Safety and costs of initiating angiotensin converting enzyme inhibitors for heart failure in primary care: analysis of individual patient data from studies of left ventricular dysfunction

James Mason, Philip Young, Nick Freemantle, Richard Hobbs

Abstract

Objective To estimate the costs and consequences of diagnosing symptomatic heart failure with left ventricular systolic dysfunction and initiating angiotensin converting enzyme inhibitors in primary care.

Design Analysis of individual patient data from studies of left ventricular dysfunction (SOLVD) to identify complications during test dose and titration phases.

Setting Two randomised controlled trials in secondary care.

Participants 7487 patients taking a test dose of enalapril at enrolment to the treatment and prevention trials; 2569 patients with clinical signs of heart failure and established left ventricular dysfunction entered the treatment trial.

Main outcome measures Discontinuation during the test dose period. Discontinuation or reduction of dose during the first year of treatment for heart failure. Costs of diagnosis and titration of treatment.

Results During the test dose phase, 585 patients (7.8%) reported side effects; 136 (1.8%) of these discontinued because of severe side effects. During the titration phase, compared with placebo, enalapril was associated with an increased risk of dose reduction due to hypotension (odds ratio 2.09, 95% confidence interval 1.15 to 3.82). However, overall, there was no difference in the rates of side effects leading to dose reduction or withdrawal between the enalapril and placebo groups. The costs of diagnosing heart failure with left ventricular systolic dysfunction and initiating and titrating an angiotensin converting enzyme inhibitor in primary care are £300 to £400.

Conclusions Treatment with angiotensin converting enzyme inhibitors can be safely started for patients with heart failure and left ventricular systolic dysfunction in primary care.

Introduction

The use of angiotensin converting enzyme inhibitors in patients with heart failure characterised by left ventricular systolic dysfunction is supported by good evidence on effectiveness and cost effectiveness.[1 2] A meta-analysis of 39 randomised trials estimated that treatment with an angiotensin converting enzyme inhibitor was associated with a 17% reduction in the risk of death (95% confidence interval 10% to 24%).[3] This reduction in mortality is highly cost effective, with a robust estimate of the cost per life year gained ranging between £0 and £10 000 depending on the assumptions made.

The positive findings from recent add-on trials of β blockers in patients with heart failure[4 5] and of spironolactone in severe heart failure[6] have confirmed the place of angiotensin converting enzyme inhibitors in the treatment of heart failure. Treatment with angiotensin converting enzyme inhibitors plus β blockers in patients with heart failure and left ventricular systolic dysfunction is estimated to reduce annual mortality by 5%.[7]

Despite the evidence for their effectiveness, angiotensin converting enzyme inhibitors are underused in primary care.[8 9] This may be partly due to the haphazard availability of diagnostic investigation, particularly echocardiography, resulting in diagnostic uncertainty. However, a trial of ramipril in 10 000 patients at increased cardiovascular risk but without signs of left ventricular systolic dysfunction indicates that modest benefits may be achieved even in this group of patients,[10] and so some imprecision in diagnosis may be acceptable. Many doctors are also concerned about the risk of hypotension and renal damage.[11 12] These problems were reported when angiotensin converting enzyme inhibitors were introduced in the late 1980s and were due to high initial dosing in patients with compromised renal function.

In this paper we examine the risks associated with starting treatment in over 7000 patients with left ventricular systolic dysfunction challenged with an angiotensin converting enzyme inhibitor in the studies of left ventricular dysfunction (SOLVD).[2 13] We also examine the need for reduction in dose and discontinuation during the first year for over 2500 patients with heart failure and left ventricular systolic dysfunction. Finally, we explore the resource implications and costs attributable to treatment in primary care.

Editorial by Cleland et al

Medicines Evaluation Group, Centre for Health Economics University of York, York YO10 5DD
James Mason *senior research fellow*
Philip Young *lecturer in biostatistics*
Nick Freemantle *reader in epidemiology and biostatistics*
Division of Primary Care, Public and Occupational Health, School of Medicine, University of Birmingham, Birmingham B15 2TT
Richard Hobbs *professor of primary care and general practice*
Correspondence to: J Mason jmm7@york.ac.uk

BMJ 2000;321:1113–6

Table 1 Side effects in 7487 patients during two to seven day run-in period for studies of left ventricular dysfunction

