Effect of a Pharmacist-Led Intervention on Diuretic Compliance in Heart Failure Patients: A Randomized Controlled Study

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ABSTRACT

Background: Noncompliance is a major factor in the morbidity and unnecessary hospital readmissions for patients with heart failure. Several studies have aimed to reduce rehospitalizations in heart failure patients through a comprehensive, multidisciplinary approach. Medication compliance was rarely measured in these studies or, when it was measured, the method employed was seldom valid. We aimed at determining the effect of a pharmacist-led intervention on medication compliance in patients with heart failure.

Methods: We conducted a randomized controlled trial into the effect of a pharmacist-led intervention on medication compliance in patients with heart failure (predominantly New York Heart Association [NYHA] II and III) treated with loop diuretics, presenting to a cardiology outpatient clinic or admitted to hospitals in The Netherlands. Patients in the intervention group received monthly consultations from their community pharmacist during a 6-month period. Patients in the control group received usual care. Primary endpoint was medication compliance, assessed with a medication event monitoring system, an electronic pill bottle that registers time of opening. Secondary endpoints were the number of rehospitalizations, death, and quality of life.

Results: A total of 152 patients were randomized: 74 patients to the intervention arm and 78 patients to the usual care arm. Over the 6-month study period, patients in the intervention group had 140/7656 days without use of loop diuretics compared with 337/6196 days in the usual care group (relative risk 0.33 [confidence interval (CI) 95% 0.24–0.38]). Two consecutive days of nondosing occurred on 18/7656 days in the intervention group compared with 46/6196 days in the usual care group (relative risk 0.32 [CI 95% 0.19–0.55]). There were no significant differences in rehospitalizations, mortality, or disease-specific quality of life between groups.

Conclusions: A pharmacy-led intervention can improve medication compliance in patients with moderate to severe heart failure, even in those with relatively high compliance. Future interventions should also focus at less compliant patients.

Key Words: Diuretics, adherence, drug monitoring.

Although deaths from ischemic heart disease and stroke are declining, the prevalence of heart failure is rapidly increasing.[1,2] Hospital admission rates for heart failure are high, with each new hospitalization increasing the risk for readmission.[3,4] Consequently, health care costs resulting from heart failure are increasing throughout much of the industrialized world.[5] Noncompliance is a major factor in the morbidity and unnecessary hospital readmissions for patients with heart failure, resulting mainly from a lack of patient understanding of their disease and its treatment.[6–8] Interviews with 22 elderly heart failure patients showed that fewer than half could correctly name their medication, the prescribed doses, and dosage intervals, and that a quarter was definitively noncompliant.[9] Nondosing, especially with loop diuretics, for even brief periods of 2 to 3 days, is associated with acute worsening of the clinical condition

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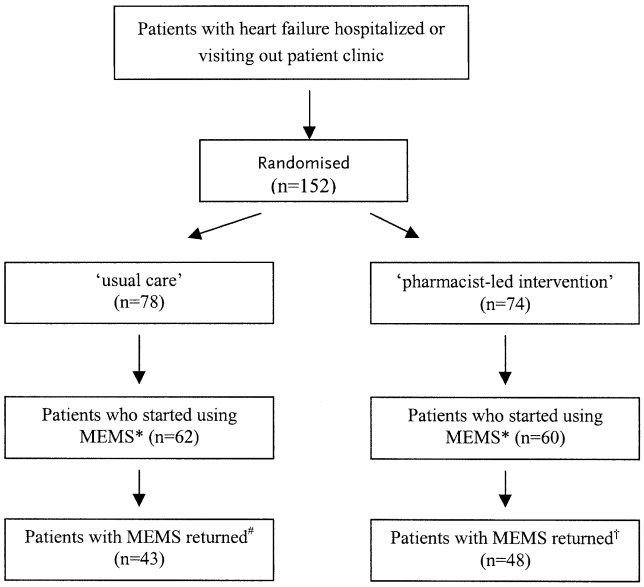

Fig. 1. Flow chart of study.

*Patients did not receive medication event monitoring systems (MEMS) for the following reasons: patient had second thoughts at visit to the pharmacy (14), pharmacy refused to cooperate (6), patient admitted to nursing home (1), and patient already used prefilled medication cassette (9).

