WORKING GROUP ON ACUTE PURCHASING

Angiotensin-Converting Enzyme (ACE) Inhibitors in Heart Failure: Reducing Mortality and Costs to the NHS

March 1998

GUIDANCE NOTE FOR PURCHASERS 98/05

Series Editor: Nick Payne

InterDEC No: 12/1998

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help Health Authorities and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise. It is chaired by Professor Sir David Hull.

The Committee recommends, on the basis of evidence provided, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by Health Authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 21 July 1998 at which this Guidance Note for Purchasers (in a draft form) was considered.

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS IN HEART FAILURE: REDUCING MORTALITY AND COSTS TO THE NHS

AUTHORS:

Cornell S J, Calvert N W, Hayes A, Channer K S, Singleton C D. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield 1998. Guidance Note for Purchasers: 98/05.

EXPERT ADVISORS TO TRENT DEC:

Dr S J Cornell, Consultant in Public Health Medicine, Doncaster Health Authority
Dr N W Calvert, Research Fellow in Health Economics, ScHARR

DECISION:

The Committee supported a wider use of ACE inhibitors and recommended that echocardiograms be made more readily available for patients where diagnosis was in doubt. The Committee also recommended that the cheaper first generation drugs should be prescribed for all new patients, but that there should be no 'blanket switch' for those patients already using an alternative product.

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Conflict of Interest None of the authors of this document has any financial interests in the drug or product being evaluated here.

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ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Institute:

- undertakes Health Services Research (HSR), adding value to the research through the networks created by the Institute;
- provides advice and support to NHS staff on undertaking Health Services Research;
- provides a consultancy service to NHS bodies on service problems;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

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Professor C E D Chilvers (Nottingham); and
Professor M Clarke (Leicester).

Professor Clarke currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within The University of Sheffield in conjunction with The School of Health and Related Research (ScHARR).

FOREWORD

The Trent Working Group on Acute Purchasing was set up to enable purchasers to share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy. The Group is facilitated by The School of Health and Related Research (ScHARR), part of the Trent Institute for Health Services Research, the ScHARR Support Team being led by Professor Ron Akehurst and Dr Nick Payne, Consultant Senior Lecturer in Public Health Medicine.

The process employed operates as follows. A list of topics for consideration by the Group is recommended by the purchasing authorities in Trent and approved by the Purchasing Authorities Chief Executives (PACE) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic assisted by a support team from ScHARR, which provides help including literature searching, health economics and modelling. A seminar is led by the public health consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been reviewed by the Trent DEC, chaired by Professor Sir David Hull.

In order to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions, The Trent Institute's Working Group on Acute Purchasing has joined a wider collaboration, InterDEC, with units in other regions. These are: The Wessex Institute for Health Research and Development, The Scottish Health Purchasing Information Centre (SHPIC) and The University of Birmingham Department of Public Health and Epidemiology.

Professor R L Akehurst,
Chairman, Trent Working Group on Acute Purchasing.

CONTENTS **Page**

LIST OF TABLES AND FIGURES **Page**

EXECUTIVE SUMMARY

Heart failure is a significant health problem in the UK and is estimated to consume about 1% of the NHS budget. It causes high morbidity and mortality. Treatment with Angiotensin-Converting Enzyme (ACE) Inhibitors can reduce symptomatic deterioration and hospitalisation, delay death, and improve quality of life. The weight of evidence indicates that the effects on reduced hospitalisation mean that the health gain associated with the use of ACE Inhibitors can be achieved with potential resource savings. Research has indicated that the benefits of ACE Inhibitors are class and not drug specific and, as such, cheaper ACE Inhibitors are expected to be more cost-effective than more expensive ones.

This paper addresses two primary questions:

1. Can the wider use of ACE Inhibitors lead to NHS resource savings (real or notional) through reduced demand for in-patient hospitalisations?

2. Can savings be made by substituting more expensive ACE Inhibitors with less expensive brands for all conditions for which ACE Inhibitors are prescribed (including hypertension and incipient heart failure following myocardial infarction)?

Question 1

Analysis addressing the first issue indicates that, in an average health authority of population 500,000, extending the use of ACE Inhibitors to treat all patients who could benefit would prevent an estimated 42 premature deaths per annum and could save a potential £400,000 in 'year one' with even greater savings expected in subsequent years. The modelled bed day savings are estimated at around 13 beds for this population. Modelling excludes potential resource savings from any reduced demand for GP and out-patient attendances. Sensitivity analysis indicates large margins for error in input assumptions before the modelled potential savings are eliminated. However, the paper notes that savings are largely potential rather than real, in that it can be difficult to convert in-patient bed day savings into actual cash savings.

Certain types of chronic heart failure (e.g. due to left ventricular dysfunction) and early forms of heart failure can be difficult to detect in the community and can lead to significant amounts of over-diagnosis and inappropriate prescribing of ACE Inhibitors and diuretics. The paper acknowledges the need for good access to echocardiography to improve

diagnosis of heart failure, thus preventing over-prescribing of diuretics and ACE Inhibitors. The analysis includes the cost of echocardiography, but ignores potential savings from more appropriate prescribing, giving further weight to the likelihood of a potential net resource saving result. Other potential costs, such as induced demand for echocardiography and extended life treatment, are thought to be well within the margins of the sensitivity analyses used.

The paper acknowledges, but does not explore explicitly, the potential costs of increased renal failure due to combination therapy of ACE Inhibitors with Non-Steroidal Anti-inflammatory Drugs (NSAIDS) in the elderly population and a theoretical risk for patients with unilateral renal artery stenosis.

A policy of more extensive prescribing of ACE Inhibitors for the treatment of heart failure would need a co-ordinated and managed implementation. The Sheffield Framework for Appropriate Care Throughout Sheffield (FACTS) project and the Promoting Action on Clinical Effectiveness (PACE) project in North Derbyshire are both well placed to contribute to this. Implementation costs are likely to be substantial, though not prohibitive. Such implementation costs and the costs of diagnostic tests may require pump-priming monies in some districts.

Question 2

The second part of the paper indicates a wide range of estimated potential savings and costs of switching between brands of ACE Inhibitors. The analysis required a number of assumptions to allow for the paucity of appropriately detailed prescribing data. The weight of evidence is that cost savings could be made, but that these may not be substantial. Energies might be better directed at ensuring that new patients are initiated on to the less expensive formulations.

1. INTRODUCTION

1.1 Background

Heart failure is a syndrome usually caused by myocardial or valvular dysfunction. The typical symptoms include shortness of breath, tiredness and signs of fluid retention with ankle swelling and crepitations in the chest. However, these are the signs of established heart failure. Many patients may have demonstrable evidence of left ventricular dysfunction (LVD) or clinically transient heart failure, for example, following a myocardial infarction, without developing overt signs of heart failure for months or years.

1.2 Prognosis and Mortality

Published research shows a range of mortality rates. For example, Framingham data[1] suggest two year mortality rates of 37% and 38% for men and women respectively. At six years, these mortality rates increase to 82% and 67% respectively, four to eight times that of the general population. Using the New York Heart Association (NYHA) severity scale, the annual death rate with respect to severity is estimated to be Grade I - 7.5%, Grade II - 12.5%, Grade III - 15%, and Grade IV - 40%.[2]

In a study in a district general hospital, Parameshwar and colleagues[3] noted that 4.9% of medical admissions had heart failure. Of these, 44% died within the first year (30% whilst in hospital) and 41% had coronary heart disease (CHD) as the aetiology of their heart failure. The average length of stay (LOS) in hospital was 16.7 days, with a range of 1 to 33 days. Other studies note death rates of 10-20% for mild heart failure and 40-60% for severe heart failure within the first year.[4,5]

1.3 Prevalence and Incidence

The size of the problem is difficult to quantify. Dargie et al.[6] state that there are few data on causes, prevalence and incidence with no reliable data on consultations for definite heart failure in general practice. This is because studies of prevalence and incidence use different criteria for diagnosis and, generally, base the estimates on either self-reported or clinical diagnoses. O'Connell and Moore express similar sentiments.[7]

1.3.1 Prevalence

Prevalence figures for the general population range from 0.091%,[3] 0.4%,[8] 1.5% to 3%,[9] and 0.88% to 1.2%.[10] In a small practice-based study, using positive echocardiography as the diagnostic criterion, a prevalence rate of 0.84% with 95% confidence intervals (CI) of 0.72% to 0.98% was found in a general population.[11] Age specific figures range from 2%[12] for 25-74 year olds, 2.1% for heart failure in 50 year olds and 13% for heart failure in 67 year olds,[13] to varying rates within different age groups - 0.8% (50-59), 2.3% (60-69), 4.9% (70-79) and 9.1% (80-89).[1] Smith states that most of the studies in the United States suggest a prevalence of 1% in the general population.[14] McMurray estimated that there were about 570,000 people with heart failure in the UK (equivalent to about 1% prevalence).[15] Of those with definite heart failure, studies suggest different proportions for those meeting the NYHA criteria of severity, with Grade IV being the most severe; e.g.: 35% NYHA I, 35% II, 25% III, 5% IV,[2] and 50% NYHA I, 25% II, 15% III, 10% IV.[16]

1.3.2 Incidence

As with prevalence, the estimates for incidence vary widely. In a Finnish study[17] the incidence in the 45-74 year age group was 0.4% per annum in men and 0.1% per annum in women. The Framingham study[1] suggested incidence rates of 0.3% per annum for men and 0.2% per annum in women aged between 35 and 64 years and 1% and 0.8% per annum respectively for 65 - 94 year old men and women. Similar figures were derived by Erickson[13], suggesting an overall incidence of 0.55% per annum for 50 to 67 year olds.

