Persistent Use of Evidence-Based Pharmacotherapy in Heart Failure Is Associated With Improved Outcomes

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Background—Undertreatment with recommended pharmacotherapy is a common problem in heart failure and may influence prognosis. We studied initiation and persistence of evidence-based pharmacotherapy in 107 092 patients discharged after first hospitalization for heart failure in Denmark from 1995 to 2004.

Methods and Results—Prescriptions of dispensed medication and mortality were identified by an individual-level linkage of nationwide registers. Inclusion was irrespective of left ventricular function. Treatment with renin-angiotensin inhibitors (eg, angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers), β-blockers, spironolactone, and statins was initiated in 43%, 27%, 19%, and 19% of patients, respectively. Patients who did not initiate treatment within 90 days of discharge had a low probability of later treatment initiation. Treatment dosages were in general only 50% of target dosages and were not increased during long-term treatment. Short breaks in therapy were common, but most patients reinitiated treatment. Five years after initiation of treatment, 79% patients were still on renin-angiotensin inhibitors, 65% on β-blockers, 56% on spironolactone, and 83% on statins. Notably, multiple drug treatment and increased severity of heart failure was associated with persistence of treatment. Nonpersistence with renin-angiotensin inhibitors, β-blockers, and statins was associated with increased mortality with hazard ratios for death of 1.37 (95% CI, 1.31 to 1.42), 1.25 (95% CI, 1.19 to 1.32), 1.88 (95% CI, 1.67 to 2.12), respectively.

Conclusions—Persistence of treatment was high once medication was started, but treatment dosages were below recommended dosages. Increased severity of heart failure or increased number of concomitant medications did not worsen persistence, but nonpersistence identified a high-risk population of patients who required special attention. A focused effort on early treatment initiation, appropriate dosages, and persistence with the regimen is likely to provide long-term benefit. (***Circulation*. 2007;116:737-744.**)

Key Words: heart failure ■ compliance/adherence ■ drugs ■ mortality ■ prognosis ■ epidemiology

Treatment with inhibitors of the renin-angiotensin system (RASi; eg, angiotensin-converting enzyme inhibitors and angiotensin-2 receptor blockers), β-blockers, and spironolactone are the cornerstones of modern medical management of heart failure (HF) with reduced left ventricular ejection fraction.[1] Additionally, many of these patients may benefit from statin treatment.[2,3] Nevertheless, surveys have demonstrated substantial underuse of these medications, and underuse has been associated with adverse events and impaired prognosis.[4–6] Comprehensive studies of the nature of underuse are necessary to know whether underuse is caused by lack of initiation, underdosing, or early discontinuation. Also, multiple drug treatment is perceived to reduce persistence of treatment, but this issue has only been partly explored in HF.

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In the present study we analyzed the medical treatment of all 107 092 Danish patients who survived a first hospitalization for HF between 1995 and 2004. We studied time to initiation of treatment after discharge, used dosages, persistence of treatment, and the effect of polypharmacy and disease severity on persistence. Furthermore, we analyzed the association between persistence of treatment and mortality.

Received December 4, 2006; accepted May 29, 2007.

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Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.106.669101**

Methods

The Danish Data Protection Agency approved the present study (No. 2003-54-1269). No ethical approval is required for retrospective registry studies in Denmark.

Population

Patients >30 years of age who were discharged alive between 1995 and 2004 after their first hospitalization for HF (*International Classification of Diseases,* 10th Revision [*ICD*-10] codes I11.0, I50, I42, and J81 as primary or secondary diagnosis) were identified in the Danish National Patient Registry, which registers all hospitalizations in Denmark since 1978. Each hospitalization is registered with 1 primary diagnosis and appropriate secondary diagnoses according to *ICD*-10 (before 1994, *ICD*-8). To ensure a homogenous history of patients, we required that the HF hospitalization was the first within a 17-year period. Each patient's vital status as of December 31, 2004, was obtained from the Central Population Registry.

Medical Treatment

The Danish Registry of Medicinal Product Statistics registers all prescriptions dispensed from Danish pharmacies since 1995. In Denmark the national health security system covers all inhabitants and partially reimburses drug expenses (with a maximum copayment for each individual of ≈US $500 a year). Therefore pharmacies are required to register all prescriptions dispensed, which ensures complete registration, and the reimbursement results in minimal incentive for patients to obtain medication through other sources. Coding is according to the Anatomic Therapeutical Chemical (ATC) system. The registry includes information about date of dispensing, strength and formulation, quantity dispensed, and the affiliation of the doctor who issues the prescription.

We defined initiation of treatment if prescriptions were claimed as follows: RASi (ie, angiotensin-converting enzyme inhibitors and angiotensin-2 antagonists; ATC C09), β-blockers (ATC C07), and spironolactone (ATC C03D) within 90 days from discharge, and statins (ATC C10AA) within 180 days from discharge. Treatment status up to 6 months before hospitalization was determined for all drugs.

