Drug therapy in heart failure: studies on prescribing, drug induced problems and compliance

MARCEL LOUIS BOUVY

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Drug therapy in heart failure: studies on prescribing, drug induced problems and compliance

Farmacotherapie bij hartfalen: onderzoek naar voorschrijven, geneesmiddel geïnduceerde problemen en therapietrouw

(met een samenvatting in het Nederlands)

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[1]

Scope of the thesis

An 'epidemic' of heart failure is emerging as a consequence of an ageing population and increased survival of patients with acute coronary artery disease.[1, 3] Rising rates of hospitalisations for heart failure mean considerable increases in health care expenses, with heart failure already accounting for 1% of Western health care expenditure.[3, 4] It was recently reported that the increase in hospitalisations for heart failure may have reached its peak in the mid-nineties.[5] Policies aimed at keeping patients out of the hospital, including specialist nurse- or physician-led outpatient clinics, may have been instrumental in this. Nevertheless, heart failure will undoubtedly remain an important cause of morbidity, mortality and impairment of quality of life in the elderly. The prevalence of heart failure, estimated in the general population at 3-20 per 1000 persons, increases strongly with age; with prevalence in patients over 65 years estimated at 10%. This implies that the 'average' Dutch general practitioner (GP) takes care of at least 20 patients with heart failure and the average Dutch community pharmacist will 'know' about 100 patients with heart failure.[4, 6, 7]

Heart failure: the syndrome and its aetiology

Heart failure is not a clearly definable disease, but a syndrome with various aetiologies. The failing heart is unable to supply an adequate amount of (oxygenated) blood to all organs and tissues. Depending on the severity of heart failure, patients will experience complaints after (severe) exertion or even at rest. Fatigue and decreased ability to exert are the most important symptoms of heart failure. Unfortunately, these symptoms also apply to a variety of other disorders and thus contribute to the difficulties in diagnosing heart failure.[4, 8] More specific symptom for heart failure is the presence of fluid retention. Fluid retention in the extremities causes ankle oedema, pulmonary fluid retention causes breathlessness, and intestinal fluid retention causes nausea, anorexia and gastrointestinal discomfort.[9] The diagnosis of heart failure depends on the presence of these symptoms, as well as objective evidence of cardiac dysfunction. In primary care where diagnostic tests such as electrocardiography and echocardiography are not routinely available, heart

failure is often missed or diagnosed incorrectly.[3] In the majority of patients in Western societies with heart failure, impaired left ventricular function is attributable to coronary artery disease.[10] Other important causes of heart failure are long-term hypertension, arrhythmias (especially atrial fibrillation), valve disease, anaemia, thyroid disorders and alcohol-abuse.[11]

Pathophysiology and drug treatment

Until 1960, heart failure was attributed to decreased renal perfusion and treatment was aimed at improving renal perfusion by rest and lifting legs.[12] Since then, different types of diuretics have been employed and have remained a cornerstone in heart failure therapy in preventing congestion. In the early 1960's, the hemodynamical concept of heart failure became increasingly significant, emphasising the importance of impaired left ventricular function in heart failure. Consequently, the use of drugs with a positive inotropic effect, such as digoxin, was advocated, while negative inotropic agents, such as beta-blockers, were contra-indicated. Digoxin had been available for almost 200 years. As its benefits were attributed to a positive effect on cardiac function, new drugs (such as phosphodiesterase-inhibitors and dopamine agonists) were developed that improved cardiac contractility. However, these drugs were found not to reduce mortality. Presently, it is assumed that the positive effects of digoxin result mostly from its ability to normalise arrhythmias, frequent in heart failure patients.
Since the 1990's, the important role of neurohumoral changes in the progression of heart failure has become apparent. The main neurohumoral changes concern the activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. These neurohumoral changes improve peripheral tissue perfusion in the short term, but have a deleterious effect on cardiac function in the long term.[12, 13] This new paradigm led to new strategies in the drug treatment of heart failure. Therapeutic interventions aimed at reducing the increased neurohumoral activity have proven to be successful in slowing down the progression of heart failure. Several studies have shown positive effects of Angiotensin Converting Enzyme (ACE)

inhibitors on morbidity and mortality in heart failure. ACE inhibitors have therefore become standard treatment.[14-16]
Beta-blockers were originally considered contra-indicated because of their negative inotropic and chronotropic effects. By now, however, the beneficial effect of beta-blockers in reducing the negative effects of increased sympathetic activity has been established and given beta-blockers a prominent position in the treatment of mild to moderate heart failure.[17, 18]
Furthermore, it has been shown that addition of the aldosterone-antagonist, spironolactone, to a regimen of ACE inhibitors, digoxin and loop diuretics further reduces mortality and morbidity.[19]
In recent years, more has become known of the role of apoptosis and the remodelling of the endothelium in heart failure. This further strengthened the importance of available agents, such as ACE inhibitors and beta-blockers, while it also stimulated the development of new agents.[20]

Prognosis of heart failure: high mortality and frequent hospital admissions

Heart failure has the lowest 5-year survival of all common diseases, with the exception of lung cancer.[21] The 5-year survival after a diagnosis of heart failure is approximately 50 %. The survival of patients with severe heart failure (NYHA IV) is even lower (2-year survival of 20-40%). Patients discharged after hospital admission for heart failure are frequently readmitted within 6 months.[22-24] These frequent readmissions are responsible for the major part of the health care expenditure in heart failure.[7, 25] In a study among 17 448 elderly patients admitted for congestive heart failure, 26% was older than 85 years and the average duration of hospital admission was 7 days. In the 6 months following hospital discharge, 44% was readmitted at least once, 16% readmitted twice or more, and 24% died. Heart failure was the most common reason for readmission (18%), followed by pneumonia and myocardial infarction (3.8% and 3.5%, respectively).[26] Several studies have identified determinants of early mortality and morbidity in patients with heart failure (Table 1).

Table 1. Determinants of death and re-hospitalisation in heart failure

	Determinants of re-hospitalisation							Determinants of early mortality				
	Chin[60*]	Krumholz[61]	Krumholz[26]	Philbin[62]	Rich[29]	Struthers[63]	Vinson[22]	Scrutinio[64]	Zugck[65]	Aaronson[66]	Cowie[67]	Jiang[68]
Determinants	(1997)	(2000)	(1997)	(2001)	(1995)	(2000)	(1990)	(1994)	(2001)	(1997)	(2000)	(2001)
age											X	X
single marital status	X											
social deprivation						X						
male sex			X									
lower socio-economic class				X								
lower systolic blood pressure	X				X					X	X	
uncontrolled hypertension							X					
mean arterial pressure									X	X		
absence of new ST-T-wave changes	X											
heart rate									X	X		
intraventricular conduction delay									X	X		
left ventricular ejection fraction								X	X	X		
renal function		X			X						X	
lower serum sodium					X				X	X		
myocardial ischaemia							X	X	X	X		X
crepitations											X	
NYHA class								X				X
peak oxygen uptake									X	X		
co-morbidity index	X											
diabetes		X			X							
depression												X
prior hospital admissions		X	X				X					
length of stay in the hospital			X									
prior heart failure		X					X					

*determinants of readmission or death

Vinson et al found a 3-month readmission rate of 47% in patients older than 70. They reported that more than half of these readmissions could have been avoided.[22] Several other studies have suggested that many (re)admissions to the hospital can be prevented.[27, 28] A variety of reasons for (unnecessary) readmissions have been reported, including:

- Erroneous pharmacotherapy: e.g. under-use of medication with proven benefits such as ACE inhibitors; overuse of harmful medication such as Non-Steroid Anti-Inflammatory Drugs (NSAIDS)
- Poor patient compliance, with regard to both drug and non-drug (such as dietary) interventions
- Patient's lack of knowledge of heart failure and its treatment
- Adverse drug reactions (especially renal dysfunction and electrolyte disturbances)
- Sub-optimal use of medical care; e.g. failure in seeking medical attention when acute symptoms of fluid retention occur
- Rapid clinical deterioration after discharge from the hospital
- Inadequate planning of hospital discharge and lack of social support after discharge
- Inadequate medical follow-up after hospital discharge

Disease management in heart failure

The factors mentioned above are key issues for disease management programs for heart failure patients. These programs strive to reduce hospital readmissions, improve quality of life, increase survival and reduce health care costs. Patients are generally enrolled in these disease management programs during their stay in the hospital. Available disease management programs include the following elements:

- Patient counselling and education of heart failure (e.g. diet, exercise, fluid intake, alcohol use, smoking)
- Optimising medication according to latest insights and supporting patient compliance with therapy
- Patient education on how to act when heart failure deteriorates (e.g. when weight increases suddenly or ankle oedema occurs)
- Arranging home care and social support for patients after discharge from the hospital
- Extensive follow-up by specially trained nurses or other medical personnel after discharge from the hospital

Specialist nurses (who also provide patient information leaflets) run most of these disease management programs, but other health care providers, such as cardiologists, general practitioners, dieticians, district nurses, social workers and pharmacists can also be involved. Disease management in heart failure has been found to improve prognosis (Tables 2-5). Although the design and quality of these studies vary considerably, convincing evidence comes from several controlled trials (Table 3). A number of the larger studies showed marked improvements in hospital readmissions and mortality.[29-31] Other outcomes that were positively influenced included patient's functional status, quality of life, medication compliance and benchmarks for the quality of treatment such as the dose of ACE inhibitors reached. Some studies also evaluated the effects on health care expenditure of heart failure programs. Heart failure programs turned out to be cost effective in that the costs of the programs, consisting of an increase in scheduled clinic visits and other regular care, are off set by savings from the reductions in the number of hospital admissions.[29, 32-34]

Table 2. Before-after studies aimed at improving prognosis in heart failure

author	no. of patients	follow-up (months)	outcomes	in the year before the intervention*	after the intervention	significant improvement
Kornowski[69] (1995)	42	12	1. total no. of hospital admissions	3.2 ± 1.5 hosp/year	1.2 ± 1.6 hosp/year	yes
			2. mean duration of hospital stay	26 ± 14 days/year	6 ±7 days/year	yes
Shah[70] (1998)	27	12	1. hospitalisation rate	0.8 per patient/year	0.4 per patient/year	no
			2. duration of hospital stay	9.5 days per patient/year	0.8 days per patient/year	
West[71] (1997)	51	4.5 ± 1.5	1. heart failure (hf) readmissions	1.12/year	0.15/year	no
			2. daily dietary sodium intake	3 393 mg	2 088 mg	
			3. mean daily lisinopril dose	17 mg	23 mg	
Fonarow[33] (1997)	214	6	1. total no. of hospital admissions		0.29/patient	
			2. improvement of functional status			
			3. savings in hospital readmission costs		$9 800/patient	
Martens[72] (1997)	924	3	1. decrease in hf readmissions		36%	
Rauh[73] (1999)	347		1. hf readmissions			yes
			2. length of stay			
			3. costs			
Smith[74] (1997)	21	6	1. hf readmissions	14	2	
			2. hf emergency visits	8	0	
			3. change in nyha class	2.6	2.2	
Whellan[34] (2001)	117	4.7 (mean)	1. patients using beta-blockers	52%	76%	yes
			2. patients on target dose of beta-blockers	6%	13%	yes
			3. hospitalisation rate	1.5 per patient/year	0 per patient/year	yes
			4. no. of clinic visits	4.3 patient/year	9.8 patient/year	yes
			5. average savings		$8 571 per patient/year	
Hanumanthu[75] (1997)	134	1-12	1. patients with hospitalisation	94%	44%	yes
			2. hf readmissions (1 year follow-up)	97	30	yes

*Measurements in the same patients in the year before the intervention

Table 3. Controlled studies aimed at improving prognosis in heart failure

Author	No. of patients	Follow-up (months)	Outcomes	Intervention group	Control group	Significant improvement
Schneider[76] (1993)	54	1	1. total no. of hospital admissions	2 (7.7%)	8 (28.6%)	yes
Rich[77] (1993)	98	3	1. patients with readmissions	33.3 %	45.7%	no
			2. mean duration of hospital stay	4.3	5.7	no
			3. mean no. of days until first readmission	31.8 ± 5.1	42.1 ± 7.3	no
Kostis[78] (1994)	20	3	1. exercise tolerance	+182 ± 139 seconds	+91 ± 76 seconds	yes
			2. Beck depression inventory score	-5.0 ± 4.2	+2.0 ± 4.2	yes
			3. Hamilton scale scores of anxiety	-5.2 ± 5.4	+6.0 ± 2.6	yes
			4. Hamilton scale scores of depression	-6.6 ± 10.1	+5.0 ± 5.0	yes
			5. weight loss	-4.37 ± 4.50 kg	-1.35 ± 1.44 kg	yes
Rich[29] (1995)	282	3	1. total no. of hospital admissions	53 (37.3%)	94 (67.1%)	yes
			2. patients with ≥ 1 readmission	41 (28.9%)	59 (42.1%)	yes
			3. patients with ≥ 2 readmissions	9 (6.3%)	23 (16.4%)	yes
			4. mean duration of hospital stay	3.9	6.2	yes
			5. total no. of days in hospital	556	865	yes
			6. overall mortality	13	17	no
			7. cost	$ 4 815 per patient	$ 5 275 per patient	yes
Cline[79] (1998)	190	12	1. hospitalisation rate	0.7 per patient/year	1.1 per patient/year	no
			2. duration of hospital stay	4.2 per patient/year	8.2 per patient/year	no
			3. mean no. of days until first readmission	141	106	yes
			4. cost	$ 2 294	$ 3 594	yes
			5. mortality	24 (30%)	31 (28%)	no

Table 3. Controlled studies aimed at improving prognosis in heart failure (continued)

Author	No. of patients	Follow-up (months)	Outcomes	Intervention group	Control group	Significant improvement
Stewart[80] (1998)	97	6	1. total unplanned hospital readmissions	36	63	yes
			2. total no. of readmitted patients	24 (49%)	31 (64.6%)	no
			3. total stay in hospital	261 days	452 days	yes
			4. mortality	6 (12.2%)	12 (25%)	no
Stewart[32] (1999)	97	18	1. total unplanned hospital readmissions	64	125	yes
			2. frequency of unplanned readmissions plus mortality	1.4±1.3/patient	2.7±2.8/patient	yes
			3. hospitalisation rate	2.5±2.7/patient	4.5±4.8/patient	yes
			4. cost of hospital-based care	Aust $5 100/patient	Aust $10 600/patient	yes
Stewart[31] (1999)	200	6	1. total unplanned hospital readmissions	68	118	yes
			2. total stay in hospital	460 days	1173 days	yes
			3. mortality	18	28	no
Jaarsma[81] (1999)	179	9	1. self-care abilities and behaviour			yes
			2. hospital readmissions	31 (37%)	47 (50%)	no
			3. visits to the emergency heart centre	14 (24%)	26 (38%)	no
Blue[30] (2001)	165	12	1. patients with HF readmissions	12 (14%)	26 (32%)	yes
			2. patients with HF readmissions or death	31 (37%)	43 (53%)	yes

The role of the pharmacist in disease management in heart failure

Pharmacists were included in several multidisciplinary intervention studies.[31] Only a few studies focussed on the individual role of the pharmacist in improving outcomes in heart failure.[35, 36] Table 4 shows a summary of these studies. Both hospital and community pharmacists were involved in managing heart failure patients. Studies with hospital pharmacists tended to focus on the role of pharmacists in choosing the appropriate drug regimen and dosages, while studies with community pharmacists focussed on improving compliance and the patient's knowledge of heart failure.

Optimising drug therapy

An important element of disease management programs is optimising medication according to prevailing evidence. In most disease management programs, cardiologists determine the drug regimen. Clinical pharmacists also play a role in judging the patient's (co-)medication.[35, 37-39] Several studies have shown that despite the demonstrated therapeutic value of ACE inhibitors and beta-blockers, the dissemination of this evidence in the treatment of patients with heart failure is low.[40-45] Moreover, studies suggest that when ACE inhibitors and beta-blockers are initiated dosages were not appropriate and discontinuation rates were high, reducing the number of patients with optimal therapy during the recommended time period.[46-48] Almost one third of hospitalised patients stopped taking their ACE inhibitor within 6 months of hospital discharge.[47]

Table 4. Overview of studies on the role of the pharmacist in the management of heart failure

Author	No. of patients	Follow-up (months)	Outcomes	Intervention group	Control group	Significant improvement
Before-after studies (same patients followed before and after the intervention)						
Stoner[39] (1998)	23	1.5	1. Quality of life			no
			2. Increase in total dose of ACE inhibitors	96%		
			3. Reduction of hospital cost	$292 per patient		
			4. Hospital stay	0.1 day per patient	0.8 day per patient	
Luzier[37] (2000)			1. Re-hospitalisation frequency	35%	63%	yes
			2. Total cost of re-hospitalisations	$ 3 800	$9 800	
Controlled studies						
Gattis[35] (1999)	181	6	1. All-cause mortality and HF clinical events	4	16	yes
		(median)	2. Median fraction of ACE inhibitor target dose	1.0	0.5	yes
			3. Use of other vasodilators	75%	26%	yes
Goodyer[58] (1995)	100	3	1. Medication compliance (tablet count)	93% (SD 11.7)	51% (SD 31.5)	yes
			2. 6-minute exercise test	+20 meters	-22 meters	yes
			3. Distance till breathlessness	+26 meters	-19 meters	yes
			4. Patients without oedema	81%	49%	yes
Rainville[82] (1997)	34	12	1. Patients with hospital admissions	4 (23.5%)	10 (58.8%)	yes
Varma[83] (1999)	83		1. Hospital admissions	14	27	yes
			2. Emergency room visits	15	7	no
			3. Hospital admissions	38	35	no
Linne[36] (1999)	130	6	1. Knowledge score (28 points questionnaire)	17.2	14.3	yes

Table 5. Overview of studies aimed at improving medication compliance in heart failure

Author	No. of patients	Follow-up (months)	Outcomes	Intervention group	Control group	Significant improvement
Controlled studies						
Fulmer[84] (1999)	50	2	1. patients with hospital admissions	35%	63%	yes
			2. total charges of re-hospitalisations	$ 3 800	$ 9 800	
Rich[23] (1996)	156	1	1. overall compliance rate during the first 30 days	87.9±12.0%	81.1±17.2%	yes
			2. compliance rate of ≥ 80%	85.0%	69.7%	yes
Goodyer[58] (1995)	100	3	1. medication compliance (tablet count)	93±11.7%	51±31.5%	yes

Improving medication compliance

Apart from initiating the appropriate therapeutic regimen, it is important to ascertain that the patient follows the regimen. Non-compliance with prescribed medication can have serious consequences: Even a few consecutive days (as short as 2-3 days) of not taking loop diuretics can cause acute worsening of the clinical condition, possibly leading to hospital admission.[49] Studies suggest that medication compliance in heart failure is low. It is estimated that non-compliance contributes to 15-65% of hospital readmissions.[27, 50-57] Improving medication compliance is, therefore, another important element of disease management programs. Most available studies did not include appropriate measurements of compliance. It is assumed, however, that the reduction in hospital (re)admissions in disease management programs for heart failure patients is partly caused by improvement in compliance with medication and life style interventions, such as dietary advice. Studies that did include measurements of medication compliance reported improvements.[58] Table 5 provides a summary of studies assessing effects on compliance to drug therapy in heart failure.

Outline of thesis

Overview of the topic

In **Chapter 1**, the changes in the epidemiology, drug treatment and management of heart failure are given. Emerging evidence of the benefits of several drugs has made treatment of heart failure more rewarding, but also more complex. Most patients with heart failure are 70 years and older and have a history of ischaemic heart disease and several co-morbidities. Hypertension, arrhythmias, diabetes and obstructive pulmonary disease occur more frequently in heart failure patients than in the elderly population at large. The treatment of both heart failure and these co-morbidities leads to the use of a broad range of very powerful medicines. The inappropriate use of these medicines can lead to several drug related problems that can have a major impact on the outcome of pharmacotherapy.[85] These problems can be directly related to the use of the drug(s) (e.g. adverse drug reactions and interactions), related to the health care system (e.g. prescribing and dispensing errors) or related to suboptimal use by the patient (e.g. non-compliance and early discontinuation of drug therapy).

An overview of changes in the drug treatment of heart failure between 1990 and 1998 is presented in **Chapter 2**, and addresses a range of drug-related problems in patients with chronic heart disease.

Discontinuation

Premature discontinuation of drugs with proven efficacy can be considered as non-compliance. A study of the continuation of several medications initiated during hospital admission for heart failure and intended for long-term use is presented (**Chapter 2**). Discontinuation of spironolactone is studied in more detail (**Chapter 3**).

Under-utilisation

Utilisation of cardiovascular drugs in patients discharged after hospitalisation for heart failure between 1990 and 1998 is studied in **Chapter 2**. As ischaemic heart disease is the most important cause of heart failure in western societies, special consideration is given to under-utilisation of acetylsalicylic acid in patients with ischaemic heart disease (**Chapter 4**).

Medication compliance

Previous studies showed a two-fold risk for recurrent heart failure hospitalisations in patients with poor refill patterns of their loop diuretics.[59] Since non-compliance with loop diuretics, is prone to lead to acute exacerbations in patients with heart failure[49], we studied compliance with these diuretics with the use of Medication Event Monitoring Systems (MEMS®). Moreover, the effect of a pharmacist-led intervention on compliance is studied in a randomised trial (**Chapter 5**).

Drug-induced problems

Patients with congestive heart failure often have obstructive pulmonary disease. Moreover breathlessness in heart failure could be mistaken for pulmonary problems. Thus, the use of sympathomimetics in heart failure is relatively common. Sympathomimetics can increase heart rate, even when administered by inhalation. Heart failure patients might be more susceptible to the development of arrhythmias after an increase in heart rate. Therefore, the effect of sympathomimetics on the occurrence of arrhythmias in heart failure patients is studied in **Chapter 6**.

A considerable proportion of patients with heart failure suffer from arrhythmias. Refractory arrhythmias are often treated with amiodarone: an effective drug with many side effects. The incidence of thyroid disorders after the start of amiodarone is studied in **Chapter 7**.

Since heart failure patients use a wide variety of drugs, they are at increased risk of drug interactions. NSAIDs are among the most commonly prescribed drugs in the elderly. Although these drugs are relatively safe, they can affect renal function in compromised patients. The effect of NSAIDs on renal function in patients using ACE inhibitors is studied in **Chapter 8**.

Predicting mortality

Several studies have identified factors that are associated with higher mortality in heart failure (Table 1). To our knowledge, studies that developed a comprehensive model incorporating different prognostic determinants are not available. In **Chapter 9**, a model, applicable to every-day medical practice, is developed which enables prediction of survival in patients with heart failure.

In **Chapter 10**, the results of the studies compiled in this thesis are discussed in the context of current medical practice, evidence and guidelines. Suggestions to improve management and pharmacotherapy in heart failure, for both physicians and pharmacists, are provided.

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Evidence based drug therapy?

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Patterns of pharmacotherapy in patients after first hospitalisation for heart failure

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ABSTRACT

Objective To evaluate the impact of new medical treatments for heart failure between 1990 and 1998.

Methods A retrospective cohort study of 2 764 patients with a first hospital admission for heart failure between 1990 and 1998. The percentage of patients treated with different cardiovascular drugs after hospitalisation was calculated and compared over time.

Results Use of loop diuretics remained steady around 80%, digoxin decreased from 57.6% to 42.7%, ACE inhibitors showed a slight increase from 49.8% to 54.8%, beta-blockers almost tripled from 11.3% to 28.7%, low-dose prophylactic acetylsalicylic acid (ASA) quadrupled from 9.9 to 39.9%. Kaplan-Meier survival estimates showed highest continuation rates of drug treatment for antithrombotics and diuretics, intermediate for digoxin and ACE inhibitors and low for beta-blockers. More than a quarter of the users discontinued beta-blockers in the first year after hospitalisation.

