

Eplerenone: the evidence for its place in the treatment of heart failure after myocardial infarction

Carole Nadin

Core Medical Publishing, Knutsford, UK

Abstract

Introduction: Heart failure is a frequent complication after acute myocardial infarction (MI) and carries a poor prognosis. Current treatments inhibit the renin-angiotensin-aldosterone system but suppression of aldosterone may be incomplete. The aldosterone antagonist spironolactone has been shown to improve survival in patients with chronic, severe heart failure. Eplerenone is a selective aldosterone antagonist expected to have a lower incidence of hormonal side effects than spironolactone.

Aims: To assess the evidence on the therapeutic value of eplerenone for treatment of heart failure in adults.

Evidence review: The evidence base consists of one large double-blind placebo-controlled multicenter randomized trial in over 6000 patients with postmyocardial infarction (MI) heart failure, comparing eplerenone plus standard therapy with placebo plus standard therapy. All the main outcomes were patient-oriented. Evidence from this trial shows that eplerenone improves survival and reduces cardiovascular hospitalization/mortality, compared with standard treatment alone. The incidence of hormonal side effects is no greater than with placebo. The risk of hyperkalemia is significantly increased, especially in patients with low creatinine clearance. Eplerenone was both more effective and more costly than standard treatment alone. The cost-effectiveness ratio has been estimated at \$US10 402–21 876 per life-year gained.

Place in therapy: Eplerenone reduces mortality compared with current treatment alone in patients with post-MI heart failure, at additional cost. Direct comparative evidence is needed to assess its efficacy versus spironolactone. It may be valuable in patients who are intolerant to the hormonal side effects of spironolactone.

Key words: eplerenone, evidence, heart failure, left ventricular dysfunction, myocardial infarction, survival

Core evidence place in therapy summary for eplerenone as an addition to standard therapy in adult patients with heart failure after myocardial infarction

Outcome measure	Evidence	Implications
Patient-oriented evidence		
Decrease in all-cause mortality	Clear	Improved survival with add-on eplerenone compared with standard therapy alone
Decrease in combined cardiovascular mortality/hospitalization	Clear	Lower risk with add-on eplerenone compared with standard therapy alone
Decrease in cardiovascular mortality	Substantial	Lower risk with add-on eplerenone compared with standard therapy alone
Decrease in sudden cardiac death	Substantial	Lower risk with add-on eplerenone compared with standard therapy alone
Decrease in combined all-cause mortality/hospitalization	Substantial	Lower risk with add-on eplerenone compared with standard therapy alone
Decrease in cardiovascular hospitalization	Substantial	No significant difference between add-on eplerenone and standard therapy alone
Incidence of hormonal side effects	Substantial	No greater incidence with eplerenone than with placebo
Reduction in length of stay	Limited	Shorter length of stay with add-on eplerenone compared with standard therapy alone in patients hospitalized for heart failure
Improvement in quality of life	Limited	No significant difference in utility score between eplerenone and standard therapy alone at 12 months
Reduction of symptom burden	No evidence	
Prevention of progression to poor functional status	No evidence	

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...table continued		
Outcome measure	Evidence	Implications
Disease-oriented evidence		
Incidence of hyperkalemia	Clear	Eplerenone is associated with an increased risk of hyperkalemia, especially in patients with creatinine clearance <50 mL/min Serum potassium and creatinine clearance should be carefully monitored throughout eplerenone therapy and prompt dose adjustment made if required
Economic evidence		
Cost effectiveness	Clear	Addition of eplerenone is more costly and more effective than standard therapy alone, \$US10 402–21 876 per life-year gained

Scope, aims, and objectives

Eplerenone (Inspra[®], Pfizer) is a selective aldosterone antagonist first developed for the treatment of hypertension and approved by the US Food and Drug Administration (FDA) in October 2003 for the treatment of adults with heart failure occurring after a myocardial infarction (MI).

Eplerenone has higher selectivity for aldosterone (mineralocorticoid) receptors and lower affinity for androgen and progesterone receptors compared with the existing aldosterone antagonist, spironolactone. As a result, eplerenone should provide effective aldosterone blockade with a lower incidence of hormonal side effects than spironolactone, which should lead to improved tolerability.

This article reviews the evidence base for the clinical use of eplerenone in adult patients with post-MI heart failure. Use of eplerenone in children or in other conditions, such as hypertension, is outside the scope of this review.

Methods

English-language literature searches were conducted on March 2–4, 2005 in the following databases, searching from the beginning of the database to date unless otherwise stated. The search strategy was “(eplerenone OR Inspra) AND (heart AND failure)” unless otherwise stated:

- PubMed, <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>, 1966 to date. Search strategy “(eplerenone OR Inspra) AND (heart AND failure OR CHF),” which was expanded by Automatic Term Mapping to “((‘eplerenone’[Substance Name] OR eplerenone[Text Word]) OR (‘eplerenone’[Substance Name] OR Inspra[Text Word])) AND ((‘heart’[MeSH Terms] OR heart[Text Word]) AND failure[All Fields] OR (‘congestive heart failure’[Text Word] OR ‘heart failure, congestive’[MeSH Terms] OR CHF[Text Word])) AND English[Lang]”
- EMBASE, <http://www.datastarweb.com>, 1974 to date. Search strategy: “((eplerenone OR Inspra) AND (heart AND failure OR CHF)) AND LG=EN AND HUMAN=YES”
- Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluations Database (NHSEED), Health

Technology Assessment (HTA), www.york.ac.uk/inst/crd/darehp.htm. All three databases were searched together. All fields searched

- NHS HTA, www.ncchta.org. Search strategy “eplerenone OR Inspra”
- National Guideline Clearing House, www.guideline.gov
- National Institute for Health and Clinical Excellence (NICE), www.nice.org.uk. Search strategy “eplerenone OR Inspra”
- Cochrane Database of Systematic Reviews (CDSR), www.cochrane.org/index0.htm. Entire site searched. Search strategy “eplerenone OR Inspra”
- Clinical Evidence (BMJ), www.clinicalevidence.com. Search strategy “eplerenone OR Inspra”
- www.clinicaltrials.gov. Search strategy “eplerenone OR Inspra”
- www.clinicalstudyresults.org. Search strategy “eplerenone OR Inspra”

After removal of duplicates, a total of 279 records were identified. Records were manually reviewed and 275 were excluded for the following reasons: nonsystematic reviews (n=170), animal studies (n=11), studies in other diseases (n=24), studies in children (n=1), letters, editorials, news items, comments and corrections (n=42), conference reviews (n=5), articles about other drugs or treatments (n=19), and articles not investigating the clinical use of eplerenone in heart failure (n=3). One clinical trial, one economic evaluation, and two articles describing their design rationale remained and were included in the evidence base (Table 1).

Online abstracts from the following congresses were searched using the search strategy “eplerenone” unless otherwise stated:

- American Heart Association, all conferences from 2001 to 2003, <http://aha.agora.com/abstractviewer/search.asp>
- European Society of Cardiology 2003 held August 30 to September 3, 2003, Vienna, Austria. <http://www.escardio.org/knowledge/congresses/abstracts/>

Table 1 | Evidence base included in the review

Category	Number of records	
	Full papers	Abstracts
Initial search	279	36
records excluded	275	29
records included	4	7 ^a
Additional papers identified	0	1
Search update, new records	69	1
records excluded	69	1
records included	0	0
Publications not available on databases and supplied by manufacturer	2	1 ^b
Level 1 clinical evidence (systematic review, meta analysis)	0	0
Level 2 clinical evidence (RCT)	3 ^c	7
Level ≥3 clinical evidence	0	0
trials other than RCT		
case reports		
Economic evidence	1	1
Total records included	6	8

^aOne of these abstracts later replaced by presentation with corrected data supplied by manufacturer, and one replaced by a full paper.
^bPresentation.
^cPlus 2 describing design and rationale.
For definitions of levels of evidence, see Editorial Information on inside back cover.
RCT, randomized controlled trial.

- European Society of Cardiology Heart Failure Update held June 12–15, 2004, Wroclaw, Poland.
<http://www.escardio.org/knowledge/congresses/abstracts/>
- European Society of Cardiology 2004 held August 28 to September 1 2004, Munich, Germany.
<http://www.escardio.org/knowledge/congresses/abstracts/>

Nineteen abstracts were identified and available online, of which 15 were excluded because they were animal studies (n=14) or did not investigate the clinical effect of eplerenone (n=1), and four were included (Table 1).

Meeting abstracts from 2002 or later were identified by searching BIOSIS Previews, <http://www.datastarweb.com>, 1996 to date, using the search strategy “(eplerenone OR Inspra) AND (heart AND failure OR CHF) AND PT=MEETING\$ AND LG=EN AND (YEAR=2002 OR YEAR=2003 OR YEAR=2004 OR YEAR=2005).” A total of 20 abstracts were retrieved, of which three were duplicates of abstracts already identified from the online abstracts of the congresses listed above, leaving 17 nonduplicates. Of these, 14 were excluded for the following reasons: animal studies (n=8), studies in other diseases (n=3),

review (1), duplicate publications of data presented in full papers (2), and the remaining 3 were included. One additional abstract was identified from the reference list of a review paper and included (Table 1).

The searches were updated on July 21–25, 2005. A total of 70 new records were identified, of which all 70 were excluded for the following reasons: animal studies (n=2); studies on other drugs (n=3); letters, notes, and editorials (n=5); articles that did not investigate the clinical use of eplerenone (n=1); and nonsystematic reviews (n=59). The manufacturer, Pfizer, provided one additional full paper (Ravis et al. 2005) which replaced an earlier abstract (Ravis et al. 2004), a further full paper (Pitt et al. in press), and a presentation with corrected data (Gheorghiadu et al. 2004b) which replaced an earlier abstract (Gheorghiadu et al. 2004a) (Table 1).

Disease overview

Heart failure is a complex clinical syndrome (Hunt et al. 2001; Remme & Swedberg 2001). The most common form is chronic heart failure; acute heart failure is sometimes used to mean acute pulmonary edema or cardiogenic shock, but the use of the term is discouraged (Remme & Swedberg 2001). The European Society for Cardiology Task Force on Heart Failure considered that no definition of chronic heart failure is entirely satisfactory, but proposed the following: “heart failure is a pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues” (Remme & Swedberg 2001).

