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ORIGINAL PAPER

Trends in prescribing for heart failure in Dutch primary care from 1996 to 2000

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SUMMARY

Purpose The aim of this study is to explore trends in primary care prescribing for chronic heart failure (CHF) over a 5-year period (1996–2000).

Methods This study consisted of repeated cross-sectional surveys in a dynamic cohort from the Integrated Primary Care Information (IPCI) primary care database. The cohort comprised all patients aged ≥ 55 years with a CHF diagnosis and prescribed a cardiovascular medication during the study period. The point prevalence per calendar year was determined for each of the main drug groups used to treat CHF.

Results The study population consisted of 3121 CHF patients. Small increases were seen in the percentage of CHF patients prescribed spironolactone (4.6%, 95% CI: 2.3–6.9%), β-blockers (6.1%, 95% CI: 2.6–9.5%) and angiotensin II antagonists (6.8%, 95% CI: 5.1–8.6%) during the study period, while the prescribing of digoxin decreased (-4.4%, 95% CI: -8.2 to -0.7). Prescribing of diuretics (difference: -0.7% 95% CI: -2.7–4.2) and ACE inhibitors (difference: 4.0% 95% CI: -0.1–8.2%) remained unchanged.

Conclusions Prescription of some drug groups for CHF increased. However, given the new scientific evidence that has emerged in past 15 years regarding CHF pharmacotherapy, the changes observed were less than expected. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — chronic heart failure; drug treatment; general practice; ACE inhibitor; β-blockers

BACKGROUND

During the past 15 years, large international clinical trials have established new scientific evidence in terms of improved prognosis and quality of life for several drug groups that are commonly used for the treatment of chronic heart failure (CHF) (Table 1). Angiotensin converting enzyme inhibitors (ACEI), β-blockers and spironolactone have all been shown to improve the symptoms and prognosis of CHF patients, while scientific evidence regarding the use of digoxin for the treatment of CHF showed improved quality of life and a reduction in hospital admissions.[1–6,7]

During the same period, it has become apparent that despite the advances reported in the scientific literature, prescribing for CHF in daily practice is suboptimal.[8–10] Studies on the use of ACEI for CHF in both primary and secondary care have shown delays in the uptake of clinical trials information into clinical

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Table 1. Major clinical trials for heart failure

Drug group	Trial	Publication year	Major findings
Diuretics	No large RCTs		
ACEI	Consensus[1]	1987	31% ↓ in mortality
	SOLVD 1[2]	1991	16% ↓ in mortality
			26% ↓ in hospital admissions
β-blocker	CIBIS-I[3]	1994	34% ↓ in hospital admissions
	MERIT-HF[4]	1999	34% ↓ in mortality
Digoxin	DIG study[6]	1997	28% ↓ in hospital admissions
			No effect on mortality
Spironolactone	RALES[5]	1999	27% ↓ in mortality
			35% ↓ in hospital admissions
Angiotensin II antagonists	ELITE 2[7]	2000	No difference in mortality between losartan and captopril

practice[11] and such delays are also likely to exist for other drug groups. While a time-lag is known to exist between the publication of new trials and the adoption of new therapies into clinical practice, the length of this time-lag is unknown as changes in prescribing behaviour are usually assessed for limited time periods following a targeted intervention.[12] It has been suggested that specialists incorporate new evidence in their daily practice faster than general practitioners (GPs).[13] However, since the majority of CHF patients are treated in primary care, the uptake of new evidence by GPs is an important issue. Given the major advances regarding optimal heart failure management that have occurred during the past 15 years, it could be expected that corresponding changes would be seen in primary care in the way drugs are prescribed for CHF. While multiple studies have reported low utilisation and little change in the use of ACE inhibitors for the treatment of heart failure, little is known regarding the way other drug groups such as the β-blockers and digoxin are prescribed.[8,14–16] The aim of this study is to explore changes in prescribing for CHF over a 5-year period (1996–2000) focusing primarily on the incorporation of new scientific evidence from clinical trials into daily practice.

METHODS

Setting and study population

In this study, we used computerised medical records from the Integrated Primary Care Information (IPCI) database. This is a longitudinal observational primary care database containing electronic medical records for patients registered with participating Dutch GPs.[17] The IPCI database was established in 1992. The number of practices contributing to the database increased from 50 in 1996 to 106 in 2000 and the number of patients registered with these practices also increased from 163 673 to 322 952 during this period.

