ORIGINAL ARTICLES

A survey of the dose of ACE inhibitors prescribed by general physicians for patients with heart failure

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Abstract

Aim—To describe the pattern of angiotensin converting enzyme (ACE) inhibitor doses prescribed by general physicians for patients with chronic heart failure and to review the current evidence favouring the use of higher doses.

Design—A retrospective survey of the medications of 125 patients with chronic heart failure (in both inpatient and outpatient settings) was carried out between December 1999 and February 2000.

Results—Altogether 18.4% of patients surveyed were receiving no ACE inhibitor, the majority of these (65%) having a contraindication to such an agent. Of those patients who were prescribed an ACE inhibitor, 65% were receiving a high dose. The majority of patients who were prescribed a low dose of ACE inhibitor had no identifiable contraindication to receiving a higher dose. Of all patients with chronic heart failure studied, 25% were receiving either no ACE inhibitor or only a low dose in the absence of contraindication.

Conclusion—Since no objectively measurable variable has been shown to share a clear relationship with the outcome benefits of ACE inhibitors, no convenient and reliable assessment exists for determining when an adequate dose has been reached for each patient. There is an abundance of evidence favouring high dose ACE inhibitors in heart failure; evidence for the role of low doses is much less clear. The fact that only half of the patients with chronic heart failure were found to be receiving a high dose of ACE inhibitor is probably testimony to inaccurate perceptions and unreliable assumptions among physicians. It is likely that a change in current prescribing patterns would benefit patients with chronic heart failure.

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Keywords: ACE inhibitors; dosing regimen; heart failure

The morbidity and mortality benefits of angiotensin converting enzyme (ACE) inhibitors in heart failure are well established.^{1–5} We recognise the importance of evidence based practice when making treatment decisions and hence

the translation of the findings of large, well conducted trials into routine clinical activity. In line with such practice ACE inhibitors have been incorporated into the model therapeutic regimen for chronic heart failure, although it would seem that these agents continue to be underused.^{6–9}

A matter which has gained increasing attention is the dose of ACE inhibitor which should be prescribed. The major mortality studies, which have established the role of these agents in chronic heart failure, used large doses; 50%–100% of the maximum recommended dose in each case was typically set as the target therapy. For example in SAVE,⁵ 150 mg of captopril was used and in AIRE,¹⁰ 10 mg of ramipril was target therapy. The evidence for enalapril, drawn largely from CONSENSUS¹ and SOLVD,² referred to a target dose of 20 mg.

The main argument against prescribing low dose ACE inhibitors is that while there is a strong body of evidence to support high doses, the efficacy of low dose regimens is less well established; after CONSENSUS,¹ large doses of ACE inhibitors were used in subsequent trials.¹¹

We examined the prescribing pattern of general physicians at Belfast City Hospital with regard to the frequency with which heart failure patients received ACE inhibitors and what doses were prescribed.

Method

The records of the last 125 patients whose inpatient or outpatient episode was coded with a primary diagnosis of heart failure were studied. A retrospective analysis began with episodes during February 2000; the “final” chart related to an episode in December 1999 with none of the other episodes predating this. In line with the mortality studies referred to we considered a high dose to be 50%–100% of the maximum dose of any ACE inhibitor (table 1).

Data collected for the purpose of this study were:

(1) Whether the patient was on an ACE inhibitor and, if so, the specific dose.

(2) When the patient was on either no ACE inhibitor or a low dose, the records were reviewed to assess: (i) whether the patient had been recently started on the drug at a low dose and may have been in the process of increasing dose titration; (ii) whether there was evidence of intention to review the dose; (iii) whether

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Table 1 Target (high) doses of ACE inhibitors

Drug	Target (high) dose range
Trandolapril	2–4 mg
Captopril	150–300 mg
Enalapril	20–40 mg
Lisinopril	20–40 mg
Perindopril	4–8 mg
Ramipril	10–20 mg
Quinapril	20–40 mg
Fosinopril	20–40 mg

there was reasonable contraindication to increasing the dose (box 1).

If any of the above characteristics were identified a specific patient episode was not judged to have fallen short of an acceptable dosing standard and was therefore recorded in the high dose group.

Results

Altogether 18.4% of patients studied were not receiving an ACE inhibitor; 35% of this group had no identifiable contraindication.

Of the patients who did receive an ACE inhibitor, 65% were receiving a high dose. Of the 35% who received a low dose, the majority (64%) had no identifiable contraindication to having the dose increased. A total of 18.5% of all patients on an ACE inhibitor were on a low dose without contraindication to a higher dose.

