4 HEART FAILURE

Everyone with heart failure should be recognised and offered appropriate evidence based care.

NICE guidelines have recently been published on the management of **chronic heart failure in adults in primary and secondary care**[i]. The guidelines include over 90 recommendations with algorithms for diagnosis and for pharmacological treatment. The following recommendations were identified as priorities for implementation:

Diagnosis

- The basis for historical diagnoses of heart failure should be reviewed, and only patients whose diagnosis is confirmed should be managed in accordance with the guideline
- Doppler 2D echocardiograhic examination should be performed to exclude important valve disease, assess the systolic (and diastolic) function of the (left) ventricle and detect intracardiac shunts

Treatment

- All patients with heart failure due to left ventricular systolic dysfunction should be considered for treatment with an ACE inhibitor
- Beta blockers licensed for use in heart failure should be initiated in patients with heart failure due to left ventricular systolic dysfunction after diuretic and ACE inhibitor therapy (regardless of whether or not symptoms persist)

Monitoring

All patients with chronic heart failure require monitoring. This monitoring should include:

- a clinical assessment of functional capacity, fluid status, cardiac rhythm, and cognitive and nutritional status
- a review of medication, including need for changes and possible side effects
- serum urea, electrolytes and creatinine

Discharge

- Patients with heart failure should generally be discharged from hospital only when their clinical condition is stable and the management plan is optimised
- The primary care team, patient and carer must be aware of the management plan

Supporting patients and carers

- Management of heart failure should be seen as a shared responsibility between patient and healthcare professional

i. National Institute for Clinical Excellence. *Chronic Heart Failure: Management of Chronic Heart Failure in Adults in Primary and Secondary Care*. London: NICE, July 2003
http://www.nice.org.uk/pdf/Full_HF_Guideline.pdf [full guideline]
http://www.nice.org.uk/pdf/CG5NICEguideline.pdf [NICE guideline]
[accessed 22.12.03]
(Evidence based guideline – systematic literature search to 2002 for specific study types based on clinical questions set out by the technical team)

4 HEART FAILURE

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

A recent UK population based study using echocardiographic screening reported that CHF was present in approximately 3% of the population. Another recent study assessed all new incident cases of clinically diagnosed heart failure within the catchment population as 1.3 per 1000 population per year. This almost certainly considerably underestimates the true incidence because of the difficulty of diagnosing heart failure mainly because of the non-specific symptoms. [paragraph 7.3]

Despite a general reduction in CHD throughout the Western World, there has been a major increase in the number of hospital admissions with chronic heart failure… Heart failure is now the principal cause of acute hospital admission in the over 65s. The increase in prevalence is partly a result of the ageing population (a trend which will ensure that the increasing prevalence of heart failure will continue whatever measures we take), but age specific rates are also increasing. The reason(s) for this are not clear. [paragraph 7.4]

Chronic heart failure has major implications for survival. Overall, affected individuals have a mortality rate 3-4 times that of their peers, but in severe heart failure, the 1-year mortality exceeds 50% despite modern therapy. In this respect, it has prognostic implications worse than most cancers. It is also produces greater morbidity than most other chronic disorders. It is clear that chronic heart failure has major health economic consequences, likely to increase markedly over the next two decades at least. [paragraph 7.5]

What are the most recent data for Wales and the UK?

The *statements* | The *evidence*

4.1. Prevalence and Incidence of heart failure

4.1a. The crude **incidence** of heart failure in the general population world-wide (unadjusted for age) ranges from 1-5 cases per 1000 population per annum. The crude **prevalence** of heart failure ranges from 3-20 per 1000. Both incidence and prevalence rise sharply with age. The majority of new cases of heart failure arise in those aged over 70 years[i].

UK based prevalence studies of symptomatic heart failure using clinical criteria suggest prevalence rates for heart failure of 0.06% for those aged under 65 years[ii] and 2.8%[ii] or 0.8%[iii] for those aged 65 years and over. The overall prevalence in the general practice population was estimated as 0.39%[ii] and 0.15%[iii].

A UK prevalence study of left-ventricular systolic dysfunction in men and women aged 25-74 estimated by **echocardiography** suggested a prevalence of 2.9% overall with symptoms of heart failure in 1.5% of the population[iv].

i. Cowie MR. Annotated references in epidemiology. *European Journal of Heart Failure* 1999; 1: 101-107

(Type IV evidence – annotated summary of epidemiological studies based on a systematic review of the literature to July 1998. No details given of critical appraisal techniques)

ii. Parameshwar J, Shackell MM, Richardson A, Poole-Wilson PA, Sutton GC. Prevalence of heart failure in three general practices in North West London. *British Journal of General Practice* 1992; **42**: 287-289

(Type IV evidence – cross sectional practice record survey in 1988 of 30,204 patients served by three general practices in London. Heart failure was defined through diuretic drug prescription confirmed by chest radiograph in 87% and electrocardiogram in 89% of cases.)

iii. Mair FS, Crowley TS, Bundred PE. Prevalence, aetiology and management of heart failure in general practice. *British Journal of General Practice* 1996; **46**: 77-79

(Type IV evidence – cross sectional medical record review in 1994 of 17,400 patients from general practice in Liverpool. Heart failure was diagnosed by clinical criteria)

iv. McDonagh TA, Morrison CE, Lawrence A *et al*. Symptomatic and asymptomatic left-ventricular systolic dysfunction in an urban population. *Lancet* 1997; **350**: 829-833

(Type IV evidence – cross sectional survey in Glasgow during 1992. Left-ventricular systolic function was assessed by echocardiography in a random sample of 2,000 men and women aged 25-74. 83% of those invited took part (n=1,640). LV systolic dysfunction was defined as an LV ejection fraction of £ 30%)

The *statements*

The *evidence*

4.1b. Using a strict case-definition, during 1995/1996 in the UK, the **incidence** rate of **heart failure** increased from 0.02 per 1000 population per year in those aged 25-34 years to 11.6 in those aged 85 years and over. The incidence was higher in males than females (age adjusted incidence ratio, 1.75 (95% CI 1.34-2.29, p<0.0001)). The primary aetiologies were coronary heart disease (36%), unknown (34%), hypertension (14%), valve disease (7%), atrial fibrillation alone (5%) and other (5%)[i].

An updated study found an incidence rate of 1.2 per 1,000 population **aged 25 or over** per year. Coronary artery disease was the cause of 52% (95% CI, 43-61%) of incident heart failure in the general population under 75 years. Clinical assessment without angiography under-estimated the proportion of patients with coronary artery disease who may benefit from revascularisation[ii].

Another study found that the overall incidence rate for GP diagnosed heart failure in **40-84 year-olds** was 4.4 per 1000 person-years in men and 3.9 per 1,000 person years in women. The incidence increased sharply with age in both sexes. The relative risk of heart failure was 2.1 (95% CI, 1.7-2.6) among men compared with women less than 65 years old and 1.3 (95% CI, 1.2-1.4) above the age of 65. Smoking, hypertension, diabetes, obesity were independently associated with heart failure as well as history of distant dyspnoea[iii].

i. Cowie MR, Wood DA, Coats AJS *et al*. Incidence and aetiology of heart failure: a population-based study. *European Heart Journal* 1999; **20**: 421-428

(Type IV evidence – analysis of patients with heart failure presenting to 82 general practitioners in London between April 1995 and December 1996. On the basis of clinical assessment, electrocardiography, chest radiography and transthoracic echocardiography, a panel of three cardiologists decided that 220 patients met the case definition of new heart failure)

ii. Fox KF, Cowie MR, Wood DA *et al*. Coronary artery disease as the cause of incident heart failure in the population. *European Heart Journal* 2001; **22**: 228-236

(Type IV evidence – Analysis of all incident cases of heart failure in a population of 292,000 in South London by monitoring patients admitted to hospital and through a rapid access heart failure clinic; case ascertainment as in reference i. 332 incident cases were identified during a 15 month period. The presence and severity of coronary artery disease was identified by coronary angiography in patients under 75 years)

iii. Johansson S, Wallander M-A, Ruigómez A, Alberto L, Rodríguez G. Incidence of newly diagnosed heart failure in UK general practice. *European Journal of Heart Failure* 2001; **3**: 225-231

(Type IV evidence – retrospective cohort study. To estimate incidence rates, patients (aged 40-84 years) were identified from the UK General Practice Research Database, as newly diagnosed with heart failure by their GP in 1996 (n=3,123). A random sample of heart failure patients (n=1,200) were sent a questionnaire and a nested case-control study was performed to assess risk factors for heart failure)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence*. Cardiff: National Assembly for Wales, July 2001

Currently chronic heart failure is markedly under diagnosed in general practice. [paragraph 7.6]

The combination of clinical history, examination, plasma BNP and ECG and chest x-ray would enable general practitioners to identify those patients who have chronic heart failure… It has been considered by some that the optimal solution would be to provide rapid access heart failure clinics to which GPs can refer patients with suspected heart failure for full assessment (including echocardiography where appropriate)… Open access echocardiography clinics have been piloted in several countries and are popular with GPs. [paragraph 7.11]

What are the best screening/diagnosis/decisions aids for GPs?

Where/how indications for echocardiography?

The reading of the echocardiography varies with technician reporting being undertaken with a quality assurance in place in a few DGHs. [paragraph 7.12]

What are the best quality assurance methods for echocardiography?

It will be necessary to take into account the time-scale for reporting the pilot research study on the opportunity provided by Brain Natriuretic Peptide (BNP) screening, a blood test which is specific to heart failure. [paragraph 7.11]

What is the latest evidence for screening by BNP?

The *statements* | The *evidence*

4.2 Diagnosis/screening/decision aids for general practice

4.2a. In three general practice surveys in the UK only 34%, 34% and 29% respectively of patients with suspected heart failure were referred for **echocardiography**[i,ii,iii].

The main barrier to the use of echocardiograms in the diagnosis of heart failure in one study was **lack of open access**[i].

In another study, **echocardiography** was less likely to be performed in older patients (test for trend, p=0.04 in women and 0.02 in men)[ii].

continued

i. Hickling JA, Nazareth I, Rogers S. The barriers to effective management of heart failure in general practice. *British Journal of General Practice* 2001; **51**: 615-618

(Type IV evidence – retrospective case-note analysis and nominal group technique to elicit general practitioners' perceptions of the reasons for differences between observed and recommended practice. Data were collected from ten Medical Research Council General Practice Framework practices in the North Thames Region. The dates of the survey and practice meetings were not given)

ii. Hood S, Taylor S, Roeves A *et al*. Are there age and sex differences in the investigation and treatment of heart failure? A population-based study. *British Journal of General Practice* 2000; **50**: 559-563

(Type IV evidence – retrospective case-note review, during 1997/1998, of prevalent cases in 16 general practices in West London. Data were collected for nine practices. 583 patients (57% women) with a diagnosis of heart failure were reviewed. The mean age of patients was 78 years (SD 9.5))

iii. Johansson S, Wallander M-A, Ruigómez A, Alberto L, Rodríguez G. Incidence of newly diagnosed heart failure in UK general practice. *European Journal of Heart Failure* 2001; **3**: 225-231

(Type IV evidence – retrospective cohort study. To estimate incidence rates, patients (aged 40-84 years) were identified from the UK General Practice Research Database, as newly diagnosed with heart failure by their GP in 1996 (n=3,123). A random sample of heart failure patients (n=1,200) were sent a questionnaire and a nested case-control study was performed to assess risk factors for heart failure)

The *statements*

The *evidence*

4.2a continued from previous page

A qualitative study found that general practitioners experience three categories of difficulty in diagnosing and managing heart failure. The first is uncertainty about clinical practice, including lack of confidence in establishing an accurate diagnosis and using drug therapies in patients who are often elderly and frail with comorbidities and polypharmacy. The second is a lack of awareness of relevant research evidence in what is perceived as a complex and rapidly changing field. The third category consists of influences of individual preference and local organisational factors such as the availability of diagnostic services and resources[iv].

iv. Fuat A, Hungin APS, Murphy JJ. Barriers to accurate diagnosis and effective management of heart failure in primary care: qualitative study. *British Medical Journal* 2003; **326**: 196-201 **http://bmj.bmjjournals.com/cgi/content/full/326/7382/196** [accessed 22.12.03]

(Type IV evidence – qualitative study using focus groups with 30 general practitioners from four primary care groups in North East England)

4.2b. In a 15-month study, it was found that a **Rapid Access Heart Failure Clinic** provided rapid assessment, prompt diagnosis and early introduction of life prolonging therapy for patients presenting with suspected heart failure in primary care[i]. *The service represents a benchmark of clinical care, against which other strategies for the diagnosis and management of heart failure can be evaluated*[i].

i. Fox KF, Cowie MR, Wood DA, Coats AJS, Poole-Wilson PH, Sutton GC. A rapid access heart failure clinic provides a prompt diagnosis and appropriate management of new heart failure presenting in the community. *European Journal of Heart Failure* 2000; **2**: 423-429

(Type IV evidence – service description and analysis of a heart failure clinic at a district general hospital in London. Assessment by a specialist registrar included history, examination, chest x-ray, electrocardiogram (ECG) and echocardiogram)

4.2c. Primary care physicians across **Europe** make limited use of objective investigations such as echocardiography. Most patients are diagnosed on symptoms and signs alone, with only 32% having further investigations or referral[i].

Caveats: The date of the survey was not given. Responses were by self-report and may not accord with actual clinical practice. Response rates from most countries were very low (although information from 300 randomly selected practices across Europe was obtained)

i. Hobbs FDR, Jones MI, Allan TF, Wilson S, Tobias R. European survey of primary care physician perceptions on heart failure diagnosis and management (Euro-HF). *European Heart Journal* 2000; **21**: 1877-1887

(Type IV evidence – Qualitative, postal questionnaire-based, validated survey in the native tongue of a random sample of 200 primary care physicians in each of five European countries (France, Germany, Italy, The Netherlands and Spain) and of 250 UK primary care physicians. All response rates were ≤ 26% other than the UK, where the response rate was 56%)

The *statements*

The *evidence*

Echocardiography techniques

4.2d. **Echocardiography** to assess left-ventricular performance and valve structure and function and ECG are critical steps in the evaluation and management of patients with suspected or clinically evident heart failure[i]. **Guidelines** for the clinical application of echocardiography are available[ii].

i. Khunti K, Baker R, Grimshaw G. Diagnosis of patients with chronic heart failure in primary care: usefulness of history, examination, and investigations. *British Journal of General Practice* 2000; **50**: 50-54

(Type V evidence – expert opinion based on a systematic review of the literature, Medline only searched to 1998)

ii. Cheitlin MD, Alpert JS, Armstrong WF *et al*. ACC/AHA guidelines for the clinical application of echocardiography: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (committee on clinical application of echocardiography). *Journal of the American College of Cardiology* 1997;**29**:862-79 **http://www.americanheart.org/presenter.jhtml?identifier=1782** [accessed 22.12.03]

(Type V evidence - expert opinion)

B-type natriuretic peptide (Brain natriuretic peptide)

4.2e. In a population at **high risk for heart failure, N-terminal pro-brain natriuretic peptide** (BNP) had the strongest correlation with reduced left ventricular wall motion index. A BNP > 275 pmol l^{-1} predicted left ventricular wall motion index ≤ 1.2 with a sensitivity of 93.8%, a specificity of 55% and a negative predictive value of 93%. The authors concluded that the **electrocardiogram** had a poor predictive value for left ventricular systolic dysfunction in this population and that BNP can usefully predict patients with a reduced left ventricular wall motion index in whom echocardiographic examination may be appropriate[i].

i. Talwar S, Squire IB, Davies JE, Barnett DB, Ng LL. Plasma M-terminal pro-brain natriuretic peptide and the ECG in the assessment of left-ventricular systolic dysfunction in a high-risk population. *European Heart Journal* 1999; **20**: 1736-1744

(Type IV evidence – cross sectional study of 243 patients referred for echocardiography. The relationship between left ventricular wall motion index (relationship previously reported for left ventricular ejection fraction) and log N-terminal pro-brain natriuretic peptide, plus various potential confounders was examined using regression analysis)

The *statements*

The *evidence*

4.2f. In patients with symptoms suspected by a general practitioner to be due to heart failure, plasma **brain natriuretic peptide (BNP)** concentration seems to be a useful indicator of which patients are likely to have heart failure and require further clinical assessment[i,ii,iii].