To quantify the severity of HF in the statistical models, patients were classified into 4 groups according to the average daily dosage of loop-diuretics (ATC C03C) during the first 90 days after discharge (furosemide-equivalent dosage: furosemide 40 mg=bumetanide 1 mg): Group I, 0 to 39 mg; Group II, 40 to 80 mg; Group III, 81 to 160 mg; and Group IV, >160 m). In multivariable analysis there was a linear trend between dosage of loop-diuretic and mortality ($P<0.0001$), which is in accordance with other studies.[7] Pharmacologically treated diabetes was identified from prescriptions of hypoglycemic medication such as oral or insulin (ATC A10) 90 days before admission to 90 days after discharge.

Persistence of Treatment and Dosage

Persistence of treatment was estimated by identification of subsequent prescription claims. Nonpersistence was defined as a break in therapy of ≥90 days among patients who survived for at least 90 days after discontinuation of therapy. As another measure of persistence we studied the proportion of patients alive who were on treatment on each day. These methods have been described in details previously.[8] Dosages used were calculated and compared with recommended target dosages.[1]

Statistical Analysis

Times from hospital discharge to initiation of therapy were evaluated with Kaplan-Meier estimators (censored for death). Trends in treatment initiation and mortality across calendar years were examined with logistic regression models, which included the calendar year as a continuous variable. Multivariable analyses of time to first break in therapy of ≥90 days and mortality were performed with Cox proportional hazard models. All models were adjusted for age, gender, calendar year, severity of HF, concomitant medical treatment, and comorbidity (Table 1). Furthermore, in the analysis of mortality, breaks in therapy of ≥90 days were included in the proportional hazard models as a time-dependent covariate, which indicated that patients were only considered at risk during breaks in treatment that extended beyond 90 days. Model assumptions, such as linearity of continuous variables, the proportional hazard assumption, and lack of interactions, were tested and found valid unless

TABLE 1. Baseline Characteristics

Characteristics	N	%
Total patients (mean age±SD, y)	107 092 (74.8±11.6)	
Male (mean age±SD, y)	55 368 (72.3±11.7)	51.7
Female (mean age±SD, y)	51 724 (77.6±10.8)	48.3
Year of first hospitalization for HF		
1995 to 1996	19 789	18.5
1997 to 1998	19 996	18,6
1999 to 2000	22 588	21.1
2001 to 2002	23 257	21.7
2003 to 2004	21 462	20.1
Discharge diagnosis at first HF hospitalization (*ICD*-10)		
Hypertensive HF (I11.0)	2 605	2.4
Cardiomyopathy (I42)	4 418	4.1
Decompensated HF (I50.0 to I50.1)	32 736	30.7
Unspecified HF (I50.9)	64 024	59.8
Acute pulmonary edema (J81.9)	3 309	3.1
Familial status		
Living alone	58 102	54.3
Comorbidity		
MI at index admission for HF	9 246	8.6
History of prior MI	26 053	24.3
Cerbrovascular disease	7 982	7.5
Peripheral vascular disease	2 736	2.6
Diabetes with complications	5 862	5.5
Malignancy	4 034	3.8
Cardiac dysrhythmias	28 709	26.8
Renal failure	3 272	3.1
COPD	16 534	15.4
Severity group*		
Group I	26 543	24,8
Group II	42 547	39.7
Group III	24 817	23.2
Group IV	13 185	12.3
Treatment		
β-Blocker†	29 084	27.2
RASi†	46 191	44.1
Spironolactone†	20 166	18.8
Statin‡	13 084	12.2
Antidiabetics§	13 387	12.5
Loop-diuretics§	86 636	80.9

ICD-10 indicates *International Classification of Diseases,* 10th Revision; COPD, chronic obstructive pulmonary disease.

*According to average daily dosage of loop-diuretic (furosemide) in the first 90 days after discharge (Group I, 0 to 39 mg; Group II, 40 to 80 mg; Group III, 81 to 160 mg; Group IV, >160 mg).

†At least 1 prescription claimed within 90 days from discharge.

‡At least 1 prescription claimed within 180 days from discharge

§At least 1 prescription claimed between 90 days before admission and 90 days after discharge.

otherwise indicated. All analyses were performed with SAS software, version 9.1 (SAS Institute, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

There were 122 663 patients with a first hospitalization for HF from 1995 to 2004; 107 092 (87.3%) patients were discharged alive and included in the present study. A total of 123 (0.1%) patients were lost to follow-up (emigrated) and were censored at the time of disappearance. Baseline characteristics are shown in Table 1.

