Effects of heart failure management programmes

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(met een samenvatting in het Nederlands)

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Introduction and aims of this thesis

■ Introduction

Heart failure is a complex syndrome, characterized by symptoms such as shortness of breath at rest or during exertion and /or fatigue, and signs of fluid retention such as pulmonary congestion or ankle swelling and objective evidence of an abnormality of the structure or function of the heart at rest.[1]
The most common causes of heart failure are coronary artery disease and hypertension (70%). In addition, other causes are valve disease (10%), tachyarrhythmia such as atrial fibrillation (3%), cardiomyopathies (10%), alcohol, drugs, endocrine diseases and some more rare causes, such as some congenital diseases.[1,2]
The condition of chronic heart failure (CHF) presents a large and growing public health problem.[2,3] The prevalence of heart failure in the population at large is 2 to 3%. The prevalence steeply increases with age: in 70 to 80 year old people it is estimated at 10 to 20%.[1] As a result of the ageing of the population, improved treatment options for patients with cardiovascular disease, notably coronary artery disease and heart failure, and more effective prevention in those at high risk, the prevalence of heart failure is increasing. Of individuals aged 55, almost 1 in 3 will develop heart failure during their remaining lifespan.[4,5] Heart failure has a poor prognosis, with only 35% to 60 % surviving 5 years after the initial diagnosis.[4,5] This makes heart failure also an economic burden for society, that takes up 1-2% of health care budget, of which a major proportion (70%) is spent on (re)hospitalisations for heart failure.[6] A prospective study of patients hospitalised for heart failure showed that about 50% of early readmissions were preventable, with factors such as poor compliance with medication or diet, sub-optimal discharge planning and follow-up, and inadequate self-management by patients in case of worsening symptoms of heart failure being the most important determinants of deterioration.[7] There is no doubt that patients with heart failure, and their family and carers are in need of adequate information, education and support when the heart failure is diagnosed as well as during follow-up. Heart failure disease management programmes, in which a nurse and/or a clinician provide education and counselling about HF and symptoms of worsening, fluid regulation and low-salt diet, management of weight and drug therapy, exercise and psychosocial well-being and in which the medication regimen is optimised, could be the answer.

■ Heart failure management programmes

What is the evidence for the Netherlands?

Many randomised studies of heart failure management programmes (HFMP) have been performed in the United States, Australia and Europe[8-30], with considerable differences in patient characteristics, setting, intervention, sample size, follow-up period and outcome parameters. Many of these studies reported a reduction in readmissions for heart failure and in the overall readmission rates. As a consequence, a large number of heart failure clinics, either directed by a nurse or a multidisciplinary clinic of health care professionals, had been initiated in the Netherlands, without compelling evidence that HFMP work in the Dutch situation. The applicability of the results of available studies to countries with a primary-care based healthcare system, such as Denmark, the United Kingdom and the Netherlands and with easy access to medical care is debatable. The question arises whether a heart failure 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 clinical guidelines for primary care physicians for many chronic diseases, including heart failure. In addition, in several articles it had been suggested that greater benefit could be expected from a heart failure management programme, if, apart from an experienced cardiovascular nurse, also a clinician, trained in heart failure, would be more directly involved.[22,25,29] The effects of a heart failure management programme with an intensive, standardised intervention by a team including a combination of a cardiovascular nurse and a clinician had not been assessed yet. Both arguments were a justification for our prospective, randomised, parallel group trial, aimed at estimating the effects of an intensive physician-and-nurse-directed intervention on hospitalisation for worsening heart failure and/or all cause mortality and functional status in the Netherlands. In addition, it is important that the effects of such a management programme are compared to the costs involved to allow for an evidence-based decision whether such programmes should be implemented or not.

Importance of adherence and persistence

Adherence is defined by the World Health Organisation (WHO) as the extent to which a person's behaviour (taking medication, following diet, and/or executing lifestyle changes) coincides with agreed recommendations from a health care provider.[31] Although many studies have shown that pharmacotherapy can reduce morbidity and mortality in heart failure[32,33], adherence of prescribers to guideline-recommendations concerning heart failure medication (prescriber adherence) remains low.[34] In addition, low

adherence to prescribed medication regimens by patients is considered a major cause in mortality, morbidity and hospital readmissions in patients with heart failure. Heart failure management programmes with patient education and counseling, improved dosing schedules and improved communication between physician and patient may increase adherence to pharmacotherapy by prescribers and by patients with heart failure.[35,36] However, valid and precise quantification of the effect of a heart failure management programme on prescriber and patient adherence is virtually lacking. Specifically, most earlier studies did not include valid measurements of adherence (such as computerised pharmacy refill data) and the follow-up period was short (1-6 months). It is important to distinguish two different aspects of patient compliance with prescribed medication regimens; *patient adherence*, i.e., how the patients execute the prescribed medication regimen in terms of missed dosages, and *persistence*, i.e., how long patients continue to take the prescribed medicines.[37]

A role for changes in (NT-pro)BNP in monitoring patients with heart failure?

Brain natriuretic peptide (BNP) is a cardiac neurohormone mainly secreted by the cardiomyocytes of the cardiac ventricles as a response to ventricular volume expansion and pressure overload.[38] ProBNP is cleaved into BNP and the hormonally inactive remnant NTpro-BNP. These neurohormones have been shown to be elevated in patients with heart failure and related to the severity of the disease.[39] (NTpro-)BNP has an established role in the diagnosis and prognosis of heart failure.[40-45] More recently (NTpro-)BNP is being studied as a potential marker to tailor heart failure therapy.[46-52] Troughton et al, in a small study (n=69), showed that NTpro-BNP-guided treatment of HF reduces cardiovascular events and delays time to first event ($p=0.034$).[49] In a study by Jourdain et al, BNP-guided drug titration reduced the risk of CHF related death or hospitalisation for HF, mainly through an increase in ACE-inhibitor and beta-blocker dosages ($p<0.001$).[50] Heart failure treatment, however, is not also given to the patient to reduce cardiovascular events or hospitalisations, but also to improve a patients' quality of life. Therefore, it is relevant for clinicians to know whether long-term changes in (NTpro-)BNP are accompanied by changes in for patients more relevant variables, such as quality of life and functional status. To determine the quality of life perception in our study we used the disease-specific Minnesota Living With Heart Failure questionnaire (MLWHF)[53] and the physical and mental health composite score (PCS and MCS) of the MOS 36-item Short-Form Health Survey (SF-36), a health-related quality of life questionnaire[54].

■ The outline of this thesis

This thesis primarily focuses on heart failure management programmes in general and on a heart failure management programme directed by a physician and a nurse in the Netherlands in particular. In **Chapter 2** a literature search of randomised studies of heart failure management programmes is presented and essential methodological aspects, in particular the population involved, the sample size, follow-up period, setting, type of intervention and outcome parameters are discussed critically. Methodological limitations of these studies include the short follow-up periods and relatively small sample size, whereas heterogeneity in setting and intervention programmes hamper the applicability of the results. Finally, the rationale and the design of the DEAL-HF study (the Deventer-Alkmaar Heart Failure study) is presented.
In **Chapter 3** the results of the DEAL-HF study, a parallel group, randomised, controlled trial are presented. The aim of the trial was to determine whether an intensive 1-year intervention at a heart failure clinic by a combination of a clinician and a cardiovascular nurse, both trained in heart failure, reduces the incidence of hospitalisation for worsening heart failure and/or all cause mortality and improves functional status and quality of life in patients with heart failure, NYHA classification III or IV.
In **Chapter 4** the effects of the physician-and-nurse-directed heart failure programme, on adherence by the prescriber and on patient adherence and persistence are reported.
In **Chapter 5** we studied, using data from the DEAL-HF study, the correlation between long-term changes in the neurohormone NTpro-BNP and changes in quality of life and functional status in heart failure.
In **Chapter 6**, the effects of the physician-and-nurse-directed heart failure programme in patients with heart failure NYHA III or IV are compared with the costs involved .
Finally, the findings from the studies included in this thesis are discussed in the light of the current discussion whether heart failure programmes (and which programmes) should be implemented on a large scale and suggestions for future research to fill the remaining knowledge gaps are provided (**Chapter 7**).

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Heart failure programmes in countries with a primary care-based health care system. Are additional trials necessary? Design of the DEAL-HF study.

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■ Abstract

Background: Several randomised studies of heart failure (HF) management programmes in the United States, Australia and Europe have shown a considerable reduction in hospitalisation rates for HF. In this article, a comprehensive review of these studies will be provided and their applicability to countries, with a primary care-based healthcare system, will be discussed. In addition, the design of the Deventer-Alkmaar HF Project (DEAL-HF), a randomised study of the effect of a nurse and physician-directed intervention over 1 year in The Netherlands, will also be presented.
Aim: To discuss the applicability of the results of available studies on heart failure management programmes to countries with well-structured primary care facilities and to determine whether additional trials should be conducted in these countries.
Methods: We performed a literature search in PubMed. In a review of the available studies, essential methodological aspects, in particular, the population involved, the sample size, follow-up period, setting, type of intervention, and the outcome parameters, are discussed critically. Also, the applicability of these studies to countries with a primary care-based healthcare system and easy access to medical care is evaluated.
Conclusion: Applicability of the results of the available studies on the efficacy of heart failure management programmes to countries with a primary care-based health care system is doubtful. An efficacy trial in a country with a well-established primary care-based healthcare system, such as The Netherlands, is due to report soon (DEAL-HF).

Keywords: Heart failure; HF management programmes; Education

■ Introduction

In recent years, several randomised studies of heart failure management programmes in the United States[1-6], Australia[7-9] and Europe[10-14] have reported a considerable reduction in readmissions for heart failure and total readmissions. However, many of these studies are characterised by limited sample size, short follow-up period or limited accessibility to the healthcare system in the respective country. Furthermore, the setting and interventions of the heart failure management programmes differ considerably. Evidence of the cost-effectiveness and impact on outcomes of these programmes in countries with a primary care-based healthcare system and easy access to healthcare is not readily available. In this article, we will critically discuss the published randomised trials assessing the effectiveness of heart failure management programmes. Apart from methodological issues, the applicability

of the results of these studies to the European situation will be discussed. Finally, we present the rationale and design of the randomised, prospective trial, the Deventer–Alkmaar Heart Failure Clinic Project (DEAL-HF), which aims to evaluate the effect of a heart failure outpatient clinic in a country with an easy access primary care-based healthcare system.

■ Randomised studies of heart failure management programmes

We performed a literature search in PubMed of randomised trials published in English, assessing the effect of heart failure management programmes. In 2001, a metaanalysis was published of 11 of such trials.[15] Since this publication, many more relevant publications of randomised controlled trials have been reported. In Table 1, the characteristics of most of these trials are reported.[1,3-14,16-23] All trials are designed as prospective, randomised, controlled trials, thus minimising the possibility of bias. The important methodological aspects of these studies are as follows: (1) Patient characteristics: Most patients included in the trials were males (55%), and the mean age was 72.8 years. The seriousness of the disease varied from mild to very serious, NYHA I–IV, in the available studies (I–IV: two studies; II–IV: nine studies; III–IV: five studies; IV: one study). Not all studies provided information on the NYHA classification. (2) Setting: The setting of these heart failure management programmes varied widely and included primary care clinics, outpatient clinics, home visits, telephone monitoring and televideocare. Most studies were performed in countries with a less well-organised primary care system and more difficult access to medical care than in European countries with a wellestablished primary care-based health care system, such as Denmark, the United Kingdom and The Netherlands. (3) Intervention: Only few studies provided a precise description of the intervention and the intensity, thus limiting the applicability of the intervention. Some clinics were run by a nurse only, some by a nurse and a physician and some by a nurse and a multidisciplinary team. The number of visits related to the interventions also differed considerably. In addition, most studies tested multiple interventions, making it difficult to discern the optimal, i.e., most effective, combination of interventions. (4) Sample size: The sample size of the majority of the available studies was limited (mean: 190 patients; range: 60–504 patients). (5) Follow-up period: The follow-up period of most of the available studies was 6 months or less. One study reported a long-term effect after 4.2 years. (6) Outcome parameters: The outcome parameters studied varied greatly and included readmission rates, time to readmission, readmission-free survival and the combined endpoint readmission for CHF and/or allcause mortality. The findings of 21 randomised trials of the effect of heart failure management

Table 1 Characteristics of randomised trials of the effect of heart failure management programs

	No. of pat. interv./ UC duration intervention	Mean age/ male (%)	NYHA/ mean LVEF	(a) HF nurse, (b) cardiol. cons., (c) HF-trained. physician, (d) pharmacist, (e) dietician, (f) soc. services, (g) primary care physician, (h) remedial couns, (i) monitoring by caregivers, (j) physiotherapy	(a) inhospital education, (b) HFclinic	(a) home-based intervention, (b) primary care, (c) tel. contact, (d) telemonitoring	No of visits	Intervention: (a) (inhospital) education about CHF, (b) its treatment, (c) signs of worsening HF (fluid retention), (d) diet, (e) weight, (f) medication recommendations (self-management), (g) early discharge planning, (h) repeated reinforcements, (i) booklet, (j) exercise regimen, (k) group education
Rich 1995, USA	142/140 3 months	79 years/ male: 36.5%	II–IV/ 42.5%	a) CV nurse, b+ c− d− e+ f+ g− h− i+	a+ b−	a+ b− c+ d−	NA	a+ b+ c+ d+ e+ f+ g+ h+ i+ j− k−
Weinberger 1996, USA	249/255 6 months	63 years/ male: NA	I–IV/ NA	a) Primary care nurse, b− c− d− e− f− g+ h− i−	a+ b−	a− b+ c+ d−	3	a+ b+ c+ d+ e? f? g? h− i− j− k−
Stewart 1998, Australia	49/48 6 months	75 years/ male: 48%	II–IV/ 38.5%	a+ b− c− d+ e− f− g+ h+ i+	a+ b−	a) 0nce b− c− d−	2	a+ b+ c+ d ? e ? f+ g ? h− i− j− k−
Serxner 1999, USA	55/54 3 months	71 years/ male :NA	NA/NA	a+ b− c− d− e− f− g− h− i−	a+ b−	a) As needed, b− c− d−	1	a− b− c− d− e− f− g− h− i) mailed education information, j− k−
Stewart 1999, Australia	100/100 6 months	76 years/ male: 62%	II–IV/ 37%	a+ b+ c− d− e− f− g+ h+ i+	a) All patients b−	a) Once and if needed, b) consultation c+ d−	1	a) All patients b− c+ d+ e+ f+ g) all pat, h− i− j+ k−
Naylor 1999, USA	30/30HF of 363 elders 1 mth; fu 6mth	75 years/ male: 50%	NA/NA	a+ b− c− d− e− f− g− h− i−	a+ b−	a+ b+ c− d−	7	a+ b+ c+ d+ e+ f+ g+ h+ i+ j− k−
Moser 2000, USA	N=136	70 years/ male: 48%	NA/NA	a+ /?	a+ b−	a+/ ?	NA	a+ b+ c+ d+ e+ f+ g− h+ i− j− k−
Doughty 2002, NZ	100/97 12 months	73 years/ male: 60.5%	III–IV/ 32.2%	a+ b+ c− d− e− f− g+ h− i−	a− b+	a− b+ c+ d−	N>5	a+ b+ c+ d+ e+ f+ g− h+ i+ j− k+
Krumholz 2002, USA	44/44 12 months	74 years/ male: 57%	NA/ 37.5%	a+ b− c− d− e− f− g− h− i−	a− b+	a) if needed, b− c− d+	HFclinic 2× , telemon 16×	a+ b+ c+ d+ e+ f− g− h+ i+ j− k−
Riegel 2002, USA	130/228 6 months	72 years/ male :49%	III–IV/ 42.7%	a+(=telephonic case manager) if needed advice from others	a− b−	a− b− c− d+	Telemo nitoring 17×	a+ b+ c+ d+ e+ f+ g− h+ i− j− k−

Table 1 (cont.)

Stewart 2002, Australia	149/148 fu : 4.2 years	75 years/ male: 56%	II–IV/ 38%	a+ b) 2nd study+ c− d) 1st study + e− f− g+ h+ i+	a) 1st study b−	a) 1x and if needed b) consultation + c) 2nd study+ d−	1–2, if needed more	See 1st and 2nd study
Harrison 2002, Canada	92/100; 2weeks after discharge fu: 12 weeks	76 years/ male :54.5%	II–IV/ NA	a) Hospital nurse + homecare nurse, b− c− d− e− f+ g− h− i−	a) transitional care (TC) on top of standard care b−	a) TC, b− c− d−	2 (?)	a+ b+ c+ d+ e+ f+ g+ h+ i− j− k−
Kasper 2002, USA	102/98 6 months	63.5 years/ male :60.5%	(II) III–IV/ 27.3%	a+ and telephone nurse, b+ c− d− e− f− g+ h− i−	a− b+	a) if needed, b+ c− d+	HFclinic: ≥6 Telemon. ≥12	a) All pat. b) all pat. c+ d) all pat. e+ f+ g− h+ i+ j+ k− (many facilities provided)
European studies								
Cline 1998, Sweden	80/110 12 months	76 years/ male: 50.5%	II–IV/ 33.7%	a+ b+ c− d− e− f− g− h− i−	a+ b+	a− b− c+ d−	≥3	a+ b+ c+ d+ e+ f+ g+ h+ i− j− k+
Ekman 1998, Sweden	79/79 6 months	80 years male: 42%	III–IV/ 40.5%	a+ b− c+ d+ e− f− g− h− i−	a− b+	a− b− c+ d−	≥1	a+ b+ c+ d+ e+ f+ g− h+ i+ j− k−
Jaarsma 1999, Netherlands	84/95 10 days	72 years male: 60%	III–IV/ 35%	a+ b− c− d− e− f− g− h− i−	a+ b−	a) once, b− c) once after 1 week, d−	2+ 1 tel. call	a+ b+ c+ d+ e+ f+ g+ h+ i− j− k−
Bleu 2001, UK	84/81 12 months	75 years/ male: 57.5%	II–IV/ NA	a+ b) other healthcare and social workers if needed	a+ b−	a+ b− c+ d−	NA	a+ b+ c+ d+ e+ f) by HF nurse g− h+ i+ j− k−
Martensson 2001, Sweden	78/75 12 months	79 years/ male: 54%	II–IV/ NA	a+/−	a− b−	a+ b− c− d+	Homevisits ≥3× Telemon 10×	a+ b c+ d+ e+ f+ g− h+ i+, CDROM, j− k−
McDonald 2002, Ireland	51/47 3 months	70.8 years/ male: 66%	IV/ 37%	a+ b− c− d− e+ f− g− h− i−	a+ b+	a− b− c+ d−	Telem. 12× HFclinic: ≥2	a+ b+ c+ d+ e+ f+ g− h+ i− j− k−

Table 1 (cont.)

