ACE INHIBITORS IN THE TREATMENT OF CHRONIC HEART FAILURE: EFFECTIVE AND COST-EFFECTIVE

Chronic heart failure (CHF) is the syndrome of breathlessness, fatigue and fluid retention resulting in an impaired ability of the heart to pump properly. The commonest causes are coronary heart disease (CHD) and primary heart muscle diseases (cardiomyopathies), with heart valve disease less common. Heart failure is over-diagnosed (especially in the elderly) and is best confirmed using cardiac ultrasound [1]. Only a minority of people in the community with suspected CHF receive this investigation [2].

The size of the problem

The size of the CHF problem in a health authority with a population of 250,000 and based on a prevalence of 1% [3,4] is shown below:-

| Number of heart failure patients | 2,500 |
| Number of new cases a year (incident cases) | 750 |
| Number of deaths a year | 1,000 |
| Number of hospital admissions a year | 660 |
| Number of GP consultations (3 per year) | 7,500 |

CHF is a serious condition with mortality ranging from 50% over 5 years in mild heart failure [3] to 60% per year in severe cases [5]; these figures are higher than breast and prostate cancer death rates.

About 1% of the NHS budget is devoted to CHF, with 60% spent on hospital admissions [6]. Between 25% and 30% of heart failure patients are admitted every year and CHF accounts for 5% of all medical admissions to hospital [7]. Quality of life for heart failure sufferers is poor and worse than some other chronic diseases such as diabetes and chronic lung disease [8]. The CHF problem will increase (the so-called heart failure epidemic [9]) because of the impact of treatment on other forms of CHD (for example thrombolysis) and the ageing population.

Using ACE inhibitors in CHF

Treatment of CHF aims to improve:-

- Symptoms
- Functional capacity
- Quality of life
- Prognosis (survival)

If the cause of heart failure is atrial fibrillation, irregular beating of the heart, the first choice medicine remains digoxin, as it has been for hundreds of years. Diuretics are the most effective treatment for heart failure symptoms [8], but do not improve prognosis. A number of randomised trials have convincingly demonstrated that angiotensin converting enzyme inhibitors (ACEIs) improve symptoms and survival in all grades of heart failure when given with diuretics [8]. A number of ACEIs have been used in trials and the results suggest that the effect is class rather than drug specific. However, enalapril is the best studied drug at present but there are cheaper alternatives (such as ramipril).

The results of two major RCTs involving enalapril demonstrate the beneficial effects. One RCT involved 253 patients with severe congestive heart failure; half were treated with enalapril 2.5 to 40 mg per day. There was a 40% reduction in mortality risk (95% confidence intervals 5-26%); the largest reduction in mortality was seen in patients with progressive heart failure (22% risk reduction, 95% CI 6-35%). There was a significant reduction in the number of hospital admissions with enalapril by about 30%.

The second RCT involved 2569 patients with chronic heart failure and reduced left ventricular ejection fractions treated with 2.5 to 20 mg enalapril per day with a follow up averaging 41 months. Enalapril use resulted in a 16% reduction in mortality risk (95% confidence intervals 5-26%); the largest reduction in mortality was seen in patients with progressive heart failure (22% risk reduction, 95% CI 6-35%). There was a significant reduction in the number of hospital admissions with enalapril by about 30%.

A comparison of the effectiveness of some of the commonly used cardiovascular drugs demonstrates the beneficial effects of enalapril, as shown in the Table overleaf.
Everyone with CHF who has been stabilised with diuretics should be considered for having an ACEI added to their therapy, unless there are specific contraindications (such as aortic stenosis [10]). Currently, only about 10% of CHF patients are on ACEI.

In a health authority of 250,000 people, around 40 deaths and 300 hospital admissions could be prevented each year using ACEIs.

Most people (around 98%) could have treatment started in general practice [11], especially as three ACEIs are licensed for this purpose. Fears about hypotension and renal failure (which meant more people starting treatment in hospital) have been overstated, especially when first doses are low and sensible guidelines followed to detect patients at risk [8].

### Problems with ACEIs

These medicines are generally well tolerated and some of the early problems were because of the high doses used. Cough is a well known problem, but is also common with people with CHF who aren’t treated (31% of controls and 37% of enalapril treated patients in trials) and is less of a problem than in patients given ACEIs for hypertension. However, only 1% of people stopped treatment because of their cough. Other adverse effects include rash, taste disturbance and impaired renal function.

### Current areas of uncertainty for ACEIs

There are two areas of uncertainty, firstly whether asymptomatic people with left ventricular dysfunction should be treated, and secondly, what is the optimal therapeutic dose. Studies are in progress to answer these questions.