Medical Treatment

Initiation of treatment is depicted in Figure 1. At least 1 prescription of RASi within 90 days from discharge was claimed by 46 191 (43.1%) patients (35.9% in 1995 and 49.6% in 2004; $P<0.0001$). The corresponding figures were 29 084 (27.2%) patients for β-blockers (12.1% in 1995 and 42.7% in 2004; $P<0.0001$), 20 166 (18.8%) patients for spironolactone (9.8% in 1995 and 24.9% in 2004; $P<0.0001$), and 13 084 (12.2%) patients for statins (2.0% in 1995 and 26.9% in 2004; $P<0.0001$). β-Blockers documented for the treatment of HF (ie, carvedilol, metoprolol [mainly metoprolol-succinate], and bisoprolol) comprised 76.7% of all β-blockers used, an increase from 46.3% in 1995 to 93.9% in 2004 ($P<0.0001$). Of those patients who claimed a prescription within 90 days of discharge, 44.0%, 46.4%, 23.9%, and 52.9% were treated with a RASi, β-blocker, spironolactone, or statin, respectively, before admission. For patients who initiated treatment within 90 days of discharge, 75% to 82% of the prescriptions were issued by a hospital physician, and for patients who started later prescriptions were equally distributed among general practitioners and hospital physicians. For all drugs under study, treatment was started within the first few months and rarely started later (Figure 2).

Dosages

There was a considerable underdosing of RASi and β-blockers compared with recommended target dosages (Table 2).[1] Furthermore, dosages were likely to remain unchanged from start of treatment onward except for carvedilol, which was uptitrated as recommended.

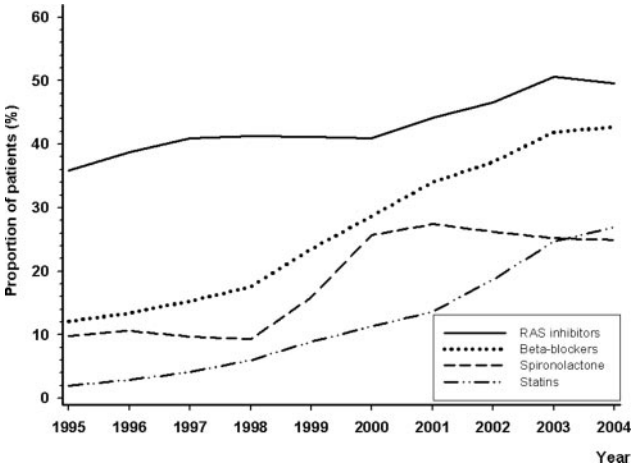

Figure 1. Patients who survived first HF hospitalization and claimed a prescription of RASi, β-blockers, or spironolactone within 90 days or statin within 180 days from discharge.

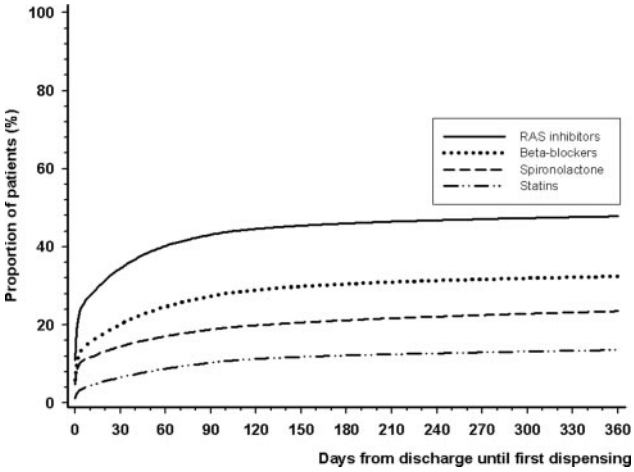

Figure 2. Cumulative frequency of patients who survived first HF hospitalization and claimed at least 1 prescription of β-blocker, RASi, spironolactone, or statin within the first year after discharge (censored for death).

Persistence of Treatment

Breaks in treatment of short duration were common, but the majority of patients reinitiated treatment (Table 3). The multivariable Cox proportional hazard analysis showed that persistence of β-blocker and spironolactone treatment improved through the period (Table 4). Men had poorer spironolactone persistence than women, but higher persistence of RASi. Increasing age was associated with lower persistence of RASi, spironolactone, and statins. Patients who lived alone generally had lower persistence of treatment than patients who lived with a partner. Concomitant use of spironolactone and RASi was associated with lower persistence of treatment, compared with patients who received only 1 of these drugs. Multiple concomitant medications were associated with increased persistence of RASi, β-blockers, and statins. There was an interaction between age and number of concomitant drugs ($P<0.0001$) for spironolactone. Age-stratified analysis demonstrated only significant difference in persistence of spironolactone treatment among patients >75 years old ($P<0.0001$). Patients who received treatment prior to the HF admission had higher persistence of treatment compared with patients who had not previously received treatment. Patients who received higher dosages of a loop-diuretic (a proxy for severity of HF) did not have poorer persistence with any of the drugs. The persistence of treatment is depicted in Figure 3. After 5 years of treatment 79%, 65%, 56%, and 83% still used RASi, β-blockers, spironolactone, and statins.