In one study, cut-off values chosen to give negative predictive values for heart failure of 98% (Atrial natriuretic peptide, ANP ≥ 18.1 pmol/L, N-terminal (NT)-ANP ≥ 537.6 pmol/L, brain natriuretic peptide, BNP ≥ 22.2 pmol/L), the sensitivity, specificity, and positive predictive value for ANP were 97%, 72% and 55%; for NT-ANP 97%, 66% and 54%; and for BNP 97%, 84% and 70%[i].

In a second study, concentrations of N-terminal atrial natriuretic peptide and BNP were significantly higher in participants with left-ventricular systolic dysfunction (2.8 ng/mL [IQR 1.8-4.6] and 24.0 pg/mL [18.0-33.0] than in those without - 1.3 ng/mL [0.9-1.8] and 7.7 pg/mL [3.4-13.0]; each $p<0.001$). A BNP concentration of 17.9 pg/mL or more gave a sensitivity of 77% and specificity of 87% in all participants, and 92% and 72% in participants aged 55 years or older[ii].

i. Cowie MR, Struthers AD, Wood AD *et al*. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997; **350**: 1349-1353

(Type IV evidence – UK population based study to examine the predictive value of plasma atrial (ANP and N-terminal ANP) and B-type (BNP) natriuretic peptides in 122 patients with a new primary-care diagnosis of heart failure)

ii. McDonagh TA, Robb SD, Murdoch DR *et al*. Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 1998; **351**: 9-13

(Type IV evidence – analysis of electrocardiograms, echocardiograms, completed questionnaires, and available blood samples of a population sample of 1,252 subjects (aged 25-74) from family physicians' lists in Glasgow, UK)

iii. Krishnaswamy P, Lubien E, Clopton P *et al*. Utility of B-natriuretic peptide levels in identifying patients with left ventricular systolic or diastolic dysfunction. *American Journal of Medicine* 2001; **111**: 274-279

(Type IV evidence – comparison, in the US, of the ability of BNP to predict echocardiographic abnormalities of ventricular function in 253 patients diagnosed with abnormal left ventricular function (aged 69±11 years, 96% male) and 147 patients diagnosed with normal left ventricular function (aged 60±12 years, 97% male))

4.2g. In clinical practice, **BNP testing** is best used as a 'rule out' test for suspected cases of new heart failure in breathless patients presenting to either the outpatient or emergency care settings[i,ii], it is not a replacement for echocardiography and full cardiological assessment will be required for patients with an elevated BNP concentration[i]. Although work is ongoing in establishing the 'normal' values of BNP, in this clinical setting, heart failure appears to be highly unlikely below a plasma concentration of 100 pg/ml[i].

i. Cowie MR, Jourdain P, Maisel A *et al*. Clinical applications of B-type natriuretic peptide (BNP) testing. *European Heart Journal* 2003; **24**: 1710-1718

(Type V evidence – expert review)

ii. Hobbs FDR, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. *British Medical Journal* 2002; **324**: 1498-1503 **http://bmj.bmjjournals.com/cgi/content/full/324/7352/1498** [accessed 22.12.03]

(Type IV evidence – community cohort study of the performance of NT-proBNP in 591 randomly selected patients over the age of 45 from four randomly selected general practices in the West Midlands. Patients were stratified for age and socio-economic status and fell into four cohorts (general population, with an existing clinical label of heart failure, with a prescription for diuretics, or deemed at high risk of heart failure))

The *statements* | The *evidence*

Diastolic heart failure

4.2h. An expert review of the diagnosis and prognosis of **diastolic heart failure** is available[i].

A review in *Clinical Evidence* concluded that treatments for diastolic heart failure are of unknown effectiveness[ii].

i. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I. Diagnosis, prognosis, and measurement of diastolic function. *Circulation* 2002; **105**: 1387-1393
(Type V evidence – expert review)

ii. McKelvie R. Heart Failure. [Search date October 2003] In: *Clinical Evidence* January 2003
(Type V evidence – expert opinion based on a systematic review of the literature)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence*. Cardiff: National Assembly for Wales, July 2001

ACE inhibitors (Angiotensin converting enzyme inhibitors) were shown to improve both symptoms and survival in CHF over a decade ago. Despite this less than 30% of all patients who might benefit from these medicines in the UK actually receive them.

Even more seriously, audits of hospital discharge records have revealed that even in patients discharged from hospital with a heart failure diagnosis, less than 50% leave hospital taking these medicines. Even when the medicines are prescribed, they are frequently given in doses much lower than those employed in the major clinical trials. The recently reported ATLAS study demonstrates that such low dose regimens confer only about 50% of the potential benefit in terms of mortality reduction, hospital admission rate and quality of life achievable with a higher dose. The reasons for this under-dosing are multifactorial but include largely unfounded concerns about side effects at higher dosage and a failure to increase the dosage because of the necessity for close supervision of the patient, monitoring of clinical status and electrolytes. [paragraph 7.7]

What is the latest evidence to guide use of ACE inhibitors?

What is the latest evidence concerning the number of patients who receive ACE inhibitors?

The *statements* | The *evidence*

4.3 ACE inhibitors

4.3a. **Angiotensin converting enzyme (ACE) inhibitors** reduce mortality and morbidity in patients with chronic heart failure. Overall there was a statistically significant reduction in mortality (odds ratio=0.77, 95% CI 0.67-0.88) However this benefit may be limited to patients with relatively poor left ventricular ejection fraction. A consistent effect among a broad range of patients and different ACE inhibitors is seen suggesting a class effect of these drugs. The largest reductions with treatment are observed in the first 90 days[i].

i. Garg R, Yusuf S. Overview of randomised trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *Journal of the American Medical Association* 1995; **273**:1450-56.
(Type I evidence - systematic review and meta-analysis of 7,105 patients in 32 trials comparing ACE inhibitors (benazepril, captopril, cilazapril, enalapril, lisinopril, perindopril, quinapril and ramipril) with placebo)

The *statements*

The *evidence*

4.3b. A Cochrane review is underway to appraise the effectiveness of **angiotensin converting enzyme inhibitors** in patients with heart failure[i].

i. Cleland JFG, Freemantle N, Eastaugh JL, Eccles M, Mason J, Harrison J. Angiotensin converting enzyme inhibitors for heart failure. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software

(Type I evidence - systematic review and meta-analysis of randomised controlled trials, in progress)

4.3c. ACE inhibitors can be started safely in **primary care** for patients with heart failure and left ventricular systolic dysfunction, following exclusion of high risk patients requiring hospitalisation[i,ii].

During the test dose phase of the SOLVD trials 585 patients (7.8%) reported side effects; 136 (1.8%) of these discontinued because of severe side effects. During the titration phase, compared with placebo, enalapril was associated with a increased risk of dose reduction due to hypotension (odds ratio=2.09, 95% CI 1.15-3.82). However, overall there was no difference in the rates of side effects leading to dose reduction or withdrawal between the enalapril and placebo groups[i].

i. Mason J, Young P, Freemantle N, Hobbs R. Safety and costs of initiating angiotensin converting enzyme inhibitors for heart failure in primary care: analysis of individual patient data from studies of left ventricular dysfunction. *British Medical Journal* 2000 ;**321** :1113-1116 **http://bmj.bmjjournals.com/cgi/content/full/321/7269/1113** [accessed 22.12.03]

(Type IV evidence – retrospective analysis of patient data from the SOLVD trials)

ii. Dargie HJ, McMurray JJV. Diagnosis and management of heart failure. British Medical Journal 1994; 308: 321-28 **http://bmj.bmjjournals.com/cgi/content/full/308/6924/321** [accessed 22.12.03]

(Type V evidence - expert opinion based on a review of the literature)

The *statements*

The *evidence*

4.3d. **Enalapril** therapy is associated with a significant reduction in the risk of hospitalisation for heart failure among **white** patients with left ventricular dysfunction, but not among similar **black** patients[i,ii]. Therapy, as compared with placebo, was associated with a 44% (95% CI 27%-57%) reduction among white patients (p<0.001) but with no significant reduction among black patients (p=0.74)[i].

In V-HeFT II, only white patients showed a mortality reduction from **enalapril** therapy compared with **hydralazine plus isosorbide dinitrate (H-I)** therapy (p=0.02)[ii].

Caveats: There were some baseline differences between black and white patients in both V-HeFT trials. The results come from unpowered sub-set analyses and should be viewed only as hypothesis generating.

Published reanalyses of ACE-inhibitor and beta-blocker trials in heart failure provide weak data to support a lack of benefit in black patients. Firm conclusions cannot be drawn until prospective trials, with planned analyses of the effect of race, have been performed[iii].

i. Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. *New England Journal of Medicine* 2001; **344**: 1351-1357

(Type IV evidence – matched cohort study pooling data from two large randomised controlled trials (the Studies of Left Ventricular Dysfunction, SOLVD) comparing enalapril with placebo. A total of 1,196 white patients (580 from the prevention trial and 616 from the treatment trial) were matched with 800 black patients (404 from the prevention trial and 396 from the treatment trial). The average duration of follow-up was 35 months in the prevention trial and 33 months in the treatment trial)

ii. Carson P, Ziesche S, Johnson G, Cohn JN; for the Vasodilator-Heart Failure Trial Study Group. Racial differences in response to therapy for heart failure: Analysis of the Vasodilator-Heart Failure Trials. *Journal of Cardiac Failure* 1999; **5(3)**: 178-187

(Type II evidence – retrospective analysis of outcomes for black and white patients in the V-HeFT I and V-HeFT II trials)

iii. Kalus JS, Nappi JM. Role of race in the pharmacotherapy of heart failure. *Annals of Pharmacotherapy* 2002; **36**: 471-478

(Type IV evidence – systematic review (literature search to May 2001) for, and retrospective analysis of, data from randomised controlled trials)

4.3e. **Long-term ACE inhibitors** lead to lower rates of mortality, myocardial infarction, and hospital admission for heart failure in patients with left-ventricular dysfunction or heart failure with or without a recent myocardial infarct. In the three post-infarction trials (n=5,966), mortality was lower with ACE inhibitors than with placebo (odds ratio, OR=0.74, 95% CI 0.66-0.83), as were the rates of readmission for heart failure (0.73, 0.63-0.85), reinfarction (0.80, 0.69-0.94) or the composite of these events (0.75, 0.67-0.83; all p<0.001). For all five trials the ACE-inhibitor group had lower rates of death than the placebo group (0.80, 0.74-0.87) and lower rates of reinfarction (0.79, 0.70-0.89), readmission for heart failure (0.67, 0.61-0.74), and the composite of these events (0.72, 0.67-0.78; all p<0.0001). The benefits were observed early after the start of therapy and persisted long term. The benefits of treatment on all outcomes were independent of age, sex, and baseline use of diuretics, aspirin, and beta-blockers. Although there was a trend towards greater reduction in risk of death or readmission for heart failure in patients with lower ejection fractions, benefit was apparent over the range examined[i].

i. Flather MD, Yusuf S, Køber L *et al*; for the ACE-Inhibitor Myocardial Infarction Collaborative Group. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 2000; **355(9215)**: 1575-81

(Type I evidence – systematic review of five long-term randomised trials with more than 1,000 subjects (12,763 patients in all) followed up for an average of 35 months. Trials included were: SAVE, AIRE, SOLVD treatment & prevention, TRACE)

The *statements*

The *evidence*

4.3f In comparison to a low dose, therapy with a **high dose of captopril** tends to improve the long-term clinical outcome of patients with mild to moderate heart failure without significantly more toxicity. A relative difference of 29% in the rates of heart failure worsening was observed between the two doses, 31.5% and 22.4% for low and high dose (p=0.088) respectively[i].

Treatment with high dose also showed a trend to benefit as compared to low dose in reducing the number of hospitalisations for all causes from 22.4 to 14.5% (p=0.1) and for congestive heart failure from 14.7 to 7.2% (p=0.06); moreover, the incidence of fatal and nonfatal cardiac events showed a trend in favour of the high dose of 22% (p=0.142). The total number of adverse events was comparable for both doses, but dizziness and hypotension were a little more frequently reported in the high-dose group. Serum creatinine values showed no significant changes either in the low-dose or in the high-dose group[i].

Caveat: The open label design and direct involvement by the manufacturer could have introduced potential for bias. Most results suggested a trend but were not significant.

i. Clement DL, De Buyzere M, Tomas M, Vanavermaete G; on behalf of the CHIPS investigators. Long-term effects of clinical outcome with low and high dose in the Captopril in Heart Insufficient Patients Study (CHIPS). *Acta Cardiologica* 2000; **55(1)**: 1-7

(Type II evidence – one year randomised controlled trial of 298 patients with mild to moderate heart failure (New York Heart Association classes I, II and III) assigned to low dose (25 mg b.i.d.) or high dose (50 mg b.i.d.) captopril. The mean follow-up period was 12 months)

The *statements*

The *evidence*

4.3g **High-dose lisinopril** (32.5 to 35 mg daily) for patients with CHF was more effective than low-dose lisinopril (2.5 to 5.0 mg daily) for reducing the combined end points of all-cause mortality combined with hospitalisation but the groups did not differ for all-cause mortality or CV mortality. Patients in the high-dose group had a significant 12% lower risk of all cause mortality combined with all-cause hospitalisation (p=0.002) and 24% fewer hospitalisations for heart failure (p=0.002) than patients in the low-dose group[i].

Long-term high-dose lisinopril was as effective and well-tolerated in **high-risk patients**, including those with diabetes mellitus, as for the ATLAS study population as a whole[ii,iii].

i. Packer M, Poole-Wilson PA, Armstrong PW *et al*; on behalf of the ATLAS Study Group. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999; **100**: 2312-2318

(Type II evidence – randomised, blinded, controlled trial of 3,164 patients (mean age 63.6 years, 80% men, NYHA classes II, III or IV and LV ejection fraction ≤ 30%). 100% follow-up was obtained over three years. An intention-to-treat analysis was used.

Reviewed in: High-dose lisinopril was more effective than low-dose for reducing combined mortality and cardiovascular events in CHF. *ACP Journal Club* 2000; **133(1)**: 4)

ii. Rydén L, Armstrong PW, Cleland JGF *et al*; on behalf of the ATLAS Study Group. Efficacy and safety of high-dose lisinopril in chronic heart failure patients at high cardiovascular risk, including those with diabetes mellitus. Results from the ATLAS trial. *European Heart Journal* 2000; **21**: 1967-1978

iii. Massie BM, Armstrong PW, Cleland JGF *et al*. Toleration of high doses of angiotensin-converting enzyme inhibitors in patients with chronic heart failure. Results from the ATLAS trial. *Archives of Internal Medicine* 2001; **161**: 165-171

(ii and iii. Type II evidence - retrospective sub-group analysis of 3164 high-risk patients in the ATLAS trial. Patients considered to be at high-risk were those with blood pressure <120 mm Hg, creatinine ≥ 1.5 mg/dL, age ≥ 70 years, or with diabetes mellitus at baseline)

4.3h. The NETWORK trial did not demonstrate a relationship between dose of **enalapril** and clinical outcome in patients with heart failure selected from both primary care and hospital practice. The number of patients reaching the primary end-point (death, heart failure related hospitalisation or worsening heart failure) was 12.3% in the 2.5mg twice daily group, 12.9% in the 5mg twice daily group and 14.7% in the 10mg twice daily group[i].
Caveat: The authors were surprised not to detect a dose-response.

i. The NETWORK Investigators. Clinical outcome with enalapril in symptomatic chronic heart failure: a dose comparison. *European Heart Journal* 1998; **19**: 481-489

(Type II evidence – 24 week randomised controlled trial of 1,532 patients (mean age = 70 and 65% male) from primary care (n=619) and hospital sources (n=913). Patients (65% in NYHA class II and 35% in classes III or IV) were randomised to receive enalapril, 2.5mg, 5mg or 10mg doses twice daily. Analysis was by intention-to-treat)

4.3i A review of the use of **perindopril** for congestive heart failure is available[i].

i. Sonnenblick EH. Perindopril treatment for congestive heart failure. *American Journal of Cardiology* 2001; **88(suppl)**: 19i-27i

(Type V – expert review)

The *statements*

The *evidence*

ACE inhibitor/ aspirin interactions?