1.4 Size of Problem in a 'Typical' District

Reported estimates of prevalence of heart failure range from as low as 0.09%[3] to 3%[14] with a commonly used average prevalence rate of 1%[14]. For a 'typical' district of 500,000 population, these rates imply estimates of numbers of affected population ranging from 455 to 15,000, with a central estimate of 5,000 heart failure patients.

Published age-specific incidence rates applied to a population of 500,000 with a Standard European demographic profile produce the following estimates of incidence:-

Finnish study[17]	370	for 45 to 74 years of age;
Erickson[13]	825	for 50 to 67 years of age;
Framingham[1]	1,000	for 35 to 74 years of age.

In a study of heart failure patients in North Derbyshire, which has a demographic profile similar to the Standard European profile and a higher than average mortality rate from coronary heart disease, the following data were recorded:

- 92% of heart failure patients were diagnosed clinically;
- 16% had had an echocardiogram;
- 45% were taking Angiotensin-Converting Enzyme (ACE) Inhibitors - 57% of these had been started in hospital;
- 54% of those taking ACE Inhibitors had urea and electrolytes (U&E) checked at the beginning of therapy but only 39% of these were rechecked within the first six weeks of therapy;
- Average hospital length of stay was 12.5 days (median 6.5).

North Derbyshire Health Authority collated this information as part of a King's Fund Promoting Action on Clinical Effectiveness (PACE) project, using heart failure as the example, (see Appendix 1).

In a study in the Kensington and Chelsea Health Authority District[18]:

- 47% of patients diagnosed clinically with heart failure were taking ACE Inhibitors;
- 31% had had an echocardiogram.

These studies demonstrate, as with many other treatments, that not all patients who could benefit from a given therapy do in fact receive such treatment. The reasons for this would need to be researched, but they are likely to include: failure to follow-up appropriate patients by GPs (which may be a result of lack of time and/or the resources to spend trawling patient notes in order to identify suitable patients); failure to attend on the part of patients; and lack of appreciation of the benefits and the effectiveness of ACE Inhibitors.

McMurray and colleagues[15] estimated the total cost of treating heart failure in the UK to be £360m in 1990/91 including:-

Hospitalisation costs	59.5%
Investigations	16%
Drug Therapy	7.5%

This £360m represented over 1% of the total NHS budget.

Wheeldon and colleagues,[11] in a retrospective study of patient records over a period of five years between 1985 and 1990, found that heart failure patients admitted to a coronary care unit, a general medical ward or a geriatric ward, generated 81, 14 and 66 GP visits per patient respectively. For patients seen in an out-patient department in cardiology, general medicine or geriatrics there were 22, 7 and 266 GP visits respectively. In estimating the cost of heart failure to the NHS, McMurray[15] allowed for four GP consultations per patient per year.

In summary, heart failure is a sizeable problem affecting over half a million people in the UK and accounting for considerable use of NHS resources in terms of bed usage, physician time and drug usage. It is a serious disease with a greater than 50% mortality after five years.

2. USE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN THE TREATMENT OF HEART FAILURE: SUMMARY OF EVIDENCE OF EFFECTIVENESS

ACE Inhibitors were introduced initially in the early eighties. Originally, they were used for the treatment of hypertension and overt congestive cardiac failure, but are now also used for incipient heart failure as occurs particularly following an acute myocardial infarction. In the early days, it was advised that commencement of treatment should be in hospital under consultant supervision. This was because of the potential for causing or exaggerating hypertension and deteriorating renal function. They may also cause potassium retention in those patients with renal impairment or taking diuretics. However, hospital admission is no longer thought to be justified for the majority of cases and initiation of treatment in primary care is acceptable provided that there is careful monitoring of renal function. Following the initial development of captopril, there are now a number of preparations on the market. More recently, there has been the emergence of Angiotensin II inhibitors. These are thought to have similar actions to the earlier drugs but with fewer side effects, particularly with respect to cough development. Their efficacy in heart failure has not yet been established.

2.1 Clinical Efficacy of ACE Inhibitors

Several studies demonstrate the clinical efficacy of ACE Inhibitors in different conditions: in primary heart failure;[19,20,21,22,4] for patients with LVD with symptoms of heart failure;[23] for patients with poor LVD but without symptoms of heart failure;[24,25] for patients with symptoms of heart failure following myocardial infarction etc;[5,26,27] for all patients after myocardial infarction;[28,29] and in hypertension.[30,31] Some key trials are summarised in Table 1. The efficacy is confirmed by Garg's meta-analysis.[32] However, in a meta-analysis of eleven randomised controlled trials, Nony et al.[33] failed to show benefit in patients with heart failure not related to (ischaemic) CHD. There are a number of consensus statements and guidelines recommending the use of ACE Inhibitors in heart failure.[34,35,36] However, there is evidence of poor management in patients who are diagnosed as having heart failure, both in terms of inadequate diagnosis[17,11] and, of those who are diagnosed, inadequate treatment.[37] In one study, only 32% of those suspected of having heart failure had objective evidence of LVD,[17] and up to 47% (37% in males and 73% in women) of diagnoses were erroneous in work elsewhere.[11] Another study found that only 56% of those prescribed diuretics by their GP for presumed heart failure, fulfilled the criteria for diagnosis of congestive cardiac failure. Of these, 74% had been referred to hospital for investigation. However, only 31% of these

had had an echocardiogram. This means that only about 14% of all those treated for congestive cardiac failure had had a definitive investigation and diagnosis.[37]

Table 1 Use of ACE Inhibitors in Heart Failure

Study	Number of Patients P T	Patient Group	Drug Used	Length of Study Follow-up	Changes in Overall Mortality Rates P T	Changes in Rates of Hospitalisation P T
Cohn V-Heft II[21] Data from the study used to compare with results from V-Heft I [38]	273 403	Men, 18-75 years old with symptomatic heart failure Left Ventricular (LV) ejection fraction <0.45	Enalapril 20 mg daily	4 years	54% 42% mortality ARR* 12% at 4 years	
CONSENSUS[22]	126 127	Men and women. Clinical diagnosis of severe (NYHA IV) heart failure	Enalapril 5-40mg daily	Average 6 months	52% 36% mortality ARR 16% at 1 year	
SOLVD[4]	1284 1285	Men and women. Symptomatic heart failure LV ejection fractions < 0.35	Enalapril 2.5-10mg twice daily	Average 42 months	40% 35% mortality ARR 5% at 4 years	64% 54% ARR 10% in hospitalisation rate without death
Captopril Digoxin Multicenter Research Group[19]	100 104	Men and women <75 years old. Symptomatic heart failure LV ejection fraction <= 0.4	Captopril 25-50mg three times daily	6 months		11% 4.7% ARR 6.3% in hospitalisation

ARR = absolute risk reduction P = placebo group T = treatment group

3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

This paper focuses on two questions:

1. Does the use of ACE Inhibitors in heart failure reduce the overall patient treatment costs?

2. Are there financial savings to be made by switching from expensive ACE Inhibitors to cheaper ones **–** whatever the indication for therapy?

This section of the paper has been sub-divided into three main sub-sections.

- The first sub-section reports the evidence found in the literature for cost-effectiveness of using ACE Inhibitors for patients with heart failure.

- The second sub-section directly addresses question 1 and describes the results of modelling the costs and potential resource savings of treating those heart failure patients in a 'typical' English health district who are not currently on ACE Inhibitor therapy, but who would benefit from such treatment. Emphasis is on the cost-savings which would result from reduced in-patient hospitalisations.

- The third sub-section addresses question 2 and identifies a number of resource implication scenarios from substituting more expensive ACE Inhibitor formulations with cheaper, but equally effective, ACE Inhibitors for conditions including heart failure and hypertension.

3.1 Cost and Benefit Evidence from the Literature

3.1.1 Introduction

The studies conducted to assess the clinical effectiveness of ACE Inhibitors vary greatly in the characteristics of the patients studied in terms of: age, sex, symptoms of heart failure, duration and degree of heart failure, association with myocardial infarction, and in the end points of hospitalisation, death and progression to heart failure. Thus, the assessment of costs and potential savings of the management of heart failure is problematic.

There have been a small number of economic analyses investigating the use of ACE Inhibitors for heart failure. These are summarised in this sub-section by looking at the total burden of illness, more general cost-effectiveness issues, and, given the focus of the question addressed in this section, giving some specific focus to the benefits from reduced hospitalisation. The SOLVD treatment trial[4] has been used as the basis for nearly all published economic analyses because of the large numbers recruited into it.

3.1.2 Burden of Illness

In their paper of 1993, McMurray et al. produced a burden of illness model, which estimated the direct total cost of heart failure to the NHS to be in the region of £360m (1990/91 prices), that is, around 1% of the NHS budget.[15] Some 60% of this figure was attributed to the direct costs of hospitalisation. This expenditure is expected to rise largely as a result of the ageing of the population.

Results published in Bandolier[39] (based on the work by McMurray et al.[15]) indicate the potential costs and benefits over a one year period to a health authority of 250,000 residents. Cost estimates range from a net saving of £60,000 to a net cost of £76,000 depending on a 2% or 40% day case initiation assumption respectively. Bandolier[39] reports that around 40 deaths and 300 hospital admissions could be prevented each year through the appropriate use of ACE Inhibitors.

3.1.3 General Cost-effectiveness

Effectively, this paper already accepts that the case for the cost-effectiveness of ACE Inhibitors in the treatment of heart failure is proven. However, the reported evidence from published papers is summarised below.

The cost-effectiveness of medical technologies is usually represented using a cost-effectiveness ratio, such as, a cost per life year gained (LYG). However, if an intervention is found to produce net savings, it is not usual to present cost-effectiveness ratios because of the negative numerator.