Mortality

The in-hospital-mortality fell from 14.5% in 1995 to 11.1% in 2004 ($P<0.0001$) and the 1-year mortality fell from 38.7% to 34.5% (1995 to 2003; $P<0.0001$). Except for spironolactone, nonpersistence with RASi, β-blockers, and statins was associated with increased mortality (Table 5). We repeated the analysis in subgroups according to whether the discharge

TABLE 2. Average Daily Dosages of the Most Frequently Used RASi, β-Blockers, Spironolactone, and Statins in Patients With HF During Different Periods From Start of Treatment

		Average Daily Dosage, mg				
Medication	%*	0 to 30 d	31 to 180 d	181 to 360 d	3 to 5 y	Target Dosage, mg†
Metoprolol‡	59.4%	75 (50 to 125)	75 (50 to 100)	75 (50 to 100)	75 (50 to 100)	200
Carvedilol	12.1%	12.5 (6.25 to 25)	18.75 (9.37 to 37.5)	25 (12.5 to 50)	25 (12.5 to 50)	50
Bisoprolol	5.5%	5 (3.75 to 10)	5 (2.5 to 7.5)	5 (5 to 10)	5 (5 to 10)	10
Other	23.0%	...	...	...	...	...
RASi						
Trandolapril	24.8%	2 (1 to 4)	2 (1 to 3)	2 (1 to 4)	2 (2 to 4)	4
Ramipril	19.8%	5 (3.125 to 7.5)	5 (2.5 to 10)	5 (3.125 to 10)	5 (3.75 to 10)	10
Enalapril	16.0%	10 (7.5 to 20)	10 (5 to 20)	10 (5 to 20)	10 (7.5 to 20)	20
Captopril	11.7%	37.5 (25 to 62.5)	37.5 (25 to 62.5)	37.5 (25 to 62.5)	50 (25 to 62.5)	150
Losartan	9.6%	50 (25 to 75)	50 (25 to 75)	50 (50 to 75)	50 (50 to 75)	50
Candesartan	1.5%	8 (6 to 16)	8 (6 to 16)	8 (8 to 16)	8 (8 to 16)	32
Valsartan	0.6%	120 (80 to 160)	120 (80 to 160)	120 (80 to 160)	80 (80 to 160)	320
Other	16.0%	...	...	...	...	...
Spironolactone	100%	37.5 (25 to 62.5)	37.5 (25 to 50)	25 (25 to 50)	37.5 (25 to 50)	25
Statins						
Simvastatin	64.7%	20 (20 to 40)	20 (20 to 40)	20 (20 to 40)	20 (20 to 40)	40
Atorvastatin	15.2%	20 (10 to 20)	20 (10 to 20)	20 (10 to 20)	20 (20 to 40)	80
Prava-statin	13.0%	40 (20 to 40)	40 (20 to 40)	40 (20 to 40)	40 (20 to 40)	40
Other	7.1%	...	...	...	...	...

Values expressed as median (interquartile range) unless otherwise noted.
*Proportion of all medications within each class, used during the observation time.
†Dosages recommended in guidelines and used in major clinical trials.
‡Mainly metroprolol-succinate.

coding of HF was listed as primary or secondary diagnosis and found no differences in outcome.

Discussion

The present nationwide study addresses initiation and persistence of evidence-based pharmacological treatment among an unselected cohort of patients with HF. The study has the following main findings: 1) treatment is usually initiated shortly after discharge and relatively few patients initiate treatment later; 2) if treatment is initiated early, persistence of treatment is high; 3) dosages used are generally far below recommended dosages and rarely uptitrated during long-term treatment; 4) increased severity and increased number of concomitant medications are associated with high persistence of treatment; and 5) nonpersistence with pharmacological treatment in HF identifies a high-risk population that requires particular attention.

In the Danish Investigations of Arrhythmia and Mortality on Dofetilide HF (DIAMOND-HF) study, consecutive patients hospitalized for HF from 1995 to 1996 were screened and 45% had left ventricular dysfunction, 60% were in New York Heart Association class III or IV, 38% had previous myocardial infarction (MI), and 57% had known ischemic heart disease.[9] To put these data in perspective with the current cohort, >50% qualify for treatment with β-blockers, RASi, and spironolactone and up to 60% for statin treatment, which exceeds the average level in the present study.[1] However, treatment initiation in-

TABLE 3. Proportion of Patients With HF on RASi, β-Blocker, Spironolactone, or Statin Therapy Who Experienced a Break of ≥7, 30, 90, or 180 Days Within 5 Years of Treatment and the Proportion Who Reinitiated Therapy Within 1 Year After a Break

	Proportion Who Experienced a Break				Proportion Who Reinitiated Treatment Within 1 Year After a Break			
Length of Break	β-Blocker	RASi	Spironolactone	Statin	β-Blocker	RASi	Spironolactone	Statin
≥7 days	96.2	95.3	98.0	96.7	91.0	94.1	88.2	97.2
≥30 days	68.6	59.5	80.7	71.6	73.3	77.9	72.2	91.9
≥90 days	45.6	36.0	58.5	34.2	47.8	52.5	47.9	74.8
≥180 days	36.7	27.7	48.7	20.4	27.1	31.0	28.6	45.1

Values are expressed as percentages.