There is no objective definition of heart failure, and diagnosis relies on clinical judgment (Remme & Swedberg 2001). The American College of Cardiology/American Heart Association (ACC/AHA) Task Force considered the key symptoms of heart failure to be dyspnea and fatigue (which may result in impaired exercise tolerance) and fluid retention (which may lead to pulmonary and/or peripheral edema) (Hunt et al. 2001). The severity of heart failure is most commonly assessed using the New York Heart Association (NYHA) functional classification (Hunt et al. 2001):

- class I, patients have symptoms of heart failure only at exertion levels that would limit normal individuals
- class II, patients have symptoms of heart failure on ordinary exertion
- class III, patients have symptoms of heart failure on less than ordinary exertion
- class IV, patients have symptoms of heart failure at rest.

In addition, the ACC/AHA Task Force has proposed a complementary classification that considers heart failure as a progressive disease (Table 2); patients are expected to progress from one stage to the next unless progression is slowed or

Table 2 | American College of Cardiology/American Heart Association (ACC/AHA) Task Force classification of heart failure stages (adapted from Hunt et al. 2001)

Stage	Description
A	Patients at high risk of developing heart failure but with no identified structural abnormalities and no symptoms
B	Patients with structural abnormalities but no symptoms of heart failure
C	Patients with symptoms of heart failure associated with structural abnormalities
D	Patients with advanced structural abnormalities and marked symptoms of heart failure at rest

stopped by medical treatment (Hunt et al. 2001). The NYHA functional classification relates primarily to patients in stages C and D of the ACC/AHA classification (Hunt et al. 2001).

Heart failure can result from any cardiac disorder that impairs the ability of the ventricle to fill with or eject blood, but the most common underlying cause is coronary artery (or heart) disease (Hunt et al. 2001). It includes acute MI, other acute ischemic coronary disease, angina pectoris, atherosclerotic cardiovascular disease, and all other forms of heart disease (AHA 2004). This review is concerned with heart failure occurring as a complication after MI.

Burden of disease

The British Heart Foundation (BHF) estimates that the incidence rate for MI in the UK is approximately 600 per 100 000 men aged 30–69 years and approximately 200 per 100 000 women of the same age (BHF 2005). The prevalence of MI (i.e. the number of people who have had an MI and survived) in the UK is estimated at approximately 4% of men and 2% of women (BHF 2005). In the USA, the prevalence of MI was estimated at 5% in men and 2.3% in women in 2002 (AHA 2004). Mortality data collected and published by the World Health Organization (WHO) show considerable international variations, with higher rates of MI mortality in Northern Europe than in Southern Europe and low MI mortality in Japan (Table 3) (WHO 2005).

Around half of people experiencing an MI die within 28 days (case fatality rate) in the UK (BHF 2005). Comparison of a population survey in Oxfordshire in 1994–1995 with a previous survey in the same region in 1966–1967 showed that case fatality had significantly ($P<0.05$) improved over the period by 28% in men and 32% in women (Volmink et al. 1998). Data from the National Registry of Myocardial Infarction show a similar improving trend in the USA; in-hospital mortality after MI declined from 11.2% to 9.4% ($P=0.0001$) between 1990 and 1999 (Rogers et al. 2000).

Table 3 | Mortality from acute myocardial infarction [adapted from World Health Organization (WHO) 2005]

Country	Year ^a	Mortality rate per 100 000 population, acute myocardial infarction	
		Men	Women
France	2000	51.1	35.5
Italy	2001	72.8	49
Japan	2002	40.7	32
Spain	2001	72.6	48.4
Sweden	2001	145.4	110.5
UK	2002	104.9	80.7
USA	2000	72.7	64.6

^aMost recent year in the online database.

Heart failure is a common complication following MI (Cleland et al. 2005). The VALIANT registry of over 5000 MI patients in nine countries in 1999–2001 (part of the VALIANT [VALsartan in acute myocardial INfarcTion] clinical trial) found that 42% of patients had heart failure and/or left ventricular systolic dysfunction during hospitalization (Velazquez et al. 2004). Data from over 60 000 MI patients enrolled in four trials of fibrinolytic therapy showed that 29% had mild-to-moderate heart failure (Hasdai et al. 2003). The AHA estimates that within 6 years after a recognized MI, 22% of men and 46% of women will be disabled by heart failure (AHA 2004).

The prevalence of heart failure and the number of hospital admissions for the disease is increasing in Europe and the USA (Haldeman et al. 1999; Szucs 2000; Stewart et al. 2002). This partly reflects the increasing average age of the population in most Western countries, as heart failure becomes increasingly common with advancing age (Remme & Swedberg 2001). It may also reflect the increased success of treatment for acute MI, such as thrombolytic therapy, as more patients survive the initial event and thus remain alive and at potential risk of developing complications (Szucs 2000). Improved management strategies for heart failure, resulting in improved survival, also tend to increase the number of patients living with the condition (Szucs 2000).

Patients who develop heart failure after MI have a worse prognosis than patients who do not. In the VALIANT registry, the in-hospital mortality rate was 13% in MI patients with heart failure and/or left ventricular systolic dysfunction during hospitalization, compared with 2.3% in patients without ($P<0.001$) (Velazquez et al. 2004). After adjustment for baseline risk factors, patients with heart failure and/or left ventricular systolic dysfunction were over four times more likely to die before discharge than patients without (hazard ratio 4.12, 95% confidence interval 3.08, 5.56) (Velazquez et al. 2004). Mild-to-moderate heart failure after MI is also associated with increased mortality; 30-day mortality was 8% for patients with mild-to-moderate heart failure, compared with 2% for patients without (Hasdai et al. 2003).

Even if systolic function is preserved the mortality risk remains elevated; a study of 3166 MI patients in Denmark reported 1-year mortality rates of 6% for patients without heart failure, 22% for patients with heart failure and preserved systolic function, and 35% for patients with heart failure and systolic dysfunction ($P < 0.0001$) (Møller et al. 2003). In the US National Registry of Myocardial Infarction, patients presenting with heart failure as a complication of ST-elevation MI were at higher risk for in-hospital death than patients without heart failure (21.4% compared with 7.2%, $P < 0.0005$) (Wu et al. 2002). In a population survey of 1915 patients with MI in Minnesota, median survival after the development of heart failure was 4 years, with a worse outcome in patients with impaired left ventricular ejection fraction (Hellermann et al. 2005). When patients with all acute coronary syndromes (not just MI) were considered, patients with heart failure on admission to hospital had higher mortality in hospital (12% compared with 2.9%, $P < 0.0001$) and at 6 months after discharge (8.5% compared with 2.8%, $P < 0.0001$) than patients without heart failure (Steg et al. 2004). Health-related quality of life, measured with the Nottingham Health Profile, was impaired in a sample of elderly patients with heart failure compared with a healthy reference population matched for age and sex (Cline et al. 1999). In patients with post-MI heart failure, poorer health status as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) was associated with higher 1-year risk of cardiovascular mortality or hospitalization (Soto et al. 2004).

As well as elevated mortality risk, patients with heart failure after MI are also less likely to return to paid work than patients with MI but without heart failure. In a small population survey of 89 patients with MI in the Midwestern USA, 33% of patients who did not return to work had heart failure, compared with only 3% of patients who did return to paid work ($P < 0.001$) (McBurney et al. 2004).

The economic burden of heart failure is substantial. It has been estimated that treating heart failure accounts for 1–2% of the total healthcare budget in France, The Netherlands, and the UK (Cleland 1998; Stewart et al. 2002). In the USA, the total inpatient and outpatient cost for heart failure in 1991 was estimated at \$US38.1 billion, 5.4% of the total healthcare budget (Hunt et al. 2001). The total direct cost of heart failure to the UK National Health Service (NHS) has been estimated at £716 million in 1995 (Stewart et al. 2002). The largest component of cost (69%) was hospital treatment, and the cost of prescribed medications was estimated at 18%. The large proportion attributable to hospital costs appears to be consistent across other European countries, including Sweden and Switzerland (Szucs 2000). In addition to these costs, Stewart et al. (2002) also estimated that a further £751 million was incurred in the UK for long-term nursing home care and hospitalizations with a secondary diagnosis of heart failure.

Certain subgroups of patients account for a disproportionately large percentage of costs. Clearly, since hospitalization is the major cost component, patients who require hospital treatment comprise such a subgroup (Szucs 2000). It has also been estimated that patients with more severe heart failure (NYHA class III or IV) consume over 90% of the total medical costs of heart failure (Szucs 2000).

No cost or economic data were identified relating specifically to patients with heart failure as a post-MI complication, as opposed to patients with heart failure from other causes. However, a study based on a decision-analysis model applied to eight European countries found that the follow-up costs for the first year after MI (excluding the acute costs of treating the initial event) ranged from €2050 per patient in Portugal to €8631 per patient in Austria (Levy et al. 2003). In the USA, the cost of MI after the acute treatment phase has been estimated at \$US1678 per patient per year in patients with diabetes mellitus (O'Brien et al. 2003), and \$US19 840 per patient over 10 years in patients undergoing cardiac catheterization (Eisenstein et al. 2001).

Pathophysiology

The pathophysiology underlying the symptoms of heart failure is not fully understood (Remme & Swedberg 2001), and symptom severity does not necessarily relate to the degree of cardiac function (Hunt et al. 2001). The development of heart failure is considered to be a progressive process, characterized by structural changes in the heart and especially in the left ventricle, resulting in an increase in ventricular wall thickness (Hunt et al. 2001). This process is referred to as left ventricular hypertrophy or cardiac remodeling, and may be an important contributor to the development and worsening of symptoms (Hunt et al. 2001). However, there are diverse mechanisms for heart failure progression, and the exact role of remodeling is not fully understood.

Heart failure can be considered as an inappropriate response of the systems that normally regulate blood pressure and blood volume, of which the renin-angiotensin-aldosterone system is a particularly important component (Fig. 1).

