strömberg et al[13] the HF clinic was staffed by nurses, with delegated responsibility for making protocol-led changes in medications. If treatment needed to be optimised, a cardiologist was consulted. The first follow-up visit was planned 2-3 weeks after discharge and the 106 patients were followed for 12 months. Most patients visited the HF clinic only once. A major effect on mortality was observed after 12 months (7 vs. 20, p=0.005). The intervention group had fewer admissions and days in hospital during the first 3 months, but there was not a long-term effect. This may have been due to the noticeable high (37%) mortality in the control group. A more intensive follow-up would possibly have resulted in a more long-term benefit.

Several limitations of this study should be discussed. First, although we had a reasonable response from 30 % of the screened patients (51% of the 473 eligible patient's), many suitable patients were not enrolled for various reasons (fig.1). The baseline characteristics, however, show the applicability of this intervention. The modest differences between the included, the total and the not-included group can possibly be explained by the presence of slightly older women in the excluded group. Second, this study with a follow-up of 12 months does not answer the question of whether and how intensively the intervention should be continued. Third, our results cannot easily be extrapolated to other HF clinics, because most of these do not include a team of a nurse in close, standardised co-operation with a HF physician. Fourth, it should be emphasised that some information bias may have occurred because, inherent to this type of intervention study, patients can not be blinded to the intervention. We, however, feel that any bias is likely to be limited, because the effects of the intervention on the outcomes most likely to be influenced, such as quality of life measures, were modest.

In the last decade, the attention given to HF management has increased considerably. The standard of care for heart failure in The Netherlands, although not optimal[33,34], is already reasonably good in both primary care and secondary care. This is illustrated by the fact that at the start of the study 97% of the patients received ACE inhibitors or ARBs and 65% received β-blockers. The justification for our study was the question of whether a HF management programme with an intensive intervention according to protocol, by a combination of a HF clinician and cardiovascular nurse, would be able to provide additional benefits, even in a country with a primary care-based healthcare system, in which general practitioners act as gatekeepers for secondary care and with high quality primary care guidelines for many chronic diseases, including HF. The answer to this question is undoubtedly positive. Such an intensive management programme substantially reduces hospitalisation for HF and/or all cause mortality, while improving LVEF, NYHA class, quality of life and self-care behaviour, and achieving a reduction in costs.

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