TABLE 4. Multivariable Cox Proportional Hazard Analysis of Time to First Break in Treatment of ≥90 Days (Proxy for Nonpersistence) in HF

	β-Blockers			RASi			Spironolactone			Statins		
Covariate	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
1995 to 1996*	1.00	...	...	1.00	...	...	1.00	...	...	1.00	...	...
1997 to 1998	0.89	0.83 to 0.96	0.004	1.04	0.98 to 1.10	0.24	0.90	0.80 to 0.99	0.04	0.89	0.74 to 1.08	0.25
1999 to 2000	0.80	0.74 to 0.86	<0.0001	1.12	1.05 to 1.19	0.0005	0.78	0.71 to 0.85	<0.0001	1.10	0.92 to 1.31	0.32
2001 to 2002	0.66	0.61 to 0.71	<0.0001	1.04	0.98 to 1.12	0.22	0.78	0.71 to 0.86	<0.0001	0.99	0.83 to 1.19	0.92
2003-2004	0.58	0.52-0.64	<0.0001	1.02	0.93-1.11	0.73	0.78	0.70 to 0.88	<0.0001	0.90	0.73 to 1.09	0.27
Gender												
Women*	1.00	...	...	1.00	...	...	1.00	...	...	1.00	...	...
Men	1.06	1.01 to 1.11	0.03	0.95	0.91 to 0.99	0.01	1.20	1.13 to 1.27	<0.0001	1.02	0.93 to 1.11	0.70
Age												
30 to 59 years*	1.00	...	...	1.00	...	...	1.00	...	...	1.00	...	...
60 to 69 years	1.01	0.94 to 1.08	0.77	1.04	0.97 to 1.11	0.32	1.03	0.94 to 1.12	0.53	0.86	0.77 to 0.95	0.004
70 to 79 years	1.05	0.98 to 1.12	0.14	1.29	1.21 to 1.37	<0.0001	1.14	1.05 to 1.23	0.001	0.94	0.84 to 1.05	0.27
≥80 years	1.01	0.93 to 1.09	0.87	1.48	1.38 to 1.58	<0.0001	1.21	1.11 to 1.32	<0.0001	1.27	1.08 to 1.50	0.003
Familial status												
Living with partner*	1.00	...	...	1.00	...	...	1.00	...	...	1.00	...	...
Living alone	1.06	1.01 to 1.12	0.02	1.08	1.04 to 1.13	0.0003	1.05	0.99 to 1.11	0.08	1.22	1.12 to 1.33	<0.0001
Concomitant treatment†												
β-Blocker	...	...	...	0.92	0.88 to 0.96	0.0001	1.03	0.98 to 1.10	0.26	0.83	0.76 to 0.90	<0.0001
RASi	0.89	0.84 to 0.93	<0.0001	...	...	...	1.25	1.18 to 1.32	<0.0001	0.95	0.87 to 1.03	0.21
Spironolactone	1.01	0.95 to 1.07	0.72	1.19	1.13 to 1.25	<0.0001	...	...	...	1.00	0.90 to 1.10	0.98
Statins	0.82	0.77 to 0.87	<0.0001	0.86	0.81 to 0.92	<0.0001	1.01	0.94-1.08	0.87	...	...	...
Antidiabetics	0.92	0.86 to 0.99	0.03	0.97	0.92 to 1.03	0.29	1.11	1.03 to 1.19	0.005	0.90	0.81 to 1.01	0.07
Prior treatment†	0.75	0.71 to 0.79	<0.0001	0.86	0.83 to 0.90	<0.0001	0.69	0.65 to 0.74	<0.0001	0.64	0.59 to 0.70	<0.0001
Severity group‡												
Group I*	1.00	...	...	1.00	...	...	1.00	...	...	1.00	...	...
Group II	1.03	0.98 to 1.10	0.27	1.00	0.94 to 1.06	0.93	0.98	0.89 to 1.07	0.61	0.99	0.89 to 1.09	0.78
Group III	0.97	0.91 to 1.04	0.44	1.04	0.98 to 1.11	0.21	0.85	0.77 to 0.93	0.001	0.86	0.76 to 0.97	0.02
Group IV	1.03	0.93 to 1.13	0.60	1.14	1.05 to 1.24	0.002	0.72	0.64 to 0.81	<0.0001	0.80	0.67 to 0.95	0.01
No. of concomitant drugs§												
No concomitant drug*	1.00	...	...	1.00	...	...	1.00‖	...	...	1.00	...	...
1 drug	0.95	0.89 to 0.99	0.05	1.06	1.01 to 1.11	0.01	1.27	1.19 to 1.36	<0.0001	0.88	0.78 to 0.99	0.05
2 drugs	0.80	0.75 to 0.86	<0.0001	0.94	0.89 to 1.01	0.10	1.36	1.26 to 1.48	<0.0001	0.82	0.73 to 0.94	0.003
3 drugs	0.75	0.66 to 0.84	<0.0001	0.84	0.74 to 0.96	0.01	1.28	1.15 to 1.42	<0.0001	0.73	0.62 to 0.86	0.0002