Twenty five per cent of all patients with chronic heart failure studied received either no ACE inhibitor or only a low dose, in the absence of contraindication to high dose ACE inhibitor therapy.

The data are summarised in table 2.

Discussion

RATES OF ACE INHIBITOR PRESCRIBING

Chronic heart failure is a major public health issue, with a general prevalence of 0.4%–2.0% in the UK and among the elderly approximately 10%.¹² It bears significant implications for resource utilisation and hence there is good reason to optimise treatment of afflicted patients. The cost effectiveness of ACE inhibitors in chronic heart failure is well established with one published study suggesting that optimal use of these agents would avoid a considerable number of hospitalisations and deaths to the extent that the saving due to the former would result in a net cost per year of life saved well below accepted cost effectiveness thresholds.¹³

The 80%–90% rates of ACE inhibitor tolerance proposed by mortality studies were quite well reflected in the prescribing rates we measured, although several authors have commented that these are not commonly achieved. Approximately 12% of patients in our study were not on such an agent due to contraindication and a further 6.5% were not receiving ACE inhibitor therapy without clear cause. Davie and McMurray reported an omission rate of around twice this in an earlier study⁸ and data gathered in 1994 in a community health-care setting,¹² although limited, estimated an

Box 1: Accepted contraindications to high dose ACE inhibitor

- Serum potassium >5 mmol/l.
- Serum creatinine >221 µmol/l.
- Symptomatic hypotension.
- Renovascular disease.
- Aortic outflow obstruction.
- Intolerance to adverse effects (for example, cough).
- Allergy.

omission rate of approximately 80%. It is difficult to resist the inference that prescribing rates are likely to have improved during the past few years.

Houghton and Cowley surveyed general practitioners' attitudes relating to chronic heart failure management.¹⁴ They reported that 98% of respondents were familiar with the outcome benefits of ACE inhibitors, however, almost half of respondents expressed concerns about the adverse effects of this group of drugs; those expressing such concern were less likely to initiate treatment. These data point towards failure to prescribe being related more to fear of doing harm than ignorance of potential benefit; of course other considerations are relevant such as the availability of diagnostic equipment.¹⁵ Chin and colleagues found that general practitioners and general physicians tend to underuse these agents when compared with cardiologists, particularly in the setting of heart failure either post-myocardial infarction or in the asymptomatic patient.¹⁶

DOSE OF ACE INHIBITORS PRESCRIBED

Given the difficulties in establishing a clear dose-response relationship for ACE inhibitors among patients with chronic heart failure there has been a widely held belief among clinicians that the effects of these agents are not dose dependent.¹⁷ However, a determinable relationship between dose and suppression of cardiovascular hormones has been identified.^{17–19}

The ATLAS investigators set out to establish whether the increased neurohumoral effects of higher dose ACE inhibitors would translate into improved patient outcomes.²⁰ The primary end point of all-cause mortality during the study period (39–58 months) was 8% lower among the high dose group; this did not reach statistical significance. However, reduction in combined risk of death or hospitalisation (a secondary end point) was significant, at 12%. In addition there was a 24% reduction in cardiovascular hospitalisations among the high dose group.

It is interesting that there was no greater improvement in New York Heart Association (NYHA) class among the high dose group; this raises the important matter of symptom relief not providing an adequate guide to the dose required for optimisation of outcome benefit. By way of contrast, however, another study found high dose enalapril to produce better effects on symptoms than low dose.²¹ It is not

Table 2 ACE inhibitor prescribing pattern in patients with chronic heart failure: summary

Drug	No of patients on drug	No on high dose	Minimum daily dose (mg)	Maximum daily dose (mg)	Mean daily dose (mg)
Trandolapril	43	32	0.5	4	2.4
Perindopril	25	17	2	8	4.0
Lisinopril	19	9	2.5	40	18.8
Quinapril	6	4	10	40	25.0
Captopril	4	0	37.5	75	56.25
Ramipril	3	3	10	20	16.67
Fosinopril	1	1	40	40	40.0
Enalapril	1	1	20	20	20.0
None	23				

unreasonable to accept that the dose-response curve for symptoms is different from that which applies to mortality; it has been previously suggested that symptoms may be governed more by haemodynamic effects and mortality more so by neurohormonal effects.⁷ In addition we should bear in mind that symptoms are subjective and their interpretation leaves room for bias.