Capomolla 2002, Italy	112/122 12 months	56 years/ male: 83%	I–IV/ 29%	a+ b+ c− d− e+ f+ g− h− i− a− b+ j+	a− b− c+ d−	NA	a+ b+ c+ d+ e+ f+ g− h+ i ? j+ k−
Strömberg 2003, Sweden	52/54 12 months	77.5 years/ male: 61%	II–IV/ NA	a+ b+ c− d− e− f− g− h− i− a− b+	a− b− c− d−	At least one	a+ b+ c+ d+ e+ f+ g− h+ i+ j− k−
Bruggink 2004, Netherlands	120/120 12 months	70 years/ male: 76%	III–IV/ 31%	a+ b) if needed, c+ d− e+ a− b+ f− g− h− i−	a− b− c+ d−	HFclinic 9× Tel. contact 1×	a+ b+ c+ d+ e− f+ g− h+ i+ j) exercise advice, k−

Table 2 Results of randomised trials of the effect of heart failure management programmes

	Endpoints (Re)admis-sions and/or death	**HF (re)adm. and/or death**	**Total (re)admissions**	**(Re)admissions for HF**	**Time to first (re)admission**	**Days in hospital**	**Death**	**Event-free survival**	**QoL/self-care**	Costs of care
Rich 1995, USA	NA	NA	Sign. ↓ (44% reduction) in interv. gr.	Sign. ↓ (56% reduction) in interv gr.	NA	Sign. ↓ in intervention gr.	No sign. difference	↑ in intervent. gr. (p=0.09)	Sign. ↑ in interv. gr.	↓ in interv. gr.
Weinberger 1996, USA	NA	NA	Sign. ↑ in intervention group	NA	NA	Sign. ↑ in intervention group	NA	NA	No sign. difference/	
Stewart 1998, Australia	Sign. ↓ unplanned readm. and out-of-hospita † in intervention group	NA	Sign. ↓ of unplanned readm. in intervention group (sign. fewer multiple unpl. readmissions)	NA	No difference	Sign. ↓ of unplanned days in hospital in intervention group	↓ in inter v. gr. (p=0.11)	Sign. ↑ in intervention gr.	No sign. difference/	No sign. difference
Serxner 1999, USA	NA	NA	↓ in intervention group	NA	NA	NA	NA	NA	NA	↓
Stewart 1999, Australia	Sign. ↓ (40%) of unpl. readm and out- hospital †in interv gr	No sign. difference	Sign. ↓ of unplanned readm. in intervention gr.	No difference in unplanned readm. for HF	Sign. ↑ in interv. gr.	Sign. ↓ of unplanned days in hospital intervention group	No sign. difference	Sign. ↑ in intervention group	No difference after 6months/	Trend to ↓
Naylor 1999, USA	NA	NA	Sign. ↓ in the complete intervention gr	NA	Sign. ↑ in interv. gr.	Sign. ↓ in complete intervention group	NA	NA	No sign. Difference/	Sign. ↓ in complete interv. Gr

Table 2 (cont.)

Moser 2000, USA	NA	NA	NA	Sign. ↓ in CCM gr. with+without PLVF	NA	Sign. ↓ idem	NA	NA	Sign. ↑ Idem/	Sign. ↓ idem
Doughty 2002, NZ	No sign. difference	No sign. difference	(sign. fewer multiple readm)	No sign difference	No sign. difference	NS	No sign. difference	No sign. difference	Sign. ↑ in ph. sc	No sign. difference
Krumholz 2002, USA	Sign. ↓ in intervention gr.	Sign. ↓(HF+ CVD readm/†)	↓ in intervention gr. (39% reduction)	↓ in intervention gr. (48% reduction)	↓ in intervention gr.	↓ in intervention gr. (p=0.09)	No sign. difference	Sign. ↑ in intervent. gr.	NA	↓ in interv. gr.
Riegel 2002, USA	NA	NA	No sign. difference	Sign. ↓ in hosp. rates for HF (48% reduction)	NA	NS	NA	NA	NA	↓ in interv. gr.
Stewart 2002, Australia	Sign. ↓ unpl. readm.+ out-hosp.† in interv	NA	Sign. ↓ of unpl. readm. in intervention gr.	NA	See 1st and 2nd study	NS	↓ in interv. gr.(p=0.06)	Sign. ↑ eventfree surv +surviv. alone	NA	Sign. ↓ in interv. gr.
Harrison 2002 , Canada	NA	NA	NS (p=0.26)	NA	NA	NA	NA	NA	MLHFQ sign. ↑ SF-36: NS	NS
Kasper 2002, USA	↓ in intervention group (p=0.13)	↓ in interv. gr. (p=0.09)	↓ in intervention group (NS)	↓ in intervention group (NS)	NA	NA	↓ (p=0.14)	NA	Sign. ↑ in interv. gr	Similar
European studies										
Cline 1998, Sweden	NS	NA	↓ in intervention group (p=0.08)	NA	Sign. ↑ in interv. gr. (p< 0.05)	↓ in intervention group (p=0.07)	No difference	NS	No difference	↓ in interv. gr. (p=0.07)

Table 2 (cont.)

Ekman 1998, Sweden	No difference	NA	No difference	NA	NA	No difference	No difference	No difference	NA
Jaarsma 1999, Netherlands	NA	NA	No sign. difference; (↓ of pat's readm.≥ once (p=0.06))	NA	NA	No difference	↑ in interv. gr.	NA	No effect QoL /sign. ↑ of self-care scores
Bleu 2001, UK	↓ in ntervention gr. (p=0.075)	Sign. ↓ interv gr. (p=0.033)	Sign. ↓ in intervention gr. (p=0.018)	Sign. ↓ in interv. gr. (p=0.0004)	NA	↓ in interv. gr. (p=0.08) Sign. ↓ for CHF (p=0.005)	similar	Sign. ↑ interv. gr.	NA
Martensson 2001, Sweden	NA	NA	NA	NA	NA	NA	NA	NA	Sign. ↑/sign. ↓ depress.
McDonald 2002, Ireland	NA	Sign. ↓ interv. Gr.(p=0.04)	NA	Sign. ↓ in intervention Group (p<0.01)	NA	NA	Similar/ few events	NA	No sign. ↑ (p=0.11)
Capomolla 2002, Italy	NA	NA	Sign. ↓ in intervention group (p<0,00001)	NA	NA	NA	Card death sign. ↓	NA	NA
Strömberg 2003, Sweden	Sign. ↓ of patients with events (p=0.03)	NA	↓ in intervention gr.(3 months p=0.047; 12 months p=0.06)	NA	NA	Sign. ↓ in intervention gr. (p=0.02)	Sign. ↓ intervgr (p=.005)	NA	Sign. ↑ self-care score (p=0.01)

programmes are summarised in Table 2. Five studies showed a statistically significant reduction in the combined endpoint of readmissions and/or mortality, irrespective of the reason[5,7-9,14], and two studies reported a statistically significant reduction in the combined endpoint of readmission rates for heart failure and/or death.[11,12] In seven studies, a reduction in the readmission rate, irrespective of cause[1,2,7-9,11,13] was observed, and a reduction of readmissions for heart failure was demonstrated in five studies.[1,4,6,11,12] A statistically significant decrease in the number of days spent in hospital was reported in five studies.[1,4,7,8,14] Stewart et al.[8,9] demonstrated a prolonged eventfree survival in two studies involving follow-up periods of 18 months and 4.2 years, respectively. Strömberg et al.[14] was the first to show a significant reduction in mortality rate related to a heart failure management programme. In four studies[1,4,20,23], an improvement in quality of life was shown, and two studies reported an improvement in self-care scores.[14,22] Significant cost-savings by a heart failure management programme were reported in three studies.[4,6,9] In summary, in 15 of the 21 studies, a positive impact on one of the primary outcome parameters was observed, while in three studies[18,21,22], no effect was shown. In one study[16], the heart failure management programme actually increased the total readmission rates and the number of the days spent in the hospital.

Applicability of the available studies to countries with a primary care-based healthcare system and easy access to medical care.

For several reasons, the applicability of these abovementioned data on heart failure management programmes to a country with a relatively strong primary care system is debatable.

Firstly, in health care systems with a strong primary care basis, such as Denmark, the United Kingdom and The Netherlands, the general practitioner is still the first physician to diagnose and treat most complaints/illnesses and to decide on referral to hospital specialists—the gatekeeping function—in contrast to, for example, the US. More than 50% of patients with heart failure in The Netherlands will be diagnosed and treated by their GP.[24] Thus, some aspects of heart failure management are, at least potentially, taken care of by the general practitioner, e.g., regular supervision and support of patients with severe heart failure and easy access to medical care when heart failure symptoms worsen. This would imply that room for improvement by counseling in a heart failure management programme would be smaller in these European countries as compared to countries with less well-structured primary care facilities. It should be noted, however, that two recent studies showed that the diagnosis and treatment of heart failure by general practitioners in The Netherlands and other European countries are far from

optimal. Our group showed a relatively, albeit understandably, low number of additional investigations, such as echocardiography (12% vs. 97% in secondary care), in patients with suspected heart failure in primary care. In addition, lower prescription rates of "evidence-based" medication are seen in "GP patients" in comparison with patients managed by a cardiologist.[25] These data confirm the results of the "IMPROVEMENT of Heart Failure Programme", an international survey conducted in 15 countries.[26]

A second aspect concerns the changes that have taken place in the treatment of heart failure over the last decade as a result of the positive outcomes of large studies of ACE inhibitors, beta-blockers and spironolactone. Although there is still underuse and underdosing of these drugs, their benefits will certainly influence the outcomes of current studies of heart failure management. In addition, in recent years, the greater awareness of the importance of heart failure by physicians and improved education of the patient leading to better understanding and compliance by the patient may have reduced the number of hospitalisations and improved survival, making extrapolation of the results of previous studies to the present questionable.[27] Several studies (e.g., in The Netherlands and Scotland) reported a peak in hospitalisation rates for heart failure as the principle diagnosis around 1993, after which a decline was noted in subsequent years.[28,29] This recent change in hospitalisation rates for heart failure could partly be attributed to improvements in the treatment of heart failure and could result in less potential for clinical improvement from heart failure management programmes. Thirdly, the previously mentioned limitations of some studies, in particular the short follow-up periods, the relatively small sample sizes and the variety in setting and intervention programmes, are reasons why it is not advisable to uncritically implement heart failure management programs in countries with a different healthcare system. In summary, the value of a heart failure management programme as a positive addition to a healthcare system with a strong primary care remains to be proven. This is the justification for the DEAL-HF study (Deventer– Alkmaar Heart Failure Clinic Project) which commenced in 2000 in The Netherlands. The design of this study is presented below. In contrast to most earlier studies, a trained cardiovascular nurse and an experienced heart failure physician worked closely together in our heart failure management programme. Other important differences from earlier studies include the fact that, in previous studies, patients could only be included if they were hospitalised for heart failure, while in our study, NYHA class III–IV outpatients were also included. Furthermore, the selection criteria in DEAL-HF were not particularly stringent, so that the patient characteristics more accurately reflect those of "real life" heart failure patients. Finally, DEAL-HF includes both patients with symptomatic left ventricular systolic

dysfunction and patients with symptomatic heart failure with preserved left ventricular systolic function.

■ Deventer–Alkmaar Heart Failure Project (DEAL-HF)

The Cardiology Department of the Deventer Hospital in The Netherlands is undertaking a prospective, randomised, parallel group trial to determine the effects of a nurse and physician-directed multidisciplinary intervention in a country with a relatively strong primary care system. The follow-up period is 1 year. Outcome parameters included rates of hospitalisation for worsening heart failure and/or all cause mortality; rates of hospitalisation for worsening heart failure and/or cardiovascular mortality; ventricular function and plasma neurohormone level (NT-proBNP), quality of life, time to first event, compliance to medication and costs of care. The trial is being performed in collaboration with the Julius Center for Health Sciences and Primary Care of the University Medical Center in Utrecht, The Netherlands and the Cardiology Department of the Groningen University Hospital in Groningen, The Netherlands. In March 2002, the Cardiology Department of the medical Center Alkmaar joined the project. Patients were only recruited in Deventer and Alkmaar, which are both regional teaching hospitals.

■ Methods

Patients

Inpatients and outpatients with New York Heart Association Class III or IV heart failure who gave written informed consent were eligible for the study. Diagnosis of heart failure was established by typical clinical signs and symptoms of heart failure in conjunction with radiographic and/or echocardiographic findings of a reduced left ventricular systolic function (LVEF≤45%) or preserved left ventricular systolic function (diastolic dysfunction), according to the guidelines for the diagnosis of heart failure of the European Society of Cardiology. The criteria for exclusion included dementia or psychiatric illness, discharge to or stay in a nursing home, disease other than HF with an expected survival of less than one year, participation in another intervention study, planned hospitalisation or ongoing hospitalisation and kidney function replacement therapy.

Randomisation

The study was approved by the local ethics committees. Following screening, eligible patients were randomised by computer-generated allocation to either the intervention group or the control group.

Intervention group

The intervention consists of an intensive follow-up of the patient, with their caregiver, at a heart failure outpatient clinic (nine visits performed at increasing time intervals). An experienced cardiovascular nurse and a trained heart failure physician directed each visit. Visits commence within a week of hospital discharge or referral from the outpatient clinic (Table 3). Comprehensive education[30] and counseling is given to help patients and caregivers to acquire the knowledge, skills and motivation needed to comply with the treatment programme and participate in self-care.[31] Intervention includes the following components:

- verbal and written education and counseling with emphasis on behavioural strategies to increase compliance;
- vigilant follow-up of patient's condition;
- checking and optimisation of medical therapy, assessment of ECG and lab results;
- increased access to health care providers (extra visits whenever needed, telephone calls);
- early attention to signs and symptoms of fluid overload;
- coordination with home healthcare, primary care and cardiologist, if needed;
- one dietician consultation (more if needed);
- self-care (adjustment of diuretics, patient diary).

Patient education covers the following areas:

- what is heart failure, and what causes this patient's heart failure;
- differences between expected and serious symptoms and how to monitor them;
- most common symptoms before hospitalisation for CHF: dyspnea, edema, fatigue, cough, chest pain, sudden weight gain, difficult breathing while sleeping, palpitations[32];
- reason for each type of medication, how to take it routinely and how to improve compliance;
- importance of risk factor modification;
- specific sodium, fluid and alcohol restrictions with individualized diet;
- importance of daily self-measurement of patient's weight and of weight gain and loss;
- exercise and rest recommendations;
- how to change his/her behavior;
- how to cope with his/her disease (psychosocial care).

Table 3 DEAL-HF study design

	Period A Screening/ enrollment	Period B												
	Vis 1	Vis 2 tel. contact 3 days	Vis 3 week 1	Vis 4 week 3 ±1 week	Vis 5 week 5 ±1 week	Vis 6 week 7 ±1 week	Vis 7 week 11 ±1 week	Vis 8 month 6 ±1 week	Vis 9 month 9 ±1 week	Vis 10 month 12 final vis	Extra vis nurse	Extra vis nurse+ phys.	Tel. cont.	Home visit
Inf. cons	X													
Nurse contact instructions	X	X	X	X	X	X	X	X	X	X	X	X		
Doctor contact	X		X	X		X	X	X	X	X		X		
Full history	X													
Abb. history		X	X	X	X	X	X	X	X	X	X	X		
Full phys. examination	X		X	X		X	X	X	X	X		X		
Brief phys. examination				X	X		X		X		±			
Full lab panel	X						X			X				
Abbr. lab panel			X	X	X	X	X	X	X		±	±		
ECG	X		X			X	X	X	X	X	±	±		
LVEF	X						X			X				
NYHA class	X		X	X	X	X	X	X	X	X	X	X		
Quality of life assessment	X						X			X				
Record/(adjust) medication	X	X	X	X	X	X	X	X	X	X	X	X		
Compliance		X	X	X	X	X	X	X	X	X	X	X		
Randomisation	X													
Letter to GP, homecare, pharmacist	X									X				
X–thorax	X													

In addition, patients are taught the following skills:

- how to recognize symptoms;
- what signs and symptoms are important;
- how to respond to symptoms in a timely manner;
- when to call their health care provider;
- how to sort food into high- and low-sodium groups.[33,34]

Repetition and individualized care are provided.

- The duration of the first two visits at the outpatient clinic is 1 h each. The nurse takes the patient's history, measures weight, pulse and blood pressure and starts the education programme. A patient diary with documentation on all relevant items is provided. An overall assessment is conducted by the physician for 30 min (introduction, physical examination, ECG, electrolytes, anemia and kidney function check and medication check with optimisation if needed). Then the nurse and physician develop a treatment plan. The nurse contacts homecare services if needed, and an appointment for a dietician consultation is made.
- Three days after the first visit, the nurse will make a telephone call to check on the patient.
- At the regular follow-up visits (7× 15–30 min, at increasing time intervals) at the outpatient clinic, education, counseling, check-up and reinforcement pertaining to the abovementioned items are provided by the nurse (Table 3). The nurse also performs a short physical examination and assesses the social circumstances of the patient. Six of the visits are combined nurse–physician visits (6× 15 min for the physician; see Table 3). The patient is first seen by the nurse and then, after a short review, by the physician. The physician assesses the clinical condition, performs a physical examination, monitors the laboratory results and ECG, checks and optimises the (medical) treatment regimen and, together with the nurse, performs the overall assessment. When a change of medication is initiated, the patient visits the heart failure clinic again after 2 weeks. In case of worsening heart failure, leading to additional drug therapy, the patient is seen at the heart failure clinic within 1–3 days. If deemed necessary, serious complications will be discussed with one of the cardiologists during the same visit.
- Patients included in the intervention group can always phone and/or visit the outpatient clinic, with a limited possibility of home visits by the nurse or physician if a patient is unable to visit the hospital.

The duration of the intervention period is 1 year. The flowchart summarises the visit schedule and the assessments at each visit (Table 3).

Control group

Patients in the control group receive usual care, including (non protocolised) outpatient visits, according to the requirements of each individual cardiologist in the Cardiology Department of the Deventer or Alkmaar hospital and care as usual from their general practitioner and possibly other health care professionals.

Outcome assessments

At baseline, 3 and 12 months plasma samples for neurohormone tests (NT-proBNP) will be taken, echocardiography will be performed to assess ventricular function (and stored on videotape) and quality of life questionnaires and NYHA classifications (by the physician) will be assessed in both patient groups, to determine if the intervention, by possibly improving fluid balance and cardiac performance, influences these outcome parameters. The hospital pharmacist will organize 3-monthly overviews of medication (collected by the patient or caregivers) for all patients in order to determine patients' drug compliance. Hospitalisations are tracked by means of patient recall, chart review and hospital databases. A clinical endpoint committee will judge all causes of hospitalisation and death.

Primary and secondary outcomes

The combined primary endpoints are; occurrence of hospitalisation for worsening heart failure and/or all cause mortality and occurrence of hospitalisation for worsening heart failure and/or cardiovascular mortality; ventricular function (left ventricular ejection fraction), plasma neurohormone level (NT-proBNP), NYHA functional class and quality of life assessment. Secondary endpoints include time to death or hospitalisation, costeffectiveness analysis and utilization of heart failure medication (diuretics, ACEi/AII antagonists, beta-blockers, spironolactone, digoxin) and adherence to prescribed medication.

Quality of life

Quality of life will be evaluated using the Rand 36 quality of life questionnaire[35], while disease-specific quality of life will be assessed by the Minnesota Living with Heart Failure questionnaire.[36]

Sample size
Calculation of the sample size (236 patients) is based on the assumption of a reduction of the primary outcome (occurrence of hospitalisation for worsening heart failure and/or all cause mortality) of 50%, with an alpha of 5%, a discriminating power of 80% and an estimated 30% of hospitalisation or mortality in the control group. The total number of patients required in each treatment arm is 118.

Study organization
The Deventer Hospital and the Alkmaar Medical Centre are participating in this study in collaboration with the University Medical Center Utrecht and the Cardiology Department, Groningen University Hospital, The Netherlands.
The last (240th) patient was recruited in April 2003. Data analyses will start in May 2004.