All covariates presented in Table 4 were included in the Cox regression. HR indicates hazard ratio.

*Reference.

†Nonusers as reference.

‡According to average daily dosage of loop-diuretic (furosemide) in the first 90 days after discharge (Group I, 0 to 39 mg; Group II, 40 to 80 mg; Group III, 81 to 160 mg; Group IV, >160 mg).

‖Interaction with age ($P<0.0001$); age-stratified analysis showed no difference among patients ≤75 years old (*P* for trend=0.23).

§Additional proportional-hazard model where concomitant drugs were left out.

creased substantially between 1995 and 2004 (Figure 1). This indicates that physicians increasingly complied with recommendations, along with increased availability of diagnostic methods to estimate left ventricular ejection fraction (ie, echocardiography). Additionally, there was a shift toward β-blockers with documented survival benefit in HF (ie, metoprolol, bisoprolol, and carvedilol) from 1995 to 2004, but use of other β-blockers probably reflects treatment of concomitant diseases. Notably, among patients who did not previously receive treatment, the first prescription was predominantly issued by hospital physicians. This could reflect an initiative during hospitalization, importance of hospital outpatient clinics, or increased availability of dedicated HF clinics in Denmark.

The dosages used were generally below recommended target dosages (Table 2).[1] Also, dosages were rarely uptitrated, with the exception of the β-blocker carvedilol, which was the first β-blocker documented for treatment of HF and primarily prescribed by specialists in cardiology. The dosages of β-blockers and most RASi were 50% or less of recommended dosages.[1] Statin dosages were also low, although it is difficult to determine

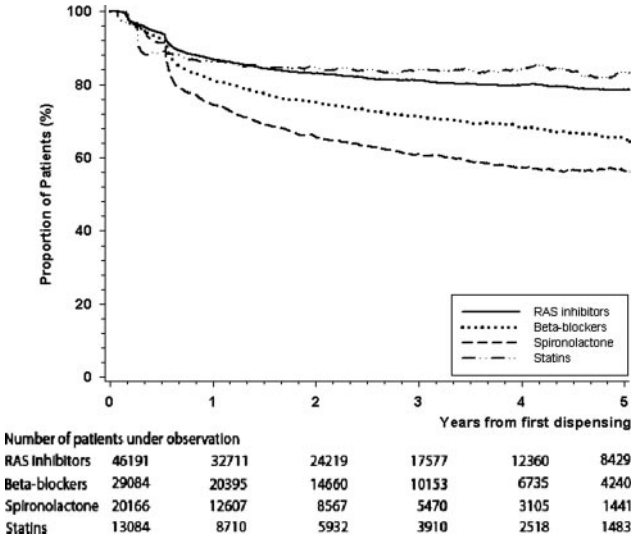

Figure 3. Long-term persistence with RASi, β-blocker, spironolactone, or statin in patients with HF: the proportion of patients alive who were on treatment on each day.

the correct dosage because we lack information on lipid levels. However, because clinical trials comprise selected populations, the current results may therefore reflect dosages generally used in an unselected HF population.

After 5 years of treatment, 79% of patients were still on RASi, 65% were on β-blockers, 56% were on spironolactone, and 83% were on statins (Figure 3). Breaks in therapy were common, but patients who experienced breaks of shorter duration usually reinitiated therapy (Table 3). Even for breaks of 90 days or longer, ≈50% reinitiated treatment within 1 year. This clearly demonstrates that breaks in treatment are a dynamic factor, in contrast to many studies that consider a break in treatment equivalent to discontinuation of treatment. Notably, persistence of β-blocker and spironolactone treatment improved during the study period (Table 4) along with an increasing number of patients who initiated treatment. Gender differences were reflected in poorer RASi persistence among women, who more often experience cough,[10] and lower spironolactone persistence among men, who often experience gynecomasty.[11] Increasing age was associated with lower persistence of RASi, spironolactone, and statin treatment, and patients who lived alone also had generally lower persistence of treatment. Poorer persistence of statin treatment in elderly patients could relate to socioeconomic factors, because statins were still fairly expensive during the study period. Risk of renal side effects and hyperkalemia in older patients could explain low persistence for treatment with RASi or spironolactone, as well as for combination treatment with RASi and spironolactone in this population.[12] Notably, an increased number of concomitant medications was associated with persistence of treatment, an important finding because treatment of HF often involves polypharmacy. Also, increased severity of HF did not worsen persistence, in contrast to studies that demonstrated risk–treatment mismatch in the pharmacotherapy of HF.[13] This is in accordance with other studies, which have found no association between HF functional class or number of concomitant medications and poorer persistence.[5,14]