The CONSENSUS trial[22] showed a 31% relative reduction in mortality at 12 months for heart failure patients treated with ACE Inhibitors. The mortality gains for those patients with progressive heart failure were more like 50%. In the larger SOLVD[4] study (sample 2,569), patients with mild to moderate heart failure were followed-up over a four year period. Those

randomised to the treatment group (2.5mg to 20mg enalapril) had a relative reduction in mortality risk of 16% (95% CI of 5%-26%). The largest reduction was seen in the progressive heart failure population, that is, a 22% risk reduction (6%- 35%).[4]

Hart et al.[40] investigated the cost-effectiveness of enalapril in the treatment of mild to moderate heart failure patients in the UK, using the results of the SOLVD study. The LYG, discounted at 6% over four years, was estimated at 0.137 per patient. The LYG figure may have been under-estimated given that 25% of the patients intended for treatment by placebo were being treated with enalapril by the end of the study.

Hart's simple one way sensitivity analysis showed direct NHS costs per life year saved varying from net savings of £200 per patient to a net cost of £3,100 per LYG (1990/91 prices). The savings are primarily a result of reduced hospitalisations as discussed below. Hart's more central estimate of cost per LYG is given as £251, although the results are very sensitive to whether initiation of treatment is in the primary or secondary sector. The SOLVD team recommended that 40% of heart failure patients required one day of in-patient initiation. The latter scenario was the baseline assumption used to derive the £251 per LYG estimate in the Hart paper[40]. In fact only 1.2% of patients in the trial required an in-patient admission to initiate treatment.[4] Consequently, the already small costs per LYG in the 'central' scenario are likely to be over-estimated.

An Australian study[41] again used the SOLVD treatment trial results to undertake an economic analysis. Allowing for differences in methodologies, the results are broadly similar to those found by Hart et al. in the UK.[40]

A Dutch study used Markovian modelling techniques to examine the 10 year effects of ACE Inhibitor treatment for congestive heart failure (CHF).[9,42] Again, the analysis was based on the SOLVD trial and includes extrapolations of treatment effects beyond the four year trial period. The analysis showed net cost savings across a range of sensitivities and, as such, no cost-effectiveness ratios were calculated. These conclusions support the case for this paper to analyse savings rather than cost-effectiveness per se.

3.1.4 Effects on Hospital Admissions

Use of ACE Inhibitors in the treatment of heart failure secondary to LVD may improve symptoms, prolong life, prevent hospitalisation, and improve quality of life. Any treatment which improves symptoms can be expected to reduce hospitalisations and, therefore,

potentially save money. Given the relatively low cost of ACE Inhibitor treatment compared with hospitalisation, it is possible that this intervention has the potential to be a cost-saving or cost neutral option, and it is the effect on hospitalisations which is likely to be pivotal to any economic evaluation.

Of the major ACE Inhibitor trials, seven have collated data on hospitalisation and these are listed in a recent publication.[43] The SOLVD treatment trial probably has the most useful information about hospitalisation effects because of the larger sample size (2,569 patients), the broadly representative population characteristics, and the longer length of follow-up (22-55 months, mean 41.4 months). The fact that the SOLVD trial excluded severe heart failure patients could mean that the potential effects of ACE Inhibitors are under-estimated using the results of this study.

It is unfortunate, given the pivotal role of the hospitalisation effect, that the different studies report widely differing non-treatment hospitalisation rates, 'relative' risk reductions (RRR)[a] and absolute risk reductions (ARR)[b] of hospitalisation following treatment with ACE Inhibitors. This is in part due to the trials being concerned with different patient groups. However, it is also due to the published papers not being explicit enough about the reported definition of hospitalisation. Specifically, some papers report the proportion of patients hospitalised, whereas others report the total number of hospitalisations. A significant proportion of heart failure patients have more than one episode of hospitalisation in a given period. This distinction is important in the context of the current paper, because Section 3.2 is concerned with the effect of ACE Inhibitors on reducing demand for hospital resources in total. As such, this paper is more concerned with analysing the total reduction in hospitalisations and not simply the number of patients with reduced hospitalisations.

To illustrate the point about the variations and confusion in reported hospitalisation effects in the published papers, the following all purport to be reporting the results from the SOLVD trial. Bandolier,[39] for example, reports that the SOLVD trial indicates a 30% RRR for hospitalisations. Davie and McMurray[43] also report a 30% RRR for hospitalisations from 22 per 100 patient years down to 15.4 per 100 patient years in the SOLVD treatment group (ARR = 6.6 per 100 patient years). Hart,[40] on the other hand, also reporting the results of the SOLVD trial, indicates that the RRR of hospitalisation from heart failure is 23.9% from 0.67

[a] RRR - The proportional reduction in rates of bad events between experimental and control participants in a trial, calculated as (Experimental Event Rate - Control Event Rate) / Control Event Rate.

hospitalisations per patient per year in the placebo group to 0.51 for the treatment group (ARR = 0.16 per patient per year). Our own analysis of the published SOLVD results show a RRR of hospitalisation from heart failure of 15.5% from 0.64 hospitalisations per patient per year in the placebo group to 0.54 for the treatment group (ARR = 0.10 per patient per year). The SOLVD investigators report that treating 1,000 patients with mild to moderate heart failure for three years with an ACE Inhibitor would prevent about 50 premature deaths and 350 hospitalisations.[4] The interpretation of the SOLVD hospitalisation analysis reported by Hart and the authors of this paper is thus in line with the analysis presented by SOLVD themselves.

In the CONSENSUS 1 trial[22] (sample size 253) patients with severe heart failure randomised to 2.5mg-40mg enalapril had significantly fewer hospital admissions and spent fewer days in hospital than the placebo group. That is, 7.3 admissions per 1,000 days at risk with 15% of study days in hospital, compared with 10.1 admissions per 1,000 days at risk with 19.6% of study days in hospital respectively.[21]

3.1.5 Summary

The discussion in Section 3.1 has demonstrated the significant resource burden of heart failure in the UK, that is, around 1% of the NHS budget with 60% of this being attributed to hospitalisation costs.

Hospitalisation costs play a pivotal role in the economic analysis of ACE Inhibitors for heart failure therapy. The most useful source of hospitalisation information from the trial data is that provided by the SOLVD treatment trial. However, it is also one of the most misinterpreted pieces of information presented in subsequently published papers. This paper has noted the relevance of the hospitalisation effects of ACE Inhibitors reported by the SOLVD trial, and as subsequently interpreted by Hart and ourselves.

Economic analyses from the UK and around the world have demonstrated the likelihood of cost savings from the treatment of heart failure patients with ACE Inhibitors. The main UK study by Hart et al.[40] had a central scenario with a small cost per LYG but was based upon relatively pessimistic assumptions about the need for day case treatment initiation. The analysis published in Bandolier[39] indicated how changing the initiation assumption changes the balance of resource usage from net costs to net savings. The body of evidence from the

[b] ARR - The absolute reduction in rates of bad events between experimental and control participants in a trial, calculated as (Experimental Event Rate - Control Event Rate)

literature is in favour of the likelihood of ACE Inhibitor therapy for heart failure resulting in net resource savings, supporting the relevance of question 1 posed in the current paper (see page 9).

3.2 Modelling the Net Cost Effects of ACE Inhibitor Therapy in a 'Typical' District

3.2.1 Methodology

A simple spreadsheet model has been built to analyse the economic impact of the use of ACE Inhibitors in a standard English health district with a population of 500,000. The model has the following key variables:

- Prevalence of congestive heart failure;
- Proportion of congestive heart failure patients already on ACE Inhibitors;
- Proportion of congestive heart failure patients not suitable for treatment with ACE Inhibitors;
- ACE Inhibitor drug costs;
- Echocardiography test costs;
- Additional GP visits and U&E tests required;
- Proportion of ACE Inhibitor patients initiated in hospital;
- Existing hospitalisation rate per patient year;
- Percentage reduction in hospitalisations from ACE Inhibitor use;
- Average in-patient LOS;
- Percentage reduction in LOS following the use of ACE Inhibitors;
- Average cost per in-patient day.

The following analysis requires a number of assumptions. A simple (non-age specific) prevalence rate for the whole population is assumed, and a proportion of these patients are assumed to be prescribed ACE Inhibitors already. Of the remaining population, a proportion will be assumed to be unsuitable for treatment with ACE Inhibitors, due to contraindications. These assumptions will identify a population of heart failure patients who are suitable for treatment with ACE Inhibitors, but who currently do not take the drug. In economists' terms, this is the identified marginal population.

The cost of treating these patients with ACE Inhibitors is estimated in the model by estimating the annual ACE Inhibitor drug treatment cost and making assumptions about the additional number of GP consultations required to undertake U&E tests. The latter are

usually undertaken before initial treatment with a low dosage ACE Inhibitor and every time the dosage is increased in the first months of treatment. Each patient to be considered for treatment with ACE Inhibitors is also assumed to require an echocardiogram to confirm the diagnosis of heart failure. The model requires an assumption about the proportion of heart failure patients who require hospitalisation for ACE Inhibitor initiation.

Mainly because of inadequate data, the model assumes that cost savings result only from reduced demand for secondary sector in-patient hospitalisation. That is, any reduced demand for GP consultations, out-patient visits, non-ACE Inhibitor drug costs etc., is excluded, although it is acknowledged that such savings may not be insignificant. In this respect, the model will under-estimate the potential cost savings of ACE Inhibitor treatment for the given population.

The model examines only the 'year one' costs and savings of ACE Inhibitor treatment. Reasons for restricting the analysis to 'year one' include the fact that most of the key source data are aggregated and, consequently, it was felt that a more detailed modelling exercise involving time estimates of treatment effects might be 'over-working' the available data. The costs of increasing the use of ACE Inhibitors are likely to be significantly higher in 'year one' compared with subsequent years because of the need to treat the existing stock of patients who could benefit from treatment. This is likely to have consequences in terms of the increased need for investment in drugs, echocardiography, and U&E testing for example. Subsequent years' costs will be dependent largely on new demand for treatment, which will be determined by only the year on year incidence of heart failure.