Side effect	No (%) of patients	No (%) who discontinued treatment
Any	585 (7.8)	136 (1.8)
Hypotension	148 (2.0)	37 (0.5)
Altered taste	75 (1.0)	7 (0.1)
Rash	45 (0.6)	11 (0.1)
Other problem	294 (3.9)	81 (1.1)
Non-compliance	80 (1.1)	—

Table 2 Predictors of discontinuation of enalapril during run-in period

Predictor	Odds ratio (95% CI)	P value
Age	1.02 (1.00 to 1.04)	0.016
Ejection fraction	0.97 (0.95 to 1.00)	0.042
Packed cell volume	0.93 (0.90 to 0.96)	0.0001
NYHA class III/IV*	1.62 (1.07 to 2.45)	0.023

*New York Heart Association

Participants and methods

We used individual patient data from the studies of left ventricular dysfunction database to quantify important side effects during initiation of the angiotensin converting enzyme inhibitor enalapril, and data on the subset of patients enrolled in the treatment trial to quantify complications during the first year of treatment. The database has been described in some detail.[2 13 14] It comprises patients under the age of 80 (at entry) with left ventricular systolic dysfunction defined as an ejection fraction below 35%. Patients were excluded if they had haemodynamically unstable valvular disease requiring surgery, unstable angina pectoris, angina serious enough to require revascularisation, myocardial infarction in the past month, severe pulmonary disease, serum creatinine concentration >177 μmol/l, or any disease that might substantially shorten survival or impede participation. Patients were initially identified for possible inclusion by reviewing medical records and the logbooks of invasive and non-invasive laboratories or by referral by private physicians. Patients were challenged with a single blind trial dose of enalapril 2.5 mg twice daily for two to seven days. Patients who met the entry criteria, tolerated the test dose, and had symptoms of heart failure were recruited to the treatment trial.[2] Those who tolerated the test dose but did not have objective symptoms of heart failure were recruited to the prevention trial.[13]

Table 3 Demographic characteristics of patients in treatment trial

Variable	No of patients	Mean (SD)	Range
Packed cell volume (%)	2507	42.21 (4.86)	12-58
Diastolic blood pressure (mm Hg)	2562	76.84 (10.27)	40-124
Age (years)	2561	60.92 (9.89)	23.1-80.8
New York Heart Association class:			
I	283 (11.0%)	—	—
II	1457 (56.7%)	—	—
III	783 (30.5%)	—	—
IV	45 (1.8%)	—	—

We used generalised linear models, with a logit link and binomial error, to identify factors that predicted problems leading to discontinuation during the test dose period and discontinuation or dose reduction during the first year of treatment. Specifically, we examined the importance of age, ejection fraction, systolic blood pressure, sex, serum creatinine concentration, packed cell volume, New York Heart Association score, and serum sodium concentration. In line with standard approaches to model development, only those factors that independently predicted outcome were included in the final models.[15] All analyses were conducted with SAS 6.12.[16]

Rates are discussed with reference to a hypothetical cohort of patients that is investigated for treatment of heart failure. Investigation is based on the algorithm from the North of England guideline.[3] The costs of initiating angiotensin converting enzyme inhibitors for heart failure are set against the long term cost effectiveness of treatment. Costs of titration are explored with enalapril and lisinopril, the two most commonly prescribed angiotensin converting enzyme inhibitors in England. All costs are based on the 1999 average NHS costs.[17]

Results

In total, 7487 patients took the test dose of enalapril in screening for the trials. Of these, 585 (7.8%) reported side effects and a further 80 patients (1.1%) did not comply (table 1). The most commonly reported problems were hypotension (2.0%), altered taste (1.0%), and rash (0.6%). A larger group of patients had unspecified problems (3.9%). Only 136 (1.8%) patients reported side effects severe enough to stop taking enalapril during the run-in period.

Age, ejection fraction, packed cell volume, and New York Heart Association score of III or IV all independently predicted discontinuation, and there were no interaction terms (table 2). Thus, overall the risk of dropping out of treatment with enalapril was under 2%. Older patients with more severe heart failure, including severely impaired left ventricular systolic dysfunction and anaemia, were twice as likely to discontinue as other patients.

Symptoms in first year of treatment

A total of 2569 patients were randomised to enalapril or placebo in the treatment trial. Most patients had mild heart failure according to the New York Heart Association classification, and the average age of patients was lower than found in English primary care, which is about 80 (table 3).