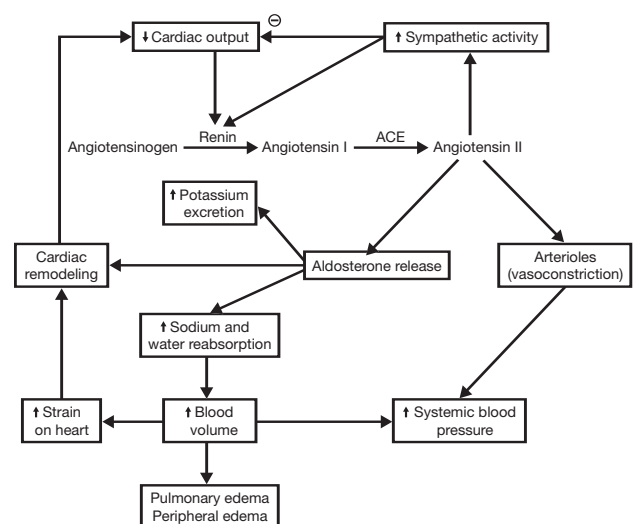


Fig. 1 | The renin-angiotensin-aldosterone system and the pathophysiology of heart failure. ACE, angiotensin-converting enzyme

Injury to the heart (e.g. from MI) reduces cardiac output (the volume of blood pumped per minute), which in turn reduces the flow of blood around the body and tends to reduce arterial blood pressure. Reduced blood flow to the kidneys stimulates the release of renin, an enzyme which converts angiotensinogen to angiotensin I. A second enzyme, angiotensin-converting enzyme (ACE), found mainly in the lungs, converts angiotensin I to angiotensin II. Angiotensin II has numerous actions on the cardiovascular system (Remme 1999). It increases sympathetic nerve activity, which in turn increases heart rate and tends to increase cardiac output. Sympathetic stimulation can also increase renin release. Angiotensin II also acts as a peripheral vasoconstrictor, causing blood vessels to narrow and thus tending to increase arterial blood pressure, and stimulates release of aldosterone from the adrenal cortex.

Aldosterone is a steroid hormone (sometimes referred to as a mineralocorticoid, because its main effects are on mineral balance) that acts on the kidney tubule to increase reabsorption of salt and water and indirectly increases potassium excretion. The increase in salt and water retention increases blood volume, which tends to increase both cardiac output and blood pressure. In healthy individuals and acute situations, restoration of cardiac output and blood pressure to normal inhibits renin release and switches off the renin-angiotensin-aldosterone system. However, renin-angiotensin-aldosterone production also occurs locally in tissues such as the heart, blood vessels, and kidneys, and these local systems may become progressively and chronically activated (Remme 1999). Chronic activation of the renin-angiotensin-aldosterone system is maladaptive and may contribute to the characteristic symptoms of heart failure. Fluid retention results in peripheral and pulmonary edema, and pulmonary edema may give rise to breathlessness. Vasoconstriction limits the blood flow to muscles and may contribute to impaired exercise tolerance. Fluid retention and increased blood pressure increase the strain on the heart, which in turn tends to promote cardiac remodeling as the ventricular muscle mass increases to meet the increased load. Angiotensin II also has direct effects on cardiac remodeling (Remme 1999).

There is evidence that aldosterone may also contribute directly to cardiac remodeling and damage to other organs. Aldosterone-generating enzymes and aldosterone receptors have been identified in heart muscle and blood vessels, indicating that these tissues can synthesize and respond to aldosterone independently of the adrenal gland (Pitt et al. 2003c).

In animal models, aldosterone in combination with a high-salt diet is associated with increased oxidative stress, inflammation of coronary blood vessels, cardiac hypertrophy, cardiac fibrosis and necrosis, renal vascular damage, and proteinuria (Rocha & Funder 2002; Rudolph et al. 2004; Shieh et al. 2004). These effects could contribute to the development of cardiac remodeling, nephrosclerosis, and stroke (Rocha & Funder 2002). Aldosterone-induced cardiac fibrosis increases the stiffness of the ventricle, which may contribute to the development of ventricular dysfunction and heart failure (Struthers 2002), and in clinical studies plasma aldosterone concentrations have been correlated with left ventricular hypertrophy, vascular stiffness, and mortality

(Rudolph et al. 2004). Aldosterone has also been shown to increase tissue levels of ACE, endothelin, and norepinephrine (noradrenaline) (Pitt et al. 2003c). In the blood vessels, aldosterone has been shown to inhibit fibrinolysis and to reduce endothelial nitric oxide (which in turn reduces the ability of the blood vessels to relax in response to vasodilator agents), and may mediate tissue injury by a variety of mechanisms (Struthers 2002). Aldosterone may also block the reuptake of norepinephrine and other catecholamines in the heart, thus potentiating the effect of sympathetic nervous system stimulation and possibly contributing to the development of cardiac arrhythmias and sudden cardiac death (Struthers 2002). Aldosterone can also decrease the sensitivity of pressure receptors in animals and humans, and this may also be linked to arrhythmias (Struthers 2004).

Current therapy options

Treatment guidelines have been published for the management of patients with heart failure in the USA (Hunt et al. 2001) and Europe (Remme & Swedberg 2001; Swedberg et al. 2005). US guidelines for the management of ST-elevation MI (Antman et al. 2004) also refer to the treatment of heart failure as a post-MI complication.

The main classes of drugs used in heart failure treatment are ACE inhibitors, angiotensin II receptor antagonists, diuretics, digoxin, spironolactone, beta blockers, and hydralazine/isosorbide dinitrate (ICSI 2004) (Table 4). The recent update to the European guidelines (Swedberg et al. 2005) recommends aldosterone receptor antagonists in addition to ACE inhibitors, beta blockers and diuretics.

According to the European guidelines (Swedberg et al. 2005), the aims of treatment for heart failure include:

- prevention of disease development and progression
- improved or maintained health-related quality of life
- improved survival.

There is broad agreement between the drugs recommended in the US guidelines and European guidelines for heart failure (Hunt et al. 2001; Remme & Swedberg 2001; Swedberg et al. 2005). The US guidelines recommend a combination of four classes of drugs (ACE inhibitors, beta blockers, diuretics, and digitalis) for routine management of patients with symptomatic left ventricular dysfunction, based on evidence and/or generally agreed effectiveness (Hunt et al. 2001). In addition, the guidelines also recommend the following drugs as being probably useful/effective but with a lower level of evidence in support:

- spironolactone in patients with class IV heart failure symptoms, preserved renal function and normal serum potassium
- angiotensin II receptor antagonists instead of ACE inhibitors in patients receiving digitalis, diuretics, and beta blockers and who cannot be given an ACE inhibitor because of cough or angioedema

Table 4 | Current pharmacologic treatments in heart failure [adapted from Institute for Clinical Systems Improvement (ICSI) 2004]

Drug class	Subsets of patients	Characteristics
Systolic dysfunction		
ACE inhibitors	NYHA class I–IV	Slow disease progression Improve exercise capacity Reduce hospitalizations and mortality May induce cough and/or rash Contraindicated if serum potassium >5.5 mmol/L, in pregnancy, in patients with severe renal artery stenosis and patients with symptomatic hypotension
Angiotensin II receptor antagonists	NYHA class I–IV	Improve cardiac output Preferred alternative in patients with ACE inhibitor-induced cough, unless high serum potassium and/or renal dysfunction is present
Hydralazine/isosorbide dinitrate	Patients intolerant to ACE inhibitors	In patients with ACE inhibitor-induced cough an angiotensin II receptor antagonist is preferred because of greater ease of use Alternative to ACE inhibitors if serum potassium is elevated
Diuretics	Patients with fluid overload	Diuretics should not be sole therapy Monitor for fluid and electrolyte balance, including potassium, magnesium, blood urea nitrogen, and creatinine
Spironolactone	NYHA class III–IV	May induce hormonal side effects, e.g. painful gynecomastia in men
Digoxin	NYHA class II–IV, patients with atrial fibrillation, left ventricular dilatation, high filling pressure	Improves symptoms, exercise tolerance, and quality of life No effect on mortality Requires monitoring of serum levels due to potential toxicity
Beta blockers	Stable NYHA class I–IV	Reduce mortality and hospitalization Improve exercise tolerance May take several months for beneficial effects to develop May produce bradycardia and/or atrioventricular block
Diastolic dysfunction		
ACE inhibitors	NYHA class I–IV	May cause serious hypotension; use with caution
Diuretics	Patients with fluid retention	May cause orthostatic hypotension; use with caution
Beta blockers	Patients with atrial fibrillation	Requires higher dose than in systolic dysfunction

ACE, angiotensin-converting enzyme; ICSI, Institute for Clinical Systems Improvement; NYHA, New York Heart Association.

- hydralazine and a nitrate in patients receiving digitalis, diuretics, and beta blockers and who cannot be given an ACE inhibitor because of hypotension or renal insufficiency.

The recent European guidelines provide broadly similar recommendations, though they recommend aldosterone antagonists in addition to ACE inhibitors, beta blockers, and diuretics in patients with NYHA class III–IV heart failure and in patients with post-MI heart failure with left ventricular systolic dysfunction and signs of heart failure or diabetes (Swedberg et al. 2005).

The guidelines for treatment of ST-elevation MI are consistent with those for heart failure. They recommend early use of beta blockers and long-term treatment with an ACE inhibitor (or an angiotensin II receptor antagonist in patients who cannot tolerate ACE inhibitors) in patients recovering from MI (Antman et al. 2004). Aldosterone receptor antagonists are also recommended

in patients who are already receiving an ACE inhibitor, who have a left ventricular ejection fraction of $\leq 40\%$ and symptomatic heart failure or diabetes, and who do not have significant renal dysfunction or elevated serum potassium (Antman et al. 2004).

Unmet needs

Despite the availability of numerous treatments and the publication of practice guidelines for their use, there is still room for improvement in the management of heart failure. Hospital admissions due to heart failure increased in the USA between 1985 and 1995 according to data from the National Hospital Discharge Survey (Haldeman et al. 1999), and current treatment guidelines consider that mortality due to the disease is increasing (Hunt et al. 2001; Remme & Swedberg 2001). The VALIANT registry study found that treatment of patients with heart failure and/or left ventricular systolic dysfunction as a post-MI complication often failed to meet guideline recommendations (Velazquez et al. 2004).