Also, 'year one' costs for items such as echocardiograms and other diagnostic tests should ideally be discounted over the increased survival time of treated patients. The fact that they have not been means a further front loading of the costs into 'year one'. Consequently, the decision to base the model on the 'year one' costs and savings will bias the results towards higher costs of implementing the treatment policy.

3.2.2 A Central Scenario

Prevalence

The range of prevalence for heart failure reported in this paper is from 0.1% to 3%, although this will be representative of a whole range of severities. The most commonly quoted

population prevalence is 1%[40] and this figure will be used as the central assumption scenario for modelling.

Already on ACE Inhibitors

A number of the papers from the early 1990s suggested that somewhere in the region of 10% of heart failure patients were already being treated with ACE Inhibitors. Recent work by North Derbyshire Health Authority indicates that that figure has risen to around 40% of its own heart failure population. Dr Joanne Carter of the Kiverton Park Medical Practice in Rotherham has indicated in personal correspondence that 36% of the practice's own heart failure patients are already on ACE Inhibitors. This figure has been achieved without a concerted drive to achieve it and the practice feels that it can achieve a much higher proportion. The model's central scenario assumes that 40% of heart failure patients are already being treated with ACE Inhibitors.

Unsuitable for Treatment with ACE Inhibitors

There is little published evidence about the proportion of heart failure patients unsuitable for treatment with ACE Inhibitors due to contraindications and side-effects. Mair et al.[44] report that 13.5% of 266 heart failure patients are unsuitable for ACE Inhibitors. Our central scenario assumes 10% unsuitable.

Potential Unmet Demand

With a population of 500,000, the central scenario assumes, therefore, that a population of 2,500 heart failure patients (i.e. 500,000 x 1% prevalence x 50% suitable but not currently treated) is eligible for treatment with ACE Inhibitors. This is, in effect, the marginal (incremental) population to be analysed.

ACE Inhibitor Prescribing Cost

One of the recommendations from this paper is that patients be initiated onto ACE Inhibitors using ramipril, as it is one of the cheaper ACE Inhibitors on the market. The central case scenario assumes that the average dosage prescribed will be 2.5mg. At a cost of 26.9p per 2.5mg tablet, the drug cost per patient per annum is assumed to be £98.19. Therefore, the marginal drug cost of treating the assumed 2,500 new patients is estimated at £245,475 per annum.

Echocardiogram Costs

The central scenario assumes that each potential new ACE Inhibitor prescribed patient will receive one echocardiogram to confirm a diagnosis of heart failure. North Derbyshire Health

Authority has indicated an estimated cost per echocardiogram of £40 per test. This figure is used in the central scenario modelling, giving a total marginal cost of £100,000.

Initiation Costs

The SOLVD trial recommended that 40% of potential ACE Inhibitor heart failure patients be initiated onto the drug as short-stay in-patients. At the conclusion of the trial, however, only 1.2% of patients with mild to moderate heart failure had required initiation in hospital. As time has passed, it is now accepted that the vast majority of patients presenting to their GP with suspected heart failure can be initiated onto ACE Inhibitors in the primary care setting. The central scenario assumes that 2% of patients require initiation in hospital. These patients have been costed assuming a generic one day in-patient stay.[c] The other 98% of patients are initiated by GPs at a cost per patient of £10.30.[d] The resulting marginal cost of initiation for the population is estimated at £35,288.

U&E Costs

It is good clinical practice for a potential ACE Inhibitor patient to undergo a U&E test prior to starting treatment with ACE Inhibitors. This would be followed by another test within two weeks of treatment commencing. It is also common practice to start patients on a low dose, subsequently increasing the dose if, and when, necessary. Each increase in dosage should be accompanied by another U&E test. Each patient would also be expected to have a U&E test once a year. However, assuming that our marginal group of patients is currently on diuretics, and that diuretic patients are also expected to have an annual U&E test, the annual U&E test for the new ACE Inhibitor prescribed patients is not an additional expense and, therefore, should not be included as a marginal cost in our economic analysis. The central case scenario assumes that a new ACE Inhibitor patient has an additional three U&E tests in 'year one'. These tests have been costed in the model by assuming one GP visit (again costed at £10.30 per consultation) and one laboratory test at £4.20 per test.[e] The total marginal cost for U&E testing in the central case scenario in 'year one' amounts to £108,750. As the need to change the dose after 'year one' is unlikely, the demand for U&E tests after 'year one' will be incidence led and, therefore, significantly less than in 'year one'.

[c] Netten and Dennett.[56] Cost per generic in-patient day (1997) = £195.19 inflated by 3%.
[d] Netten and Dennett.[56] Cost per GP consultation (1997) inflated by 3%.
[e] £4.20 is the cost of a laboratory test for a GP fundholder quoted by Central Sheffield University Hospitals Trust Biochemistry Dept.

Total Marginal Cost of Central Case Assumptions

Assuming that these costs account for all the additional costs of treatment with ACE Inhibitors, the gross cost of the central scenario is modelled at £489,513 in 'year one'.

Cost Savings

The model assumes that the cost savings from treatment with ACE Inhibitors result only from reduced in-patient hospitalisations. Any potential savings from reduced out-patient visits and reduced demand for GP time are not considered, although it is acknowledged that they could be significant.

Hart[40] reports that the hospitalisation rate per patient per year for the control placebo group in the SOLVD study was 0.67 per patient per year. Our own estimate of the same figure using the results reported by SOLVD is 0.64. Hart reports the RRR of hospitalisation for the ACE Inhibitor treatment group from the SOLVD study to be 23.9%, that is, an implied hospitalisation rate of 0.51 per patient per annum for the ACE Inhibitor treatment group (an implied ARR of 0.16 per patient per year). Our own estimate of the treatment group hospitalisation rate using the results reported by SOLVD is 0.54 per person per annum, that is, a RRR of 15.5% (ARR = 0.10 per patient per year). The original SOLVD paper itself concludes that it would expect 1,000 mild to moderate heart failure patients treated with ACE Inhibitors for a period of three years to experience 300 fewer hospitalisations. Assuming a central case scenario of 0.65 hospitalisations per patient per year for the non-treatment group, the conclusions reported in the SOLVD paper imply that the RRR for hospitalisations is about 18% (ARR = 0.12 per patient per year). These latter figures are used to form the central case scenario assumption for hospitalisation effects, and are a compromise between Hart's and our own interpretations of the hospitalisation effects reported by SOLVD.

Work undertaken in North Derbyshire indicates that the average LOS for heart failure patients is 12.15 days. In addition to ACE Inhibitor treatment reducing admission rates for heart failure patients, North Derbyshire has indicated that treatment is associated with a 5% shortening of average LOS. Using these hospitalisation risk reduction and LOS assumptions, the model estimates that 4,363 bed days would be saved per annum by treating 2,500 heart failure patients with ACE Inhibitors. Using a crude cost per in-patient day of £201[f], this implies an estimated potential saving of £877,255 per annum.

[f] Netten and Dennett.[56] Cost per generic in-patient day (1997) = £195.19 inflated by 3%.

Net Savings from Central Scenario

The results of modelling the central scenario imply potential savings of £387,743. The input assumptions and the outputs for the central scenario are summarised in Table 2 below.

Table 2 Summary of Central Scenario Assumptions and Model Outputs

Variable	Central Scenario Assumptions and Outputs
Prevalence	1%
Proportion already on ACE Inhibitors	40%
Proportion not suitable for ACE Inhibitors	10%
UNMET DEMAND	**2,500 Heart Failure Patients**
ACE Inhibitor cost per patient per annum	£98.19
Echocardiograms per ACE Inhibitor patient	1
Cost per Echocardiogram	£40
Additional U&E tests per ACE Inhibitor patient	3
U&E test cost (GP + Analysis)	£14.50
Proportion initiated in hospital	2%
Cost per hospital initiation	£201.05
TOTAL MARGINAL COST	**£489,513**
IP rate per patient per annum (no-treatment group)	0.65
RRR of hospitalisation from ACE Inhibitors	18%
ARR of hospitalisation from ACE Inhibitors	0.12 per patient per year
Average LOS for heart failure	12.15 days
Average LOS reduction from ACE Inhibitors	5%
Cost per in-patient bed day	£201.05
NET IN-PATIENT COST	**- £877,255**
NET MARGINAL COST	**- £387,743**

The use of the word ‘potential’ is deliberate, in that it indicates not only uncertainty around the central scenario, but draws attention to the fact that the in-patient savings will not automatically translate to financial savings to the commissioners of health care. Having said this, the bed day savings should not be dismissed. With a 90% occupancy assumption, the bed day savings amount to 13.3 beds (about half of an average sized ward’s bed allocation).

Premature Deaths Prevented

On the basis of 50 premature deaths prevented for every 1,000 patients treated for three years,[4] and assuming that this converts to 16.67 deaths prevented per 1,000 patients treated per annum, treatment of the 2,500 central case patients would prevent 42 premature deaths per annum.

3.2.3 Sensitivity analysis

The effects on net marginal savings can be modelled by changing the assumed values of key input variables used in the central scenario. The sensitivity to demand is investigated using simple single variable sensitivity analysis. The cost and saving variable sensitivities are examined by investigating by how much the input assumptions need to change in order to eliminate the potential net savings which result from the central scenario assumptions.

Demand

The relationship between prevalence and net savings is a proportional one. That is, changing the prevalence assumption by x% increases the resulting net savings by x%. For example, doubling the prevalence from 1% to 2% doubles the net savings from £388,000 to £776,000.