#MEMS were not returned for the following reasons: died (10) or MEMS lost (9).

†MEMS were not returned for the following reasons: died (9) or MEMS lost (3).

and hospital admission.[10] A 2-fold risk for recurrent hospitalizations for heart failure patients with poor refill patterns has been reported.[11]

Several studies have aimed to improve outcomes through a comprehensive, multidisciplinary approach to reduce rehospitalizations for heart failure patients.[12–19] However, medication compliance was rarely measured in these studies or, when it was measured, the method employed was seldom valid. Two studies that did measure compliance showed an improvement in the intervention group, using tablet counts.[20,21] Only 1 study used a more sophisticated method to assess medication compliance with medication event monitoring systems (MEMS). But it involved a relatively small sample of 50 patients and only 2 months of follow-up.[22]

Specialist nurses have played a major role in previous intervention studies of heart failure patients.[12,19,22,23] A few studies have included a pharmacist in a multidisciplinary intervention to improve compliance.[19,24,25] Although other smaller studies have evaluated the independent role of pharmacists, they have used inadequate methodology to assess compliance and specially trained hospital or research pharmacists in the intervention.[20,26,27] In our randomized controlled study, we determined the effect of a community pharmacist-led intervention on medication compliance in heart failure patients. The study included 7 hospitals and 79 pharmacists in The Netherlands.

Subjects and Methods

Selection Criteria

Only patients treated with loop diuretics were eligible for inclusion into the study. Patients had been admitted to 1 of the participating hospitals for heart failure (ICD-9, 428) or attended a specialist outpatient heart failure clinic. The diagnosis of heart failure was validated with patient's hospital records and included cardiac imaging findings. Patients who had severe psychiatric problems or dementia, planned admission to a nursing home, did not take care of their own medication (eg, filled or administered by relatives or district nurses), or life expectancy of less than 3 months were excluded from the study. Patients were recruited between July 1998 and February 2000.

Intervention Program and Usual Care Group

Cardiologists informed patients about the study. Upon written consent, investigators were notified and randomly allocated patients, using a computer-generated randomization scheme, to one of the two arms: intervention or usual care. Patient's pharmacy and general practitioner (GP) were notified of their participation in the study. Pharmacists received training for the intervention that consisted of a structured interview on the patient's first visit to the community pharmacy after inclusion into study. A computerized medication history was used to discuss drug use, reasons for noncompliance—such as possible adverse drug reactions and difficulties to integrate medication use in daily life—to reinforce medication compliance. A short report of this interview was forwarded to the GP. Pharmacists then contacted patients on a monthly basis for a maximum of 6 months. Patients in the usual care group did not receive the structured interview or monthly follow-up.

Compliance Measurement

All patients who agreed to take part in the study received their loop diuretics in a MEMS, a medicine-container with a microchip that recorded the time and date of opening. The MEMS container was filled by the patient's regular pharmacy. At the end of follow-up, containers were collected by pharmacists and sent in for computer-based reading and evaluation. Hospital records were used to obtain patients' actual dosing scheme. Patients filled in a questionnaire on their use of the MEMS. We allowed for patients to "shift" dosing from morning to evening. We assessed days without any dosing during scheduled dosing. When patients were temporarily advised to use the diuretic intermittently, this was not considered noncompliance.

Additional Data Collection

Hospital records were screened to validate patient's diagnosis and evaluate rehospitalizations and death. Data on deaths, hospital, and nursing home admissions were also collected from patients' GPs. Pharmacists provided data on prescription drugs' use. Complete follow-up for at least 6 months was available in all patients. In the Netherlands, pharmacy records are virtually complete because of loyalty of patients to a single pharmacy.[28] At the start and end of study, patients were required to submit questionnaires on quality of life (Dartmouth Primary Care Cooperative Information Project/World Organization of National Colleges, Academies, and Academic Associations of General Practice/Family Physicians [COOP-WONCA] and Minnesota Living With Heart Failure Questionnaire [MHFQ]).