In the Netherlands, patients register with a single GP who has a gatekeeper role in coordinating their medical care. GPs contributing to the IPCI database are not permitted to use paper records in addition to their electronic medical records. Thus, the records held by each GP can be considered complete for each patient. A maximum of 3 months medication can be prescribed on a single prescription. Patients referred to a specialist may initially receive drug treatment from the specialist and then generally return to their GP for further medication supply.

Data source

Data in the IPCI database are coded and anonymous and the system complies with European guidelines on the use of confidential data for medical research.[17] Records for each patient include age and sex, symptoms, diagnoses, laboratory tests and results, information on specialist referrals and hospital admissions, GP notes and prescription details. The prescription data include drug name, strength, dosage form, dose, quantity prescribed and indication. Diagnoses and symptoms are entered either as free text or are coded according to the International Classification for Primary Care (ICPC).[18] Medications are coded according to the Anatomical Therapeutic Chemical (ATC) classification.[19]

Cohort definition

Patients with a diagnosis of CHF who were prescribed a cardiovascular medication (ATC code: C*) during the study period were identified from the medical files using either the ICPC coded diagnoses or free text. All potential heart failure patients younger than 55 were excluded. Patients with a CHF diagnosis who were not prescribed a cardiovascular medication were also excluded since an untreated CHF diagnosis may

indicate diagnostic uncertainty on behalf of the prescriber. We defined CHF as a diagnosis recorded by the GP rather than limiting the definition to a diagnosis of left ventricular dysfunction confirmed by ECHO, since a pilot study ($n = 769$) showed that less than 20% ($n = 144$) of patients had undergone an ECHO. We recruited CHF patients treated with any cardiovascular medication to ensure that patients treated with drugs other than those in which we were interested were also included. Patients entered follow-up when all of the following conditions were fulfilled: diagnosis of CHF, 6 months of valid history (registered for 6 months and GP participating in IPCI for at least 6 months). Follow-up ended on the earliest of the following dates: end of the study period, death, transfer to a non-participating GP or last data drawn.

Outcome measurement

To explore trends in the pharmacological management of CHF in primary care, we calculated the point prevalence for specific drugs in the dynamic cohort in the years 1996–2000. For each year, the first Wednesday in October was used as the prevalence index date. On each prevalence index date, the cohort of CHF patients still actively followed at that date was divided into new and old patients. A CHF patient was considered a *new patient* if their first CHF diagnosis was within the 6 months preceding the index date and an *old patient* if the initial CHF diagnosis was made more than 6 months before the index date.

Exposure definition

The main drug groups investigated in this study were those recommended in the 1997 European Society of Cardiology guideline for the treatment of Heart Failure[20] which was the European guideline current at the time of the study. The drug groups included were diuretics, ACEI, β-blockers, digoxin, angiotensin II antagonists and spironolactone. The diuretic groups available in the Netherlands at the time of the study were chlorthalidone, chlorothiazide, hydrochlorothiazide, indapamide, mefruside, bumetanide, furosemide, ethacrynic acid, amiloride, triamterene, triamterene/epitizide, triamterene/hydrochlorothiazide and potassium canrenoate. Patients were considered current users of a drug on the prevalence index date if they had received a prescription for one of the selected drug groups in a 6-month time window prior to the index date. A 6-month time window was chosen since the maximum period that may be supplied by one prescription in the Netherlands is 3 months. Thus, within a 6-month period, it can be expected that a patient currently using a medication would be issued with at least one prescription for that drug.

