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Extended short report

Determinants of failure to prescribe target doses of angiotensin-converting enzyme inhibitors for heart failure

Juliet Manyemba*, Arduino A. Mangoni, Keith W. Pettingale, Stephen H.D. Jackson

Department of Health Care of the Elderly, Clinical Age Research Unit, Guy's King's and St. Thomas School of Medicine, King's College Hospital, London SE5 9PJ, UK

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1. Background

Angiotensin-converting enzyme (ACE) inhibitors reduce mortality, frequency of hospitalisation for heart failure and slow the progression of left ventricular systolic dysfunction [1,2]. These benefits are independent of baseline use of diuretics, aspirin and beta-blockers and of the type of ACE inhibitor prescribed. Since the original descriptions of outcome benefit from ACE inhibitors, attention has been focussed on examining the dose–response relationship.

The ATLAS study demonstrated reduction in the combined endpoint of mortality and hospitalisation (hazard ratio 0.85, 95% CI 0.78–0.93) with lisinopril 32.5–35 mg daily vs. 2.5–5 mg daily but there is no significant benefit in all-cause mortality and cardiovascular mortality [3]. The NETWORK trial, conducted by general practitioners and hospital physicians in the UK, compared low dose enalapril (5 mg) with intermediate dose (10 mg) and high dose (20 mg) in patients aged 18–85 years with NYHA class II–IV [4]. The study did not demonstrate a relationship between dose of enalapril and clinical outcome (hospitalisation for heart failure, worsening heart failure, death). However, this study had limited power since it treated patients for only 6 months and reported few deaths and hospitalisations. An American study of elderly patients discharged from hospital on ACE inhibitors showed significantly lower mortality at 1 year in patients treated with high dose ACE inhibitors (enalapril 20 mg a day, lisinopril 20 mg a day and captopril 150 mg a day) [5]. The results of the ongoing ACHIEVE trial comparing quinapril 10 vs. 40 mg are awaited. In the meantime the target doses used in the major trials (Table 2) remain the evidence-based doses to achieve benefit.

Most patients with chronic heart failure are now receiving ACE inhibitors. However, the doses prescribed are lower than the target doses shown to be beneficial in clinical trials [6]. Chronic heart failure is prevalent in elderly patients and is a major cause of mortality, morbidity and hospitalisation in this population [7,8]. However, elderly patients with heart failure are under-represented in clinical trials. For example, the mean age of patients was 59 years in the SOLVD trial, 71 years in the CONSENSUS trial and 64 in the ATLAS trial [3,9,10]. They are less likely to be treated with an ACE inhibitor or if they do receive them, are often treated with less than target doses [11].

Previous work has focussed on estimating prevalence of ACE inhibitor use and prescription of target doses [12,13]. However, there are limited data on factors contributing to the use of lower than target doses of ACE inhibitors and hence we have sought to identify these factors.

2. Aim

To determine factors associated with prescription of lower than target doses of ACE inhibitors in patients with chronic heart failure.

3. Methods

We studied case notes of all heart failure patients attending King's College Hospital (Dulwich) medical outpatient clinics from January to September 2001. Patients who had been admitted with heart failure in the preceding 4 months were excluded. This was based on

*Corresponding author. Tel.: +44-207-346-3420; fax: +44-207-346-3441.

E-mail address: juliet.manyemba@kcl.ac.uk (J. Manyemba).

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Table 1
Characteristics of 136 patients being treated as outpatients for heart failure

Demographic characteristics	
Age (years)	78.8±9.4 (range 52–100)
Sex (male/female)	50/86
Comorbidity (*number*)[a]	
Diabetes	31
Falls, dizziness or syncope	30
Stroke/TIA	18
Co-prescriptions (*number*)	
Diuretics	113
Digoxin	42
Nitrates	33
Calcium channel blockers	22
Spironolactone	19
Beta-blockers	17

[a] Ischaemic heart disease was the cause of heart failure in 68 of the 70 cases where aetiology of heart failure was documented.

Table 2
ACE inhibitors prescribed, target doses and proportion of patients receiving target doses

Drug	No. of patients (%)	Target dose (mg/day)	No. receiving target dose (%)
Enalapril	23 (17)	20	6 (26.1)
Lisinopril	16 (12)	20	6 (37.5)
Ramipril	52 (38)	10	19 (36.5)
Perindopril	11 (8)	4	4 (36.4)
Captopril	3 (2)	150	0
Total	105	–	–

the assumption that such patients might still be undergoing dose-escalation. Age, gender, type and dose of ACE inhibitor (if any) prescribed, co-morbidity and other heart failure medication prescribed were recorded. We performed backward stepwise conditional logistic regression using SPSS version 10.0 to identify determinants of sub-target ACE inhibitor dosage. The following variables were entered into the model: age, sex, systolic blood pressure, other cardiac medication and past history of stroke, diabetes and falls.

