ELSEVIER

The European Journal of Heart Failure 5 (2003) 195–200

The European Journal of Heart Failure

www.elsevier.com/locate/heafai

Patterns of pharmacotherapy in patients hospitalised for congestive heart failure

Marcel L. Bouvy[a,b,*], Eibert R. Heerdink[a], Hubert G.M. Leufkens[a], Arno W. Hoes[c]

[a]*Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), P.O. Box 80082, 3508 TB Utrecht, The Netherlands*

[b]*SIR Institute for Pharmacy Practice Research, Leiden, The Netherlands*

[c]*Julius Centre for Health Sciences and Primary Care, University Medical Centre, Utrecht, The Netherlands*

Received 15 April 2002; received in revised form 16 July 2002; accepted 17 September 2002

Abstract

Background: In the 1990s, a number of cardiovascular drugs were evaluated in randomised clinical trials. Treatment guidelines for heart failure were modified to include these evidence-based treatments. *Aim:* To evaluate the impact of new medical treatments for heart failure between 1990 and 1998. *Methods and results:* A retrospective cohort study of 2764 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. Use of loop diuretics remained steady approximately 80%, digoxin decreased from 57.6 to 42.7%, angiotensin converting enzyme (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 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.

Keywords: ACE-inhibitors; Beta-blockers; Diuretics; Digoxin; Antithrombotics; Heart failure; Medication patterns; Persistence of therapy

1. Introduction

The ‘epidemic’ of increasing rates of heart failure, thought to have peaked in the mid-1990s, still remains an important cause of morbidity and mortality in the elderly today [1–3]. In the 1990s, a number of cardiovascular drugs, such as digoxin, angiotensin converting enzyme (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 heart failure patients [5–8]. Beta-blockers were shown to provide similar benefits [9–12]. Treatment guidelines for heart failure were modified to include these evidence-based treatments. Attempts should be made to initiate ACE inhibitors or beta-blockers in all patients with heart failure [13]. 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 been repeatedly reported to be low [14–17]. 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 [18,19]. As an example, one third of hospitalised patients stopped taking their ACE inhibitor within 6 months of hospital discharge [18].

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 [14,19–21]. Hospital-based

*Corresponding author. Tel.: +31-30-2537324; fax: +31-30-2539166.

E-mail address: m.bouvy@pharm.uu.nl (M.L. Bouvy).

1388-9842/03/$ - see front matter
PII: S1388-9842(02)00256-8

studies, especially in specialised heart centres, show higher uptake of use of ACE inhibitors and beta-blockers [21–25]. 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 for 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.

2. Methods

2.1. 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. In the PHARMO system, data from all community pharmacies in a number of medium-sized cities in the Netherlands are collected. These data are virtually complete (99%). Pharmacy data and hospital discharge data are anonymously linked using gender, date of birth and general practitioner code. This linking has been shown to be very accurate [26]. We selected a cohort of 3822 patients with at first hospitalisation for heart failure according to discharge diagnosis between 1990 and 1998 (icd 428). The heart failure discharge diagnoses were validated in a separate study and were shown to be accurate [27]. Patients were excluded because of death during the hospitalisation ($n=456$) or because it was not possible to link hospital and pharmacy data ($n=602$; e.g. patients who 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 classification.

2.2. Exposure definition

A patient was defined as a user when there was at least one prescription for any drug dispensed 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. Patients who disappeared from the cohort either because they died, moved outside the scope of PHARMO or for other reasons were censored.

2.3. 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 1990–1992, 1993–1995, and 1996–1998 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) the 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.

3. Results

3.1. Study population

The study cohort comprised 2764 patients with a first hospitalisation for heart failure, with 6805 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).

3.2. 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 approximately 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.

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 ASA	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

3.3. Drug treatment before and after hospitalisation for heart failure

There was an increase in the use of ACE inhibitors, diuretics, digoxin, antithrombotics and nitrates after hospitalisation in all three cohorts between 1990 and 1998 (Figs. 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.

3.4. 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 ($\approx$28% discontinued beta-blockers in the first year after hospitalisation) (Fig. 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, i.e. at least 2 and 3 prescriptions per year, this led to slightly lower percentages. Patterns, however, remained the same (data not shown).