### Direct costs of introducing ACEIs

The impact of introducing ACEIs to patients with CHF in a health authority of 250,000 people over 1 year have been calculated based on published economic analyses [6,12]. The analysis suggests that a net saving could be made by introducing an ACEI to patients if the 98% in whom it was appropriate had treatment started in general practice. The balance between overall savings and costs depends on the proportion of patients whose treatment is initiated by the GP:

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Cost</th>
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<tbody>
<tr>
<td>If 40% of patients admitted as day cases for treatment initiation</td>
<td>£76,000 input</td>
</tr>
<tr>
<td>If 2% of patients admitted as day cases for treatment initiation</td>
<td>£60,000 saving</td>
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</table>
Note: SOLVD results [11] for reduced admission rates, improved survival and usual enalapril dose (20 mg od). Includes capital and revenue costs of an extra echocardiogram machine plus costs of echoes for every patient with CHF. These will be less in subsequent years. Two extra visits to GP per patient per year for monitoring therapy (Fourth National GP Morbidity Survey), extra biochemical tests (to exclude renal impairment) are included. Costs are direct NHS costs for 1990/1 [6,12].

Conclusion

Large improvements in the quality and quantity of life for people with CHF could be achieved by using ACEIs appropriately. Treatment could be introduced at minimal cost to the NHS and might achieve savings. However, costs and savings would be unevenly distributed: primary care would pick up most of the prescribing costs and no apparent savings; the acute sector would pick up capital and revenue costs of echocardiography and any potential savings from reduced hospital admissions. If we are to encourage evidence-based prescribing in this area, these issues need addressing soon.

Dr Simon Sanderson
Senior Registrar in Public Health Medicine
Cambridge and Huntingdon Health Commission

References:


Questions to be answered

Q: What need is met by this treatment?
A: Improved quality and length of life for CHF patients, coupled with likely savings for the NHS.

Q: What happens at present?
A: Only about 10% of CHF patients receive ACEIs. Most could have the medicine safely prescribed for them.

Q: How does this improve effectiveness or quality?
A: Each health district of 250,000 could reduce deaths by 40 a year and hospital admissions by 300 per year.

Q: What is the capital cost?
A: Small - probably one echocardiogram per district.

Q: What is the revenue cost per case?
A: The revenue cost per case of CHF treated with ACEIs is £300 per year.

Q: What is the likely total cost per million population? (capital or depreciation plus cost/case times number of cases)
A: About £3.6 million.

Q: Will this increase or decrease total cost of secondary care?
A: Secondary care costs could be reduced by around £800,000 in an authority of 250,000 if the expected reduction in hospital admissions occurs.

Q: What is the effect on total cost?
A: Could be as high as an increase in £900,000 (revenue plus capital/depreciation) in an authority of 250,000 if 40% of patients were admitted to hospital for initiation of treatment. The lower the proportion of patients admitted to hospital for initiation of treatment, the lower would be the effect on total cost.

Q: What cost savings are likely?
A: Cost savings as high as £60,000 could be achieved in an authority of 250,000 if only 2% of patients have treatment initiated in hospital as inpatients and if the expected reduction in hospital admissions occurs.

Advice to health authorities and GP fundholders

1 Will increase quality and effectiveness.
2 Will increase/decrease total cost of care.
3 Include in specification.
**LAXATIVES: DIFFERENT ASPECTS OF THE SAME SUBJECT**

The Medicines Resource Centre (MeReC) Bulletins from Liverpool began in June 1990 after publication of the DoH working paper on improving prescribing. Free to GPs, the bulletins provide immediately usable information on medicines and their effectiveness. The June 1994 bulletin on the treatment of constipation [1] is typical: a clear statement of the problem, executive summary, background and treatments available and graphics with comparative costs of different treatment choices.

However, there are other aspects to laxative use and constipation. In the UK some 10 million prescriptions are written annually for laxatives, and many more non-prescription laxatives are taken. Two studies from the early '90s are worth considering with the MeReC bulletin.

**A better way to go?**

It is now well accepted that increased fibre in the diet represents a better way of preventing constipation, rather than uncontrolled, often excessive use of laxatives by people with a poor diet. The elderly particularly have a low fibre intake, with concomitant increased prevalence of constipation. Wholemeal bread, fruit and vegetable consumption is better than taking laxatives.

An Australian study from 1991 [2] examined the effects on laxative sales of two methods of promoting increased consumption of wholemeal/wholegrain bread by the elderly. These studies of community intervention were conducted in three small towns on the mid-north coast of New South Wales.