Analysis

Point prevalence of specific drug use was calculated each year by dividing the number of CHF patients currently treated with the specified cardiovascular medication by the total number of CHF patients who were registered on the prevalence index date for the year. Point prevalence was calculated overall and then stratified for old and new patients. Changes in the prevalence estimates (2000–1996) were calculated for each drug group during the 5-year period and 95% confidence intervals (95% CI) given around all prevalence difference estimates. Confidence intervals were calculated according to the methods outlined in Bland *et al.* (2000)[21] using CIA (Confidence Interval Analysis for Windows 2nd edition) software.[22]

RESULTS

From the source population of approximately 63 000 persons aged 55 years or over in the IPCI database, we identified 3121 patients with a CHF diagnosis who were treated with a cardiovascular medication during the period 1996–2000. Overall, the mean age of the CHF patients increased 1.2 years (95% CI: 0.4–2.0) during the study period, from 77.3 years in 1996 to 78.4 years in 2000. When separated into new and old patients, no increase in age was seen for the new patients. For this group, the mean age was 76.7 years (95% CI: 75.6–78.0) in 1996 and 77.4 years (95% CI: 76.2–78.7) in 2000. For the old patients, the mean age increased from 77.5 years (95% CI: 76.7–78.2) in 1996 to 78.6 years (95% CI: 78.1–79.0) in 2000. The proportion of male patients treated for heart failure increased slightly throughout the 5-year period from 41.3% (95% CI: 37.9–44.6) in 1996, to 44.3% (95% CI: 41.9–46.7) in 2000. Similar increases were observed for both the new patients and the old patients.

Figure 1 shows the prescribing trends observed for the selected heart failure drug groups during the study period. Trends for all CHF patients are seen in Figure 1a, new CHF patients in Figure 1b and old CHF patients in Figure 1c. The trends observed for all patients and for old patients were comparable.

No significant change was seen in the prevalence of patients prescribed a diuretic or an ACEI during 1996–2000 (Table 2). There was a significant increase in prescription of spironolactone, β-blockers and angiotensin

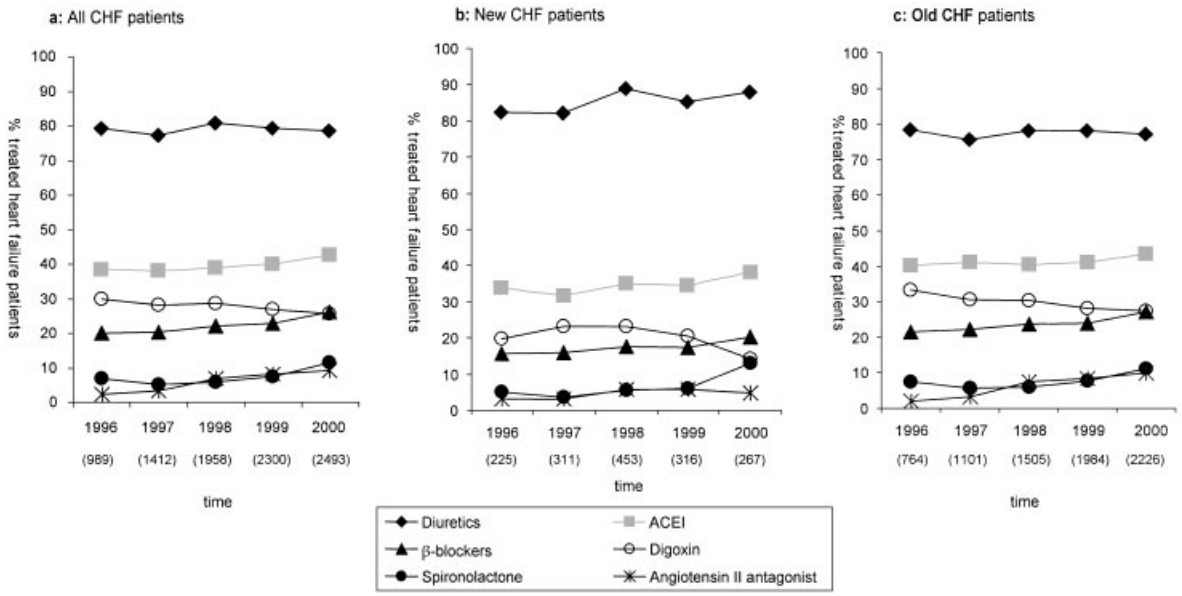

Figure 1. Prescribing of selected cardiovascular medications for heart failure patients. Figures present the number of CHF patients prescribed each drug as a percentage of all CHF patients treated in primary care with the number of CHF patients for each year is presented in parentheses.