We examined the reported side effects that led to a reduction in dose and the extent that these may be attributable to treatment. Side effects included altered taste, rash, pulmonary embolism, azotaemia, and hypotension (table 4). Enalapril was associated with a greater risk of dose reduction due to hypotension: odds ratio 2.09 (95% confidence interval 1.15 to 3.82). Overall, there was no difference in the rates of side effects leading to dose reduction or withdrawal between the enalapril and placebo groups (number of withdrawals 302/1232 *v* 278/1224, odds ratio 1.11 (0.91 to 1.34); number of withdrawals or reductions in dose 328 *v* 332, 0.98 (0.81 to 1.17)).

Resource implications of definitive diagnosis

The best way to identify patients with impaired left ventricular function is by echocardiography or radionuclide measurement. However, if these facilities are unavailable, medical history, response to diuretics, chest radiography, and electrocardiography can be used to identify patients likely to have heart failure. We based our costs on the diagnostic algorithm derived by the North of England guideline group,[3] although its sensitivity and specificity in primary care is not known.

The cost of investigating a patient presenting in primary care with suspected heart failure will depend on the diagnostic options available. If open access echocardiography is available, the costs might be simply those of referral to the service plus one unscheduled visit to the general practitioner to discuss the results. Without open access, patients with an uncertain clinical diagnosis have to be referred to hospital for a definitive diagnosis. Based on average 1999 NHS unit costs for a cardiology outpatient appointment and a general practice consultation, the approximate costs of formal diagnosis of a patient are £88 (table 5).[17] Costs of diagnostic procedures are not reported nationally in England, although a recent study indicated that echocardiography costs about the same as an outpatient attendance.[18] A clinical diagnosis of suspected heart failure is confirmed in about half of cases by echocardiography.[9 19 20] This implies that the cost per case confirmed might be £176, although this does not take account of other abnormalities that might be detected by echocardiography, such as valvular disease.

Resource implications of starting treatment

Before patients with heart failure start treatment with angiotensin converting enzyme inhibitors in primary care they must have their blood pressure measured and a serum profile obtained to determine whether they require referral.[3 21] Referral to hospital for supervised initiation of treatment is advised when patients have above normal sodium or creatinine concentrations or systolic blood pressure, require high doses of diuretic, or show symptoms of severe heart failure. Older patients and those with severe peripheral vascular disease may also need referral.

Patients should be started on a small dose of an angiotensin converting enzyme inhibitor (such as enalapril 2.5 mg twice daily or lisinopril 2.5 mg once daily) with the goal of reaching the doses used in large scale clinical trials (enalapril 10 mg twice daily or lisinopril 20 mg once daily). Older patients and those at high risk of first dose hypotension should be given a small test dose of a short acting drug and monitored closely for two hours.[22 23] Blood pressure, renal function, and serum potassium measurements should be repeated one week after starting treatment and one week after each increase in dose. Patients should then be monitored at least annually. Treatment may need to be decreased or stopped if test results become abnormal.

Table 5 shows the NHS costs of this initiation and titration process. Our model suggests that the cost per patient started on angiotensin converting enzyme inhibitors is about £320, although several factors could lower this cost, such as preavailable echocardiographic findings. Use of lisinopril instead of enalapril requires an additional titration step and leads to a cost per patient initiated of £360. The costs of managing adverse events when starting treatment are not known. However, the studies of left ventricular dysfunction found that side effects are rare and self limiting. We conducted a sensitivity analysis using the range of angiotensin converting enzyme inhibitors and titration schedules listed in the *British National Formulary*.[24] This gave costs between £300 and £400, similar to those for enalapril.

We could not estimate the cost of referral for initiation and titration of angiotensin converting enzyme inhibitors by a cardiologist. No cost data are available for such a referral, and it is unclear whether the titration process, once started would be handed back to the general practitioner to complete.

Table 4 Side effects leading to reduction in dose of enalapril during first year of treatment

Side effect	No in enalapril group (n=1284)	No in placebo group (n=1285)	Odds ratio (95% CI)
Altered taste	1	2	0.50 (0.05 to 5.52)
Rash	3	4	0.75 (0.17 to 3.36)
Pulmonary embolism	4	3	1.34 (0.30 to 5.99)
Azotaemia	12	11	1.09 (0.48 to 2.49)
Hypotension	33	16	2.09 (1.15 to 3.82)
Total	53	36	1.49 (0.97 to 2.30)

Table 5 Costs of diagnosing heart failure and initiating and titrating angiotensin converting enzyme inhibitor therapy