Conclusions We observed an increase in the prescribing of several important drug classes, reflecting changes in treatment guidelines during the study period. However, our findings show that not all patients were receiving optimal treatment. More research into the reasons for this is warranted.

Introduction

The 'epidemic' of increasing rates of heart failure, thought to have peaked in the mid-1990's, still remains an important cause of morbidity and mortality in the elderly today.[1-3] In the 1990's, a number of cardiovascular drugs, such as digoxin, ACE inhibitors and beta-blockers, were evaluated in randomised clinical trials. The DIG trial showed that digoxin reduced the rate of hospitalisation both overall and for worsening heart failure.[4] ACE inhibitors were shown to reduce mortality in moderate to severe heart failure patients.[5-8] Beta-blockers were also shown to provide benefit.[9-12] Treatment guidelines for heart failure were modified to include these evidence-based treatments. Despite an initial increase in the numbers of patients treated using these drugs, the dissemination of the evidence-based treatments to routine clinical practice has repeatedly been reported to be low.[13-16] Discontinuation rates among patients have been reported to be high when ACE inhibitors and beta-blockers are started, further reducing the percentage of patients receiving optimal therapy during a recommended time period.[17, 18] As an example, one third of hospitalised patients stopped taking their ACE inhibitor within 6 months of hospital discharge.[17]

There are large differences between studies examining prescriptions of drug therapy for patients with heart failure. Population-based studies have reported high rates for under-utilisation of evidence-based therapy for patients with heart failure.[13, 18-20] Hospital-based studies, especially in specialised heart centres, showed higher uptake of use of ACE inhibitors and beta-blockers.[20-24] However, as most studies of prescribing and drug utilisation in patients with heart failure are cross-sectional, they do not always present data on continuation of therapy after hospital discharge.

This study aimed to evaluate the impact of new medical treatments of heart failure on the actual pharmacotherapy patients received after a first hospital admission for heart failure between 1990 and 1998. We also described the changes in cardiovascular drug treatment before and after hospitalisation for heart failure.

Methods

Patients and data

Data were retrieved from the PHARMO record linkage system - a database containing drug-dispensing records from community pharmacies and linked hospital discharge records of a defined population of 300 000 residents of six medium-sized cities in The Netherlands.[25] We selected a cohort of 3 822 patients with at first hospitalisation for heart failure between 1990 and 1998 (ICD 428). Patients were excluded because of death during the hospitalisation (456) or because it was not possible to link hospital and pharmacy data (602; e.g. because patients did not collect their medication in the community pharmacy such as nursing home residents). Medication histories were collected from 1989 to 1999. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification.

Exposure definition

A patient was defined as a user when there was at least one prescription for any drug in the 6 months after hospitalisation for heart failure. Continuous use was defined as the presence of at least one prescription for any drug in every year after the first hospitalisation.

Analysis

We calculated the percentage of patients using several cardiovascular drugs in the 6 months after the first hospitalisation for heart failure between 1990 and 1998. Then, 3 cohorts of patients admitted between 1990 to 1992, 1993 to 1995, and 1996 to 1998 were formed.The percentages of patients using cardiovascular drugs in the 6 months before and after the first hospitalisation for heart failure and also in the years before and after the hospitalisation in the different cohorts were determined. The percentages calculated for these three cohorts are an aggregate of patients starting, continuing, discontinuing and restarting (sometimes after hospital readmission) of drugs. We used Kaplan-Meier survival estimation to evaluate continuation of drug therapy for individual patients who started drugs after hospitalisation for heart failure.All analyses were performed with Microsoft Excel 97, Microsoft Visual FoxPro 6.0 and SPSS (SPSS for Windows 10.0) software.

Results

Study population

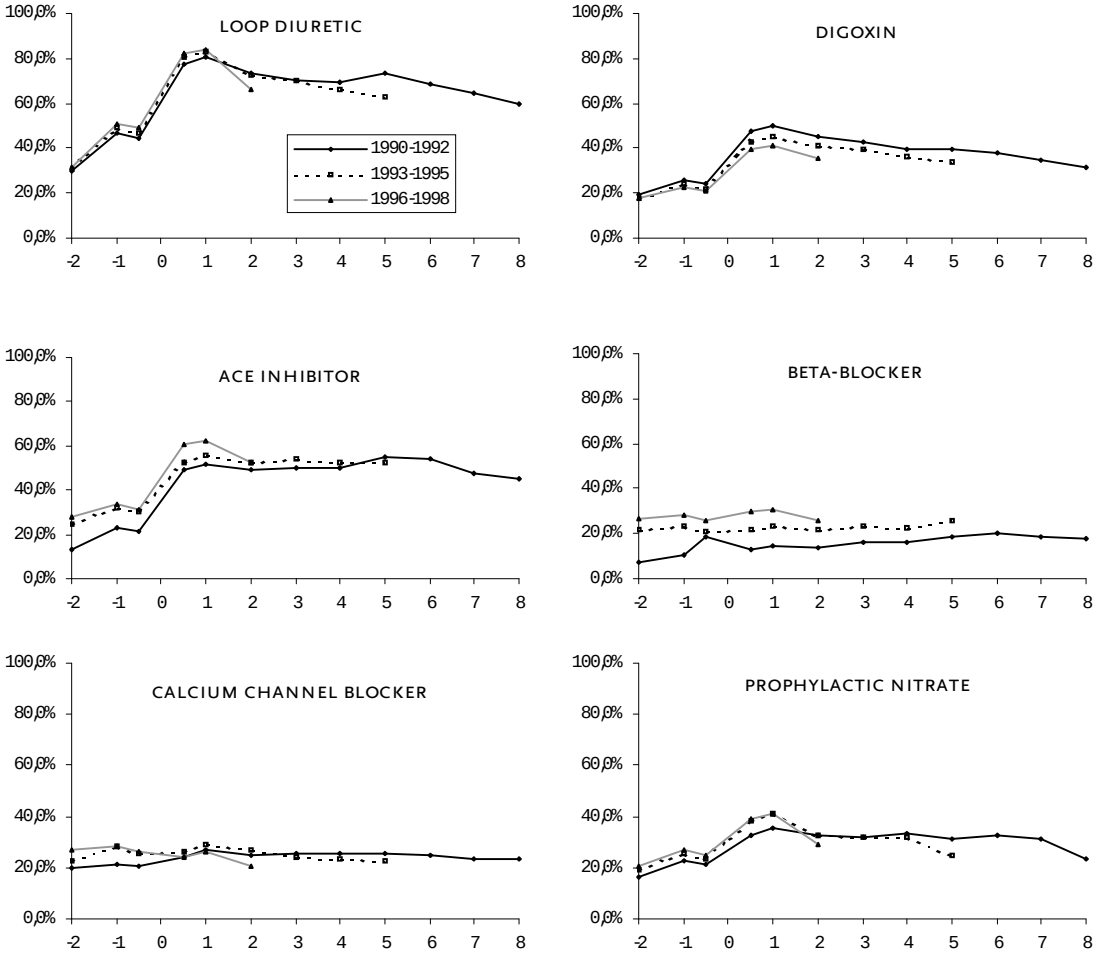
The study cohort comprised 2 764 patients with a first hospitalisation for heart failure, with 6 805 person-years of follow-up after hospitalisation (mean follow-up period 2.5 years per patient). The age and gender distribution among patients admitted to the hospital remained constant during the study period (Table 1).

Table 1. Drug treatment of patients in 6 months after hospital admission for heart failure

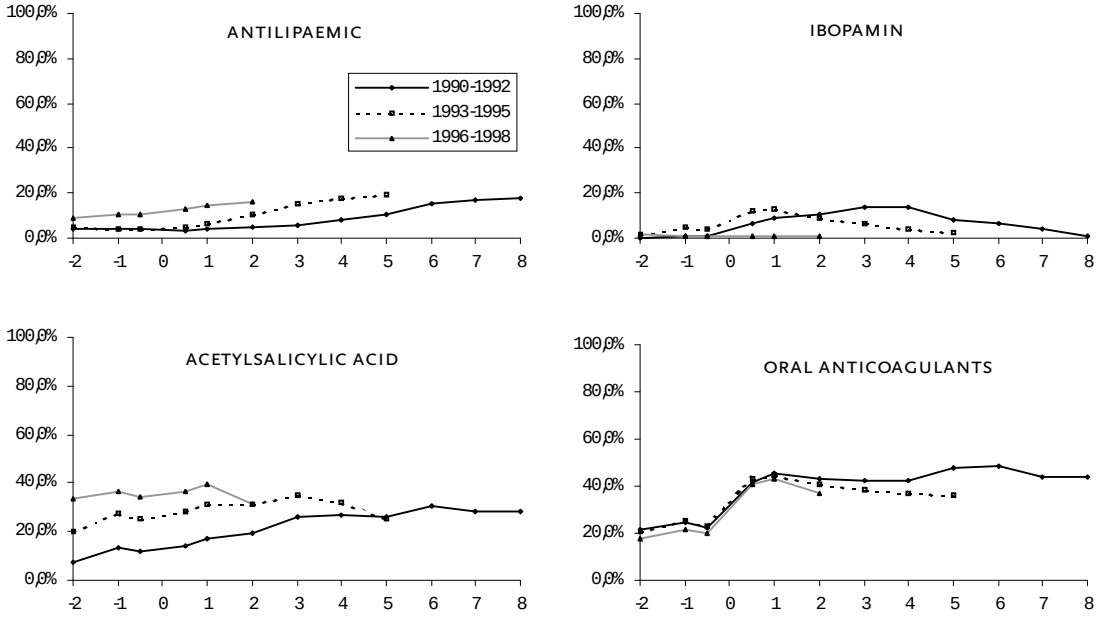
	1990	1991	1992	1993	1994	1995	1996	1997	1998
admissions (n)	283	250	291	323	288	331	300	342	356
female (%)	51.6	46.0	49.8	42.1	53.1	47.1	48.3	44.7	49.4
average age (yr)	74.4	72.6	72.0	72.5	74.3	72.3	73.0	73.1	73.6
medication (%)									
loop diuretic	79.9	74.4	74.2	74.9	82.3	79.8	78.0	80.4	80.6
ace inhibitor	49.8	43.6	50.5	47.1	51.7	54.1	63.7	59.1	54.8
aii antagonist						0.6	3.3	5.3	6.5
digoxin	51.9	42.0	45.7	37.8	43.4	44.4	40.3	37.1	37.6
beta-blocker	11.3	12.4	14.8	19.2	20.8	23.0	25.3	31.9	28.7
spironolactone	11.3	10.0	8.9	8.0	10.8	11.8	10.3	9.6	8.4
anticoagulant	34.3	38.8	49.5	40.9	43.4	41.7	44.0	36.8	39.6
low dose acetylsalicylic acid	9.9	13.2	18.6	21.1	27.8	34.4	31.7	35.4	39.9
calcium channel blocker	25.8	19.2	26.1	26.3	25.0	26.3	22.7	21.9	26.1
ibopamin	1.1	5.2	13.1	11.5	13.5	9.7	0.3	1.2	0.6
prophylactic nitrate	27.9	32.8	35.4	31.6	42.0	39.6	36.7	37.7	38.5
antilipaemic	2.1	4.4	3.8	3.7	2.8	6.3	11.0	10.8	14.9

Changes in drug treatment after hospitalisation for heart failure

Table 1 shows the changing patterns of cardiovascular drug use after hospital discharge for heart failure during the years 1990-1998. During this time, loop diuretics remained the most frequently used drugs for heart failure (80% of patients).The use of ACE inhibitors increased from 49.8% in patients in 1990 to 54.8% in 1998. Angiotensin II (AII) antagonists were first prescribed in 1995 and were used by 6.5% of patients in 1998. The use of digoxin decreased from 51.9 to 37.6% during the study period. Over this time, use of beta-blockers almost tripled from 11.3% to 28.7%. The use of oral anticoagulants increased slightly from 34.3 to 39.6% while the use of low dose prophylactic acetylsalicylic acid (ASA) nearly quadrupled from 9.9 to 39.9%. The use of calcium channel blockers remained constant at about 25%. The use of ibopamin, the only available inotropic agent for chronic use in The Netherlands, increased from 1.1 to 13.5% between 1990 and 1994 and subsequently decreased to 0.6% in 1998. The use of prophylactic nitrates (mostly isosorbidedinitrate) increased from 27.9% in 1990 to 38.5% in 1998. There was also a clear increase in the use of antilipaemics from 2.1% in 1990 to 14.9% in 1998.



Figures 1-6. Use of medication in the years before (-2, -1, -0.5) and after (0.5-8) first hospitalisation for heart failure



Figures 7-10. Use of medication in the years before (-2, -1, -0.5) and after (0.5-8) first hospitalisation for heart failure

Drug treatment before and after hospitalisation for heart failure

There was an increase in the use of ACE inhibitors, diuretics, digoxin, antithrombotics, nitrates and calcium channel blockers after hospitalisation in all three cohorts between 1990 and 1998 (Figure 1-10). Use of beta-blockers decreased between 1990 and 1992, with a slight increase thereafter. The use of antilipaemics increased over time, but was not related to the year of the hospital admission.

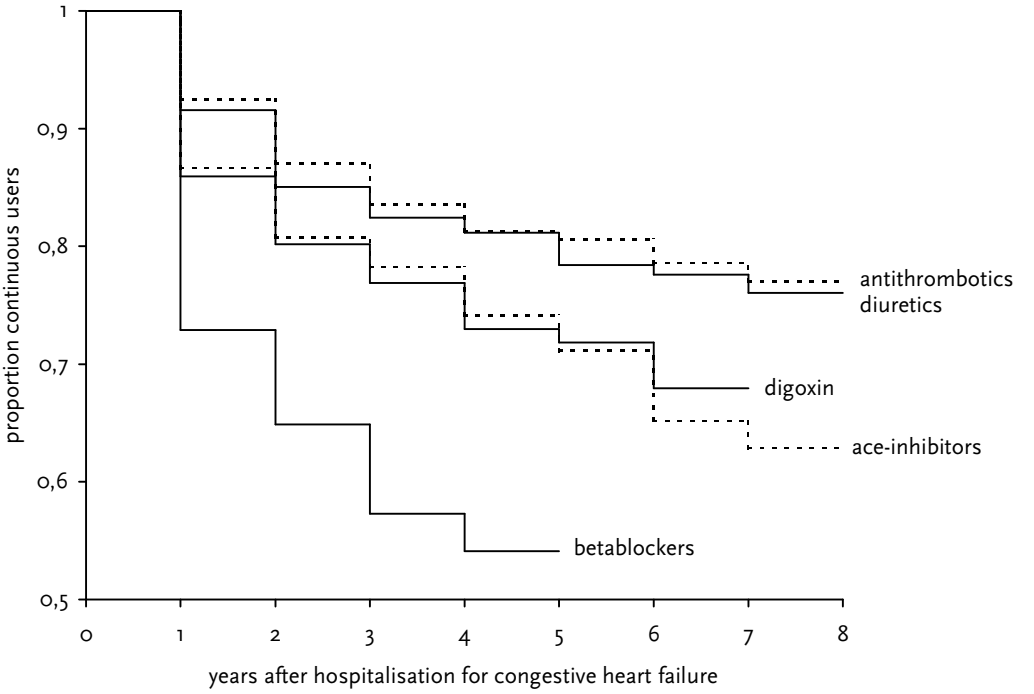


Figure 11. Long term continuation of therapy

Continuation of drug treatment started after hospitalisation for heart failure

Highest continuation rates were observed for antithrombotics and diuretics, intermediate continuation for digoxin and ACE inhibitors and low continuation patterns for beta-blockers (approximately 28% discontinued beta-blockers in the first year after hospitalisation) (Figure 11).

The definition of patients as (continuous) users when there was at least one prescription for a drug in a year may have led to some overestimation of (continuous) use since some patients did not collect enough prescriptions to cover the whole year. When we applied more strict definitions for continued

use as at least 2 and 3 prescriptions per year, this led to slightly lower percentages. Patterns, however, remained the same (data not shown).

Discussion

There have been considerable changes in the treatment of heart failure patients between 1990 and 1998; changes which are reflected in an increased number of drugs available and evidence-based guidelines to support physicians in the use of these drugs in practice. This study of the patterns of pharmacotherpay reveals that there is under-use of drugs and premature discontinuation of prescribing.

Although our results showed a slight increase in the number of heart failure patients receiving ACE inhibitors after discharge form hospital, there appeared to be a large proportion who did not receive them. This would suggest that ACE inhibitors were still not initiated in many subjects that might benefit. Strikingly the use of ACE inhibitors even showed a small decrease at the end of the 1990's when the use of AII antagonists showed a rise. This could indicate a tendency to switch patients with troublesome side effects from ACE inhibitors to AII antagonists, despite the fact that the treatment of heart failure patients with AII antagonist monotherapy is not evidence based. Our figures showed a slightly lower uptake of ACE inhibitors than other hospital-based studies.[21-24] Unlike our study, these previous studies were performed in hospitals with special interest in heart failure treatment. An alternative explanation may be that a small proportion of patients who were prescribed ACE inhibitors in our study did not fill the prescriptions they received in the hospital.

We found that the number of patients that received beta-blockers after hospital admission almost tripled, but was still low. This finding is in accordance with other studies and may be related to the fact that many elderly patients with heart failure do not tolerate beta-blockers or that physicians are reluctant to initiate beta-blockers because of the potential of initial worsening of heart failure symptoms.[26]

Digoxin has been used as a drug for more than 200 years and still remains an important drug in heart failure treatment, its use decreased only slightly over our study period.
The increase and decrease of the use of ibopamin shown in our study reflects the quick uptake and fall of this inotropic after findings of observational studies and the early stop of the PRIME II-trial.[27, 28]
The use of oral anticoagulants has always been relatively high in The Netherlands where there is a sophisticated system for monitoring international normalised ratio (INR). The increase in the use of ASA is striking, since there are no recent trials proving a mortality benefit for the use of ASA in heart failure. Observational studies, however, do support the use of ASA in heart failure.[29] Moreover it is plausible that the majority of patients with heart failure have coronary artery disease and therefore another indication for treatment with ASA
There are no studies that have proven a mortality benefit of calcium channel blockers in heart failure. Although long-acting dihydropyridines can probably be given safely to patients with heart failure who need additional treatment for angina pectoris or hypertension[30, 31], it seems unlikely that 25% of patients need calcium channel blockers.
Our study showed that hospitalisation for heart failure has a major impact on patients' medication. When we compared the use of cardiovascular drugs before and after a patient's first hospitalisation for heart failure, a steep increase in the use of several drugs was noted (Figure 1-10). The increase in drug use after hospitalisation shows the major influence of cardiologists on drug treatment in patients with heart failure.
Loop-diuretics were continued in most patients. This is probably related to the severity of heart failure; patients often need diuretics to diminish symptoms related to fluid retention.
Continuation of treatment with ACE inhibitors was higher than reported in literature[17], but we observed high discontinuation rates for beta-blockers especially in the first year of use. The reason for this may be the beta-blocker related initial worsening of heart failure symptoms.[26] Alternatively, some patients may have stopped using beta-blockers because of adverse drug

reactions. As a consequence, many patients might be denied maximum morbidity and mortality reducing therapy.
Our study was performed in patients with at least one hospitalisation for heart failure and, consequently, will have led to a selection of patients with relatively severe heart failure. This study is therefore not fully applicable to patients with less severe heart failure in the community.

Conclusion

Cardiovascular pharmacotherapy in the 1990's has been strongly influenced by hospitalisation for heart failure. Treatments using drugs with proven effect on morbidity and mortality have increased, but some drugs such as ACE inhibitors and beta-blockers, in particular, may still be under used. More research into the reasons why patients are not prescribed these drugs or discontinue using them is warranted.

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[3]

Long term therapy with spironolactone

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Abstract

Objective to evaluate the duration of therapy with spironolactone in daily practice.

Methods a retrospective follow-up of a cohort of patients with a first prescription for spironolactone between January 1, 1990 and December 31, 1996 and at least one hospital discharge for heart failure in the preceding year.

Results 243 patients met the inclusion criteria and were followed until the end of data collection. The average starting dosage of spironolactone was 55 mg. 143 patients (58.8%) discontinued spironolactone therapy before the end of follow-up. 98 patients (40.8%) discontinued within 6 months of follow-up. Of the 137 patients (56.4%) who did use spironolactone and an ACE inhibitor concomitantly, only 45 (32.8%) continued this combination until the end of follow-up. The remainder of the patients discontinued either the ACE inhibitor (10.9%) or spironolactone (12.4%) or both (43.8%).

Conclusion while the reasons for discontinuation remain unclear, our data suggest that it is difficult to keep patients on spironolactone, in particular when combined with ACE inhibitors. It is not certain whether these findings from past spironolactone use can be extrapolated to future use. Patients in the general population received higher average spironolactone dosages compared to the RALES study (55 mg vs. 26 mg), possibly resulting in more adverse effects and partly explaining the high discontinuation rate.

Introduction

In August 1999 the results of the Randomised Aldactone Evaluation Study (RALES) were released electronically ahead of a publication in the New England Journal of Medicine on September 3 1999.[1] RALES was an adequately designed trial to study the effects of spironolactone in patients with heart failure. It suggested that patients with advanced heart failure should preferably be treated with an Angiotensin Converting Enzyme (ACE) inhibitor in combination with spironolactone.

This publication was accompanied by extensive media coverage and led to an increase in spironolactone prescriptions in patients with severe congestive heart failure.

The study results suggested that patients benefit mainly from long-term use of spironolactone (mean follow-up in RALES was 24 months). However, spironolactone use has both bothersome (e.g. gynaecomastia; 10% of men in RALES) and serious (e.g. hyperkalemia and renal disturbances) side effects. Notably the combination with ACE inhibitors can lead to severe hyperkalemia and renal dysfunction.[2] In RALES, patients with already high serum potassium or creatinine were excluded. Moreover serum potassium and kidney function was measured every 4 weeks during the first 12 weeks and every 3 months thereafter for up to 1 year. Literature also suggests that a combination of ACE inhibitors and spironolactone is feasible provided that renal function is normal and serum potassium concentration is closely monitored.[3] Patients using this combination might develop serious renal dysfunction and hyperkalemia when they are not monitored regularly. This could lead to premature termination of therapy. Furthermore, discontinuation rates of new therapies and especially cardiovascular medications in the general population are reported to be high.[4-6] This could also contribute to a sub-optimal duration of therapy with spironolactone.

Indications for the favourable effects of spironolactone in patients with heart failure has been available for several years.[7-9] Therefore spironolactone was already used in patients with advanced heart failure (e.g. NYHA class III-IV), matching the study population of RALES. We studied a cohort of heart failure

patients who received a first prescription for spironolactone in order to evaluate the duration of spironolactone therapy in these patients.

Methods

Data were used from the PHARMO ongoing record linkage system, a database containing drug dispensing records from community pharmacies and linked hospital discharge records of a defined 300 000 residents population of 6 medium-sized cities in The Netherlands.[10]

Medication histories and hospital data were collected from 1990 to 1999. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification.[11] Hospital discharge records were coded according to the International Classification of Diseases, 9th Edition (ICD-9). Clinical modification codes were also utilised.

We included a cohort of patients with a first-time prescription for spironolactone in the period from January 1, 1990 until December 31, 1996 and at least one primary hospital discharge for heart failure in the preceding year. We detected 2,024 patients with a primary hospital discharge for heart failure. Of these patients 316 received a prescription for spironolactone within one year after hospital discharge. Of the latter we had a follow-up of at least 6 months for 243 patients. These 243 patients were followed until the end of data collection (June 30, 1999) or until their disappearance from the database, indicating a move to a city outside the scope of PHARMO, institutionalisation or death.

The discontinuation of spironolactone or ACE inhibitors was defined as the absence of dispensing of either spironolactone or an ACE inhibitor by the pharmacist, in the presence of other drug-dispensing for at least 6 months. Duration of therapy was determined by dividing the number of dispensed doses by the dosage regimen. A simultaneous start was defined as the start of an ACE inhibitor and spironolactone on the same day.