4.3j There is only weak evidence of any reduction in the benefit of **ACE-inhibitor** therapy when added to **aspirin**[i,ii].

Results from analyses of all trials, except SOLVD, did not suggest any significant differences between the proportional reductions in risk with ACE inhibitor therapy in the presence or absence of aspirin for the major clinical outcomes (death, myocardial infarction, stroke, hospital admission for congestive heart failure, or revascularisation, p=0.15) or in any of its individual components, except myocardial infarction (p=0.01)[i].

In another systematic review, no substantial clinical evidence could be found that **aspirin** diminishes the benefits of angiotension-converting enzyme inhibitors in heart failure[ii]

i. Teo KK, Yusuf S, Pfeffer M *et al*. ACE Inhibitors Collaborative Group. Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin : a systematic review. *Lancet* 2002 ; **360(9339)** : 1037-1043

(Type I evidence – systematic overview of data for 22,060 patients from six long-term randomised controlled trials of ACE inhibitors)

ii. Mysak T, Cadario B. Acetylsalicylic acid and angiotensin-converting enzyme inhibitors in heart failure: A serious hemodynamic interaction? A systematic critique. *Canadian Journal of Hospital Pharmacy* 2001; **54**: 83-95

(Type I evidence – narrative systematic review of 20 English language papers, literature search to January 2000, including retrospective analyses of randomised controlled trial data)

4.3k Among coronary artery disease patients with and without heart failure who are treated with **ACE inhibitors**, the use of **aspirin** was associated with lower mortality than treatment without aspirin. After a mean follow-up of five years, patients with heart failure taking aspirin experienced lower mortality than patients who did not (24% vs 35%, p=0.001). After adjustment for some, but not all, confounders treatment with aspirin was still associated with lower mortality (Relative Risk = 0.70, 95% CI, 0.49-0.99)[i].
Caveats: This is a post-hoc analysis on groups with different characteristics. These results are supported by some studies but conflict with others and this may relate, for example, to a variation in population characteristics, or to the relatively low doses of aspirin (250 mg) used by the patients in this study.

i. Leor J, Reicher-Reiss H, Goldbourt U *et al*. Aspirin and mortality in patients treated with angiotensin-converting enzyme inhibitors: a cohort study of 11,575 patients with coronary artery disease. *Journal of the American College of Cardiology* 1999; **33(7)**: 1920-1925

(Type IV evidence – an analysis of mortality data from 11,575 patients screened for the Bezafibrate Infarction Prevention trial. A subgroup analysis of 464 patients with congestive heart failure (NYHA classes II-IV) treated with ACE inhibitors revealed 221 patients (48%) on aspirin and 243 patients not on aspirin)

The *statements*

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Underdosing of ACE inhibitors

4.3l. **Underdosing** of ACE inhibitors has been noted in both primary and hospital care in the UK[i,ii,iii].

In one UK general practice survey, 47% of patients with probable heart failure were prescribed **angiotensin-converting enzyme (ACE)-inhibitors.** The main barrier to the use of ACE-inhibitors was GPs' concerns about their possible adverse effects[i].
Caveat: The dates of the survey and practice meetings were not given.

In another UK general practice survey, angiotensin-converting enzyme (ACE) inhibitor treatment, recorded in 54% of patients, **decreased with age** in both sexes ($p<0.001$). Patients whose heart failure had been entirely managed in primary care were less likely to have been prescribed an ACE inhibitor (36% compared with 64% who had been seen in hospital, $p<0.0001$). Patients were also more likely to have been prescribed an ACE inhibitor if they had had an echocardiogram compared to those who had not (72% versus 46%, $p<0.0001$)[ii].

In a **hospital study**, of all patients with chronic heart failure studied, 25% were receiving either no ACE inhibitor or only a low dose in the absence of contraindications[iii].

i. Hickling JA, Nazareth I, Rogers S. The barriers to effective management of heart failure in general practice. *British Journal of General Practice* 2001; **51**: 615-618

(Type IV evidence – retrospective case-note analysis and nominal group technique to elicit general practitioners' perceptions of the reasons for differences between observed and recommended practice. Data were collected from ten Medical Research Council General Practice Framework practices in the North Thames Region)

ii. Hood S, Taylor S, Roeves A *et al*. Are there age and sex differences in the investigation and treatment of heart failure? A population-based study. *British Journal of General Practice* 2000; **50**: 559-563

(Type IV evidence – retrospective case-note review, during 1997/1998, of prevalent cases in 16 general practices in West London. Data were collected for nine practices. 583 patients (57% women) with a diagnosis of heart failure were reviewed. The mean age of patients was 78 years (SD 9.5))

iii. McMullan R, Silke B. A survey of the dose of ACE inhibitors prescribed by general physicians for patients with heart failure. *Postgraduate Medical Journal* 2001; **77**: 765-768

(Type IV evidence – retrospective study of hospital records for 125 patients with heart failure, in Belfast between December 1999 and February 2000)

4.3m. In a survey of primary care practice in **Europe**, only 47-62% of patients were prescribed ACE-inhibitors, and at doses below those identified as effective in trials. Most prescribing doctors (91%) believed there was strong evidence of reduced mortality in heart failure patients using ACE inhibitors, but 51% also considered that **ACE inhibitors** have substantial risks with their use[i].
Caveats: The date of the survey was not given. Responses were by self-report and may not accord with actual clinical practice. Response rates from most countries were very low (although information from 300 randomly selected practices across Europe was obtained).

i. Hobbs FDR, Jones MI, Allan TF, Wilson S, Tobias R. European survey of primary care physician perceptions on heart failure diagnosis and management (Euro-HF). *European Heart Journal* 2000; **21**: 1877-1887

(Type IV evidence – Qualitative, postal questionnaire-based, validated survey in the native tongue of a random sample of 200 primary care physicians in each of five European countries (France, Germany, Italy, The Netherlands and Spain) and of 250 UK primary care physicians. All response rates were ≤ 26% other than the UK, where the response rate was 56%)

The *statements*

The *evidence*

Cost-effectiveness of ACE inhibitors

4.3n. Economic analyses suggest ACE inhibitors are **cost-effective** therapy[i,ii,iii]. The balance between overall savings and costs depends on the proportion of patients whose treatment is initiated by the general practitioner[i].

i. ACE Inhibitors in the treatment of chronic heart failure: Effective and cost-effective. *Bandolier* 1994, Number 8. Volume 1 Issue 8
http://www.jr2.ox.ac.uk/bandolier/band8/b8-1.html
[accessed 22.12.03
(Type IV evidence - economic analyses based on data from randomised controlled trials)

ii. Sculpher MJ, Poole L, Cleland J *et al*. Low doses vs. high doses of the angiotensin converting-enzyme inhibitor lisinopril in chronic heart failure: a cost-effectiveness analysis based on the Assessment of Treatment with Lisinopril and Survival (ATLAS) study. *European Journal of Heart Failure* 2000; **2**: 447-454
(Type IV evidence – cost-effectiveness analysis using data from the ATLAS study)

iii. Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care. London: National Institute for Clinical Excellence, 2003 pp.101-105
http://www.nice.org.uk/pdf/Full_HF_Guideline.pdf
[accessed 22.12.03]
(Evidence based guideline)

ACE inhibitors versus angiotensin II receptor blockers. See Section 4.10

4.4 ACE inhibition after myocardial infarction

4.4a. Long-term treatment with **trandolapril** in patients with reduced left ventricular function soon **after myocardial infarction** significantly reduced the risk of overall mortality, mortality from cardiovascular causes, sudden death, and the development of severe heart failure. The relative risk of death (RR) in the trandolapril group, as compared with the placebo group, was 0.78 (95% CI 0.67-0.91, p=0.001). Trandolapril also reduced the risk of death from cardiovascular causes (RR=0.75, 95% CI 0.63-0.89, p=0.001) and sudden death (RR=0.76, 95% CI 0.59-0.98, p=0.03). The relative risk of progression to severe heart failure was 0.71 (95% CI 0.56-0.89, p=0.003). In contrast, the risk of recurrent myocardial infarction was not significantly reduced (RR=0.86, 95% CI 0.66-1.13, p=0.29)[i].

i. Køber L, Torp-Pedersen C, Carlsen JE *et al*; for the Trandolapril Cardiac Evaluation (TRACE) study group. A clinical trial of the angiotensin-converting enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *New England Journal of Medicine* 1995; **333**: 1670-1676
(Type II evidence – randomised controlled trial of 1,749 patients with echocardiographic evidence of left ventricular systolic dysfunction (ejection fraction ≤ 35%) assigned to oral trandolapril or placebo 3 to 7 days after myocardial infarction. The mean follow-up period was 26 months (range 24-50 months). Mortality analyses were performed on an intention-to-treat basis)

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4.4b. ACE inhibition after myocardial infarction complicated by left ventricular dysfunction appears to be of considerable importance in patients with **diabetes mellitus** by saving lives and substantially reducing the risk of progression to severe heart failure. Treatment with trandolapril resulted in a relative risk (RR) of death from any cause for the diabetic group of 0.64 (95% CI, 0.45-0.91) versus 0.82 (0.69-0.97) for the nondiabetic group. In the diabetic group, trandolapril reduced the risk of progression to severe heart failure markedly (RR=0.38, 0.21-0.67) and no significant reduction of this end point was found in the nondiabetic group[i].

i. Gustafsson I, Torp-Pedersen C, Køber L, Gustafsson F, Hildebrandt P; on behalf of the TRACE Study Group. Effect of the angiotensin-converting enzyme inhibitor trandolapril on mortality and morbidity in diabetic patients with left ventricular dysfunction after acute myocardial infarction. *Journal of the American College of Cardiology* 1999; **34(1)**: 83-89

(Type II evidence – retrospective analysis of data from the Trandolapril Cardiac Evaluation (TRACE) trial. See above. A history of diabetes was found in 237 (14%) of the 1,749 patients)

4.4c. The addition of **eplerenone** (aldosterone blockade) to optimal medical therapy reduces morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure[i].

During a mean follow up of 16 months, the relative risk of death in the treatment versus placebo group was 0.85 (95% CI 0.75-0.96, p=0.008). The relative risk of death due to cardiovascular causes was 0.83 (95% CI 0.72-0.94, p=0.005) and the relative risk of cardiovascular death or hospitalisation for cardiovascular causes was 0.87 (95% CI 0.79-0.95, p=0.002). The rate of serious hyperkalemia was 5.5% in the eplerenone group and 3.9% in the placebo group (p=0.002), whereas the rate of hypokalemia was 8.4% in the eplerenone group and 13.1% in the placebo group (p<0.001)[i].

i. Pitt B, Remme W, Zannad F *et al*; for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *New England Journal of Medicine* 2003; **348**: 1309-1321

(Type II evidence – double-blind randomised controlled trial, EPHESUS, of 6,632 patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure, assigned to eplerenone (25 mg/day initially, titrated to a maximum of 50 mg/day) or placebo)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence*. Cardiff: National Assembly for Wales, July 2001

More recent trials have demonstrated improvements in mortality from a number of other medicines. [paragraph 7.7]

Latest evidence concerning other therapies?

See also Section 4.20 for severe heart failure

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4.5 Diuretics

4.5a. **Diuretics** are an effective symptomatic treatment for acute and chronic heart failure[i,ii]. Compared to active control, **diuretics** appear to reduce the risk of worsening disease and improve exercise capacity (standardised mean difference between diuretic and active control groups = 0.37, 95% 0.10-0.64, p=0.007). Compared to placebo, diuretics reduce the risk of death and worsening heart failure compared to placebo (odds ratio for death=0.25, 95% CI 0.07-0.84, p=0.03)[i].
Caveats: The data should be viewed with caution. Included studies were small. No unpublished studies were sought. Trials with a cross-over design were included.

i. Faris R, Flather M, Purcell H, Henein M, Poole-Wilson P, Coats A. Current evidence supporting the role of diuretics in heart failure: a meta analysis of randomised controlled trials. *International Journal of Cardiology* 2002; **82**: 149-158
(Type I evidence – systematic review, literature search to 1999, of 18 randomised trials (928 patients in all). Mortality data were available for three of the placebo controlled trials (n=221) and exercise capacity data were available for six trials of diuretic versus active control)

ii. Dargie HJ, McMurray JJV. Diagnosis and management of heart failure. *British Medical Journal* 1994; **308**: 321-28 **http://bmj.bmjjournals.com/cgi/content/full/308/6924/321** [accessed 22.12.03]
(Type V evidence - expert opinion)

4.5b. Cochrane reviews are underway to summarise the current evidence for **conventional diuretic therapy**[i] and to compare **continuous infusion** with **bolus injection** of loop diuretics[ii]

i. Faris R, Flather MD, Purcell H, Heinan MY, Poole-Wilson P, Coats AJS. Diuretics for heart failure. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software
(Type I evidence – ongoing systematic review and meta-analysis of randomised trials)

ii. Salvador DRK, Rey NR, Ramos GC, Punzalan FER. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software
(Type I evidence – ongoing systematic review and meta-analysis of randomised trials)

4.5c. Despite the higher acquisition cost of **torasemide** over **furosemide**, pharmacoeconomic analyses have shown that torasemide is likely to reduce overall treatment costs of chronic heart failure by reducing hospital admissions and readmissions[i].
Caveat: It is not possible to tell whether the included publications were assessed for quality by the authors.

i. Young M, Plosker GL. Torasemide. A pharmacoeconomic review of its use in chronic heart failure. *PharmacoEconomics* 2001; **19(6)**: 679-703
(Type IV evidence – narrative systematic review, literature search to May 2001, of economic analyses)

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4.6 Beta-blockers

4.6a. **Beta-blocker** therapy is associated with clinically meaningful reductions in mortality and morbidity in patients with stable congestive heart failure and should be routinely offered to all patients similar to those included in trials (most of which excluded patients with severe heart failure)[i,ii,iii].

From one recent meta-analysis, the best estimates are 3.8 lives saved and 4 fewer hospitalisations per 100 patients treated during the first year after therapy[i].

In another review, including many of the same trials, the odds ratio for death with beta-blocker compared to control was 0.63 (95% CI 0.55-0.72, p<0.00001)[ii].

Issues that remain unclarified include the mechanisms through which beta-blockers may improve cardiac function and their tolerability and efficacy in specific groups of patients (such as those with asymptomatic left ventricular dysfunction, severe heart failure, the elderly, or those with left ventricular diastolic dysfunction).

i. Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure. A Bayesian meta-analysis. *Annals of Internal Medicine* 2001; 134: 550-560

(Type I evidence – systematic review, literature search to July 2000, and meta-analysis, using a Bayesian hierarchical (random effects) model of 22 trials involving 10,135 patients. The trials that reported in 1999-2000 (CIBIS II, MERIT-HF, RESOLVD) are included as well as earlier trials)

ii. Shibata MC, Flather MD, Wang D. Systematic review of the impact of beta-blockers on mortality and hospital admissions in heart failure. *European Journal of Heart Failure* 2001; **3**: 351-357

(Type I evidence – systematic review, literature search of Medline and meeting abstracts to January 2000, of 22 randomised controlled trials involving 10,480 patients. CIBIS II & MERIT are included as well as earlier trials. The trials had an average length of treatment of 11 months)

iii. Foody JM, Farrell MH, Krumholz HM. Beta-blocker therapy in heart failure. Scientific review. *Journal of the American Medical Association* 2002; **287**: 883-889

(Type V evidence – expert review of large randomised controlled trials (with n≥ 300) and clinical guidelines)

4.6b. Statistically and clinically significant improvement, including a statistically significant reduction in mortality, have been noted in patients receiving therapy with either **bisoprolol, carvedilol**, or **metoprolol**[i,ii]. The trial results were homogeneous, and pooled analysis revealed a reduction in the risk of total mortality (odds ratio=0.66, 95% CI 0.58-0.75) and sudden death (OR=0.61, 95% CI 0.5-0.75) for patients receiving beta-blocker therapy[i].

i. Lee S, Spencer A. Beta-blockers to reduce mortality in patients with systolic dysfunction. A meta-analysis. The *Journal of Family Practice* 2001; **50(6)**: 499-504

(Type I evidence – systematic review, literature search to February 2000, of six double-blind randomised controlled trials looking at bisoprolol (CIBIS I & II), carvedilol (AUZ & US Carvedilol) and metoprolol (MDC & MERIT-HF))

ii. Metra M, Nodari S, D'Aloia A, Bontempi L, Boldi E, Del Cas O. A rationale for the use of beta-blockers as standard treatment for heart failure. *American Heart Journal* 2000; **139(3)**: 511-21.