	£
Diagnosis	
General practice opportunistic screen at annual health check	0.00
Echocardiography or referral for cardiological assessment	70.00
General practice assessment visit (to discuss test results)	18.00
Cost of diagnostic work up	88.00
Cost per case detected (assuming half of patients require angiotensin converting enzyme inhibitors)	176.00
Initiation and titration in general practice	
Nurse appointment (measure blood pressure and take blood)	9.14
Analysis of blood	8.00
General practitioner consultation* (view test results, start treatment or refer to cardiologist)	18.00
Start enalapril 2.5 mg twice daily (weeks 1-2)	5.60
Nurse follow up (start of week 2; measure blood pressure and take blood)	9.14
Analysis of blood	8.00
General pracitioner follow up (start of week 3; view test results, measure blood pressure, and increase dose)	18.00
Second dose of enalapril 5 mg twice daily (weeks 3-4)	7.51
Nurse follow up (start of week 4; measure blood pressure and take blood)	9.14
Analysis of blood	8.00
General practitioner follow up (start of week 5; view test results, measure blood pressure, and increase dose)	18.00
Final and long term dose of enalapril 10 mg twice daily (weeks 5-6)	10.53
Nurse follow up (start of week 6; measure blood pressure and take blood)†	9.14
Analysis of blood	8.00
Total cost of initiation and titration	146.20
Cost per patient started on angiotensin converting enzyme inhibitor‡	322.20

*Cost per surgery consultation including practice expense, overhead and qualification elements.[19]
†No subsequent general practitioner consultation is assumed if test values are normal.
‡Cost per patient contact including qualification element.[19]

Discussion

Our analysis of individual patient data from the studies of left ventricular dysfunction shows that introduction of angiotensin converting enzyme inhibitors rarely causes problems. None of the 7487 patients in the initiation phase had a lasting or life threatening event, and in the first year of treatment withdrawal and dose

What is already known on this topic

Angiotensin converting enzyme inhibitors delay disease progression and reduce mortality and serious morbidity in patients with heart failure associated with left ventricular systolic dysfunction

Despite the good evidence of their benefits, these drugs are underused in primary care

What this study adds

Less than 2% of patients receiving a test dose of enalapril reported side effects severe enough to stop treatment

Older patients and those with more severe heart failure are at increased risk of side effects leading to discontinuation

Diagnosing heart failure with left ventricular systolic dysfunction and starting treatment costs £300-£400 per patient

reduction were similar for enalapril and placebo. Intolerance of a test dose was uncommon, occurring in less than 2% of patients, although older patients with severe heart disease were more likely to withdraw.

Our finding relate only to patients younger than 80. However, nearly half of the patients with a clinical diagnosis of heart failure on an average general practice list will be over 80 years of age.[3] Additionally, patients were excluded if they had serious comorbidity or were unlikely to comply, which does not fully reflect patients managed in primary care.

The management pathway shown in table 5 represents reflects current evidence based guidance on best practice. Since the validity of a clinical diagnosis of heart failure in primary care is low (25-50% accuracy),[25 26] a diagnosis of heart failure requires objective evidence of cardiac abnormality.[27] Patients in primary care should at least have electrocardiography as a normal recording will usually exclude left ventricular dysfunction.[28 29] Ideally, general practitioners should have open access to echocardiography.

These data show that the costs of identifying patients and starting treatment are small and do not adversely affect the overall estimates of cost effectiveness of angiotensin converting enzyme inhibitors for heart failure with left ventricular systolic dysfunction (£0-£10 000 per life saved).[3] Doctors' perceptions of the risks of these drugs in patients with heart failure are exaggerated.

We thank the SOLVD investigators for access to their patient data.

Contributors: JM analysed the resource implications of diagnosis and starting treatment, assisted with the interpretation of the trial data, and cowrote the paper. PY analysed the trial data and cowrote the paper. NF had the original idea for study, obtained the trial data, wrote a protocol, helped with the analysis of the trial data, and wrote the first draft of the paper. RH assisted with the interpretation of trial data and resource implications, provided clinical interpretation, and cowrote the paper. NF is the guarantor.

Funding: This study was funded through an unrestricted research grant from Servier Laboratories.

Competing interests: JM and NF have received fees and expenses for research and consultancy work from pharmaceutical companies who manufacture treatments for heart failure, from the Department of Health, and from medical charities. RH is a member of the European Society of Cardiology working party on heart failure, is chair-elect of the British Primary Care Cardiovascular Society, and has received travel sponsorship and honorariums from several biotechnology and pharmaceutical companies with cardiovascular products for plenary talks and attending major cardiology scientific congresses and conferences.