Steering committee
Prof. A.W. Hoes, MD, PhD, chairman; Prof. D.J. van Veldhuisen, MD, PhD; P.W.F. Bruggink-André de la Porte, MD, principal investigator; D.J.A. Lok, MD, J. van Wijngaarden, MD, PhD and J.H. Cornel, MD, PhD.

Endpoint committee
A panel of three independent cardiologists from other hospitals will decide about the cause of hospitalisation and death. The panel will be blinded for the patient's intervention arm.

After study follow-up measurements
After the study period of 1 year, data on (re) admission, morbidity and mortality of both groups will still be collected by means of 6-monthly telephone calls.

■ Summary

The results of the DEAL-HF study will contribute to our knowledge of the effect of a heart failure clinic, directed by a trained cardiovascular nurse and a specialised heart failure physician, with an intensive intervention over 1 year, in a country with a relatively strong primary care system.

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3

Added value of a physician-and-nurse-directed heart failure clinic: results from the Deventer-Alkmaar heart failure study.

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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 end point) and improves functional status (including left ventricular ejection fraction, New York Heart Association (NYHA) class and quality of life) in patients with 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 9 scheduled patient contacts-at day 3 by telephone, and at weeks 1, 3, 5, 7 and at months 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 from the hospital 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-month 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 to 0.81; p = 0.001). There was an improvement in left ventricular ejection fraction (LVEF) in the intervention group (plus 2.6%) compared with 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 b-blockers, quality of life, self-care behaviour and healthcare 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 healthcare costs, even in a country with a primary-care-based healthcare system.

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 readmissions 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] hampers the applicability of the 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, standardised 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, randomised parallel group trial aimed at estimating the effects of an intensive physician-and-nurse-directed intervention on hospitalisation for worsening HF and/or allcause 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 highquality 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 outpatient clinic, with the 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, 1 year, participation in another trial, being under ongoing 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 1 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, together with the nurse, proposed a treatment regimen. At the regular follow-up visits at weeks 5 and 7, and at months 3, 6, 9 and 12, the nurse provided counselling, 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 the 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) 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 patients completed quality of life questionnaires at baseline and after 3 and 12 months. Healthrelated 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 reviews. 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 hospitalisation. 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

Table 1 Baseline characteristics of the study patients

Characteristics	Intervention group (n = 118)	Control group (n = 122)
Demography		
Mean (SD) age (years)	70 (10)	71 (10)
Male	78 (66%)	96 (79%)
Living alone	23 (20%)	21 (17%)
CHF		
Aetiology of CHF: ischaemia	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%
Comorbidity*		
Ischaemic 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%
Hypercholesterolaemia	54%	43%
Laboratory values		
NT-proBNP (pmol/l)(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 (mm Hg)	123	125
Mean diastolic blood pressure (mm Hg)	73	76
Mean heart rate (bpm)	79	78
Medication at entry		
Diuretics	97%	96%
ACE inhibitor	84%	88%
ARB	14%	8%
ß-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%
NSAIDs	3%	5%

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; NSAIDs, non-steroid anti-inflammatory drugs; NT-proBNP, N-terminal prohormone brain natriuretic peptide; NYHA, New York Heart Association; PTCA, percutaneous transluminal coronary angioplasty.
*More than one item possible; † Values are medians; ‡ To convert from pmol/l to pg/ml, multiply by 8.457.

were prespecified in the protocol.[8] The primary end point was the composite of incidence of hospitalisation for worsening HF and/or 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 a 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 the not normally distributed continuous variables. The differences in change in quality of life scores were compared by the Wilcoxon rank-sum test. The 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 to April 2003 (figure 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 hospitalisation). Among the 797 patients, the reasons that 103 did not participate included the presence of a variety of non-cardiac 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 (51% (30% of the 797 screened patients)) eligible patients gave written informed consent and were randomly allocated to the intervention group (n=118) or to the usual care group (n=122; figure 1). Of these, 31% were hospitalised due to HF at the time of recruitment and 69% were 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 was 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% of the patients 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.

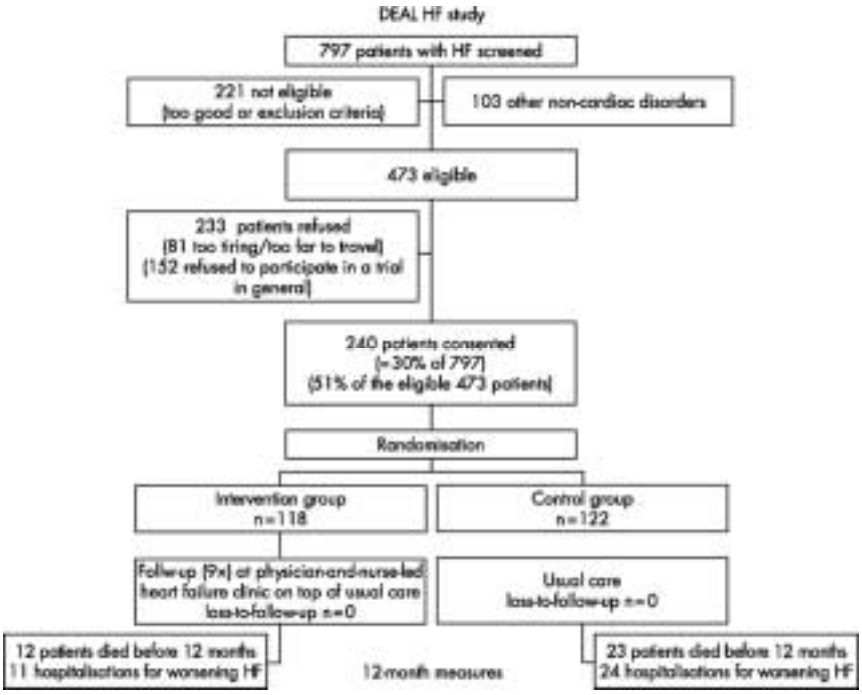

Figure 1. Flow chart of the trial

Effect on hospitalisation for worsening HF and/or allcause 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.

Ventricular function and NYHA classification

After 3 months, there was no difference (p=0.22) in LVEF between the intervention and the usual care groups. 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 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).

Quality of life

Improvement in the 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 the baseline in the intervention group compared with 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; Z=20.848; p=0.397) and 12 months (U=5604; Z=21.699; p=0.089; table 3)). The values of the natural logarithm of NT-proBNP in the intervention group versus 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, after both 3 and 12 months of follow-up (table 3). 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 b-blockers. Importantly, the maximally reached dose of b-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 group and 1.43 in the usual care group (p,0.001). The number of days in the 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 in the usual care group (€202.728 (US$270.648, £137.338) was €137.682 (US$183.834, £93.279). The total cost for the HF clinic programme (for the salary of the HF nurse, HF physician and the dietician, and for the extra lab and ECGs) was €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). Adjustment for the baseline difference in sex between the intervention and usual care groups did not change the results presented above.

Table 2 Effect of a nurse-and-physician-directed heart failure clinic on hospitalisation, death and days in hospital

Variable	Intervention group (incidence rate) n = 118	Usual care group n = 122	Rate ratio (95% CI)	RD (95% CI; NNT)
Hospitalisation for CHF and/or death	23 (20.7 per 100 patient years)	47 (42.2 per 100 patient years)	0.49 (0.30 to 0.81)	0.215 (0.07 to 0.36; 5)
Death (all-cause)	12 (10.8 per 100 patient years)	23 (20.6 per 100 patient years)	0.52 (0.26 to 1.05)	0.098 (10)
Days in hospital	359 (324 per 100 patient years)	644 (578 per 100 patient years)	0.56 (0.49 to 0.64)	2.54 (0.4)

CHF, congestive heart failure; NNT, numbers needed to treat; RD, rate difference.

Table 3 Effect of a nurse-and-physician-directed heart failure clinic on left ventricular ejection fraction, New York Heart Association class, N-terminal prohormone- pro-brain natriuretic peptide, quality of life and self-care behaviour

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

Table 3 (cont.)

Total score at 12 months	23.8	30.2	<0.001
Creatinine levels (µmol/l)			
At baseline	123	130	0.144
At 3 months	124	132	0.08
At 12 months	121	138	0.002

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal prohormone brain natriuretic peptide; SF36, Short Form 36.

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

Table 4. Utilisation of medication

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

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NS, not significant.
For the ACE inhibitors, the dosages were converted to an enalapril-equivalent dose, for the angiotensin receptor blockers (ARBs) to a valsartan-equivalent dose and for the ß-blockers to a metoprolol-succinate-equivalent dose.

■ 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 b-blockers, quality of life and healthcare costs.

Compared with 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 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.[11,13,19,26,28-30] 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 utilisation 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 up 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 no long-term effect. This may have been due to the noticeably 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 patients), many suitable patients were not enrolled for various reasons (figure 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 cooperation 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 cannot 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 b-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 a cardiovascular nurse, would be able to provide additional benefits, even in a country with a primary-carebased 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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4

Effect of a physician-and-nurse-directed heart failure clinic on prescriber adherence, patient adherence and persistence of medication: a randomised controlled trial.

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■ Abstract

Aim: To quantify the effect of a physician-and-nurse-directed heart failure (HF) clinic on prescriber adherence and patient adherence and persistence to HF pharmacotherapy.
Background: Adherence to guideline-recommended HF medication by prescribers and adherence to prescribed medication by patients remains low. HF clinics have been reported to improve adherence, but appropriate quantification of this effect is lacking.
Methods: We studied 185 HF patients of a cohort of 240, recruited in a 1-year prospective, randomized HF study, evaluating a protocolised HF clinic intervention by a clinician and a cardiovascular nurse. Adherence and persistence with pharmacotherapy was calculated by means of rates of prescription refills at local pharmacies.
Results: Prescription of spironolactone was larger after 3 and 6 months in the intervention group (49.4% vs. 32.6%, p= 0.022 and 45.9% vs. 30.8%, p= 0.039). The average maximal dose reached, of BB was higher in the intervention group (141.2 mg vs. 115.8 mg metoprolol-equivalent, p= 0.031). 82.4% of patients during and at end of follow-up in the intervention group used ≥ 50% of recommended dose of BB, compared to 67.1% of control-patients (p= 0.040 and p= 0.040). No effect on prescription of ACE-i or ARB was observed. Patient adherence and persistence with pharmacotherapy were similar in both groups.
Conclusion: A physician-and-nurse-directed heart failure clinic did result in an increased beta-blocker dose and an increased number of patients using spironolactone. This may have been an important contributor to the observed improved clinical outcomes. It did not improve the, already (sub)optimal, use or dosage of ACE-i or ARB.

■ Introduction

Heart failure (HF) is common and an important cause of hospitalisation and death.[1,2] Although many studies have shown that pharmacotherapy can reduce morbidity and mortality in CHF[3,4], adherence of prescribers to guideline-recommendations concerning HF medication (prescriber adherence) remains low.[5,6] In addition, low adherence to prescribed medication regimens by patients is a major factor in mortality, morbidity and hospital readmissions for patients with HF.[7,8] Randomised trials have shown that patient education and counseling, improved dosing schedules and improved communication between physician and patient (which are interventions included in heart failure clinics) may increase adherence to pharmacotherapy by HF patients.[9-17]

However, valid and precise quantification of the effect on prescriber and patient adherence in HF is virtually lacking. Specifically, most studies did not include valid measurements of adherence (such as computerised pharmacy refill data) and the follow-up period was short (1-6 months). Nonadherence during short-term follow-up is found to be less than 30%, while nonadherence increases to 50% with long-term treatment and follow-up.[18]
It is important to distinguish two different aspects of patient compliance with prescribed medication regimens[19]; *patient adherence*, i.e., how the patients execute the prescribed medication regimen in terms of missed dosages, and *persistence,* i.e., how long patients continue to take the prescribed medicines.
We quantified the effect of a one-year physician-and-nurse-directed HF clinic intervention on prescriber adherence to the treatment guidelines and on patient adherence and persistence with pharmacotherapy in a randomised controlled trial in patients with HF, NYHA III-IV, using computerised pharmacy refill data.

■ Methods

Patients
The DEAL-HF study is a parallel group, randomised controlled trial to determine whether a regular, intensive intervention at a HF clinic by a combination of a cardiovascular nurse and a HF clinician reduces the primary endpoint "the composite of incidence of hospitalisation for worsening HF and/or all cause mortality". The local Ethics Committees of the participating Deventer and Alkmaar hospitals approved the study. The design and major findings of the study are discussed in detail elsewhere.[20,21] 240 Patients either hospitalised or visiting the cardiology outpatient clinic, with NYHA III or IV HF, who gave written informed consent, were eligible for the DEAL-HF 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 (LVEF≤45%) or of a preserved left ventricular systolic function with diastolic dysfunction according to the 2001 guidelines for the diagnosis of HF of the European Society of Cardiology.[4] Exclusion criteria were dementia or psychiatric illness, discharge to or stay in a nursing home, disease other than HF with an expected survival of less than one year, participation in another randomised trial, ongoing or planned hospitalisation and kidney function replacement therapy. Following screening, eligible patients were randomised by computer-generated allocation to either the intervention group or the control group. Patients were recruited between March 2000 and April 2003 with a follow-up of one year. Only patients of the Deventer Hospital were

asked informed consent to collect data concerning HF medication prescription according to the guidelines, and patient adherence to and persistence with medication by means of rates of prescription refills at their local pharmacy.

Intervention

The intervention of the DEAL-HF study, performed on top of 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 following hospital discharge or referral from the outpatient clinic with a telephone call. At the first (at week 1) and second visit (at week 3) to the HF clinic, verbal and written comprehensive education was given about the disease and the aetiology, about medication, possible side effects, and about adherence to pharmacotherapy and diet. Patients were advised about individualised diet with salt- and fluid restriction, weight control, early recognition of worsening HF, when to call a health care provider and about physical exercise and rest. A patient diary was given. Easy access to the HF clinic was offered during working hours. At the regular follow-up visits at week 5, week 7, months 3, 6, 9 and 12, the nurse provided counselling, check-up and reinforcement of the education and performed a short physical examination. She checked the utilisation and dose of the prescribed medication At six of the nine follow-up visits, the physician assessed the condition of the patient, including electrolytes and kidney function, tolerance of medication and side-effects, optimised (medical) treatment according to guidelines and performed an overall assessment together with the nurse. The intervention was described in more detail elsewhere.[20, 21]

Control Group

The cardiologists of the Deventer cardiology department have a special interest in HF. They treated the HF patients randomised to routine care, according to their "usual care". Their routine care was largely according to the guidelines for the treatment of HF of the European Society of Cardiology (version 2001)[4] with optimal application of medical therapy including aiming at target or high dose of HF medication (See baseline chronic medication use). Since it was our aim to compare the intervention with routine care, we did not develop a specific protocol for the management of the control group of the DEAL-HF study. All cardiologists treated patients from the control group at their outpatient clinic.

Medication

In this sub-study of the DEAL-HF we investigated the data of the following medication for patients with HF: angiotensin-converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARB), beta receptor blockers (BB) and spironolactone. For all patients of the Deventer Hospital, computerised prescription claims files were collected at the community pharmacies from one year before inclusion up to two years following inclusion, through PHARMO, a record linkage system containing drug-dispensing records from community pharmacies.[22] Data from community pharmacies that did not participate in PHARMO were added, by extraction from their electronic medication files.

Prescriber adherence (adherence to HF medication guidelines by prescriber): several parameters of prescriber adherence were included:

1) HF drug prescription rate. This was calculated by dividing the number of patients in both groups that, according to the pharmacy records, filled an ACE-i or ARB, BB and spironolactone prescription at baseline, 3, 6, 9 and 12 months by the total number of patients in each group in the sub-study at those moments in time.
2) The maximum dosages reached at any point during the study and at the end of the study.
3) The proportion of the recommended dose according to international guidelines that these maximum dosages represented. For the ACE-i the dosages were converted to enalapril-equivalent dose for comparison, for the ARBs to valsartan-equivalent dose and for the beta-blockers to metoprolol-equivalent dose for comparison.[23]
4) The proportion of patients that reached the internationally recommended dosages at any point in time during the study for both groups.
5) The proportion of patients that was prescribed this recommended dose at the end of the study.

Patient adherence and persistence with HF pharmacotherapy:

Patient adherence to HF medication was calculated by dividing the sum of the durations of the prescriptions during the study period by the time between the start date of the first prescription and the end date of the last prescription for which an end date was available or end of study. Hospitalized days were deducted from the follow-up time.
The persistence with HF medication was calculated as the time between the first recorded use of a drug during the follow-up, and the drug discontinuation date. A maximum gap of 90 days was allowed for (regarding both adherence

and persistence) between two prescriptions, because in the Netherlands prescriptions have a maximum length of 90 days.[24]

Statistics

Statistical analysis was conducted according to the "intention to treat" principle. For the change in non-normally distributed continuous variables, the Mann-Whitney-U test was used for the between-group comparisons. Time from first recorded use until discontinuation date of a drug was defined as the persistence, for which a hazard ratio was calculated using Cox' proportional hazards model.

■ Results

We collected data of 185 of the 221 patients of the Deventer hospital in the DEAL-HF study. Of 36 patients data on rates of prescription refills were not available at the pharmacies because of a change of their computer systems at the time of our study. The mean age of the 185 patients was 71 years. The percentage of male patients was 71%, mean ejection fraction was 31.5% and 96% was in NYHA functional class III (Table 1).

Prescriber adherence

The prescription of ACE-i or ARB and BB increased in both the intervention and the usual care group during follow-up. The prescription of ACE-i and/or ARB at baseline in the intervention group compared to the control group was 88.9% respectively 87.4% (p=0.749) and at 12 months 97.5% respectively 91.4 % (p=0.716). BB prescription at baseline in the intervention group compared to the control group was 74.4% respectively 68.4% (p=0.852) and at 12 months 80.3% respectively 76.5% (p=0.174). The prescription of spironolactone showed a statistically significant difference at 3 and 6 months between the intervention group and the control group (49.4% vs. 32.6%, p= 0.022 and 45.9% vs. 30.8%, p= 0.039) and a non-significant difference at 9 and 12 months (45.8% vs. 34.8% p=0.177 and 49.4% vs. 39.5% p=0.132) (Table 2). The maximum reached recommended doses of ACE-i, ARB and spironolactone were comparable between the groups. The average maximum dose, in % of the recommended dose, of BB, reached at any time during the study was 70.6% (141.2 mg metoprololsuccinate-equivalent) in the intervention group and 57.9% (115.8 mg metoprololsuccinate-equivalent, p= 0.031) in the control group (Table 3). At the end of the follow-up period the average dose of BB was 69.9% of the recommended dose (Table 4) for the intervention group compared to 56.5% in the control group (p=0.09). Of the patients in the intervention group, 82.4% used ≥ 50% of the recommended

Table 1 Baseline characteristics of 185 patients with moderate to severe HF.