(Type V evidence – expert narrative review of placebo-controlled, double-blind studies looking at the effects of beta-blockers in patients with heart failure (almost 10,000 patients in all))

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4.6c. A Cochrane review is underway to examine the effectiveness of **beta blockers** in patients with heart failure[i].

i. Cleland JFG, Freemantle N, Eastaugh JL, Young P, Harrison J. Beta-blockers for heart failure. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software

(Type I evidence - systematic review and meta-analysis of randomised trials)

4.6d. Published reanalyses of ACE-inhibitor and beta-blocker trials in heart failure provide weak data to support a lack of benefit in **black patients**. *Firm conclusions cannot be drawn until prospective trials, with planned analyses of the effect of race, have been performed*[i].

i. Kalus JS, Nappi JM. Role of race in the pharmacotherapy of heart failure. *Annals of Pharmacotherapy* 2002; **36**: 471-478

(Type IV evidence – systematic review (literature search to May 2001) for, and retrospective analysis of, data from randomised controlled trials)

4.6e. In **CIBIS-2**, medical events were significantly influenced by treatment withdrawal. Analysis of survival curves in patients who permanently discontinued treatment showed that bisoprolol did not reduce mortality compared with placebo in this population (relative risk=1.03, 95% CI 0.67-1.59, p=0.88). Recurrent nonlethal events were reduced by bisoprolol. All attempts to resume bisoprolol therapy should be made if temporary withdrawal is clinically required[i].

i. Funck-Brentano C, Lancar R, Hansen S, Hohnloser SH, Vanoli E; for the CIBIS-2 Investigators. Predictors of medical events and of their competitive interactions in the Cardiac Insufficiency Bisoprolol Study 2 (CIBIS-2). *American Heart Journal* 2001; **142**: 989-997

(Type IV evidence – Use of a Cox model for censored data (and competitive risk analysis) to analyse the relations among baseline variables, medical events, and their interactions with treatment, within the context of the CIBIS-2 randomised controlled trial)

4.6f. Sub-group analysis of the CIBIS II trial, showed that **high risk patients** benefited equally from beta-blockade with bisoprolol as patients without these complications or drugs[i].

i. Erdmann E, Lechat P, Verkenne P, Wiemann H. Results from post-hoc analyses of the CIBIS II trial: effect of bisoprolol in high-risk patient groups with chronic heart failure. *European Journal of Heart Failure* 2001; **3**: 469-479

(Type II evidence – retrospective sub-group analysis of the CIBIS II trial. Patients were included in the analysis if they were ≥ 71 years, had type 2 diabetes mellitus, renal impairment, severe heart failure (NYHA class IV) or were taking either amiodarone, aldosterone antagonists or digitalis as concomitant medication (2,647 patients). An intention-to-treat analysis was used)

4.6g. Regardless of beta-blocker treatment and baseline clinical profile, **female sex** is a significant predictor of survival in patients with congestive heart failure. After adjustment for baseline differences, all-cause mortality was significantly reduced by 36% in women compared with that in men (hazard ratio=0.64, 95% CI 0.47-0.86, p=0.003)[i].

i. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P; on behalf of the CIBIS II Investigators. Sex differences in the prognosis of congestive heart failure. Results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Circulation* 2001; **103**: 375-380

(Type IV evidence – observational study of the influence of female sex on outcomes in the CIBIS II study)

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4.6h. A recent randomised controlled trial suggests that **carvedilol** extends survival compared to **metoprolol**[iii]. The all-cause mortality was 34% (512 of 1511) for carvedilol and 40% (600 of 1518) for metoprolol (hazard ratio 0.83 [95% CI, 0.74-0.93], p=0.0017). The reduction of all-cause mortality was consistent across predefined subgroups. The composite endpoint of mortality or all-cause admission occurred in 1116 (74%) of 1511 on carvedilol and in 1160 (76%) of 1518 on metoprolol (0.94 [0.86-1.02], p=0.122). Incidence of side-effects and drug withdrawals did not differ by much between the two study groups[i].

i. Poole-Wilson PA, Swedberg K, Cleland JG *et al*. Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003; **362(9377)**: 7-13

(Type II evidence – randomised controlled trial, mean study duration 58 months (SD 6), of 3,029 patients, mean age 62 years (SD 11). 1511 randomised to treatment with carvedilol (target dose 25 mg twice daily) and 1,518 to metoprolol (metoprolol tartrate, target dose 50 mg twice daily). Patients were required to have chronic heart failure (NYHA II-IV), previous admission for a cardiovascular reason, an ejection fraction of less than 0.35, and to have been treated optimally with diuretics and angiotensin-converting enzyme inhibitors unless not tolerated. The mean ejection fraction was 0.26 (0.07) and the mean age 62 years (11))

4.6i. The effect of **beta-blockade** appears to be **additive** to that of **ACE** inhibition[i].

i. Sharpe N. Benefit of beta-blockers for heart failure: proven in 1999. *Lancet* 1999; **353**: 1988-1989

(Type V evidence – expert commentary on the CIBIS II and MERIT-HF trials)

4.6j. A trial is underway to evaluate the effects of **nebivolol** compared with placebo, in addition to background therapy, in clinically stable elderly patients (≥ 70 years) with chronic heart failure, with or without impairment of left ventricular systolic function[i].

i. Randomised trial of nebivolol in elderly patients with heart failure (SENIORS). End date: 1 June 2003. MREC reference: MREC/00/8/49
Lead centre: National Heart and Lung Institute, Imperial College London.

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4.6k. For patients with **hypertension and left ventricular hypertrophy, losartan** (an angiotensin II receptor antagonist) prevents more cardiovascular morbidity and death than **atenolol** (a beta-blocker) for a similar reduction in blood pressure and is better tolerated. Blood pressure fell by 30.2/16.6 (SD 18.5/10.1) and 29.1/16.8 mm Hg (19.2/10.1) in the losartan and atenolol groups respectively. The primary composite endpoint (cardiovascular mortality, stroke and myocardial infarction) for losartan was 23.8 per 1000 patient years and 27.9 per 1000 patients years for atenolol (relative risk 0.87, 95% CI 0.77-0.98, p=0.021). The discontinuation in losartan versus atenolol groups for all adverse events was significantly less common (p<0.0001). New onset diabetes was less frequent with losartan[i].

For the subset of patients with **isolated systolic hypertension** and left ventricular hypertrophy the data also suggested that losartan is superior to atenolol for treatment. The primary composite endpoint (see above) was reduced by 25% with losartan compared with atenolol (relative risk, 0.75 95% CI 0.56-1.01)[ii].

i. Dahlöf B, Devereux RB, Kjeldsen SE *et al*; for the LIFE study group. Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE): a randomised trail against atenolol. *Lancet* 2002; **359**: 995-1003

(Type II evidence – double-blind, randomised, parallel-group trail in 9,193 participants aged 55-80 years with essential hypertension and left ventricular hypertrophy to compare losartan- with atenolol-based antihypertensive treatment with at least four year follow-up. An intention to treat analysis was used)

ii. Kjeldson SE, Dahlöf B, Devereux RB *et al*; for the LIFE study group. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy. *Journal of the American Medical Association* 2002; **288**: 1491-1498

(Type II evidence – analysis of 1326 men and women from the above trial with isolated systolic hypertension and electrocardiographically documented left ventricular hypertrophy)

Beta-blocker therapy after myocardial infarction

4.6l. The relative benefit of **beta-blockers** on mortality **after a myocardial infarction** is similar in the presence or absence of heart failure but the absolute benefit may be greater in the former. Overall treatment with a beta-blocker was associated with a 22.6% reduction in the odds of death (95% CI, 11%-32.3%). In the analysis that included heart failure as a factor, treatment with a beta-blocker was associated with a non-significant interaction with the presence of heart failure. However, because the group including heart failure patients were at higher risk, the absolute benefit of treatment with beta-blockers appeared greater in this group. *Current clinical practice has changed radically from the time when the majority of these trials were conducted (eg prior to the widespread use of ACE inhibitors). Further trial evidence would be desirable to confirm the value of beta-blockers for contemporary clinical practice, and to examine any variations in individual therapies within the beta-blocker class*[i].

i. Houghton T, Freemantle N, Cleland JGF. Are beta-blockers effective in patients who develop heart failure soon after myocardial infarction? A meta-regression analysis of randomised trials. *European Journal of Heart Failure* 2000; **2(3)**: 333-40.

(Type I evidence – systematic review and meta-analysis of 17 randomised controlled trials, without cross-over, with beta-blocker treatment lasting more than one month and with 50 or more patients)

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4.6m. In patients treated long-term after an acute myocardial infarction complicated by left ventricular systolic dysfunction, **carvedilol** reduced the frequency of all-cause and cardiovascular mortality and recurrent non-fatal myocardial infarctions. These beneficial effects are additional to those of evidence-based treatments for acute MI, including ACE-inhibitors. Although there was no difference between groups for the combined end-points of all-cause mortality or hospital admission for cardiovascular problems (hazard ratio=0.92, 95% CI 0.80-1.07) all-cause mortality alone was lower in the carvedilol group (HR=0.77, 95% CI 0.60-0.98, p=0.03)[i].

i. The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001; **357**: 1385-1390

(Type II evidence – randomised controlled, double-blind, trial of 1,959 patients with left ventricular ejection fraction ≤ 40% 3-21 days (mean 10 days) after an acute myocardial infarction. Patients were randomised to placebo or carvedilol (progressively increased to a maximum of 25 mg twice daily) and all had received ACE inhibitor therapy for at least 48 hours prior to randomisation. Follow-up was for a mean of 1.3 years. An intention to treat analysis was used)

4.7 Antiarrythmic therapies

4.7a. A review in *Clinical Evidence* concluded that **amiodarone** is of **unknown** effectiveness for the treatment of heart failure[i]. Systematic reviews found weak evidence suggesting that amiodarone versus placebo may reduce mortality. For example, one review suggested an overall reduction in mortality of 13% (odds ratio=0.87, 95% CI 0.78-0.99, p=0.030)[ii]. However, expert advice is that no firm conclusions about effects of amiodarone in people with heart failure can be drawn[i].

i. Samuel R. Heart Failure. [Search date October 2002] In: *Clinical Evidence* January 2003

(Type V evidence – expert opinion based on a systematic review of the literature)

ii. Amiodarone Trials Meta-Analysis Investigators. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6,500 patients in randomised trials. *Lancet* 1997; **350**: 1417-1424

(Type I evidence – systematic review and meta-analysis of eight randomised controlled trials post-myocardial infarction and five randomised controlled trials of patients with heart failure (6,553 patients in all))

4.7b. A review in Clinical Evidence concluded that **non-amiodarone antiarrythmic drugs** were likely to be ineffective or harmful[i].

i. Samuel R. Heart Failure. [Search date October 2002] In: *Clinical Evidence* January 2003

(Type V evidence – expert opinion based on a systematic review of the literature)

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4.7c. There is a paucity of controlled clinical trial data for the management of **atrial fibrillation** (AF) among patients with **heart failure** (HF). The interaction between AF and heart failure means that neither can be treated optimally without treating both. For patients with acute AF ventricular rate control, anticoagulation and treatment of HF should be pursued simultaneously before cardioversion is attempted. Digoxin is relatively ineffective at controlling ventricular response and for cardioversion. Intravenous diltiazem is rapidly effective in controlling ventricular rate and limited evidence suggests it is safe. Amiodarone controls ventricular rate rapidly and increases the rate of cardioversion. There are insufficient data to conclude that immediate anti-coagulation, transoesophageal echocardiography to exclude atrial thrombi followed by immediate cardioversion is an appropriate strategy. Evidence based guidelines, including an algorithm for management, are provided[i].

The **Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial** is underway to determine whether restoring and maintaining sinus rhythm significantly reduces cardiovascular mortality compared with a rate-control strategy in patients with atrial fibrillation and CHF[ii].

The *evidence*

i. Khand AU, Rankin AC, Kaye GC, Cleland JGF. Systematic review of the management of atrial fibrillation in patients with heart failure. *European Heart Journal* 2000; **21(8)**: 614-32.

(Type I evidence – evidence based guidelines from a systematic review of studies investigating the management of AF in patients with heart failure published between 1967 to 1998. Eight studies pertaining to acute and twenty-four pertaining to chronic AF)

ii. Anonymous. Rationale and design of a study assessing treatment strategies of atrial fibrillation in patients with heart failure: the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial. *American Heart Journal* 2002; **144(4)**: 597-607

(Ongoing multicentre randomised controlled trial that will randomize 1,450 patients with CHF with left ventricular ejection fraction < or =35% and atrial fibrillation to 1 of 2 treatment strategies: (1) rhythm control with the use of electrical cardioversion combined with antiarrhythmic drugs (amiodarone or other class III agents), (2) rate control with the use of beta-blockers, digoxin, or pacemaker and AV nodal ablation)

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4.8 Digoxin/digitalis

4.8a. **Digitalis** has a useful role in the treatment of patients with congestive heart failure who are in normal sinus rhythm. There was no difference in mortality between treatment and control groups but digitalis therapy was associated with a lower rate of hospitalisation (odds ratio, OR=0.68, 95% CI 0.61-0.75) and of clinical deterioration (OR=0.29, 95% CI 0.20-0.42)[i].

The largest trial in this review found that **digoxin** therapy for patients with heart failure in sinus rhythm is associated with fewer hospital admissions than placebo (26.8% vs. 34.7%, risk ratio 0.72; 95% CI 0.66-0.79; p<0.001), a borderline reduced risk of death from worsening heart failure (11.6% vs. 13.2%, risk ratio 0.88; 95% CI 0.77-1.01; p=0.06) but no difference in overall mortality (34.8% vs. 35.1%, risk ratio 0.99; 95% CI 0.91-1.07; p=0.80)[ii].

A review in *Clinical Evidence* concluded that **digitalis** improves morbidity in people already receiving diuretics and ACE-inhibitors[iii].

i. Hood WB, Dans A, Guyatt GH, Jaeschke R, McMurray JJV. Digitalis for treatment of congestive heart failure in patients in sinus rhythm. Cochrane Review. [Most recent update: 28 November 2001] In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software (most recent update 30 May 2001) **http://www.update-software.com/abstracts/ab002901.htm** [accessed 22.12.03]

(Type I evidence - systematic review, search to June 2000, and meta-analysis of 11 randomised controlled trials. 8 trials (n=7,744) for mortality outcomes, 4 trials (n=7,262) for hospitalisation and 10 trials (n=1085) for clinical deterioration)

ii. The Digitalis Investigation Group (DIG). The effect of digoxin on mortality and morbidity in patients with heart failure. *New England Journal of Medicine* 1997;**336**:525-33

(Type II evidence - randomised controlled trial of 6,800 patients in sinus rhythm with ejection fractions <0.45 randomised to digoxin or placebo in addition to diuretics and ACE inhibitors)

iii. McKelvie R. Heart Failure. [Search date October 2003] In: *Clinical Evidence* January 2003

(Type V evidence – expert opinion based on a systematic review of the literature)

4.9 Phosphodiesterase inhibitors

4.9a. **Phosphodiesterase inhibitors** are associated with a non-significant increased mortality at minimum follow-up of three months in patients with chronic heart failure. Analysis of studies excluding vesnarinone found a significant increase in mortality of 41% (95% CI 11%-79%)[i].

i. Nony P, Boissel JP, Lievre M *et al*. Evaluation of the effect of phosphodiesterase inhibitors on mortality in chronic heart failure patients: a meta-analysis. *European Journal of Clinical Pharmacology* 1994; **46**:191-96.