1 CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. *N Engl J Med.* 1987;316:1429-35.
2 SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302.
3 Eccles M, Freemantle N, Mason JM for the North of England Evidence Based Guideline Development Project. Evidence based clinical practice guideline: angiotensin converting inhibitors in the primary care management of adults with symptomatic heart failure. *BMJ* 1998;316:1369-75.
4 CIBIS-II Investigators and Committees. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9-13.
5 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;353:2001-7.
6 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne W, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17.
7 Cleland JGF, Freemantle N, McGowan J, Clark A. The evidence for β blockers equals that for angiotensin converting enzyme inhibitors in heart failure. *BMJ* 1999;318:824-5.
8 Mair FS, Crowley TS, Bundred PE. Prevalence, aetiology and management of heart failure in general practice. *Br J Gen Pract* 1996;46:77-9.
9 Clark KW, Gray D, Hampton JR. Evidence of inadequate investigation and treatment of patients with heart failure. *Br Heart J* 1994;71:584-7.
10 Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on death from cardiovascular causes, myocardial infarction, and stroke in high-risk patients. *N Engl J Med* 2000;342:145-53.
11 Houghton AR, Cowley AJ. Why are angiotensin converting enzyme inhibitors underutilised in the treatment of heart failure by primary care practitioners? *Int J Cardiology* 1997;59:7-10.
12 Hobbs FDR, Wilson S, Jones MI, Tobias RS, Allan TF, Fletcher M. European survey (EuroHF) of primary care physician perceptions and practice in heart failure diagnosis and management [abstract No 1444]. *Eur Heart J* (in press).
13 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.
14 SOLVD Investigators. Studies of left ventricular dysfunction (SOLVD)—rationale, design and methods: two trials that evaluate the effect of enalapril in patients with reduced ejection fraction. *Am J Cardiol* 1990;66:315-22.
15 McCullagh P, Nelder JA. Generalized linear models. 2nd ed. London: Chapman and Hall, 1989.
16 SAS Institute. *SAS-Stat users guide. Version 6.* Cary, NC: SAS, 1990.
17 Netten A, Dennett J, Knight J. *Unit costs of health and social care 1999.* Canterbury: Personal Social Services Research Unit, University of Kent, 1999.
18 Lightowlers S, McGuire A. Cost-effectiveness of anticoagulation in non-rheumatic atrial fibrillation in the primary prevention of ischemic stroke. *Stroke* 1998;29:1827-32.
19 Wheeldon NM, MacDonald TM, Flucker CJ, McKendrick AD, McDevitt DG, Struthers AD et al. Echocardiography in chronic heart failure in the community. *Q J Med* 1993;86:17-23.
20 Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.
21 Agency for Health Care Policy and Research. *Heart failure: evaluation and care of patients with left-ventricular systolic dysfunction.* Maryland: AHCPR, 1994. (Clinical practice guideline 11.)
22 Frank GJ. The safety of ACE inhibitors for the treatment of hypertension and congestive heart failure. *Cardiology* 1989;76(suppl 2):56-7.
23 O'Neill CJ, Bowes SG, Sullens CM, Royston JP, Hunt WB, Denham MJ, et al. Evaluation of the safety of enalapril in the treatment of heart failure in the very old. *Eur J Clin Pharmacol* 1988;35:143-50.
24 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British national formulary.* London: BMA/RPS, 1999. (No 38.)
25 Weeldon NM, McDonald TM, Fluker CJ, McKendrick AD, McDevitt DG, Struthers AD. Echocardiography in chronic heart failure in the community. *Q J Med* 1993;86:17-20.
26 Remes J, Miettinen H, Reunanen A, Pyorala K. Validity of clinical diagnosis of heart failure in primary health care. *Eur Heart J* 1991;12:315-21.
27 Task Force on Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis of heart failure. *Eur Heart J* 1995;16:741-51.
28 Davie AP, Francis CM, Love MP, Caruana L, Starkey IR, Shaw TRD, et al. Value of an electrocardiogram in identifying heart failure due to left ventricular systolic dysfunction. *BMJ* 1996;312:222.
29 NETWORK Investigators. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. *Eur Heart J* 1998;19:481-9.

(Accepted 3 August 2000)