Table 1. Baseline Characteristics of Participants*

	Pharmacy-Led Intervention (n = 74)	Usual Care (n = 78)
Age (y)	69.1 ± 10.2	70.2 ± 11.2
Male	53 (72)	47 (60)
NYHA class†		
1	6 (9)	7 (11)
2	22 (34)	33 (50)
3	33 (51)	24 (36)
4	4 (6)	2 (3)
Years after diagnosis of heart failure	2.1 ± 2.5	2.1 ± 2.6
Visiting heart failure clinic	53 (72)	50 (64)
Comorbidity		
Myocardial infarction	42 (57)	39 (50)
Hypertension	26 (35)	35 (45)
Arrhythmias	36 (49)	46 (59)
Renal insufficiency	10 (14)	9 (11)
Diabetes	20 (27)	23 (30)
Obstructive pulmonary disease	13 (18)	16 (21)
Laboratory		
Creatinine (μmol/L)	124 ± 39	136 ± 64
Sodium (mmol/L)	140 ± 3	140 ± 4
Potassium (mmol/L)	4.3 ± 0.5	4.3 ± 0.5
Hemoglobin (mmol/L)	8.3 ± 0.9	8.1 ± 1.2
Body mass index	26 ± 4	26 ± 5
Systolic blood pressure (mm Hg)	124 ± 23	124 ± 22
Diastolic blood pressure (mm Hg)	73 ± 11	76 ± 13
Cardiovascular medication at inclusion		
ACE inhibitor	50 (68)	48 (62)
Acetylsalicylic acid or anticoagulant	65 (88)	64 (82)
All antagonist	14 (19)	12 (15)
Antiarrhytmic	12 (16)	6 (8)
β-blocker	27 (37)	33 (42)
Calcium entry blocker	6 (8)	6 (8)
Cholesterol lowering agent	22 (30)	16 (21)
Digoxin	37 (50)	33 (42)
Organic nitrate	31 (42)	30 (39)
Spironolactone	28 (38)	25 (32)
Type of diuretic		
Furosemide	54 (73)	54 (69)
Bumetanide	20 (27)	24 (31)
Average PDD‡	2.9	3.3
Initial dosage schedule		
Once daily	43 (58)	44 (56)
Twice daily	25 (34)	31 (40)
> twice daily	6 (8)	3 (4)

NYHA, New York Heart Association; ACE, angiotensin converting enzyme; PDD, prescribed daily dose.
*All values are numbers (percentages) ± SD.
†Data on NYHA class were missing in 21 patients.
‡furosemide 40 mg or bumetanide 1 mg = 1.

Outcomes

The primary endpoint measured was medication compliance over the period that the patient used the MEMS up to a maximum period of 6 months. Noncompliance was expressed as the number of days without any loop diuretic when the prescription was at least once daily. Variability in timing of the doses during the day was not considered as noncompliance. Periods with 2 or more consecutive days of nondosing were recorded separately. The percentage of days with an actual opening of the MEMS for a scheduled diuretic was calculated and binomial comparisons were made on two cut-off values (80% and 95%).

Secondary endpoints followed were the number of rehospitalizations, death, and quality of life, which were assessed both with a generic instrument (Dartmouth COOP Functional Assessment Charts/WONCA)[29] and a specific heart failure instrument (MHFQ).[30]

Sample Size

For the primary endpoint, a conservative estimation of compliance based on data from Rich et al was used, expecting a difference in compliance between the usual care and intervention groups of 6.8%.[21] We used *t*-tests with a standard deviation of compliance of 15%.[21] With a power of 80% and a confidence interval of 95%, we had to include 76 patients in both arms.

Data Analysis

Relative risks, expressed as rate ratios, with 95% confidence interval were used to compare the occurrence of missing dosages in the intervention group and usual care group. In addition the cumulated incidence of mortality and readmission was compared. Finally the change in quality of life was compared using *t*-tests.