4. Results

We identified 147 patients who attended medical outpatients with heart failure during the 9-month period. Eleven of these were excluded because they were on angiotensin receptor antagonists instead of an ACE inhibitor. We present data on the remaining 136 patients with a mean age of 78.8 years and range 52–100 years (Table 1). One hundred and five of them (77.2%) were on ACE inhibitors and only 35 (33.3%) received target doses (Table 2). The reasons that were documented for not using ACE inhibitors were a contraindication in 13 and lack of evidence of left ventricular systolic dysfunction in 13. In the remaining 5 patients the reasons for not using an ACE inhibitor were not documented (Table 3).

Table 3
Documented reasons for not prescribing ACE inhibitors

Reason	No. of patients
ACE inhibitor contraindicated	
Renal impairment (renovascular disease in 1 patient)	6
Aortic stenosis	2
Mitral stenosis	1
Adverse drug reactions to ACE inhibitor	
Hyperkalaemia	2
Dry cough	1
Hypotension	1
ACE inhibitor not indicated	
Diastolic dysfunction	2
Normal left ventricular systolic function on echo	3
Heart failure secondary to fast atrial fibrillation	3
Awaiting echo to assess left ventricular function	5
Reason not documented	5
Total	31

Increasing age was associated with prescription of lower doses of ACE inhibitors (OR 0.46; 95% CI 0.26–0.79) (Table 4) ($P=0.006$), i.e. an older patient was less than half as likely to get target doses of an ACE inhibitor as a patient a decade younger. Seventy-three of the patients (54%) were older than 80 years. Further analysis did not show a difference in the ACE inhibitor dosage used between those under 80 years of age and those who were over 80 years of age. The data also showed

Table 4
Final logistic regression model

Variable	Regression coefficient	Standard error	Odds ratio	95% CI	*P*-value
Age (years)	−0.78	0.28	0.46	0.26–0.79	0.006
SBP (mmHg)	1.714	0.76	5.55	1.25–24.6	0.024
Constant	3.724	2.160	41.4	–	–

that patients with a systolic blood pressure greater than 120 mmHg were at least five times more likely to receive target doses of ACE inhibitors than patients with a systolic blood pressure less than 120 mmHg (OR 5.55; 95% CI 1.25–24.6, $P=0.024$).

The other factors (history of falls, stroke, diabetes, serum creatinine concentration, type of ACE inhibitor prescribed and use of other heart failure medication) were not significantly associated with whether or not target doses of ACE inhibitors were prescribed. None of the patients received an angiotensin 2 receptor antagonist in addition to an ACE inhibitor. Therefore angiotensin 2 receptor antagonist co-prescription was not the reason for not using maximum doses of ACE inhibitors. Approximately 95% of patients lived in their own homes and the remainder lived in care homes. Because of the small number of patients in care homes it was not possible to determine whether place of residence determined the dosage of ACE inhibitor prescribed.

5. Discussion

This study showed a rate of ACE inhibitor use of 77%. In only 5 patients (3.7%), was an appropriate reason for not giving an ACE inhibitor not documented. Thus use or non-use of ACE inhibitor was appropriate in 96.3% of the patients. However, there was a low rate of achieving target dosage (33%). The patients fell within a broad age range of 52–100 years and there was a trend to use lower doses in older patients. The Cardiovascular Health Study of over 5000 community dwelling adults aged 65 years or older with heart failure also showed use of captopril, enalapril and lisinopril at doses which were below target [11]. Similarly, a previous retrospective medical record review of over 500 Medicare beneficiaries who were 65 years or older discharged from hospital on an ACE inhibitor, showed an even lower rate of target dose usage (19%) [5]. This decreased with increasing age and was 24% in those aged 65–74 years, 20% in those aged 75–84 years and 11% in those aged 85 years or older. The determinants of ACE inhibitor dosage in the Medicare beneficiaries were previous ACE inhibitor use and the presence of hypertension.

In the ATLAS trial, patients aged 70 years or older receiving high-dose lisinopril experienced hypotension and dizziness serious enough to warrant withdrawal in 2.3% compared to 1.5% in those younger than 70 years of age [14]. The other major trials did not provide data on adverse events by age.

The main limitation of this study was the use of retrospective medical records review, where the quality of information obtained depended on what was recorded at the time of consultation. For example, other factors, which may contribute to drug prescription in the elderly, such as cognitive function and activities of daily living, were not reported. Another limitation to our study was the unavailability of data on the degree of left ventricular dysfunction, which made it impossible to analyse the ACE inhibitor dosage by degree of left ventricular failure. However, the current evidence base suggests that the elderly are just as likely to benefit from optimal dosing of ACE inhibitors, as demonstrated in randomised clinical trials as younger patients. Therefore whether the tendency to use lower doses is due to a perceived or real ability of elderly patients to tolerate ACE inhibitors still needs further investigation.

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