(Type I evidence - systematic review of 2,732 patients in 13 randomised controlled trials of phosphodiesterase inhibitors: amrinone, milrinone, enoximone, indolidan, vesnarinone, pimobendan)

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4.9b. A Cochrane review is underway to examine the data from all randomised controlled trials of **phosphodiesterase III inhibitors** versus placebo in patients symptomatic with chronic heart disease[i].

i. Nony P, Martin F. Phosphodiesterase III inhibitors for heart failure. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software

(Type I evidence – ongoing systematic review and meta-analysis of randomised controlled double-blind trials with a minimum follow-up of 3 months, and using an intention to treat strategy)

4.10 Angiotensin receptor blockers

4.10a. A meta-analysis could not confirm that **angiotensin receptor blockers** (ARBs) are superior in reducing all-cause mortality or heart failure hospitalisation in patients with symptomatic heart failure, particularly when compared with ACE inhibitors (ACEIs). However the use of ARBs as monotherapy in the absence of ACEIs or as combination therapy with ACEIs appears promising[i].

There was a non-significant trend in benefit when ARBs were given in the absence of background ACEI therapy. When compared directly with ACEIs, ARBs were not superior in reducing either mortality (odds ratio 1.09, 95% CI 0.92-1.29) or hospitalisation (0.95, 0.80-1.13). In contrast, the combination therapy of ARBs and ACEIs was superior to ACEIs alone in reducing hospitalisation (0.74, 0.64-0.86) but not mortality (1.04, 0.91-1.20)[i].

A Cochrane review is underway to examine the effectiveness of **angiotensin receptor blockers** in patients with heart failure[ii].

i. Jong P, Demers C, McKelvie R, Liu PP. Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. *Journal of the American College of Cardiology* 2002; **39(3)**: 463-470

(Type I evidence – systematic review, literature search to May 2001, of 17 randomised controlled trials involving 12,469 patients)

ii. Jong P, Demers C, McKelvie R, Liu P. Angiotensin receptor blockers for heart failure. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software

(Type I evidence – ongoing systematic review and meta-analysis of randomised trials)

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4.10b. **Losartan** (an angiotensin II receptor blocker) was not superior to **captopril** (an ACE inhibitor) in improving survival in elderly heart failure patients, but was significantly better tolerated. There were no significant differences in all-cause mortality or sudden death/resuscitated arrests between the two treatment groups (hazard ratios 1.13, 95% CI 0.95-1.35, p=0.16 and 1.25, 95% CI 0.98-1.60, p=0.08 respectively). Significantly fewer patients in the losartan group (excluding those who died) discontinued study treatment because of adverse effects (9.7% vs 14.7%, p<0.001), including cough (0.3% vs 2.7%)[i].

The authors concluded that ACE inhibitors should be the initial treatment for heart failure, although angiotensin II receptor antagonists may be useful to block the renin aldosterone system when ACE inhibitors are not tolerated[i].

i. Pitt B, Poole-Wilson PA, Segal R *et al*; on behalf of the ELITE II Investigators. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial - the losartan heart failure survival study – ELITE II. *Lancet* 2000; **355**: 1582-1587

(Type II evidence – randomised, double-blind, controlled trial of 3,152 patients (aged 60 years of older, mean age 71.6 years) with symptomatic heart failure (New York Heart Association Classes II-IV and a left-ventricular ejection fraction of ≤ 40%). Subjects, stratified for beta-blocker use, were randomised to either 12.5 mg losartan, titrated as tolerated to 50 mg once daily, or 12.5 mg captopril, titrated as tolerated to 50 mg three times daily. Median follow-up was 555 days. An intention-to-treat analysis was used.)

4.10c. In patients with stable, mild-to-moderate heart failure, **enalapril** could be replaced by **telmisartan** for a period of 12 weeks without deterioration in exercise capacity or clinical statusi. There were no statistically significant differences in exercise tolerance between the groups. There was a small but significant increase in blood pressure in all but the 80 mg telmisartan groups, compared to enalapril. Both drugs had similar adverse effect profiles. Cough occurred in 5.6% of the enalapril patients and in 3% of telmisartan patients (not significant)[i].
Caveat: Short term trial. *Studies of greater duration are needed to establish the survival benefits of telmisartan and other angiotensin converting enzyme inhibitors as long-term replacement therapy for ACE-inhibitors*[i]

i. Dunselman PHJM. Effects of the replacement of the angiotensin converting enzyme inhibitor enalapril by the angiotensin II receptor blocker telmisartan in patients with congestive heart failure. The replacement of angiotensin converting enzyme inhibition (REPLACE) investigators. *International Journal of Cardiology* 2001; **77**: 131-138

(Type II evidence – double-blind randomised controlled trial of 378 patients being treated with enalapril (mean age 64±9 years) randomised to once-daily treatment with telmisartan 10, 20, 40, 80mg or continuation with enalapril 10 mg twice daily. Patients had NYHA class II or III heart failure and a left-ventricular function ≤ 40%. An intention to treat analysis was used for 367 patients included in the efficacy analysis)

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4.10d. **Valsartan**, compared to placebo, significantly reduced the combined end point of mortality and morbidity and improved clinical signs and symptoms in patients with heart failure, when added to prescribed therapy. Overall mortality was similar between the two groups. The incidence of the combined end-point of mortality and morbidity was 13.2% lower with valsartan (relative risk=0.87; 97.5% CI 0.77-0.97; p=0.009) predominantly because of the lower number of patients hospitalised for heart failure[i].

Caveat: There are **serious concerns** with this trial. It is unclear if follow-up was complete and/or if an intention-to-treat analysis was used. In a post-hoc analysis of the combined end point and mortality in subgroups defined according to base-line treatment with ACE inhibitors or beta-blockers, valsartan had a favourable effect in patients receiving neither or one of these types of drugs but an adverse effect in patients receiving both types of drugs.

i. Cohn JN, Tognoni G; for the Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *New England Journal of Medicine* 2001; **345(23)**: 1667-1675

(Type II evidence – randomised controlled trial of 5,010 patients with New York Heart Association classes II to IV heart failure, while receiving all standard therapy, receiving treatment with valsartan, 160 mg twice daily, or placebo. Average follow up period: 23 months)

4.10e. **Candesartan** was generally well tolerated and significantly reduced cardiovascular deaths and hospital admissions for heart failure. Ejection fraction or treatment at baseline did not alter these effects[i].

The covariate adjusted hazard ratio was just significant for all deaths (0.90, 95% CI 0.82-0.99, p=0.032) and for cardiovascular deaths (0.87, 95% CI 0.78-0.96, p=0.006). The unadjusted hazard ratios were 0.91 (0.83-1.00, p=0.55) and 0.88 (0.79-0.97, p=0.012) respectively. Hospital admissions for heart failure were 20% versus 24% (p<0.0001). There was no significant heterogeneity for candesartan results across the component trials. More patients discontinued candesartan than placebo because of concerns about renal function, hypotension and hyperkalaemia[i].

Caveat: The sponsor was closely involved with the data analysis and interpretation but data analyses were independently verified.

i. Pfeffer MA, Swedberg K, Granger CB *et al*. for the CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *The Lancet* 2003; **362**: 759-766

(Type II evidence – double-blind randomised controlled trials comparing candesartan with placebo in three distinct populations: Patients with left-ventricular ejection fraction (LVEF) ≤ 40% who were not receiving ACE inhibitors because of previous intolerance or who were currently receiving ACE inhibitors, and patients with LVEF >40%. 7601 patients (7,599 with data) were assigned candesartan (titrated to 32 mg/day, n=3,803) or matching placebo (n=3,796) and followed up for at least two years)

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4.11 Inotropic agents

4.11a. On the basis of the available evidence, the routine use of **inotropes** as heart failure therapy is **not** indicated in either the acute or chronic setting[i,ii].

Potentially appropriate uses of inotropes include temporary treatment of diuretic-refractory acute heart failure decompensations or as a bridge to definitive treatment such as revascularisation or cardiac transplantation. Inotropes may also be appropriate as a palliative measure in patients with truly end-stage heart failure[ii].

i. Cuffe MS, Califf RM, Adams KF *et al*; for the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbation of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbations of chronic heart failure. *Journal of the American Medical Association* 2002; **287**: 1541-1547

(Type II evidence – randomised, double-blind, placebo-controlled trial of 951 patients admitted with an exacerbation of systolic heart failure not requiring intravenous inotropic support (mean age, 65 years, 92% with baseline NYHA calls III-IV, mean left ventricular ejection fraction, 23%. Patients were randomised to a 48-hour infusion of milrinone (0.5 _g/kg per minute) or placebo)

ii. Felker GM, O'Connor CM. Inotropic therapy for heart failure: An evidence-based approach. *American Heart Journal* 2001; **142**: 393-401

(Type V evidence – expert opinion based on a well-referenced literature review)

4.11b. **Class I antiarrhythmic agents, non-glycoside positive inotropic drugs**, and **calcium channel blockers** with negative inotropic actions are associated with increased risk of death, and they should be avoided in patients with heart failure[i].

i. Lonn E, McKelvie R. Drug treatment in heart failure. *British Medical Journal* 2000; **320(7243)**: 1188-1192 **http://bmj.bmjjournals.com/cgi/content/full/320/7243/1188** [accessed 22.12.03]

(Type V evidence – expert opinion based on a systematic review of randomised controlled trials and a study of meta-analyses and reviews in heart failure (Medline searched from 1966-1999))

4.12 Anticoagulants

4.12a. Evidence from randomised controlled and observational studies found a reduction in mortality and cardiovascular events with **anticoagulants** compared to control in patients with heart failure[i].

Caveat: Effectiveness is unknown. Some studies were very old; results were also contradictory and should be interpreted with caution. *A large randomised controlled trial, the Warfarin Antiplatelet Therapy in Chronic Heart Failure (WATCH) study (n=4,500) is in progress*[ii].

i. Lip GYH, Gibbs CR. Anticoagulation for heart failure in sinus rhythm. In: The Cochrane Library, Issue 1 2003. Oxford: Update Software (most recent update 21 August 2001) **http://www.update-software.com/abstracts/ab003336.htm** [accessed 22.12.03]

(Type I evidence – systematic review, literature search to 2000, of one pilot randomised controlled trial, three prospective studies (all over 50 years old) and four retrospective non-randomised studies)

ii. Warfarin and antiplatelet therapy study in chronic heart failure (the WATCH study). End date: 1 April 2005. MREC Reference: MREC/98/0/10
Lead centre: Castle Hill Hospital, Cottingham, E. Yorkshire.

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4.12b. At present there is no evidence from long-term randomised controlled trials to recommend use of **aspirin** to prevent thromboembolism in patients with heart failure in sinus rhythm. A possible interaction with ACE inhibitors may reduce the efficacy of aspirin although this evidence is from retrospective analyses of trial cohorts (see statements 4.3h-4.3j). There is also no evidence to indicate superior effects from oral anticoagulation, when compared to aspirin[i]

i. Lip GYH, Gibbs CR. Antiplatelet agents versus control or anticoagulation for heart failure in sinus rhythm. [Most recent update: 8 August 2001] In: The Cochrane Library, Issue 1 2003. Oxford: Update Software **http://www.update-software.com/abstracts/ab003333.htm** [accessed 22.12.03]

(Type I evidence – systematic review, literature search to 2000, of one randomised controlled trial and three retrospective non-randomised cohort studies from the V-HeFT, SOLVD and SAVE trials)

4.13 Calcium channel blockers

4.13a. An analysis of the non-randomised clinical use of **calcium channel blockers** in the **post-myocardial infarction** population with left ventricular dysfunction did **not** identify either a clinical deterioration or improvement with respect to subsequent cardiovascular events.

For all causes of mortality, the relative risk (RR) for calcium channel blocker users versus nonusers was 0.96 (95% CI, 0.78-1.17). In the SAVE placebo and captopril groups, the RRs for the development of severe heart failure among the calcium channel blocker users versus nonusers were 0.95 (95% CI, 0.72-1.25) and 1.23 (95% CI, 0.88-1.71) respectively. A similar neutral result held for patients with and without a history of hypertension. Furthermore, calcium channel blockers did not alter the benefit of the angiotensin converting enzyme inhibitor, captopril[i].

i. Hager WD, Davis BR, Riba A *et al*. Absence of a deleterious effect of calcium channel blockers in patients with left ventricular dysfunction after myocardial infarction: The SAVE Study experience. *American Heart Journal* 1998; **135(3)**: 406-413

(Type IV evidence – prospective examination of the effect of calcium channel blocker use in 940 patients taking and 1,180 patients not taking this therapy 24 hours before randomisation to placebo or captopril in the Survival and Ventricular Enlargement (SAVE) Trial. Average follow-up = 42 months. All patients had a left ventricular ejection fraction of ≤ 40% but those with overt clinical heart failure or persistent myocardial ischemia were excluded)

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4.13b. The addition of 10 mg/day **amlodipine** to standard therapy in patients with heart failure is associated with **no** significant improvement in exercise time compared with placebo therapy over a 12-week period[i].

i. Udelson JE, DeAbate A, Berk M *et al*. Effects of amlodipine on exercise tolerance, quality of life, and left ventricular function in patients with heart failure from left ventricular systolic dysfunction. *American Heart Journal* 2000; **139(3)**: 503-510

(Type II evidence – randomised, double-blind, controlled trial of 437 patients with stable heart failure (NYHA Classes II-IV and an LV ejection fraction of ≤ 35%). Subjects were assigned to amlodipine (10 mg/day) or placebo. The results of two similar studies were combined. In the first, amlodipine or placebo was initially titrated from 5 to 10 mg/d in patients who were receiving a combination of digoxin, diuretics and/or ACE inhibitors, if tolerated (n=192). In the second, 10 mg amlodipine was compared with placebo (without titration) in patients who were required to receive digoxin, diuretics and ACE inhibitors (n=245). Patients were eligible for the first protocol if intolerance to ACE inhibitors had been demonstrated. All patients followed a low sodium diet throughout the study. An intention-to-treat analysis was used)

4.13c. **Second generation dihydropyridine calcium channel blockers** slightly increase cardiac index, left ventricular ejection fraction, and exercise treadmill test in patients with chronic heart failure, and do not increase norepinephrine levels. A 6% reduction in mortality was found. Although not significantly different from 0%, it does indicate that these drugs do not increase mortality in this category of patients[i].

Caveats: Inadequate search strategy (single database to 1997 and no search for unpublished studies) and some results plots suggest that publication bias may be a problem with this review.

i. Cleophas TJ, van Marum R. Meta-analysis of efficacy and safety of second-generation dihydropyridine calcium channel blockers in heart failure. *American Journal of Cardiology* 2001; **87(4)**: 487-490

(Type I evidence – systematic review, Medline search only to 1997, of 18 studies. 13 studies included in the meta-analysis. The drugs studied were: felodipine, nicardipine, amlodipine, nisoldipine, isradipine and lacidipine)

4.14 Spironolactone

4.14a. **Spironolactone**, in addition to standard therapy, substantially reduces the risk of both morbidity and death among patients with **severe heart failure**[i]. See also statement 4.20f.