The towns had populations of 1400 to 1800; one was used as a control (CON), while in two others a community organisation strategy (COS) involving the media, community activities and social marketing principles using the theme “Bread: It’s a Great Way to Go” was compared with a patient education strategy (PES) through local doctors to patients over 55 years.

The main outcome measures were the sales of wholemeal/wholegrain bread and laxatives before and after the 4-month campaigns.

**Results**

The effectiveness of the community organisation strategy compared with patient education strategy was overwhelming. The PES community was no different from the control community, with trivial changes in sales of bread and laxatives. By contrast the COS community recorded a 60% increase in bread sales and a 60% fall in laxative sales - highly significant results before a statistical test was even thought of.

**What is COS?**

The COS included the media, community events, bread pricing and social marketing. The centrepiece was a pamphlet with the theme “Bread: It’s a Great Way to Go” which provided detailed information about bread and its benefits as well as tips for using bread.

Those are the details given in this short report in the Medical Journal of Australia. They don’t tell us how much cheaper was the bread - implied by their reference to bread pricing. However, the implication is that the small community of Harrington (population 1659, 40% over 55 years) was subjected to a powerful advertising blitz about the value of bread. It is a shame that the advertising cost per person was not given: it would be interesting to compare with other heavily advertised health promotion messages.

**Laxative induced diarrhoea**

Another aspect of laxative use in populations is the abuse of laxatives by individuals. If a patient complains of diarrhoea, the GP or gastroenterologist may consider an idiopathic origin, but the very patient most likely to be abusing laxatives is most likely to be economical with the truth when asked directly.

**How big is the problem?**

A 1992 study from Glasgow provides the answer [3]. Glasgow is fortunate in having superb biochemistry services, and as part of this a laxative screening service using urine...
samples was established and offered to gastroenterologists covering the West and Central belt of Scotland.

In 49 patients referred to the gastroenterology clinic from GPs for the investigation of diarrhoea, in two patients (4%) the complaint was found to be self-induced.

In 10 patients who had already been extensively investigated for diarrhoea of unknown origin, two (20%) gave positive urine tests for laxatives.

**What are the costs and savings?**

In eight patients in whom the diagnosis of idiopathic laxative use was unsuspected, an average of £2,807 (range £60 - £10,709) was spent on tests which would have been unnecessary had an earlier laxative screen been performed.

A laxative screen can be conducted on a urine sample using simple thin layer chromatography by any biochemistry laboratory at a cost of about £40. Glasgow estimated that the cost of performing a laxative screen on all patients presenting with diarrhoea was estimated at £600 for each laxative abuser detected compared with unnecessary expenditure of £2,807 per laxative abuser without screening, an 80% saving per laxative abuser.

**Conclusion**

Perhaps it would be sensible to perform laxative screens on all new patients referred for investigation of diarrhoea.

**References:**

1 The treatment of constipation. MeReC Bulletin vol. 5, no 6, June 1994. Medical Resources Centre, Hamilton House, 24 Pall Mall, Liverpool L3 6AL.

**PROSTACYCLIN IN PRIMARY PULMONARY HYPERTENSION**

Primary pulmonary hypertension is a rare disease, affecting about one person in 150,000 at any one time. Its cause is not known. Blood vessels in the lungs become diseased leading to a rise in blood pressure in them, and in arteries leading to the lungs. In its milder form it can be managed with familiar drugs such as calcium antagonists and anti-coagulants, but it is often progressive, in which case treatment with prostacyclin (epoprostenol, PGI2) is sometimes used.

Patients with severe disease may be offered heart-lung transplantation. Prostacyclin is licensed as an anticoagulant for use during renal dialysis, but not for primary pulmonary hypertension. There is no evidence that the drug alters the progress of the disease; it acts as an inhibitor of platelet aggregation and may prevent pulmonary thrombosis, an important complication of the disease.

**Is prostacyclin treatment effective?**

Only three controlled studies comparing prostacyclin with conventional treatment which report the impact of this drug on clinical outcomes have been published. Two reported randomised trials. The first [1] showed an improvement in haemodynamic variables and symptoms, but was too short to examine survival. The second [2] showed that the addition of prostacyclin improved walking distance, quality of life and survival to twelve weeks (0/41 versus 8/40, p=0.0029). This second study is published only in abstract, making thorough appraisal impossible.

A third paper [3] investigated 44 patients at a British hospital; in 25 the decision to purchase prostacyclin treatment was made by the patients’ health authority, and in 19 the decision was not to purchase, so the treatment decision was not randomised. A group of historical controls from the Mayo Clinic comprised patients studied before the drug was available. In terms of prognosis at outset the historical controls were in a more favourable position than the British patients, while the untreated British controls may have had a slightly better outlook than the treated patients.