Table 5 | Effects of eplerenone on all-cause mortality and combined cardiovascular mortality/hospitalization (adapted from Pitt et al. 2003b; level 2 evidence)

Outcome	
All-cause mortality	Combined cardiovascular mortality/hospitalization ^a
Lower with eplerenone ($P=0.008$)	Lower with eplerenone ($P=0.002$)
Relative risk 0.85 (95% CI 0.75, 0.96)	Relative risk 0.87 (95% CI 0.79, 0.95)
<p>Patients were randomized to receive standard therapy plus either placebo (n=3313) or eplerenone (25 mg/day for 4 weeks, then titrating up to a target dose of 50 mg/day, n=3319) in a double-blind trial, with a mean of 16 months of follow-up. Standard therapy included ACE inhibitors or angiotensin II receptor antagonists (87%), diuretics (60%), aspirin (88%), beta blockers (75%), and coronary reperfusion therapy (45%).</p> <p>^aHospitalization was defined as a nonfatal event causing or prolonging hospitalization.</p> <p>CI, confidence interval.</p>	

One problem may relate to the phenomenon of “aldosterone escape.” Although ACE inhibitor treatment produces an acute reduction in serum aldosterone levels, the level of aldosterone rises again in long-term therapy and may return to baseline in some patients (Struthers 2004). Aldosterone escape has been linked to increased risk of cardiovascular events and reduced exercise capacity, and has been suggested as a possible mechanism for the blunting of the beneficial effects of ACE inhibitors over time (Struthers 2004). The mechanism of aldosterone escape is unclear, but may be related to non-ACE-dependent pathways for synthesis of angiotensin II (e.g. chymase), and/or direct synthesis of aldosterone in tissues such as the brain, heart, and blood vessels (Struthers 2004).

Recognition of aldosterone escape has resulted in increased interest in aldosterone antagonists, since these agents directly block the action of aldosterone. Pivotal in this research was the Randomized Aldactone Evaluation Study (RALES) (Pitt et al. 1999). This study randomized 1663 patients with chronic severe heart failure and a left ventricular ejection fraction of $\leq 35\%$ to double-blind treatment with either the aldosterone antagonist spironolactone (25 mg/day) or placebo, in addition to standard treatment with ACE inhibitors, loop diuretics, and (in most cases) digoxin. It was terminated early after an interim analysis revealed that addition of spironolactone reduced all-cause mortality by 30%, reduced hospitalization for worsening heart failure by 35%, and improved NYHA functional classification, compared with standard treatment alone (all $P < 0.001$) (Pitt et al. 1999).

However, spironolactone is not without drawbacks. It has affinity for androgen and progesterone receptors as well as aldosterone (mineralocorticoid) receptors, so it can be associated with troublesome hormonal side effects such as gynecomastia, breast pain and impotence in men and abnormal vaginal bleeding in women. In RALES, gynecomastia or breast pain occurred in 10% of men treated with spironolactone, compared with 1% of placebo-treated men ($P < 0.001$), causing 10 men in the spironolactone group to discontinue treatment (Pitt et al. 1999). Furthermore, because one of the effects of aldosterone is to increase potassium excretion, suppression of the renin-angiotensin-aldosterone system by ACE inhibitors, angiotensin II receptor antagonists, or aldosterone antagonists tends to promote potassium

retention. Impaired renal function may also promote potassium retention, as the ability of the kidney to excrete excess potassium is reduced, and mild-to-moderate renal insufficiency is common in patients with advanced heart failure, especially in patients with concomitant conditions such as diabetes (Sica et al. 2003). The combination of drug therapy and impaired renal function means that hyperkalemia is not uncommon in patients with heart failure, and may be a serious complication as it can increase the risk of cardiac arrhythmias and sudden cardiac death (Sica et al. 2003). Strategies for minimizing hyperkalemia include restriction of dietary potassium intake, and dose reduction or temporary withdrawal of drugs that suppress the renin-angiotensin-aldosterone system. Aldosterone receptor antagonist treatment is at greatest risk of inducing hyperkalemia in patients with moderate renal impairment and serum potassium of ≥ 4.5 mmol/L (Sica et al. 2003). In patients with more advanced renal failure, the risk of hyperkalemia has limited the use of aldosterone antagonists (McLaughlin et al. 2004). However, in patients with end-stage renal disease (ESRD) the effects of aldosterone blockade on potassium excretion should be minimal, since there is little or no renal excretion to be affected. Limited evidence from a small number of patients indicates that the risk of hyperkalemia with aldosterone antagonists may indeed be lower in ESRD patients, although further studies are required (McLaughlin et al. 2004). A recent pharmacokinetic study reported that after single or multiple dosing with 100 mg/day eplerenone, approximately 10% of the administered dose was removed by hemodialysis (Ravis et al. 2005). This study also concluded that no dose adjustment of eplerenone is necessary in patients with renal dysfunction (Ravis et al. 2005).

The ideal treatment for heart failure would therefore have an effect on some or all of the following outcomes compared with current treatment: reduction in mortality; reduction in cardiovascular morbidity; improvement in symptoms, functional status and/or health-related quality of life; attenuation of heart failure progression; reduction in the need for hospitalization; reduction in overall costs and/or demonstrated cost effectiveness; improved patient tolerability (e.g. low incidence of side effects that lead to discontinuation of therapy); and low risk of hyperkalemia.

Clinical evidence with eplerenone

The evidence base for the use of eplerenone in post-MI heart failure currently consists of one large double-blind randomized controlled trial (RCT), the Eplerenone Postacute myocardial infarction Heart Failure Efficacy and Survival Study (EPHESUS) (Pitt et al. 2001; Pitt et al. 2003b). This study was conducted in over 6000 patients with a mean follow-up of 16 months. The primary outcomes were all-cause mortality and a combined endpoint of cardiovascular death or hospitalization for cardiovascular causes (heart failure, MI, stroke, or ventricular arrhythmia). Both of these are clearly patient-oriented outcomes. The secondary efficacy outcomes (all-cause hospitalization/mortality, cardiovascular mortality, and cardiovascular hospitalizations) provide further patient-oriented evidence. Data on symptoms, functional status, and health-related quality of life were also collected during the study (Spertus et al. 2002), though as yet these results have not been published. Disease-oriented outcomes included the incidence of hyperkalemia (Pitt et al. 2003b). The study was also designed to investigate additional disease-oriented outcomes including cardiac remodeling, heart rate variability, neurohormonal profile, collagen metabolism, thrombolytic balance, vascular compliance, and proteinuria (Pitt et al. 2001), although as yet the results for these outcome measures have not been published as full papers.

All-cause mortality

All-cause mortality was one of the two primary endpoints in EPHESUS, and the study was powered to have a chance of 88.3% of detecting a reduction in all-cause mortality of 18.5% for eplerenone compared with placebo at a significance level of 0.04 (Pitt et al. 2001). EPHESUS reported clear evidence that addition of eplerenone to standard therapy produced a significant reduction in all-cause mortality, compared with placebo plus standard therapy (Table 5). Standard therapy in EPHESUS consisted of optimal medical treatment for MI as selected by the investigators. At baseline, ACE inhibitors or angiotensin II receptor antagonists were used in 87% of patients, beta blockers

in 75%, aspirin in 88%, and diuretics in 60%. In addition, 45% of patients received reperfusion therapy or revascularization (Pitt et al. 2003b). This pattern of treatment is broadly in line with that recommended in treatment guidelines for post-MI patients and patients with heart failure (see Current therapy options section), and indicates that the survival benefit conferred by adding eplerenone represents a therapeutic gain over the survival benefit that can be achieved with current treatment. The dose of eplerenone chosen, 25 mg/day for 4 weeks then titrated up to a maximum of 50 mg/day, was lower than that required for significant hemodynamic and/or diuretic effects (Pitt et al. 2001), and suggests that the survival benefit was due to direct effects of aldosterone blockade rather than to effects on blood volume or pressure (see Disease overview section).

A further analysis showed that the survival benefit of eplerenone was apparent at 30 days after randomization (Pitt et al. in press).

Combined cardiovascular hospitalization/mortality

EPHESUS provided clear evidence that addition of eplerenone to standard therapy also reduced the combined risk of death or hospitalization from cardiovascular causes (Table 5), which was the other of the two primary endpoints in the study.

Combined all-cause hospitalization/mortality

Eplerenone significantly reduced the risk of hospitalization or death from any cause, compared with standard treatment alone (Table 6). This was a secondary endpoint in the EPHESUS trial.

Cardiovascular mortality

EPHESUS showed that eplerenone reduced the risk of death from cardiovascular causes by 17% compared with standard therapy alone (Table 6). Eplerenone also significantly reduced the risk of sudden cardiac death. There was no statistically significant reduction in the risk of death from acute MI, heart failure, stroke, or other cardiovascular causes with eplerenone (Table 6).

Table 6 | Effects of eplerenone on combined all-cause mortality/hospitalization and cardiovascular mortality (adapted from Pitt et al. 2003b; level 2 evidence)

		Outcome				
All-cause mortality/hospitalization ^a	Cardiovascular mortality due to:					
	Any cause	Sudden cardiac death	AMI	Heart failure	Stroke	Other
Lower with eplerenone ($P=0.02$) Relative risk 0.92 (95% CI 0.86, 0.98)	Lower with eplerenone ($P=0.005$) Relative risk 0.83 (95% CI 0.72, 0.94)	Lower with eplerenone ($P=0.03$) Relative risk 0.79 (95% CI 0.64, 0.97)	NSD	NSD	NSD	NSD

Patients were randomized to receive standard therapy plus either placebo (n=3313) or eplerenone (25 mg/day for 4 weeks, then titrating up to a target dose of 50 mg/day, n=3319) in a double-blind trial, with a mean of 16 months of follow-up. Standard therapy included ACE inhibitors or angiotensin II receptor antagonists (87%), diuretics (60%), aspirin (88%), beta blockers (75%), and coronary reperfusion therapy (45%).