Characteristics	Intervention group	Control group
Demography		
Mean age (years)	71±10	71±10
Male	58(64%)	75(79%)
Living alone	20(22%)	15(16%)
CHF		
Aetiology CHF: Ischemia	58%	62%
Prior admissions for CHF	50%	55%
Mean LVEF*	31%	32%
Systolic dysfunction	99%	98%
Diastolic dysfunction	37%	30%
NYHA III†	97%	95%
NYHA IV	3%	5%
Co-Morbidity ‡		
Ischemic heart disease	59%	54%
COPD**	34%	30%
Current smoker/ ex-smoker	12 % /54%	14% /47%
Diabetes mellitus	33%	28%
Anemia	20%	12%
Hypercholesterolemia	53%	46%
Laboratory values		
NT proBNP (pg/ml) ††,‡‡	408/3451	464/3924
Potassium (mmol/l)	4.4	4.3
Creatinine (µmol/l)	120	130
Micro albumin./creatinine ratio(mg/mmol)	23	23
Blood urea nitrogen (mmol/l)	11	11
Mean systolic blood pressure (mmHg)	124	126
Mean diastolic blood pressure (mmHg)	73	76
Mean heart rate (bpm)	79	79

*LVEF= Left Ventricular Ejection Fraction; †NYHA= New York Heart Association classification
‡ More than one item possible; **COPD= Chronic Obstructive Pulmonary Disease; †† Values are medians ‡‡To convert from pmol/l to pg/ml multiply by 8.457;

dose of BB, both during follow-up and at the end of the trial, compared to 67.1% of patients in the control group (p= 0.040 and p= 0.040, respectively) (Table 3).

Patient adherence and persistence

In the intervention group, > 80% adherence was achieved by 84% of the patients on ACE-i, 81% of the BB users and by 100% of the patients on spironolactone, as compared to respectively 82%, 78% and 100% in the usual care group (NS). The median patient adherences to ACE-i, ARB, BB and spironolactone in the intervention group were 98%, 95%, 94% and 100% and

Table 2 Medication prescriptions at baseline, 3, 6 and 12 months

	Intervention					Control				
Medication	baseline	3 months	6 months	9 months	12 months	baseline	3 months	6 months	9 months	12 months
Total n	90	87	85	83	81	95	92	91	89	81
Any RAS blocker	n=80	80	81	78	79	83	86	83	81	74
	88,89%	91,95%	95,29%	93,98%	97,53%	87,37%	93,48%	91,21%	91,01%	91,36%
Ace-inhibitor	71	71	72	68	68	76	79	74	72	64
	78,89%	81,61%	84,71%	81,93%	83,95%	80,00%	85,86%	81,32%	80,90%	79,01%
AII-antagonist	9	9	9	10	11	7	7	9	9	10
	10,00%	10,34%	10,59%	12,05%	13,58%	7,37%	7,61%	9,89%	10,11%	12,35%
Beta-blocker	67	67	67	65	65	65	64	64	62	62
	74,44%	77,01%	78,82%	78,31%	80,25%	68,42%	69,57%	70,33%	69,66%	76,54%
Diuretic	83	83	81	70	70	84	84	85	84	76
	92,22%	95,40%	95,29%	84,34%	86,42%	88,42%	91,30%	93,41%	94,38%	93,83%
Spironolac tone	32	43	39	38	40	27	30	28	31	32
	35,55%	**49,43%***	**45,89%***	45,78%	49,38%	28,42%	32,61%	30,76%	34,83%	39,51%

* Significant difference with control group ($p<0.05$)

Table 3 Patients reaching recommended doses during follow-up

Medication	At any time during follow-up			At end of follow-up		
	Avg max dose†	N patients = 100% recommended dose	N patients ≥50% recommended dose	Avg dose†	N patients = 100% recommended dose	N patients ≥ 50% recommended dose
Intervention						
Any RAS blocker	69,7	40/80 (50,0%)	61/80 (76.3%)	67,3	29/80 (36,3%)	61/80 (76.3%)
Ace-inhibitor	69,4	36/71 (50,7%)	53/71 (74,6%)	69,2	28/71 (39,4%)	53/71 (74,6%)
AII-antagonist	65,9	4/11 (36,4%)	9/11 (81,8%)	50,0	1/11 (9,1%)	9/11 (81,8%)
Beta-blocker	**70,6‡**	31/68 (45,6%)	**56/68 (82,4%)‡**	69,9	30/68 (44,1%)	**56/68 (82,4%)‡**
Spironolactone	86,1	31/43 (72,1%)	43/43 (100%)	86,1	31/43 (72,1%)	43/43 (100%)
Control						
Any RAS blocker	69,4	35/84 (41,7%)	64/84 (76,2%)	65,9	30/84 (35,7%)	64/84 (76,2%)
Ace-inhibitor	70,8	33/77 (42,6%)	60/77 (77,9%)	67,0	28/77 (36,4%)	60/77 (77,9%)
AII-antagonist	61,4	4/11 (36,4%)	7/11 (63,6%)	53,8	3/11 (27,3%)	7/11 (63,6%)
Beta-blocker	57,9	23/70 (32,9%)	47/70 (67,1%)	56,5	21/70 (30,0%)	47/70 (67,1%)
Spironolactone	104,2	27/36 (75,0%)	36/36 (100%)	104,2	27/36 (75,0%)	36/36 (100%)

† in % of recommended dose

‡ significant difference with control group ($p<0.05$)

Table 4 Recommended maximum dose according to international guidelines[4] of heart failure medication (ACE-i, ARB, BB) used in the DEAL HF study

Medication	Recommended maximal dose
Enalapril	20 mg
Captopril	150 mg
Fosinopril	40 mg
Lisinopril	20 mg
Perindopril	8 mg
Ramipril	10 mg
Valsartan	320 mg
Candesartan	32 mg
Losartan	100 mg
Metoprolol	200 mg
Carvedilol	50 mg
Bisoprolol	10 mg
Spironolactone	25 mg

Table 5 Patient adherence* and persistence**

	Intervention			Control		
	Avg adherence	Median adherence	Avg persistence (days)	Avg adherence	Median adherence	Avg persistence (days)
ACE inhibitor	0.89 (p=0.441)	0.98	343 (p=0.917)	0.92	0.97	342
AII inhibitor	0.91 (p=0.092)	0.95	321 (p=0.374)	1.02	1.01	280
Beta-blocker	0.88 (p=0.275)	0.94	330 (p=0.433)	0.95	0.92	318
Diuretic	1.00 (p=0.610	0.96	341 (p=0.213)	0.97	0.95	328
Spironolactone	0.94 (p=0.862)	1.00	259 (p=0.620)	0.93	1.00	245

p-values for independent t-test intervention vs. control

* calculated by dividing the sum of the durations of the prescriptions during the study interval by the time between the start date of the first prescription and the end date of the last prescription for which an end date was available in that interval or end of study. The days in hospital were deducted from the follow-up time.

** persistence was calculated as the time between the first recorded use of a drug during the follow-up, and the drug discontinuation date, difference between intervention and control group expressed through the Cox' proportional hazards model.

in the control group 97%, 100%, 92%, and 100%, respectively (Table 5). The Cox' regression survival curves showed that the hazard ratio (HR) for persistence to ACE-i was 1.57 (0.51-4.80), indicating that patients in the intervention group had a non-significant 50% increased probability of being persistent to ACE-i compared to the patients in the control group. The corresponding HRs for BB was 1.63 (0.63-4.20) and for spironolactone 0.58 (0.20-1.64). The 95% CI's, however, were wide.

■ Discussion

We did not find a clear effect of a physician-and-nurse-directed 1-year intervention on the prescription of ACE-i or ARB. However, the prescription of spironolactone showed a statistically significant difference at 3 and 6 months between the intervention group and the control group (49.4% vs. 32.6%, p= 0.022 and 45.9% vs. 30.8%, p= 0.039). In addition the average maximum dose (in % of the recommended dose) of BB, reached at any time during the study, was higher in the intervention group (70.6% (141.2 mg metoprololsuccinate-equivalent)) than in the control group (57.9%(115.8 mg metoprololsuccinate-equivalent, p= 0.031)) as was the proportion of the patients in the intervention group, that used ≥ 50% of the recommended dose of BB (82.4%), both during follow-up and at the end of the trial, compared to 67.1% of patients in the control group (p= 0.040 and p= 0.040). This study demonstrated already at baseline a high prescriber adherence to the treatment guidelines in both groups, especially for any renin-angiotensin blocker and diuretics and to a lesser extend for BB. Furthermore, the study showed a very high patient adherence in both the intervention and usual care group (average > 90% for all studied medications) and a high persistence with no statistically significant difference in patient adherence and persistence between the two groups. In our study we used rates of refilling prescriptions to measure patient adherence. This assessment of adherence and persistence is not ideal. Patient adherence to medication can be measured by using pill counts[9,10], self report[7,25], a medicine-container with a microchip (MEMS)[12], blood and urine samples or rates of refilling prescriptions.[13] Apart from (logistically impossible) regular blood and urine samples, the electronic monitoring system is described as costly but most accurate, where the prescription refill data provide an acceptable approximation.[15] In one study, pharmacy records showed the highest correlation with MEMS compared to other adherence measures.[26] We were unable to include MEMS measurements in our study, but the prescription refills, as were used in this study, are considered as a reasonable, next best alternative.[26] In our original article we collected these data through patient self report, a method that has the potential for

overestimating true medication use. These data indeed showed a somewhat higher reported medication use.

Several phenomena may have contributed to the high patient adherence and persistence rates in our study. First, while giving informed consent, patients also agreed that data on prescription refills at their local pharmacy were going to be collected. This could have made patients of both groups more aware about the importance of collecting and taking medication (Hawthorne effect[27]). Second, although the control group did not receive the study intervention, it appeared that they more often visited their cardiologist than the intervention group.[21] This could have improved patient adherence in the control group. It did not however improve the prescription of spironolactone and the maximal dose of BB during the study as much as the intervention did.

The intervention of our original study was comparable to the intervention by Rich et al.[28] Rich et al assessed medication adherence during a short period of 30 days by pill counts. He also found a high average patient adherence in both groups, 87.9% in the intervention group and 81.1% in the usual care group ($p=0.003$) in this short period.[10] Both groups in our study showed a high adherence and persistence after 12 months. This shows, in accordance with the data of Van der Wal et al[25], an improvement in long-term patient medication adherence in general in the cardiology practice in the Netherlands in comparison with previous international data.[18,29] Bouvy et al used MEMS to measure adherence to loop diuretic therapy in a pharmacist-led intervention. Comparable to our study, he also found a high baseline patient adherence in both the intervention and the usual care group. Although adherence was high in both groups, they found a significant improvement of the adherence in the intervention group. In contrast to our study, they did not focus on drugs with a proven beneficial effect on prognosis in heart failure such as BB, ACE-i and spironolactone.[12] Another intensive, pharmacy-based intervention by Murray et al for outpatients with heart failure, using MEMS, improved patient adherence to cardiovascular medication and decreased health care use during a 9-months intervention[16], although the effect disappeared, during the 3 months after the intervention ceased. The patient population of this study differed strongly from our patient population (Table 1) and included low income patients, mean age 62 years, 66% women, mean LVEF of 50%, with heart failure, confirmed by their primary care physician.

Several limitations of this study should be discussed. First, of 36 patients data on rates of prescription refills were not available at the pharmacy because of a change of their computer systems at the time of our study. However, the baseline characteristics of this group of patients were comparable with the data of the original study.

Second, collecting data through rates of prescription refills would be a limitation if patients would collect their medications at different pharmacies. In general, however, patients in The Netherlands collect their medications from a single pharmacy. Furthermore, hospitalised patients do not receive drugs from the hospital at discharge. We can regard this system as a closed pharmacy system.[15] Third, as we mentioned before, to measure patient adherence and persistence by using prescription refills, is not the optimal method, but a good alternative. Fourth, adherence to pharmacotherapy by prescribers and patients was embedded in "a whole package" intervention programme and therefore might not quite have received the attention that it would have received, had it been independently studied. Our approach, however, is more in accordance with the way HF clinics work in daily practice. Our multidisciplinary heart failure management programme involved an intensive intervention, directed by a physician and a nurse. It has been suggested that greater benefit could be expected if a clinician, trained in HF, is more directly involved in these programmes.[30,31] The results of our study support this. The improvement of the physician adherence in the intervention group of prescription of spironolactone and of the average maximal dose of BB, drugs that beneficially influence the natural history of heart failure, is likely to have contributed to the positive outcome of our original study. This is in accordance with the effect of bisoprolol in the CIBIS II trial[32] (RRR 34% of total mortality) and metoprolol CR/XL in the MERIT-HF trial[33] (RRR 34% of total mortality) and the effect of spironolactone in the RALES trial[34] with 30% relative risk reduction (RRR) of HF death and sudden death and 35% RRR of hospitalisation for worsening HF. It also agrees with the study of Dobre et al[35], that indicates that higher doses of the BB Nebivolol (medium to target) appear to give a better effect on the combined endpoint mortality and hospitalisation. Despite the positive results of these large trials prescription of spironolactone and the dosing of beta-blockers are still not optimal. Our study showed that a physician-and-nurse-directed HF clinic is helpful in improving the prescription of these HF medications.

We conclude that a physician-and-nurse-directed HF clinic can improve the prescription of spironolactone and the dose of BB in patients with HF. This may be an important contributor to the prognostic benefit of this intervention.

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5

Correlation between long-term changes in NT-proBNP and changes in quality of life and functional status in heart failure

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■ Abstract

Background: Brain Natriuretic Peptide (BNP) has an established role in the diagnosis and prognosis of heart failure (HF). Whether, however, long-term changes in (NT-pro)BNP are accompanied by changes in other variables relevant for patients, such as quality of life and functional status, remains unknown.
Methods: We examined the correlation between absolute and relative long-term changes in NT-proBNP with changes in quality-of-life, measured with the Minnesota Living With HF Questionnaire (MLWHFQ), the physical (PCS) and mental composite score (MCS) of the MOS 36-item Short-Form Health Survey (SF-36), functional status (NYHA class) and echoparameters at 3 and 12 months in 237 patients with chronic HF, (NYHA III-IV).
Results: Absolute and relative long-term changes in NT-proBNP were modestly, but statistically significantly correlated with absolute and relative changes in the MLWHFQ, PCS and MCS of the SF-36, in NYHA class, and with echo parameters.
Conclusion: This study in a representative sample of patients with advanced HF shows that long-term changes in (NT-pro)BNP are accompanied by long-term changes in quality of life, functional status and echo parameters.
Keywords: correlation, long-term changes, NT-proBNP, quality-of-life

■ Introduction

Neurohormonal activation plays a pivotal role in the diagnosis of heart failure and reflects the severity of ventricular dysfunction.[1-6] NT-proBNP and BNP have been widely studied as potential diagnostic markers and both have also been shown to provide prognostic information in patients with heart failure beyond other measures including functional status and echocardiographic parameters.[7-9] Several studies reported that changes in neurohormone levels over time are associated with corresponding changes in mortality and morbidity.[10-12] A study of Yan et al.[11] showed a statistically significant correlation between serial measurements of neurohormones and changes in left ventricular ejection fraction (LVEF) and ventricular volumes after 17 and 43 weeks. Changes in BNP may be considered a biological marker for changes in left ventricular wall stress.[10] With the growing interest in the potential value of BNP-guided therapy[13-15], determining the correlation of BNP-changes with clinically relevant changes in quality of life and functional status becomes even more important to guide patient management. Luther et al[16] showed no correlation between changes in BNP with corresponding changes in the disease-related Kansas City Cardiomyopathy Questionnaire (KCCQ), but the

follow-up period was only 6 weeks. Importantly, the correlation between long-term changes in (NT-pro)BNP with changes in for patients more relevant variables, such as quality of life and functional status, remains unknown. Therefore, our aim was to study whether long-term changes in amino-terminal brain natriuretic peptide (NT-proBNP) are accompanied by changes in quality of life and a functional parameter such as New York Heart Association (NYHA) class. In addition the correlation with echo parameters, such as Left Ventricular Ejection Fraction (LVEF), Left Ventricular End Diastolic- and End Systolic Diameter (LVEDD, LVESD) was assessed.

■ Methods

Patients

Our study is a sub-study of the DEAL-HF (Deventer – Alkmaar Heart Failure Clinic Study[17-18]), a parallel group, randomised controlled trial to determine whether a regular, intensive (9 visits) 1-year intervention at a heart failure (HF) clinic by a combination of a clinician and a cardiovascular nurse reduces the primary endpoint "the composite of incidence of hospitalisation for worsening HF and/or all cause mortality". The study was performed between 2000 and 2004 in two cardiology departments in the Netherlands. 240 Patients with NYHA Class III or IV heart failure either after discharge from HF admission or visiting the cardiology outpatient clinic, were eligible for the study. A diagnosis of HF was established by typical 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 a preserved left ventricular systolic function, according to the 2001 guidelines for the diagnosis of HF of the European Society of Cardiology.[19] The exclusion criteria were dementia or psychiatric illness, discharge to or staying in a nursing home, any disease other than HF with an expected survival of < 1 year, participation in another trial, ongoing or planned hospitalisation, or undergoing kidney function replacement therapy. The Ethical committee of both hospitals approved the study and all patients provided written informed consent. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and the 2001 guidelines for HF of the European Society of Cardiology.[19] The results of the trial were described in detail elsewhere.[18]

Data collection

For this sub-study, at baseline, 3 and 12 months NT-proBNP levels, quality of life questionnaires, NYHA class and echo parameters were determined. Samples to assess plasma NT-proBNP levels were collected in chilled disposable tubes, containing aprotinin. After centrifugation at 4 °C, plasma samples were stored at -70 °C. NT-proBNP levels were determined by an immunoelectrochemiluminisence method (Elecsys 2010; Roche Diagnostics, Basel, Switzerland) and expressed in pg/ml. The clinicians, who assigned NYHA class and the administrators of the quality of life questionnaires were blinded for the quality of life questionnaires, NYHA classification, and NT-proBNP levels.

Disease-specific quality of life perception was evaluated by means of the Minnesota Living With Heart Failure Questionnaire (MLWHFQ)[20] with higher scores indicating worse quality of life. Health-related quality of life perception was assessed using the physical and mental health composite score (PCS and MCS) of the MOS 36-item Short-Form Health Survey (SF-36)[21], with higher scores indicating better perceived physical or mental functioning. Left Ventricular Ejection Fraction (LVEF), Left Ventricular End Diastolic- and End Systolic Diameter (LVEDD and LVESD) were measured either with a Philips Sonos 5500 or a Philips NZE28 Sonos 7500- Live 3D echo machine (biplane Simpson's method). If it was not possible to measure LVEF during echocardiography, radionuclide ventriculography was used.

Statistical analysis

Neurohormone concentrations at baseline exhibited a logarithmic-normal distribution and were log transformed before parametric correlation. Changes in NT-proBNP over time were normally distributed and not log transformed. Pearson correlation coefficients were calculated for the correlation between absolute, short (0 to 3 months) - and long-term (0 to 12 months), changes in NT-proBNP on the one hand, and absolute, short- and long-term, changes in quality of life, NYHA class and echo parameters on the other hand. Spearman correlation coefficients were calculated between relative changes in NT-proBNP after 3 and 12 months and the corresponding relative changes in the same set of items, such as quality of life. The correlation analyses were performed in the combined two arms of the clinical trial as well as in both arms separately.