Table 1. Comparison of characteristics of patients in this study with the RALES population

	THIS STUDY	RALES
STUDY DESIGN	OBSERVATIONAL	RANDOMISED CONTROLLED TRIAL
SETTING	THE NETHERLANDS	195 CENTRES IN 15 COUNTRIES
NO. OF PATIENTS RECEIVING SPIRONOLACTONE	243	822
SEX		
MALE	123 (50.6%)	603 (73%)
FEMALE	120 (49.4%)	219 (27%)
AVERAGE AGE	72.6 YR.	65 YR.
AGE DISTRIBUTION		
<-60	24 (9.9%)	NOT GIVEN
60-70	56 (23.0%)	
70-80	99 (40.7%)	
80-90	64 (26.3%)	
CO-MEDICATION AT START OF SPIRONOLACTONE		
LOOP DIURETICS	231 (95.0%)	100%
ACE INHIBITORS	146 (60.1%)	95%
DIGOXIN	127 (52.3%)	75%
ACETYLSALICYLIC ACID	49 (20.2%)	36%
ORAL ANTICOAGULANTS	134 (55.1%)	NOT GIVEN
POTASSIUM SUPPLEMENTS	22 (9.1%)	29%
BETA-BLOCKERS	40 (16.5%)	11%

Results

We identified 243 patients meeting the inclusion criteria. Basic characteristics of the patients are given in Table 1. Patients were predominantly older than 70 years. There was an equal distribution among sexes and a broad use of co-medication.

We found that 143 patients (58.8%) discontinued spironolactone therapy before the end of follow-up (Table 2). 98 patients (40.8%) discontinued within 6 months of follow-up.

Furthermore, we saw that 106 patients (43.6%) received no ACE inhibitor prescription together with spironolactone. Of the 137 patients (56.4%) who did use spironolactone and an ACE inhibitor concomitantly, only 45 (32.8%) continued this combination until the end of follow-up. The remainder of the patients discontinued either the ACE inhibitor (10.9%) or spironolactone (12.4%) or both (43.8%).

Table 2. Follow-up of patients with severe heart failure who were prescribed spironolactone between 1990-1996

	N=243
use of spironolactone continued until end of follow-up	100 (41.2%)
average duration of spironolactone use	304 days
use of spironolactone discontinued before end of follow-up	143 (58.8%)
average duration of spironolactone use	208 days
spironolactone dose at first prescription	
25 mg	60 (24.7%)
50 mg	117 (48.2%)
100 mg	66 (27.2%)
did not use an ACE inhibitor at the start of spironolactone	86 (35.4%)
ACE inhibitor use at start of spironolactone therapy	(N=137)
started ACE inhibitor simultaneously with spironolactone	11 (4.5%)
continued ACE inhibitor at the start of spironolactone	126 (51.9%)
discontinued ACE inhibitor at the start of spironolactone	20 (8.2%)
continued use of ACE inhibitors and spironolactone until end of follow-up	45 (32.8%)

Discussion

Basic characteristics of the patients were slightly different from the RALES population. Patients were older and our cohort consisted of a higher percentage of women (Table 2). The differences in basic characteristics may be due to the fact that heart failure patients admitted to clinical trials tend to be relatively young healthy men.[12] Differences in medication use can be partly explained by regional differences.[13]

The use of loop diuretics and ACE inhibitor was an inclusion criterion in RALES. It is therefore not surprising that this use is higher than in our study. Use of acetylsalicylic acid was lower in our population. However a large proportion of our population were using oral anticoagulants.

The relatively high use of oral anticoagulants can be attributed to the highly organised form of International Normalised Ratio (INR) monitoring in The Netherlands. Striking is also the high use of potassium supplements in RALES. This could indicate some selection of patients with a tendency to hypokalemia in RALES.

With nearly 60% of patients discontinuing spironolactone, our data suggest that it is difficult to maintain patients on this drug, in particular in combination with ACE inhibitors. In RALES only 214 (26%) patients discontinued spironolactone. A partial explanation for the higher discontinuation rate we find could be that patients in our population received higher average spironolactone dosages compared to RALES (55 mg vs. 26 mg), possibly resulting in more adverse effects.

Although our data do not provide the reasons for discontinuation, we suspect that patients in the general population do not receive the same amount of monitoring and follow-up as patients in RALES. Close monitoring has been shown to be important in the management of heart failure patients.[14, 15] Serum creatinine- and potassium monitoring is recommended for spironolactone users.[16] Emphasis on monitoring of patients with heart failure is crucial, especially for the success of adding spironolactone to therapy in clinical practice. The fact that in daily practice a relatively older population seems to be exposed to these drug-combinations makes monitoring even more important. Besides monitoring electrolytes and renal function, attention

should also be given to other reasons for patients' discontinuations, such as perceived adverse reactions, patient attitudes to medication, lack of social support and treatment beliefs.[17]

Conclusion

Currently there are three major classes of drugs available that have been shown to reduce morbidity and mortality in heart failure patients: ACE inhibitors[18], beta-blockers[19] and spironolactone.[1] The use of these drugs in combination with a wide variety of medications necessitates close monitoring and an individual approach to patient therapy. Health professionals should be aware of this need for attention in heart failure patients. Pharmacists might play a helpful role in this process.[20] Further research – at least in The Netherlands – is needed to monitor the actual use of these drugs in the general population with heart failure.

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[4]

Underutilisation of evidence-based treatment: women with angina pectoris receive less antiplatelet treatment than men

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Abstract

In a study investigating the prevalence of underprescription of platelet therapy for women with angina pectoris, the complete medication histories of patients were examined and indicators of possible comorbidity and comedication were recorded. A higher percentage of women than men were not treated with any form of antithrombotic treatment (37% versus 18%), suggesting a serious, and possibly hazardous, undertreatment with acetylsalicylic acid (ASA) in women compared with men.

Introduction

Ischemic Heart Disease (IHD) is the leading cause of mortality in the industrialized countries. The incidence of IHD, especially among women, has been rising gradually in the past 10 years.[1] Despite this, several studies have shown a relative under-use of proven effective medical therapy among older and female patients with IHD, possibly owing to a perceived lower risk of serious cardiovascular events for these patients.[2-6] The underprescription of antiplatelet therapy with acetylsalicylic acid (ASA) in the secondary prevention of IHD could lead to preventable increased morbidity and mortality among women and elderly. Underutilisation of ASA can cause unnecessary myocardial ischemia and impaired ventricular function, ultimately leading to symptomatic heart failure. This study investigates the prevalence of antiplatelet treatment in patients diagnosed with angina pectoris.

Methods

Patients from four separate pharmacies, treated by 28 different general practioners (GPs) were included. Of the 28 GPs, 13 were female and 14 were active in group practices: this is not unrepresentative for The Netherlands. All 368 patients from practices with participating GPs given multiple nitrate prescriptions in 1996 and/or a code for angina pectoris in the patient database shared by the physician and the pharmacist were included. The patients' physician confirmed the diagnosis of angina pectoris in 346 (94.0%) cases and only these patients were included in the study. Complete medication histories of the patients were available and we investigated whether patients were being treated with antiplatelet agents at the end of the inclusion period. Indicators of possible comorbidity and comedication were recorded from the medication histories.

A proportion of patients with angina pectoris received anticoagulants for other indications (e.g. myocardial infarction or atrial fibrillation). In these patients antiplatelet drugs are not indicated, therefore these patients were analysed separately. We compared patients cases (patients not treated with antiplatelets or anticoagulants) with controls (patients receiving antiplatelet treatment) in a case-control design. We calculated odds ratios on the association between patients' co-factors and lack of treatment with antiplatelet agents. Multiple logistic regression was used to adjust for possible confounding factors.

Results

Of 346 patients with a diagnosis of angina pectoris, a total of 66 (19.1%) were treated with anticoagulants (either phenprocoumon or acenocoumarol; 6 in combination with low dose ASA) and 189 (54.6%) with low dose ASA (30-250 mg/day). A significantly higher percentage of women versus men was not treated with any form of antithrombotic treatment 37.7% vs 18.0%.
Table 1 shows possible co-factors associated with non-treatment with antiplatelet drugs. After adjustment using logistic regression including all factors mentioned in Table 1, female sex remained significantly associated with lack of treatment with antiplatelet agents, resulting in a 2.5-fold increased risk. In a separate analysis we found approximately the same difference in the use of anticoagulants. The lower usage of antiplatelet drugs wasn't explained by an increased use of anticoagulants.
Further adjustment for the presence of diabetes, a risk factor for IHD with a twofold higher incidence in women or the presence of asthma/COPD which could be a contra-indication for prescribing ASA, did not influence the results. Cholesterol lowering agents also seemed to be used less frequently by women (p=0.06) (data not shown). There was a trend for a lower use of ASA in the elderly, although this was not statistically significant after adjustment.

Table 1. factors associated with non-treatment with antiplatelet therapy in 346 patients diagnosed with angina pectoris

	all patients (n=346) n (%)	no anti-thrombotics (n=91) n(%)	asa (n=189) n(%)	anti-coagulant (n=66) n(%)	no treatment versus asa	
					unadjusted or [ci 95%]*	adjusted* or [ci 95%]
male	200 (57.8)	36 (39.6)	125 (66.1)	39(59.1)	ref.	ref.
female	146 (42.2)	55 (60.4)	64 (33.9)	27(40.9)	3.0 [1.8-5.0]	2.5 [1.4-4.4]
age (year)						
<-59	68 (19.6)	9 (9.9)	48(25.4)	11(16.7)	ref.	ref.
60-74	150 (43.4)	37 (40.7)	82 (43.4)	31(47.0)	2.4 [1.1-5.4]	1.8 [0.8-4.4]
75->	128 (37.0)	45 (49.5)	59 (31.2)	24(36.4)	4.1 [1.8-9.2]	2.2 [0.9-5.5]
comorbidity						
diabetes	52 (15.0)	14 (15.4)	20 (10.6)	18 (27.3)	1.5 [0.7-3.2]	1.6 [0.7-3.5]
asthma/copd	35 (10.1)	12 (13.2)	17 (9.0)	6 (9.1)	1.5 [0.7-3.4]	1.7 [0.7-4.1]
other medication						
nitrate (rescue)	208 (60.1)	44 (48.4)	117 (61.9)	47 (71.2)	0.6 [0.3-1.0]	0.6 [0.3-1.0]
nitrate (maintenance)	142 (41.0)	35 (38.5)	77 (40.7)	30 (45.4)	0.9 [0.5-1.5]	0.9 [0.5-1.6]
beta-blocker	137 (39.6)	31 (34.1)	79 (41.8)	27 (40.9)	0.7 [0.4-1.2]	0.9 [0.5-1.6]
digoxin	38 (11.0)	5 (5.5)	15 (7.9)	18 (27.3)	0.7 [0.2-1.9]	0.7 [0.2-2.3]
diuretic	113 (32.7)	28 (30.8)	48 (25.4)	37 (56.1)	1.3 [0.8-2.3]	1.1 [0.5-2.1]
ace inhibitor	98 (28.3)	21 (23.1)	42 (22.2)	35 (53.0)	1.0 [0.6-1.9]	0.9 [0.5-1.9]
calcium channel blocker	138 (39.9)	32 (27.5)	79 (41.8)	27 (40.9)	0.8 [0.5-1.3]	0.9 [0.5-1.5]
antilipaemic drug	101 (29.2)	11 (12.1)	66 (34.9)	24 (36.4)	0.3 [0.1-0.5]	0.4 [0.2-0.8]

Discussion

Preventive therapy with 80 mg ASA is included in the Dutch standards of treatment of angina pectoris for all patients. Less extensive treatment of women with IHD has been described frequently in literature.[2-6] Our results suggest that women receive less prophylactic therapy for angina pectoris compared with men.

The diagnosis of angina pectoris in general practice is subjective. Although GPs confirmed the diagnosis angina pectoris, the severity of the complaints could differ between patients. However no differences in the use of other anti-anginal drugs e.g. beta-blockers, long-acting nitrates and calcium channel blockers, were found, indicating comparable severity of disease in patients between men and women. The finding that cholesterol lowering agents (also prophylactic agents) seemed to be used less frequently by women, adds to the theory that physicians are less likely to prescribe prophylactic drugs to women with IHD. We thought that female GPs might be more likely to prescribe ASA to women. Also new standards of treatment might be accepted earlier in group practices. However, we found no association with sex of the GP, or the fact that the GP worked in a group practice, with prescribing of ASA.

Peptic ulcer disease could be a potential confounder. However, Dutch standards do not see peptic ulcer disease as an absolute contraindication for the use of low dose ASA. Furthermore as the incidence of peptic ulcer disease is higher among men compared with women, this would only strenghten our findings.

Low dose ASA for the prevention of IHD is seldom purchased over the counter in The Netherlands, owing to the fact that this drug is fully reimbursed. If some patients did purchase ASA over the counter it is highly unlikely that this behaviour wil be different between men and women, making confounding by non-prescription use unlikely.

When patients are diagnosed with angina pectoris and subsequently treated with anti-anginal medication, antiplatelet drugs should also be prescribed. This study suggest a serious and possibly hazardous undertreatment with the relatively cheap antiplatelet agent ASA in women with angina pectoris compared with men. In the long run this can lead to preventable myocardial ischemia and loss of ventricular function. Ultimately contributing to the increase in heart failure in the female population.

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Compliance in heart failure therapy

[5]

Effect of a pharmacist-led intervention on medication compliance in heart failure patients: a randomised-controlled study

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Abstract

Objective To determine the effect of a pharmacist-led intervention on medication compliance in patients with heart failure.

Design Randomised-controlled trial.

Setting 7 hospitals and 79 pharmacies in The Netherlands

Participants Patients with heart failure (predominantly NYHA II and III) treated with loop diuretics, presenting to a cardiology outpatient clinic or admitted to hospital.

Intervention 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.

Main outcome measures Primary endpoint was medication compliance, assessed with a Medication Event Monitoring System (MEMS®), an electronic pill bottle that registers time of opening. Secondary endpoints were the number of re-hospitalisations, death and quality of life.

Results 152 patients were randomised: 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 140/7,656 days without use of loop diuretics compared to 337/6,196 days in the usual care group (relative risk 0.33; CI 95% [0.24-0.38]). Two consecutive days of non-dosing occurred on 18/7,656 days in the intervention group compared to 46/6,196 days in the usual care group (relative risk 0.32; CI 95% [0.19-0.55]). There were no significant differences in re-hospitalisations, mortality and disease-specific quality of life between groups.

Conclusion 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.

Introduction

Although deaths from ischaemic 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 hospitalisation increasing the risk for readmission.[3, 4] Consequently, health care costs due to heart failure are increasing throughout much of the industrialised world.[5] Non-compliance 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 less than half could correctly name their medication, the prescribed doses and dosage intervals, and a quarter was definitively non-compliant.[9] Non-dosing, especially with loop diuretics, for even brief periods of 2-3 days, is associated with acute worsening of the clinical condition and hospital admission.[10] A two-fold risk for recurrent hospitalisations 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 re-hospitalisations 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 one 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 randomised-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.

Participants and Methods

Selection criteria

Only patients treated with loop diuretics were eligible for inclusion into the study. Patients had been admitted to one 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 and/or dementia, planned admission to a nursing home, did not take care of their own medication (e.g. filled or administered by relatives or district nurses) and/or life expectancy of less than 3 months, were excluded from the study.

Intervention program and usual care group

Cardiologists informed patients about the study. Upon written consent, investigators were notified and randomly allocated patients 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 computerised medication history was used to discuss drug use, reasons for non-compliance, 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 Medication Event Monitoring System (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. The patients filled in a questionnaire on their use of the MEMS.

Additional data collection

Hospital records were screened in order to validate patient's diagnosis and evaluate re-hospitalisations and death. Data on deaths, hospital and nursing home admissions were also collected from patient's GP. Pharmacists provided data on prescription drugs' use. In The Netherlands, pharmacy records are virtually complete due to loyalty of patients to one pharmacy.[28] At the start and end of study, patients were required to submit questionnaires on quality of life (COOP-WONCA and Minnesota Living with Heart Failure Questionnaire (MHFQ)).

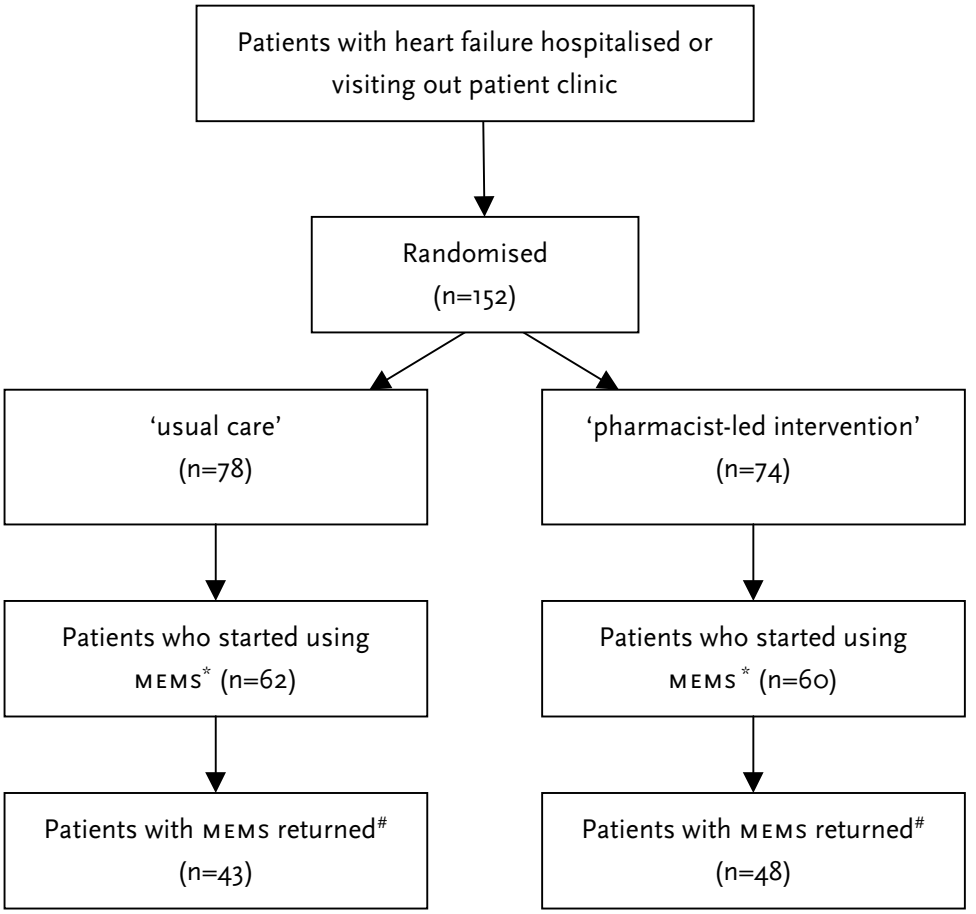

Figure 1. Flow-chart of study

*Patients did not receive 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 pre-filled medication cassette (9).

#MEMS were not returned for the following reasons: died (19), or MEMS lost (12).

Outcomes

The primary endpoint measured was medication compliance over the period that the patient used the MEMS upto a maximum period of 6 months. Non-compliance 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 non-compliance. Periods with two or more consecutive days of non-dosing were recorded separately. Secondary endpoints followed were the number of re-hospitalisations, 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-test 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-test. Multivariate logistic regression was performed to adjust for possible incomparability (despite randomisation) in prognostic factors between the intervention and usual care group. All analyses were done on an intention to treat basis, with SPSS (SPSS for Windows, 10.0) software.

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

June 1998

Mon	Tue	Wed	Thr	Fri	Sat	Sun
1	2	3	4	5	6 1	7 1
8 1	9 1	10 1	11 1	12 1	13 1	14 1
15 0	16 2	17 1	18 1	19 1	20 1	21 1
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July 1998

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August 1998

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10 0	11 0	12 1	13 1	14 0	15 1	16 1
17 1	18 2	19 1	20 1	21 0	22 1	23 1
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September 1998

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7 2	8 0	9 1	10 1	11 0	12 1	13 0
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CHRONOLOGY

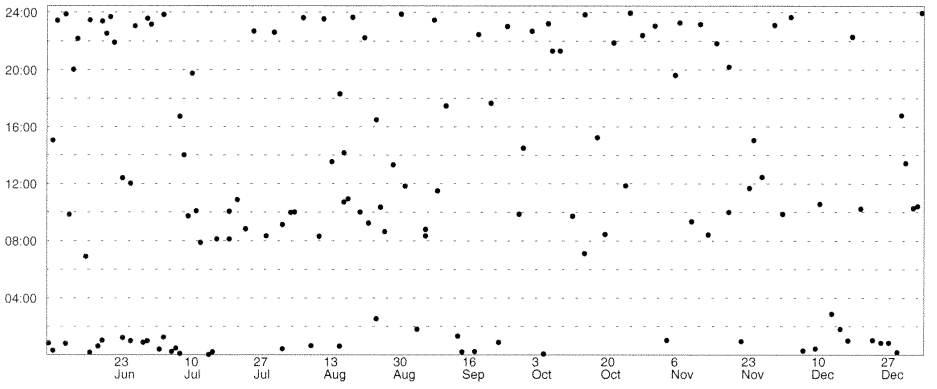

Figure 2. First example of mems compliance data

The calendar shows the number of doses taken on each day. The chronology shows the time at opening of the container. Patient in Figure 2 is taking his medication irregularly and has several days of missed dosages.

March 1999

Mon	Tue	Wed	Thr	Fri	Sat	Sun
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16 **0**	17 **2**	18 **2**	19 **2**	20 **2**	21 **2**
22 **2**	23 **2**	24 **2**	25 **2**	26 **2**	27 **2**	28 **2**
29 **2**	30 **2**	31 **2**				

April 1999

Mon	Tue	Wed	Thr	Fri	Sat	Sun
			1 **2**	2 **2**	3 **2**	4 **2**
5 **2**	6 **2**	7 **2**	8 **2**	9 **2**	10 **2**	11 **2**
12 **3**	13 **2**	14 **2**	15 **2**	16 **2**	17 **2**	18 **2**
19 **2**	20 **2**	21 **2**	22 **2**	23 **2**	24 **2**	25 **2**
26 **2**	27 **2**	28 **2**	29 **2**	30 **2**		

May 1999

Mon	Tue	Wed	Thr	Fri	Sat	Sun
					1 **2**	2 **2**
3 **2**	4 **2**	5 **2**	6 **2**	7 **2**	8 **2**	9 **2**
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17 **2**	18 **2**	19 **2**	20 **2**	21 **2**	22 **2**	23 **2**
24 **2**	25 **2**	26 **2**	27 **2**	28 **2**	29 **2**	30 **2**
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June 1999

Mon	Tue	Wed	Thr	Fri	Sat	Sun
	1 **2**	2 **2**	3 **2**	4 **2**	5 **2**	6 **2**
7 **3**	8 **2**	9 **2**	10 **2**	11 **2**	12 **1**	13 **2**
14 **2**	15 **2**	16 **2**	17 **2**	18 **2**	19 **2**	20 **3**
21 **2**	22 **2**	23 **2**	24 **3**	25 **2**	26 **2**	27 **2**
28 **2**	29 **2**	30 **2**				

CHRONOLOGY

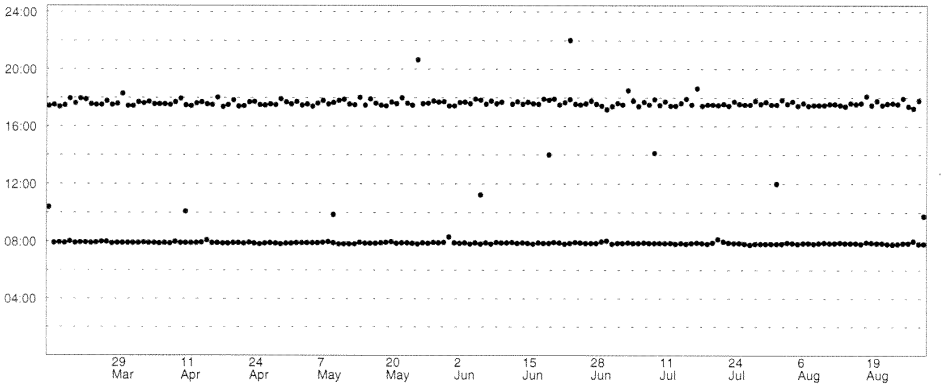

Figure 3. Second example of MEMS compliance data

The calendar shows the number of doses taken on each day. The chronology shows the time at opening of the container. Patient in Figure 3 is taking his medication very regularly at 8.00 and 17.00.