It is noteworthy that successful treatment outcomes were achieved with the maximum dose of 4 mg of trandolapril in the TRACE study,²² however, it is disappointing that it was not possible within the remit of this trial to examine the effects of the lower doses prescribed. Critically a smaller study found that elderly patients with chronic heart failure receiving high dose ACE inhibitor experienced a lower incidence of adverse clinical events than those receiving a low dose.²³

Readmission intervals have been found to be greater with high dose enalapril while a dose of 5 mg or less did not influence readmission rate.²⁴ Since ATLAS supports such a finding,²⁰ one must therefore consider the resultant financial impact of prescribed dose of ACE inhibitors.

By way of opposing evidence, the NET-WORK investigators compared 5 mg, 10 mg, and 20 mg of enalapril and were unable to demonstrate a significant relationship between dose and death, hospitalisation, or worsening heart failure.²⁵ Although this study was satisfactorily powered, it had a wide 95% confidence interval and was smaller than ATLAS.

On balance, therefore, it can be concluded that the evidence available weighs in favour of the practice of titrating the dose of ACE inhibitor to the target doses used in the major mortality trials.

Referring once again to the 1994 general practitioner data,¹² the mean doses of ACE inhibitor prescribed were lower than those measured in this study. The mean daily doses recorded in 1994 were: captopril 50 mg, enalapril 8 mg, and lisinopril 9.2 mg. In our study, we found the mean doses to be 56.25 mg, 20 mg, and 18.8 mg, respectively.

Although the range of agents recorded most recently was markedly different, if one compares the drug doses on the basis of potency there is suggestion of a favourable shift.

Chin and colleagues observed that cardiologists were more likely than generalists to increase ACE inhibitors to the target doses used in the major survival studies.¹⁶ The findings of Davie and McMurray⁸ were also consistent with this. This may be explained by

Box 2: Learning points

- In the mortality studies that established the outcome benefits of ACE inhibitors in heart failure, large doses were used.
- The efficacy of low dose regimens is less clear.
- There exists a determinable dose-response relationship that is evident in terms of both biological markers and patient outcomes.
- No objectively measured variable has been identified for determining when, for each patient, an adequate dose has been reached.
- There is, however, an absence of evidence to support a clear mortality benefit of higher doses despite the other identified outcome benefits.
- ACE inhibitors are still felt to be under-used despite improvement in prescribing rates and apparent dose increases in recent years.
- In our study, a substantial proportion of patients were identified who may benefit from more intense ACE inhibitor therapy.

greater familiarity with current evidence and opinion combined with greater experience of prescribing such agents, resulting in a more realistic perspective on the risk of adverse effects and familiarity with the management of these. It would be unreasonable to suggest that all patients with chronic heart failure should be managed by cardiologists on this basis; the resource allocation equation could not easily be balanced.

Interesting data are available which show that although the incidence of ACE inhibitor prescribing is similar throughout Europe, there is marked variation in the proportion of patients receiving high doses between various European countries.²⁶ On average, 25% of Europeans receive high doses; in the UK 35% of patients were on a high dose (the highest of all European countries), compared with only 17% in Belgium (the lowest). The authors of this study were unable to identify differences between patient populations that may account for this. In our study 53% of patients reached such a dose.

Although this pan-European study did not incorporate within the data the number of patients who were unable to tolerate high doses, this may be a critical issue. It enables the identification of those patients not on a high dose without good reason; this is the group which we ought to target with a view to improving our performance.

Conclusion

The evidence available is consistent with the recommendation seen to recur in the medical literature—that is, to titrate the dose of ACE inhibitor to the highest tolerated by each patient, aiming to at least meet the target doses of the major mortality studies.^{27–29} The problem is that the typical dose prescribed in current

common practice falls well short of this. Critically, the findings of our study suggest that around 25% of patients with chronic heart failure are receiving a suboptimal dose of ACE inhibitor without good reason. There also remains some room for improving the proportion of patients started on an ACE inhibitor.

Underdosing of ACE inhibitors may be explained by several possible factors. The most important is, perhaps, the perception that low dose is as effective as high dose and carries a much lower risk of adverse effects. This may be reinforced by the assumption that effect on symptoms is a reliable parameter for measuring the effect on mortality and frequency of hospitalisation. There is lack of sound evidence to support these perceptions.^{14–20} Furthermore, no objectively measurable quantity (such as fall in arterial pressure) has been shown to share a clear relationship with the outcome benefits of ACE inhibitors. Therefore no convenient or reliable assessment exists for determining when an adequate dose has been reached for each patient. Human nature is such that we often prefer to try to measure the benefits of each intervention in each patient, rather than accepting the findings of clinical trials without positive feedback from the patient before us at the time.

Improved awareness of the imbalance between the strong evidence supporting high dose therapy and the paucity of sound evidence in support of lower dose regimens should encourage a practice of aiming higher while we await further data.

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