TABLE 5. Multivariable Cox Proportional Hazard Analysis of Risk of Death Related to Nonpersistence With Pharmacological Treatment (Break in Treatment ≥90 Days) in HF

Drug	HR*	95% CI	*P*
RASi	1.37	1.31 to 1.42	<0.0001
β-Blocker	1.25	1.19 to 1.32	<0.0001
Spironolactone	0.95	0.89 to 1.00	0.07
Statins	1.88	1.67 to 2.12	<0.0001

*Adjusted for age, year, sex, concomitant medical treatment, severity (loop-diuretic dosage), and comorbidity.

Comprehensive studies on persistence of pharmacotherapy in HF are sparse. Most studies comprise small selected cohorts with short follow-up, and differences in methods, definitions, and outcomes make direct comparison difficult. Studies on different HF populations demonstrate long-term compliance with RASi to be between 56% and 92%.[5,15,16] One study reported 5-year compliance with angiotensin-converting enzyme inhibitor to be 75% and with β-blockers to be 53%.[17] In a cohort that attended HF clinics only, 10% of patients discontinued β-blocker treatment after 2 years,[18] and in another similar study 34% discontinued spironolactone within 1 year.[19] In a study on HF patients in clinical practice, 77% of patients were on β-blockers after 1 year, and importantly severity of HF did not increase discontinuation of β-blocker treatment.[14] Studies on HF patients have observed similar underdosing of angiotensin-converting enzyme inhibitors and β-blockers.[16,20] In a previous study of treatment after MI in Denmark, the persistence and underdosing of treatment was comparable to the present results.[8] In the present study only 8.6% of the patients had the diagnosis of MI at the index HF admission, and 24.3% had any history of prior MI; thus, similar results from these 2 studies do not reflect overlapping populations.

Nonpersistence with RASi, β-blockers, and statins was associated with higher mortality and hence identified a high-risk group of patients with HF (Table 5). There is a possibility that increased mortality was partly caused by confounding-by-indication (ie, sicker patients could not tolerate medication and therefore discontinued treatment, shortly before death). However, we used conservative measures of nonpersistence in our analysis where only breaks in treatment of ≥90 days were considered as risks. Thus patients who died after a shorter break in therapy were censored in the mortality analyses, which thereby avoids the possibility that patients who stopped treatment because of increased morbidity in the proximity of death would bias the relative risk estimates. Another possible explanation of worse prognosis in patients who had breaks in treatment is "the healthy adherer effect" (ie, patients who have better persistence of treatment also have healthier lifestyles than patients with poorer persistence, and therefore good persistence of treatment is a surrogate marker for overall healthier behavior).[21] The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) trial demonstrated that patients with good compliance with either candesartan or placebo had equal prognosis, and all patients with poor compliance had worse prognosis.[5] Ho et al reported almost 4-fold increased mortality in patients who discontinued treatment after MI and nonadherence increased mortality and hospitalization rates in patients with diabetes.[22,23] Newby et al found that, in patients with coronary heart disease and HF, consistent treatment

with angiotensin-converting enzyme inhibitors was associated with a 25% reduction in mortality.[15] Also, consistent use of β-blockers and lipid-lowering drugs reduced mortality by 37% and 48%, respectively, but were not analyzed separately for HF. Furthermore, Rasmussen et al found that the healthy adherer effect did not explain all of the mortality difference between high- and low-adherence post-MI patients.[24] This certainly reflects effects far beyond that of simple treatment withdrawal, thus the term "compliance" is an integrated measure of the entire clinical situation. It is intriguing that nonpersistence with spironolactone is not associated with increased mortality. In the Randomized Aldactone Evaluation Study (RALES), spironolactone treatment reduced mortality in severe HF by 30%.[11] But later studies have demonstrated increased risk of hyperkalemia[12,19] and increased mortality associated with spironolactone treatment in chronic HF,[25] which could explain why the benefit of spironolactone treatment is not reflected in increased mortality in nonpersistent patients.

We observed a decrease in in-hospital mortality, which is intriguing because there were no major improvements in acute HF treatment during the study period. This could be a carry-over effect of increased focus on the treatment of chronic HF, or reflecting improvements in treatment of other important cardiovascular diseases such as acute MI.