*Table 1. Baseline characteristics of participants**

	Pharmacy led intervention (n=74)	Usual care (n=78)
Age (year)	69.1±10.2	70.2±11.2
Male	53 (72)	47 (60)
NYHA class#		
I	6 (9)	7 (11)
II	22 (34)	33 (50)
III	33 (51)	24 (36)
IV	4 (6)	2 (3)
Years after diagnosis of heart failure	2.1±2.5	2.1±2.6
Co-morbidity		
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/liter)	124±39	136±64
Sodium (mmol/liter)	140±3	140±4
Potassium (mmol/liter)	4.3±0.5	4.3±0.5
Haemoglobin (mmol/liter)	8.3±0.9	8.1±1.2
Body-mass index	26±4	26±5
Systolic blood pressure (mmHg)	124±23	124±22
Diastolic blood pressure (mmHg)	73±11	76±13
Cardiovascular medication at inclusion		
ACE inhibitor	50 (68)	48 (62)
Acetylsalicylic acid or anticoagulant	65 (88)	64 (82)
AII antagonist	14 (19)	12 (15)
Antiarrhythmic	12 (16)	6 (8)
Beta-blocker	27 (37)	33 (42)
Calcium channel blocker	6 (8)	6 (8)
Antilipaemic	22 (30)	16 (21)
Digoxin	37 (50)	33 (42)
Organic nitrate	31 (42)	30 (39)
Spironolactone	28 (38)	25 (32)

* All values are numbers (percentages) ± SD.

Data on NYHA class were missing in 21 patients.

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 (Figure 1). Patients were predominantly male and NYHA class II and III. Co-morbidities and co-medication in both groups were comparable (Table 1).

Primary outcome

Examples of MEMS-data for two patients are given in Figures 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 140/7,656 days without use of loop diuretics compared to 337/6,196 days in the usual care group (relative risk 0.33; CI 95% [0.24-0.38]).

*Table 2. Compliance in patients with MEMS-data**

	PHARMACY LED INTERVENTION (N=48)	USUAL CARE (N=43)	RELATIVE RISK
MEAN AGE (YEARS)	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	7 656	6 196	
DAYS WITHOUT DOSING	140/7,656	337/6,196	0.3 [0.2-0.4]
≥ 2 CONSECUTIVE DAYS WITHOUT DOSING	18/7,656	46/6,196	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]

*All values are numbers (percentages).

Two consecutive days without use of diuretics occurred 18/7,656 days in the intervention group compared to 46/6,196 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 did not indicate the presence of such differences.

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 vs. 24.4% of patients in the usual care group were either readmitted or dead (p value > 0.05) (Table 3).

*Table 3. Morbidity and mortality in all patients during the follow-up period**

	USUAL CARE N=78	INTERVENTION N=74	RELATIVE RISK
DEATH	16 (21)	10 (14)	0.6 [0.3-1.4]
NUMBER OF PATIENTS WITH EITHER DEATH OR HOSPITALISATION FOR HEART FAILURE	19 (24)	19 (26)	1.1 [0.5-2.2]
TOTAL NUMBER OF HOSPITALISATIONS	42 (332 DAYS)	32 (465 DAYS)	P=0.4#
HEART FAILURE	15 (259 DAYS)	16 (163 DAYS)	P=0.4#
OTHER CARDIOVASCULAR DISEASE	5 (19 DAYS)	6 (132 DAYS)	P=0.7#
PLANNED READMISSION	19 (37 DAYS)	5 (25 DAYS)	P=0.4#
OTHER HOSPITAL ADMISSION	3 (17 DAYS)	5 (145 DAYS)	P=0.4#

*All values are numbers (percentages or days is hospital).

#p-values given on number of hospitalisations; p-values on number of hospital days are also > 0.05.

*Table 4. Quality of life in patients with available questionnaires**

	Pharmacy-led intervention			Usual care			p-value
	Baseline	6 months	Change#	Baseline	6 months	Change#	
	N=58	N=40	N=40	N=56	N=30	N=30	
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	0.03
MHFQ‡	40.1±21.6	33.8±22.3	-2.3±14.1	49.0±23.4	35.9±21.4	-11±22.8	0.07
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	0.07
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	0.6

*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.

†Dartmouth COOP/WONCA charts

‡Minnesota Heart Failure Questionnaire

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 medication compliance for patients with moderate to severe heart failure. Compliance was found to be unexpectedly high in both the intervention and the usual care groups (mean >90%). Other studies have suggested that non-compliance 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 specialised 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 ACE inhibitors, beta-blockers and spironolactone at baseline.

For informed consent, all eligible patients received preliminary written and oral information before entry into our study. It is possible that deliberate non-compliant patients chose not to participate. Consenting patients have been shown to be dissimilar to non-consenting patients.[31] The selection of patients with a positive attitude towards healthcare may be useful in randomised clinical trials testing new medication but dilutes the effect of more pragmatic 'care-interventions'. 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 counselling 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 two 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 to 17.1% in our study. They report 0.93 admissions/patient compared to 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 randomised nurse-led intervention study in heart failure performed in The Netherlands up to now did not find effects on 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, the fact 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 regression to the mean. 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 specialised 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 design created certain logistical 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 (Figure 1). Especially misplacement of the MEMS device by the patient occurred more frequently in the usual care group. 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.

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 non-compliance. Since 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 co-operation of the community pharmacist with other health care providers, as in this study, would be prerequisites.

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Drug induced problems in heart failure

[6]

Use of sympathomimetic drugs leads to increased risk of hospitalisation for arrhythmias in patients with congestive heart failure

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Abstract

Background Sympathomimetic agents have a direct positive chronotropic effect on heart rate and may cause hypokalaemia, even when administered by inhalation. In selected patients (e.g. patients with heart failure) this can lead to arrhythmias. Despite the potential adverse effects of these agents, they are used frequently in patients with heart failure, due to a high incidence of respiratory co-morbidity.

Objective To investigate the effects of sympathomimetics on the incidence of hospitalisations for arrhythmias in patients with heart failure.

Methods In a cohort of 1 208 patients with a validated hospital discharge diagnosis of heart failure, we identified 149 cases with a readmission for arrhythmias, and compared these in a nested matched case-control design with 149 controls from the remainder of the cohort with no hospital readmission for any cardiac cause. Conditional logistic regression was used to calculate the risk for hospitalisation for arrhythmias associated with exposure to sympathomimetic agents, expressed as odds ratios.

Results Of 149 case patients, a total of 33 (22.1%) were treated with any sympathomimetic agent, and 6 patients (4.0%) were treated with systemic sympathomimetics. The use of any sympathomimetic drug was associated with an increased risk of admission for arrhythmia (odds ratio, 4.0; CI 95% [1.0-15.1]). For systemic sympathomimetic drugs, the corresponding odds ratio was 15.7; CI 95% [1.1-228.0].

Conclusions The results of this study strongly suggest an increased risk of hospitalisation for arrhythmias in patients with heart failure treated with sympathomimetic drugs. Sympathomimetics should be given under close surveillance to patients with heart failure.

INTRODUCTION

Arrhythmias can be induced or aggravated by a variety of drugs, which include cardiotonic drugs (digoxin, sympathomimetics, and antiarrhythmics), and by drugs that lower plasma potassium levels, such as diuretics and corticosteroids. A special group comprises drugs that lengthen QT interval and can lead to induction of torsade de pointes (e.g. antihistamines, antidepressants, macrolide antibiotics, cisapride, and antipsychotics).[1]
Sympathomimetic drugs have a direct positive chronotropic effect that can promote arrhythmia. Moreover, sympathomimetics can induce hypokalaemia, further increasing the risk for arrhythmias.[2, 3] Studies on chronotropic and hypokalaemic effects of sympathomimetics have shown small but significant effects, which can even be induced by inhalation of sympathomimetics.[4, 5] At the introduction of selective β_2-sympathomimetics, a limited number of small-scale studies suggested that these drugs could be safely used in patients with chronic obstructive pulmonary disease (COPD).[6] Evidence, however, accumulates that arrhythmias due to systemic use of sympathomimetics do occur occasionally.[7, 8] Even the occurrence of arrhythmias after inhalation of sympathomimetics has incidentally been reported.
Elderly patients and patients with heart failure, renal or hepatic dysfunction, electrolyte disturbance (hypokalaemia, hypomagnesia), or a history of arrhythmias are probably more prone to the proarrhythmic effect of sympathomimetics.[10] Moreover, patients with heart failure often use diuretics. The hypokalaemic response to diuretics could be additive to that of sympathomimetics.[11, 12]
Cardiac arrest and arrhythmia are the major causes of death in patients with heart failure.[13] Despite the potential negative effects of sympathomimetics in patients with heart failure, they often receive such drugs, due to a high incidence of respiratory co-morbidity (in particular COPD). This study investigates the effects of sympathomimetics on the incidence of hospitalisations due to arrhythmias in patients with heart failure.

Patients and methods

Setting

Data were used from the PHARMO record linkage system, a database containing drug dispensing records from community pharmacies and linked hospital discharge records of a defined population of 300 000 residents of 6 medium-sized cities in The Netherlands.[14]
Medication histories and hospital data were collected from 1986 to 1992. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification. Hospital discharge records were coded according to the International Classification of Diseases, Ninth Revision (ICD-9). Clinical modification codes were used.[15]

Patients

A total of 1 208 patients with a validated hospital discharge diagnosis for heart failure were included in the study.[16] These patients were followed up for a total of 5 038 person-years (mean follow-up, 4.2 years per patient). In this cohort we identified a total of 454 readmissions for cardiac causes, including myocardial infarction, angina pectoris, arrhythmias, and heart failure. We found 149 patients with a re-hospitalisation for arrhythmias (cases). For each case, a control was sampled randomly from the remainder of the cohort who were not readmitted for any cardiac cause and matched according to follow-up time. An index date was assigned to each control matching the hospitalisation date of the case.

exposure definition

A patient was defined as exposed when there was at least 1 prescription filled for a given drug in the 3 months before hospital admission for the cases or the corresponding index date for the controls.

DATA ANALYSIS

We performed a nested case-control analysis comparing exposure in cases vs. controls. Odds ratios (ORs) were calculated for exposure to sympathomimetic agents, at the time of the hospitalisation due to arrhythmias (cases) or matched index date (controls). Conditional logistic regression techniques were applied to adjust for potential confounders. All statistical analyses were performed with Egret software (Egret for Windows, version 2.0, Cytel Software Corporation).

COVARIATES

This study was done in a group of patients with a high frequency of co-morbidity. Arrhythmia is a common complication in patients with heart failure. Left ventricular hypertrophy and local ischaemia of heart tissue may contribute to arrhythmogenic effects.
Arrhythmias frequently occur in patients with COPD. An important risk factor is the occurrence of hypoxemia in patients with COPD. An increased risk for hospital admissions for arrhythmias could therefore be related to the underlying disease instead of the use of sympathomimetics. On the other hand, sympathomimetics can also aggravate the effects of hypoxemia.[17]
In addition, a broad range of drugs could affect the occurrence of arrhythmias by direct effect on heart rate (e.g. Angiotensin Converting Enzyme (ACE) inhibitors, beta-blockers, calcium channel blockers, digoxin, antiarrhythmics, and ibopamin), blood potassium levels (e.g. ACE inhibitors, corticosteroids, diuretics, and laxatives), or QT interval (e.g. antihistaminic drugs, antidepressants, antipsychotics, macrolides, and cisapride).
We corrected for potential confounders by including the number of hospital admissions for arrhythmias, myocardial infarction, angina pectoris, asthma, and COPD in the year preceding the hospitalisation for heart failure and the use of aforementioned drugs in the 3 months prior to the hospital admission in a multiple regression model.

*Table 1. Age, gender, preceding hospitalisations and type of arrhythmias according to the use of sympathomimetic agents**

	NO SYMPATHOMIMETICS (N=248)	USE OF SYMPATHOMIMETICS (N=50)
AGE		
<-64	32 (12.9)	5 (10)
65-74	89 (35.9)	14 (28)
75->	127 (51.2)	31 (62)
MALE	109 (44.0)	37 (74)
HOSPITAL ADMISSIONS IN PRECEDING YEAR		
GENERAL	85 (34.3)	16 (32)
WITH ARRHYTHMIA	22 (8.9)	4 (8)
WITH COPD, ASTHMA OR EMPHYSEMA	3 (1.2)	8 (16)
WITH MYOCARDIAL INFARCTION	12 (4.8)	3 (6)
WITH ANGINA PECTORIS	7 (2.8)	1 (2)
TYPE OF ARRHYTHMIA DURING FOLLOW-UP†		
PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA	2 (0.8)	1 (2)
PAROXYSMAL VENTRICULAR TACHYCARDIA	15 (6.0)	0
PAROXYSMAL TACHYCARDIA	1 (0.4)	0
ATRIAL FIBRILLATION	73 (29)	25 (50)
ATRIAL FLUTTER	6 (2.4)	1 (2)
VENTRICULAR FIBRILLATION	14 (5.6)	2 (4)
CARDIAC ARREST	7 (2.8)	0
PREMATURE HEARTBEATS	2 (0.8)	3 (6)
SINO-ATRIAL KNOT DYSFUNCTION	1 (0.4)	1 (2)
CARDIAC DYSRYTHMIA	6 (2.4)	2 (4)
CARDIAC DYSRYTHMIA, NOS.	2 (0.8)	0

*Values are number (percentage) of patients.

The observation period for the no sympathomimetics group was 414 days and for the sympathomimetics group was 535 days.

COPD indicates chronic obstructive pulmonary disease; NOS. indicates not otherwise specified

†The total number of arrhythmias exceeds 149, because of multiple types of arrhythmia during one hospital admission.

*Table 2. Co-medication according to the use of sympathomimetic agents**

	NO SYMPATHOMIMETICS (N=248)	USE OF SYMPATHOMIMETICS (N=50)
SYSTEMIC CORTICOSTEROID	7 (2.8)	6 (12)
INHALATION CORTICOSTEROID	5 (2.0)	18 (36)
DIGOXIN	109 (44.0)	33 (66)
ORAL ANTICOAGULANT	127 (51.2)	17 (34)
VERAPAMIL OR DILTIAZEM	44 (17.7)	13 (26)
DIHYDROPYRIDINE	29 (11.7)	6 (12)
ACE INHIBITOR	119 (48.0)	21 (42)
BETA-BLOCKER	30 (12.1)	5 (10)
IBOPAMIN	8 (3.2)	1 (2)
LAXATIVE	22 (8.9)	9 (18)
ANTIARRHYTHMIC	26 (10.5)	6 (12)
THIAZIDE DIURETIC	2 (0.8)	1 (2)
THIAZIDE + POTASSIUM SPARING DIURETIC	32 (12.9)	5 (10)
LOOP DIURETIC	171 (69.0)	35 (70)
POTASSIUM SPARING DIURETIC	53 (21.4)	11 (22)
NITRATE	118 (47.6)	18 (36)
ANY PROARRHYTHMIC DRUG‡	14 (5.6)	3 (6)
ANTIDIABETIC DRUG	51 (20.6)	5 (10)

*Values are number (percentage) of patients. The observation period for the no sympathomimetics group was 414 days and for the sympathomimetics group was 535 days. ACE indicates angiotensin converting enzyme. ‡antipsychotic, antidepressant, antihistaminic, macrolide or cisapride)

RESULTS

Tables 1 and 2 detail the general characteristics of the study population. The majority of arrhythmias were classified as atrial fibrillation (n=98, 60%). The other frequently seen arrhythmias were ventricular tachycardia (n=15, 9%) and fibrillation (n=16, 10%). The characteristics of users of sympathomimetics differed in some aspects from patients not using these drugs (e.g. sex, use of corticosteroids, and prior hospital admissions for COPD). The following inhalation sympathomimetics were used: albuterol, 94% of all prescriptions;

and terbutaline sulfate, 6% of all prescriptions. Systemic sympathomimetics used were albuterol in 74% and terbutaline in 26%. There was only 1 nasal sympathomimetic used, which was xylometazoline hydrochloride.

Table 3. Association between use of sympathomimetic agents and risk of hospitalisation for arrhythmias

	no (%)		odds ratio (confidence interval 95%)	
	cases (n=149)	controls (n=149)	Crude	Adjusted†
current use of any sympathomimetic	33 (22.1)	17 (11.4)	2.2 [1.2-4.3]	4.0 [1.0-15.1]
systemic sympathomimetic	6 (4.0)	1 (0.7)	6.0 [0.7-49.8]	15.7 [1.1-228]
inhalation sympathomimetic	21 (14.1)	12 (8.1)	1.8 [0.9-3.8]	2.4 [0.5-13.1]
nasal sympathomimetic	2 (1.3)	1 (0.7)	2.0 [0.2-22.1]	3.5 [0.2-70.5]
theophyllin	14 (9.4)	12 (8.1)	1.2 [0.5-2.6]	1.4 [0.3-5.7]

†adjusted for age, sex, prior hospital admissions (for arrhythmia, chronic obstructive pulmonary disease, asthma, emphysema, myocardial infarction or angina pectoris) in the preceding year and concomitant use of corticosteroids, digoxin, oral anticoagulants, calcium channel blocker, ACE inhibitors, beta-blockers, ibopamin, laxatives, antiarrhythmics, (potassium-sparing) diuretics, nitrates, any proarrhythmic drugs (antipsychotic, antidepressant, antihistaminic, macrolide or cisapride), antidiabetics

Of the 149 cases 33 (22%) and of the 147 controls 17 (11%) were treated with any sympathomimetic agent, yielding a crude OR of 2.2 (CI 95% [1.2-4.3]). We adjusted for a number of possible confounders, notably, sex, age, prior hospitalisations for arrhythmia, asthma, COPD, myocardial infarction, and angina pectoris. In addition, we adjusted for the use of a broad range of drugs that may have direct proarrhythmic effects, give rise to hyperkalemia or hypokalaemia, or are markers for a history of rhythm disturbances, such as digoxin, calcium channel blocker, beta-blockers, oral anticoagulants, antiarrhythmics, ACE inhibitors, corticosteroids, laxatives, diuretics, nitrates, neuroleptics, H_1-antihistamines, antidepressants, and ibopamin. Adjusted ORs were 4.0 (CI 95% [1.0-15.1]) for the use of any sympathomimetic drug and

15.7 (CI 95% [1.1-228]) for the use of systemic sympathomimetic drugs (Table 3). Separate ORs for inhalation and nasal sympathomimetics and theophyllin were not significantly associated with hospitalisation for arrhythmia.

Discussion

Our results strongly suggest an increased risk (OR 4.0; CI 95% [1.0-15.1]) for hospitalisation for arrhythmias in patients with heart failure using sympathomimetic drugs. This risk was much higher (OR 15.7; CI 95% [1.1-228]) in patients using systemic sympathomimetics than in patients using inhalation sympathomimetics (OR 2.4; CI 95% [0.5-13.1]). Possibly due to the relative small number of patients, the risk found for the inhalation group was not statistically significant, but data suggest that use of sympathomimetics by inhalation also leads to an increase in the risk of arrhythmia.

Surprisingly, we did not find an increased risk for arrhythmias in patients taking theophyllin. This is difficult to explain, since the hypokalaemic and heart rate effects of theophyllin are well known. Perhaps, physicians are familiar with these effects and only prescribe theophyllin for low-risk patients. Moreover, theophyllin is usually prescribed as a maintenance dose, while sympathomimetics are probably more often used 'on demand'. Patients with acute dyspnea due to heart failure could overuse these bronchodilators, while they are already more susceptible to develop arrhythmias.

In this study there were no patients using long-acting sympathomimetics. Studies suggest that these drugs have systemic effects comparable to those of short-acting sympathomimetics.[18] More research on their effects in patients with heart failure is warranted.

We did not have direct data on the severity of heart failure. However, we tried to compensate for this by correcting for a variety of co-medications and previous hospitalisations that we see as 'proxies' for the severity of heart failure. After adjustment for possible confounders such as sex, age, prior hospitalisations for arrhythmia, asthma, COPD, myocardial infarction, angina pectoris, and the use of a broad range of co-medications, the OR remained increased. These findings are suggestive of a causal relation between use of

sympathomimetics and arrhythmias. We were not able to control for caffeine use, which could also be a confounder.
This study was conducted in a selected group of seriously ill patients. Use of β_2-sympathomimetics is generally safe in patients with asthma or COPD.[19] However, patients with severe cardiac co-morbidity are probably more prone to their systemic effects.
Sudden death – often due to arrhythmias – is the major cause for mortality in patients with heart failure. This study was not designed to reveal the incidence of sudden death outside the hospital. The effects of sympathomimetics could therefore even be more deleterious. In this light, it seems important to avoid every possible factor that could lead to arrhythmias in these patients. Due to the high rate of co-morbidity, the complete avoidance of sympathomimetics is often not possible. However, the necessity of the use of sympathomimetics should be evaluated critically. The beneficial effects of bronchodilators in patients with heart failure and shortness of breath should be clearly documented by pulmonary function test before these drugs are prescribed. Oral sympathomimetics should be avoided in all patients. When patients have problems with inhalation, extra attention should be given to inhalation instruction. Potassium levels should be measured regularly and the clinician should be alert for the occurrence of arrhythmias.

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[6.1]

Baseline rates of disease may account for some arrhythmia risk

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Bouvy et al[1] recently reported a link between the use of sympathomimetic agents and arrhythmias in patients with congestive heart failure. As the authors pointed out, the pharmacologic properties of sympathomimetics and the physiologic features of arrhythmias and congestive heart failure make the link not wholly unexpected. The trial was well conducted and provides useful and needed information for weighing the benefits of treating one disease with the risk of worsening another. The attributed odds ratio of 2.2 for the occurrence of arrhythmias requiring hospitalisation, however, may be a little high.

Not surprisingly, the use of sympathomimetics (albuterol and terbutaline) selected for a population with pulmonary disease. This was most evident by the fact that 48.0% of sympathomimetic users vs. 4.8% of non-sympathomimetic users were prescribed inhaled or systemic corticosteroids. While corticosteroids are increasingly used for the treatment of pulmonary disease, they remain a mainstay of therapy for asthma,[2] which may carry with it some inherent risk of arrhythmias.

Recently, asthma has been linked to the long QT syndrome, with a significantly higher prevalence among patients with longer QT intervals.[3] A strong epidemiologic link between asthma and dilated cardiomyopathy has been demonstrated,[4] as have focal conduction abnormalities in the hearts of subjects with asthma who have died suddenly.[5] Thus, while more research is needed to clarify the link between asthma and cardiac conduction abnormalities, it is becoming clear that a link does exist.

Because there were twice as many sympathomimetic users in the case group (33 patients) as compared with controls (17 patients), it is important to know if that reflected a baseline difference in the incidence of asthma between the groups. Bouvy et al[1] list that 16.0% of sympathomimetic users vs. 1.2% of nonusers were admitted for exacerbations of asthma or chronic obstructive pulmonary disease in the year preceding the trial, but baseline rates of disease in cases vs. controls are not listed. If such a difference exists, the observed odds ratio of 2.2 may partially represent a disease selection bias and not entirely a pharmacologic cause and effect.