Table 2. Changes in the treatment of heart failure in primary care from 1996 to 2000. Presented as percentage of patients

	All patients			Old patients			New patients		
	1996 ($n=989$)	2000 ($n=24$)	Difference (95% CI)	1996 ($n=764$)	2000 ($n=2226$)	Difference (95% CI)	1996 ($n=225$)	2000 ($n=267$)	Difference (95% CI)
Diuretics (excluding)	79.2	78.5	−0.7 (−2.7 to 4.2)	78.3	77.1	−1.2 (−5.1 to 2.7)	82.3	87.9	5.6 (−1.2 to 12.3)
ACEIs	38.6	42.6	4.0 (−0.1 to 8.2)	40.1	43.4	3.3 (−1.3 to 8.0)	33.8	38.1	4.3 (−4.8 to 13.3)
β-blockers	20.0	26.1	6.1 (2.6 to 9.5)	21.4	27.0	5.6 (1.7 to 9.6)	15.7	20.3	4.7 (−2.6 to 11.9)
Digoxin	29.9	25.5	−4.4 (−8.2 to −0.7)	33.2	27.3	−5.8 (−10.2 to −1.5)	19.7	14.3	−5.4 (−12.6 to 1.7)
Spironolactone	6.8	11.4	4.6 (2.3 to 6.9)	7.4	11.2	3.8 (1.1 to 6.4)	5.1	13.0	7.9 (2.6 to 13.2)
Angiotensin II antagonists	2.2	9.0	6.8 (5.1 to 8.6)	1.9	9.8	7.8 (5.9 to 9.7)	3.0	4.8	1.7 (−1.9 to 5.4)

II antagonists for old CHF patients. However, for the new patients only, the percentage of patients prescribed spironolactone increased significantly. The percentage of new and old CHF patients prescribed digoxin decreased during the 5-year study period.

CONCLUSIONS

In this study, we examined prescribing trends for the treatment of CHF in Dutch primary care over a 5-year period, from 1996 to 2000. Internationally, considerable change has taken place over the past 15 years based on the outcome from various clinical trials regarding what is considered optimal CHF pharmacotherapy. We expected that these changes reported in the scientific evidence would be reflected in changes in prescribing. However, while the use of many drug groups for the treatment of heart failure increased from 1996 to 2000, the changes observed in drug use did not appear to follow the changes regarding optimal treatment published in the scientific literature.

Evidence regarding the benefits of ACEIs in the treatment of CHF was first established in 1987 with the publication of the Consensus trial.[1] With further studies strengthening their position in heart failure, the ACEIs are currently considered first-line therapy for all heart failure patients.[2] Despite this wealth of evidence, the percentage of patients treated with an ACEI in our study population was low. The total number of heart failure patients treated with an ACEI did increase by 4% during the study period, however, this increase was not statistically significant. Given the strength of the evidence supporting the use of ACEIs in the treatment of heart failure, a greater increase in the use of ACEIs for CHF was expected. While the main focus of this study was to investigate changes in prescribing over time and not to compare treatment patterns for new and old patients, our results indicate that ACEIs appear to be prescribed more often for the treatment of old cases of CHF rather than being initiated in newly diagnosed CHF patients. Further studies are needed to fully investigate this difference and to elucidate possible factors that may be responsible for it.

While little change was seen in the prescribing of the ACEIs, a considerable increase was observed with respect to the angiotensin II antagonists. Use of this drug group increased from 2.2% in CHF patients in 1996 to 9.0% in 2000. Angiotensin II antagonists were first introduced onto the Dutch market in 1995, and by 2000, six were available in the Netherlands. Clinical trials have shown that these agents are equivalent, not superior to the ACEIs for the treatment of heart failure and they are generally recommended only as alternatives to ACEIs for patients unable to tolerate ACEIs.[21] The increase seen in this population is consistent with the introduction of a new drug group onto the market.[22,23] While prescribing of angiotensin II antagonists increased for both new and old CHF patients, a larger increase was seen for old cases of CHF patients.