Varying the assumed 40% of heart failure patients already on ACE Inhibitors from 20% to 60% changes the modelled net savings from £543,000 to £233,000 respectively. Thus, for every absolute 10% increase in this input assumption, there is a corresponding reduction in net savings of around £80,000, and vice versa. The latter is also true for any changes in the assumed value for the proportion of heart failure patients not suitable for ACE Inhibitor therapy.

Costs and Savings

Simple one-way sensitivity analysis can be used to illustrate by how much individual variable assumptions need to change in order to eliminate the net savings modelled in the central scenario. The results of the analysis are presented in Table 3.

Table 3 Required Changes in Individual Input Assumptions in the Central Scenario in Order to Eliminate Modelled Potential Savings

Input Variable	Central Scenario Assumption	Sensitivity Assumption	Relative Percentage Change Required
ACE Inhibitor drug cost per patient per annum	£98.19	£235.29	+240%
Echocardiograms per patient	1	4.9	+490%
Cost per Echocardiogram	£40	£195	+488%
U&E tests per patient	3	13.7	+457%
Initiated in hospital	2%	83.3%	+4,165%
Non-treatment hospitalisation rate	65%	36%	-45%
RRR of hospitalisation	18%	7.7%	-57%
ARR of hospitalisation	0.12	0.05	-57%
Cost per in-patient day	£201	£111	-45%

The analysis shows, for example, that in order to eliminate the potential net savings of the central scenario, the assumed ACE Inhibitor drug costs per patient per annum would have to increase by 240% from £98 to £235. Likewise, the cost per echocardiogram would need to rise by almost 500% from £40 to £195 before the net cost saving result is eliminated.

The hospitalisation assumptions are pivotal to the analysis, and represent the area of most uncertainty and confusion in the literature. The sensitivity analysis indicates that the hospitalisation assumption for the untreated patients would have to be reduced from 0.65 per patient per annum in the central case to 0.36. The latter is very low compared with the figure reported in the SOLVD trial, although the trial was concerned only with patients who had mild to moderate heart failure. The implications for the number of hospitalisations avoided, is that it would be about one third of the reduction reported by SOLVD.

Likewise, the central scenario assumption for the hospitalisation RRR following treatment with ACE Inhibitors would need to be lowered from 18% to 7.7%, the ARR being lowered

from 0.12 to 0.05 per patient per annum. Again the implication is that the hospitalisations saved would need to be less than a third of those reported by SOLVD.

In summary, the sensitivity analysis indicates that the assumptions of the central case scenario would have to change substantially in order to eliminate the net saving result of the central scenario. The question is almost certainly “how big are the potential savings?” rather than “will there be any?”

3.2.4 Discussion and Conclusions

In summary, modelling has indicated that managing heart failure patients according to good clinical practice, that is, using echocardiographic investigation and treatment using ACE Inhibitors can be achieved with potential marginal cost savings. The central case scenario implies that, for a population of 500,000, an additional 42 premature deaths could be prevented per annum with a potential net cost saving of around £388,000 in ‘year one’. This modelling is based explicitly on a number of simplifying assumptions. Net savings may be greater or smaller than those modelled in the central scenario for a number of reasons.

The exclusion of potential savings from reduced demand for out-patient and GP attendances through the use of ACE Inhibitors clearly implies that the modelled savings are under-estimated in the central case.

Also, the demand and costs for U&E tests and echocardiography have been ‘front loaded’ into ‘year one’, which means that the actual net costs could be even lower than those indicated by the results of the modelled central scenario. For example, LVD is difficult to identify solely on the basis of signs and symptoms. The costs of echocardiography to improve and confirm diagnosis have been modelled by assuming one test per new ACE Inhibitor patient, to allow for the fact that echocardiograms are required once per patient before the initiation of treatment. The model indicates that the demand for echocardiograms in ‘year one’ is estimated to cost £100,000 (£40 x 2,500 patients). Thereafter, the cost of echocardiograms will be restricted to potential new incidence of heart failure patients. Assuming an incidence rate for heart failure of between 0.15% and 0.3%, the annual cost of echocardiography for heart failure after ‘year one’ is estimated at between £27,000 and £54,000 per annum.

In addition, it would have been quite legitimate to have constructed the model so that the estimated marginal cost of £100,000 for echocardiography was annualised over the

expected lifetime of the patients. Assuming a 5% discount rate and a survival period of five years, for example, implies a repayment annuity of £23,097 per annum. This figure is significantly lower than our £100,000 'year one' costing assumption.

The increased use of echocardiography could result in potential savings from the reduction or avoidance of inappropriate or over-prescribing of diuretics and ACE Inhibitors for mis-diagnosed patients. The Francis study,[45] for example, demonstrated that 45% of diuretic patients had inappropriate treatment withdrawn following investigation by echocardiogram. These potential cost savings have not been modelled in this paper. A follow-up paper from the Edinburgh team has subsequently recommended screening out the need for echocardiography with pre-tests using electrocardiography.[46] This option could result in a more cost-effective use of resources by reducing the demand for echocardiography by as much as 50%. Also, there are a number of new initiatives underway concerned with screening for, and the diagnosis of, heart failure. These involve the detection of peptide hormones in the blood, which have raised levels when the heart begins to fail. The potential implications for echocardiography of such initiatives will need to be monitored.

The model does not allow for the possibility of induced extra demand for echocardiography for patients subsequently confirmed not to have heart failure. This induced demand will mean increased costs of echocardiography per heart failure patient detected. A recent study in Scotland showed inappropriate referral rates for open access echocardiography to be as low as 12%.[45] Such a figure is well within the sensitivity range for the 'echocardiograms per patient' variable as demonstrated in Table 3.

Because of the relatively high level of aggregation of the source data, modelling has been deliberately kept simple. The analysis has been confined to the 'year one' costs and benefits of treating heart failure patients with ACE Inhibitors. The model does not fully address issues associated with treatment over the lifetime of the patient. As such, the model does not account for changes in the reduction in risk of hospitalisation over time, nor does it account for the costs of treating patients who live longer because of their improved health state. Work already reported in this paper, which does model the life-time effects of ACE Inhibitor treatment, indicates that the cost-effectiveness of ACE Inhibitors, in terms of discounted LYG, is very favourable. Life years may even be gained with cost savings. The sensitivity analysis presented in this paper also indicates that there are wide margins for error in the assumed values for the input variables of the model before the resulting potential savings are eliminated.

The analysis does not address the issue of potential resource implications from increased incidence of renal failure in the elderly resulting from combination therapy of ACE Inhibitors with Non-Steroidal Anti-inflammatory Drugs (NSAIDS). The latter needs to be monitored carefully because such effects could have considerable resource consequences. Also, there is a possible theoretical risk for patients with unilateral renal artery stenosis which will require longer-term monitoring, and may mean that screening for this condition is a wise precaution for patients at high risk.[46] The latter group includes hypertensive patients over 50 years of age and those with peripheral vascular disease, diabetes, or coronary artery disease.

The SOLVD study excluded frail elderly patients and patients with severe heart failure. If the hospitalisation gains from treatment with ACE Inhibitors are lower for these groups of patients than those found in the SOLVD sample, then the hospitalisation savings indicated by our modelling will have been over-estimated.

It is important to point out that the modelled bed day savings, whilst clearly a true opportunity cost saving, will not automatically accrue to the purchasers as cash savings, unless they can be incorporated into contracting. The benefits are more likely to manifest themselves in the form of reduced waiting times and increased bed capacity in wards no longer occupied by heart failure patients. Having said this, the marginal implications could be significant if a large Trust is looking to reduce demand for 13 beds in order to be able to close a ward. Alternatively, reduced demand for 13 beds could prevent, or at least delay, the need to build a new ward and, thus, avoid all the associated capital and other marginal costs. Any actual release of hospital resources would need to be managed locally.

The implementation of a policy of wider treatment of ACE Inhibitors and the increased use of echocardiography (with or without other diagnostic tests) needs to be thought through and managed. Information and training may need to be given to GPs, and will inevitably require additional resources. Appendix 2 outlines how such a planned approach might be created using the lessons learned by the FACTS project team following the implementation of a policy to prescribe aspirin to patients at high risk of heart attack and stroke. FACTS (in personal correspondence) have indicated that the costs of implementing policies such as the aspirin policy are unlikely to be more than £100,000 in a 'typical' district. Such costs would need to be made available up front, but still imply a potential net savings result even in 'year one'.

The main issues surrounding the increased use of echocardiography include:-

- open access versus a consultant led service;
- use of pre-testing using x-rays and electrocardiograms.

Increased demand for these diagnostic services may mean that pump-priming monies need to be made available in those districts where the marginal change in demand requires capital investment.

In summary, modelling has demonstrated that managing heart failure patients appropriately using diagnostic echocardiography and treatment with ACE Inhibitors is not only beneficial in health terms, but is likely to be achieved with a potential net resource saving. These costs and savings will fall unequally on the primary and secondary care sector, and the savings are essentially potential in cash terms to the purchaser. The recent White Paper's[48] proposals to hand over unified budgets to Primary Care Groups (PCGs) will mean that the primary versus secondary balance of financial gains and burdens will be less of an issue than is the case under existing financial arrangements. A number of variables have not been included in the model which, on balance, is likely to mean even greater potential savings. The case for implementing a policy of wider treatment with ACE Inhibitors appears very strong, although its implementation will require careful planning, management, and possibly, some pump-priming monies.

3.3 Are there Financial Savings to be Made by Switching from Expensive ACE Inhibitors to Cheaper Ones – Whatever the Indication for Therapy?