■ Results

Patients had a mean age of 70.5 (SD ± 10 years), 72.6 % was male and in 63% of the patients coronary artery disease was the primary cause of heart failure (table 1).
NT-proBNP levels and quality of life values showed an improvement over time from baseline to 12 months (table 2). Absolute changes in NT-proBNP from baseline to 3 months showed a modest, but statistically significant correlation with corresponding changes in the MLWHFQ (r=.181, p= .014) and changes in NYHA class (r= .235, p= .001). Absolute changes in NT-proBNP from baseline to 12 months showed a comparable correlation with changes in the MLWHFQ (r= .257, p= .001), PCS and MCS of the SF-36 (r=-.245, p=.001 respectively r=-.158, p=.032), in NYHA class (r= .281, p< .001), LVEF (r=-.173, p=.024), and LVESD (r=.239, p=.009). Relative changes in NT-proBNP from baseline to 3 months were also accompanied by changes in MLWHFQ (r=.254, p<.001), PCS of the SF-36 (r=-.195, p=.005), NYHA class (r=.253, p<.001), LVEF (r=-.246, p=.003), and LVESD (r=.207, p=.018). Similar correlations were found between the relative changes in these parameters from baseline to 12 months (Table 3). Most of the correlations were somewhat stronger in the usual care group than in the intervention group (Table 4).

Table 1 Baseline characteristics of the study patients

Variable	N=237
Mean age (years)	70.5±10
Male	172(72.6%)
Aetiology CHF: Ischemia	63%
LVEF*	31% ± 9
LVEDD‡	64 ± 8.4
LVESD‖	49.6 ± 9
Systolic dysfunction	98%
NYHA† III /IV	96% / 4%
Atrial fibrillation	25%
Hypertension	39%
COPD**	28%
Diabetes mellitus	30%
Hypercholesterolemia	48%
Blood pressure (mmHg)	124 / 74
Mean heart rate (bpm)	78
NT-proBNP Mean/Median/ IQR ¶ (pg/ml) ‡‡	3890/ 2129/ 973-4516
Haemoglobin (mmol/l)	8.4
Hs-CRP (mg/L)	12.7
Creatinine (µmol/l)	126
Diuretics	96%
ACE inhibitor	85%
Angiotensin receptor blocker	11%
Beta-blocker	64%
Spironolactone	32%
Statins	38%
MLWHFQ ⊥ (total score)	42.3
SF-36 (PCS)∞	39
SF-36 (MCS)•	67

*LVEF= Left Ventricular Ejection Fraction; LVEDD=Left Ventricular End Diastolic Diameter, ‖LVESD=Left Ventricular End Systolic Diameter; †NYHA= New York Heart Association classification; **COPD= Chronic Obstructive Pulmonary Disease; ‡‡To convert from pmol/l to pg/ml multiply by 8.457; ¶ IQR= Interquartile Range; ⊥ Minnesota Living With Heart Failure Questionnaire. ∞ Physical Composite Score of the RAND-36 ; • Mental Composite Score of the RAND-36.

Table 2 Values and long-term changes of NT-proBNP and other for HF relevant variables at baseline, 3 and 12 months.

Variables (without worst rank)	Baseline n=237	3mnths n=211	12 months n=189	Δ 3mths - baseline n=211	Δ 12 mths - baseline n=189
NT-proBNP* (pg/ml) ‡‡	3890 ± 5353	3011± 3848	2453 ± 2960	- 330 ± 3078	- 761 ± 3112
MLWHFQ	42.5 ± 20.6	32.5 ± 18.3	32.2 ± 19.4	- 9.8± 18.7	- 9.6 ± 21.3
SF-36 PCS	39 ± 22.9	42.3 ± 25	41.9 ± 24.5	3.4 ± 16.3	2.8 ± 19.2
SF-36 MCS	67 ± 19.1	70.8 ± 17.8	70 ± 20.3	3.9 ± 14.8	3.1 ± 18.4
NYHA class	I -	I 2.6%	I 6.3%		
	II -	II 32.8%	II 45.3%		
	III 96%	III 62.6%	III 47.4%		
	IV 4%	IV 2.1%	IV 1%		
LVEF (%)	31 ± 9.4	33 ± 10.7	36.4 ± 11.9	2.7 ± 9.4	5.5 ± 10.9
LVEDD (mm)	64.1 ± 8.3	62.9 ± 8.2	61.5 ± 8.4	- 1.1 ± 4.5	- 2.4 ± 5.4
LVESD (mm)	49.6 ± 9.3	47.6 ± 10.0	45.3 ± 9.4	- 2.5 ±6.8	- 4.6 ± 8.1

*Actual levels (mean ± SD) are presented. ‡‡To convert from pmol/l to pg/ml multiply by 8.457;

Table 4 Correlations between absolute changes in NT-proBNP after 3 and 12 months with other for HF relevant variables for intervention and usual care group.

Variables that are compared			Intervention		Usual care	
			r	p	r	p
ΔproBNP	-ΔMLWHF	3 mths-baseline	.194	.059	.145	.173
ΔproBNP	-ΔSF-36 PCS	3 mths-baseline	-.017	.864	-.285	.004
ΔproBNP	-ΔSF-36 MCS	3 mths-baseline	.048	.630	-.241	.015
ΔproBNP	-ΔNYHA	3 mths-baseline	.176	.071	.320	.003
ΔproBNP	-ΔLVEF	3 mths-baseline	-.037	.755	-254	.032
ΔproBNP	-ΔLVEDD	3 mths-baseline	.005	.962	.098	.358
ΔproBNP	-ΔLVESD	3 mths-baseline	.105	.389	.165	.204
ΔproBNP	-ΔMLWHF	12 mths-baseline	.120	.264	.463	<.001
ΔproBNP	-ΔSF-36 PCS	12 mths-baseline	-.163	.108	-.383	<.001
ΔproBNP	-ΔSF-36 MCS	12 mths-baseline	-.100	.328	-.249	.020
ΔproBNP	-ΔNYHA	12 mths-baseline	.211	.035	.455	<.001
ΔproBNP	-ΔLVEF	12 mths-baseline	-.130	.214	-.236	.040
ΔproBNP	-ΔLVEDD	12 mths-baseline	.138	.198	.139	.219
ΔproBNP	-ΔLVESD	12 mths-baseline	.298	.016	.099	.478

Table 3 Correlations between NT-proBNP at baseline and absolute and relative changes in NT-proBNP after 3 and 12 months with absolute and relative changes in other clinically relevant variables.

Variables	lnNT-proBNP at baseline	Variables	ΔNT-proBNP 3 mths – baseline	Variables	ΔNT-proBNP 12 mths – baseline	Variables	% ΔNT-proBNP 3 mths – baseline	Variables	% ΔNT-proBNP 12 mths – baseline
MLWHFQ	r= .095	Δ MLWHFQ	r= .181	Δ MLWHFQ	r= .257	%Δ MLWHFQ	r= .254	%Δ MLWHFQ	r= .165
	p= .170	3 months -baseline	p= .014	12 months -baseline	p= .001	3 months -baseline	p< .001	12 months -baseline	p= .034
SF-36 PCS	r= -.163	Δ SF-36 PCS	r= -.130	Δ SF-36 PCS	r= -.245	%Δ SF-36 PCS	r= -.195	%Δ SF-36 PCS	r= -.197
	p= .015	3 months -baseline	p= .062	12 months -baseline	p= .001	3 months -baseline	p= .005	12 months -baseline	p= .007
SF-36 MCS	r= .029	Δ SF-36 MCS	r= -.076	Δ SF-36 MCS	r= -.158	%ΔSF-36 MCS	r= -.046	%Δ SF-36 MCS	r= -.144
	p= .672	3 months -baseline	p= .275	12 months -baseline	p= .032	3 months -baseline	p= .515	12 months -baseline	p= .050
NYHA	r= .213	Δ NYHA	r= .235	Δ NYHA	r= .281	%Δ NYHA	r= .253	%Δ NYHA	r= .153
	p= .001	3 months -baseline	p= .001	12 months -baseline	p < .001	3 months -baseline	p < .001	12 months -baseline	p = .038
LVEF	r= -.392	Δ LVEF	r= - .159	Δ LVEF	r= -.173	%Δ LVEF	r= -.246	%Δ LVEF	r= -.327
	p< .001	3 months -baseline	p= .058	12months -baseline	p= .024	3 months -baseline	p= .003	12months -baseline	p< .001
LVEDD	r= .195	Δ LVEDD	r= .053	Δ LVEDD	r= .143	%Δ LVEDD	r= .102	%Δ LVEDD	r= .212
	p= .004	3 months -baseline	p= .473	12 months -baseline	p= .064	3 months -baseline	p= .170	12 months -baseline	p= .006
LVESD	r= .137	Δ LVESD	r= .126	Δ LVESD	r= .239	%Δ LVESD	r= .207	%Δ LVESD	r= .396
	p= .078	3 months -baseline	p= .154	12 months -baseline	p= .009	3 months -baseline	p= .018	12 months -baseline	p< .001

■ Discussion

The present data demonstrate that changes in NT-proBNP over a longer time are correlated, albeit modestly, with time corresponding changes in clinically relevant variables such as HF- related quality of life perception (MLWHFQ), health related quality of life perception (SF-36, physical and mental composite score) as well as NYHA class.

Because BNP is more and more considered an important parameter to guide patient management in heart failure[13], understanding whether long-term changes in (NT-pro)BNP are accompanied by changes in for patients more appealing and relevant variables, such as quality of life and functional status, is important. In an earlier study, including 342 patients with systolic HF, the correlation between changes in BNP with changes in the HF-related Kansas City Cardiomyopathy Questionnaire (KCCQ) over a short period of 6 ± 2 weeks was determined.[16] No correlation between BNP with health status over this short time was found. Also in our study, no correlation between changes in NT-proBNP with the changes in the health related SF-36 questionnaire (PCS and MCS) were found after 3 months, but we did observe a, statistically significant correlation between changes in NT-proBNP and changes in the HF-related MLWHFQ. We also found a correlation between (relative) changes in NT-proBNP and (relative) changes in MLWHFQ and (relative) changes in the SF-36 questionnaire (mainly the physical score, lesser the mental score) after 12 months. These results suggest that it takes time before patients' quality of life perception and NT-proBNP reflect changes, either improvement or deterioration, in left ventricular function. In agreement with other studies[22,23] we found a correlation at baseline of NT-proBNP and LVEF and NYHA class. The statistically significant correlation between changes in NT-proBNP and changes in LVEF and LVESD over a longer time is in line with the findings of Yan et al.[11]

Our separate analysis in the two arms of the clinical trial revealed a stronger correlation between changes in NT-proBNP and changes in quality of life in the usual care group than in the intervention group. Thus, in a more intensive intervention/treatment the correlation seems to decrease. This could be explained in different ways: either the improvement of quality of life perception is more pronounced than the improvement of the NT-proBNP in the intervention group (irrespective of changes in the functioning of the heart) or the opposite. This decreasing correlation between changes in NT-proBNP and changes in quality of life in the intervention group is in line with our finding in the clinical trial. Here we observed that the improvement in NT-proBNP was accompanied by a similar improvement of quality of life in the usual care group, while in the intervention group the improvement of quality

of life was larger than the improvement in NT-proBNP.[18] It should be emphasized that our study did not aim to and was therefore not designed to answer the question whether there is a *causal* relationship between changes in NT-proBNP and changes in quality of life, functional status or other for HF relevant measures. Our aim was not to determine whether changes in NT-proBNP *caused* changes in these parameters, but whether NT-proBNP changes (brought about by, e.g., improved management of heart failure) can be expected to coincide with changes in quality of life and functional status. Thus, confounding was a non-issue and no multivariate analyses were performed.[24]

Several limitations of our study should be discussed. First, we decided to combine the two arms of this clinical trial. One could argue, that the "natural correlation" between changes of NT-proBNP with changes in health status and functional status should be assessed in the control group of a trial, where no interventions are initiated and thus the "natural history" can be observed. However, the control group in our trial received multiple interventions, according to the guidelines for HF of the European Society of Cardiology.[19] An analysis restricted to this usual care group though, identified indeed stronger correlations between changes in NT-proBNP with changes in health- and functional parameters (table 4). As discussed before, quality of life perception is more possitively influenced by the heart failure clinic intervention than the NT-proBNP is, resulting in a decreasing correlation. The correlations between the changes in the usual care group are stronger and probably more likely to reflect the real relationship. Second we used the MLWHF and the SF-36 quality of life questionnaires. We, therefore, cannot make a comparison with the KCCQ used in the earlier study.

We conclude that our findings in this study in a representative sample of patients with advanced heart failure indicate that long-term changes in (NT-pro)BNP, apart from reflecting morbidity and mortality, are likely to also be accompanied by similar changes in quality of life, functional status and echo parameters. These findings will be of interest to those health care professionals considering the use of natriuretic peptides in tailoring interventions in heart failure patients.

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Cost-effectiveness of a physician-and-nurse-directed heart failure clinic. Results from the DEAL-HF study

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■ Abstract

Background: Crude estimates of costs and effects alongside the Deventer-Alkmaar-Heart-Failure-study (DEAL-HF) suggest a favourable balance between costs and effects of an intensive follow up program. A more detailed analysis, with emphasis on the uncertainties is warranted.
Methods: Subsequently, survival, disease severity, health related quality of life, utility, quality adjusted life years (QALYs) and costs are addressed based on data collected alongside the trial. The time horizon is one year. Disease severity is addressed by the New York Heart Association (NYHA) categorisation; health related quality of life by the Minnesota Living with Heart Failure questionnaire and the SF36. Utility is derived from the SF36. QALYs are estimated by combining utility estimates with survival. Costs are limited to direct medical costs. Programme costs are estimated as a lump sum on the basis of data from the hospital administration. Other costs are estimates by multiplying volumes of resource utilisation with unit costs estimates from the literature.
Results: Expected survival time during year 1 follow up increases with 0.025 year (95% CI:(-0.020; 0.071)). Changes in disease severity (NYHA classification) are in significant favour of the intervention group. When disregarding the effects on survival the average increase in SF 36 (scale 0-100) is 5.6 points better (P-value 0.062) in the intervention group points and 5.2 (P-value 0.108) with the MLWHF (scale 105-0). The gain in QALYs is estimated at 0.032 (95% CI: (-0.018,+0.078)). Cost savings per patient are estimated at -€2,484 (-€5,328; -€145). The probability that the intervention is cost saving is estimated at 98%, the probability that it gains QALYs at 87%.
Conclusion: A more detailed analysis of the costs and effects alongside the DEAL HF study confirms the earlier conclusion and leaves little doubt that intensive follow up treatment may be associated with cost savings and additional effectiveness.

■ Introduction

Heart failure (HF) is a life-threatening syndrome and prognosis is poor[1] despite new pharmacological[2,3] and non-pharmacological therapies.[4] Because HF affects 1-3% of the adult population, it is an important public health problem.[5-7] Disease Management Programs (DMPs) try to improve morbidity and mortality by means of education, regular follow-up at home or at an outpatient clinic, and by adherence to the international guidelines for the treatment of HF.[8-10] Randomised and non-randomised studies show conflicting results on the cost-effectiveness of DMPs.[11-20]

We have previously reported that an intensive HF management programme, directed by a physician and a nurse, substantially reduced hospitalisations for HF and/or all cause mortality.[21] In this sub study we investigate the cost-effectiveness of this programme in further detail. Subsequently we address survival, disease severity, health related quality of life, utility, quality adjusted life years (QALYs) and costs. Disease severity is assessed by the clinician using the New York Heart Association (NYHA) categorisation. Health related quality of life is assessed by using a disease specific questionnaire - the Minnesota Living with Heart Failure questionnaire (MLHF)[22] – and a generic questionnaire - the SF36. Utility is derived from the SF36.[23] The balance between costs and effects is addressed by assessing the costs per QALY, where QALYs are estimated by combining utility estimates with survival. Based on the results that have been reported previously, we will especially focus on the uncertainties surrounding the various outcomes.

■ Methods

Patients

The DEAL-HF study was a parallel group, randomised controlled trial designed to determine whether a regular, intensive intervention at a heart failure (HF) clinic delivered by a clinician and a cardiovascular nurse reduces the primary endpoint of "the composite of incidence of hospitalisation for worsening HF and/or all cause mortality".[24] The local Ethics Committees of the participating Deventer and Alkmaar hospitals approved the study. 240 patients with NYHA class III or IV who were either hospitalised or visiting the cardiology outpatient clinic, were eligible for the DEAL-HF study. All patients gave written informed consent. A diagnosis of HF was established by typical clinical signs and symptoms in conjunction with echocardiographic or radionuclide ventriculographic findings of a reduced left ventricular systolic function (LVEF≤45%) or of a preserved left ventricular systolic function with diastolic dysfunction according to the 2001 guidelines of the European Society of Cardiology for the diagnosis of HF.[25] After screening, eligible patients were randomised by computer-generated allocation to either the intervention group or the control group. Patients were recruited between March 2000 and April 2003 with a follow-up of one year.

The Intervention group

The intervention of the DEAL-HF study, performed in addition to usual care, consisted of an intensive follow-up of patients for one year at a HF outpatient clinic led by a HF physician and a cardiovascular nurse. The actual intervention commenced with a telephone call within a week following

hospital discharge or referral from the outpatient clinic. At the first two visits to the HF clinic (weeks 1 and 3), comprehensive verbal and written education about HF and disease management was given to the patient. An appointment with a dietician was also scheduled. Easy access to the HF clinic was offered during working hours. At the regular follow-up visits at week 5, week 7, months 3, 6, 9 and 12, the nurse provided counselling, check-up, reinforcement of the education, and a short physical examination. At six of the nine follow-up visits, the physician assessed the condition of the patient, including electrolytes and kidney function, tolerance of medication and side-effects, optimised (medical) treatment and performed an overall assessment together with the nurse. The intervention has been described in greater detail elsewhere.[21,24]

The Control Group

The cardiologists of the Deventer and Alkmaar cardiology department treated the patients randomised to routine care according to their "usual care". Their routine care is largely based upon the guidelines for the treatment of heart failure (the European Society of Cardiology - version 2001)[25] which include optimal application of medical therapy including target doses or high doses of heart failure medication. All cardiologists from the two hospitals saw patients from the control group at their outpatient clinic.

Effectiveness

Effectiveness was expressed in terms of differences in life years gained, disease severity, quality of life, utility and QALYs. Survival was estimated by integration of the area under Kaplan Meier survival curves and life years gained were estimated by subtraction. Disease severity was assessed by the clinician using the NYHA classification. Quality of life was assessed by the patient using the SF36 and MLHF questionnaires. Utility was derived from the SF36 and QALYs were obtained by integrating individual utility over individual survival.

Data about disease severity and quality of life were collected at baseline, 3 months, and 12 months.

The SF 36 is a generic questionnaire consisting of 35 questions covering 8 dimensions of health: physical and social functioning, physical and emotional role functioning, vitality, psychological functioning, pain, and general health. Additionally, there is a question concerning the change in health over the last year. Scores vary between 0 and 100 within each dimension and the summary score is obtained as an average of the scores on the 8 dimensions. Here, 100 is the best and 0 the worst possible score. The Minnesota Living with Heart Failure questionnaire is a disease specific instrument which contains 21

questions asking to what extent heart failure has limited the patient in living as desired. The overall score is obtained by summating the responses to all questions. Zero is the best possible score and 105 the worst. A physical dimension score and an emotional dimension score can be obtained by summing up the answers of 8 or 5 selected questions respectively.
The results from the SF36 were transformed into utility estimates using the algorithm by Brazier.[26] QALYs were obtained by linear interpolation of the utility scores at baseline, 3 months and 12 months. When patients die, their utility was set at 0 from the moment of their death and onwards and utility estimates were again obtained by linear interpolation between the last observation and the time of death.