^aHospitalization was defined as a nonfatal event causing or prolonging hospitalization.

AMI, acute myocardial infarction; CI, confidence interval; NSD, not statistically significantly different.

Table 7 | Effects of eplerenone on all-cause and cardiovascular hospitalization (adapted from Pitt et al. 2003b; level 2 evidence)

Outcome					
All-cause hospitalization ^a	Hospitalization due to:				
	Any cardiovascular cause	AMI	Heart failure	Stroke	Ventricular arrhythmia
NSD	NSD	NSD	Lower with eplerenone ($P=0.03$) Relative risk 0.85 (95% CI 0.74, 0.99)	NSD	NSD

Patients were randomized to receive standard therapy plus either placebo (n=3313) or eplerenone (25 mg/day for 4 weeks, then titrating up to a target dose of 50 mg/day, n=3319) in a double-blind trial, with a mean of 16 months of follow-up. Standard therapy included ACE inhibitors or angiotensin II receptor antagonists (87%), diuretics (60%), aspirin (88%), beta blockers (75%), and coronary reperfusion therapy (45%).

^aHospitalization was defined as a nonfatal event causing or prolonging hospitalization.

AMI, acute myocardial infarction; CI, confidence interval; NSD, not statistically significantly different.

All-cause hospitalization

Addition of eplerenone did not reduce the risk of all-cause hospitalization, compared with standard treatment alone (Table 7). When the number of episodes of all-cause hospitalization was assessed (rather than the number of patients hospitalized), there was also no statistically significant difference between the treatment groups ($P=0.12$) (Pitt et al. 2003b).

Cardiovascular hospitalization

Eplerenone reduced the risk of hospitalization for heart failure, compared with standard therapy alone, but showed no statistically significant difference for the risk of hospitalization for acute MI, stroke, ventricular arrhythmia, or any cardiovascular cause (Table 7). When the data were analyzed in terms of number of episodes of hospitalization a similar pattern was seen, except that the difference in the number of episodes of hospitalization for any cardiovascular event also reached statistical significance ($P=0.03$) (Pitt et al. 2003b).

Tolerability

There was no statistically significant difference between the EPHEBUS treatment groups in the percentage of patients with adverse events, and the number who discontinued due to adverse events was also similar (Table 8). Eplerenone was also no more likely than placebo to be associated with hormonal adverse effects such as gynecomastia and impotence in men or breast pain in women (Table 8). This contrasts with the result for spironolactone in RALES, where 10% of men reported gynecomastia or breast pain (Pitt et al. 1999).

Hyperkalemia

Clear evidence from the main analysis of EPHEBUS and a *post-hoc* analysis showed that eplerenone was associated with a significantly higher incidence of hyperkalemia (defined as serum potassium >5.5 mmol/L) and serious hyperkalemia (defined as serum potassium ≥ 6 mmol/L) (Table 9). More patients in the eplerenone group had to be hospitalized for treatment of hyperkalemia, compared with the group receiving standard

therapy alone (Table 9). However, only one death in the placebo group and none in the eplerenone group was attributed to hyperkalemia. The *post-hoc* analysis of EPHEBUS investigated "worst-case assumptions" in which any sudden deaths or deaths of unknown cause were included in the analysis of deaths possibly linked to hyperkalemia, and found that eplerenone was still associated with significantly lower mortality than standard therapy alone (Table 9). These data suggest that eplerenone-induced hyperkalemia was nonfatal and that the survival benefit with eplerenone outweighed any risk due to hyperkalemia, at least under the conditions of a clinical trial.

Length of stay

A retrospective analysis examined the length of hospital stay in EPHEBUS patients who were hospitalized for heart failure (n=828) (Gheorghide et al. 2004b). The mean length of stay per hospitalization episode was significantly shorter in eplerenone-treated patients than in patients receiving standard treatment alone (9.2 days compared with 10.8 days, $P=0.012$). The total number of days hospitalized for heart failure was also significantly lower in the eplerenone group than the standard treatment alone group (13.3 days compared with 16.9 days, $P=0.0009$) (Gheorghide et al. 2004b).

Osteopontin

A group of 476 patients in EPHEBUS were randomized to a substudy investigating the prognostic value of various laboratory parameters at baseline (Ketelslegers et al. 2004a). This study found that patients who died during the study had significantly ($P<0.05$) higher baseline levels of aldosterone, cortisol, renin, vasopressin, natriuretic peptides, interleukin-6, osteopontin, C-reactive protein, and type I collagen, compared with patients who survived (Ketelslegers et al. 2004a). A further analysis examined the effect of eplerenone on serum osteopontin (a cytokine associated with inflammation) in 193 patients receiving standard therapy alone and 195 patients receiving eplerenone (Ketelslegers et al. 2004b). At baseline, there was no significant difference between the groups in serum osteopontin. However, after 9 months the mean osteopontin level in the eplerenone group was

Table 8 | Tolerability of eplerenone (adapted from Pitt et al. 2003b; level 2 evidence)

Outcome				
Discontinuations due to AEs (number of patients)	Any AE	Gynecomastia in men	Impotence in men	Breast pain in women
Placebo 149	Placebo 79.5%	Placebo 0.6%	Placebo 0.9%	Placebo 0.3%
Eplerenone 147 ^a	Eplerenone 78.9%	Eplerenone 0.5%	Eplerenone 0.9%	Eplerenone 0.1%
	NSD	NSD	NSD	NSD

Patients were randomized to receive standard therapy plus either placebo (n=3313) or eplerenone (25 mg/day for 4 weeks, then titrating up to a target dose of 50 mg/day, n=3319) in a double-blind trial, with a mean of 16 months of follow-up. Standard therapy could include ACE inhibitors or angiotensin II receptor antagonists (87%), diuretics (60%), aspirin (88%), beta blockers (75%), and coronary reperfusion therapy (45%).

^aNo between-group comparison reported.

AE, adverse event; NSD, not statistically significantly different.

significantly lower than that in the placebo group (376.2 ng/mL compared with 423.9 ng/mL, $P<0.01$) (Ketelslegers et al. 2004b). However, the clinical significance of this finding is unclear.

Health status and health-related quality of life

Utility assesses the relative value of the patient's health state on a scale where 0=dead and 1=perfect health. Negative utility scores are possible, as some health states may be considered worse than death. Utility scores were obtained from a subgroup of 1123 patients from English-speaking countries at 12 months into the EPHEUS trial, using the EuroQoL(EQ)-5D instrument (Weintraub et al. 2005). The mean utility score was slightly higher in the eplerenone group than in the group receiving standard therapy alone at 12 months (0.802 compared with 0.779), but the difference was not statistically significant (Weintraub et al. 2005).

Other measures of health status, functional impairment and health-related quality of life were included in the design of EPHEUS (Spertus et al. 2002). Results have been published showing that the overall score at 4 weeks on the Kansas City Cardiomyopathy Questionnaire, a disease-specific health status measure, correlated significantly ($P<0.001$) with 1-year cardiovascular mortality or hospitalization in a cohort of 1516 patients from the study (Soto et al. 2004). However, no results have yet been published comparing health status in eplerenone-treated patients with that in patients receiving standard therapy only.

Economic evidence

EPHEUS included an economic analysis, and this provided good evidence that addition of eplerenone to standard treatment was both more effective and more costly than standard treatment alone. Data on healthcare resource use (hospitalization, outpatient procedures, and drugs) were collected prospectively during the trial, and combined with unit costs for the USA (Weintraub et al. 2005) or The Netherlands (Zhang & Weintraub 2004) to estimate total direct healthcare costs during the trial period. The US analysis has been fully published (Weintraub et al. 2005), while the analysis using Dutch costs has been published only in abstract form (Zhang & Weintraub 2004).

For the US analysis, an investigator who was blind to treatment group assigned all hospitalizations to a Medicare Diagnosis-Related Group (DRG) and coded outpatient procedures according to the current Medicare fee schedule. Costs for these items were estimated based on 2001 Medicare fees and reimbursement rates. All medications were costed using the US average wholesale price for 2001, except eplerenone which was assigned its average wholesale price for 2004, and all medications were assumed to continue for the duration of follow-up for each patient. The eplerenone cost was \$US3.60 per patient per day. Costs were calculated for the average duration of follow-up (16 months). Life-years lost for those patients who died during the trial period were estimated using survival data from three different epidemiologic studies: the Framingham Heart Study, Saskatchewan Health database, and the Worcester Heart Attack Registry. Patients who survived during the trial period were considered to have 0 life-years lost. The difference between life-years lost in the eplerenone and placebo groups gave the number of life-years gained with eplerenone. Lifetime cost-effectiveness ratios (\$US per life-year gained) were estimated from the number of life-years gained and the projected lifetime costs. Costs beyond the EPHEUS trial period were estimated by projecting forward the costs in years 2 and 3 of the trial. All costs and life-years were discounted by 3% per year.

As discussed earlier, utility scores were obtained from a subgroup of 1123 patients from English-speaking countries at 12 months into the trial, using the EQ-5D questionnaire. The number of life-years lost was multiplied by the mean utility score in each treatment group to estimate the number of quality-adjusted life-years (QALYs) lost. As the utility scores were derived only from a subgroup of patients this was considered to be a sensitivity analysis, with the estimate of cost per life-year gained being the main analysis (Weintraub et al. 2005).

The Dutch analysis appeared to use similar methods, except that the discount rate was 4% per year, costs for eplerenone were not presented, and only the Framingham Heart Study and Saskatchewan Health database were used to estimate life-years gained (Zhang & Weintraub 2004). However, the information available in the abstract is limited.