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[6.2]

In reply

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We appreciate the valuable comments of Dr. Williams. Confounding by indication is a potential source of bias in observational studies. The overrepresentation of patients with pulmonary disease in a study may increase susceptibility for cardiac arrhythmias found in the results. In our study[1] we attempted to adjust for the severity of pulmonary disease by including the use of any corticosteroid and previous hospitalisations for pulmonary disease in the multiple regression analysis.

Williams suggests that asthma has recently been linked to the long QT syndrome and could therefore be responsible for arrhythmias resulting in readmission in our study population. In our analysis we have totalled all pulmonary conditions (International Classification of Diseases, Ninth Revision, Clinical Modification codes 491, 492, 493, 496).

Chronic obstructive pulmonary disease represented most of these conditions (8 of 11 patients); 2 patients were diagnosed as having both asthma and chronic pulmonary disease, and 1 patient had emphysema. The 2 patients with both asthma and chronic obstructive pulmonary disease had a re-hospitalisation for arrhythmias. One of them used inhalation sympathomimetic agents, and the other used only inhalation corticosteroids. These findings do not support an important independent role of asthma in the aetiology of arrhythmias in these patients.

The effects of treatment with inhalation corticosteroids in patients with chronic obstructive pulmonary disease are limited compared with the beneficial effects of inhaled corticosteroids in patients with asthma.

In The Netherlands, inhaled corticosteroids are used relatively more frequently in both chronic obstructive pulmonary disease[2] and asthma[3] than in most countries. We did not report the independent odds ratios for the use of corticosteroids, but these were not significantly increased: the odds ratio for any corticosteroid use was 1.5 (CI 95% [0.7-3.4]); for systemic corticosteroid use, 1.6 (CI 95% [0.5-5.9]); and for inhaled corticosteroid use 1.3 (CI 95% [0.5-3.4]). These odds ratios support the fact that our results are not severely biased.

We cannot rule out residual confounding completely. Because most patients with pulmonary disease will use sympathomimetics, a synergistic effect of disease and treatment cannot be excluded. In essence it does not really matter whether the increased incidence of arrhythmias is caused by sympathomimetic use only or by the effect of sympathomimetics in patients with pulmonary disease who are more susceptible to the development of arrhythmias. The conclusion remains that sympathomimetics should be used with caution in patients with heart failure.

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[7]

Amiodarone induced thyroid-dysfunction associated with cumulative dose

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Abstract

Objective To obtain risk-estimates of thyroid disorder in patients starting amiodarone.

Methods We followed a cohort of 5 522 patients with a first prescription for an anti-arrhythmic drug and no previous use of thyroid drugs. Within this cohort we conducted a nested case control analysis. Cases were defined as all patients who started a thyreomimetic or thyreostatic drug no sooner than 3 months after the start of an anti-arrhythmic drug. Controls were patients with a comparable follow-up period not receiving any thyroid drugs during the observation period.

Results We identified 123 cases that started thyreostatic drugs and 96 cases that started a thyreomimetic drug. In users of amiodarone we found an adjusted odds ratio of 6.3 (CI 95% [3.9-10.2]) for hyperthyroidism and 6.6 (CI 95% [3.9-11.1]) for hypothyroid disease compared to users of other antiarrhythmics. Patients who were exposed to a cumulative dose exceeding 144 gram of amiodarone had an adjusted odds ratio of 12.9 (CI 95% [6.1-27.3]) for the development of hyperthyroid disease. The dose response for development of hypothyroidism was less pronounced.

Conclusions We observed an increased risk for thyroid disorder on the high end of that reported in literature. The risk on thyroid disorder increased with exposure to higher cumulative doses. Clinicians should keep in mind the possibility of development of thyroid disorders in patients on treatment with amiodarone even after several years of use.

Introduction

Due to ageing of the population and decreased cardiovascular mortality in patients with acute coronary artery disease the incidence of both congestive heart failure and arrhythmias is increasing.[1-3] Sudden death is the major cause of death in patients with congestive heart failure and is frequently associated with (ventricular) arrhythmias.

Since class I antiarrhythmic drugs have proarrhythmic effects and increase mortality, amiodarone or implantable cardioverter defibrillators (ICD) are the preferred treatment for ventricular arrhythmias. Amiodarone is considered less likely to give rise to secondary arrhythmias and may especially be beneficial in patients with advanced heart failure and rapid resting heart rates. Especially patients with refractory atrial fibrillation and ventricular arrhythmias are frequently treated with amiodarone.[4] Approximately 10% of patients with congestive heart failure receive treatment with amiodarone.[5]

However several serious side effects such as pneumonitis, skin reactions, liver function abnormalities and thyroid disorders have been reported after exposure to amiodarone.[6] These toxic effects seem to be related to the total dose of amiodarone administrated.[7] Alterations in thyroid hormone metabolism during treatment with amiodarone have been reported for many years.[8]

Thyroid disorders may occur in patients with pre-existing thyroid abnormalities and in subjects with apparently normal thyroid glands.[9] Several mechanisms for amiodarone-induced thyroid dysfunction are postulated. Amiodarone is structurally related to thyroid hormones and can inhibit the conversion of thyroxin to triiodothyronine. Each molecule of amiodarone contains two atoms of iodine. Because of this high iodine content, amiodarone can inhibit thyroid hormone synthesis and secretion. Conversely, especially in regions with low intake of iodine (e.g. The Netherlands and most European countries) this high iodine content of amiodarone also leads to excessive thyroid hormone synthesis and subsequent hyperthyroidism. Inflammation is an alternative etiologic mechanism for the development of hyperthyroidism.[10]

Data on the incidence of amiodarone induced thyroid disorders are conflicting. An incidence between 4 and 20% is reported.[11-13] This variability in risk probably arises from several factors such as the duration of treatment and the cumulative dose of amiodarone. Different estimates of the risk of amiodarone induced thyroid disorders could also arise from the fact that some studies counted all patients with thyroid-hormones elevations, while other studies only counted patients with clinical manifestations of thyroid disorder. This study aims to obtain reliable risk estimates on amiodarone induced thyroid disorders in a large cohort of patients with a long follow-up period.

Patients and Methods

Patients and data

Data were retrieved from the PHARMO record linkage system, a database containing drug dispensing records from community pharmacies and linked hospital discharge records of a defined population of 300 000 residents of 6 medium-sized cities in The Netherlands.[14] Medication histories were collected from 1986 to 1999. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification.

We selected a cohort of 17 228 patients with at least one prescription for an antiarrhythmic drug (ATC-code C01AA01-C01AX99 (digoxin and related drugs), C01BA01-C01BX99 (other antiarrhythmics) or C07AA07 (sotalol)). Patients with a follow-up of less than 1 year, less than 180 days use of antiarrhythmics and a history of thyreostatic or thyreomimetic drugs in the year before the start of the anti-arrhythmic drug were excluded from the cohort. The remaining study cohort consisted of 5 522 patients representing 21 730 person-years of follow-up (mean follow-up period 3.9 years). Within this cohort a nested case-control analysis was performed.

cases and controls

Patients receiving a prescription for a thyreostatic drug (carbimazole, thiamazole or propylthiouracil) with or without a simultaneous or succeeding prescription for a thyreomimetic drug, were considered treated for hyperthyroidism. Patients receiving a thyreomimetic drug (levothyroxine or triiodothyronine) without a simultaneous or preceding thyreostatic drug were considered treated for hypothyroid disorder. Patients, within the cohort of patients receiving antiarrhythmics, who did not receive any thyroid-drugs served as controls. The date of the start of a thyreostatic or thyreomimetic drug was the index date of the cases. We assigned an index date to controls comparable to the calculated average time in the follow-up of the cases.

Exposure definition

A patient was defined as a current user when there was at least one prescription for amiodarone filled in the 3 months before the start of the use of a thyroid drug. To assess the presence of a dose response relationship we calculated the total amount of amiodarone dispensed to the patient before the start of a thyroid drug. The average maintenance dose of amiodarone was 200 mg. We therefore categorised exposure into less than 72 gram (less than 360 tablets of 200 mg; i.e. approximately 1 year of use), between 72 and 144 gram (between 360 and 720 tablets of 200 mg; i.e. between 1 and 2 years of use) and more than 144 gram (more than 720 tablets of 200 mg; i.e. more than 2 years of regular use).

Data analysis

We performed a nested case-control analysis comparing exposure in cases versus controls. Odds ratios were calculated for exposure to amiodarone before the start of the use of a thyroid drug (cases) or matched index date (controls). We calculated odds ratios both for current and prior use of amiodarone. Multivariate unconditional logistic regression analysis was performed to adjust for potential confounders such as age, sex and anti-arrhythmic co-medication.

Kaplan-Meier survival curves were depicted to express the percentage of amiodarone treated patients in whom treatment for either hyperthyroid or hypothyroid disease was initiated as a function of time.
All statistical analyses were performed with Egret (Egret for Windows, 2.0) and SPSS (SPSS for Windows, 10.0) software.

Results

In the cohort of 5 522 patients exposed to any anti-arrhythmic drug we identified 123 cases that started thyreostatic drugs (carbimazole, thiamazole or propylthiouracil with or without a thyreomimetic drug) and 96 cases that started a thyreomimetic drug (levothyroxine or triiodothyronine, without a thyreostatic drug).

Hyperthyroid disease

The use of amiodarone was associated with an increased risk for hyperthyroidism; crude odds ratio 4.9 (CI 95% [3.0-7.8]), adjusted odds ratio 6.3 (CI 95% [3.4-8.4]). In patients who were exposed to more than 144 gram (720 doses of 200 mg) the adjusted odds ratio was 12.9 (CI 95% [6.1-27.3]) (Table 1). 3.5 years after initiation of amiodarone therapy almost 13% of patients had developed hyperthyroidism. Most patients develop hyperthyroidism between 2 and 3 years after the start of amiodarone (Figure 1).
Since the incidence of hyperthyroid disease is higher for women, we stratified for gender (Table 1). The crude odds ratios for men and women were comparable, although slightly higher in men than women (6.8 vs. 4.6). However we did not find a dose response relationship in women and a very clear dose response relationship in men (Table 1).

Table 1. Association between use of amiodarone and risk of hyperthyroid dysfunction

	cases (n=123)		controls (n=5 303)		crude OR [ci 95%]	adjusted OR* [ci 95%]
current use of amiodarone	24	19.5%	250	4.7%	4.9 [3.0-7.8]	6.3 [3.9-10.2]
prior use of amiodarone	28	22.8%	328	6.2%	4.5 [2.8-7.1]	5.4 [3.4-8.4]
total use < 72 gram	10	8.1%	171	3.2%	3.1 [1.5-6.3]	3.4 [1.7-6.8]
total use 72-144 gram	8	6.5%	100	1.9%	4.2 [1.8-9.2]	4.9 [2.2-10.5]
total use >144 gram	10	8.1%	57	1.1%	9.2 [4.3-19.3]	12.9 [6.1-27.3]
stratified for gender						
female	88	71.5%	2 559	48.3%	ref.	ref.
current use of amiodarone	11	12.5%	78	3.0%	4.5 [2.2-9.2]	4.8 [2.4-9.5]
prior use of amiodarone	15	17.0%	109	4.3%	4.6 [2.4-8.6]	4.9 [2.7-8.9]
total use < 72 gram	7	8.0%	58	2.3%	4.0 [1.6-9.6]	4.0 [1.8-9.2]
total use 72-144 gram	6	6.8%	34	1.3%	5.9 [2.2-15.3]	6.7 [2.6-16.9]
total use >144 gram	2	2.3%	17	0.7%	3.9 [0.6-18.3]	4.4 [1.0-19.9]
male	35	28.5%	2 744	51.7%	0.4 [0.2-0.6]†	0.3 [0.2-0.5]†
current use of amiodarone	13	37.1%	172	6.3%	8.8 [4.1-18.7]	8.2 [4.0-16.9]
prior use of amiodarone	13	37.1%	219	8.0%	6.8 [3.2-14.4]	6.2 [3.0-12.6]
total use < 72 gram	3	8.6%	113	4.1%	2.7 [0.7-10.9]	2.7 [0.8-9.2]
total use 72-144 gram	2	5.7%	66	2.5%	3.5 [0.6-15.7]	3.5 [0.8-15.5]
total use >144 gram	8	22.9%	40	1.5%	20.6 [8.8-58.4]	20.7 [8.4-51.2]

*Adjustment was made by multivariate logistic regression. Model contained gender, age, prior use of digoxin, sotalol, or any other anti-arrhythmic.

†male vs. female

Hypothyroidism

The use of amiodarone was associated with an increased risk for hypothyroidism as well; crude odds ratio 5.7 (CI 95% [3.4-9.4]), adjusted odds ratio 6.6 (CI 95% [3.9-11.1]). Unlike the development of hyperthyroidism we could not find a clear association between the total exposure to amiodarone (in gram) and the risk for developing hypothyroid disease (Table 2).

Table 2. Association between use of amiodarone and risk of hypothyroid dysfunction

	cases		controls		crude OR	adjusted OR*
	(N=96)		(N=5 303)		[CI 95%]	[CI 95%]
current use of amiodarone	21	21.9%	249	4.7%	5.7 [3.4-9.4]	6.6 [3.9-11.1]
prior use of amiodarone	23	23.9%	336	6.3%	4.7 [2.9-7.5]	5.0 [3.0-8.3]
total use < 72 gram	7	7.3%	163	3.1%	2.9 [1.2-6.4]	3.2 [1.4-7.1]
total use 72-144 gram	10	10.4%	97	1.8%	6.9 [3.5-13.8]	8.5 [4.2-17.5]
total use >144 gram	5	5.2%	74	1.4%	4.5 [1.8-11.5]	4.8 [1.9-12.5]
Stratified for gender						
Female	66	68.8%	2 559	48.3%	ref.	ref.
current use of amiodarone	11	16.7%	83	3.2%	6.0 [2.8-12.3]	6.3 [3.2-12.7]
prior use of amiodarone	12	18.2%	114	4.5%	4.8 [2.3-9.5]	5.0 [2.6-9.8]
total use < 72 gram	4	6.1%	59	2.3%	3.1 [0.9-9.2]	3.4 [1.2-9.7]
total use 72-144 gram	6	9.1%	27	1.1%	10.1 [3.6-27.0]	10.6 [4.1-27.4]
total use >144 gram	2	3.0%	28	1.1%	3.2 [0.5-14.5]	3.3 [0.8-14.4]
Male	30	31.3%	2 744	51.7%	0.4 [0.3-0.7]†	0.3 [0.2-0.5]†
current use of amiodarone	10	33.3%	166	6.0%	7.8 [3.3-17.8]	7.4 [3.4-16.5]
prior use of amiodarone	10	33.3%	220	8.0%	5.7 [2.5-13.1]	6.0 [2.8-13.0]
total use < 72 gram	3	10.0%	104	3.8%	3.6 [0.8-13.2]	3.2 [0.9-10.9]
total use 72-144 gram	4	13.3%	70	2.6%	7.2 [2.0-23.1]	7.0 [2.3-21.4]
total use >144 gram	3	10.0%	46	1.7%	8.2 [1.9-30.7]	7.6 [2.1-27.0]

*Adjustment was made by multivariate logistic regression. Model contained gender, age, prior use of digoxin, sotalol, or any other anti-arrhythmic.

†male vs. female

4 years after initiation of amiodarone therapy approximately 10% of patients had developed hypothyroidism. Most patients developed hypothyroidism within 2 years (Figure 1).
Since the incidence of hyperthyroid disease is higher for women, we stratified for gender (Table 2). The crude odds ratios for men and women were comparable, although slightly higher in men than women (7.4 vs. 6.3). The data showed a tendency to develop hypothyroid disease at higher exposure to amiodarone in men (Table 2).

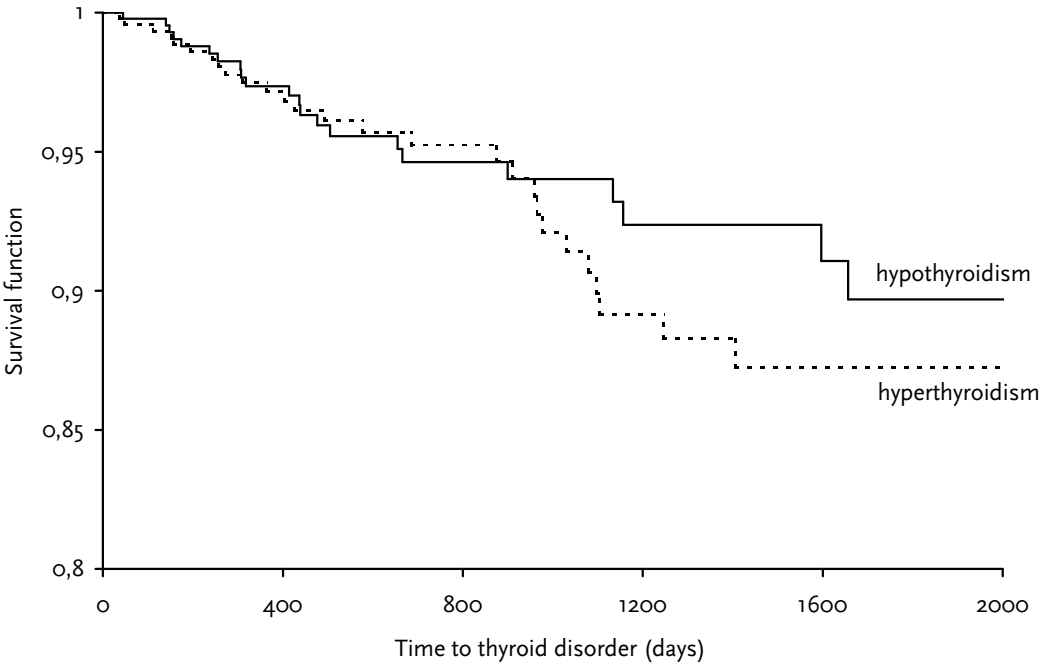

Figure 1. Time to thyroid disorder

Discussion

In this study we found an increased risk of 6.3 (CI 95% [3.9-10.2]) for hyperthyroidism and 6.6 (CI 95% [3.9-11.1]) for hypothyroid disease comparing current users of amiodarone with users of other antiarrhythmics. Moreover, the results show a very clear relationship between the total exposure to amiodarone and the development of hyperthyroid disorder.

Although conventional pharmacological therapy (synthetic (anti)thyroid drugs) is not always effective in amiodarone induced thyroid disease, all patients will initially be treated with pharmacotherapy.[15] So this should not underestimate the presented risk. The use of these drugs as an indicator of hyper- or hypothyroid disease seems therefore appropriate. However since amiodarone induced thyroid disorders can be subclinical and will not always be recognised, this study only reveals cases that are treated for thyroid disorders. We therefore underestimated the absolute risk for thyroid disorders, but this is unlikely to have influenced the odds ratios.

Thyroid disorders are more frequent in females than males.[16] Arrhythmias on the other hand are more frequent in men than women. Gender could therefore be an important confounder. The relation between thyroid disorders and age is less clear. Yet the relation between age and arrhythmias is definite. Both gender and age have therefore been included in our logistic regression. Previous research suggested that female sex was a risk factor for development of thyroid disorder in users of amiodarone.[17] It is generally known that female gender is a risk factor for thyroid-disease.[16] Stratification showed that risk estimates for thyroid disorder for men and women were comparable. This suggests that although women have a higher baseline risk on thyroid disorder, the relative risk when using amiodarone is not higher in women. Furthermore it is interesting to see that women tend to develop thyroid disorder when they are exposed to lower total doses than men. This could imply either that women are more sensitive to develop thyroid disorder or that relative doses in women are higher than in men, due to lower body weight of women. This warrants research into differential dosing of amiodarone in both sexes.

Arrhythmias such as atrial fibrillation can be secondary to a thyroid disorder. It is not uncommon that patients are primarily treated for an arrhythmia, that later turn out to arise from a thyroid disorder.[10] This would lead to increased risk estimates when comparing the risk on thyroid-disorder in patients receiving amiodarone with patients not receiving antiarrhythmic drugs. We therefore restricted our study to a cohort of patient treated with antiarrhythmics.

Since this is a non-randomised study the possibility of confounding by indication should be examined. Apart from including potential confounders in a multivariate model, we explored this possibility by calculating odds ratios for several other antiarrhythmics prescribed in our cohort. We did not find any increased risk on thyroid disorders in users of other antiarrhythmics except an association between use of digoxin and hyperthyroid disease (adjusted odds ratio of 1.7 (CI 95% [1.1-2.5]). In our view this moderately increased risk may indeed be due to confounding by indication. This type of confounding will probably not apply to amiodarone, since this drug will not be prescribed as first line therapy in patients presenting with arrhythmias.

Another source for potential confounding is co-medication that has been linked to thyroid disorders. Best documented are thyroid disorders due to use of lithium, interferon and iodine-containing x-ray contrast liquids. We did not include the use of this co-medication in our logistic regression since the use of these drugs is not frequent in our population.

In daily practice two strategies in patients receiving long term amiodarone seem appropriate: Either regular control of serum thyroid hormone levels at least twice a year or continuous attention for clinical symptoms of thyroid disorder. Withdrawal of amiodarone could be considered when thyroid disorders occur. In many cases continuation of therapy will be preferable. Amiodarone-induced hypothyroidism is treated with levothyroxine and hyperthyroidism with anti-thyroid drugs. Thyroidectomy is an option in case of resistance to treatment with anti-thyroid drugs. Thyroidectomy can also be considered when continued use of amiodarone is desired.

The study shows an incidence of thyroid disease that is on the higher end of earlier literature reports. Probably this is related to the relative long follow-up

period. In our opinion our study may even underestimate the absolute risk for amiodarone related thyroid disorder.

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Start of Non-Steroid Anti-Inflammatory Drugs increases the risk of renal dysfunction in users of Angiotensin Converting Enzyme inhibitors

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Abstract

Background Although relatively safe, both Non-Steroid Anti-Inflammatory Drugs (NSAIDs) and Angiotensin Converting Enzyme (ACE) inhibitors can cause renal dysfunction in compromised patients. Case reports indicate that the combination of ACE inhibitors and NSAIDs increases the risk on renal dysfunction. It is not known how often and when renal dysfunction occurs in patients using a combination of ACE inhibitors and NSAIDs.

Objective To investigate the effects of NSAIDs on the incidence of hospitalisations due to renal dysfunction in patients treated with ACE inhibitors.

Methods We designed a case-control study nested within a cohort of users of ACE inhibitors. All patients in the cohort had at least two consecutive prescriptions for an ACE inhibitor. The risk for hospitalisation for renal dysfunction associated with exposure to NSAIDs in patients receiving ACE inhibitors was expressed as odds ratios.

Results 144 cases were admitted for renal insufficiency during use of ACE inhibitors. 1 189 randomly sampled controls did not have any hospital admission for renal dysfunction during use of ACE inhibitors. Of 144 cases a total of 32 (22.2%) received NSAIDs in the 90 days before hospital admission for renal dysfunction compared to 236 (19.8%) of 1 189 controls. Recent start (<90 days) of a NSAID was associated with an increased risk of admission for renal dysfunction: adjusted OR: 2.2 (CI 95% [1.1-4.5]). For patients who started NSAIDs and were dispensed at least 3 prescriptions in the 90 days preceding hospitalisation an adjusted OR of 7.1 (CI 95% [1.8-28.7]) was observed.

Conclusions This study strongly suggests an increased risk for hospitalisation for renal insufficiency in patients receiving ACE inhibitors who start using NSAIDs. Especially patients receiving several prescriptions for NSAIDs in a short period of time are at risk.