ACE Inhibitors are generally expensive, costing from £60 to £240 per year of treatment depending on the drug and the dose. The Angiotensin II drugs range from £180 to £240 per year and are, therefore, generally more expensive than the first generation ACE Inhibitors.[49,50] The Drug and Therapeutics Bulletin[49] recommended prescribing the original three, captopril, enalapril and lisinopril, as there appeared to be little to choose between these and the multiplicity of newer products. Currently, however, ramipril is reportedly cheaper for a year's course of treatment - between £72 and £115.[50] It is thought, therefore, that switching patients to ramipril will result in considerable savings.

There is evidence that the benefits from ACE Inhibitors are due to a class effect and not related to specific preparations.[51,52] Studies have also been performed to show that it is safe

to convert from one preparation to another.[53,54] Therefore, if there are economic grounds for recommending that patients be changed to ramipril, there is evidence to support the clinical safety of such a policy.

To test the hypothesis that there are savings to be made by changing people from their current ACE Inhibitor to ramipril, certain information is required:

1. The number of people taking an ACE Inhibitor.
2. The number of people who should be taking ACE Inhibitors – particularly in respect of heart failure.
3. Which drug is being taken and for what clinical indication.
4. What dose of the drug is being taken.
5. What the recommended doses are for each clinical indication.
6. What the equivalent dose of ramipril would be for each patient.
7. The cost of each drug at whatever dose is used.

However, the only piece of information known for certain is item 7.

For most GP practices, information on items 1, 3, and 4 is either readily available on computer or could be discovered by searching patient records or by a combination of the two. However, at a health authority level this information is not available unless a deliberate attempt, as in North Derbyshire, has been made to ask practices to provide it. Even so, the number of patients who may be receiving inadequate doses of ACE Inhibitors is unknown. Such patients may need to increase their dose and, hence, this may increase the cost of ACE Inhibitor prescribing. However, this may be off-set by a number of patients currently prescribed an ACE Inhibitor, who may not require this particular type of drug if their diagnosis of heart failure is wrong and, hence, may be able to stop taking ACE Inhibitors.

Although there are recommendations from the drug companies concerning therapeutic dosage, generally speaking this is supplied as a range with a starting dose and a maximum level. There are recommended dosages based on those used in the main trials. There may be marked differences between the dosage patients take of the same drug for the same indication.

Item 5 is probably not definable. Although the number of patients with heart failure can be estimated, an attempt to identify the number of patients with hypertension and in whom ACE Inhibitors would also be indicated, would be much less reliable. Issue 6 also remains unresolved.

Analysis of PACT Data

Prescribing Analysis and Cost (PACT) data supplied by the Prescription Pricing Authority are provided both at district and practice levels, in varying degrees of detail. At district level, it indicates the number of items (prescriptions) for a particular drug, which strength was prescribed, and the number of tablets prescribed. The cost is then calculated. However, problems include:

- The number of patients receiving prescriptions cannot be calculated reliably. (Doctors may prescribe different quantities of tablets and different numbers of prescriptions for patients taking the same drug, at the same dose and for the same reason).

- ACE Inhibitors are prescribed for hypertension, incipient heart failure (as occurs after an acute myocardial infarction), as well as CHF, and it is not possible to identify how many prescriptions are for which indication.

- The therapeutic dose for the same drug may differ for each of these indications.

- The cost of the drug, per milligram, varies according to strength i.e. the cost of a low strength tablet is relatively more expensive than a stronger tablet, but the actual cost of the stronger preparation will be greater. Thus, the therapeutic dose of a preparation is crucial to assessing its cost-effectiveness.

The steps in the analytical process were as follows:

- PACT data for Sheffield GPs for the quarter July to September 1997 were obtained. The total prescribing population for Sheffield GPs is 543,000.

- The defined daily dose (DDD) based on the World Health Organisation (WHO)[55] recommendations (see Table 4), was used to calculate the total number of DDDs for ACE Inhibitor prescribing in Sheffield. For example, the DDD of captopril is 50mg daily. Therefore, 50mg are 1 DDD and 25mg is 0.5 DDD. ACE Inhibitor/diuretic drug combinations were excluded.

- The total prescribing cost for Sheffield GPs for ACE Inhibitors was calculated. The second generation ACE Inhibitors were totalled separately as there are no recommendations concerning DDDs for these drugs.

- The current costs of the ACE Inhibitors most commonly prescribed are shown in Table 5.

- All the calculations relate to one quarter only, unless otherwise stated.

NB: There may be aspects of Sheffield's prescribing profile which are not typical of other areas and, therefore, the results of this analysis should be considered with this in mind.

Table 4 Defined Daily Doses of ACE Inhibitors[55]

ACE Inhibitor	DDD mg
Benazepril	7.5
Captopril	50.0
Cilazapril	2.5
Delapril	30.0
Enalapril	10.0
Fosinopril	15.0
Lisinopril	10.0
Moexipril	15.0
Perindopril	4.0
Quinapril	15.0
Ramipril	2.5
Spirapril,	6.0
Trandolapril	2.0

Table 5 Current Cost of 28 Days' Treatment of the Four ACE Inhibitors Most Commonly Prescribed[50]

ACE Inhibitor	Cost of 28 days' treatment (£)
Ramipril 1.25mg	5.30
Captopril 12.5mg bd (twice daily)	5.79
Captopril 25mg bd	6.93
Ramipril 2.5mg	7.51
Lisinopril 2.5mg	7.64
Enalapril 5mg	7.86
Captopril 50mg bd	9.34
Ramipril 5mg	9.55
Enalapril 10mg	11.03
Lisinopril 10mg	11.83
Enalapril 20mg	13.10
Lisinopril 20mg	13.38
Ramipril 10mg	19.10
Enalapril 40mg	26.20
Lisinopril 40mg	26.76

The analysis is based on the residual data after excluding the information for patients already on captopril, ramipril, and the second generation ACE Inhibitors. The reasons for this are:

1. Captopril is given two or three times daily. Changing to a once daily dosage of ramipril may not be straightforward. Also generic captopril is cheaper than ramipril. Therefore, there is no saving to be made by changing these patients to ramipril. Those taking a proprietary brand of captopril should probably be encouraged to change to the generic variety.
2. Those patients already on ramipril will not be changed and, therefore, there are no savings to be made from these patients.
3. There is no DDD for the second generation ACE Inhibitors. Although they are more expensive, they represent only a small proportion of ACE Inhibitor prescribing at the moment, and so would contribute little to any overall potential savings.

Table 6 shows the summary of the PACT data for Sheffield GP prescribing for the quarter July to September 1997. It also shows the number of DDDs available for exchange and the total cost from which savings might be made.

The total number of DDDs available for exchange is: 921,664.

The total cost of ACE Inhibitor prescribing, from which savings might be realised is: £341,046

Table 6 Summary of PACT Prescribing Data for Sheffield GPs: July to September 1997

Drug			Cost (£)	Total no. DDDs
Captopril			73,065	228,755
Cilazapril			6,162	19,196
Enalapril			175,453	528,486
Fosinopril			14,740	28,316
Lisinopril			129,654	308,572
Losartan			19,438	30,201
Perindopril			6,973	14,466
Quinapril			4,564	16,138
Ramipril			26,774	134,838
Trandolapril			3,497	6,488
Valsartan			493	952

TOTAL 1:		460,818	1,316,410
TOTAL 2:	total excluding ACE Inhibitor second generation	440,886	1,285,257
TOTAL 3:	total 2 excluding ramipril	414,112	1,150,419
TOTAL 4:	total 2 excluding captopril	367,821	1,056,502
TOTAL 5:	total 2 excluding ramipril and captopril	341,046	921,664

The following paragraphs discuss a number of possible scenarios for changing the current profile of ACE Inhibitor prescribing to the use of ramipril. A number of caveats and explanations for the different scenarios are highlighted. The results are shown in Table 7 and the calculations behind them are set out in Appendix 3.

Scenario 1: *If the 921,664 DDDs were to be directly replaced by ramipril 2.5mg – low maintenance regime:*

Potential savings are £667,406 per annum for a population of just over 543,000 with a similar CHD profile i.e. savings of 37.8 % of ACE Inhibitor budget.

1. This total saving is unlikely as some patients will not wish to change and others will not be satisfied by a change even if they agree to it initially.

2. A proportion of patients will require 5mg or even 10mg daily which will increase the cost.

3. This figure may be increased because of patients on lower doses, but decreased by patients on higher doses.

Scenario 2: *If the 921,664 DDDs were to be replaced by ramipril 5mg – high maintenance regime:*

Potential savings are £107,034 per annum for a population of just over 543,000 with a similar CHD profile i.e. savings of 6% of ACE Inhibitor budget.

Thus, the potential savings by this methodology are likely to be somewhere in between scenarios 1 and 2.

However, analysis of the Sheffield PACT data shows that 75% of prescribing is for the 5mg preparation (see below). This suggests that the average dose of ramipril is not 2.5mg but 5mg once or even twice daily. The Prescribing Support Unit in Leeds, by calculating the average daily dose (ADD) for ACE Inhibitors, confirms this. For all ACE Inhibitor preparations, the ADD is the same as the DDD, as defined by the WHO, except for ramipril. The ADD for ramipril is 5mg and not 2.5mg. Thus, the potential savings are likely to be nearer those of scenario 2.

Scenario 3: *If the 921,664 DDDs were to be replaced in the same proportions as ramipril is currently prescribed in this population, i.e.*

3.1% for 1.25mg preparation
21.8% for 2.5mg preparation
75.1% for 5mg preparation

Potential savings are £181,280 per annum for a population of just over 543,000 with a similar CHD profile i.e. savings of 10% of ACE Inhibitor budget.