The British patients (together) had a relative risk of death of 0.56 (95% confidence interval 0.31 to 1.00) compared with historical untreated controls from the Mayo Clinic. Among the British cohort, prostacyclin doubled the time on the waiting list for heart-lung transplantation or to death (from 8 to 17 months). Deaths differed little between groups (9/25 compared with 9/19); prostacyclin apparently increased the chances of transplantation but the numbers were very small (7/25 compared with 3/19) and the difference was not significant.

The total number of patients on prostacyclin in all these studies was 149, and the results can only be regarded as preliminary. It is not clear how the patients who were treated differed from those who were not, but such differences may explain differences in outcome. There is an obvious need for a much larger, adequately reported randomised controlled trial of prostacyclin, since random allocation is the only way to exclude differences between groups of patients. Postponing transplantation is not necessarily desirable since it leaves the patient symptomatic for longer and defers rather than removes the need for transplantation surgery, thus only helping match supply and demand of donor organs in the short term.

**How much does prostacyclin cost?**

A vial of prostacyclin contains 0.5 mg and costs £103. The drug is infused continuously into a central vein and the minimum requirement is two vials a day. This costs £75,800 a year. As patients deteriorate their requirement rises, sometimes up to 12 or 15 vials per day, costing up to £500,000 per year. Nearly all these costs are for patients treated outside hospital. At the moment, specialist units using prostacyclin estimate that about one patient per health authority will be recommended to receive prostacyclin at any
one time. Nearly all of these are assessed for transplant, but those doing well on prostacyclin are not considered urgent cases for transplantation.

What should purchasers do?

This is a very expensive treatment for a rare but often fatal disease. The evidence of efficacy is scanty and at the moment the drug can only be used experimentally rather than as part of evaluated and accepted routine clinical practice. However, the number of patients is very small and unlikely to rise.

Purchasers should encourage the entry of patients into a large randomised controlled trial. In the meantime prostacyclin for primary pulmonary hypertension should not be purchased.

Dr Tom Dent
Senior Registrar in Public Health Medicine
Cambridge and Huntingdon Health Commission

References:

Questions to be answered

Q: What need is met by this treatment?
A: Possibly increasing life span, and chance of transplantation in a group of patients with a rare disease.

Q: What happens at present?
A: Prostacyclin is only given by specialist units.

Q: What is the revenue cost per case?
A: From £75,000 to £500,000 per year per case.
Q: Will this increase effectiveness or quality.
A: On present evidence this is unlikely.

Q: Is more information needed?
A: Yes. RCT with appropriate numbers is needed.

Advice to health authorities and GP fundholders

1. Will not increase quality or effectiveness.
2. Will increase total cost of care.
3. Patients treated should be part of a well-organised RCT.

Reader’s points

The June edition of Bandolier 5 reviewed the role of cholesterol screening and the treatment of hypercholesterolaemia. It concluded that screening will not make a contribution to the lowering of overall mortality rates and should be discouraged whilst treatment should be targeted at those patients with the highest overall risk of coronary heart disease. I agree with this, but not with your endorsement of the conclusions of a recently published meta-analysis of cholesterol lowering treatments (Smith, Song & Sheldon, BMJ 1993; 36: 1367-73) which suggested that the likely benefit of treatment was restricted to patients with an annual coronary heart disease mortality rate exceeding 5%.

Implementation of this finding in clinical practice would result in some highly questionable decisions. For instance, lipid lowering drug therapy might be prescribed to men aged more than 80 years since their annual CHD mortality exceeds 3.3%. Drug treatment would be denied to men aged 35-44 years with familial hypercholesterolaemia in whom the annual incidence of fatal coronary heart disease is 1.1%, and the cumulative risk in this condition of a fatal or non fatal myocardial infarction by the age 60 years is about 50%.

The explanation for these anomalous conclusions is that the meta-analysis cited included trials with subjects ranging in age from 18-70 years. Epidemiological principles - and common sense - suggest that the absolute risk of coronary heart disease is unhelpful in determining whether drug treatment is appropriate unless age-specific incidence is taken into account.

Dr Andrew Neil
Radcliffe Infirmary
Oxford

Using the evidence

Northamptonshire project on stroke

Bandolier 3 (April ’94) reviewed the Northamptonshire GRiP project on Stroke rehabilitation. Marie-Josée Blais of the Northamptonshire Directorate of Public Health Medicine has now published a stroke literature review which Bandolier is delighted to recommend to its readers, though to call it a literature review grossly understates its quality and value.