Costs
To assess economic and utilisation outcomes, patient medical records were reviewed covering the period of the patient's enrolment in the trial. Patient recall and patient's diaries were also used to assess these outcomes. A distinction was made between programme costs and patient-related costs.
The programme costs consisted of the salary costs of the people involved in the intervention (the physician, the nurse and the dietician) and the costs of routine ECGs and lab-tests associated with the programme. All programme costs were calculated as a lump-sum for one year.
Patient-related costs were the costs of hospital days, visits to the GP, cardiologist, and other specialists, and home nursing. Hospital days were broken down into days on the general ward and days on the ICU/CCU. Volumes of resource utilisation were obtained from hospital records and patient interviews. Unit costs were estimated using the Dutch guidelines for cost calculations[27] and inflated to 2008 prices using a general consumer price index. To assess whether potential differences in hospital days are a result of more or less hospitalisations and/or of more or less hospital days per hospitalisation an analysis was carried out of the relationship between the number of hospital days and the patients' NYHA classification after 3 months.

Cost effectiveness
The balance between costs and effects is addressed by estimating additional costs per QALY gained. On the basis of earlier publications one may expect cost savings in combination with additional effectiveness with the intervention. Therefore, the report will be limited to the estimated probabilities that cost and effects will be in each of the four quadrants of the cost-effectiveness plane.[28] The quadrants correspond with the probability of the intervention being more expensive and more effective (north-east), cost

saving and more effective (south-east), more expensive and less effective (north-west) and cost saving but less effective (south-west).

Statistical analysis

Cumulative survival functions with and without the intervention were estimated using Kaplan-Meier curves and differences were tested using a Wilcoxon-test. The surface under the curves was used to estimate life years gained and bootstrapping was used to estimate 95% confidence intervals surrounding the difference.[29]

Changes in disease severity were addressed by the distribution of patients in the NYHA classes in time and by the probability that a patient's NYHA class improved, stayed the same, or worsened, excluding patients who died. Again, bootstrapping was used to estimate the 95% confidence intervals.

Quality of life as measured by the SF36 summary score, the SF36 utility score, and the Minnesota summary score was compared at baseline, 3 months and 12 months using pair wise T-tests. Similar analyses were also carried out on the differential changes between baseline and 3 months, 3 months and 12 months and baseline and 12 months.

QALYs were calculated by integrating the interpolated utility scores over the time that patients were alive. Differences in QALYs were tested by bootstrapping.

Hospitalisation costs were calculated per patient as the product of volumes of resource utilisation and unit costs. To estimate uncertainty margins a simulation approach was followed in which each patient in the intervention-group was allocated fixed costs, which were varied by ± 10% using a Beta (2,2) distribution. This was then subsequently divided by a number of patients drawn from another Beta (2,2) distribution transformed to (100, 136). (The choice of Beta(2,2) implies that approximately 95% of the density is to be found within 10% and 90% of the interval). Similar uncertainty margins were calculated for the unit costs associated with the number of days spent in hospital.

The resulting 95% uncertainty margins surrounding the differences in costs were obtained by a combination of bootstrapping and, within each bootstrap, drawing from the uncertainty distributions surrounding the unit costs and the programme costs.

Hospitalisation days were analysed as a function of treatment and NYHA-classification using a zero-inflated Poisson-regression. This implies a simultaneous analysis of the probability that hospitalisation was needed and subsequently (if this is indeed the case) of the number of hospital-days. The latter analysis aims to identify whether observed differences are due to the need for hospital treatment, the length of hospital treatment, or both.

The uncertainty surrounding the balance between costs and effects was addressed by combining bootstrap approaches to calculate the 95% confidence intervals surrounding costs and QALYs. The results from 5000 bootstraps were presented in the cost effectiveness plane and probabilities were estimated for each quadrant.[28]

■ Results

Figure 1 illustrates the Kaplan-Meier estimates of all-cause mortality. The surface under the intervention curve (blue solid line), measures 343 days, the surface under the control curve (red dotted line) 334 days. Life years gained with the intervention during the first year are estimated at 0.025 years (95% CI:(-0.020; 0.071)), or 9 days (95% CI: (-7.5; 25.9)).

It is noted that while the P-value from the Wilcoxon test for differences in survival is under 0.05, 0 is within the limits of our 95% confidence interval surrounding the number of life years gained during the first year, and so the probability of no gains is not excluded here.

The results in Figure 1 also show that the intervention is associated with improving NYHA categories and with keeping patients in the better NYHA classes. Table 1 presents the probabilities of improvement in NYHA, staying in the same category, and worsening in NYHA category.

In all comparisons of NYHA class over time, larger improvements are found in the intervention group. Given that the transitions to death have been disregarded in these estimates and also that the lower limits of the 95% confidence interval of the differences are positive, one may conclude that there is a statistically significant improvement in disease severity – as assessed by the clinician using the NYHA classification - next to an improvement in survival.

Table 2 presents Health Related Quality of Life results as measured by the SF-36 and the Minnesota-living with heart failure questionnaire and where data are treated as missing after patients died.

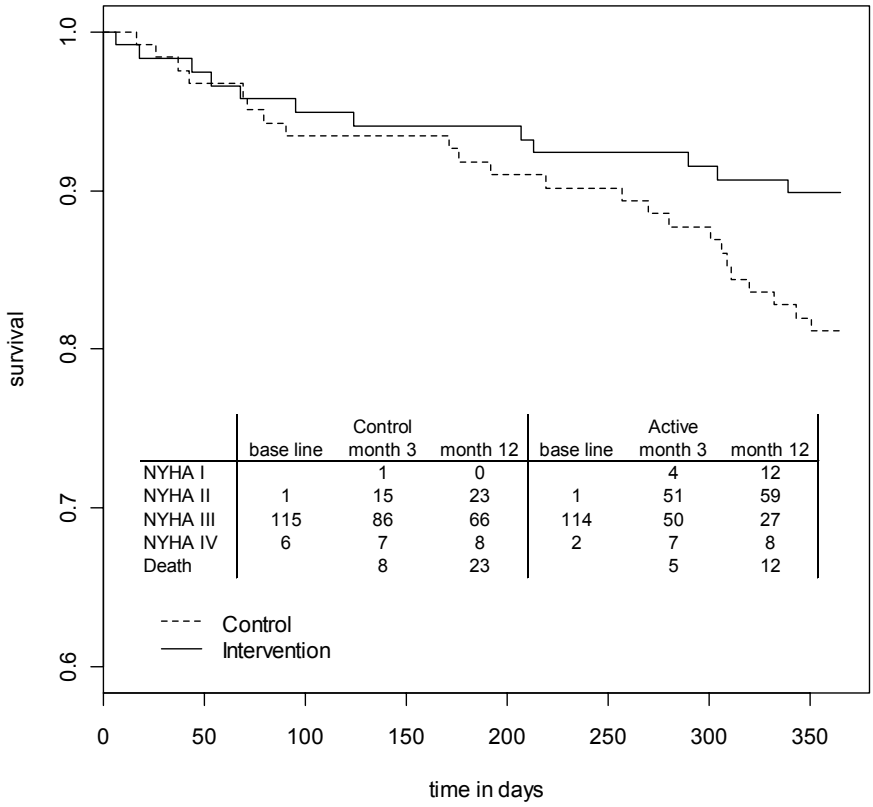

Figure 1 Survival and NYHA class in time

Table 1 Probability to change in terms of NYHA class (excluding mortality)

		Control	Intervention	Intervention-control
baseline vs. month 3	worsen	6.4% (2.8%; 10.5%)	6.3% (2.8% ; 10.2%)	-0.2% (-5.6% ; 5.7%)
	stay	76.1% (69.5%; 82.8%)	43.8% (35.9%; 51.5%)	-32.4% (-42.9% ; -22.2%)
	improve	17.4% (11.3%; 23.6%)	50.0% (41.7% ; 57.8%)	32.6% (22.8% ; 43.1%)
month 3 vs. month 12	worsen	14.7% (9.0%; 21.1%)	9.5% (5.2% ; 14.2%)	-5.2% (-12.7% ; 2.5%)
	stay	70.5% (62.4% ; 77.9%)	56.2% (48.5% ; 64.4%)	-14.3% (-25.7% ; -3.2%)
	improve	14.7% (9.3% ; 21.3%)	34.3% (26.6% ; 41.9%)	19.5% (9.0% ; 28.9%)
baseline vs. month 12	worsen	11.1% (6.2% ; 16.5%)	6.7% (2.9% ; 11.1%)	-4.4% (-11.0% ; 2.1%)
	stay	63.6% (55.9% ; 71.6%)	24.8% (17.9% ; 31.6%)	-38.9% (-49.5% ; -28.3%)
	improve	25.3% (18.2% ; 32.6%)	68.6% (60.7% ; 75.7%)	43.3% (32.4% ; 53.4%)

At three months significant improvements are seen in the SF36 summary score and the Minnesota LWHF summary score. No statistically significant effects were found in the SF36-utility score. Surprisingly – in light of the significant changes in NYHA - none of the changes in self-reported assessments at month 12 are statistically significant.

Table 2 Health related quality of life (non-survivors as missing)

	Control				Intervention				
	mean	**5%**	**95%**	**N**	**Mean**	**5%**	**95%**	**N**	**P-value**
SF36 summary score									
Baseline	46.77	22.32	70.70	90	45.12	22.80	76.30	97	0.506
3 months	50.16	21.24	81.11	97	54.13	25.41	85.11	104	0.126
12 months	52.34	18.56	87.76	87	56.30	29.50	82.89	101	0.167
Δ3 months-baseline	4.19	-16.77	26.24	79	9.19	-19.00	37.99	90	0.039
Δ12 months-baseline	5.64	-13.53	43.09	69	11.25	-22.64	34.80	85	0.062
SF36 utility score									
Baseline	0.5986	0.4438	0.7192	87	0.6024	0.4720	0.7190	95	0.767
3 months	0.6192	0.5125	0.7206	85	0.6229	0.4761	0.7320	91	0.745
12 months	0.6118	0.4966	0.7704	70	0.6216	0.4871	0.7345	85	0.465
Δ3 months-baseline	0.0279	-0.1132	0.1593	69	0.0125	-0.0916	0.1243	75	0.221
Δ12 months-baseline	0.0215	-0.1178	0.1828	54	0.0134	-0.0958	0.1488	72	0.609
Minnesota LWHF									
Baseline	42.62	11.35	75.60	103	42.47	10.00	78.20	112	0.958
3 months	36.23	6.70	61.00	98	28.75	4.00	69.00	102	0.004
12 months	34.51	2.45	60.00	86	30.21	3.60	65.40	97	0.135
Δ3 months-baseline	-6.15	-40.40	16.35	91	-13.22	-42.25	15.00	99	0.009
Δ12 months-baseline	-6.76	-40.00	22.75	79	-11.98	-44.10	25.30	94	0.108

Table 3 presents the estimates when the SF summary score is set at zero and the Minnesota LWHF score at its maximum (105) after patients have died. Now the differences after 12 months are statistically significant at the 5% level. Additionally, we present the results in terms of QALYs when the SF 36 data are transformed into utilities according to the algorithm proposed by Brazier et. al.[25]

Here, while the difference in QALYs seems significant between months 3 and 12, this is not the case between months 0 and 3 or when considering the whole one year period. The number of QALYs gained at 12 months is estimated at 0.032 (95% CI: (-0.018,+0.078)). This is 0.07 a year more than the

difference in life years gained, suggesting that the intervention combines gains in survival with gains in quality of life. As with survival, the 95% confidence interval includes 0, not excluding the point of no QALY gains.
Table 4 presents the estimates of costs with and without the intervention. It is estimated that 1/3 of the programme can be run by a clinician, 1/3 by a nurse and 1/10 by a dietician. Costs of additional ECGs are estimated at €2,000 and of additional lab-tests at €5,000. As such, the fixed costs of the intervention are estimated at €61,673.

Table 3 Health related quality of life (non survivors set at worst score) and QALY's

	Control				Intervention				
	mean	**5%**	**95%**	**N**	**mean**	**5%**	**95%**	**N**	**P-value**
SF36 Summary score									
Baseline	46.77	22.32	70.70	90	45.12	22.80	76.30	97	0.506
3 months	46.34	0.00	81.04	105	51.65	10.57	84.14	109	0.074
12 months	41.39	0.00	81.98	110	50.32	0.00	89.08	113	0.012
Minnesota LWHF									
Baseline	42.62	11.35	75.60	103	42.47	10.00	78.20	112	0.958
3 months	41.42	8.00	105.00	106	32.32	3.30	95.40	107	0.007
12 months	49.39	4.00	105.00	109	38.44	3.80	105.00	109	0.012
QALYs gained									
Baseline-month 3	0.147	0.100	0.175	71	0.147	0.104	0.177	78	0.939
Month 3-month 12	0.386	0.000	0.574	78	0.437	0.000	0.562	83	0.045
Baseline-month 12	0.553	0.372	0.718	59	0.585	0.091	0.728	70	0.269

Table 4 Estimates of costs

	Intervention	Control	Unit costs	Intervention	Control	Intervention–control (95% CI)	
N	118	122					
Intervention	1	0	€ 61,673	€ 522	€ 0	€ 522	(€449; €607)
ICU/CCU days	2/5	27/73	€ 2,746	€ 163	€ 2,251	-€ 2,088	(-€3,610; -€777)
General ward days	352	568	€ 569	€ 1,697	€ 2,537	-€ 840	(-€2,456; €504)
Total hospital days	359	644		€ 1,860	€ 4,787	-€ 2,928	(-€5,745; -€586)
Primary care physician	129	131	€ 40	€ 48	€ 50	-€ 2	(-€12; €8)
Cardiologist	84	149	€ 175	€ 137	€ 251	-€ 113	(-€157; -€70)
Other physician	86	65	€ 175	€ 141	€ 109	€ 31	(-€8; €72)
Home care nurse	22	16	€ 96	€ 20	€ 15	€ 5	(-€8; €19)
Total Costs						-€ 2,484	(-€5,328; -€145)

The results indicate that the programme will lead to significant cost savings on the ICU and CCU wards and that additional savings may be expected on the general ward, albeit with broader uncertainty margins. Total savings per patient are estimated at € 2,484 with a 95% confidence interval that has a lower limit of €145.

It needs to be noted that the results are slightly skewed by one patient in the control group who was in hospital for 138 days of which 18 were spent in the ICU. When this patient is removed from the analysis, total costs are estimated at -€1,532 (95% CI: (-€3,411; €187)). But even in this case, one finds an upper 95% limit which may be considered acceptable.

An additional analysis was carried out to examine whether the effect on hospital days was due to a lower probability of hospitalisation, a lower number of days spent in hospital, or to a combination of the two. The results from the zero-inflated Poisson regression are presented in table 5. This adds a logistic regression (estimating an additional probability to not be hospitalised) to a Poisson regression (estimating the number of days in hospital as a Poisson process). The estimates show that neither NYHA nor treatment has a significant effect on the probability to be hospitalised (as measured by the logistic regression), Contrarily, both indicate a significant effect on the Poisson-part suggesting a significant effect on the number of hospital days.

Table 5 Hospital days as the result form a zero-inflated Poisson process: parameter estimates

		Coefficient	Standard error	P-value
Logistic regression	(Intercept)	1.65	0.68	0.0151
	NYHA month3	-0.14	0.21	0.4934
	Intervention	-0.37	0.33	0.2719
Poisson regression	(Intercept)	2.24	0.18	<2E-16
	NYHA month3	0.21	0.056	0.00016
	Intervention	-0.49	0.078	2.27E-10

The balance between costs and effects is illustrated in figure 2. The probability that the intervention is cost saving is estimated at 98%, the probability that it gains QALYs at 87%.

■ Discussion

In an earlier report the costs of the programme discussed here were estimated at €50,246 and the savings due to less hospitalisations at €137,682, a difference of €741 per patient. Here, with updated unit cost estimates (cost of CCU and ICU at €2,746 per day instead of €1,146 and the costs of a day on the general ward at €569 instead of €162), and including the costs of some additional visits, savings are estimated at €2,484 per patient. In one patient, €952 of savings were observed but even when this patient is left out of the analysis, the balance between costs and effects still seems favourable.

When considering the effects of the programme on disease severity as assessed by the clinicians, results are spectacularly positive even when disregarding the effects on survival. Effects are slightly less impressive when considering patient-reported outcomes from the SF36 and the Minnesota LWHF questionnaire (with non-survivors missing). The only statistically significant difference is found at 3 months in the SF36 and the Minnesota LWHF questionnaires. However, when the non-survivors are set at worst score (SF summary score at zero, MLWHF score at 105) the differences after 12 months are statistically significant, which is conform the results of the earlier report. When translating the SF36 into utilities no statistically significant effects are found.

One might wonder whether this may have been expected. Patients are kept alive due to the programme and one might expect that average quality of life would decrease due to keeping these patients alive. However, quality of life increases in all measures, albeit not significantly. This is once more reflected in the more substantial increase in QALYs than in life years gained. While the average utility per day is about 0.6, the average number of QALYs gained is

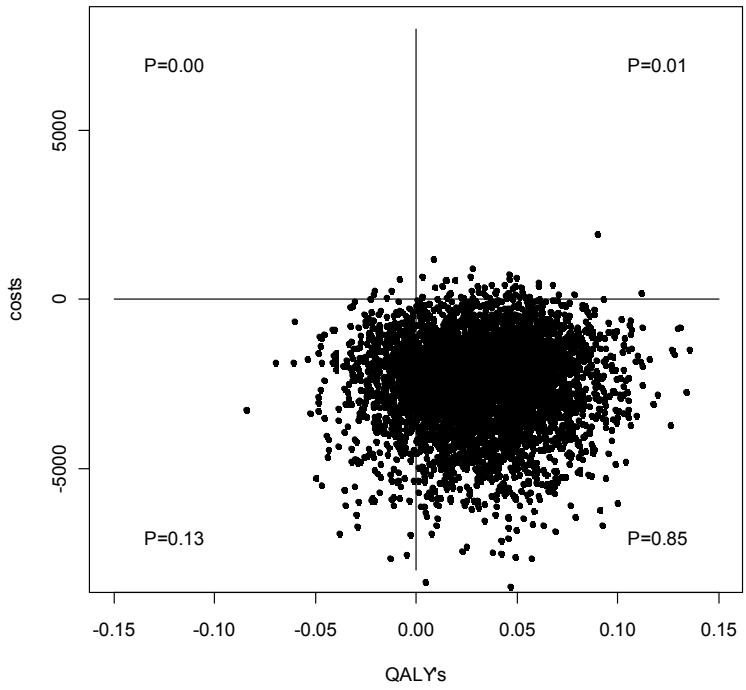

Figure 2 Uncertainty distribution of costs and effects; bootstrap results

0.0325 vs. 0.025 life years or 12 vs. 9 days. Now, one may argue that 12 days per patient may only be small but one may want to consider that this is 3.2 QALYs per 100 patients in the programme. Moreover, for each 100 patients, an additional €248,400 is saved. Therefore, not only are there 3.2 QALYs gained per 100 patients in the programme, one might send each QALY home with an additional €77,625 (i.e.248,400 / 3.2). That sounds like value for money.

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7

General discussion

■ Heart failure management programmes: what works for whom, when and how?