4. Discussion

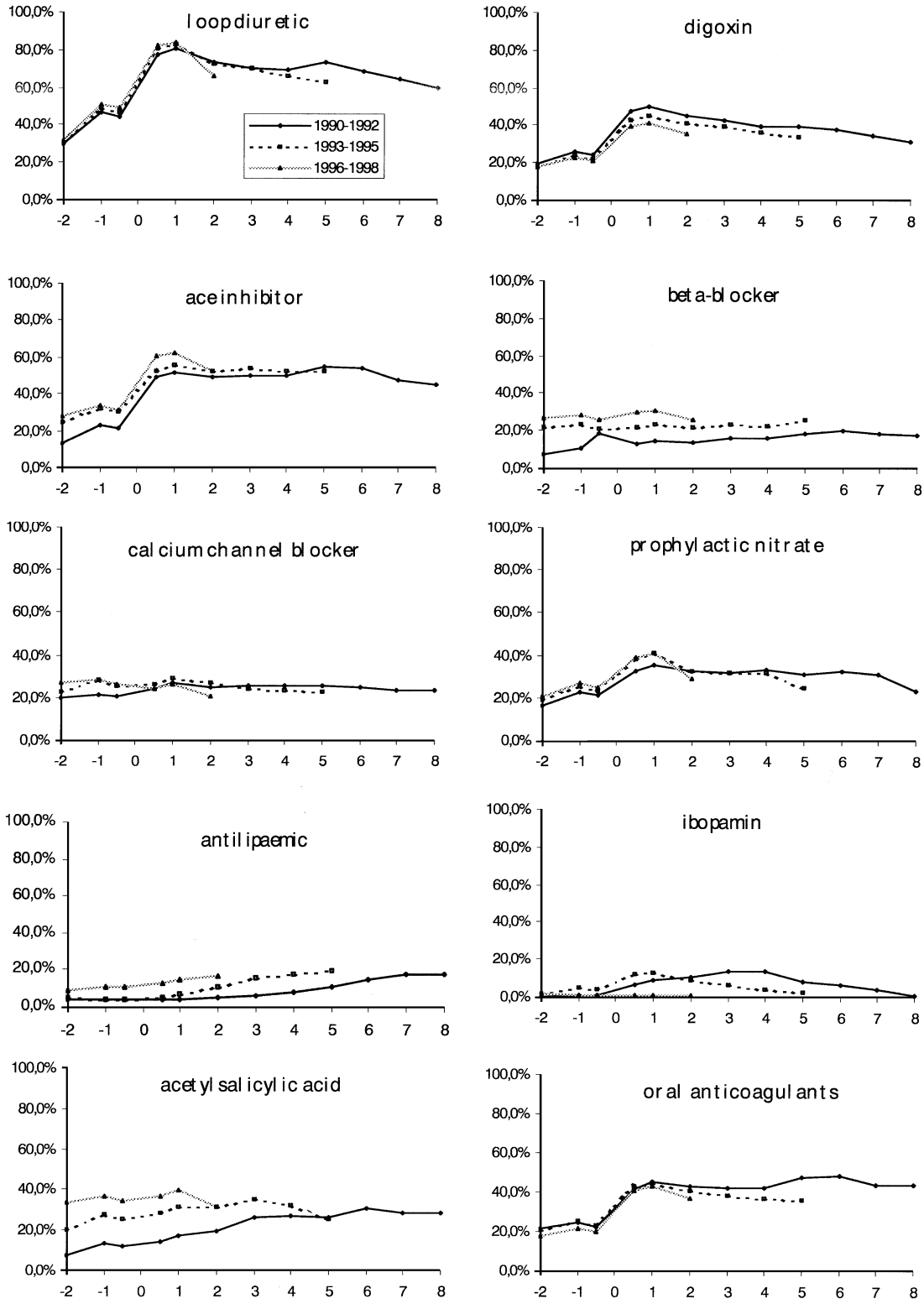
There have been considerable changes in the treatment of heart failure patients between 1990 and 1998; changes which are reflected in an increased number of drugs available and evidence-based guidelines to support physicians in the use of these drugs in practice. This study of the patterns of pharmacotherapy 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 who might benefit. Strikingly, the use of ACE inhibitors even showed a small decrease at the end of the 1990s 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 [22–25]. 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 [28].

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 in use of ibopamin shown in our study reflects the quick uptake and fall of this



Figs. 1–10. Use of medication in the years before (−2, −1, −0.5) and after (0.5–8) first hospitalisation for heart failure.

inotropic agent after the findings of observational studies and the early termination of the PRIME II-trial [29,30].