Background

The positive effects of Angiotensin Converting Enzyme (ACE) inhibitors in hypertension and diminished left ventricular function are well established. ACE inhibitors block the conversion of angiotensin I to angiotensin II. Angiotensin II has a vasoconstrictive effect on the efferent arteriole. ACE inhibitors can blunt this vasoconstrictive effect and diminish efferent arteriolar resistance. By dilating the efferent renal arteriolar glomerular filtration rate (GFR) can decrease. This can lead to moderate increases in serum creatinine. These changes are usually no reason to withdraw ACE inhibitor therapy.[1, 2] However, in special situations such as renal artery obstruction, low cardiac output or hypovolemia severe renal dysfunction can occur. Renal dysfunction during treatment with ACE inhibitors is not uncommon in daily practice.[3]

The effects of moderate use of Non-Steroid Anti-Inflammatory Drugs (NSAIDS) on renal function in relatively healthy persons, not using ACE inhibitors, are probably negligible.[4] However several studies have shown that the use of NSAIDS is associated with an increased risk for acute renal failure (ARF).[5] Although the absolute risk on renal dysfunction in the general population is low, this risk could increase substantially in patients with already compromised renal function or using concurrent potentially nephrotoxic medication.[6] Even use of topical NSAIDS can lead to renal failure in compromised patients.[7] Use of both NSAIDS and ACE inhibitors is a common cause of acute renal failure. In a study of 109 patients with hospital admissions for acute renal failure, ARF was drug related in 39 patients. Either NSAIDS or ACE inhibitors were the cause of ARF in 24 and 8 patients respectively.[8]

The combination of NSAIDS and ACE inhibitors can result in ARF as a consequence of decreased glomerular filtration by their combined effects on renal blood flow. NSAIDS inhibit cyclo-oxygenase (COX) and thereby reduce the production of renal vasodilating prostaglandins. This phenomenon is especially important in kidneys dependent on these vasodilating effects of prostaglandins. ACE inhibitors inhibit the vasoconstrictor effect of angiotensin II on the efferent arteriole and make control of glomerular filtration more dependent on prostaglandins.[9, 10]

Other risk factors of renal insufficiency such as pre-existing renal disease, congestive heart failure, ageing, and hypovolemia increase nephrotoxicity during the simultaneous use of ACE inhibitors and NSAIDs.
Both NSAIDs and ACE inhibitors are frequently used in the general population. We aimed at quantifying the risk on hospital admission for renal dysfunction in patients using NSAIDs while exposed to ACE inhibitors.

Patients and Methods

Setting

Data were used from the PHARMO record linkage system, a database containing drug dispensing records from community pharmacies and linked hospital discharge records of a defined population of 300 000 residents of 6 medium-sized cities in The Netherlands. Medication histories and hospital data were collected from 1987 to 1998. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification. Hospital discharge records were coded according to the International Classification of Diseases, 9th Ed., clinical modification.

Patients

Within a cohort of ACE inhibitor users, older than 40, with at least 2 consecutive prescriptions for an ACE inhibitor we identified 144 cases, admitted to the hospital because of renal insufficiency (ICD 584 or 586) during the use of an ACE inhibitor. From the remainder of the cohort we randomly sampled (case:control ratio 1:8) 1 189 controls without any hospital admission for renal problems (ICD 580 to 588). An index date was assigned to each control matching the hospitalisation date of the case.

Exposure definition

A patient was defined as a current user when there was at least one prescription filled for a given drug in the 3 months before hospital admission for the cases or the corresponding index date for the controls.
A patient was defined as a former user when there was at least one prescription for a given drug between 3 and 12 months before hospital admission for the cases or the corresponding index date for the controls.
New use or start of use was defined as current use without former use.

Data analysis

We performed a case-control analysis comparing exposure in cases vs. controls. Odds ratios were calculated for exposure to NSAIDs, at the time of the hospitalisation due to renal dysfunction (cases) or matched index date (controls). Since age, gender, co-morbidity and co-medication can influence the occurrence of renal dysfunction and may be associated with NSAID-use, and thus, may confound the relationship between NSAID-use and renal dysfunction, we applied multivariable logistic regression techniques to adjust for these potential confounders. All statistical analysis was performed with Egret (Egret for Windows 2.0) software.

Table 1. Comparison between patients using ACE inhibitors who were admitted to hospital for renal dysfunction (cases) and a random sample of patients not admitted for renal dysfunction (controls)

	CASES N=144		CONTROLS N=1 189	
AGE CATEGORY				
<60 YEARS	18	12.5%	395	33.2%
60-69 YEARS	23	23.6%	333	28.0%
70 > YEARS	92	63.9%	461	38.8%
MALE	92	63.9%	540	45.4%
CO-MORBIDITY				
DIABETES	43	29.9%	203	17.1%
HISTORY OF HEART FAILURE HOSPITAL ADMISSION	38	26.4%	66	5.6%
MEDICATION USED IN 90 DAYS BEFORE INDEX DATE				
LOOP DIURETIC	96	66.7%	288	24.2%
THIAZIDE DIURETIC	4	2.8%	64	5.4%
SPIRONOLACTONE	21	14.6%	44	3.7%
ANTIBIOTIC	53	36.8%	172	14.5%
ANTI-GOUT DRUG	14	9.7%	23	1.9%
CORTICOSTEROID	11	7.6%	61	5.1%
DIGOXIN	52	36.1%	138	11.6%
LOW DOSE ACETYLSALICYLIC ACID	40	27.8%	286	24.1%

Results

In total 144 hospital admissions for renal insufficiency were observed. The majority of these were classified as renal insufficiency not otherwise specified (ICD-9 586 (132/144)). 12 out of 144 admissions were coded ICD-9 584 for acute renal insufficiency.

Table 2. Association between use of non-steroid anti-inflammatory drugs (NSAIDs) and risk on hospitalisation for renal dysfunction

	cases		controls		crude odds ratio	adjusted odds ratio
	n=144		n=1 189		[CI 95%]	[CI 95%]
exposition to NSAIDs in 90 days before index date	32	22.2%	236	19.8%	1.2 [0.7-1.8]	0.9 [0.6-1.5]
former use of NSAIDs in year before index date	38	26.4%	385	32.4%	0.7 [0.5-1.1]	0.7 [0.4-1.1]
start of NSAIDs in 90 days before index date	13	9.0%	53	4.5%	2.1 [1.1-4.2]	2.2 [1.1-4.5]
start of NSAIDs in 90 days before index date and at least three prescriptions in this period	5	3.5%	5	0.4%	8.5 [2.1-34.4]	7.1 [1.8-28.7]

*adjusted for age and gender, prior hospital admissions for heart failure, diabetes and for concomitant use of diuretics, low dose ASA, antibiotics, acetaminophen, epoetin, corticosteroids, opioids, digoxin, anti-gout drugs and duration of use of ACE inhibitor.

Of the 144 cases and 1 189 controls 32 (22.2%) and 236 (19.8%) respectively were treated with any NSAID in the 90 days preceding the hospital admission or index date. There was no increased risk for renal dysfunction related hospital admission for current use of NSAIDs (crude odds ratio (OR) 1.2; CI 95% [0.7-1.8]). However, the start of a NSAID in the 90 days prior to hospital admission for renal dysfunction was associated with an increased risk (crude OR 2.1; CI 95% [1.1-4.2]) (Table 2).

Cases and controls showed some differences in age, gender, co-morbidity and co-medication (Table 1). Adjustment for these potential confounders did not change the OR for start of a NSAID: 2.2 (CI 95% [1.1-4.5]). In order to determine a dose response relationship we calculated separate ORs for patients who started NSAIDs and received three or more prescriptions within 90 days before the hospitalisation. Adjusted OR in this subgroup was 7.1 (CI 95% [1.8-28.7]).

Discussion

This study suggests an increased risk (OR 2.2; CI 95% [1.1-4.5]) for hospitalisation for renal insufficiency in patients using ACE inhibitors who start a NSAID. In addition, a dose response relationship seems present. In this study only the effect on renal function requiring hospital admission was assessed. Smaller decrease of renal function, not leading to hospital admission, will probably occur much more frequently.

Covariates and possible confounders

Since this is a non-randomised study there will always be a risk for confounding. Renal function as well as NSAID use is related to age, gender and a broad range of co-morbidities and medications. Age itself or co-morbidity often reduces renal function in elderly patients.[11]
Our analysis showed several differences between patients with hospital admissions for renal dysfunction and controls. Notably patients with renal dysfunction were older, more often male and more frequently had a history of heart failure and diabetes. Also patients with renal dysfunction used several drugs (loop diuretics, spironolactone, digoxin, anti-gout drugs and antibiotics) more frequently. Patients with a hospitalisation for renal dysfunction used ACE inhibitors for a longer period of time, probably reflecting more serious underlying disease.

We corrected for potential confounders by including age, gender, diabetes, any hospital admission for heart failure, the use of aforementioned drugs in the 3 months prior to the index date and the duration of treatment with ACE inhibitors in the multiple regression model. We also adjusted for the use of five other drugs (low dose acetylsalicylic acid (ASA), acetaminophen, opioids, corticosteroids and epoetin) that may be associated with the presence of renal disease on the one hand an the use of NSAIDs on the other hand. After adjustment for these possible confounders the odds ratios did not change appreciably. These findings remain suggestive of a causal relation between starting NSAIDs and hospital admission for renal dysfunction in users of ACE inhibitors. Since information on important confounders was available, we believe that the chance of important residual confounding is negligible.
We were only partly able to take into account over-the-counter (OTC) use of NSAIDs. However we expect that this use is relatively low, since NSAIDs were reimbursed fully in The Netherlands in the study period and most Dutch (elderly) patients used these drugs on prescription. NSAIDs bought in the pharmacy will often be added to the medication history of the patient. Only NSAIDs bought in so called druggists will not be found in patients' medication history. Even when some patients did use OTC NSAIDs it is unlikely that OTC use will be unevenly distributed among cases and controls. Therefore we do not expect OTC use of NSAIDs will influence our findings.

Conclusion

NSAIDs are often combined with ACE inhibitors without deterioration of renal function. However this study strongly suggests an increased risk on hospitalisation for renal dysfunction in patients treated with ACE inhibitors who start using NSAIDs. Especially patients who receive several prescriptions for NSAIDs in a short period of time are at increased risk for renal dysfunction. Use of NSAIDs should be avoided as much as possible in patients receiving ACE inhibitors. Acetaminophen seems to be preferred as an alternative for NSAIDs. Preliminary data from COX-2-selective inhibitors suggest that they also affect renal prostaglandins.[12, 13] Renal failure has already been reported after high doses of COX-2 inhibitors.[14] Therefore, the same precautions should be exercised with their use as with traditional NSAIDs. Literature suggests that renal function is only monitored in 30% of patients after the start of ACE inhibitors.[3] This study emphasises the importance of monitoring renal function in patients already using ACE inhibitors who start NSAIDs.

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Prediction of mortality in heart failure patients

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Predicting mortality in patients with heart failure; a pragmatic approach

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Abstract

Background Patients with heart failure have a poor prognosis. Several studies investigated factors that predict early death in these patients. Predictive models combining several prognostic determinants and enabling identification of patients with high and low mortality risk are, however, scarce.
Objective To develop a comprehensive and easily applicable prognostic model predicting mortality risk in patients with moderate to severe heart failure.
Methods 152 outpatients with heart failure or patients admitted to hospital because of heart failure that were included in a randomised trial to assess the impact of a pharmacist-led intervention to improve drug compliance were followed for at least 18 months. Multivariable logistic regression modelling was used to evaluate which information from history, physical examination (e.g. blood pressure), medication used and quality-of-life questionnaires independently contributed to the prediction of death. Area under receiver operating characteristic curves (AUC) were used to estimate the predictive ability of the prognostic models.
Results During the 18 months of follow-up, a total of 51 patients (34%) died. Independent predictors for mortality were presence of diabetes mellitus, a history of renal dysfunction (or lower creatinine (clearance)), NYHA class III or IV, lower weight or body mass index, lower blood pressure, ankle oedema and higher scores on a disease–specific quality of life questionnaire. Use of beta-blockers was predictive of better prognosis. These factors were used to derive various prediction formulas. A model based only on medical history, weight, presence of oedema and lower blood pressure had an AUC of 0.77. Addition of use of beta-blockers to this model improved the AUC to 0.80. Addition of NYHA class increased the AUC to 0.84. Data on quality of life did not improve the AUC further (AUC 0.85).
Conclusions A prognostic model produced on the basis of easily obtainable information from medical history and physical examination can adequately stratify heart failure patients according to their short-term risk of death.

Introduction

Mortality among patients with heart failure discharged from hospital has repeatedly been reported to be high.[1-4] Several studies investigated determinants of early death or re-hospitalisation in these patients. A wide variety of factors is reported to be associated with an increased risk for hospitalisation or death, including demographic factors (e.g. male gender and single marital status), clinical characteristics (e.g. lower systolic blood pressure, renal dysfunction), history of heart failure (e.g. previous hospital admissions) and co-morbidity (e.g. diabetes and depression).[2, 5-8] Some of these studies focused on invasive and non-invasive test results (such as echocardiographically determined ejection fraction) that are not widely available for all patients, notably for those mainly managed in primary care.[5-7] The aim of this study is to develop a comprehensive and easily applicable prognostic model predicting the risk of death in patients with heart failure, based on information that is readily available in the medical practice.

Methods

Patients and prognostic determinants

The study group consisted of 152 patients enrolled in a randomised controlled trial evaluating the effect of a pharmacist-led intervention on medication compliance in patients with heart failure. All patients in the study were treated with loop diuretics and were either admitted to one of the participating hospitals because of heart failure (ICD-9, 428) or were treated in a specialised out patient heart failure clinic. The diagnosis heart failure was validated with patient's hospital records, including cardiac imaging findings. Patients with severe psychiatric problems and/or dementia, patients with a planned admission to a nursing home, patients who did not take care of their own medication (e.g. filled or administered by relatives or district nurses) and patients with a life expectancy of less than three months were excluded from the study.
Patients were enrolled in 7 hospitals in the province of Utrecht, The Netherlands (1 university hospital and 6 regional hospitals). The majority of patients (70%) was enrolled in two large (>500 beds) regional hospitals. The prognostic model was developed in all 152 patients included in the study.
As potential prognostic determinants, information from the patients' medical history, physical examination and laboratory tests was obtained from hospital charts, while quality of life was assessed by using a generic questionnaire (COOP/WONCA charts) and a disease specific questionnaire (Minnesota Living with Heart Failure Questionnaire (MHFQ)). Information on survival during the 18 months follow-up period was retrieved from patients' hospital charts and through patients' general practitioner and community pharmacy.

Data analysis

First, crude risk ratios for 18-months mortality were calculated for all potential prognostic determinants. Continuous variables were initially analysed without categorisation but various cut-off values were evaluated as well. All factors with a p-value < 0.10 and age and sex were included in multivariable logistic regression analyses.

Models were constructed in accordance to the chronology in which predictors are available in clinical practice. Hence, we first included all variables from patient history into an overall 'history model'. Model reduction was performed by excluding variables with p-values > 0.10. The reduced 'history model' was consecutively extended with data from physical examination, e.g. body mass index, blood pressure parameters, and laboratory data to evaluate their added value in the prediction of death. Of each model, the reliability (goodness of fit) was quantified using the Hosmer & Lemeshow test.[9] The predicted values from the logistic regression model were used to construct receiver operating characteristic (ROC) curves and to calculate the area under the ROC curves (AUC).[10] The ROC area is a suitable parameter to summarise the discriminative or predictive value and can range from 0.5 (no discrimination, like a coin flip) to 1.0 (perfect discrimination). Subsequently, to obtain an easily applicable prediction rule, the adjusted regression coefficients of the model were multiplied by a factor 10 and rounded to the nearest integer.

Missing values

Deleting subjects with a missing value on one of the predictors included in the multivariable model (so-called complete case analyses) commonly leads to biased results and surely to a loss of power.[11, 12] To decrease bias and to increase statistical efficiency, it is better to impute these missings rather than doing a complete case analyses.[11, 12] Accordingly, we imputed our missing data using the expectation maximisation method available in SPSS (SPSS for Windows, version 10.0, SPSS Inc.) software. Such imputation is based on the correlation between each variable with missing values and all other variables as estimated from the set of complete subjects.

Table 1. Crude association of potential prognostic determinants with 18 months-mortality in heart failure patients

	survivors		deaths		95% ci	p value
	n=101		n=51			
mean age (yr.)	69		72		1.0 [1.0-1.1]	0.07
female	67	66.3%	33	64.7%	1.1 [0.5-2.2]	0.84
nyha* class						
i or ii	56	67.5%	12	25.0%	Ref.	
iii or iv	27	32.5%	36	75.0%	6.2 [2.8-13.8]	0.000
co-morbidity						
obstructive pulmonary disease	18	17.8%	11	21.6%	1.3 [0.5-2.9]	0.58
diabetes	24	23.8%	19	37.3%	1.9 [0.9-4.0]	0.08
arrhythmias	50	49.5%	32	62.7%	1.7 [0.9-3.4]	0.12
myocardial infarction	51	50.5%	30	58.8%	1.4 [0.7-2.8]	0.33
cardiac valve abnormalities	69	68.3%	35	68.6%	1.0 [0.5-2.1]	0.97
renal insufficiency	7	6.9%	12	23.5%	4.1 [1.5-11.3]	0.006
pacemaker	11	10.9%	7	13.7%	1.3 [0.5-3.6]	0.61
physical examination and laboratory data						
ankle oedema	34	33.7%	25	49.0%	1.9 [1.0-3.0]	0.07
diastolic bp# below 70 mm hg	19	18.8%	15	29.4%	1.8 [0.8-3.9]	0.14
systolic bp# below 110 mm hg	17	16.8%	15	29.4%	2.1 [0.9-4.6]	0.08
pulse rate (min^{-1})	78±15		81±15		1.01 [0.99-1.04]	0.30
weight (kg)	79±15		72±15		0.97 [0.94-0.99]	0.009
body mass index (kg/m^2)	27±5		24±4		0.87 [0.79-0.96]	0.007
haemoglobin (mmol/litre)	8.3±1.1		8.0±1.1		0.83 [0.6-1.15]	0.26
mean creatinine (µmol/litre)	120±43		142±73		1.01 [1.0-1.02]	0.01
mean creatinine clearance (ml/min)	61±26		45±23		0.97 [0.95-0.99]	0.0007
mean serum sodium (mmol/litre)	140±4		139±4		0.91 [0.83-1.0]	0.06
mean serum potassium (mmol/litre)	4.3±0.5		4.3±0.5		1.33 [0.68-2.61]	0.41

Table 1. Crude association of potential prognostic determinants with 18 months-mortality in heart failure patients (continued)

	SURVIVORS N=101		DEATHS N=51		95% CI	P VALUE
MEDICATION AT BASELINE						
THIAZIDE DIURETIC	1	1.0%	3	5.9%	6.3 [0.6-61.7]	0.12
POTASSIUM SPARING DIURETIC	12	11.9%	8	15.7%	1.4 [0.5-3.6]	0.50
ACE INHIBITOR	66	65.3%	32	62.7%	0.9 [0.4-1.8]	0.75
AII ANTAGONIST	21	20.8%	5	9.8%	0.4 [0.1-1.2]	0.10
SPIRONOLACTONE	35	34.7%	18	35.3%	1.0 [0.5-2.1]	0.94
BETA-BLOCKER	49	48.5%	11	21.6%	0.3 [0.1-0.6]	0.002
ACETYLSALICYLIC ACID	25	24.8%	16	31.4%	1.4 [0.7-2.9]	0.39
ANTICOAGULANT	68	67.3%	28	54.9%	0.6 [0.3-1.2]	0.14
DIGOXIN	43	42.6%	27	52.9%	1.5 [0.8-3.0]	0.23
AMIODARONE	8	7.9%	5	9.8%	1.3 [0.4-4.1]	0.70
NITRATE (PROPHYLACTIC)	39	38.6%	22	43.1%	1.2 [0.6-2.4]	0.59
ANTILIPAEMIC	29	28.7%	9	17.6%	0.5 [0.2-1.2]	0.14
QUALITY OF LIFE SCORE						
MEAN COOP/WONCA† SCORE	21±5		22±4		1.04 [0.96-1.14]	0.31
MEAN MHFQ‡ SCORE	42±23		52±21		1.02 [1.00-1.04]	0.02

All values are means (± standard deviation) or proportions

*New York Heart Association; # BP=blood pressure

†Dartmouth COOP/WONCA charts

‡Minnesota Heart Failure Questionnaire

Table 2. Independent predictors of 18 month mortality

characteristics	clinical model	clinical model + medication at baseline	clinical model + medication at baseline + nyha -class	clinical model + medication at baseline + nyha -class + quality of life
	odds ratio [ci 90%]	odds ratio [ci 90%]	odds ratio [ci 90%]	odds ratio [ci 90%]
age	1.00 [0.98-1.04]	1.01 [0.97-1.04]	1.00 [0.97-1.04]	1.00 [0.97-1.04]
male sex	0.67 [0.31-1.43]	1.52 [0.69-3.34]	1.04 [0.44-2.47]	1.27 [0.52-3.09]
history of diabetes	2.35 [1.17-4.77]	2.37 [1.15-4.85]	2.53 [1.19-5.38]	2.76 [1.26-6.07]
history of renal insufficiency	4.02 [1.56-10.38]	5.22 [1.88-14.45]	4.14 [1.49-11.48]	3.69 [1.28-10.63]
ankle oedema	2.82 [1.40-5.71]	2.81 [1.36-5.82]	1.99 [0.89-4.42]	1.62 [0.72-3.65]
weight	0.96 [0.93-0.98]	0.96 [0.94-0.99]	0.96 [0.93-0.99]	0.96 [0.93-0.99]
lower systolic (<110) or diastolic (<70) blood pressure	2.16 [1.09-4.25]	2.10 [1.05-4.22]	1.94 [0.93-4.04]	1.81 [0.85-3.83]
non-use of beta-blockers		3.68 [1.73-7.84]	3.40 [1.52-7.59]	3.21 [1.43-7.23]
nyha† class iii or iv			4.91 [2.33-10.34]	4.18 [1.95-8.96]
mhfq‡-score > 37				3.24 [1.38-7.62]
roc area [ci 95%]	0.77 [0.69-0.84]	0.80 [0.72-0.87]	0.84 [0.77-0.90]#	0.85 [0.79-0.92]##

without oedema and lower systolic or diastolic blood pressure auc = 0.82

without oedema and lower systolic or diastolic blood pressure auc = 0.84

†New York Heart Association ‡Minnesota Heart Failure Questionnaire

Results

Within the 18 months follow-up period 51 (34%) of the 152 heart failure patients died; mortality at 6 and 12 months was 26 (17%) and 43 (28%). Table 1 shows the results of the crude association with 18-months mortality of all potential prognostic determinants. Strongest predictors of mortality were NYHA classification, Minnesota Heart Failure Score, renal dysfunction and (non-)use of beta-blockers.

The overall clinical model (i.e. first column of Table 2) had an AUC of 0.77. The inclusion of use of beta-blockers in this model improved the AUC to 0.80, while the introduction of NYHA class III or IV further improved the AUC to 0.84. The introduction of the Minnesota Heart Failure Score yielded a predictive accuracy with an AUC of 0.85. The fit of all models was good: p-values of the Hosmer & Lemeshow statistic ranged from 0.2 to 0.9.

Table 3. Regression coefficient and score of each predictor included in model 2

predictor	regression coefficient	score#
age (per year)	0.006	0.06
male sex	-0.42	+4
history of diabetes	0.86	+9
history of renal insufficiency	1.65	+17
ankle oedema	1.03	+10
weight (per kg)	-0.04	-0.4
lower systolic or diastolic blood pressure*	0.74	+7
absence of use of beta-blockers	-1.30	+13

*diastolic blood pressure <70 mm Hg or systolic blood pressure <110 mm Hg
The score per predictor is obtained by multiplying the regression coefficient by 10, and then rounded to nearest integer.