Publication of the CIBIS study in 1994 revolutionised the use of β-blockers for the treatment of CHF, reporting a 34% decrease in mortality with the use of bisoprolol.[3] This finding was reinforced with the publication of the MERIT-HF study.[3,4] Guidelines from the European Society of Cardiology published in 1997 recommend the use of β-blockers in CHF but only under specialist care. The current European guidelines (2001) recommend the use of β-blockers in patients with moderate heart failure.[20,26] While the prescription of β-blockers for heart failure patients has steadily increased since 1996, their use in primary care is still low. Since many CHF patients have coexisting cardiovascular conditions such as hypertension or myocardial infarction for which β-blockers are also indicated,[23,24] it is possible that β-blockers prescribed to the CHF patients in this study were actually for the treatment of comorbid conditions rather than for CHF. One factor contributing to the slow adoption of the new clinical trial evidence for β-blockers is that these have traditionally been contraindicated for use in heart failure patients. The Dutch primary care heart failure guideline, published in 1995, recommended that these agents should not be used in heart failure patients, even for the treatment of comorbid conditions.[27] That no significant increase was seen in the prescription of β-blockers to new CHF patients may further be explained by differences in CHF severity between new and old patients. Many new patients may present with less severe heart failure and may be adequately treated with ACEI monotherapy.

The only drug group to show a decrease in use during the 5-year study period was digoxin. Evidence from the DIG study published in 1997 showed that while digoxin had no effect on CHF mortality, it did reduce hospital admissions and improve quality of life.[6] Nevertheless, the use of digoxin decreased from 29.4% of all heart failure patients in 1996 to 25.5% in 2000. Similar decreases were seen with respect to the prescribing of digoxin for both new and old patients. The Dutch primary care guideline for the treatment of heart failure recommends digoxin as first-line therapy for CHF patients with co-existing atrial fibrillation.[27] However, prior to the introduction of the ACEIs, first-line treatment for CHF in primary care generally consisted of a combination of diuretics and digoxin. The decrease in the use of digoxin for CHF patients that was observed in this study most likely reflects these changes in the role of digoxin with respect to treatment of CHF in primary care.

Prescribing of spironolactone increased significantly for both new and old patients. Publication of the RALES study in 1999 demonstrated the benefits of spironolactone as an adjuvant therapy along with ACEI and diuretics for patients with moderate to severe heart failure.[5] Overall, prescribing of spironolactone appeared to decline from 1996 to 1998 and then increased again from 1999. While this increase occurs around the time of the publication of the RALES trial, in this study we are unable to establish a causal effect. Interestingly, similar increases in the use of spironolactone were observed for both new and old patients.

Traditionally, diuretics have been seen as first-line therapy for the treatment of CHF and while there are no major clinical trials involving these agents,

their role in alleviating the symptoms of heart failure is well established. As could be expected, no significant change was seen in the prescription of diuretics. Prescribing of diuretics was slightly higher for new CHF patients than for old patients but this most likely relates to an increased need for reducing volume overload among newly diagnosed patients.

In this study, we have focused on the treatment of CHF in Dutch primary care since in the Netherlands the GP has a central role in the coordination of patient care. Previous studies have shown that heart failure patients in the Netherlands are less often treated with digoxin but more often with ACE inhibitors or β-blockers than in other countries in Western Europe.[28] However, drug use observed in this study is comparable with that reported in other European primary care CHF populations.[29,30]

A repeated cross-sectional survey design based on a dynamic cohort was chosen to examine changes in the drug-use point prevalence during a 5-year period. An important consideration for the choice of this design is the high mortality associated with CHF. Average survival time for a CHF patient is less than 5 years, rendering a traditional cohort design unsuitable for providing an overview of changes in the treatment over a 5-year period. Furthermore, we were interested in prescribing trends for both old and newly diagnosed CHF patients. We defined a current drug user as a heart failure patient who received a prescription for a particular drug in the 6-month time window prior to the index date each year. The difference between definitions of a current user based on treatment duration and methods based on any prescription during a 12-month time window prior to the index date differ by less than 5%.[31] It is expected that the 6-month time window used in this study would further lower this difference.