The use of oral anticoagulants has always been relatively high in The Netherlands where there is a sophisticated system for monitoring international normalised ratio. 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

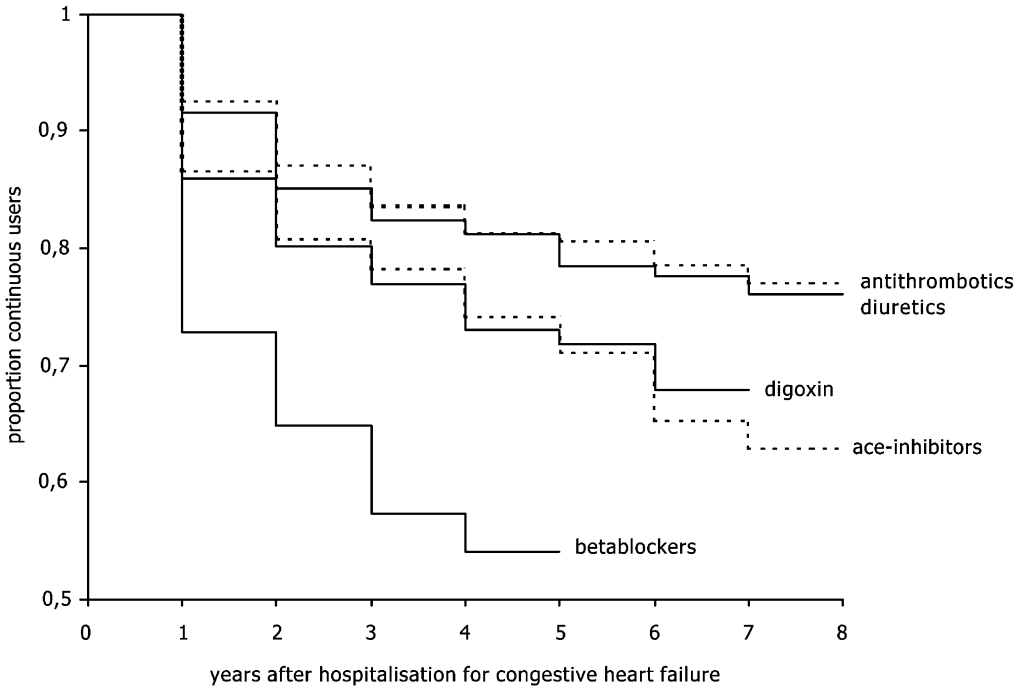


Fig. 11. Long term continuation of therapy.

studies, however, do support the use of ASA in heart failure [31]. 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 [32,33], it seems unlikely that 25% of patients need calcium channel blockers. Calcium channel blockers are prescribed most often for indications other than heart failure, in particular ischaemic heart disease, hypertension and atrial fibrillation. The use of calcium channel blockers in patients with heart failure should always be reconsidered.

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 (Figs. 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 Ref. [18], 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 [28]. 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.

5. Conclusion

Cardiovascular pharmacotherapy in the 1990s 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.

References

[1] Hoes AW, Mosterd A, Grobbee DE. An epidemic of heart failure? Recent evidence from Europe. Eur Heart J 1998;19(Suppl. L):L2–L9.

[2] Reitsma JB, Dalstra JA, Bonsel GJ, et al. Cardiovascular disease in The Netherlands, 1975 to 1995: decline in mortality, but increasing numbers of patients with chronic conditions. Heart 1999;82:52–6.

[3] Stewart S, MacIntyre K, MacLeod MM, Bailey AE, Capewell S, McMurray JJ. Trends in hospitalization for heart failure in Scotland, 1990–1996. An epidemic that has reached its peak? Eur Heart J 2001;22:209–17.

[4] Digitalis Investigation Group (DIG). The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525–33.

[5] SOLVD investigators. Effect of enalapril on survival in patients with reduced left ventri-cular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293–302.

[6] SOLVD investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left-ventricular ejection fractions. N Engl J Med 1992;327:685–91.

[7] CONSENSUS trial study group. Effects of enalapril on mortality in severe congestive heart failure. N Engl J Med 1987;316:1429–35.

[8] Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349–55.

[9] Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–8.

[10] Effect of metoprolol cr/xl in chronic heart failure: Metoprolol cr/xl Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999;353:2001–7.

[11] The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9–13.

[12] Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709–17.