Spironolactone is recommended for all patients with class III or IV heart failure who are already being treated with a diuretic and ACE inhibitor, with or without digoxin[i].

i. Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care. London: National Institute for Clinical Excellence, July 2003
http://www.nice.org.uk/pdf/Full_HF_Guideline.pdf
[full guideline]

http://www.nice.org.uk/pdf/CG5NICEguideline.pdf
[NICE guideline]

[accessed 22.12.03]

(Evidence based guideline – systematic literature search to 2002 for specific study types based on clinical questions set out by the technical team)

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4.15 *Crataegus* extract

4.15a. A trial to investigate the influence of the herbal drug ***Crataegus* Special Extract WS 1442** (hawthorn leaves with flowers) on mortality of patients suffering from heart failure should report in 2003[i].

i. Holubarsch CJF, Colucci WS, Meinertz T, Gaus W, Tendera M. Survival and prognosis: Investigation of Crataegus Extract WS1442 in congestive heart failure (SPICE) – rationale, study design and study protocol. *European Journal of Heart Failure* 2000; **2**: 431-437

(Type II evidence – ongoing randomised, double-blind, controlled trial of up to 2300 patients with NYHA class II-III heart failure and left ventricular function ≤ 35% randomised to Special Extract WS1442 standardised to 84.3 mg of oligomeric procyanidines or matched placebo per day in addition to standard therapy)

4.16 General expert advice on choice of drug therapy

4.16a. The recently published NICE guidelines include an **algorithm for pharmacological treatment**. Priorities for implementation from the Guidelines are summarised at the beginning of this chapter[i].

i. Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care. London: National Institute for Clinical Excellence, July 2003
http://www.nice.org.uk/pdf/Full_HF_Guideline.pdf
[full guideline]

http://www.nice.org.uk/pdf/CG5NICEguideline.pdf
[NICE guideline]

[accessed 22.12.03]

(Evidence based guideline – systematic literature search to 2002 for specific study types based on clinical questions set out by the technical team)

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4.16b. **Adherence with medication** may reduce mortality and morbidity in patients with or at risk for coronary artery disease or congestive heart failure. Among 12 studies that compared hospitalisation rates and mortality between adherers and nonadherers, seven showed a significant relationship between medication adherence and outcomes. Three studies showed that adherence to placebo was associated with improved outcomes, suggesting that adherent behaviour may be a marker of better prognosis or confers a protective effect on patients with coronary heart disease[i].

In heart failure patients 50% of hospital admissions are related to poor medical and dietary compliance; medication compliance ranges between 20%-58% and dietary compliance ranges between 22%-51.4%[ii]. Advice, based on research findings, to enhance compliance is[ii]:

- promote self-management
- establish patient contracts with behavioural expectations
- reduce barriers by resolving the difficulties the patient may have that are interfering with compliance
- mobilise professional and social support
- elicit patients' concerns related to heart failure and treatment plan
- identify ways to modify the treatment plan that will increase the likelihood of compliance.

i. McDermott MM, Schmitt B, Wallner E. Impact of medication nonadherence on coronary heart disease outcomes. A critical review. *Archives of Internal Medicine* 1997; **157**: 1921-1929

(Type IV evidence – systematic review of medication adherence in 20 studies with positive outcomes for the trial drug (randomised controlled trials, cohort and case-control studies)

Reviewed in: Review: Medication adherence may reduce mortality and morbidity. *ACP Journal Club* 1998; **128**: 53)

ii. Evangelista LS, Dracup K. A closer look at compliance research in heart failure patients in the last decade. *Progress in Cardiovascular Nursing* 2000; **15(3)**: 97-103

(Type V evidence – review of published studies)

4.16c. A review is available of economic and **cost-effectiveness** studies in heart failure research relating to digoxin, ACE inhibitors, beta blockers, disease management and transplantation[i].

i. Weintraub WS, Cole J, Tooley JF. Cost and cost-effectiveness studies in heart failure research. *American Heart Journal* 2002; **143**: 565-576

(Type V evidence – expert opinion and a succinct summary of 10 economic studies)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence.* Cardiff: National Assembly for Wales, July 2001

A variety of non pharmacological therapies such as exercise training, surgical revascularisation, biventricular pacing and cardiac transplantation are also of proven value in selected cases. [paragraph 7.7]

- *What is the evidence for non-pharmacological treatments?*
- *What is the appropriate level of exercise?*
- *For how long should an exercise programme continue?*
- *Where should a programme of exercise for heart failure be undertaken and how should such a programme be monitored for adverse effects?*

Tertiary heart failure units are important in the development and assessment of new therapeutic strategies for those with severe chronic heart failure both pharmacological and non pharmacological (e.g. left ventricular pacing, left ventricular assist devices, myocardial reduction surgery), and in the decision making process regarding revascularisation using techniques such as Radionuclide Imaging or Positron Emission Tomography and Stress Echocardiology. [paragraph 7.9]

Latest evidence for surgical approaches?

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4.17 Non pharmacological therapies

Exercise training

4.17a. **Short-term physical exercise training** in selected subgroups of patients with chronic heart failure has physiological benefits and positive effects on quality of life[i].

Caveat: The review highlighted the problem of clinical trials that include participants who are not representative of the general population of heart failure patients seen in primary care.

Further research to examine the long-term physical benefits of exercise training in terms of morbidity and mortality is required.

i. Lloyd-Williams F, Mair FS, Leitner M. Exercise training and heart failure: a systematic review of current evidence. *British Journal of General Practice* 2002; **52(474)**: 47-55

(Type I evidence – narrative systematic review, literature search to December 2000, of papers published in English; 14 randomised controlled trials, 8 cross-over studies, two non-randomised trials and seven pre-test, post-test studies)

4.17b. A Cochrane review is underway to examine the effectiveness of **exercise based rehabilitation programmes** for patients with heart failure[i].

i. Rees K, Taylor RS, Ebrahim S. Exercise based rehabilitation for heart failure (Protocol) In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software

(Type I evidence – ongoing systematic review and meta-analysis of randomised trials)

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4.17c. A series of expert recommendations for **exercise training** in chronic heart failure patients are available[i].

i. Working Group on Cardiac Rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology. Recommendations for exercise training in chronic heart failure patients. *European Heart Journal* 2001; **22(2)**: 125-135
(Type V evidence – well referenced expert review)

4.17d. No single **instrument** has emerged as the leader in evaluating health related quality-of-life (HR-QOL) outcomes in patients with congestive heart failure (CHF). Results of recently published clinical trials indicate pharmacological and non-pharmacological interventions can have a positive impact on HR-QOL. The primary domain affected by treatment appears to be the performance of daily activities, which may or may not be accompanied by improvements in well-being. Thus, *functional status should be considered a primary HR-QOL target in clinical prevention trials, with well-being a secondary outcome. Preference-based or utility assessment, ethnic-group differences in treatment effectiveness, caregiver burden and cost effectiveness are understudied outcomes in CHF research*[i].

i. Leidy NK, Rentz AM, Zyczynski TM. Evaluating health-related quality-of-life outcomes in patients with congestive heart failure. A review of recent randomised controlled trials. *Pharmacoeconomics* 1999; **15(1)**: 19-46
(Type V evidence – expert discussion based on a systematic review, literature search of Medline and reference list follow-up only to October 1998, of 41 randomised controlled trials of pharmacological and other treatments for heart failure. All examined HR-QOL as a specific outcome)

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Surgical revascularisation

4.17e. **Coronary artery bypass** grafting improves survival and functional outcome (improvement in ejection fraction) in males with moderate to severe heart failure and concomitant limiting angina with a likely mortality reduction of between 30% and 50%. There is insufficient evidence of benefit for women, for men without angina, or of benefit from angioplasty[i].
Caveat: Conclusions based on the three highest quality primary studies, one showing no difference and one compromised by unadjusted baseline differences. The mortality reduction may differ from the 30% to 50% reported.

There is a strong association between **myocardial viability on non-invasive testing** and improved survival after revascularisation in patients with chronic coronary artery disease and left ventricular dysfunction. In patients with viability, revascularisation was associated with a 79.6% reduced in annual mortality (16% vs 3.2%; p<0.0001) compared with medical treatment. Patients without viability had intermediate mortality, tending towards higher rates with revascularisation versus medical therapy (7.7% vs 6.2%; not significant)[ii].

i. Baker DW, Jones RJ, Hodges J, Massie B M, Konstam MA, Rose EA. Management of heart failure III: the role of revascularisation in the treatment of patients with moderate or severe left ventricular systolic dysfunction. *Journal of the American Medical Association* 1994;**272**:1528-34.

(Type IV evidence - narrative review of 2691 patients (80% male) with moderate to severe left ventricular dysfunction in eight cohort studies of CABG vs. medical treatment.)

ii. Allman KC, Shaw LJ, Hachamovitch R, Udelson JE. Myocardial viability testing and impact of revascularization on prognosis in patients with coronary artery disease and left ventricular dysfunction: a meta-analysis. *Journal of the American College of Cardiology* 2002; **39**: 1151-1158

(Type IV evidence – systematic review, literature search of Medline only to August 1999, of 24 viability studies reporting patient survival using thallium perfusion imaging, F-18 fluorodeoxyglucose metabolic imaging or dobutamine echocardiography. 3,088 patients (2,228 men) with ejection fraction 32±8%, followed for 25±10 months)

4.17f. A trial in underway to determine whether **revascularisation** should be considered only in cases of unresponsiveness to medical therapy[i].

i. Heart failure revascularisation Trial (HEART UK). National Research Register ID: N0084105624. End date: 31 December 2010. n=650
Main centre: Castle Hill Hospital, Nr Hull.

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Implantable cardioverter defibrillators and cardiac resynchronisation (by biventricular pacing)

4.17g. **Implantable cardioverter defibrillators** are likely to be beneficial for people with heart failure and near fatal arrhythmias and as prophylactic use in people at high risk of arrhythmia[i,ii].

The use of implantable cardioverter defibrillators (ICDs) should be routinely considered for patients who present in the absence of a treatable cause with[i]:

1. Cardiac arrest due to either ventricular tachycardia (VT) or ventricular fibrillation (VF);
2. Spontaneous sustained VT causing syncope of significant haemodynamic compromise;
3. Sustained VT without syncopy/cardiac arrest, and who have an associated reduction in ejection fraction <35% but are no worse than Class III of the NYHA functional classification for heart failure.

ICDs should also be routinely considered for patients with[i]:

4. A history of previous myocardial infarction and non-sustained VT on Holder (24 hour ECG) monitoring plus inducible VT on electrophysiological testing plus left ventricular ejection fraction <35% but are no worse than Class III of the NYHA functional classification for heart failure.
5. A familial cardiac condition with a high risk of sudden death, including long QT syndrome, hypertrophic cardiomyopathy, Brugada syndrome, arrhythmogenic right ventricular dysplasia (ARVD) and following repair of Tetralogy of Fallot.

ICDs should **not** be routinely considered for[i]:

1. Those with spontaneous sustained VT associated with minimal symptoms and good cardiac function (EF>35%);
2. Those who present with a syncope of unknown cause (with no previous history of MI) and who have inducible VT on electrophysiological testing (EPS) in the presence of normal cardiac function (EF>35%).

The evidence for patients with syncope of unknown origin, with haemodynamically significant sustained VT or VF induced at EPS and in the presence of impaired cardiac function (EF<35%) is insufficient to recommend the use of ICDs.

i. National Institute for Clinical Excellence. *Guidance on the Use of Implantable Cardioverter Defibrillators for Arrhythmias*. Technology Appraisal Guidance No.11. London: NICE, September 2000
http://www.nice.org.uk/Docref.asp?d=10239
[accessed 22.12.03]
(Evidence-based guidance from an assessment report prepared by the Wessex Institute for Health Research and Development, submissions from manufacturers, professionals, specialists, patients & carers)

ii. McKelvie R. Heart Failure. [Search date October 2003] In: *Clinical Evidence* January 2003
(Type V evidence – expert opinion based on a systematic review of the literature)

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4.17h. Compared to treatment with **amiodarone**, for survivors of ventricular fibrillation or sustained ventricular tachycardia, there is a 28% reduction in the relative risk of death with the **implantable cardioverter defibrillator** (hazard ratio=0.72, 95% CI 0.60-0.87) that is due almost entirely to a 50% reduction in arrhythmic death[i].

i. Connolly SJ, Hallstrom AP, Cappato R *et al*; on behalf of the investigators of the AVID, CASH and CIDS studies. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. *European Heart Journal* 2000; **21(24)**: 2071-2078

(Type II evidence – pre-planned meta-analysis of amiodarone therapy versus implantable cardioverter defibrillator from three randomised controlled trials, 1,866 patients in all. The mean follow-up from the pooled data was 2.33 ± 1.89 years. An intention-to-treat analysis was used. Life-expectancy was the only outcome examined)

4.17i. **Cardiac resynchronisation** reduces mortality from progressive heart failure in patients with symptomatic left ventricular dysfunction by 51% relative to controls (odds ratio=0.49, 95% CI 0.25-0.93). Cardiac resynchronisation also reduces heart failure hospitalisation by 29% (OR=0.71, 0.53-0.96) and shows a trend towards reducing all-cause mortality (OR=0.77, 0.51-1.18)[i].

i. Bradley DJ, Bradley EA, Baughman KL *et al*. Cardiac resynchronization and death from progressive heart failure. A meta-analysis of randomized controlled trials. *Journal of the American Medical Association* 2003; **289(6)**: 730-740

(Type I evidence – systematic review and meta-analysis, literature search to May/June 2002, of four randomised controlled trials and 1,634 patients)

4.17j. **Cardiac resynchronisation therapy** (CRT) through biventricular pacing in patients with **implantable cardioverter defibrillators (ICDs)** improved quality of life, functional status, and exercise capacity in patients with moderate to severe HF, a wide QRS interval, and life-threatening arrhythmias. These improvements occurred in the context of underlying appropriate medical management without proarrhythmia or compromised ICD function[i].

At 6 months, patients assigned to CRT had a greater improvement in median (95% CI) quality of life score (-17.5 [-21 to –14] vs –11.0 [-16 to –7], p=0.02) and functional class (-1 [-1 to –1] vs 0 [-1 to 0], p=0.007) than controls but were no different in the change in distance walked in 6 minutes (55 m [44-79] vs 53 m [43-75], p =0.36)[i].
Caveat: Baseline characteristics were similar other than a higher percentage of patients with ischaemic heart disease in the control group.

i. Young JB. Abraham WT. Smith AL *et al*. Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial Investigators. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD Trial. *Journal of the American Medical Association* 2003; **289(20)**: 2685-94

(Type II evidence - randomised controlled trial of 369 patients with left ventricular ejection fraction of 35% or less, QRS duration of 130 ms, at high risk of life-threatening ventricular arrhythmias, and in NYHA class III (n = 328) or IV (n = 41) despite optimised medical treatment. Of 369 randomised patients who received devices with combined CRT and ICD capabilities, 182 were controls (ICD activated, CRT off) and 187 were in the CRT group (ICD activated, CRT on))

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4.17k. In an unpublished estimate, using the results of all clinical trials, the cost-effectiveness of the **implantable cardioverter defibrillator (ICD)** was $31,500 per life year added. The ideal candidate is at high risk of lethal ventricular arrhythmia, but otherwise not at increased risk of death. In this situation, the ICD would add several years of life and easily justify its high cost. Such patients are rare however and the more typical ICD candidates are at considerable risk of death by mechanisms other than arrhythmias. Even so, a low ejection fraction identifies patients in whom ICD placement might be more cost-effective. *If newer tests can be developed to identify patients who would benefit substantially from ICD therapy, the cost-effectiveness will be greatly improved*[i].