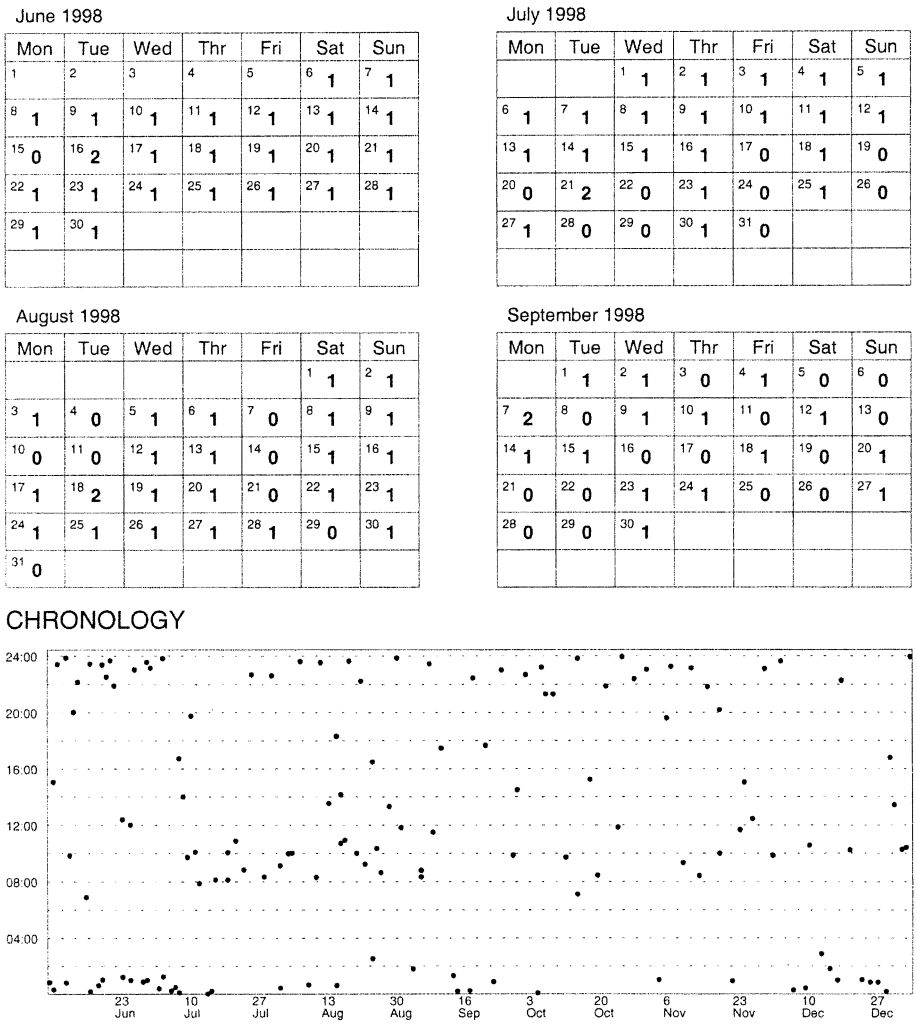

Fig. 2. First example of medication event monitoring systems' compliance data. The calendar shows the number of doses taken on each day. The chronology shows the time at opening of the container. Patient is taking his medication irregularly and has several days of missed dosages.

Multivariate logistic regression was performed to adjust for possible incomparability (despite randomization) in prognostic factors between the intervention and usual care group. All analyses were done on an intention-to-treat basis, with SPSS software (SPSS for Windows, version 10.0, SPSS Inc., Cary, NC).

Research ethics committees from University Medical Centre, Utrecht, and 6 regional hospitals approved the study.

Results

A total of 79 pharmacies participated in the study. Of the 152 patients included in the study, 78 were randomly allocated to the usual care group and 74 to the pharmacy-led intervention (Fig. 1). Patients were predominantly male and New York Heart Association (NYHA) class 2 and 3. Comorbidities and comedication in both groups were comparable. There were no differences in type, daily dose, and dosing schedule of loop diuretics (Table 1).

Primary Outcome

Examples of MEMS data for 2 patients are given in Fig. 2 and 3. The average duration of MEMS use was 143.6 days in the usual care group and 163.3 days in the intervention group. Patients in the intervention group had 140/7656 days without use of loop diuretics compared with 337/6196 days in the usual care group (relative risk 0.33 [confidence interval (CI) 95% 0.24–0.38]). Two consecutive days without use of diuretics occurred 18/7656 days in the intervention group compared with 46/6196 days in the usual care group (relative risk 0.32 [CI 95% 0.19–0.55]) (Table 2). We performed multivariate logistic regression to check whether these findings were influenced by the small discrepancies in prognostic factors between intervention and usual care group. The results of the multivariate analysis (model with age, sex, NYHA class, comorbidity, and visiting heart failure clinic) did not indicate the presence of such differences.