This highly readable monograph has 241 references, 15 tables and 10 appendices. Most important is that it extracts all the relevant information from the huge background literature they have chosen to review and lays it out clearly for the reader to benefit.

Quite apart from a superb executive summary which in a few pages outlines the problems for stroke rehabilitation, there are 10 short and punchy chapters covering topics from background and primary and secondary prevention, through delivering stroke services, to information requirements and research priorities.
There is so much information in this document; on costs, for instance, it runs from the £791 million which was the estimated cost of strokes to the NHS in 1990/1 to the £1.94 cost of an ESR in Northampton, making it impossible to review adequately. While there is a necessary local spin to this monograph, there is something in it for any geographical location. It is the best possible example of how to review a problem to ensure that all the important questions are being asked.

“Stroke: literature review” is available at £5 per copy from Dr Jill Meara, Director of Public Health, Northamptonshire HA

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**POWER AND CONFIDENCE**

Many readers will remember the sense of satisfaction they felt when they first mastered the principle of the P-value and could either themselves assert, or understand when others asserted, that a particular result was “significant” or “not significant”. The P-value is now largely dead and new methods of reporting significance have emerged.

**The rise of the confidence interval**

As the P-value has declined, so has the confidence interval increased and the confidence interval, usually set at 95% limits (though others may be used), is a visually dramatic and comprehensible way of describing the confidence that can be placed on “the result”.

Confidence intervals figure largely in many systematic reviews and meta-analyses, and Bandolier has used them in previous editions.

**The rise of power**

More recently there has been growing interest in the power of a study. This is “the probability that a study of a given size would detect a statistically significant real difference of a given magnitude” [1]. If the difference expected is a 100% reduction in mortality, a small study will have sufficient power; if the expected reduction in mortality is much smaller, say 5%, then a very much larger study must be conducted to produce a result which will have statistical significance.

Of course, the question needs still to be addressed as to whether a statistical significance is clinically important or effective.

**Post hoc power**

As the concept of power becomes more widely diffused, it is becoming increasingly common to ask in journal clubs or in letters to the editors of journals “what was the power of the study to detect the observed difference?” This may seem a sensible question to ask, but an excellent and mindstretching article by Goodman & Berlin [2] points out why this question is inappropriate, and how to place reliance on confidence intervals. Those who wish to read about trials in the original reports are well-advised to read this paper, as are those who are sufficiently well-adjusted to realise that their statistical know-how needs a brush-up.

Another important paper is that by David Moher and his colleagues in Ottawa, who reviewed 383 randomised controlled trials published in 1975, ’80, ’85 and ’90 in JAMA, Lancet and New England Journal of Medicine. Of these, 27% were classified as having negative results, but only a small fraction had sufficient power to detect relative differences of 25% or even 50%, and only 20 of the 102 reports made any statement related to the clinical significance of the observed differences.

**Educational objectives**

Those who wish to mindstretch should set themselves some objectives and here are some to consider. Someone who wishes to be an interpreter of the evidence should be able:

- to define and describe to people what is meant by the power of a study;
- to describe what is meant by confidence intervals.

**References:**


**DIFFICULT DECISIONS**

Bandolier 2 featured the first of a series of articles by David Eddy from JAMA called “Three battles to watch in the 1990s”. The second article of the series is entitled “Principles for making difficult decisions in difficult times”; like the first, it is a hard but worthwhile read.

Although directed at US healthcare systems the way in which Eddy tackles the difficulties which limited resources bring to health care delivery are equally applicable to the UK. Purchasers and providers should both take note of this powerful article - what is highlighted is the inevitable tension between the needs of the individual and the needs of the population as a whole, and the sometimes unpalatable alternative choices that result.

Eddy is careful not to overuse the word rationing - but decisions about how to make effective decisions about the use of limited healthcare resources is what this article is all about, as summarised in the figure. Whichever part of the system you occupy, this will help on good and bad days.

**Reference:**

• Why Ration?
  – because resources are limited
  – to maximise the health of the population served using the limited resources

• What is Rationing?
  – individual
  – society

• How to Ration
  – set priorities between treatments
    » rank treatments in order of benefits
      • need good quantitative estimates of benefits, harms and costs
      • empirical evidence required
        – when empirical evidence contradicts subjective, empirical takes priority
    » treatment must be
      • more effective than no treatment in improving health outcomes
      • risk:benefit better than no treatment
      • as cheap or cheaper than next best alternative

60 units of benefit to 1 person
at equal cost
30 units of benefit to each of 5 persons