In people at high risk from ventricular tachyarrhythmia estimated benefits are 0.23-0.8 additional years of life with implantable cardioverter defibrillator therapy compared with anti-arrhythmic drug therapy. At 1999/2000 prices, cost per quality-adjusted life year is estimated at £21,300 to £108,800[ii].

i. Hlatky MA, Bigger T. Cost-effectiveness of the implantable cardioverter defibrillator? *Lancet* 2001; **357**: 1817-1818

(Type V evidence – expert opinion based on review of US cost-effectiveness studies)

ii. Parkes J, Bryant J, Milne R. Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review. *Health Technology Assessment* 2000; **4(26)**: 1-81
http://www.ncchta.org/fullmono/mon426.pdf
[accessed 22.12.03]

(Type I evidence – systematic review, literature search to 1999, of seven randomised controlled trials, eight cost-effectiveness analyses (mostly older studies and based on non-UK data), and two good quality literature reviews)

4.17l. A study in the United States suggested that, based on discharge diagnoses, many patients who could benefit from **implantable cardioverter defibrillators** (ICD) are not receiving this therapy. In the base case scenario, 1,226 patients per million population were identified as potential ICD candidates. Sensitivity analyses reduced this value to a range from 736 to 1,140 ICD candidates per million population, contrasting with a usage rate of 416 per million population in the US and lower rates in other countries[i].

i. Ruskin JN, Camm AJ, Zipes DP, Hallstrom AP, McGrory-Usset ME. Implantable cardioverter defibrillator utilization based on discharge diagnoses from Medicare and managed care patients. *Journal of Cardiovascular Electrophysiology* 2002; **13**: 38-43

(Type IV evidence – historical US claims based study of Managed Care and Medicare databases (claims related to 4.6 million covered US lives during the period from July 1997 to June 1998)

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4.17m. Whilst evidence is of a variable nature in terms of quality and effectiveness, there is a trend towards greater effectiveness in **dual rather than single chamber pacing** (in terms of mortality, pacemaker symptoms and exercise capacity). The results from four economic analyses were inconclusive. *Reports from five large randomised controlled trials are awaited*[i].

i. Dretzke J, Lip G, Raftery J, Toff W, Fry-Smith A, Taylor R. Dual versus single chamber pacemaker therapy for atrioventricular block and sick sinus syndrome. Report No. 32. University of Birmingham: West Midlands Health Technology Assessment Group, 2002 **http://www.publichealth.bham.ac.uk/wmhtac/pdf/pacemaker.pdf** [accessed 22.12.03]
(Type I evidence – systematic review, literature search to June/July 2001 of 30 randomised controlled trials and four economic evaluations)

Left ventricular assist devices

4.17n. **Left ventricular assist devices** are potentially attractive in terms of the possible benefits to patients with end-stage heart failure, but the available evidence is of very poor quality and the devices are expensive. Left ventricular assist devices are evolving rapidly and experience with their use is increasing in the UK. From one analysis, if 100 patients are treated with LVADs as a bridge to transplant, they gain approximately 218 QALYs more than an equivalent group of 100 patients not treated, over 20 years. *There is a need for high quality evaluative research in this area, with duration and quality of life being primary outcomes, and talking into account current UK practice and costs*[i].

i. Christopher F, Clegg A. Left ventricular assist devices (LVADs) for end stage heart failure. Development and Evaluation Committee Report No. 103. Southampton: Wessex Institute for Health Research and Development, 1999. **http://www.hta.nhsweb.nhs.uk/rapidhta/publications.htm** [accessed 22.12.03]
(Type IV evidence – systematic review of ten cohort studies looking at LVADs as a bridge to transplant and one cohort study looking at LVADs as a bridge to myocardial recovery (literature searching completed in May 1999). A cost utility analysis was based one better quality cohort study and cost information from NHS Trusts and device manufacturers.)

4.18 Cardiac transplantation

4.18a. **Cardiac transplantation** remains the gold standard of surgical therapies for advanced and end-stage heart failure[i,ii] with the 10-year survival rate after transplantation approaching 50%[i] although there continues to be a shortage of donor organs[i].

i. Vitali E, Colombo T, Fratto P, Russo C, Bruschi G, Frigerio M. Surgical therapy in advanced heart failure. *American Journal of Cardiology* 2003; **91(suppl)**: 88F-94F
(Type V evidence – expert review)

ii. Zeltsman D, Acker MA. Surgical management of heart failure: An overview. *Annual Review of Medicine* 2002; **53**: 383-391
(Type V evidence – expert review)

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4.18b. There is some evidence that mortality is significantly lower at **high volume versus low volume** hospitals for some interventions. In individual, high quality studies, the odds of mortality (low volume vs high volume) for **cardiac transplantation** (n=7,893) were 2.06 (1.69-2.50)[i]
Caveat: It is unclear whether the quality criteria used to judge the best study for each intervention were from a validated scheme. Definitions of high volume varied between studies. Unpublished studies were not sought and publication bias cannot be excluded.

i. Dudley RA, Johansen KL, Brand R, Rennie DJ, Milstein A. Selective referral to high-volume hospitals. Estimating potentially avoidable deaths. *Journal of the American Medical Association* 2000; **283(9)**: 1159-1166
(Type V evidence – results from selected 'best' studies based on a systematic review of the literature looking at the effects of referral to low volume versus high volume hospitals on various interventions)

4.18c. The evidence base for **left ventricular reconstruction**, including the Batista and Dor procedures, along with **mitral valve repair** and **cardiomyoplasty** is currently very weak[i,ii].

i. Vitali E, Colombo T, Fratto P, Russo C, Bruschi G, Frigerio M. Surgical therapy in advanced heart failure. *American Journal of Cardiology* 2003; **91(suppl)**: 88F-94F
(Type V evidence – expert review)
ii. Zeltsman D, Acker MA. Surgical management of heart failure: An overview. *Annual Review of Medicine* 2002; **53**: 383-391
(Type V evidence – expert review)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence*. Cardiff: National Assembly for Wales, July 2001

Heart failure nurses have a major proven role to play.

A network of such… nurses established in Greater Glasgow… is proving highly successful. [paragraph 7.7]

Supporting evidence for the role of heart failure nurses?

Is there evidence that "patient education" in patients with heart failure to promote exercise works?

What was the evidence re exercise and nurses and readmission/symptom rates in the Glasgow study?

Health Authorities will plan in their Health Improvement Programmes to provide an equitable, comprehensive and cost effective heart failure service by 2005. This will include the establishment in all DGHs of appropriately staffed specialist heart failure clinics and the appointment of specialist nurses to support these clinics and work with the LHGs and the patients. [key action 24]

What is the best set up for heart failure clinics and specialist nurses?

It has also been shown that patients with heart failure benefit from the care of clinical pharmacists. [paragraph 7.7]

What is the evidence for direct involvement of clinical pharmacists in care?

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4.19 Heart failure clinics and specialist staff

Specialist heart failure nurses

4.19a. Small trials suggest that follow up after hospitalisation by **specially trained nurses** can improve survival and self-care behaviour in patients with heart failure as well as reduce the number of events, readmissions and days in hospital[i,ii,iii].

In a trial of a **nurse-led heart failure clinic** there were fewer patients with events (death or admission) after 12 months in the intervention group compared to the control group (29 vs 40, p=0.03) and fewer deaths after 12 months (7 vs 20, p=0.005). The intervention group had fewer admissions (33 vs 56, p=0.047) and days in hospital (350 vs 592, p=0.045) during the first 3 months. After 12 months the intervention was associated with a 55% decrease in admissions/patient/month (0.18 vs 0.40, p=0.06) and fewer days in hospital/patient/month (1.4 vs 3.9, p=0.02). The intervention group had significantly higher self-care scores at 3 and 12 months compared to the control group (p=0.02 and p=0.01)[i].
Caveat: Of 2000 patients screened only 106 were included in the trial although they had similar characteristics to the general heart failure population. There were significantly more patients with diabetes in the control than the intervention group. After adjustment for this the intervention group still had a significantly lower risk of death.

A **nurse-led transitional care intervention** resulted in significant improvements in health related quality of life (p=0.002 at six weeks) and less use of the emergency room (p=0.03 at 12 weeks)[ii].

In another trial of a **specialist nurse intervention** 31 patients (37%) in the intervention group died or were readmitted with heart failure compared with 45 (53%) in the usual care group (hazard ratio=0.61, 95% CI 0.33-0.96). Compared with usual care, patients in the intervention group had fewer readmissions for any reason (86 v 114, P=0.018), fewer admissions for heart failure (19 v 45, P<0.001) and spent fewer days in hospital for heart failure (mean 3.43 v 7.46 days, P=0.0051)[iii].
Caveat: This trial was carried out before good evidence for beta-blockers was available. ACE-inhibitor use was higher in the intervention than in the control group and calcium channel blocker use was higher in the usual care group.

i. Stromberg A, Martensson J, Fridlund B, Levin LA, Karlsson JE, Dahlstrom U. Nurse-led heart failure clinics improve survival and self-care behaviour in patients with heart failure: results from a prospective, randomised trial. *European Heart Journal* 2003; **24(11)**: 1014-1023

(Type II evidence – randomised controlled trial of 106 patients assigned to either follow-up at a nurse-led heart failure clinic or to usual care. The nurse-led heart failure clinic was staffed by specially educated and experienced cardiac nurses, delegated the responsibility for making protocol-led changes in medications. The first follow-up visit was 2-3 weeks after discharge. During the visit the nurse evaluated the heart failure status and the treatment, gave education about heart failure and social support to the patient and his family)

ii. Harrison MB, Browne GB, Roberts J *et al*. Quality of life of individuals with heart failure: a randomised trial of the effectiveness of two models of hospital-to-home transition. *Medical Care* 2002; **40**: 271-282

(Type II evidence – randomised controlled trial of 192 patients (mean age 76 years, 55% men) with 12 weeks follow-up after hospital discharge)

Reviewed in: Williams N. Nurse led transitional care improved health related quality of life and reduced emergency department use for heart failure.

Evidence-Based Nursing 2003; **6(1)**: 21

iii. Blue L, Lang E, McMurray JJ *et al*. Randomised controlled trial of specialist nurse intervention in heart failure. British Medical Journal 2001; 323(7315): 715-718 **http://bmj.bmjjournals.com/cgi/content/full/323/7315/715** [accessed 22.12.03]

(Type II evidence – randomised controlled trial of 165 patients admitted with heart failure. The intervention started before discharge and continued thereafter with home visits for up to one year)

Reviewed in:
ACP Journal Club 2002;**136(3)**: 87
Evidence Based Nursing 2002; **5(2)**: 55

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4.19b. For patients discharged after hospitalisation for congestive heart failure, a **nurse-run management programme** reduced the time to readmission but had no effect on the one-year mortality rate or quality of life[i].
Caveat: Since consent was obtained after randomisation, the control group was much larger than the intervention group (110 vs. 80) and those who agreed to the intervention may have been more motivated; This is a potential source of confounding. The trial was not blinded.

i. Cline CMJ, Israelsson BY, Willenheimer RB, Broms K, Erhardt LR. Cost effective management programme for heart failure reduces hospitalisation. *Heart* 1998; **80**: 442-446

(Type II evidence – randomised unblinded controlled trial with one year follow-up (in Sweden) of 206 patients. 96 were allocated to the intervention group and 80 accepted treatment. These patients and their families received specific interventions to encouragement self-management and adherence to medication, plus increased visits to outpatient visits at nurse and physician run clinics. 110 were allocated to routine clinical care)

Reviewed in: Anonymous. A nurse-run program for congestive heart failure reduced time to hospital readmission. *ACP Journal Club* 1999; **130**)

4.19c. **Home-based intervention** after hospitalisation for congestive heart failure with nurse involvement reduced out-of-hospital deaths and unplanned readmissions[i,ii].

In a cohort of **high risk patients** with congestive heart failure, beneficial effects of a **postdischarge home-based intervention** were sustained for at least 18 months, with a significant reduction in unplanned readmissions (p=0.02), total hospital stay (p=0.004) and hospital based costs (p=0.02)[i].
Caveat: Post-discharge care procedures may be quite different in the UK.

i. Stewart S, Vandentroek AJ, Pearson S, Horowitz JD. Prolonged beneficial effects of a home-based intervention on unplanned readmissions and mortality among patients with congestive heart failure. *Archives of Internal Medicine* 1999; **159**: 257-261

(Type II evidence – sub-group analysis of a randomised controlled trial (n=762 patients) with 18 months follow-up (in Australia). 97 patients (mean age 75 years, 52% women) were allocated to a home-based intervention (a single home visit by a nurse and a pharmacist to assess the need for further intervention and to ensure optimal compliance) or usual care (a visit to the patient's family physician within two-weeks of discharge))

Reviewed in: Anonymous. A home based intervention reduced out-of-hospital deaths and hospitalisations in CHF. *ACP Journal Club* 1999; **131**: 6)

ii. Stewart S, Marley JE, Horowitz JD. Effects of a multidisciplinary, home-based intervention on unplanned readmissions and survival among patients with chronic congestive heart failure: a randomised controlled study. *Lancet* 1999; **354(9184)**: 1077-1083

(Type II evidence – randomised controlled trial with six month follow-up. 200 patients were allocated to usual care or usual care plus a home-based intervention which included a structured home visit by a cardiac nurse 7 to 14 days after discharge. 88 patients accepted this visit on the day. An intention-to-treat analysis was used)

Reviewed in: Anonymous. A multidisciplinary, home-based intervention reduced deaths and readmissions in patients with chronic congestive heart failure. *ACP Journal Club* 2000; **132(3)**: 88)

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4.19d. The reduction in hospitalisations, costs and other resource use achieved using standardised **telephonic case management** in the early months after a heart failure admission is greater than that usually achieved with pharmaceutical therapy and comparable with other disease management approaches. The heart failure hospitalisation rate was 47.8% lower in the intervention group at six months (p=0.01)[i].
Caveat: An intention to treat analysis was not used.

i. Riegel B, Carlson B, Kopp Z, LePetri B, Glaser D, Unger A. Effect of a standardized nurse case-management telephone intervention on resource use in patients with chronic heart failure. *Archives of Internal Medicine* 2002; **162**: 705-712
(Type II evidence – randomized controlled trial of patients randomized to 6 months of intervention (n=130) or usual care (n=228) based on the group to which their physician was randomized)

4.19e. The **nutritional status** of heart failure patients can be improved by simple **nursing** interventions[i].
Caveat: No quality assessment of studies was carried out.
Future research should focus on controlled experimental studies to compare the outcomes of patients taking part in a fully enriched nutrition intervention and patients who are eating their normal diet[i].

i. Jacobsson A, Pihl-Lindgren E, Fridlund B. Malnutrition in patients suffering from chronic heart failure: the nurse's care. *European Journal of Heart Failure* 2001; 3: 449-456
(Type IV evidence – narrative systematic review, literature search to 1998, of 13 articles)

Appropriate staffing for heart failure care (& clinics)

4.19f. Patients with coronary heart disease or heart failure in the United States who are treated by **cardiologists** appear more likely to receive evidence-based care and probably have better outcomes than those treated by generalists. *Investigation of collaborative models of care and innovative efforts to improve the use of proven therapies by physicians are needed*[i].
Caveat: The authors noted that included studies were heterogeneous and all had methodological limitations.

i. Go AS, Rao RK, Dauterman KW, Massie BM. A systematic review of the effects of physician specialty on the treatment of coronary disease and heart failure in the United States. *American Journal of Medicine* 2000; **108**: 216-226
(Type IV evidence – systematic review, Medline only searched to 1997 plus reference list follow-up for studies relevant to the US healthcare system. 24 observational studies were selected for analysis. 6 studies included data on clinical outcomes)

4.19g. In one Italian study, **cardiologists** followed published guidelines for congestive heart failure more strictly than internists, but treated a smaller number of patients who were younger, have more severe congestive heart failure and fewer co-morbidities than those managed by internists. Patients treated by cardiologists had a mortality not significantly different from that of patients treated by internists (10% and 6% respectively, p=0.067), although congestive heart failure was more severe on admission in patients treated by cardiologists[i].

i. Belloti P, Badano LP, Acquarone N *et al*. for the OSCUR Investigators. Specialty-related differences in the epidemiology, clinical profile, management and outcome of patients hospitalised for heart failure. The OSCUR study. *European Heart Journal* 2001; **22**: 596-604
(Type IV evidence – prospective record of epidemiological and clinical data from patients with congestive heart failure consecutively admitted to 11 departments of cardiology and 12 departments of internal medicine in Northern Italy. The overall study population included 749 patients; 22% treated by cardiologists and 78% by internists)

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4.19h. For patients hospitalised with heart failure, **cardiologists' care** was associated with greater costs and resource use and no difference in survival at 30 days of follow up. Whether the trend towards better survival at longer follow-up represents differences in care of unadjusted illness severity is uncertain. The median unadjusted 1994 cost was $11,800 for patients of cardiologists and $5,000 for patients of generalists (p=0.001). The median cost increment attributable to cardiologist care after adjustment was $2,100 (42.9%, 95% CI 27.8%-59.8%)[i].