A limitation of this study is the lack of a specific diagnosis for each medication. As with many cardiovascular drugs, the agents followed in this work are all indicated in the treatment of multiple conditions and CHF patients generally have a high prevalence of comorbid cardiovascular diseases.[26] From the GP records it could not always be ascertained for which cardiovascular diagnosis a particular drug is being used and one drug may be prescribed to simultaneously treat more than one cardiovascular diagnosis in an individual patient. Increases seen in the use of some drugs may be attributable to increased use for cardiovascular comorbidities, rather than to increased use for the treatment of heart failure. However, each of the patients included in this study had a diagnosis of CHF registered in their general practice medical records. Given this, we can assume that the cardiovascular medications included in this study were either prescribed directly for heart failure or in order to treat a combination of heart failure and a comorbid condition.

While an increase was seen in the prescription of many of the drugs commonly used to treat CHF, the increases were much smaller than could be expected given the substantial changes in the evidence regarding optimal CHF treatment. Differences between the patients recruited for clinical trials and those treated in primary care may be one factor contributing towards this.[32] Heart failure patients seen in primary care are older and have more related comorbidities than those participating in clinical trials, which may influence treatment decisions.[33] These patients are also less likely to have undergone confirmatory diagnostic testing such as an ECHO which routinely forms part of the inclusion criteria for clinical trials. These differences may partly explain the low adoption of the clinical trials' evidence into daily practice. GP fears of renal impairment and hypotension have been well documented as barriers to optimal ACEI use[16,34–36] and similar concerns regarding side effects may well play a role in under-utilisation of other drug groups. This study focused on treatment for CHF in primary care. Data from a GP database was used to determine current drug use and medication prescribed by a specialist would not be routinely captured in the GP database and thus, would not have been assessed in this study. Given that in the Netherlands patients referred to a specialist generally return within 3-months to their GP for further medication supply, it is unlikely that specialist prescription would be for longer than a 3-month period.

KEY POINTS

- New scientific evidence has emerged over the past 15 years supporting the use of ACE inhibitors, β-blockers, digoxin and spironolactone in the treatment chronic heart failure but these changes are not being incorporated into daily practice.
- Despite evidence that ACE inhibitors improve both prognosis and symptoms in heart failure and are recommended as first line treatment for all heart failure patients, these drugs are only prescribed to around 40% of Dutch heart failure patients.
- This study highlights the difficulties associated with translating the scientific evidence from large randomised clinical trials into daily practice.

This study highlights the difficulties associated with translating the scientific evidence from large randomised clinical trials into daily practice. An increase was seen in the prescribing of most of the drug groups used to treat CHF during the 5-year study period. However, given the advances in the scientific literature regarding the use of these agents in the treatment of CHF, the increases in prescribing observed were lower than expected. Further studies are needed for exploring the barriers to optimal heart failure care, and interventions bridging the gap between the current evidence and daily practice appear pivotal if the management of heart failure in primary care is to improve.