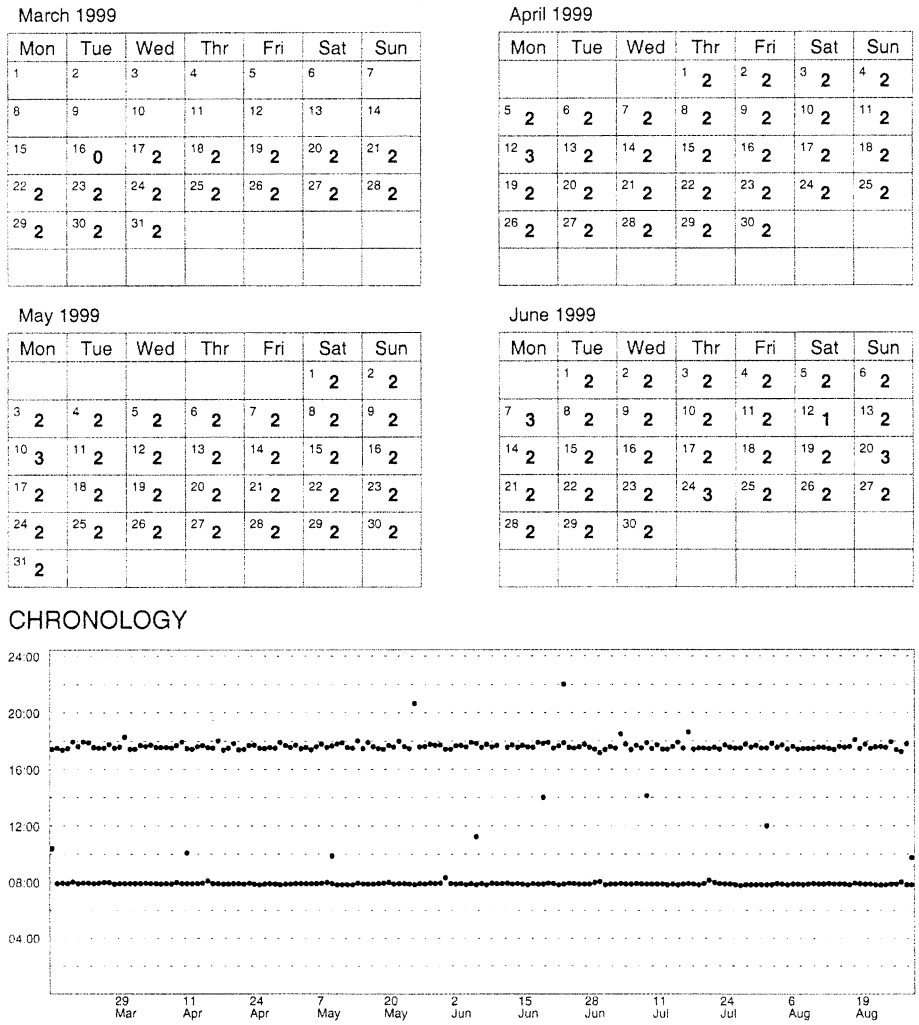

Fig. 3. Second example of medication event monitoring systems compliance data. Patient is taking medication regularly. The dots between morning and evening opening are refills from the pharmacy. The majority of patients showed dosing patterns comparable with that in this figure.

Secondary Outcomes

During the study period, 26 patients died and 64 were readmitted into hospital. At 6 months, 25.7% of the patients in the intervention group versus 24.4% of patients in the usual care group were either readmitted or dead (P value $> .05$) (Table 3). Disease-specific quality of life improved in both the intervention and usual care groups. Improvement in the usual care group tended to be higher, although this difference was not statistically significant. Generic quality of life (COOP/WONCA) measures improved in the usual care group and worsened slightly in the intervention group (Table 4).

Discussion

This study showed that a pharmacist-led intervention improves diuretic compliance for patients with moderate to severe heart failure. After multivariate analysis, allocation to the intervention group remained the only determinant that was significantly associated with higher compliance. Compliance was found to be unexpectedly high in both the intervention and the usual care groups (mean >90%). Other studies have suggested that noncompliance occurs in approximately 50% of elderly heart failure patients.[6–9] There are several explanations for the extremely high overall medication compliance in our study. A large proportion of patients (68%) also visited a specialized heart failure clinic to improve compliance with medication and diet. The impact of these visits is shown in the relatively high percentage of patients receiving angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and spironolactone at baseline.