Table 9 | Effects of eplerenone on serum potassium [level 2 evidence, main analysis of the EPHEsus study (Pitt et al. 2003b) and a *post-hoc* analysis (Pitt et al. 2004)]

Outcome						Reference
Serum potassium >5.5 mmol/L	Serum potassium ≥6 mmol/L	Hospitalization for hyperkalemia	Death due to hyperkalemia	Death due to hyperkalemia or any sudden death	Death due to hyperkalemia or any sudden death or any unknown cause	
NR	Placebo 3.9% Eplerenone 5.5% <i>P</i> =0.002	Placebo 3 patients Eplerenone 12 patients ^a	Placebo 1 patient Eplerenone 0 patients ^a	NR	NR	Pitt et al. 2003b
Placebo 11.2% Eplerenone 15.6% <i>P</i> <0.001	NR	NR	Placebo 0.3% Eplerenone 0% ^a	Placebo 6.1% Eplerenone 4.9% <i>P</i> =0.022	Placebo 6.6% Eplerenone 5.3% <i>P</i> =0.016	Pitt et al. 2004
<p>Patients were randomized to receive standard therapy plus either placebo (n=3313) or eplerenone (25 mg/day for 4 weeks, then titrating up to a target dose of 50 mg/day, n=3319) in a double-blind trial, with a mean of 16 months of follow-up. Standard therapy included ACE inhibitors or angiotensin II receptor antagonists (87%), diuretics (60%), aspirin (88%), beta blockers (75%), and coronary reperfusion therapy (45%).</p> <p>^aNo between-group comparison reported.</p> <p>NR, not reported.</p>						

In the analysis with US unit costs, the mean additional cost of eplerenone was \$US1513 per patient over the trial period. This was the only component of cost that was statistically significantly different between the eplerenone group and the group receiving standard treatment only, although there were numerical differences in hospital costs that partly offset the additional costs of eplerenone (Table 10). Fewer life-years were lost in the eplerenone group, as expected from the survival benefit demonstrated in the clinical study analysis (see Clinical evidence section). The mean number of life-years gained by addition of eplerenone was 0.1 (Framingham), 0.06 (Saskatchewan), and 0.13 (Worcester) (Weintraub et al. 2005). Thus, addition of eplerenone to standard therapy was both more effective and more costly than standard therapy alone. The cost-effectiveness ratio was \$US13 718 per life-year gained (Framingham estimate), \$US21 876 (Saskatchewan estimate), or \$US10 402 (Worcester estimate) (Weintraub et al. 2005). There was no significant difference between the treatment groups in utility scores, and the cost per QALY gained was \$US20 579 (Framingham estimate), \$US32 405 (Saskatchewan estimate), or \$US15 330 (Worcester estimate) (Weintraub et al. 2005). Whether these cost-effectiveness ratios represent acceptable use of resources depends on circumstances and policies in different healthcare systems and/or institutions and is a matter for the judgment of individual decision makers. The authors of the US economic analysis (Weintraub et al. 2005) argue that these cost-effectiveness ratios for eplerenone compare favorably with those for other interventions and with a “threshold” of \$US50 000 per life-year gained (see Resource utilization section).

The analysis with Dutch costs (Zhang & Weintraub 2004) produced a similar pattern, with numerically smaller hospital costs in the eplerenone group but no statistically significant difference (Table 10). However, this abstract did not present estimates of the cost of eplerenone, overall costs, or cost-effectiveness ratios.

No data that would allow an estimate of indirect costs were collected during EPHEsus (Weintraub et al. 2005). However, as the mean age of the EPHEsus patients was 64 years, it is likely that some would have already retired from employment and thus indirect costs may be quite small. Direct evidence is needed to assess this possibility.

Resource utilization

The evidence base for eplerenone (the EPHEsus study) relates to the use of eplerenone as an additional treatment on top of existing management strategies for post-MI heart failure. There is no evidence indicating that eplerenone could replace any of the other therapies. Thus, the acquisition cost of eplerenone would be a net addition to the drug budget for the duration of therapy. In the USA, the average wholesale price of eplerenone is \$US112.50 per patient per month (Barnes & Howard 2005), which equates to approximately \$US1350 per patient per year. The optimal duration of therapy with eplerenone is uncertain, but a period of 1–2 years has been suggested (Pitt 2003).

Hospitalization is the main component of cost in the management of heart failure (see Disease overview section). As the addition of eplerenone to standard therapy reduces the risk of cardiovascular hospitalization compared with standard therapy alone, it might be expected that the reduction in hospitalization costs could offset part or all of the additional costs of eplerenone. However, economic analyses of EPHEsus have found that the reduction in hospitalization costs in the eplerenone group was not statistically significant, and was not sufficient to offset the additional cost of the drug (see Economic evidence section). On the current evidence base, it thus seems likely that addition of eplerenone to standard therapy would result in a net increase in healthcare costs. However, the main economic analysis was conducted using US Medicare costs, and the authors suggest that as

Table 10 | Estimated costs with eplerenone (level 2 evidence, economic analyses of the EPHEMUS study with unit costs for two countries)

Country	Outcome						Reference
	Difference in mean costs per patient over 16-month mean follow-up, eplerenone minus placebo						
	Rehospitalization	Eplerenone	Other medication	Outpatient procedures	ER visits	Total	
USA	-\$US207 (95% CI -887, 504)	\$US1513	\$US55 (95% CI -67, 173)	\$US34 (95% CI -34, 105)	-\$US4 (95% CI -10, 1)	\$US1391 (95% CI 656, 2165)	Weintraub et al. 2005
The Netherlands	-€162 (95% CI -472, 136)	NR	€3.5 (95% CI -35, 42)	€44 (95% CI -63, 154)	-€3.9 (95% CI -8.8, 1.8)	NR	Zhang & Weintraub 2004

Patients were randomized to receive standard therapy plus either placebo (n=3313) or eplerenone (25 mg/day for 4 weeks, then titrating up to a target dose of 50 mg/day, n=3319) in a double-blind trial, with a mean of 16 months of follow-up. Standard therapy could include ACE inhibitors or angiotensin II receptor antagonists (87%), diuretics (60%), aspirin (88%), beta blockers (75%), and coronary reperfusion therapy (45%).
CI, confidence interval; ER, emergency room; NR, not reported.

Medicare costs tend to be lower than US managed care costs their analysis may have underestimated the potential savings in hospital costs with eplerenone (Weintraub et al. 2005). Further economic analyses using other unit costs and in other countries are required to assess this possibility.

Eplerenone has shown clear evidence of a survival benefit, and it is possible that this could translate into a reduced loss of working days and thus a reduction in indirect cost. Such a reduction in indirect cost might offset more of the eplerenone cost, although there is as yet no evidence that this is the case. The net gain in life-years with eplerenone was quite small, averaging about 0.1 life-years gained per patient (see Economic evidence section above), which may suggest that any corresponding gain in indirect costs might also be small. As heart failure is primarily a disease of elderly people, a substantial proportion of patients may no longer be economically active, and this would also tend to suggest that any gain in indirect costs may be modest.

The evidence base at present shows quite clearly that the addition of eplerenone to standard therapy is both more effective and more costly than standard therapy alone. Cost effectiveness for the addition of eplerenone in the US was estimated at \$US10 402–21 876 per life-year gained or \$US15 330–32 405 per QALY (Weintraub et al. 2005). The authors of this US economic analysis argued that the cost-effectiveness ratios for eplerenone compared favorably with those for other interventions in cardiology (Weintraub et al. 2005). For example, they cited previous cost-effectiveness estimates for captopril therapy versus no captopril in post-MI patients (\$US3700–10 400 per QALY, Tsevat et al. 1995), and implantable cardiac defibrillators versus amiodarone in survivors of cardiac arrest (\$US37 300 per QALY, Owens et al. 1997). The authors also considered that the cost effectiveness of eplerenone was below a “threshold” for acceptable cost effectiveness of \$US50 000 per life-year gained (Weintraub et al. 2005). Whether the additional benefits of eplerenone justify the additional costs is a matter for decision makers in individual healthcare systems.

Patient group/population

The EPHEMUS patient population consisted of men and women with heart failure and left ventricular systolic dysfunction 3–14 days following an acute MI (Pitt et al. 2003b). Inclusion and exclusion criteria are summarized in Table 11. The mean age was 64 years and 90% of patients were white. The mean left ventricular ejection fraction was 33% (Pitt et al. 2003b). As the EPHEMUS study provides the entire current evidence base for eplerenone in post-MI heart failure, this is the only population to which the results can be confidently applied. However, it is likely that a very high percentage of patients with post-MI heart failure would meet the selection criteria used in EPHEMUS (B. Pitt, personal communication). A substudy of 134 eplerenone-treated patients in EPHEMUS found that the pharmacokinetic behavior of eplerenone in this population was similar to that in healthy volunteers of similar age (Reid et al. 2003).

EPHEMUS included several subgroup analyses (Table 11). In general, the beneficial effects of eplerenone on both primary endpoints (all-cause mortality and combined cardiovascular hospitalization/mortality) were similar in the subgroups and in the main analysis (Pitt et al. 2003b). However, it should be noted that EPHEMUS was not powered to detect differences among subgroups.

A retrospective analysis of the 4007 EPHEMUS patients with hypertension found that addition of eplerenone reduced all-cause mortality ($P=0.001$) and combined cardiovascular mortality/hospitalization ($P=0.002$) compared with standard therapy alone (Pitt et al. 2003a).

A further retrospective analysis studied the 1483 patients with diabetes and signs of heart failure in EPHEMUS. In this subgroup, the eplerenone-treated patients had lower all-cause mortality, combined cardiovascular mortality/hospitalization, and cardiovascular mortality compared with the patients receiving standard therapy alone. However, the 95% confidence intervals

Table 11 | Patient population in the EPHEBUS study (adapted from Pitt et al. 2003b)

Inclusion criteria	<p>Acute myocardial infarction as documented by standard criteria</p> <p>Left ventricular dysfunction as documented by a left ventricular ejection fraction of $\leq 40\%$ on echocardiography, radionuclide angiography, or angiography of the left ventricle after the index acute myocardial infarction but before randomization</p> <p>Heart failure as documented by the presence of pulmonary rales, pulmonary venous congestion shown on chest radiography, or presence of a third heart sound</p> <p>In patients with diabetes, the third criterion (symptoms of heart failure) was not necessary as patients with diabetes are considered to have a risk of cardiovascular events similar to that of patients without diabetes but with symptoms of heart failure</p>
Exclusion criteria	<p>Taking potassium-sparing diuretics</p> <p>Serum creatinine concentration > 2.5 mg/dL (220 μmol/L)</p> <p>Serum potassium > 5 mmol/L</p>
Subgroups analyzed	<p>Sex</p> <p>Age (dichotomized at < 65 years)</p> <p>Pulse pressure</p> <p>Serum potassium concentration < 4 mmol/L</p> <p>Serum creatinine concentration < 1.1 mg/L</p> <p>Ejection fraction $< 35\%$</p> <p>Use of percutaneous transluminal coronary revascularization and cardiovascular medication (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, beta blockers, aspirin, diuretics, lipid-lowering agents)</p> <p>Diabetes</p> <p>Hypertension</p>

for the risk ratio included 1 for all-cause and cardiovascular mortality, indicating that statistical significance was not achieved for these endpoints (O'Keefe et al. 2004).