Strengths and Limitations

The completeness of data, which enables comprehensive follow-up for 10 years, is the main strength of the study. The Danish National Patient Registry keeps records on discharge diagnosis from all hospitals in Denmark, and the present study thus avoids selection bias, which may be present in surveys that are based on selected centers. Furthermore, the national prescription registry includes all prescriptions dispensed nationwide. Use of registries to estimate refilling of prescriptions is a reliable method to estimate long-term persistence,[26] avoids recall bias, and, because there is copayment of the medication expenses, claimed prescriptions from pharmacy indicates intention to take the medication. The Danish healthcare system is government-financed, which secures equal access to health care for all inhabitants free of charge, regardless of socioeconomic status. Similar to many Western countries, drug expenses are partially reimbursed; therefore, we believe the results can be extended to other countries. But, because persistence of treatment is highly influenced by copayment of drug expenses,[27] lower persistence of treatment cannot be excluded in healthcare systems in which copayments are higher.

There are some important limitations of the study that need to be acknowledged. The diagnosis of HF in the Danish National Patient Registry has not been validated and, because the difficulties in defining HF are evident, one may question the precision of the *ICD*-10 codes used in the present study. Two recent studies from Scotland and Canada found high accuracy of the discharge coding diagnosis of HF.[28,29] Hence, when the diagnosis of HF is established, it is accurate. The present study is based on administrative registries and do not include clinical data. Thus, precise indications and contraindications for HF treatments are not available (eg, information on left ventricular ejection fraction, which often is used for prognostic and management stratification). Furthermore, contraindications for treatment, adverse reactions, or allergies that might have caused lack of initiation or early termination are not included in the registries, which makes it difficult to state which fraction of the patients who would require therapy in an ideal setting. However, these limitations are particularly relevant to any attempt to study the fraction of patients who require therapy, but are not important in a study of treatment persistence, dosing, and changes over time, because patients started on medical therapy were considered to have the indication for treatment by the caring physician. Discontinuation of therapy can be caused by several factors, such as the decision of a caring physician to stop treatment in a patient with terminal heart failure who is approaching palliative care or that the patient is too weak to tolerate the treatment.

Conclusions and Clinical Implications

Persistence of treatment was high once treatment was started, but the dosages used were below recommended dosages. Particularly, increased severity of HF or increased number of concomitant medications was not associated with lower persistence. Nonpersistence with RASi, β-blockers, and statins in HF identifies a high-risk population of patients that requires special attention.

Therefore, hospital departments that care for patients with HF should consider early in the management which treatment is indicated for the individual patient and preferably start treatment before discharge. Furthermore, to ensure appropriate long-term management, physicians who treat HF patients need to ensure that treatment is uptitrated to recommended dosages after discharge to achieve maximal benefits of treatment. Once medication is stable, treatment will continue for many years and patient can be followed by a general practitioner, but nonpersistence with treatment might indicate the need for special attention from a specialist. Thus, a systematic effort to increase initiation of therapy and ensure titration to appropriate dosages is likely to provide major long-term benefit.

Source of Funding

The present study was supported by a research grant from the Danish Heart Foundation (No. 05-04-B46A522-22207).

Disclosures

M. Madsen has received a research grant from the Danish Pharmaceutical Foundation. Dr Torp-Pedersen has received research grants for several clinical trials related to congestive heart failure and has served as a consultant and/or on advisory boards related to congestive heart failure; he has also given several talks on the topic of congestive heart failure. He has received funds from Roche, Abbott, Cerdione, and sanofi. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Underuse of evidence-based pharmacotherapy is common in patients with heart failure and may worsen the prognosis. Studies on the nature of underuse are therefore important to identify likely targets for improvement. We studied the use and persistence of use of evidence-based pharmacotherapy in 107 092 patients discharged after first hospitalization for heart failure in Denmark between 1995 and 2004. Furthermore, we studied the association between persistence and long-term prognosis. The present study demonstrated that if treatment was started early after discharge, most patients continued treatment for long-term. If treatment was not started early after discharge, the likelihood of ever receiving treatment was low. Short breaks in treatment were common, but most patients reinitiated treatment, especially after short breaks. Treatment dosages were in general only 50% of recommended dosages and were not increased during long-term treatment. Five years after initiation of treatment, 79% of patients were still on angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, 65% on β-blockers, 56% on spironolactone, and 83% on statins. Notably, multiple drug treatment and increased severity of heart failure was not associated with poorer persistence of treatment. Nonpersistence with angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, β-blockers, and statins identified a high-risk population who required special attention and was associated with increased mortality. Therefore, hospital departments that care for patients with heart failure should consider early in the management of these patients which treatments are indicated and make arrangements for both initiation of treatment and uptitration. A focused effort on early treatment initiation, appropriate dosages, and persistence is likely to provide long-term benefit.

Persistent Use of Evidence-Based Pharmacotherapy in Heart Failure Is Associated With Improved Outcomes

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Circulation. 2007;116:737-744; originally published online July 23, 2007;
doi: 10.1161/CIRCULATIONAHA.106.669101
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539