Compliance might also be relatively high because patients might have noticed a direct symptomatic benefit of diuretics. We chose to monitor compliance with diuretics, because we hypothesized that this direct effect of diuretics could also be an argument to omit doses of diuretics. We argued that nonuse of diuretics could have direct effects on morbidity and mortality. We realize that studies into compliance with drugs with proven effect on morbidity and mortality such as

Table 2. Compliance in Patients with MEMS Data*

	Pharmacy-Led Intervention (n = 48)	Usual Care (n = 43)	Relative Risk (n = 43)
Mean age (y)	68.9	68.3	
Male	35 (73)	30 (70)	
Mean no. of days with no dosing	2.9	7.8	
Duration of use MEMS	159.5	144.1	
Total days on MEMS	7656	6196	
Days without dosing	140/7656	337/6196	0.3 (0.2–0.4)
≥2 consecutive days without dosing	18/7656	46/6196	0.3 (0.2–0.6)
Less than 80% compliance	0 (0)	6 (14)	0.5 (0.4–0.6)
Less than 95% compliance	6 (13)	16 (37)	0.3 (0.1–0.9)

MEMS, medication event monitoring system.
*All values are numbers (percentages).

Table 3. Morbidity and Mortality in All Patients During the Follow-Up Period*

	Pharmacy-Led Intervention (n = 74)	Usual Care (n = 78)	Relative Risk
Death	10 (14)	16 (21)	0.6 (0.3–1.4)
Number of patients with either death or hospitalization for heart failure	19 (26)	19 (24)	1.1 (0.5–2.2)
Total number of hospitalizations	32 (465 days)	42 (332 days)	P = .4†
Heart failure	16 (163 days)	15 (259 days)	P = .4†
Other cardiovascular disease	6 (132 days)	5 (19 days)	P = .7†
Planned readmission	5 (25 days)	19 (37 days)	P = .4†
Other hospital admission	5 (145 days)	3 (17 days)	P = .4†

*All values are numbers (percentages or days is hospital).
†P values given on number of hospitalizations; p-values on number of hospital days are also > 0.05

β-blockers and ACE inhibitors will also be very important. However, to show an effect on clinical outcomes such studies probably will need long follow up (at least as long as the original studies that have shown the effect of these drugs).

For informed consent, all eligible patients received preliminary written and oral information before entry into our study. It is possible that deliberately noncompliant patients chose not to participate. Consenting patients have been shown to be dissimilar to nonconsenting patients.[31] The selection of patients with a positive attitude toward health care may be useful in randomized clinical trials testing new medication but dilute the effect of more pragmatic "care interventions." We randomized patients instead of pharmacies; therefore, pharmacists could have patients in both the intervention and usual care group. Although we are of the opinion that cross contamination will be limited because only 27% of participating pharmacists were dispensing for both intervention and usual care groups, residual contamination will only have diluted the effect of the intervention. All patients in The Netherlands are insured for prescription drug reimbursement. So, unlike in some other countries, socioeconomic differences are less of an issue in compliance. Finally, the use of MEMS itself in the usual care group may be seen as an intervention and might also have contributed to a higher compliance.[32] Our findings are in accordance with data from Rich et al, who measured medication compliance by tablet counts and found an average compliance of 87.9% in intervention patients compared with 81.1% in the usual care group.[21]

Our study design was comparable with a study of Goodyer et al that showed that a 3-month intensive medication counseling program by a pharmacist improved compliance from 61% to 93%.[20] The only previous study of medication compliance that used MEMS showed unchanged compliance of approximately 80% in 2 intervention groups that received daily telephone or video-telephone calls and a drop in compliance from 81% to 57% in a control group.[22]

The intervention did not reduce number of hospital readmissions or deaths. The study, however, did not have sufficient power to show an effect on morbidity and mortality. Stewart et al reported a 6-month mortality of 23%, as compared with 17.1% in our study. They report 0.93 admissions/patient compared with 0.39 admissions/patient in our study; furthermore, their patients had 8.2 days/patient in hospital compared to 4.8 days/patient in our study.[19] The only randomized nurse-led intervention study in heart failure performed in the Netherlands up to now did not find effects on