Patients with low baseline creatinine clearance (< 50 mL/min) were at elevated risk for eplerenone-associated hyperkalemia in EPHEBUS. In this subgroup, the incidence of serious hyperkalemia (serum potassium ≥ 6 mmol/L) was 10.1% in eplerenone-treated patients compared with 5.9% in the patients receiving standard therapy alone ($P=0.006$) (Pitt et al. 2003b). This suggests that serum potassium needs to be monitored with special care in patients with low creatinine clearance.

A separate open-label study in 32 patients with varying degrees of renal impairment and 32 matched healthy controls found that the pharmacokinetics of eplerenone (area under the curve, total clearance, and maximum plasma concentration) following single (100 mg) or multiple dosing (100 mg/day for 5 days) were not significantly affected by renal impairment (Ravis et al. 2005). This study concluded that no adjustment of the eplerenone dose is necessary in patients with renal impairment, although dose adjustment may be required depending on the potential for clinically relevant hyperkalemia (Ravis et al. 2005).

Dosage, administration, and formulations

Eplerenone (Inspra[®]) is indicated to improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction $\leq 40\%$) and clinical evidence of congestive heart failure after an

acute MI (Anon. 2005). Inspra[®] is supplied as film-coated tablets containing 25 or 50 mg eplerenone.

Eplerenone is contraindicated in patients with serum potassium higher than 5.5 mmol/L at the beginning of treatment, and in patients with creatinine clearance ≤ 30 mL/min. Eplerenone is also contraindicated for concomitant use with potent inhibitors of cytochrome P450 3A4, including ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir (Anon. 2005).

The recommended eplerenone dosage in post-MI heart failure is 50 mg once daily. The starting dose should be 25 mg once daily, titrated to the target dose of 50 mg once daily as tolerated by the patient and preferably within 4 weeks (Anon. 2005).

Serum potassium should be measured before beginning eplerenone treatment, within the first week and at 1 month after beginning treatment or after each dose adjustment, and periodically thereafter. The eplerenone dose should be adjusted according to the serum potassium level as follows:

- serum potassium level < 5 mmol/L: increase eplerenone dose from 25 mg every other day to 25 mg once daily, or from 25 mg once daily to 50 mg once daily
- serum potassium level 5–5.4 mmol/L: no eplerenone dose adjustment

- serum potassium level 5.5–5.9 mmol/L: decrease eplerenone dose from 50 mg once daily to 25 mg once daily, or from 25 mg once daily to 25 mg every other day; if the dose is already down to 25 mg every other day, eplerenone should be withheld
- serum potassium level ≥ 6 mmol/L: withhold eplerenone.

Eplerenone may be restarted at a dose of 25 mg every other day when serum potassium levels have fallen to below 5.5 mmol/L (Anon. 2005).

No adjustment of the starting dose is recommended for elderly patients or patients with mild-to-moderate hepatic impairment.

Place in therapy

The evidence summary table at the beginning of this article summarizes the available clinical and economic evidence on eplerenone in patients with post-MI heart failure. Almost all the evidence (except for one small pharmacokinetic study) is derived from EPHESUS, a large double-blind multicenter RCT conducted in over 6000 patients. The main efficacy outcomes in EPHESUS were patient-oriented, measuring mortality and/or hospitalization. The study also collected data on other patient-oriented outcomes such as health status and functional capacity, but as yet this information does not appear to have been published. The main disease-oriented evidence related to the incidence of hyperkalemia, a well-known and potentially serious side effect of drugs that suppress the renin-angiotensin-aldosterone system.

As EPHESUS compared eplerenone plus standard therapy with standard therapy alone, the results are of clear relevance to current practice. Patients were treated with ACE inhibitors or angiotensin II receptor antagonists (87% of patients), beta blockers (75%), aspirin (88%), and diuretics (60%). In addition, 45% of patients received reperfusion therapy or revascularization (Pitt et al. 2003b). This suggests that the survival benefit produced by addition of eplerenone to standard therapy was a genuine improvement over what can be achieved by current best practice, and cannot be attributed to undertreatment in the control group. However, clinical trials are likely to have a higher degree of patient monitoring than is possible in routine practice, and are conducted in defined and selected patient populations. Whether the results can be generalized to populations of heart failure patients other than the population selected for EPHESUS requires further evidence. However, as the EPHESUS population is considered likely to represent a high proportion of patients with post-MI heart failure (B. Pitt, personal communication), the results are likely to be applicable to many, perhaps most, patients in clinical practice.

Clear evidence shows that addition of eplerenone to standard therapy improves all-cause mortality and combined cardiovascular mortality/hospitalization compared with standard therapy alone. There is also evidence of benefit on secondary endpoints including cardiovascular mortality, risk of sudden cardiac death, and combined all-cause mortality/hospitalization. There was no significant improvement on the risk of

cardiovascular hospitalization, though EPHESUS was not powered on this endpoint. The trial also provided evidence that eplerenone had an incidence of hormonal side effects that was no greater than placebo. This contrasts with the 10% incidence of hormonal side effects observed with spironolactone in the RALES study (Pitt et al. 1999), indicating that eplerenone may be better tolerated in this regard than spironolactone.

Limited evidence from a *post-hoc* analysis indicated that eplerenone treatment could be associated with a shorter length of stay in patients hospitalized for heart failure. Similarly, limited evidence from a substudy found that although eplerenone was associated with higher mean utility score (indicating better health-related quality of life) than standard therapy alone at 12 months, the difference did not reach statistical significance.

There is evidence that eplerenone treatment is associated with a higher risk of hyperkalemia than standard therapy alone, especially in patients with low creatinine clearance. In the EPHESUS study, where patients with high serum creatinine and/or potassium at baseline were excluded and where serum potassium was regularly monitored throughout treatment, evidence from a *post-hoc* analysis indicated that the hyperkalemia was nonfatal and manageable. However, this emphasizes the need for monitoring of serum potassium and dose adjustment as necessary during use of eplerenone in routine practice.

Economic analyses showed that the addition of eplerenone was more costly than standard treatment alone, as well as more effective. Although small and nonsignificant reductions in hospital costs were observed, they were not sufficient to offset the additional cost of eplerenone. The cost-effectiveness ratio in the EPHESUS population was estimated at \$US10 402–\$US21 876 per life-year gained (depending on the method used to estimate life-years). The study authors considered that this compares favorably with other cardiology interventions such as ACE inhibitor use after MI. It will be for individual decision makers to assess whether this represents acceptable value in their particular healthcare systems and institutions.

EPHESUS demonstrated clinical benefit with eplerenone in a large population (over 6000) of patients with post-MI heart failure. The population enrolled in EPHESUS is considered likely to represent a high proportion of patients with post-MI heart failure. It may be that eplerenone could also be beneficial in other populations, such as the patients with severe heart failure who benefited from spironolactone treatment in the RALES study, but there is as yet no evidence on this issue. It has been recommended that formularies should include both drugs, with eplerenone used in patients who resemble the EPHESUS population and spironolactone used in patients who resemble the RALES population (Pitt 2003; Barnes & Howard 2005). Patients receiving spironolactone who develop intolerable hormonal side effects could reasonably be given a trial of eplerenone, in the light of its low incidence of such side effects (Pitt 2003; Barnes & Howard 2005). However, at US average wholesale prices generic spironolactone is considerably cheaper

than eplerenone (\$US14–25 compared with \$US112.50 per month) (Barnes & Howard 2005). Other authorities have suggested that spironolactone could be tried first (Jessup 2003). Evidence from trials directly comparing eplerenone and spironolactone is needed to fully assess the optimum place in therapy for the two drugs, but at present no comparative data are available.

In summary, the current evidence base indicates that eplerenone improves survival and reduces cardiovascular hospitalization/mortality, compared with standard treatment alone, in patients with heart failure as a complication after acute MI. The incidence of hormonal side effects is no greater than with placebo. Eplerenone is associated with an elevated risk of hyperkalemia that necessitates regular monitoring of serum potassium and dose adjustment as required. Eplerenone is both more effective and more costly than standard treatment alone, and decision makers will need to assess whether this represents added therapeutic value in their own situations.