In the last decade the attention given to heart failure (HF) management programmes (HFMP) increased considerably. The first heart failure management programmes were received with great enthusiasm and viewed as an important contribution to improving the quality of care in patients with heart failure. Evidence from several randomised controlled trials (RCTs) suggested that these programmes could reduce all-cause mortality and hospitalisation for heart failure by 10 to 30%.[1-4] However, the setting, the contents and duration of these HF management programmes varied widely, as did the interventions in the control groups of the trials. Furthermore, the sample size was often limited and only few studies provided a detailed description of the interventions included in the HFMP and their intensity. In addition, the applicability to the European situation and especially to countries with a primary care-based health care system such as the Netherlands and the UK was uncertain.[5] The latter was on the main justification for performing the DEAL-HF (Deventer Alkmaar Heart Failure) study.[6] At about the same time, the COACH (Coordinating study Evaluating Outcomes of Advising and Counselling in Heart Failure) study, the largest trial up to date to assess the effect of a multidisciplinary HF management programme, was set up in the Netherlands.[7]

Two recent randomised HF management trials in the Netherlands

The DEAL-HF study (n=240), a prospective, randomised, parallel group 1-year trial to determine the effect of a nurse-and-physician-directed, multidisciplinary intervention in patients with NYHA III and IV HF (Table 1), found a substantial reduction of hospitalisations for HF and/or all-cause mortality (Table 2). Furthermore, a beneficial effect on functional status, the number of days in hospital and health-care costs were observed. Further analyses revealed that the beneficial effects were at least partly attributable to increased use of spironolactone and higher dosaging of beta-blockers. This implies, that even in a country with well-structured primary care facilities, there is room for improvement in the quality of care through a HF management programme.

The COACH study (n=1023), however, reported less positive results (Table 2). In the COACH study the effect of two types of HFMP (intensive (19 visits) disease management and moderate intensive (10 visits) disease management) were compared with usual care (3-4 consultations by a cardiologist) in patients with mild, moderate or severe heart failure (NYHA II, III and IV). The main outcome parameters were time to death or

Table 1. Comparison of patients and intervention in DEAL-HF and COACH study

	DEAL-HF (n=240)	COACH (n=1023)
Mean age	71 years	71 years
Female	28%	38%
LVEF	31%	34%
NYHA	III 96%; IV 4%	II 50%; III46%; IV 4%
Previous MI	55%	43%
Prior admission for HF	49%	32%
Blood Pressure	124/75	118/68
Heart rate	78	75
Atrial Fibrillation	27%	36%
Diabetes Mellitus	30%	28%
Mean e-GFR	55	55
NTpro-BNP, median, pg/ml	2139	2528
Personnel	Nurse and clinician	Nurse
Intervention	Intensive (9 vis/y)	Intensive (19 vis/1.5y, incl home vis) Moderate intensive (10 vis/1.5y)
	Usual care: not protocolised	Usual care: 3-4 vis at cardiologist/1.5y
Pharmacological therapy	Medication optimalisation	Non-pharmacological programme
Participating clinics	2	17

rehospitalisation because of HF and the number of days "lost" because of hospitalisation or death during the 18 months follow-up period. The interventions included in the two HFMP arms were primarily given by a HF nurse. Relevant characteristics of the DEAL-HF and COACH studies are given in table 1.

How can the seemingly contradictory results of the DEAL-HF and COACH study be explained? Importantly, the content of the behavioural management by the HF nurse in the DEAL-HF and the COACH study was comparable, except for the home-visits included in the most intensive HFMP arm of the COACH study. Several larger differences between the two studies could account for the contradictory findings. First, the heart failure population included differed (Table 1): the COACH study included less severely ill people, 50% NYHA II and 50% NYHA III or IV, whereas in the DEAL-HF study only patients with more severe HF (96% NYHA III, 4% NYHA IV) participated. Second, in the DEAL study the intervention was provided by a combination of a nurse and a clinician, while in the COACH study the management programmes were nurse-led. In the DEAL-study the clinician and not the nurse performed the pharmacological and clinical management of

the more severely ill people with HF. Optimisation of HF medication was a crucial part of the programme, whereas in the COACH study more emphasis was put on non-pharmacological interventions. A detailed analysis of the DEAL study findings strongly suggest that differences in uptake of drug therapy between the two comparison arms has contributed to the observed beneficial effect of the HFMP. Third, usual care in the COACH study was, in contrast with the DEAL-HF study, protocolised (3-4 visits to a cardiologist in 18 months), which could have "upgraded" the control group in the COACH study. This, together with the more intense intervention arm of the DEAL-HF study, is likely to have resulted in a larger contrast between the intervention and control groups in the DEAL-HF study. Moreover, the fact that the COACH study was performed in 17 hospitals, with varying experience in heart failure care and differences in the way the interventions included in the protocols were actually implemented may have further limited the contrast between the comparison arms in the COACH study. Such "dilution" is less likely in the DEAL study, since that study was conducted in two hospitals with a small well-trained and very dedicated staff. Fourth, the possibility of a chance finding was much larger in the DEAL study, because compared to the COACH-study the number of patients included (240 versus 1023) and the follow-up period (12 versus 18 months) was smaller. One can only speculate on which of these possible explanations truly underlies the different results of these two trials. Evidence from other trials indicates that optimisation of heart failure medication is an important contributor to the beneficial effects of heart failure management programmes.[8-11] In several articles it has been suggested that larger benefit can be expected from a HF management programme, if a clinician, trained in HF, is more directly involved.[2,12,13]

In conclusion, more emphasis on optimisation of HF medication, a combined nurse-and-physician-directed management programme and a larger contrast between intervention and usual care groups in the DEAL study probably contributed to the observed differences with the COACH-study findings. Interestingly, several other recent international HFMP studies reported similar findings as the COACH-study.[14-19] This brings up the question whether modifications of the existing programmes are needed and perhaps more individually targeted programmes are required.

Table 2 Effect of DEAL-HF and COACH study on hospitalisation, death and days in hospital

	DEAL-HF (n=240)		**COACH** (n=1023)		
	Control group (n=122)	Intensive intervention (n=118)	Control group (n=339)	Moderate intensive intervention (n=340)	Intensive intervention (n=344)
No of hosp for HF and/or death	47 (42.2 per 100 pat years)	23 (20.7 per 100 pat years) Rate Ratio (95%CI) 0.49(0.30 to 0.81)*			
No of patients with hosp for HF or death			141 (42%)	138 (41%) (p=.43)*	132 (38%) (p=.22)*
Per patient median no of days lost because of death or all cause hospitalisation			12 (25^{th} and 75^{th} perc., 0 and 173 days)	9 (25^{th} and 75^{th} perc., 0 and 88 days; p=.81*	7.5 (25^{th} and 75^{th} perc., 0 and 86.5 days; p=.49*
All cause mortality	18.8%	10.2% (p=.068)*	29%	27% (p=.39)*	24% (p=.15)*

* versus control group

■ How should management of patients with HF be organised in the future?

Although systematic reviews or meta-analyses on effects of HFMP usually report that HFMPs are beneficial, the trial results vary considerably. As mentioned earlier, explanations for these discrepancies are not straightforward. Differences in the included patient populations (eg in age, heart failure severity and co-morbidity) and large variations in the intensity, duration, content and way of delivery of the intervention programmes and of "usual care" undoubtedly play a role. Even in positive trials it is impossible to discern which components of the intervention "cocktail" are most instrumental in the observed effects.[20,21] Importantly, future programmes and effect studies should provide a more detailed and comprehensive description of the programme and usual care to allow for a more thorough analysis of the discrepancies in the observed effects and enable application of the most effective programmes in daily practice.[22,23]

Future research is needed to answer the, many, remaining questions pertaining to HFMPs. These include: (1) Why do some patients, e.g. older women, choose not to enter in a HF management programme? (2) Which are patient- (or health care professional)-related determinants of non-compliance with a HFMP? (3) Is it equally effective to provide the HFMP in the primary care setting (supported by the patient's general practitioner and a practice nurse) as in the hospital (out-patient) setting? Currently the COACH-2 study is being designed in the Netherlands with the aim to compare, in HF patients well-controlled during an outpatient HFMP, the effect of continued care at the outpatient clinic or further management in the primary care setting. (4) Should patients be targeted more individually, as was, at least partly, the case in the DEAL-HF study? Thus, the question which HFMP interventions work best for which heart failure patients and how and by whom these should be delivered can not satisfactorily be answered yet.

With the current evidence it seems best to aim at flexible systems in heart failure management programmes, "integrated care", where the involvement of individual health care professionals (eg a nurse at a HF clinic, cardiologist, general practitioner, practice nurses, community-health nurses and others such as physiotherapists, dieticians and community pharmacist) can change, dependent on the needs of the individual patient. Also the contents of the HFMP may vary. For some items (e.g. providing information about what heart failure is, its prognosis and the importance of compliance to life style

and drug interventions and the recognition of symptoms of worsening heart failure, etc) consensus exists about their benefits for patients and the important role of HFMP. Also the recently developed website for heart failure patients and their carers and family (www.heartfailurematters.org) may play a role here. Patients and their carers, in discussion with health care professionals, should have the opportunity to choose between other components of a HF management programme, with the aim to focus on those components a patient needs or prefers at that moment in time. Obviously, this approach of selection of modules of components, content, and health care providers for every individual patient requires a complex organisation. Research on the effects of such individualised care is complicated, because it should focus not only on clinically relevant outcomes, but also on the varying components of the programmes and the processes involved. Although a before-after trial, observational studies or even an n=1 study are options, a large enough randomised trial is the preferred study design. Especially, a superiority trial comparing a more individualised approach with a general ('franchise'-like) approach should be considered. Randomisation at the patient level in such studies may, however, be a challenge, because of the risk of contamination and ensuing lack of contrast between the comparison arms. Cluster randomisation, however, also has some potential disadvantages, e.g. the increased risk of confounding and increased sample size. In many earlier HFMP trials the primary outcome was mortality and/or hospitalisation. One could argue that, in view of the available evidence that certain parameters are closely linked to prognosis, surrogate endpoints could be considered. These may include recognition of symptoms of worsening HF, compliance to medication and life-style, (NTpro)BNP levels or even regular/daily self-assessment of the patient's weight, or knowledge about heart failure. With the steady increase in the number of trials evaluating the effect of HFMPs it may be possible in the future to evaluate which characteristic of trials (e.g. the intervention "cocktail" tested, the health professionals involved, the type of usual care, the patient domain included) truly modify the results of HFMP trials, by performing individual patient data (IPD) meta-analyses, i e, meta-analyses based on pooled raw trial data. To enable such IPD meta-analyses several conditions should be met, including the use of comparable endpoints and availability of detailed enough information of the potential effect modifiers of interest.[24]

There is no doubt that future research will have to reveal which heart failure management programmes are most beneficial in which patients and in particular whether more individualised care by different health-care providers can improve HF management and health outcomes at acceptable costs. The

fact that such studies will have complex designs and will be rather difficult to perform should not discourage researchers and those considering to fund these trials: the rapidly increasing population of heart failure patients needs them.

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8

Summary
Samenvatting

■ Summary

The main purpose of the studies presented in this thesis, was to assess whether an intensive 1-year intervention at a heart failure clinic for patients with heart failure, NYHA classification III or IV, reduces the incidence of hospitalisation for worsening heart failure and/or all cause mortality and improves functional status and quality of life at acceptable costs and whether the observed effects may be (partly) attributable to beneficial changes in patient adherence to drug therapy. Important differences with many previous studies were that our heart failure clinic was directed by a combination of a clinician and a heart failure nurse and that the study was performed in a country with a relatively strong primary care health-care system.
In a systematic review in the beginning of the thesis, the results of previous studies on heart failure management programmes are reviewed critically and their applicability to countries, such as the Netherlands, with well-structured primary care facilities is discussed.
In the core chapters of the thesis the main results of the Deventer-Alkmaar Heart Failure study (DEAL-HF study) are presented first. Then, several sub-studies within the DEAL-HF population are presented. First, we assessed the effect of the heart failure management programme on adherence of prescribers and patients to the medication regimes. Then we investigated the correlation between the change in a biochemical parameter, NT-proBNP, and the change in quality of life and functional class during the follow-up of the main study. Finally we studied the costs of the heart failure management programme in relation to the observed effects.

■ Review of randomised studies on the effects of heart failure management programmes.

The aim of this study (Chapter 2) was to critically review the results of randomised studies assessing the effects of heart failure management programmes, to discuss the applicability of the findings to countries with well-structured primary care facilities, such as the Netherlands and the United Kingdom, and to determine whether additional trials should be conducted in these countries. To investigate this, we retrieved all available randomised, controlled trials, published in English. Most patients included in the trials were male (55%) and the mean age was 72.8 years. The setting and especially the specific interventions included in the heart failure management programmes studied varied widely, thus limiting the generalisability of the findings. Some programmes were run by a nurse only, some by a nurse and a physician and some by a nurse and a multidisciplinary team. The number of visits differed

considerably and many studies tested multiple interventions, making it difficult to discern the most effective combination of interventions. Most studies were performed in countries with a less well-organised primary care system than for example Denmark, the United Kingdom and the Netherlands. The follow-up period of most of the available studies was 6 months or even less.
The results of 15 of the 21 randomised trials on the effect of heart failure management programmes showed a positive impact on one of the primary outcome parameters, such as the combined endpoint of readmissions and/or mortality (5 studies), readmissions for heart failure and/or mortality (2 studies), mortality (1 study), days in hospital (5 studies) and quality of life (4 studies), while in three studies no effect was shown. In one study the heart failure management programme even increased hospital readmission rate and the number of the days spent in hospital. The applicability of results from the available studies to countries with a primary care-based health care system was considered debatable limited; firstly because usual care of heart failure patients in primary care may not be comparable to the control arm in many of the available trials and secondly because of recent improvements in the management treatment of heart failure in general. Both phenomena could result in smaller effects of heart failure management programmes. As mentioned above, applicability of the findings of the available studies was further hampered by the short follow-up periods and the variety in the contents of the intervention programmes. These arguments were the justification for performing the DEAL-HF study (Deventer-Alkmaar Heart Failure Project).

■ Results of the DEAL-HF study

To determine whether a heart failure management programme with an intervention by a combination of a nurse and a physician would be able to provide additional benefits even in a country with a primary-care based health-care system we performed the Deventer-Alkmaar Heart Failure Project, a randomised study in 2 regional teaching hospitals in the Netherlands (Chapter 3). In the DEAL study the effect of a nurse-and-physician-directed intensive 1 year intervention on the incidence of hospitalisation for worsening heart failure and/or all-cause mortality in patients with moderate to severe heart failure was assessed. Additional endpoints included functional status (including left ventricular ejection fraction and NYHA class), quality of life, NT-proBNP, time of death, utilisation of heart failure medication and health care costs. The intervention consisted of 9 patient visits during one year to the heart failure outpatient clinic. Comprehensive education and information was given by the nurse about heart failure and many aspects concerning coping

with and managing of heart failure. The nurse also performed a short physical examination. In addition the physician optimised heart failure medication according to the available heart failure clinical guidelines. Nurse and physician performed an overall assessment together at six of the nine visits. There was not a special protocol for the management of patients in the control group; they received "care as usual".
The number of admissions for worsening heart failure 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 0.30 to 0.81; p= 0.001). There also was an improvement of the left ventricular ejection fraction (LVEF) in the intervention group (plus 2.6%) compared with a decrease in 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 functional class, quality of life, self-care behaviour and health care costs. The DEAL-HF study showed that a heart failure programme with an intensive intervention according protocol, by a combination of a cardiovascular nurse and a heart failure clinician, in a country with a primary-care-based healthcare system, in which general practitioners act as gatekeepers for secondary care, is able to provide additional clinical benefit.

■ Effect on prescriber adherence, patient adherence and persistence of medication.

An important element of the heart failure management programme was the optimisation of heart failure medication (Chapter 4). Many studies have shown that pharmacotherapy in heart failure can reduce morbidity and mortality. Several randomised trials demonstrated that support by a heart failure clinic may improve adherence of prescribers and patients with heart failure to pharmacotherapy. However, precise quantification of the effect on prescriber and patient adherence is virtually lacking. In the DEAL-HF study the effect of a one-year physician-and nurse-directed heart failure clinic intervention on prescriber adherence to treatment guidelines and on patient adherence and persistence with pharmacotherapy was studied in detail, using computerised pharmacy refill data The heart failure management programme did not improve the, already (sub)optimal use or dosage of ACE-i or ARB. Beta-blocker dosaging and the number of patients using spironolactone increased, however. This may have been an important contributor to the observed improved clinical outcomes.
No effect on patient adherence or persistence was seen. This may have been caused by the large number of visits to the cardiologists in the control group,

but is should be emphasized that this “intensive” care in the control group apparently did not influence the prescription of spironolactone and the maximal prescribed dosage of beta blockers.

■ Long-term changes in NT- proBNP and changes in quality of life and functional status in heart failure.

Recently, changes in the levels of the neurohormone (NTpro)BNP has been suggested as a possible tool to monitor heart failure patients. Whether changes in NT-proBNP really coincide with changes in for patients more relevant parameters such as quality of life and functional status remains unknown. To determine this possible correlation, NT-proBNP levels, disease-specific quality of life (the Minnesota Living With Heart Failure Questionnaire) and the physical and mental health composite score (PCS and MCS) of a health-related quality of life questionnaire (the MOS 36-item Short-Form Health Survey (SF-36)) were assessed in participants of the DEAL study at baseline and after 3 and 12 months (Chapter 5). Furthermore, NYHA classification and echocardiography parameters (Left Ventricular Ejection Fraction (LVEF), Left Ventricular End Diastolic- and End Systolic Diameter (LVEDD and LVESD)) were determined. Absolute changes in NT-proBNP from baseline to 12 months showed a statistically significant correlation with corresponding changes in the MLWHFQ (r= .257, p= .0010, PCS and MCS of the SF-36 (r= .245, p= .001 respectively r= -.158, p= .032), NYHA class (r= .281, p < .001), LVEF (r= -.173, p= .024) and LVESD (r= .239, p= .009). Long-term changes in NT-proBNP were indeed accompanied by similar changes in quality of life, functional status and echo parameters.

■ Costs-effectiveness

In chapter 6, a detailed comparison of the effects of this HF management programme and the costs involved is presented. Survival, disease severity, disease- and health related quality of life, utility, quality adjusted life years (QALYs) and costs were assessed with a time horizon of one year. The heart failure management programme increased expected survival time during year 1 follow up with 0.025 year (95% CI:(-0.020; 0.071)). Changes in disease severity (NYHA classification) were also in favour of the intervention group. When disregarding the effects on survival the average increase in SF 36 (scale 0-100) was 5.6 points larger in the intervention group (p-value 0.062) and the difference in change in the MLWHF (scale 105-0) was 5.2 (p-value 0.108). The gain in QALYs was estimated at 0.032 (95% CI:

-0.018,+0.078). Cost savings per patient are estimated at -€2,484 (95% CI -€5,328; -€145). The probability that the intervention is cost saving is estimated at 98% and the probability that it increases QALYs at 87%. This more detailed analysis of the costs and effects of the heart failure management programme studied in the DEAL HF study confirms that such a programme exerts beneficial clinical benefit and saves costs.

In the general discussion (Chapter 7) the seemingly contradictory results of two recent, randomised HF management trials in the Netherlands, the DEAL HF and the COACH (Coordinating study Evaluating Outcomes of Advising and Counselling in Heart Failure) study, were assessed. More emphasis on optimisation of HF medication, a combined nurse-and- physician-directed management programme and a larger contrast between intervention and usual care groups in the DEAL study probably contributed to the observed differences with the COACH-study findings. Furthermore we concluded that future research will have to reveal which heart failure management programmes are most beneficial in which patients and in particular whether more individualised care by different health-care providers can improve HF management and health outcomes at acceptable costs. We realised that such studies will have complex designs and will be rather difficult to perform, but that the rapidly increasing population of heart failure patients needs them.