Scenario 4: *If the 921,664 DDDs were to be replaced in the same proportions as ramipril is currently prescribed in this population, allowing for 25% of prescriptions being for 10mg daily:*

From PACT data it is not possible to determine the proportions of prescriptions for 5mg once and 5mg twice daily. However, looking at the prescriptions for multiples of two months supply of 5mg tablets (using 2 months supply of 5mg daily as a proxy for one month of 5mg twice daily) suggests that there is approximately a $^{2}/_{3}$ – $^{1}/_{3}$ split. As 75% of ramipril prescriptions are for the 5mg preparation, this suggests that 25% of all ramipril prescribing is for 5mg twice daily. This 25% accounts for 50% of the cost of ramipril prescribing as the cost is twice that of 5mg daily.

Thus, the cost of ramipril, allowing for 25% of prescriptions for 10mg = £373,983.

This is greater than the current prescribing costs of £341,046 and, therefore, represents a potential extra cost.

Table 7 Summary of Scenarios 1 - 4

Scenario: with Total Available DDDs Replaced by:	Costs (£)	Potential Savings per annum (£)
Scenario 1: ramipril 2.5mg	174,194	667,406
Scenario 2: ramipril 5mg	314,287	107,034
Scenario 3: ramipril in proportions of doses currently prescribed	295,726	181,280
Scenario 4: ramipril in proportions of doses currently prescribed, allowing for 25% @ 10mg daily	373,983	**-** 32,937

Caveats

1. Savings are dependent on:

   - which DDD of ramipril is used;
   - what the proportions of prescribing would be for the different doses of ramipril;
   - which strengths of ramipril are used.

2. There will be a cost for changing patients from their current ACE Inhibitor to ramipril.

Estimating the number of patients on ACE Inhibitors by dividing the number of DDDs by 365 days gives an estimate of 2,525 patients. Assuming an extra four visits to the GP to establish the change and clinical stability, at a cost per visit of £10,[56] the cost of changing these patients is 2,525 x 4 x £10 = £101,000 (for the other ACE Inhibitors 30% of prescriptions are for DDD, 42% for >DDD, 27% for < DDD).

Potentially, this eliminates the potential savings for scenarios 2 and 3 in the year of change. It must be remembered that patients will generally be on ACE Inhibitors for life, once established, and, therefore, the savings identified might be expected to accrue after the first year. The mortality remains high, even for patients on ACE Inhibitors and, therefore, the benefits gained by a mass change-over exercise may be less than the scenarios imply. However, initiating treatment using less expensive preparations will reduce significantly the prescribing costs for heart failure patients.

The prescribing profiles of the other ACE Inhibitors may be different from that of ramipril. There may be a larger percentage of patients on the smaller doses. Patients currently on ramipril may be prescribed it predominantly for heart failure and this may account for the 25% taking the higher doses. The AIRE[26] study used a dose of 5mg twice daily. If the proportion of other ACE Inhibitors is predominantly for hypertension then changing these patients to ramipril might increase the proportions on doses of less than 5mg daily. This would increase the savings.

3.3.1 Discussion and Conclusions

It would appear from the foregoing analysis that, at a dose of 5mg daily or less, ramipril is currently cheaper than other ACE Inhibitor preparations (except generic captopril). However, if the number of patients who require 5mg twice daily, is as high as 25%, this changes the pricing profile considerably, to the extent that directly changing patients to ramipril would certainly not save money and may be more expensive. Thus, the number of patients requiring more than 5mg daily, may be sufficient to change the balance of cost-effectiveness away from a recommendation to convert all patients to ramipril .

If the caveat is accepted that all patients requiring more than 5mg daily revert back to their original preparation then there are still savings to be made. This then has to be weighed against the cost of seeing patients several times to establish a change, monitoring the effects and counselling, changing about a quarter back again and so on. These costs are

likely to counter balance the potential savings in the first year. For individual practices and doctors these costs may be 'absorbed' in routine work and, therefore, only the savings in the drug budget may be apparent, rather than the lost opportunity costs in seeing 'extra' patients. However, year on year after the first year, the potential savings will probably outweigh the costs of changing patients to ramipril.

Currently, it would seem sensible to recommend starting new patients on ramipril, as about 75% of these will be on the lower dose. Those patients requiring 10mg of ramipril could then be changed to another ACE Inhibitor.

If changing patients to ramipril is to be advocated, clear protocols and methodologies will be required. Also, product developments, such as, the introduction of new drugs or the removal of patent from competing brands, such as, enalapril, will mean that the cost-effectiveness of any advocated policy will need to be reviewed constantly. For example, enalapril is currently the major ACE Inhibitor prescribed in Sheffield. Given that enalapril will soon become available generically, thus lowering its price, a policy to switch current ACE Inhibitor patients in Sheffield from enalapril to ramipril may not be seen as sensible at this point in time.

The foregoing analysis is based on Sheffield data, which may not be representative of other districts. Other districts may wish to undertake their own local analysis of PACT data and should be aware that the above conclusions drawn may not be relevant to their own locality.

The cost-effectiveness of Angiotensin II drugs is not yet established.

4. OPTIONS FOR PURCHASERS AND PROVIDERS

4.1 More Extensive Use of ACE Inhibitors

The following options are not necessarily alternatives to one another. Options 1 to 3 can be taken in any combination.

1. Increase the use of ACE Inhibitors for non-contraindicated heart failure patients. The experience of the Sheffield FACTS project and/or the North Derbyshire PACE project can be used as models for implementing the policy. The comments about the class effects of ACE Inhibitors and the implications for appropriate low cost prescribing in section 3.3 of this paper should be noted when developing policy.

2. Enhance echocardiography services to improve the diagnosis of heart failure leading to more appropriate prescribing of ACE Inhibitors and diuretics. This option may require pump-priming monies.

3. Supplement echocardiography services with pre-diagnostic tests for heart failure using chest x-ray and electrocardiograms. This pre-screening option may encourage more appropriate use of echocardiography. Again, pump-priming monies may be required in some districts.

4. Healthcare commissioners and providers need to decide whether echocardiography, x-ray, and electrocardiography are to be provided using an ‘open access’ or a consultancy-led model.

5. Maintain the status quo with all its apparent implications for inefficient use of hospital and pharmaceutical resources and loss of health gain for the population.

4.2 Substituting More Expensive for Lower Cost ACE Inhibitors

The following options are not necessarily mutually exclusive.

1. Allow current clinical practice to direct the prescribing of ACE Inhibitors in terms of both the patients who receive them and which drugs are prescribed.

2. Advocate that new patients requiring an ACE Inhibitor should currently be initiated on ramipril but, if the therapeutic dose required exceeds 5mg daily, they should be changed to a different preparation. (Enalapril will shortly come off patent so that its generic price could become similar to that of ramipril.)

3. Advocate changing patients who are on the DDD of their ACE Inhibitor (excluding captopril and ACE Inhibitor II) to 2.5 mg of ramipril.

4. Advocate changing all patients to ramipril 1.25 mg and increasing the dose as necessary, but anyone requiring more than 5 mg daily should be changed back to their previous preparation. (Assume that patients in severe heart failure are likely to require the higher dose of ramipril and, therefore, should not be changed.)

APPENDIX 1: North Derbyshire Health Authority - Promoting Action on Clinical Effectiveness Project (PACE)

Objectives

- To improve the investigation and management of patients with congestive cardiac failure in North Derbyshire.

- To develop open access provision of echocardiographic resources.

- To promote effective prescribing by increasing the prescription of ACE Inhibitors and decreasing the unnecessary prescription of loop diuretics.

- To encourage audit in order to monitor progress.

The PACE Project has employed a variety of change techniques in order to encourage the use of echocardiography and the subsequent prescribing of ACE Inhibitors where appropriate, including distributing practice information packs, audit and re-audit of the records of patients with heart failure, an education programme, and the development of open-access echocardiography services in local Trusts.

Practice Information Pack

An information pack was compiled and distributed to all the practices in North Derbyshire early in the project. This followed the format of the FACTS practice information packs on aspirin.

The pack contained information on the PACE project, the research evidence on the management of heart failure, details of the audit methodology, the prescribing of ACE Inhibitors and a cost benefit analysis on the management of heart failure patients in addition to epidemiological data and details of available open access echocardiography services.

Audit

Following a pilot study involving three GP practices, an initial audit of the records of a sample of patients diagnosed as having heart failure was undertaken involving 48 (78%) of the practices in North Derbyshire and covering 86.5% of the population.

A re-audit of a random sample of records of patients diagnosed as having heart failure has been undertaken between 15 and 24 months after the first audit, involving 49 (80%) of the

existing 61 practices, in order to establish change in clinical practice over the period of the project. Forty three practices took part in both audits.

The audit criteria were:

- All patients with suspected heart failure should have had an echocardiograph.

- All patients with proven heart failure and without contraindications should be on an ACE Inhibitor.

- All patients on ACE Inhibitors should have their U&E checked before starting and again within two weeks of starting an ACE Inhibitor.

The re-audit results show a 2% increase overall in the use of echocardiography in the diagnosis of heart failure. Although this is not a huge increase, given that the open access service at Chesterfield and North Derbyshire Royal Hospital only started in November 1997 it demonstrates the right trend. The numbers of patients referred to the service by each practice showed a large variation, with eight practices referring nearly half of those scanned, and 30% of the practices not making any referrals at all.

Overall 49% of the total sample of patients were taking ACE Inhibitors, an improvement of 4% on the initial audit. Studies have shown that the average proportion elsewhere is only around 30-35%, which indicates that a relatively high proportion of heart failure patients are treated appropriately in North Derbyshire.

Disappointingly, the audit shows that only 49% of the patients had their U&E checked before starting ACE Inhibitors (a decrease of 5% from the initial audit) and only 35% of patients have had their U&E checked within six weeks of starting ACE Inhibitors, (a decrease of 4% from the first audit). This issue will be addressed in the next series of education meetings and practice visits.