References

- AHA (American Heart Association). *Heart Disease and Stroke Statistics — 2005 Update*. Dallas, Texas. American Heart Association; 2004. Available at: www.americanheart.org (accessed March 30, 2005).
- Anon. Inspra® US Prescribing Information. Available at: www.inspra.com (accessed April 20, 2005).
- Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee to revise the 1999 guidelines on the management of patients with acute myocardial infarction). *Circulation*. 2004;110:588–636.
- Barnes BJ, Howard PA. Eplerenone: a selective aldosterone receptor antagonist for patients with heart failure. *Ann Pharmacother*. 2005;39:68–76.
- BHF (British Heart Foundation) Statistics website, <http://www.heartstats.org/topic.asp?id=18> (accessed April 26, 2005).
- Cleland JG. Health economic consequences of the pharmacological treatment of heart failure. *Eur Heart J*. 1998;19(Suppl. P):P32–P39.
- Cleland JG, Torabi A, Khan NK. Epidemiology and management of heart failure and left ventricular systolic dysfunction in the aftermath of a myocardial infarction. *Heart*. 2005;91(Suppl. 2):ii7–ii13.
- Cline CM, Willenheimer RB, Erhardt LR, Wiklund I, Israelsson BY. Health-related quality of life in elderly patients with heart failure. *Scand Cardiovasc J*. 1999;33:278–285.
- Eisenstein EL, Shaw LK, Anstrom KJ, et al. Assessing the clinical and economic burden of coronary artery disease: 1986–1998. *Med Care*. 2001;39:824–835.
- Gheorghide M, Pitt B, Chu TC, Patni R. *Length of stay for heart failure hospitalization in the eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS)*. European Society of Cardiology Heart Failure Update, Wroclaw, Poland, 12–15 June 2004a, available at: <http://cic.escardio.org/AbstractDetails.aspx?id=9868> (accessed March 3, 2005).
- Gheorghide M, Krum H, Chu TC, Patni R, Pitt B. *Concurrent treatment with eplerenone and standard HF therapy reduces the duration of heart failure hospitalization in patients with post AMI heart failure*. Presented: American Heart Association, November 6–10, 2004b, New Orleans, Louisiana.
- Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. *Am Heart J*. 1999;137:352–360.
- Hasdai D, Topol EJ, Kilaru R, et al. Frequency, patient characteristics, and outcomes of mild-to-moderate heart failure complicating ST-segment elevation acute myocardial infarction: lessons from 4 international fibrinolytic therapy trials. *Am Heart J*. 2003;145:73–79.
- Hellermann JP, Jacobsen SJ, Redfield MM, Reeder GS, Weston SA, Roger VL. Heart failure after myocardial infarction: clinical presentation and survival. *Eur J Heart Failure*. 2005;7:119–125.
- Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. *J Am Coll Cardiol*. 2001;38:2101–2113.
- ICSI (Institute for Clinical Systems Improvement). *Heart failure in adults*. Bloomington, Maryland, USA, February 2004, available at: http://www.guideline.gov/summary/summary.aspx?doc_id=4927&nbr=3514&string=eplerenone.
- Jessup M. Aldosterone blockade and heart failure. *N Engl J Med*. 2003;348:1380–1382.
- Ketelslegers J, Schiffrin E, Williams G, et al. *Biomarkers of prognosis in patients with post-acute-myocardial-infarction heart failure: results of an EPHESUS sub-study*. European Society of Cardiology Congress, Munich, Germany, August 28–September 1, 2004a, available at: <http://cic.escardio.org/AbstractDetails.aspx?id=14961> (accessed March 3, 2005).
- Ketelslegers J, Zannad F, Schiffrin E, et al. *The effect of eplerenone on the cytokine osteopontin in post-MI heart failure: an EPHESUS sub-study*. European Society of Cardiology Congress, Munich, Germany, August 28–September 1, 2004b, available at: <http://cic.escardio.org/AbstractDetails.aspx?id=14571> (accessed March 3, 2005).
- Levy E, Gabriel S, Dinet J. The comparative medical costs of atherothrombotic disease in European countries. *Pharmacoeconomics*. 2003;21:651–659.
- McBurney CR, Eagle KA, Kline-Rogers EM, Cooper JV, Smith DE, Erickson SR. Work-related outcomes after a myocardial infarction. *Pharmacotherapy*. 2004;24:1515–1523.
- McLaughlin N, Gehr TWB, Sica DA. Aldosterone-receptor antagonism and end-stage renal disease. *Curr Hypertens Rep*. 2004;6:327–330.
- Møller JE, Brendorp B, Ottesen M, et al. Congestive heart failure with preserved left ventricular systolic function after acute myocardial infarction: clinical and prognostic implications. *Eur J Heart Failure*. 2003;5:811–819.
- O'Brien JA, Patrick AR, Caro J. Estimates of direct medical costs for microvascular and macrovascular complications resulting from type 2 diabetes mellitus in the United States in 2000. *Clin Ther*. 2003;25:1017–1038.
- O'Keefe J, Zarich S, Felicetta J, et al. Eplerenone is safe and effective in diabetic patients with post-acute myocardial infarction heart failure: results from EPHESUS. *Diabetes*. 2004;53(Suppl. 2):A116 (Abstract 491-P).
- Owens DK, Sanders GD, Harris RA, et al. Cost effectiveness of implantable cardioverter defibrillators relative to amiodarone for prevention of sudden cardiac death. *Ann Intern Med*. 1997;126:1–12.
- Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med*. 1999;341:709–717.
- Pitt B, Williams G, Remme W, et al. The EPHESUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. *Cardiovasc Drugs Ther*. 2001;15:79–87.
- Pitt B. Aldosterone blockade in patients with systolic left ventricular dysfunction. *Circulation*. 2003;108:1790–1794.
- Pitt B, Krum H, Nicolau JC, et al. The EPHESUS trial: effect of eplerenone in patients with a baseline history of hypertension. *Circulation*. 2003a;108(Suppl.):IV–599 (Abstract 2727).
- Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003b;348:1309–1321.
- Pitt B, Stier CT, Rajagopalan S. Mineralocorticoid receptor blockade: new insights into the mechanism of action in patients with cardiovascular disease. *J Renin Angiotensin Aldosterone Syst*. 2003c;4:164–168.
- Pitt B, Ruilope L, Bakris G, DiCarlo L, He W, Grossman E. *Risk/benefit analysis of hyperkalemia in the eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS)*. European Society of Cardiology Heart Failure Update, Wroclaw, Poland, June 12–15, 2004, available at: <http://cic.escardio.org/AbstractDetails.aspx?id=9871> (accessed March 3, 2005).

- Pitt B, White H, Nicolau J, et al. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *Am J Coll Cardiol*. in press.
- Ravis WR, Stokes TJ, Reid S, et al. Pharmacokinetics of eplerenone after single and multiple dosing in subjects with and without renal impairment. *Clin Pharmacol Ther*. 2004;75:P37 (Abstract PI-132).
- Ravis WR, Reid S, Sica DA, Tolbert DS. Pharmacokinetics of eplerenone after single and multiple dosing in subjects with and without renal impairment. *J Clin Pharmacol*. 2005;45:810–821.
- Reid SE, Hutmacher MM, Tolbert DS, Ferry J. The pharmacokinetics of eplerenone in patients with left ventricular dysfunction/heart failure. *Pharmacotherapy*. 2003;23:1332 (Abstract 27).
- Remme WJ. Modulation of the renin-angiotensin-aldosterone system — pivotal in heart failure treatment. *Z Kardiol*. 1999;88(Suppl. 3):12–17.
- Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J*. 2001;22:1527–1560.
- Rocha R, Funder JW. The pathophysiology of aldosterone in the cardiovascular system. *Ann NY Acad Sci*. 2002;970:89–100.
- Rogers WJ, Canto JG, Lambrew CT, et al. Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2 and 3. *J Am Coll Cardiol*. 2000;36:2056–2063.
- Rudolph AE, Rocha R, McMahon EG. Aldosterone target organ protection by eplerenone. *Mol Cell Endocrinol*. 2004;217:229–238.
- Shieh FK, Kotlyar E, Sam F. Aldosterone and cardiovascular remodeling: focus on myocardial failure. *J Renin Angiotensin Aldosterone Syst*. 2004;5:3–13.
- Sica DA, Gehr TWB, Yancy C. Hyperkalemia, congestive heart failure, and aldosterone receptor antagonism. *Congest Heart Failure*. 2003;9:224–229.
- Soto GE, Jones P, Weintraub WS, Krumholz HM, Spertus JA. Prognostic value of health status in patients with heart failure after acute myocardial infarction. *Circulation*. 2004;110:546–551.
- Spertus JA, Tooley J, Jones P, et al. Expanding the outcomes in clinical trials of heart failure: the quality of life and economic components of EPHEBUS (Eplerenone's neuroHormonal Efficacy and SURvival Study). *Am Heart J*. 2002;143:636–642.
- Steg PG, Dabbous OH, Feldman LJ, et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes. Observations from the Global Registry of Acute Coronary Events (GRACE). *Circulation*. 2004;109:494–499.
- Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. *Eur J Heart Failure*. 2002;4:361–371.
- Struthers AD. Aldosterone: cardiovascular assault. *Am Heart J*. 2002;144:S2–S7.
- Struthers AD. The clinical implications of aldosterone escape in congestive heart failure. *Eur J Heart Failure*. 2004;6:539–545.
- Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). *Eur Heart J*. 2005;26:1115–1140.
- Szucs TD. The growing healthcare burden of CHF. *J Renin Angiotensin Aldosterone Syst*. 2000;1(Suppl. 1):2–6.
- Tsevat J, Duke D, Goldman L, et al. Cost-effectiveness of captopril therapy after myocardial infarction. *J Am Coll Cardiol*. 1995;26:914–919.
- Velazquez EJ, Francis GS, Armstrong PW, et al. An international perspective on heart failure and left ventricular systolic dysfunction complicating myocardial infarction: the VALIANT registry. *Eur Heart J*. 2004;25:1911–1919.
- Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, Neil HAW. Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. *Heart*. 1998;80:40–44.
- Weintraub WS, Zhang Z, Mahoney EM, et al. Cost-effectiveness of eplerenone compared with placebo in patients with myocardial infarction complicated by left ventricular dysfunction and heart failure. *Circulation*. 2005;111:1106–1113.
- WHO (World Health Organization) Statistics, Mortality Database, available at: http://www3.who.int/whosis/mort/table1_process.cfm (accessed on March 29, 2005).
- Wu AH, Parsons L, Every NR, Bates ER. Hospital outcomes in patients presenting with congestive heart failure complicating acute myocardial infarction. A report from the second National Registry of Myocardial Infarction (NORMI-2). *J Am Coll Cardiol*. 2002;40:1389–1394.
- Zhang Z, Weintraub WS. *Reduced resource use associated with aldosterone blockade (Inspra) in patients with heart failure after acute myocardial infarction: results from EPHEBUS applied to the Netherlands*. European Society of Cardiology Congress, Munich, Germany, August 28–September 1, 2004, available at: <http://cic.escardio.org/AbstractDetails.aspx?id=14962> (accessed March 3, 2005).

Correspondence: Carole Nadin, Core Medical Publishing, Mere House, Brook Street, Knutsford, Cheshire WA16 8GP, UK or at editor@coreevidence.com