Table 4. Quality of Life in Patients With Available Questionnaires*

	Pharmacy-Led Intervention			Usual Care			
	Baseline (n = 58)	6 Months (n = 40)	Change† (n = 40)	Baseline (n = 56)	6 Months (n = 30)	Change† (n = 30)	*P* value
COOP/WONCA	20.6 ± 4.8	20.4 ± 5.5	0.5 ± 3.9	22.1 ± 5.1	19.6 ± 5.4	−2.5 ± 6.4	.03
MHFQ	40.1 ± 21.6	33.8 ± 22.3	−2.3 ± 14.1	49.0 ± 23.4	35.9 ± 21.4	−11 ± 22.8	.07
Physical domain	18.5 ± 8.6	16.1 ± 9.6	−0.6 ± 5.7	22.4 ± 9.7	16.9 ± 9.6	−4.6 ± 10.4	.07
Emotional domain	8.2 ± 6.1	6.8 ± 6.6	−1.1 ± 3.8	9.3 ± 7.2	7.2 ± 6.5	−1.6 ± 5.0	.6

COOP/WONCA, Dartmouth Primary Care Cooperative Information Project/World Organization of National Colleges, Academies, and Academic Associations of General Practice/Family Physicians; MHFQ, Minnesota Heart Failure Questionnaire.
*Lower scores on the questionnaires indicate better quality of life; mean and standard deviation of scores are given.
†Change was only calculated for patients with questionnaires available at both baseline and 6 months.

use of health care resources.[33] Possibly, the "usual care" in the Netherlands, with its "gate-keeping" function of GPs, may differ from care in other countries, and thus explains the absence of an effect on use of health care resources. Finally, that this intervention mostly focussed on medication compliance and was much less extensive than multidisciplinary interventions by others[12,14,16–19] could explain the lack of an effect on morbidity.

Quality of life improved in both usual care and intervention groups, which probably reflects natural course of disease. Improvement of quality of life was especially high in patients who were included in the study shortly after a hospital admission. Quality of life as measured with the disease unspecific COOP/WONCA charts improved more in the usual care group. This greater improvement in the usual care group might be explained by the fact that fewer patients with lower quality of life in the usual care group did return the quality of life questionnaire after 6 months. Those patients in the pharmacy-led intervention were motivated by regular contacts with the pharmacist to respond to this questionnaire. We must conclude that this intervention, in the context of other interventions that the patients received (68% visited a specialized heart failure clinic) did not improve quality of life.

In other studies, patients were managed by a small number of specialist nurses, collaborating with other hospital-based professionals. In this study, although patients were enrolled in the hospital, they received intervention from their regular community pharmacists. This pragmatic approach makes it easier to apply the findings in daily practice. This design created certain logistic problems, particularly with the return of MEMS monitors from patients at highest risk of death or severe morbidity. In this way we were deprived of dosing history data that may have included crucial information (see Fig. 1). Misplacement of the MEMS device by the patient occurred more frequently in the usual care group (9 versus 3 patients). It is likely that patients who lost the MEMS device were less compliant. Missing data in these patients could have resulted in an underestimation of the effect in our study. Moreover, patients in the usual care group used MEMS devices for a shorter period (144.1 versus 159.5 days). This was caused by a higher number of patients in the usual care group that decided to stop using the MEMS before the end of the follow-up period. This could also indicate lower compliance.

Conclusion

This study showed that community pharmacists can improve medication compliance in heart failure patients, even in those starting with relatively high compliance. Future interventions need to be directed at patients at higher risk for noncompliance and should focus on improving compliance in patients using drugs that alter the natural history of heart failure such as β-blockers and ACE inhibitors. Because patients always have to visit their pharmacy to collect their medication, it seems logical to include community pharmacists in multidisciplinary interventions. Adherence of patients to one community pharmacy and cooperation of the community pharmacist with other health care providers, as in this study, would be prerequisites. Implementation of a structural role for the community pharmacist will be difficult to achieve in countries were mail-in prescriptions without direct pharmacist interactions are commonplace.

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