■ Samenvatting

Het belangrijkste doel van de studies, beschreven in dit proefschrift, was om een antwoord te krijgen op de vraag, of een intensieve begeleiding door een hartfalenpolikliniek voor patiënten met hartfalen in de NYHA classificatie III of IV, het aantal ziekenhuisopnames als gevolg van verslechterend hartfalen en/of overlijden zou kunnen verminderen, of anderszins de kwaliteit van functioneren en leven zou kunnen verbeteren tegen acceptabele kosten, en of de waargenomen effecten mogelijk (gedeeltelijk) toegeschreven zouden kunnen worden aan gunstige veranderingen in de therapietrouw van patiënten aan hun medicatie. Er waren enkele belangrijke verschillen met vele eerder uitgevoerde studies: onze hartfalenpolikliniek werd geleid door een combinatie van een clinicus en een hartfalenverpleegkundige en bovendien werd de studie uitgevoerd in een land met een betrekkelijk sterk eerstelijnszorg systeem.
In een systematisch overzicht in het begin van dit proefschrift worden de uitkomsten van eerder uitgevoerde studies over hartfalenmanagement programma's kritisch beschouwd en hun toepasbaarheid op landen met goed functionerende eerstelijnszorg faciliteiten, zoals Nederland, bestudeerd. In het belangrijkste hoofdstuk van het proefschrift worden de resultaten van het Deventer-Alkmaar Hartfalen Project (DEAL-HF studie) gepresenteerd en vervolgens verscheidene substudies binnen de DEAL-HF populatie.
Allereerst onderzochten wij de effecten van dit hartfalen management programma op de adherentie van voorschrijvers (volgens nationale en internationale richtlijnen) en patiënten aan de medicatie. Vervolgens bestudeerden wij de correlatie tussen de verandering in de biochemische parameter, NT-proBNP, en de verandering in kwaliteit van leven en functionele status gedurende de follow-up van de hoofdstudie. Tenslotte analyseerden wij de kosten van het hartfalen management programma in relatie tot de waargenomen effecten.

■ Overzicht van gerandomiseerde studies naar het effect van hartfalen management programma's.

Het doel van deze studie (Hoofdstuk 2) was om de resultaten van gerandomiseerde studies over hartfalen management programma's kritisch te bestuderen, de toepasbaarheid van deze bevindingen op landen met goed georganiseerde eerstelijnshulp faciliteiten, zoals Nederland en het Verenigd Koninkrijk te overwegen en te bepalen of het al dan niet aanbeveling zou verdienen om ook in dergelijke landen aanvullende onderzoeken uit te voeren. Hiertoe verzamelden wij alle beschikbare prospectieve, gerandomiseerde, gecontroleerde studies, gepubliceerd in PubMed in de Engelse taal. De

patiënten in deze onderzoeken waren overwegend mannelijk (55%) en de gemiddelde leeftijd was 72.8 jaar. De setting en vooral de specifieke interventies van de bestudeerde hartfalen management programma's verschilden sterk van elkaar en dit beperkte de generaliseerbaarheid van de bevindingen. Sommige programma's werden geleid alleen door een verpleegkundige, sommige door een verpleegkundige en een arts, en weer andere door een verpleegkundige en een multidisciplinair team. Het aantal bezoeken aan de polikliniek liep aanzienlijk uiteen en vele studies onderzochten meervoudige interventies, waardoor het moeilijk was om de meest effectieve combinatie van interventies te onderscheiden. De meeste studies werden uitgevoerd in landen met een minder goed georganiseerd eerstelijnshulpsysteem dan bijvoorbeeld Denemarken, het Verenigd Koninkrijk en Nederland. De follow-up periode van de meerderheid van de beschikbare studies was 6 maanden, of zelfs minder.
De resultaten van 15 van de 21 gerandomiseerde studies naar het effect van hartfalen management programma's lieten een positieve invloed zien op een van de primaire eindpunten, zoals het gecombineerde eindpunt van heropnames en/of mortaliteit (5 studies), heropnames voor hartfalen en/of mortaliteit (2 studies), mortaliteit (1 studie), aantal opnamedagen (5 studies) en kwaliteit van leven (4 studies). In 3 studies werd geen effect gemeten. In een studie nam het aantal heropnames en opnamedagen van de patiënten in het hartfalen management programma zelfs toe. Over de toepasbaarheid van de data van de beschikbare studies op landen met een relatief sterk eerstelijnszorg systeem kan men discussiëren. Ten eerste omdat de gebruikelijke zorg die hartfalen patiënten in deze landen ontvangen van de huisarts mogelijk niet vergelijkbaar is met de zorg die de controle groep krijgt in vele van de bekende studies, en ten tweede in verband met de recente verbeteringen in de behandeling van hartfalen in het algemeen. Beide aspecten zouden kunnen leiden tot een geringer effect van de hartfalen management programma's. En zoals reeds eerder genoemd, de toepasbaarheid van de resultaten van de beschikbare studies wordt verder belemmerd door de korte follow-up periodes en de verscheidenheid in inhoud van de interventieprogramma's. Deze argumenten vormden de rechtvaardiging voor het uitvoeren van de DEAL-HF studie (Deventer-Alkmaar Hartfalen Project).

■ Resultaten van de DEAL-HF studie

Om te kunnen beoordelen of een hartfalen management programma met de interventie van een combinatie van een verpleegkundige en een arts additionele voordelen zou opleveren, ook in een land met een zorgsysteem, gebaseerd op eerstelijnszorg hebben wij het Deventer-Alkmaar Hartfalen

Project, een gerandomiseerde studie in 2 regionale opleidingsziekenhuizen in Nederland, uitgevoerd (Hoofdstuk 3). In de DEAL-HF studie bestudeerden wij het effect van een intensieve interventie onder begeleiding van een verpleegkundige en een arts, gedurende een periode van 1 jaar, op het aantal ziekenhuisopnames als gevolg van verslechterend hartfalen en/of overlijden bij patiënten met matig tot ernstig hartfalen. van 2000 tot 2004. Additionele eindpunten waren het effect op functionele status (inclusief de Linker Ventrikel Ejectie Fractie en NYHA klasse), kwaliteit van leven, NT-proBNP, tijd van overlijden, gebruik van hartfalenmedicatie en kosten van zorg. De interventie bestond uit 9 bezoeken aan de hartfalenpolikliniek gedurende een jaar. Patiënten ontvingen uitgebreide instructie en informatie van de verpleegkundige omtrent hartfalen en vele aspecten van het lijden aan en omgaan met hartfalen. De verpleegkundige voerde ook een kort lichamelijk onderzoek uit. Daarnaast optimaliseerde de arts de hartfalen medicatie, overeenkomstig de beschikbare klinische richtlijnen voor de behandeling van hartfalen. Bij 6 van de negen bezoeken voerden arts en verpleegkundige samen een algemene beoordeling uit. Voor de begeleiding van de patiënten in de controlegroep bestond geen speciaal protocol. Deze patiënten ontvingen "gebruikelijke zorg".
De resultaten van onze studie lieten zien dat het aantal opnames als gevolg van verslechterend hartfalen en/of overlijden in de interventiegroep lager was dan in de controlegroep (23 vs 47; relatief risico (RR) 0.49; 95% betrouwbaarheidsinterval 0.30 tot 0.81; p=0.001). Er was ook een verbetering van de linker ventrikel ejectie fractie (LVEF) in de interventiegroep (plus 2.6%), vergeleken met een afname in de controlegroep (minus 3.1%; p=0.004). Patiënten in de interventiegroep werden opgenomen gedurende een periode van in totaal 359 dagen, vergeleken met een aantal van 644 dagen voor de patiënten in de controlegroep. Er werden ook gunstige effecten waargenomen met betrekking tot de NYHA classificatie, kwaliteit van leven, "selfcare" en zorgkosten. De DEAL-HF studie toonde aan dat een hartfalen management programma met een intensieve interventie volgens protocol, door een combinatie van een cardiovasculaire verpleegkundige en een arts in een land met een adequate eerste lijns gezondheidszorg, waarin huisartsen optreden als de "gatekeepers" voor de tweedelijns zorg, toegevoegde klinische waarde kan opleveren.

■ Effect op de adherentie van voorschrijver en patiënt aan HF medicatie

Een belangrijk element van het hartfalen management programma was de optimalisatie van hartfalen medicatie (Hoofdstuk 4).Vele studies hebben

aangetoond dat farmacotherapie bij hartfalen ziekte en overlijden kan verminderen. Verscheidene gerandomiseerde studies wezen uit dat ondersteuning door een hartfalenpolikliniek de adherentie van voorschrijvers en patiënten aan farmacotherapie kan verbeteren. Echter, exacte kwantificering van het effect op deze adherentie ontbreekt nagenoeg. In de DEAL-HF studie wordt het effect van een interventie door een hartfalenpolikliniek, geleid door een arts en verpleegkundige gedurende een jaar, op adherentie van de voorschrijver aan de behandelingsrichtlijnen, alsmede op de adherentie van de patiënt aan farmacotherapie in detail bestudeerd, met gebruikmaking van geautomatiseerde herhalingsgegevens van apotheken. Het hartfalen management programma verbeterde het reeds (sub)optimale gebruik en de dosering van ACE-i of ARB niet. Wel echter werd de dosering van bètablokkers en het aantal patiënten dat spironolactone gebruikt verbeterd. Dit zou in belangrijke mate kunnen hebben bijgedragen aan de waargenomen verbetering van de klinische resultaten. Er werd geen effect op patient-adherentie of persistentie gemeten. Dit zou een gevolg geweest kunnen zijn van een groot aantal bezoeken aan de cardioloog in de controlegroep. Echter, er moet op gewezen worden , dat deze “intensive care” in de controlegroep blijkbaar niet de prescriptie van spironolacton en de maximale dosis van de bètablokkers heeft beïnvloed.

■ Lange-termijn veranderingen in NT-proBNP en veranderingen in kwaliteit van leven en functionele status bij hartfalen

Recentelijk wordt gesuggereerd dat veranderingen in het neurohormoon (NTpro) BNP een mogelijke methode zou kunnen zijn om de conditie van patiënten met hartfalen te beoordelen.
Het blijft nog onduidelijk of deze veranderingen in NTproBNP werkelijk samenvallen met de voor patiënten meer relevante parameters zoals veranderingen in de kwaliteit van leven en functionele status. Om deze mogelijke correlatie vast te stellen, werden NTproBNP niveaus, de ziekte-specifieke kwaliteit van leven-vragenlijst (Minnesota Living With Heart Failure Questionnaire) en de fysieke en mentale “health composite score” (PCS en MCS) van een aan gezondheid gerelateerde kwaliteit van leven-vragenlijst (de MOS 36-item Short-Form Health Survey (SF-36)) beoordeeld bij deelnemers aan de DEAL-HF studie bij de start, na 3 en na 6 maanden. (Hoofdstuk 5). Vervolgens werden de NYHA classificatie en echocardiografische parameters (Linker Ventriculaire Ejectie Fractie (LVEF), Linker Ventriculaire Eind Diastolische-en Eind Systolische Diameter (LVEDD en LVESD)) bepaald. Absolute veranderingen in NTproBNP vanaf baseline tot 12 maanden lieten een statistisch significante correlatie met overeenkomstige veranderingen in de

MLWHFQ (r= .257, p= .001), PCS en MCS van de SF-36 (r= .245, p= .001 respectievelijk r=- .158, p= .032), NYHA klasse (r= .281, p< .001), LVEF (r=- .173, p= .024) en LVESD (r= .239, p= .009) zien. Lange-termijn veranderingen in NTproBNP werden inderdaad vergezeld door vergelijkbare veranderingen in kwaliteit van leven, functionele status en echo parameters.

■ Kosten-effectiviteit

In Hoofdstuk 6 geven wij een gedetailleerde vergelijking van de effecten van dit hartfalen management programma alsmede de kosten. Overleving, ernst van de ziekte, aan ziekte en gezondheid gerelateerde kwaliteit van leven, economisch nut, “Quality adjusted life years” (QALYs) en kosten worden behandeld met een tijdshorizon van1 jaar. Het hartfalen management programma verbeterde de verwachte tijd van overleven gedurende het eerste follow-up jaar met 0.025 jaar (95% CI: (-0.020; 0.071)). Veranderingen in de ernst van de ziekte (NYHA classificatie) waren significant beter bij de interventiegroep. Als we de effecten op overleven buiten beschouwing laten, was de gemiddelde toename in SF-36 (schaal 0-100) 5.6 punten groter (p-waarde 0.062) in de interventiegroep en het verschil in de verandering in de MLWHF (schaal 105-0) was 5.2 punten (p -waarde 0.108). De winst in QALYs werd geschat op 0.032 (95% CI: (-0.018,+0.078)). De kostenbesparingen per patiënt werden geschat op E 2.484 (95% CI: -E5328; -E145). De waarschijnlijkheid dat de interventie kostenbesparend is wordt op 98% geschat en de waarschijnlijkheid dat er een winst aan QALYs is op 87%. Deze meer gedetailleerde analyse van de kosten en effecten van het hartfalen management programma, in de DEAL HF studie, bevestigt dat zo’n programma van toegevoegde klinische waarde is en kostenbesparend .

■ Algemene discussie

In de algemene discussie (Hoofdstuk 7) werden de schijnbaar tegenstrijdige resultaten van twee recent uitgevoerde gerandomiseerde hartfalen management onderzoeken in Nederland, nl het DEAL-HF onderzoek en de COACH studie (Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure) in beschouwing genomen. Meer nadruk op optimalisatie van HF medicatie, een HF management programma geleid door een arts en een verpleegkundige en een groter contrast tussen interventiegroep en gebruikelijke zorggroep in de DEAL-HF studie hebben waarschijnlijk bijgedragen aan de verschillen, die gezien worden met de resultaten van het COACH onderzoek. Toekomstig onderzoek zal moeten uitwijzen welke hartfalen management programma’s meest effectief zijn in welke patiënten. En

vooral of meer individuele zorg door verschillende zorgverleners het hartfalen management en de uitkomsten verbetert tegen acceptabele kosten. Zulke studies zullen complex van ontwerp zijn en nogal moeilijk om uit te voeren. Echter, de snel groeiende populatie van patiënten met hartfalen heeft deze onderzoeken nodig.

Dankwoord

Onze patiënten, daar draait het bij een klinische studie van het begin tot het einde om!
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Met zijn scherpe analyses voor de kosten-effectiviteit van ons hartfalen management programma maakte prof.dr. B.A. van Hout duidelijk wat “value for money” is. Ben, ik wil je graag danken voor je belangrijke bijdrage aan het DEAL-HF onderzoek.

Tijdens de periode van het onderzoek had de hartfalenpoli niet kunnen draaien zonder de enorme inzet, de toewijding aan de patiënten en het continue enthousiasme van de hartfalenverpleegkundigen, in Deventer Bertie Stoel het eerste jaar en daarna Dian Pruijssers-Lamers, in Alkmaar Lammy Pol, Sonja Touw, Jeanne Hogeling-Koopman en research nurse Nel Rood. Heel veel dank daarvoor. Aan Dian nog een extra woord van dank voor al het werk dat je, naast je poliwerk, ook voor het DEAL-HF onderzoek deed. Deze klus is mede door jouw nauwkeurige werk geklaard. In Deventer voelden ook de secretaresses Petra Hemme, Alet van de Noort en later Rina Dommerholt en nu Joanneke Penninkhof-Hemeltjen zich betrokken bij het DEAL-HF

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Curriculum vitae

Pieta W.F. André de la Porte werd geboren op 14 juni 1948 in Den Haag. 3 maanden later vertrok zij met haar moeder en broertje naar Jakarta, Indonesië, waar haar vader na de kamptijd van haar ouders zich weer gevestigd had als advocaat. Op haar zesde kwam zij met moeder, broertje en zusje weer terug naar Holland. Vader volgde later. Haar lagere schooltijd volgde zij in Den Haag en later in Gorssel, omdat haar vader tot rechter in Zutphen werd benoemd. In 1967 deed zij eindexamen Gymnasium B aan het Baudartius Lyceum te Zutphen, waarna zij naar Leiden vertrok, waar zij eerst een jaar sociologie studeerde. In 1968 begon zij met de studie medicijnen in Leiden. In 1970 deed zij haar kandidaats- en in 1972 haar doctoraal examen. In deze tijd leerde zij tijdens haar onderzoekstage op het biochemisch laboratorium van prof. H.C. Hemker de beginselen van de stollingsstoornissen kennen. Tevens werkte zij een periode op de psychiatrische kliniek Endegeest. In verband met haar huwelijk in 1972 met Herman Bruggink nam zij na haar doctoraal een korte sabbatical, waarna haar semi-artsexamen in Leiden in 1974 en haar artsexamen oude stijl in 1975 aan de UVA te Amsterdam volgden. Zij mocht zich dus ook huisarts noemen. Na een klein jaar interne geneeskunde als AGNIO in het voormalig Burger Ziekenhuis volgde zij haar man naar het oosten, waar zij als AGNIO kindergeneeskunde werkte in het Spittaal Ziekenhuis van Zutphen, als consultatiebureauarts en tevens als docent op de Academie voor Fysiotherapie te Deventer. Na de geboorte van hun twee zonen, Tom en Pieter Bas in 1977 en 1978 vertrok het gezin in 1979 naar Amersham (Buckinghamshire, UK) voor een uitzending van haar echtgenoot door Kluwer, waar zij tot hun terugkeer in 1982 als parttime huisarts werkte. Terug in Nederland, nu in het ouderlijk huis in Gorssel, ging zij, na de geboorte van hun dochter Caroline in 1983, het volgende jaar werken bij de maatschap cardiologie in Deventer, eerst bij de afdeling fietsergometrie. In 1988 hielp zij drs. Dirk Lok met het opzetten van de researchafdeling in Deventer, waar zij vervolgens als parttime researcharts werkte. De huisartsgeneeskunde kon zij toch nog niet los laten, zij werkte ook parttime in twee huisartsenpraktijken in Deventer. Maar zij werden het reizen niet moe en het gezin woonde van 1991 tot 1994 in Mountain Lakes (New Jersey, USA) in verband met een benoeming van haar echtgenoot door Elsevier in de Verenigde Staten. Vanaf september 1994 werkte zij weer op de researchafdeling Cardiologie in Deventer, waar zij zich, naast organisatorische taken, vooral bezig hield met het begeleiden van patiënten in de hartfalenonderzoeken. Tevens volgde zij vele cursussen en symposia over verschillende onderwerpen in de cardiologie, maar vooral hartfalen. Dit had

tot gevolg dat zij in 1999 gevraagd werd om de hartfalenpoli op te zetten. Al brainstormend met Dirk Lok en Jan van Wijngaarden kwamen zij tot de conclusie dat het dan zeer interessant zou zijn om een gerandomiseerd onderzoek te doen naar het effect van een hartfalenpoli, geleid door een arts en een verpleegkundige, als toevoeging aan de gebruikelijke cardiologische zorg in een ziekenhuis in Nederland. Als vanzelfsprekend volgde het idee van een promotie hierop. Van maart 2000 tot april 2004 duurde de DEAL-HF studie. Dankzij de positieve resultaten van de DEAL-HF studie werd daarna de hartfalenpoli als een regulier instituut aan het Deventer Ziekenhuis erkend. Naast haar medische werk vervulde zij tijdens haar studententijd en daarna verschillende functies op het sociale vlak.