The re-audit results also show that frusemide prescribing has risen from 56% to 63% of the total and co-amilofruse has dropped significantly from 19% to only 11%.

<u>Education programme</u>

A series of formal educational meetings were held during 1997 for the GPs in each locality. The content of the meetings centred around information about the PACE Project, echocardiography as a diagnostic tool, and the results of the initial audit. The meetings were well attended involving 51 GPs from 32 (52%) of the 61 practices.

A second series of meetings is being held during 1998 when the focus will be on the use of open-access echocardiography services, including results on the analysis of the first few months of open-access services, the results of the re-audit and the management of those patients in whom the diagnosis of heart failure is not confirmed by echocardiography, but who present with similar symptoms.

A practice nurse study day has also been held in order to inform and involve the nurses of the project work and to explore with them how other members of the practice team can be involved in promoting change on the basis of evidence.

The development of open access echocardiography services

Open access echocardiography services have been developing in provider Trusts increasingly over the past 2-3 years.

North Derbyshire Health Authority, through the PACE project, has recently commissioned open access echocardiography services at Chesterfield and North Derbyshire Royal Hospital and has worked with other NHS Trusts in the development of echocardiography services (Stepping Hill, Stockport; East Cheshire and Northern General Hospital, Sheffield).

Following the success of an initial small pilot study, a larger pilot service was set up at Chesterfield and North Derbyshire Royal Hospital (CNDRH) enabling 52 GP practices from across North Derbyshire to refer patients for echocardiography. The pilot study operated for six months pending evaluation.

Monitoring data for that service suggests that usage has increased markedly over the first six months of the year. Use of the service has been evaluated and results show that the service is working well and expected outcomes are being achieved.

Analysis of the evaluation forms shows that the management of 52% of the patients has changed following echocardiography, with 29% starting a new treatment and 30% stopping a previous treatment. Thirteen per cent of the sample are now being referred to a

cardiologist whereas 73% would have been had there been no open access echocardiography service available. These figures are consistent with the findings in both the literature and in other local pilots.

At Stepping Hill, Stockport 32% of patients started a new treatment and 32% stopped an existing one compared with 29% starting and 30% stopping at CNDRH. Twenty four per cent of the patients at CNDRH stopped being prescribed a diuretic, as did 22% of the patients in the Matlock study, and 24% of the patients at Stepping Hill. In Stockport, 64% of the patients would have been referred to a cardiologist had there been no open-access service, as would 73% of the patients from CNDRH.

Further information, the results from the district-wide audit, and the outcomes in terms of patient management from the evaluation of the echocardiography service, are available from Mrs Anne Hayes, PACE Project, Public Health Department, North Derbyshire Health Authority.

APPENDIX 2: Lessons from the Framework for Appropriate Care Throughout Sheffield (FACTS) Project

Possible Implementation Strategies:

Left to themselves, different GPs will innovate at different rates, for different levels of risk and with different degrees of thoroughness. Given the potential costs and benefits, there are strategic advantages in a more coherent and planned implementation of the policy of increased use of ACE Inhibitors at a district level.

This appendix outlines how such a planned approach might be created. It incorporates the experience of the FACTS project in Sheffield in helping 66 practices in one city prescribe aspirin to several thousand patients at high risk of heart attack and stroke.

Developing a District-wide Strategy

Developing a district-wide strategy for the prescription of ACE Inhibitors can be broken down into several stages:

a) Creating a clear and credible district-wide policy stating which groups are to be targeted. If the intention is to motivate GPs then such a policy must:
   - be clear, coherent and consistent with the evidence. The decision as to which patients to target must take account of those groups of patients which practices can easily identify (see below);
   - deal explicitly and fairly with the question of prescribing costs. Policies which simply expect GPs to absorb the costs of ACE Inhibitors into their drug budgets could fail.

b) Any policy, once formulated, is more likely to be effective if it is supported by a coalition of key players. Ideally this would include:
   - key local consultants;
   - members of the Local Medical Committee;
   - Director of Public Health;

   It might also be useful to have the specific endorsement of the Chief Executive of the Health Authority for the policy.

   Such coalitions do not necessarily need to include everyone and the experience of the FACTS project shows that coalitions are often best negotiated through a series of

meetings with individuals rather than trying to get all ‘stakeholders’ together for a single, potentially fractious, meeting.

The purpose of the coalition is to ensure support for the overall principles of the policy, and to explore potential problems from the perspectives of different players. It is not to develop guidelines or detailed policies about implementation.

c) Given a clear policy endorsed by local consultants, together with an equitable strategy for dealing with prescribing costs, most GPs will want to participate. In order to do so effectively, practices will need to:
   - identify patients in target groups;
   - pull the notes;
   - exclude those who are contraindicated;
   - invite remaining patients for a consultation and preliminary counselling;
   - prescribe, if appropriate.

d) A whole series of other barriers within practices are likely to arise at this point:
   - workload - few practices have capacity for work that is likely to be seen as ‘extra’ to the demands of everyday practice;
   - difficulty identifying target patients;
   - lack of computer skills;
   - concerns about clinical aspects of ACE Inhibitors, side effects etc.

Health Authorities should seriously consider policies to address these difficulties. For example:

a) *Workload:*
   Health Authorities need to recognise this problem explicitly. They can help in two ways:
   - providing concrete help - clear, simple guidelines about what to do; stickers and prompts for notes; leaflets for patients; postage for letters; resources.
   - reducing burdens in other areas - offering implementation of the ACE Inhibitor policy as an alternative to providing any other health promotion activity and/or banding information for the year.

b) *Identifying target patients:*

There are at least two ways to identify target patients:

- use the practice computer to search for all those on particular drugs, for example, diuretics.
- use the Health Authority database to identify patients who have had a relevant diagnosis in hospital and send each practice a list.

Each of these methods has advantages and disadvantages. These need to be understood by those who draw up the district policy - selecting the right mix will be crucial if the policy is to be implemented successfully.

c) *Computer skills:*

Although most practices are computerised, the experience of the FACTS project shows that many practices have relatively poor IT skills. If implementation of the strategy requires anything more than routine computer skills, then many practices will need extra help.

d) *Concerns about clinical aspects:*

Many GPs, and practice nurses, will have clinical questions about the use of ACE Inhibitors. These need addressing both through continuing medical education (CME) meetings and, if possible, with printed material.

<u>Strategies to avoid over-prescription:</u>

One concern of Health Authorities will be to ensure that people outside the target groups do not receive ACE Inhibitors. This might be avoided by giving practices 'completion criteria', which would tell them how many people they should have on ACE Inhibitors by the end of their implementation process. Such end points could take into account both the demography of each practice and/or the prevalence of heart failure. Linking 'completion criteria' to cost-free prescribing (i.e. up to this number of new prescriptions for ACE Inhibitors will be discounted from the drug budget) would give a strong message to practices about the importance and coherence of the policy, whilst ensuring a cap to ACE Inhibitor costs at a district level.

APPENDIX 3: Calculations to Support the Analysis of Section 3.3

Scenario 1: If the 921,664 DDD were to be replaced by ramipril 2.5mg – low maintenance regime:

The cost = 921,664 x £0.189 = £174,194.5

Therefore potential savings = £341,046 - £ 174,194.5 = £166,851.5 per quarter.
i.e. £667,406 per annum.

Scenario 2: If the 921,664 DDD were to be replaced by ramipril 5mg – high maintenance regime:

The cost = 921,664 x £0.341 = £314,287
Therefore potential savings = £341,046 - £314,287 = £ 26,758 per quarter.
i.e. £107,034 per annum

Scenario 3: If the 921,664 DDD were to be replaced in the same proportions as ramipril is currently prescribed in this population:

Cost of ramipril prescribing:
3.1% for 1.25mg preparation: Cost per tablet £0.189
21.8% for 2.5mg preparation: Cost per tablet £ 0.269
75.1% for 5mg preparation∗: Cost per tablet £0.341[43]

∗ NB: 5mg may be prescribed as a double dose i.e. some 5mg prescriptions represent 10mg daily dosage

For 1.25mg	3.1% x 921,664	EDD†	= 28571.6 @ £0.189	= £5,400
For 2.5mg	21.9% x 921,664	EDD†	= 201844.4 @ £0.269	= £54,296
For 5mg	75.1% x 921,664	DDD	= 692169.7 @ £0.341	= £236,030

† *EDD = Equivalent Daily Dosage. (E.g. 25mg three times daily is an EDD of 75 mg.)*

Cost of ramipril prescribing £295,726
{at unit prices of 0.38,0.269, 0.17 for 1.25mg, 2.5mg and 5mg respectively = £10,857.2, £54,296.1, £117,668.8 = £182,824.1 = savings of £158,221.9 per quarter}

Therefore potential savings = £341,046 - £295,726 = £45,320 per quarter.
i.e. £181,280 per annum

Scenario 4: If the 921,664 DDD were to be replaced in the same proportions as ramipril is currently prescribed in this population, allowing for 25% of prescriptions being for 10mg daily:

For 1.25mg	3.1% x 921,664	DDD	= 28571.58 @ £0.189	= £5,400
For 2.5mg	21.9% x 921,664	DDD	= 201844.40 @ £0.269	= £54,296
For 5mg	50% x 921,664	DDD	= 460832.00@ £0.341	= £157143.70

Cost of ramipril prescribing for preparations of 5mg or less = £216,839.7
Cost of ramipril 5mg twice daily = 25% of 921,664 = 230416 x £0.682 (cost of 2x 5mg tablet) = £157,143.7

Thus, cost of ramipril, allowing for 25% of prescriptions being for 10mg = £373,983

This is greater than current prescribing costs of £341,046 and, therefore, represents a potential extra cost.

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