[13] Remme WJ, Swedberg K. Comprehensive guidelines for the diagnosis and treatment of chronic heart failure. Task force for the diagnosis and treatment of chronic heart failure of the European society of cardiology. Eur J Heart Fail 2002;4:11–22.

[14] Stafford RS, Saglam D, Blumenthal D. National patterns of angiotensin-converting enzyme inhibitor use in congestive heart failure. Arch Int Med 1997;157:2460–4.

[15] Sueta CA, Chowdhury M, Boccuzzi SJ, et al. Analysis of the degree of undertreatment of hyperlipidemia and congestive heart failure secondary to coronary artery disease. Am J Cardiol 1999;83:1303–7.

[16] Roe CM, Motheral BR, Teitelbaum F, Rich MW. Angiotensin-converting enzyme inhibitor compliance and dosing among patients with heart failure. Am Heart J 1999;138:818–25.

[17] Smith NL, Psaty BM, Pitt B, Garg R, Gottdiener JS, Heckbert SR. Temporal patterns in the medical treatment of congestive heart failure with angiotensin-converting enzyme inhibitors in older adults, 1989 through 1995. Arch Int Med 1998;158:1074–80.

[18] Roe CM, Motheral BR, Teitelbaum F, Rich MW. Compliance with and dosing of angiotensin-converting-enzyme inhibitors before and after hospitalization. Am J Health Syst Pharm 2000;57:139–45.

[19] Hobbs FD, Jones MI, Allan TF, Wilson S, Tobias R. European survey of primary care physician perceptions on heart failure diagnosis and management (EURO-HF). Eur Heart J 2000;21:1877–87.

[20] Simko RJ, Stanek EJ. Treatment patterns for heart failure in a primary care environment. Am J Manage Care 1997;3:1669–76.

[21] Philbin EF. Factors determining angiotensin-converting enzyme inhibitor underutilization in heart failure in a community setting. Clin Cardiol 1998;21:103–8.

[22] Rich MW, Brooks K, Luther P. Temporal trends in pharmacotherapy for congestive heart failure at an academic medical center: 1990–1995. Am Heart J 1998;135:367–72.

[23] Echemann M, Zannad F, Briancon S, et al. Determinants of angiotensin-converting enzyme inhibitor prescription in severe heart failure with left ventricular systolic dysfunction: the EPICAL study. Am Heart J 2000;139:624–31.

[24] Pearson GJ, Cooke C, Simmons WKT, Sketris I. Evaluation of the use of evidence-based angiotensin-converting enzyme inhibitor criteria for the treatment of congestive heart failure: opportunities for pharmacists to improve patient outcomes. J Clin Pharm Ther 2001;26:351–61.

[25] Taubert G, Bergmeier C, Andresen H, Senges J, Potratz J. Clinical profile and management of heart failure: rural community hospital vs. metropolitan heart center. Eur J Heart Fail 2001;3:611–7.

[26] Herings RM, Bakker A, Stricker BH, Nap G. Pharmacomorbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts. J Epidemiol Community Health 1992;46:136–40.

[27] Heerdink ER. Clustering of drug use in the elderly: population-based studies into prevalence and outcomes (Thesis). Utrecht: Utrecht University; 1995.

[28] Kennedy HL. Current utilization trends for beta-blockers in cardiovascular disease. Am J Med 2001;110(Suppl. 5A):2S–6S.

[29] Hampton JR, van Veldhuisen DJ, Kleber FX, et al. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Second prospective randomised study of ibopamine on mortality and efficacy (PRIME II) investigators. Lancet 1997;349:971–7.

[30] Feenstra J, in't Veld BA, van der Linden PD, Grobbee DE, Stricker BCh. Risk factors for mortality in users of ibopamine. Br J Clin Pharmacol 1998;46:71–7.

[31] Krumholz HM, Chen YT, Radford MJ. Aspirin and the treatment of heart failure in the elderly. Arch Int Med 2001;161:577–82.

[32] O'Connor CM, Carson PE, Miller AB, et al. Effect of amlodipine on mode of death among patients with advanced heart failure in the PRAISE trial. Prospective randomized amlodipine survival evaluation. Am J Cardiol 1998;82:881–7.

[33] de Vries RJ, van Veldhuisen DJ, Dunselman PH. Efficacy and safety of calcium channel blockers in heart failure: focus on recent trials with second-generation dihydropyridines. Am Heart J 2000;139:185–94.