Since the clinical model with information on drug therapy combines data readily available for practising clinicians we transformed this model to a scoring rule: age/17 + 4 for male + 9 for presence of diabetes + 17 for history of renal dysfunction + 10 for presence of ankle oedema + 7 for systolic blood pressure <110 or diastolic blood pressure <70 – weight/3 + 13 for absence of use of beta-blockers (Table 3). Such a scoring rule can be considered as one overall measure for predicting mortality in heart failure patients. The score was calculated for each subject by assigning points for each predictor present and adding these points. For instance, a woman of 60 years and 70 kg, with a history of renal insufficiency and diabetes and ankle oedema and a blood pressure of 130/80 and who does not use a beta-blocker receives a score of (60/17 + 9 + 17 + 10 – 70/3 +13) = 29.2. In our data, the score ranged from –32.2 to +31.7 (mean –0.3, median 0.5) and the AUC of the rule was 0.80 (CI 95% [0.72 – 0.88]).

Table 4. Distribution of patients according to the risk score derived from model 2

risk score	total[1]	incidence of mortality (%)[2]	death[3]	survival[3]
< - 15	25	12.0	3	22
-15 - -5	29	10.3	3	26
-5 – 1	24	8.3	2	22
1 – 7	26	46.2	12	14
7 – 11	25	52	13	12
> 11	23	78.3	18	5
Total	152		51	101

Values represent absolute number of patients, except for incidence of mortality (%)

1. Total number of patients per score category;

2. Observed incidence of mortality per score category;

3. Number of patients who died and survived per score category

Table 4 shows the incidence of mortality among patients across different score categories. From this table one can directly obtain the observed mortality per score category (reading horizontally). For example, of 23 subjects with a score > 11, 78.3% (n=18) died while this was only 12.0% (n=3) in the 25 subjects with a score < -15. Similarly, the positive and negative predictive values for various cut-off points can be calculated: the positive predictive value for a score >=7 is 31/48 = 65%, while the negative predictive value of a score <7 is 84/104 = 81%. Reading the table vertically provides estimates of the sensitivity and specificity at different thresholds. For example, 74 (26+25+23) subjects received a score ≥ 1. Of these, 43 (12+13+18) indeed died, correctly predicting 84% of all deaths (i.e. the sensitivity or true positive rate). Since 31 (31%) of all subjects predicted as future deaths did not die the specificity of a threshold of 1 was 100 – 31% = 69%.

Table 5. Determinants of mortality in heart failure

	Lee[14] (1986)	Middlekauff[13] (1991)	Parameshwar[15] (1992)†	Scrutinio[5] (1994)	Chin[1] (1997)	Aaronson[7] (1997)	Cowie[2] (2000)	Zugck[6] (2001)	Jiang[8] (2001)	this study
age	+	NA	o	o	o	o	+	NA	+	o
depression	NA	NA	NA	NA	NA	NA	NA	NA	+	NA
crepitations	NA	NA	NA	NA	NA	NA	+	NA	NA	NA
heart rate	o	NA	NA	NA	NA	+	o	+	NA	o
intraventricular conduction delay	NA	NA	NA	NA	NA	+	NA	+	NA	NA
nonsinus rhythm	NA	+	NA	NA	+	o	o	NA	NA	o
lower LVEF	+	+	+	+	NA	+	o	+	o	NA
lower serum sodium	+	+	+	NA	o	+	o	+	NA	o
higher serum bilirubin	+	NA	NA	NA	NA	NA	NA	NA	NA	NA
lower (systolic) blood pressure	NA	NA	NA	NA	+	+	+	NA	NA	+
higher mean arterial pressure	o	+	NA	NA	NA	+	NA	+	NA	NA
myocardial infarction or ischaemia	NA	+	o	+	o	+	o	+	+	o
higher NYHA class	NA	NA	NA	+	NA	o	o	NA	+	+
lower peak oxygen uptake	NA	NA	+	o	NA	+	NA	+	NA	NA
6 minutes walking test	NA	NA	NA	NA	NA	NA	NA	+	NA	NA
impaired renal function	+	NA	o	NA	o	o	+	NA	NA	+
systolic dysfunction	NA	NA	NA	NA	NA	NA	o	NA	NA	NA
diabetes	NA	NA	NA	NA	+	o	NA	NA	NA	+
lower body weight or BMI	NA	NA	NA	NA	NA	o	NA	NA	NA	+
ankle oedema	NA	NA	NA	NA	NA	NA	o	NA	NA	+
absence of use of beta-blockers	NA	NA	NA	NA	NA	NA	NA	NA	NA	+

+ = associated with higher mortality in multivariate analysis; o = no association in multivariate analysis; NA = not assessed

LVEF=Left Ventricular Ejection Fraction; NYHA = New York Heart Association; BMI = Body Mass Index; † combined endpoint of death or transplantation

Discussion

This study shows that a combination of easily obtainable parameters accurately predicts 18 months mortality in patients with heart failure. Except for use of beta-blockers, weight and quality-of-life score these predictors were also observed in earlier studies (Table 5).

Several studies did use multivariate logistic regression to derive predictive models.[1, 2, 5-7, 13-15] Most of these studies, however, involved highly selected mostly relatively young patient populations (e.g. patients referred for cardiac transplantation). Our study was performed in patients included in a randomised controlled trial. Although there were few in- and exclusion criteria in this trial, patients with severe psychiatric problems and/or dementia, patients with a planned admission to a nursing home, patients who did not take care of their own medication (e.g. filled or administered by relatives or district nurses) and patients with a life expectancy (in the opinion of the physician) of less than three months were excluded from the study. This made our population more typical of a group of patients mainly treated in primary care. Other studies often included variables in the multivariate logistic regression that are not widely available in heart failure patients, while the determinants included in our study are usually routinely available. These determinants turned out to at least as predictive of mortality as the more difficult to obtain determinants included in other studies.[6, 7] Our predictive values were comparable with a recent study that found age, crepitations, lower systolic blood pressure and higher creatinine levels to be most predictive of mortality.[2] This study[2], however, did not assess the presence of diabetes, which was an important predictor in our study as well as in one other study.[1]

Although for all patients either echocardiography (95%), chest x-ray (87%) or electrocardiographs (99%) were available, more specific information on these data such as ejection fraction and diastolic function were only available in 54% and 35% of the participants and were subject to large intrahospital differences. Therefore these findings were not included in the analyses.

Finally, although other studies did compose logistic regression models, they did not assess the prognostic performance of a scoring rule combining the individual predictors derived from the logistic regression model.

We did not have data on a second cohort of patients with heart failure available. Therefore we could not carry out an external validation study. Our scoring rule will be validated in another ongoing study in our group. Ideally, such a validation should take place before the model can be applied in practice.

Conclusion

Easily obtainable data on clinical features can identify a group of heart failure patients at increased risk for mortality. Although quality of life scores are independent predictors of mortality, their added prognostic value is too small to warrant quality of life measurements for such a purpose in routine clinical practice. Additional research is necessary to validate the proposed model in other populations.

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General discussion

This thesis was based on a series of pharmacoepidemiologic studies of heart failure patients, covering the dissemination of evidence-based treatment, drug-induced problems, compliance with prescribed medication, and prognosis. A variety of study designs was used: randomised trial, case-control and follow-up studies, trend analysis and prognostic modelling. Different data sources were used, including hospitals, community networks of GPs and pharmacists, a prescription record database (PHARMO), patient diaries and MEMS. In this concluding chapter, we would like to consider the questions: Where are we now? And what has been achieved?

Evidence-based drug therapy?

Chapters 2-4 focussed on the question of the extent to which new evidence has affected the pharmacotherapy used presently to treat heart failure patients. **Chapter 2** showed the considerable changes in the treatment of heart failure that took place between 1990 and 1998. Although there was a constant increase in the use of 'evidence-based' treatments, a substantial number of patients was found not to receive appropriate treatment. The use of ACE inhibitors was found to be slightly lower in our study compared to other studies, while the under-use of beta-blockers determined in our study was also reported in previous studies.[1-5] Under-utilisation may be related to the fact that physicians are reluctant to initiate beta-blockers because of the risk of initial worsening of heart failure symptoms.[6] It is also possible that the users of beta-blockers in primary care differ from participants in clinical trials. Many elderly patients with heart failure may not tolerate beta-blockers. Moreover, many physicians who trained during the last 10 years were trained with the view that beta-blockers are contra-indicated in patients with heart failure. We found that beta-blockers were frequently discontinued shortly after discharge from hospital. The reason for this may be discomforting side effects. This suggests the need for re-education of physicians on the use of beta-blockers in patients with heart failure. In particular, the adage 'start low and go slow' should be kept in mind and patients need to be informed of the initial worsening of symptoms, motivating them to continue.[7]

The premature discontinuation of an evidence-based treatment threatens a drug's clinical benefit. Although in the 'real world' fewer patients continue treatment than in clinical trials (**Chapter 2**), the number of heart failure patients continuing therapy in our studies compared favourably to other reports.[8, 9] A relevant case, underlining the gap between efficacy (controlled trials) and effectiveness ('real world'), was reported in **Chapter 3**. We found that, although spironolactone was found to be highly efficacious in a controlled setting[10], only small (41%) proportions of patients continued therapy as needed. Patients who used spironolactone and ACE inhibitors concomitantly failed to continue using both drugs for longer periods. Non-compliance in patients using this combination could be related to the occurrence of adverse drug reactions and electrolyte disturbances.[11, 12] Monitoring of serum potassium is mandatory after starting spironolactone, especially when it is used concomitantly with ACE inhibitors, and may prevent discontinuation through early dose adjustment.

In many cases, heart failure is the end stage of chronic heart disease following an ischaemic event.[13] The development of heart failure could be partly prevented by providing appropriate treatment at earlier stages. The use of acetylsalicylic acid has been proven to prevent future ischaemic events after myocardial infarction. We found that a number of patients, especially women, were less likely to receive anti-platelet therapy (**Chapter 4**), in accordance with other studies.[14] Since prognosis in women with ischaemic heart disease is comparable to that in men, more efforts should be made toward targeting appropriate treatment to more women.

The findings as reported in **Chapters 2-4** warrant important questions on the dynamics of therapeutic innovation in medical practice.[15] Evidence of prognostic benefit of the use of ACE inhibitors in heart failure has already been available for over a decade. Studies have suggested that patients not receiving ACE inhibitors are at higher mortality risk.[16] The gap between recommended and actual treatments received by heart failure patients has been amply reported.[5, 17] This is an important point, since studies have shown that if evidence-based treatment is utilised properly, risk reductions in routine

medical practice can be comparable to those found in clinical trial settings[18] Evidence of prognostic benefit of the use of ACE inhibitors in heart failure has already been available for over a decade, with studies suggesting that patients not receiving ACE inhibitors are at higher mortality risk.[16] Deviation from these evidence-based guidelines could be related to differences between patient populations in clinical trials and those in routine medical practice. In particular, patients in primary care are older, more often female and the prevalence of co-morbidities is higher.[19] More research into reasons for not prescribing evidence-based treatment is needed to assess when the observed under-utilisation is justified or not, and, thus, should be prevented. We did not look into dosing of evidence-based treatment in full detail. A numbers of studies showed that ACE inhibitors especially were given in lower dosages than applied in clinical trials.[3, 20-24] It is probable that our study patients frequently received ACE inhibitors at lower dosages than recommended. Conversely, it is possible that some patients received too high dosages of diuretics or beta-blockers.

Evidently, it is not enough to assess or even explain the lack of dissemination of evidence-based drug treatment to daily practice. There is clearly a need to explore and develop further strategies to improve prescribing according to practice guidelines as shown recently by van Eijk et al.[25]

Improving compliance with therapy

Compliance with prescribed drug regimen is the mainstay of successful pharmacotherapy. Appropriate compliance for the use of loop diuretics in patients with heart failure has been identified as a key area for improvement of clinical practice for both medical and economical reasons[26]. Pharmacy records were used to determine whether heart failure patients filled their prescriptions consistently. Using this method, it was shown that patients not regularly refilling their prescriptions for diuretics were at an increased risk of hospitalisation for heart failure.[27] However, this methodology could not assess day-to-day compliance of individual patients. We used Medication

Event Monitoring Systems (MEMS) to show that a pharmacy-led intervention could improve medication compliance in heart failure (**Chapter 5**).[28, 29]
A relatively high percentage of MEMS devices was lost during this study compared to other studies.[30, 31] There are several explanations for this phenomenon. First, this study was performed in a group of patients with high morbidity and mortality. The MEMS device was lost after a patient died or was admitted to hospital. In current studies, we use fixed labels on every MEMS stating that this container is used for research and needs to be returned. Furthermore, patients used MEMS for 6 consecutive months. Most studies using MEMS have employed these devices for much shorter periods. It is recommended that future studies especially of patients with high morbidity and mortality do not employ MEMS for longer than 3 consecutive months; when a longer follow-up period is required, another MEMS device should be provided for the next 3 month period. In our study, compliance in the control group was unexpectedly high and could be related to selection of motivated patients. Future studies should be aimed at patients with lower compliance; but it will be difficult to include these patients in randomised trials, since they will be less motivated to participate.

Drug-induced problems in heart failure

We found that patients with heart failure received on average 15 different drugs per year. Obviously, not all of these drugs are used simultaneously and the number included incidental use of medication, such as antibiotics and cough syrups. However, even incidental use of drugs may cause serious problems. We studied various examples of drug-related adverse effects and interactions of drugs frequently used by patients with heart failure. Several studies found clear correlations between the number of medications used and the number of drug-related problems, such as potential adverse drug reactions and drug interactions.[32-34] Due to the increasing numbers of heart failure patients suffering from multiple morbidities and susceptible for drug-induced disease exacerbation, we have to face long listings of potential risks:

- Digoxin intoxication by overdosing or drug interactions.[35]
- Electrolyte depletion due to diuretic overuse.[7, 36]
- Electrolyte depletion due to laxative overuse.[37-39]
- Decreased efficacy of diuretics and induction of fluid retention in patients using Non-Steroid Anti-Inflammatory Drugs (NSAIDS).[40]
- Hyperkalaemia due to combination ace inhibitors and potassium suppletion or potassium sparing diuretics, including spironolactone.[12, 41]
- Inappropriate use of sleep medication as a consequence of nocturnal dyspnoea and sleep problems.
- Increased susceptibility to arrhythmias due to QT-interval prolongating drugs.[42]
- Hyponatraemia due to combination of diuretics and serotonin reuptake inhibitors.[43]
- Hypotension due to aggressive blood pressure lowering treatment (in combination with use of nitrates and diuretics).[44]
- Gastrointestinal bleeding and occult blood loss due to use of antithrombotics (in combination with NSAIDS).[45]

Drug-induced problems are closely related to the ageing process. These problems are likely to increase in the near future with the proportionately increasing ageing population. In the studies reported in **Chapters 6-8**, we identified various determinants of important drug-induced problems. We feel

that a significant part of these iatrogenic effects could be avoided if the individual clinical situation of the heart failure patient is carefully considered in the light of the risk-benefit ratios of proposed treatments.[40, 46] Prevention of adverse drug reactions and interactions in heart failure therefore deserves closer attention. Improving communication between different physicians and between physicians and pharmacists could partly prevent these problems. This requires both investments in infrastructure (e.g. automation and availability of shared patient records) and training of physicians and pharmacists.

Prognosis of patients with heart failure

Heart failure has the lowest 5-year survival of all common diseases, with the exception of lung cancer.[47] Patients discharged after a hospital admission for heart failure are frequently readmitted within 6 months.[48, 49] Although physicians implicitly use patient-related variables to predict prognosis for an individual patient, a simple prognostic rule may further facilitate the identification of high-risk patients and, thereby, guide therapeutic management. In **Chapter 9**, the development of a pragmatic model to predict mortality in heart failure was shown. This model used information that was generally available in patient records. Although this model had very good predictive power, it awaits validation in other populations. As most factors included in the model were also found to be independent determinants of morbidity and mortality in other studies of heart failure patients, it seems plausible that the model will be applicable to other heart failure populations.[50-54]

Role of the pharmacist

We will now consider the role of the pharmacist in improving pharmaceutical care in patients with heart failure. The series of studies reported in this thesis were conducted in a pharmacy-based practice research setting, including the controlled trial as described in **Chapter 5**. Optimal drug therapy in patients with heart failure involves implementation and continuation of evidence-based therapy. Paradoxically, initiation of new drugs also increases the

potential for drug related problems.[46, 55] There is no doubt that drug treatment in the mostly elderly heart failure patient with the high prevalence of co-morbid disorders should be accompanied by comprehensive care in order to prevent drug-related problems and optimise individual pharmacotherapy. Numerous studies have shown multidisciplinary interventions were very successful in achieving improved patient outcomes.[52, 56]

For the Dutch health care setting, Leufkens and Urquhart have identified three important reasons why pharmacy-GP networks may fulfil a key role in the management of care of patients with heart failure: (i) computerized drug dispensing records are subject to financial audit because they are the basis for reimbursement; (ii) a long tradition that patients frequent a single GP and pharmacy; (iii) the lack of a strong economic incentive for between-pharmacy shopping.[57] We would like to add to these the development and implementation of so-called FTO groups[25]: community networks of collaborating GPs and pharmacists directed at the implementation of evidence-based and cost-effective prescribing. These FTO groups are fully supported by the Dutch government and health insurers and have now expanded to hospital settings as well. Both community and hospital pharmacists have been shown to be capable of judging and evaluating treatment guidelines and initiating appropriate evidence-based therapy.[3, 58-60] A recent study showed that a review of the drug regimen of elderly patients by the pharmacist resulted in significant changes in patients' drugs and saves more than the cost of the intervention without affecting the workload of GPs.[61] A recent Cochrane review concludes that a limited number of studies support the expanded roles of pharmacists in patient counselling and physician education. However, more rigorous research is needed to document the effects of outpatient pharmacist interventions.[62, 63]
Pharmacists must aid physicians and patients in sustaining drug compliance using electronic devices (i.e. MEMS) and persistence of chronic therapy and check on interactions and possible treatment of adverse events when new drugs are initiated.[64] Furthermore, pharmacists in their role as pharmacotherapy experts are in the position to weigh new research findings

on pharmacotherapy, both from trials and observational studies, and discuss those with their colleague physicians on how to treat patients with heart failure in the most cost-effective way.[65] The studies presented in this thesis provide supporting clues to expand innovation in pharmaceutical care in this direction. However, the Dutch governmental policy to stimulate market forces and competition in the health care sector for economical reasons is a possible threat to the basic requirements of this successful 'managed care' environment.[66] The detrimental impact of market forces on health care was already described by Titmuss in his comparison of the US and UK blood donation system.[67] As long as market forces remain to be seen as the cure for the health care system competing pharmacists, GPs and other health care providers may provide short-term cost savings, while elderly patients such as the heart failure patient will be the real victim.

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Summary

The prevalence of heart failure has increased considerably in the past decades and is expected to increase further in the near future. The available evidence of the benefits of several categories of drugs has made treatment of heart failure more rewarding, but also more complex. Moreover, most patients with heart failure are 70 years and older and have a history of ischaemic heart disease and several co-morbidities. The treatment of both heart failure and these co-morbidities leads to the use of a broad range of very powerful medicines. The inappropriate use of these medicines can lead to several drug related problems. Drug related problems can have a major impact on outcomes of pharmacotherapy, comprising problems directly related to the use of the drug(s) (e.g. adverse drug reactions and interactions), problems related to the health care system (e.g. prescribing and dispensing errors) and problems related to suboptimal use by the patient (e.g. non-compliance and early discontinuation of drug therapy).

Evidence based drug therapy?

This thesis started with an overview of changes in the drug treatment of heart failure in patients discharged after a first hospitalisation for heart failure between 1990 and 1998 (**Chapter 2**). The use of loop diuretics remained constant at 80 percent of discharged patients. The use of ACE inhibitors increased from 49.8% in patients with a first hospitalisation in 1990 to 54.8% in patients hospitalised in 1998. The use of digoxin decreased from 51.9 to 37.6%, whereas the use of beta-blockers almost tripled from 11.3% to 28.7% and of low dose prophylactic aspirin quadrupled from 9.9 to 39.9%. Kaplan-Meier survival estimation showed highest continuation of drug treatment for antithrombotics and diuretics, intermediate continuation for digoxin and ACE inhibitors and low continuation for beta-blockers (approximately 28% discontinued beta-blockers in the first year after hospitalisation). The observed increase in the prescription of several important drug-classes, reflects the changes in guidelines on treatment. However optimal treatment is still not given to all patients. Discontinuation of evidence-based medication started after hospital admission remains an important topic to address.

In **Chapter 3** the continuation of therapy with spironolactone with and without concomitant use of ACE inhibitors was studied in a cohort of 243 patients with a first prescription for spironolactone between 1990 and 1997 and at least one hospital discharge for heart failure in the preceding year. 143 patients (58.8%) discontinued spironolactone therapy before the end of follow-up. 98 patients (40.8%) discontinued within 6 months of follow-up. Of the 137 patients (56.4%) who did use spironolactone and an ACE inhibitor concomitantly, only 45 (32.8%) continued this combination until the end of follow-up. The remainder of the patients discontinued either the ACE inhibitor (10.9%) or spironolactone (12.4%) or both (43.8%). While the reasons for discontinuation remain unclear, these data suggest that it is difficult to keep patients on spironolactone, in particular when combined with ACE inhibitors. It is not certain whether these findings from past spironolactone use can be extrapolated to future use. Patients in the general population received higher average spironolactone dosages compared to the RALES study (55 mg vs. 26 mg), possibly resulting in more adverse effects and partly explaining the high discontinuation rate.

Ischaemic heart disease is the most important cause of heart failure in western societies. The use of antithrombotics to reduce coronary events in patients with myocardial infarction and angina pectoris is well established. Underutilisation of low dose acetylsalicylic acid (ASA) can cause unnecessary myocardial ischaemia and impaired ventricular function, ultimately leading to symptomatic heart failure. In **Chapter 4** utilisation of ASA in patients with ischaemic heart disease was investigated. A higher percentage of women than men were not treated with any form of antithrombotic treatment (37% versus 18%). This study suggests a serious and possibly hazardous undertreatment with the antiplatelet agent ASA in women with angina pectoris compared with men. In the long run this can lead to preventable myocardial ischaemia and loss of ventricular function. Ultimately contributing to an increase in heart failure in the female population.

Compliance in heart failure therapy

Previous studies showed a two-fold risk for recurrent heart failure hospitalisations in patients with poor refill patterns of their loop diuretics. In **Chapter 5** compliance with diuretics was studied with the use of Medication Event Monitoring Systems (MEMS), an electronic pill bottle that registers time of opening. Moreover the effect of a pharmacist-led intervention on compliance was studied in a randomised trial. Patients in the intervention-group received monthly consultations from their community pharmacist during a 6-month period, aiming to improve medication compliance. Patients in the control-group received usual care. 152 patients were randomised; 74 patients to the intervention and 78 patients to the usual care arm. Over the 6-month study period patients in the intervention group had 140/7,656 days without use of loop diuretics compared to 337/6,196 days in the usual care group (relative risk 0.33; CI 95% [0.24-0.38]). Two consecutive days without use of diuretics occurred on 18/7,656 days in the intervention group compared to 46/6,196 days in the usual care group (relative risk 0.32; CI 95% [0.19-0.55]). There were no significant differences in re-hospitalisations, mortality and disease specific quality of life between both groups. This study shows that a pharmacy led intervention improves medication compliance in patients with moderate to severe heart failure, even in those patients with relatively high initial compliance. Future interventions should also focus at less compliant patients.