REFERENCES

1. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; **316**: 1429–1435.
2. The 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**: 685–691.
3. The CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation* 1994; **90**: 1765–1773.
4. The MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; **353**: 2001–2007.
5. The Rales Investigators. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]). *Am J Cardiol* 1996; **78**: 902–907.
6. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; **336**: 525–533.
7. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, *et al.* Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000; **355**: 1582–1587.
8. Hobbs FD. Management of heart failure: evidence versus practice. Does current prescribing provide optimal treatment for heart failure patients? *Br J Gen Pract* 2000; **50**: 735–742.
9. Hobbs FD. Modern management of hypertension and heart failure: evidence and practice. *Heart* 2000; **84**: 35–38.
10. Horan M, Barrett F, Mulqueen M, Maurer B, Quigley P, McDonald KM. The basics of heart failure management: are they being ignored? *Eur J Heart Fail* 2000; **2**: 101–105.
11. McMurray J, Cohen-Solal A, Dietz R, Eichhorn E, Erhardt L, Hobbs R, *et al.* Practical recommendations for the use of ACE inhibitors, beta-blockers and spironolactone in heart failure: putting guidelines into practice. *Eur J Heart Fail* 2001; **3**: 495–502.
12. Haynes RB, Hayward RS, Lomas J. Bridges between health care research evidence and clinical practice. *J Am Med Inform Assoc* 1995; **2**: 342–350.
13. Wieringa NF, Denig P, de Graeff PA, Vos R. Assessment of new cardiovascular drugs. Relationships between considerations, professional characteristics, and prescribing. *Int J Technol Assess Health Care* 2001; **17**: 559–570.
14. Luzier AB, DiTusa L. Underutilization of ACE inhibitors in heart failure. *Pharmacotherapy* 1999; **19**: 1296–1307.
15. Kermani M, Dua A, Gradman AH. Underutilization and clinical benefits of angiotensin-converting enzyme inhibitors in patients with asymptomatic left ventricular dysfunction. *Am J Cardiol* 2000; **86**: 644–648.
16. Horne R, Coombes I, Davies G, Hankins M, Vincent R. Barriers to optimum management of heart failure by general practitioners. *Br J Gen Pract* 1999; **49**: 353–357.
17. Vlug AE, van der LJ, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, *et al.* Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods Inf Med* 1999; **38**: 339–344.
18. World Organisation of Family Doctors (WONCA). *ICPC-2: International Classification of Primary Care* (2nd edn). Oxford Medical Publications: Oxford, 2000.
19. WHO Collaborating Centre for Drug Statistics Methodology. *ATC Index with DDDs 1999.* WHO: Oslo, 1999.
20. Task force of the working group on heart failure of the European Society of Cardiology. The treatment of heart failure. *Eur Heart J* 1997; **18**: 736–753.
21. Bland DG, Machin D, Bryant T, Gardner M (eds). *Statistics With Confidence* (2nd edn). BMJ Books: London, UK, 2000.
22. Bland DG, Machin D, Bryant T, Gardner M (eds). *CIA (Confidence Interval Analysis for Windows) Software* (2nd edn). BMJ Books: London, UK, 2000.
23. Berry C, Norrie J, McMurray JJ. Are angiotensin II receptor blockers more efficacious than placebo in heart failure? Implications of ELITE-2. Evaluation of losartan in the elderly. *Am J Cardiol* 2001; **87**: 606–607, A9.
24. McGavock H, Webb CH, Johnston GD, Milligan E. Market penetration of new drugs in one United Kingdom region: implications for general practitioners and administrators. *BMJ* 1993; **307**: 1118–1120.
25. Martin RM. When to use a new drug. *Aust Prescr* 1998; **21**: 67–69.
26. 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.
27. Walma EP, Bakx HCA, Besselink RAM, Hamstra PWJ, Hendrick JMA, Kootte JHA, *et al.* NHG-Standaard Hartfalen (Dutch College of General Practice Heart Failure Treatment guideline). *Huisarts Wet* 1995; **38**: 471–487.
28. van-Veldhuisen DJ, Charlesworth A, Crijns HJ, Lie KI, Hampton JR. Differences in drug treatment of chronic heart failure between European countries. *Eur Heart J* 1999; **20**: 666–672.
29. Komajda M, Bouhour JB, Amouyel P, Delahaye F, Vicaut E, Croce I, *et al.* Ambulatory heart failure management in private practice in France. *Eur J Heart Fail* 2001; **3**: 503–507.
30. Mejhert M, Persson H, Edner M, Kahan T. Epidemiology of heart failure in Sweden—a national survey. *Eur J Heart Fail* 2001; **3**: 97–103.
31. Mantel-Teeuwisse AK, Klungel OH, Verschuren WM, Porsius A, de Boer A. Comparison of different methods to estimate prevalence of drug use by using pharmacy records. *J Clin Epidemiol* 2001; **54**: 1181–1186.
32. Wieringa NF, de Graeff PA, van der Werf GT, Vos R. Cardiovascular drugs: discrepancies in demographics between

pre- and post-registration use. *Eur J Clin Pharmacol* 1999; **55**: 537–544.
33. Cleland JG. Improving patient outcomes in heart failure: evidence and barriers. *Heart* 2000; **84**: 8–10.
34. Cleland JG. ACE inhibitors for the prevention and treatment of heart failure: why are they 'under-used'? *J Hum Hypertens* 1995; **9**: 435–442.
35. Houghton AR, Cowley AJ. Why are angiotensin converting enzyme inhibitors underutilised in the treatment of heart failure by general practitioners? *Int J Cardiol* 1997; **59**: 7–10.
36. Hickling JA, Nazareth I, Rogers S. The barriers to effective management of heart failure in general practice. *Br J Gen Pract* 2001; **51**: 615–618.