Drug induced problems in heart failure

Sympathomimetic bronchodilators have a direct positive chronotropic effect on heart rate and may cause hypokalaemia, even when administered by inhalation. In selected patients (e.g. patients with heart failure) this could lead to arrhythmias. Despite the potential adverse effects of these agents, they are used frequently in patients with heart failure, due to a high incidence of respiratory co-morbidity. In **Chapter 6** the effect of use of sympathomimetics on the incidence of hospitalisations for arrhythmias in 1 208 patients with heart failure was investigated. We identified 149 cases with a readmission for

arrhythmias, and compared these in a nested matched case-control design with 149 controls from the remainder of the cohort with no hospital readmission for any cardiac cause. Conditional logistic regression was used to calculate the risk for hospitalisation for arrhythmias associated with exposure to sympathomimetic agents. Of 149 case patients, a total of 33 (22.1%) were treated with any sympathomimetic agent, and 6 patients (4.0%) were treated with systemic sympathomimetics. The use of any sympathomimetic drug was associated with an increased risk of admission for arrhythmia (odds ratio (OR) 4.0; CI 95% [1.0-15.1]). For systemic sympathomimetic drugs, the corresponding odds ratio was 15.7 (CI 95% [1.1-228.0]). The results of this study strongly suggest that sympathomimetic drugs increase the risk of hospitalisation for arrhythmias in patients with heart failure. Sympathomimetics should be given under close surveillance to patients with heart failure.

In a considerable proportion of patients with heart failure arrhythmias occur. Refractory arrhythmias are often treated with amiodarone: an effective drug with, however, many side effects. In **Chapter 7** the incidence of thyroid disorders after the start of amiodarone is studied. We followed a cohort of 5 522 patients with a first prescription for an anti-arrhythmic drug and no previous use of thyroid drugs. Within this cohort we conducted a nested case control analysis. Cases were defined as all patients who started a thyreomimetic or thyreostatic drug no sooner than 3 months after the start of an anti-arrhythmic drug. Controls were patients with a comparable follow-up period not receiving any thyroid drugs during the observation period. We identified 123 cases that started thyreostatic drugs and 96 cases that started a thyreomimetic drug. In users of amiodarone we found an adjusted odds ratio of 6.3 (CI 95% [3.9-10.2]) for hyperthyroidism and 6.6 (CI 95% [3.9-11.1]) for hypothyroid disease compared to users of other anti-arrhythmics. Patients who were exposed to a cumulative dose exceeding 144 gram of amiodarone had an adjusted odds ratio of 12.9 (CI 95% [6.1-27.3]) for the development of hyperthyroid disease. The dose response for development of hypothyroidism was less pronounced. Data on the incidence of amiodarone induced thyroid

disorders are conflicting. An incidence between 4 and 20% is reported. This variability in risk probably arises from several factors such as the duration of treatment and the cumulative dose of amiodarone. We observed an increased risk for thyroid disorder on the high end of that reported in literature. Clinicians should keep in mind the possibility of development of thyroid disorders even several years after start of amiodarone.

Since heart failure patients use a wide variety of drugs they are at increased risk of drug interactions. Non-Steroid Anti-Inflammatory Drugs (NSAIDs) are among the most commonly prescribed drugs in the elderly. All heart failure patients should use ACE inhibitors. Although relatively safe, both NSAIDs and ACE inhibitors can cause renal dysfunction in compromised patients. Case reports indicate that the combination of ACE inhibitors and NSAIDs increases the risk on renal dysfunction. It is not known how often and when renal dysfunction occurs in patients using a combination of ACE inhibitors and NSAIDs. In **Chapter 8** we studied the occurrence of hospitalisation for renal dysfunction in a case-control study nested within a cohort of users of ACE inhibitors. We found an increased risk for hospitalisation for renal dysfunction in patients receiving ACE inhibitors, who recently started (<90 days) use of a NSAID (adjusted OR 2.2 (CI 95% [1.1-4.5]). For patients who started NSAIDs and were dispensed at least 3 prescriptions in the 90 days preceding hospitalisation an adjusted OR of 7.1 (CI 95% [1.8-28.7]) was observed. This study strongly suggests an increased risk for renal insufficiency in patients receiving ACE inhibitors who start using NSAIDs. Especially patients receiving several prescriptions for NSAIDs in a short period of time are at risk. Renal function in patients receiving ACE inhibitors should be monitored closely after start of a NSAID.

Prediction of mortality in heart failure patients

Patients with heart failure have a poor prognosis. Several studies investigated factors that predict early death in these patients. Predictive models combining several prognostic determinants and enabling identification of patients with high and low mortality risk are, however, scarce. In **Chapter 9** a comprehensive and easily applicable prognostic model predicting mortality risk in the 152 patients included in the DECOMP trial (**Chapter 5**) was developed. During the 18 months of follow-up, a total of 51 patients (34%) died. Independent predictors for mortality were presence of diabetes mellitus, a history of renal dysfunction (or lower creatinine (clearance)), NYHA class III or IV, lower weight or body mass index, lower blood pressure, ankle oedema and higher scores on a disease–specific quality of life questionnaire. Use of beta-blockers was predictive of better prognosis. These factors were used to derive various prediction formulas. A model based only on medical history, weight, presence of oedema and lower blood pressure had an 'area under the receiver operator curve' (AUC) of 0.77. Addition of use of beta-blockers to this model improved the AUC to 0.80. Addition of NYHA class increased the AUC to 0.84. Data on quality of life did not improve the AUC further (AUC 0.85). This study shows that a prognostic model produced on the basis of easily obtainable information from medical history and physical examination can adequately stratify heart failure patients according to their short-term risk of death.

The studies compiled in this thesis give several suggestions to improve drug treatment in patients with heart failure. It is important to get patients on the right evidence based regimens and moreover keep them on these regimens. Adverse drug reactions and interactions are common and need permanent attention. Physicians and pharmacists should cooperate to ensure patients receive optimal drug treatment.

[12]

Samenvatting

De prevalentie van hartfalen is de afgelopen decennia aanzienlijk toegenomen en de verwachting is dat deze toename nog niet tot staan is gebracht. Klinisch onderzoek heeft de afgelopen jaren aangetoond dat verschillende geneesmiddelen de morbiditeit en mortaliteit van hartfalen kunnen verlagen Er is daardoor meer mogelijk geworden op het gebied van de behandeling van hartfalen, maar die is tegelijkertijd complexer geworden. Patiënten met hartfalen zijn vaak ouder dan 70 jaar en hebben behalve een voorgeschiedenis van ischemische hartziekten, vaak bijkomende aandoeningen zoals diabetes, longziekten en nier-aandoeningen. De gelijktijdige behandeling van hartfalen en deze bijkomende aandoeningen leidt tot het gebruik van een groot aantal, sterk werkende geneesmiddelen. Onjuiste toepassing van deze middelen kan aanleiding geven tot een wijd spectrum aan geneesmiddelgerelateerde problemen, die de uitkomst van de behandeling in sterke mate kunnen beïnvloeden. Deze problemen kunnen direct gerelateerd zijn aan het gebruik van het geneesmiddel (zoals bijwerkingen en geneesmiddel-interacties), gerelateerd zijn aan de organisatie van de gezondheidszorg (zoals voorschrijf- of afleverfouten), en gerelateerd zijn aan onjuist gebruik door de patiënt zelf (zoals therapie-ontrouw en voortijdig stoppen met het geneesmiddel).

'Evidence based' toepassing van geneesmiddelen?

Dit proefschrift begint met een overzicht van de veranderingen in de behandeling met geneesmiddelen bij patiënten die tussen 1990 en 1998 voor het eerst ontslagen zijn uit het ziekenhuis na een opname voor hartfalen (**Hoofdstuk 2**). Het gebruik van lisdiuretica bleef constant bij 80 percent van de uit het ziekenhuis ontslagen patiënten. Het gebruik van ACE remmers nam toe van 49.8% bij patiënten met een eerste ziekenhuisopname in 1990, tot 54.8% bij patiënten met een eerste opname in 1998. Het gebruik van digoxine nam in dezelfde periode af van 51.9 tot 37.6%, terwijl het gebruik van bètablokkers bijna verdrievoudigde van 11.3% tot 28.7%. Het profylactisch gebruik van lage doseringen acetylsalicylzuur verviervoudigde zelfs: van 9.9 tot 39.9%.

Van de geneesmiddelen die gestart werden na een ziekenhuisopname bleken antithrombotica en diuretica het langst gecontinueerd te worden, digoxine en Angiotensine Converting Enzyme (ACE) remmers werden iets minder lang gecontinueerd en bètablokkers het minst lang (ongeveer 28% stopte binnen een jaar na de ziekenhuisopname met het gebruik van bètablokkers). De toename in het gebruik van een aantal geneesmiddelen reflecteert de veranderingen in de richtlijnen voor de behandeling van hartfalen. Veel patiënten ontvangen echter nog steeds geen optimale behandeling. Bovendien worden behandelingen nog vaak (te) vroeg gestaakt. Het is van belang om nader onderzoek te doen naar de achterliggende oorzaken hiervan. In **Hoofdstuk 3** werd specifiek gekeken naar de continuering van de behandeling met het geneesmiddel spironolacton. Hiervoor werden 243 patiënten met hartfalen gevolgd die tussen 1990 en 1997 een recept voor spironolacton hadden gekregen. Hierbij werd tevens een onderverdeling gemaakt in patiënten die tegelijkertijd wel of geen ACE remmer gebruikten. 143 patiënten (58.8%) stopten voortijdig met het gebruik van spironolacton. 98 patiënten stopten zelfs al binnen 6 maanden (40.8%). Van de 137 patiënten (56.4%) die naast spironolacton tevens een ACE remmer gebruikten, bleven slechts 45 (32.8%) deze combinatie tot het eind van de 'follow-up' volgen. De overige patiënten stopten ofwel met de ACE remmer (10.9%), of met spironolacton (12.4%), of met beide middelen (43.8%). Hoewel de redenen voor het grote aantal stoppers onbekend blijven, suggereren deze gegevens dat het moeilijk is om patiënten spironolacton te laten continueren, vooral wanneer gelijktijdig ACE remmers worden gebruikt. Het is niet zeker of deze bevindingen geëxtrapoleerd kunnen worden naar het toekomstig gebruik van spironolacton. De patiënten in dit onderzoek kregen relatief hogere doseringen spironolacton dan in het RALES onderzoek (55 mg vs. 26 mg); mogelijk traden daardoor meer bijwerkingen op, waardoor het grote aantal stoppers (deels) verklaard kan worden.

Ischemische hartziekten zijn de belangrijkste oorzaak van hartfalen in de westerse samenleving. In meerdere onderzoeken is aangetoond dat het gebruik van antithrombotica zoals lage doseringen acetylsalicylzuur (ASA), het

aantal hartinfarcten bij patiënten die al eerder een hartinfarct hebben gehad of die last hebben van angina pectoris, kan verminderen. Ondergebruik van ASA leidt daarom tot onnodige schade aan hartspierweefsel en zal op de langere termijn leiden tot een verminderde functie van het linkerventrikel en uiteindelijk tot symptomatisch hartfalen. In **Hoofdstuk 4** werd het gebruik van ASA bij patiënten met ischemische hartziekten onderzocht. Een hoger percentage vrouwen dan mannen bleek geen enkele vorm van ontstollende behandeling te krijgen (37% versus 18%). Dit onderzoek suggereert een belangrijk en potentieel ernstig ondergebruik van ASA bij vrouwen met angina pectoris. Op de lange termijn kan dit leiden tot meer schade aan het hartspierweefsel van deze vrouwen, hetgeen uiteindelijk kan bijdragen aan een toename van hartfalen bij vrouwen.

Therapietrouw bij hartfalen

Eerder onderzoek liet zien dat patiënten die hun diuretica onregelmatig ophaalden in de apotheek, een tweevoudig verhoogd risico hadden op herhaalde ziekenhuisopnamen. In **Hoofdstuk 5** werd de therapietrouw met diuretica bestudeerd met Medication Event Monitoring Systems (MEMS). Dit zijn potjes met in het dekseltje een microprocessor die het moment van openen registreert. Tegelijkertijd werd onderzocht of extra begeleiding in de vorm van maandelijkse gesprekken met de eigen apotheker van de patiënt, diens therapietrouw verbeterde. Een controlegroep kreeg deze extra informatie niet. Aan het onderzoek deden 152 patiënten mee; 74 patiënten in de interventiegroep en 78 patiënten in de controlegroep. Gedurende de onderzoeksperiode van 6 maanden gebruikten de patiënten in totaal van 140/7,656 dagen geen lisdiuretica, vergeleken met 337/6,196 dagen in de controlegroep (relatief risico 0.33; CI 95% [0.24-0.38]). Twee opeenvolgende dagen zonder gebruik van diuretica kwamen voor op 18/7,656 dagen in de interventiegroep, vergeleken met 46/6,196 dagen in de controlegroep (relatief risico 0.32; CI 95% [0.19-0.55]). Er werden geen significante veranderingen gevonden in het aantal ziekenhuisopnamen, sterfte en hartfalen gerelateerde kwaliteit van leven tussen beide groepen. Dit onderzoek toont aan dat

begeleiding door de apotheek de therapietrouw kan verbeteren bij patiënten met matig tot ernstig hartfalen, zelfs bij patiënten die al relatief therapietrouw zijn. Toekomstige interventies bij hartfalen-patiënten moeten ook patiënten insluiten die vooraf minder therapietrouw zijn.

Geneesmiddel gerelateerde problemen bij hartfalen

Sympathomimetische luchtwegverwijders hebben een rechtstreeks stimulerend effect op de hartslag en kunnen daarnaast een verlaging van het kaliumgehalte veroorzaken. Deze effecten treden zelfs op wanneer deze middelen worden toegepast per inhalatie. Bij bepaalde patiënten (zoals patiënten met hartfalen) zou dit kunnen leiden tot hartritmestoornissen. Ondanks de potentiële bijwerkingen van deze middelen worden ze frequent toegepast bij patiënten met hartfalen, omdat veel van deze patiënten tegelijkertijd aandoeningen van de luchtwegen hebben. In **Hoofdstuk 6** werd het effect van het gebruik van sympathomimetica op het optreden van ziekenhuisopnamen voor ritmestoornissen bij 1 208 patiënten met hartfalen onderzocht. Wij vonden 149 patiënten ('cases') met een heropname voor ritmestoornissen, en vergeleken hun geneesmiddelgebruik in een genest case-control onderzoek met 149 patiënten ('controls') zonder een cardiaal gerelateerde heropname. Conditionele logistische regressie werd gebruikt om het risico voor ziekenhuisopnames voor ritmestoornissen als gevolg van het gebruik van sympathomimetica te berekenen. Van de 149 'case' patiënten gebruikten er 33 (22.1%) een sympathomimeticum. 6 patiënten (4.0%) gebruikten een systemisch sympathomimeticum. Het gebruik van een sympathomimeticum was geassocieerd met een verhoogd risico op een ziekenhuisopname voor ritmestoornissen (odds ratio (OR) 4.0; CI 95% [1.0-15.1]). Voor systemische sympathomimetica werd een OR berekend van 15.7 (CI 95% [1.1-228.0]). Dit onderzoek geeft sterke aanwijzingen dat het gebruik van sympathomimetica door patiënten met hartfalen de kans op ziekenhuisopnamen wegens ritmestoornissen verhoogt. Sympathomimetica moeten daarom zeer zorgvuldig worden toegepast bij patiënten met hartfalen.

Een aanzienlijk percentage van de patiënten met hartfalen heeft last van hartritmestoornissen. Ritmestoornissen die niet onder controle te krijgen zijn met andere middelen, worden vaak behandeld met amiodaron: een effectief geneesmiddel dat echter een aantal ernstige bijwerkingen heeft.
In **Hoofdstuk 7** wordt het optreden van schildklierstoornissen na het starten met amiodaron onderzocht. We volgden 5 522 patiënten met een eerste recept voor een middel tegen hartritmestoornissen die niet eerder schildkliermiddelen gebruikten. Binnen deze groep patiënten voerden we een genest 'case controle' onderzoek uit. Als 'cases' definieerden we de patiënten die niet eerder dan 3 maanden na de start van het antiaritmicum een schildkliermiddel gingen gebruiken. Als 'controles' gebruikten we de patiënten die even lang antiaritmica gebruikten maar geen schildkliermiddel kregen. We vonden 123 patiënten die een thyreostaticum en 96 patiënten die een thyreomimeticum kregen. Het gebruik van amiodaron bleek geassocieerd met een geadjusteerde OR van 6.3 (CI 95% [3.9-10.2]) voor hyperthyroidie en 6.6 (CI 95% [3.9-11.1]) voor hypothyroidie vergeleken met gebruikers van andere antiaritmica. Patiënten die meer dan 144 gram amiodaron gebruikten, hadden een geadjusteerde OR van 12.9 (CI 95% [6.1-27.3]) voor het optreden van hyperthyroidie. De dosis respons voor het optreden van hypothyroidie was minder uitgesproken. Eerder onderzoek naar het optreden van schildklierstoornissen bij gebruik van amiodaron was tegenstrijdig. Een incidentie tussen 4 en 20% werd beschreven. Deze variatie hangt waarschijnlijk samen met verschillende factoren zoals de duur van de behandeling en de cumulatieve dosering van amiodaron. Wij vonden een risico op schildklierstoornissen dat aan de hoge kant ligt van hetgeen eerder werd gemeld. Behandelaars moeten er vooral rekening mee houden dat schildklierstoornissen nog jaren na start van het gebruik van amiodaron kunnen optreden.

Omdat patiënten met hartfalen vaak veel verschillende geneesmiddelen gebruiken, lopen zij een verhoogde kans op geneesmiddelinteracties. 'Non Steroid Anti-Inflammatory Drugs' (NSAIDS) behoren tot de meest gebruikte geneesmiddelen door ouderen. Daarnaast zouden alle patiënten met hartfalen

ACE remmers moeten gebruiken. Zowel NSAIDs als ACE remmers zijn relatief veilig, maar kunnen nierfunctiestoornissen veroorzaken bij gecompromitteerde patiënten. Er zijn individuele gevallen beschreven waarbij de combinatie van ACE remmers en NSAIDs aanleiding gaf tot nierfunctiestoornissen. Het is niet bekend hoe vaak en wanneer nierfunctiestoornissen optreden bij patiënten die zowel ACE remmers als NSAIDs gebruiken. In **Hoofdstuk 8** werd het voorkomen van ziekenhuisopnamen voor nierfunctiestoornissen onderzocht in een genest case-control onderzoek binnen een groep ACE remmer gebruikers. We vonden een verhoogde kans op ziekenhuisopnamen voor nierfunctiestoornissen bij patiënten die ACE remmers gebruikten, en recent (<90 dagen) gestart waren met een NSAID (geadjusteerde OR 2.2 (CI 95% [1.1-4.5]). Bij patiënten die recent gestart waren met een NSAID en bovendien binnen deze 90 dagen tenminste 3 recepten voor NSAID kregen voorgeschreven, vonden we een geadjusteerde OR van 7.1 (CI 95% [1.8-28.7]). Dit onderzoek geeft sterke aanwijzingen dat gebruikers van ACE remmers die starten met een NSAID, een verhoogd risico op nierfunctiestoornissen hebben. Vooral patiënten die in een korte periode meerdere recepten krijgen, lopen een verhoogd risico op nierfunctiestoornissen. De nierfunctie van gebruikers van ACE remmers die voor het eerst een NSAID krijgen, moet derhalve goed worden gecontroleerd.

Voorspellen van mortaliteit bij patiënten met hartfalen

De vooruitzichten van patiënten met hartfalen zijn slecht. Verschillende eerdere onderzoeken bekeken de factoren die voortijdige sterfte bij deze patiënten voorspellen. Er zijn echter weinig modellen gemaakt waarin verschillende voorspellende factoren worden gecombineerd en waarmee patiënten met een hoog en met een laag risico op sterfte kunnen worden geïdentificeerd. In **Hoofdstuk 9** wordt een alomvattend en eenvoudig toepasbaar prognostisch model gepresenteerd dat de sterfte voorspelt bij de 152 patiënten die werden geïncludeerd in het DECOMP onderzoek (**Hoofdstuk 5**). Gedurende 18 maanden 'follow-up' overleden in totaal 51 patiënten (34%). Onafhankelijke voorspellers van sterfte waren diabetes mellitus, een

voorgeschiedenis van nierfunctiestoornissen (of een laag creatinine of lage creatinineklaring), NYHA klasse III of IV, een lager lichaamsgewicht of lagere quetelet index, lage bloeddruk, aanwezigheid van enkel-oedeem en hogere score op een hartfalen-specifieke kwaliteit van leven vragenlijst. Het gebruik van bètablokkers bleek voorspellend voor een betere prognose. Deze voorspellers werden gebruikt om verschillende modellen te maken. Een model gebaseerd op de medische voorgeschiedenis, gewicht, aanwezigheid van enkel-oedeem en een lage bloeddruk had een 'area under the receiver operator curve' (AUC) van 0.77. Het toevoegen van het gebruik van bètablokkers aan dit model verbeterde de AUC tot 0.80. Het vervolgens toevoegen van NYHA klasse verbeterde de AUC verder tot 0.84. Het toevoegen van de kwaliteit van leven-score verbeterde de AUC amper (AUC 0.85). Dit onderzoek laat zien dat een prognostisch model, gebaseerd op makkelijk verkrijgbare informatie uit de medische historie van de patiënt en op lichamelijk onderzoek, hartfalen-patiënten op adequate wijze kan stratificeren in hoog en laag risico op sterfte op de korte termijn.

De verschillende onderzoeken die zijn samengebracht in dit proefschrift geven meerdere suggesties voor de verbetering van de behandeling met geneesmiddelen bij patiënten met hartfalen. Het is van groot belang dat patiënten die geneesmiddelen gebruiken waarvan is aangetoond dat deze de prognose verbeteren. En vooral dat zij deze middelen blijven gebruiken nadat zij er eenmaal mee gestart zijn. Bijwerkingen en geneesmiddel-interacties treden regelmatig op en vergen daarom permanente aandacht. Artsen en apothekers zouden meer moeten samenwerken om deze patiënten de optimale behandeling met geneesmiddelen te geven.

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Dankwoord

Wetenschap wordt niet meer bedreven in achterkamertjes of ivoren torentjes waar de wetenschapper in alle rust en eenzaamheid zit te ploeteren. Wetenschap speelt zich dezer dagen veeleer af binnen een gemeenschap van gelijkgestemden die vaak over de landsgrenzen reikt.
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John Urquhart is natuurlijk de therapietrouwdeskundige bij uitstek. Hij zei mij in het begin van het project eens: '*Marcel, you should try some frusemide and find how bothersome it is to keep going to the toilet for the hours to come.*' Ik heb de daad bij het woord gevoegd en op een verloren zondagmorgen dit experiment uitgevoerd. Er gebeurde helemaal niets. Althans niet meer dan anders. Waarschijnlijk moet er toch sprake zijn van enige mate van vochtretentie wil een lisdiureticum effect hebben.
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Curriculum Vitae

Marcel Louis Bouvy was born in Amsterdam, The Netherlands on oktober 24th, 1966. He finished secondary school at the 'Johan van Oldenbarnevelt' Gymnasium in Amersfoort, The Netherlands in 1984. He studied Pharmacy at Groningen University between 1984 and 1992. After his PharmD he worked shortly in community pharmacy and at the Dutch Drug Bulletin ('Geneesmiddelenbulletin'). Hereafter he fulfilled his military service as a pharmacist at the Royal Dutch Navy. In 1994 he started working both for The Netherlands Pharmacovigilance Foundation LAREB ('Landelijke Registratie Evaluatie Bijwerkingen') and for the academic community pharmacy Stevenshof in Leiden. In 1999 he left LAREB and started working for SIR (Institute for Pharmacy Practice Research) which is affiliated with the academic pharmacy Stevenshof.

Since 1993 he has been editor of the Dutch consumers book on medicine 'Geneesmiddelen in Nederland'. He has been a member of the editorial board of the Dutch pharmaceutical journal ('Pharmaceutisch Weekblad') between 1994 and 2000. Between 1997 and 2000 he was chairman of the editorial board.

The studies in this thesis were performed between 1996 and 2001.