Caveat: US costs will vary considerably from those in the UK

i. Auerbach AD, Harmel MB, Davis RB *et al*; for the SUPPORT Investigators. Resource use and survival of patients hospitalized with congestive heart failure: differences in care by specialty of attending physician. *Annals of Internal Medicine* 2000; **132(3)**: 191-200

(Type IV evidence – US cost-effectiveness analysis based on a prospective cohort study of 1,298 patients hospitalised with an exacerbation of chronic heart failure in five US teaching hospitals between 1989 and 1994)

Multidisciplinary care programmes

4.19i. **Heart failure disease management programs** (eg critical or care pathways) appear to be a cost-effective approach to reducing morbidity and enhancing quality of life in selected patients[i,ii]. Comprehensive, multidisciplinary management programmes can improve functional status and reduce the risk of hospital admission, and they may lower medical costs. In one review, five studies reported improved functional status, aerobic capacity, or patient satisfaction. Six of the studies reported a 50% to 85% reduction in the risk of hospital admission. Three studies reported economic analyses, but the aggregate economic data are weak, with suggestive but not compelling evidence of financial benefit[i].

In all studies in which a cost analysis was performed, heart failure disease management programs were found to be cost-effective[ii]. *Additional study is needed involving larger and more diverse populations to define the optimal approach to heart failure disease management*[ii].

i. Philbin EF. Comprehensive multidisciplinary programs for the management of patients with congestive heart failure. *Journal of General Internal Medicine* 1999; **14(2)**: 130-135

(Type I evidence – narrative systematic review of seven trials of programmes that encouraged patient participation for at least three months (including two randomised controlled trials) and 3,927 patients in all. Medline only searched (from 1966 to 1998) for English-language studies.)

ii. Rich MW. Heart failure disease management: A critical review. *Journal of Cardiac Failure* 1999; **5(1)**: 64-75.

(Type I evidence – narrative systematic review of 16 studies describing multidisciplinary heart failure disease management programs published in the English language literature (Medline only searched from 1983 to 1998 with reference list follow up). 6 randomised clinical trials, 8 pre-post and 2 retrospective chart review studies were included)

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4.19j. Many State Medicaid programmes in the United States have adopted **disease management programmes** for heart failure. In a narrative systematic review, of 17 studies of programmes that used re-admission rates as an outcome, rates dropped in 13, remained the same in one and increased in one. A superior quality of life was measured in 7 out of 10 studies. Of 16 reports that discussed cost-savings, 11 described savings and none reported losses associated with these programmes[i]. **Caveat:** No evidence of quality appraisal of included studies and unpublished studies were not included. Publication bias may be a problem.

i. Gillespie JL. The value of disease management – Part 1: Balancing cost and quality in the treatment of congestive heart failure. A review of disease management services for the treatment of congestive heart failure. *Disease Management* 2001; **4(2)**: 41-51

(Type I evidence – systematic review, literature search to February 2000, of 36 educational or disease management programmes, including 13 randomised controlled trials)

4.19k. An **integrated management programme** for patients with chronic heart failure improved quality of life and reduced total hospital admissions and total bed days. There was no significant difference between the intervention and control groups for the combined end-point of death or hospital readmission. The physical dimension of quality of life showed a greater improvement in the intervention group (-11.1 versus –5.8 respectively, 2P=0.015). The main effect of the intervention was attributable to the prevention of multiple admissions (56 intervention versus 95 control group, 2P=0.015) and associated reduction in bed days[i].

i. Doughty RN, Wright SP, Pearl A *et al*. Randomized, controlled trial of integrated heart failure management. The Auckland Heart Failure Management Study. *European Heart Journal* 2002; **23**: 139-146

(Type II evidence – 12 month cluster randomised-controlled trial of integrated primary/secondary care compared with usual care for 197 patients with heart failure. The intervention involved clinical review at a hospital-based heart failure clinic early after discharge, individual and group education sessions, a personal diary to record medication and body weight, information booklets and regular clinical follow-up alternating between the general practitioner and the heart failure clinic)

4.19l. The available evidence suggests that congestive heart failure is associated with a pattern of generalised **cognitive impairment** that includes memory and attention deficits. *There is, however, a paucity of systematic information about this association*[i]

i. Almeida OP, Flicker L. The mind of a failing heart: a systematic review of the association between congestive heart failure and cognitive functioning. *Internal Medicine Journal* 2001; **31**: 290-295

(Type IV evidence – systematic review, Medline only searched to June 2000 & reference list follow-up, of five heterogeneous case-control studies)

4.19m. A multi-centre study is underway to determine the value of **home monitoring** of patients with heart failure due to left ventricular systolic dysfunction at high risk of readmission[i].

i. Trans-European Network Home Monitoring Study. End date 31 July 2002. National Research Register ID: N0211068797
Lead centre: University of Hull

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4.19n. A Cochrane review is underway to assess the effectiveness of different **clinical service interventions**, which are not primarily education in focus, in preventing death and/or hospital readmission in patients who have previously been admitted to secondary care with a diagnosis of heart failure[i].

i. Taylor SJC, Underwood M, Parsons S, Falshaw M, Hood S. Clinical service organisation for heart failure. Protocol for a Cochrane Review. In: *The Cochrane Library*, Issue 1 2003. Oxford: Update Software

(Type I evidence - systematic review and meta-analysis of randomised clinical trials)

4.19o. From the available evidence, it appears that heart failure patients generally experience moderate levels of **depression**, but not greatly heightened **anxiety**. Level of social support and style of coping with the disease are, however, important prognostic factors. It is difficult to draw definitive conclusions due to the paucity of the literature[i].

i. MacMahon KMA, Lip GYH. Psychological factors in heart failure. A review of the literature. *Archives of Internal Medicine* 2002; **162**: 509-516

(Type IV evidence – systematic review, literature search to 2000, of 12 observational studies)

4.19p. **Ethanol** damage to the heart is evident if alcohol consumption exceeds 90-100 g/day. To prevent further complications from drinking and for long-term management of drinking, patients with alcohol abuse and heart failure should be treated in brief intervention and follow-up programmes. Prognosis is good even in patients with NYHA class IV heart failure caused by cardiomyopathy if complete abstinence is accomplished[i].

i. Spies CD, Sander M, Stangl K *et al*. Effects of alcohol on the heart. *Current Opinion in Critical Care* 2001; **7**: 337-343

(Type V evidence – expert review of the literature)

Pharmacists

4.19q. The application of **drug use evaluation** (DUE) criteria by **pharmacists** in hospital and community practice has the potential to improve ulitilisation and dosing of ACE-inhibitor therapy. Although clinical trials suggest that 80-90% of patients tolerate ACE-inhibitors, of those evaluated using developed DUE criteria in one small trial, only 68.6% were discharged on ACE-inhibitor therapy, and only 40% of this group reached target dose[i].

(See also Section 4.3)

i. Pearson GJ, Cooke C, Simmons WKT, Sketris I. Evaluation of the use of evidence-based angiotensin-converting enzyme inhibitor criteria for the treatment of congestive heart failure: opportunities for pharmacists to improve patient outcomes. *Journal of Clinical Pharmacy and Therapeutics* 2001; **26**: 351-361

(Type IV evidence – retrospective chart review of 138 patients discharged from a Canadian hospital during 1 March-31 July 1998 with a diagnosis of congestive heart failure using developed drug use evaluation (DUE) criteria)

The *statements*

4.19r. A small non-randomised US study suggested that optimisation of ACE inhibitor doses by a **clinical pharmacist** can improve rehospitalization rates and significantly lower cost of care in a heart failure management programme. At 180 days, rehospitalisation frequency and total charges were lower in Groups A (31% and $5,600) and B (35% and $3,800) than in Group C (63%, $p<0.004$, and $9,800, $p<0.04$)[i].
Caveats: This is a small nonrandomised study. A potential confounder is that physicians already providing or willing to accept evidence-based guidance may provide better all-round care for patients irrespective of the pharmacist's intervention.

The *evidence*

i. Luzier AB, Forrest A, Feuerstein SG, Schentag JJ, Izzo JL. Containment of heart failure hospitalisations and cost by angiotensin-converting enzyme inhibitor dosage optimisation. *American Journal of Cardiology* 2000; **86**: 519-523

(Type III evidence – prospective nonrandomised intervention study (n=110) over 180 days of patients admitted to hospital with heart failure. In Group A care (n=28) was optimal (according to current guidelines) at the beginning of the study; In Group B (n=51) the attending physician agreed to follow the clinical pharmacist's instructions; In Group C (n=31) the physician declined the intervention)

National Service Framework

National Assembly for Wales. *Tackling CHD in Wales: Implementing Through Evidence*. Cardiff: National Assembly for Wales, July 2001

Severe heart failure can be markedly improved by tailoring therapy on an individualised basis to optimise the pressure of blood within the heart chambers. [paragraph 7.8]

Best forms of tailored therapy?

The treatment of those with severe chronic heart failure is likely to advance considerably during the next few years. The recent success with heart assist devices is evidence of this. [paragraph 7.9]

Latest evidence and guidance re heart assist devices in severe heart failure?

By 2002/3 there will be agreement, with not more than two tertiary centres, to assess resistant/end stage heart failure within an agreed protocol. [key action 27]

What are the best assessment methods for resistant/end stage heart failure?

A strategy for palliative management in symptomatic end-stage heart failure will be developed. [key action 27]

What are the best palliative management protocols?

The *statements* | The *evidence*

4.20 Severe heart failure and palliative management

4.20a. In **severe heart failure** mortality is significantly reduced by **enalapril**. Averaged over the two-year duration of the trial (double-blind plus open label extension) the risk reduction was 30% (p=0.008, 95% CI 11%-46%). At ten-year follow-up, there were five survivors (all in the enalapril group) and one patient lost to follow-up. On average the beneficial effect of enalapril was maintained for several years and overall survival time was prolonged by 50% (from 521 to 781 days)[i].

i. Swedberg K, Kjekshus J, Snapinn S; for the CONSENSUS Investigators. Long-term survival in severe heart failure in patients treated with enalapril. Ten year follow-up of CONSENSUS I. *European Heart Journal* 1999; **20**: 136-139

(Type III evidence – long term results (over ten years) following a double-blind randomised controlled trial (average 183 days) plus two-year open label follow up of 253 patients with New York Heart Association Class IV heart failure with the ACE inhibitor enalapril. 135 survivors of the double-blind period were followed until death or for ten years)

4.20b. In patients with **severe heart failure, carvedilol** treatment results in a 35% decrease in the risk of death (95% CI 19%-48%, p=0.0014, adjusted for interim analyses). There was a 24% decrease in the combined risk of death or hospitalisation. Fewer patients in the carvedilol than in the placebo group withdrew because of adverse effects or for other reasons (p=0.02)[i].

In this group of patients, the relation of benefit to risk during initiation of treatment with carvedilol is similar to that seen during long-term therapy[ii].

i. Packer M, Coats AJS, Fowler MB *et al*; for the Carvedilol Prospective Randomized Cumulative Survival Study Group (COPERNICUS). Effect of carvedilol on survival in severe chronic heart failure. *New England Journal of Medicine* 2001; 344(22): 1651-1658

(Type II evidence – randomised, double-blind, controlled trial of 2,289 patients with symptoms of heart failure at rest or on minimal exertion, who were clinically euvolemic, and who had an ejection fraction of <25% randomised to a target dose of 25mg twice daily carvedilol (a beta-blocker) or placebo for a mean period of 10.4 months. During this period, standard therapy was continued. An intention-to-treat analysis was used)

ii. Krum H, Roecker EB, Mohacsi P *et al*; for the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effects of initiating carvedilol in patients with severe chronic heart failure. *Journal of the American Medical Association* 2003; **289(6)**: 712-718

(Type II evidence - analysis of results from the above trial during the first eight weeks of treatment)

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4.20c. **Beta-blocker therapy** conferred functional benefit in patients with **severe heart failure**. Bisoprolol was well tolerated without between group difference in premature withdrawals. The observed difference in mortality between groups did not reach statistical significance (Relative risk, RR=0.80, 95% CI 0.56-1.15). No significant difference was observed in sudden death rate or death related to documented ventricular tachycardia or fibrillation. Bisoprolol significantly improved functional status, reduced the number of patients requiring hospitalisation for cardiac decompensation (90 on placebo versus 61 on bisoprolol, p<0.01) and more patients improved by at least one NYHA functional class (48 on placebo versus 68 on bisoprolol, p=0.04) at the end of the follow-up period[i].

Some patients with severe heart failure derive more benefit from beta-blocker therapy than others. In the CIBIS trial, they are those patients with the lower left ventricular ejection fractions and those who have nonlethal cardiovascular events but in whom between beta-blocker therapy is not permanently discontinued. Compared with placebo, bisoprolol reduced mortality rates in patients with a left ventricular ejection fraction ≤ 20% (relative risk, RR=0.49, 95% CI 0.27-0.88, p=0.02). In patients whose baseline heart rate was in the upper tertile of distribution, permanent treatment withdrawals were less frequent in patients randomly assigned to bisoprolol than in patients randomly assigned to placebo (RR=0.50, 95% CI 0.28-0.88, p=0.02). Bisoprolol reduced the incidence of nonlethal cardiac events in patients in whom heart failure was present for at least 4 years (RR=0.44, 95% CI 0.27-0.71, p<0.01). Event history analysis revealed that among patients who died under treatment after having at least one nonlethal cardiovascular event, 20 patients were treated with placebo but only seven patients were treated with bisoprolol (RR=0.41, 95%CI, 0.17-0.98. p<0.05)[ii].

i. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation* 1994; **90**: 1765-1773

(Type II evidence – randomised controlled trial of 641 patients with chronic heart failure of various etiologies and a left ventricular ejection fraction of <40%. Patients were in New York Heart Association class III (95%) or IV (5%) at inclusion. 90% were receiving ACE-inhibitor therapy. Subjects were randomised to placebo or bisoprolol (initial dose 1.25 mg/d, increased 48 hours later to 2.5 mg/d and one month after to 5 mg/d). Mean follow-up was 1.9 years. An intention-to-treat analysis was used)

ii. Funck-Brentano C, Lancar R, Le Heuzey Y-Y, Lardoux H, Soubrié C, Lechat P. Predictors of medical events in patients enrolled in the Cardiac Insufficiency Bisoprolol Study (CIBIS): A study of the interactions between beta-blocker therapy and occurrence of critical events using analysis of competitive risks. *American Heart Journal* 2000; **139(2)**: 262-271

(Type II evidence – post-hoc analysis of baseline variables and occurrence of critical events during the CIBIS trial, see above)

4.20d. A subgroup analysis of the MERIT-HF study showed that patients with severe heart failure receive a similar mortality benefit and a similar reduction in hospitalisation for worsening heart failure with **metoprolol CR/XL** treatment as those patients included in the total study[i].

i. Goldstein S, Fagerberg B, Hjalmarson A *et al*; for the MERIT-HF Study Group. Metoprolol controlled release/extended release in patients with severe heart failure. Analysis of the experience with the MERIT-HF study. *Journal of the American College of Cardiology* 2001; **38**: 932-938

(Type II evidence – subgroup analysis of a trial for controlled/extended release metoprolol on 795 patients with NYHA functional class III/IV heart failure and left ventricular ejection fraction <0.25)

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4.20e. The calcium channel blocker **amlodipine** did not increase cardiovascular morbidity of mortality in patients with **severe heart failure**[i].

When mortality was evaluated, based on the **cause of heart failure**, there was a significant reduction in the composite end point of all-cause and cardiovascular mortality in **nonischemic** patients treated with amlodipine (hazard ratio, HR, for all-cause mortality=0.54, 95% CI 0.37-0.79). There were no significant differences in all-cause mortality or specific mode of death in heart failure patients who had ischemia (HR=1.02, 95% CI 0.81-1.29)[ii]. *Further trials that evaluate cause-specific mortality in heart failure should be done to determine the safety of amlodipine in this population*[i].

i. Packer M, O'Connor CM, Ghali JK *et al*; for the Prospective Randomized Amlodipine Survival Evaluation Study Group. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *New England Journal of* Medicine 1996; **335**: 1107-1114

(Type II evidence – randomised double-blind controlled trial of 1,153 patients with NYHA class IIIB or IV heart failure and ejection fractions of less than 30% to amlodipine or placebo for 6-33 months. The PRAISE trial. An intention to treat analysis was used)

ii. Gattis WA, O'Connor CM. Effect of amlodipine on mode of death in advanced heart failure. *Cardiology Review* 2001; **18(2)**: 13-19

(Type II/IV evidence – retrospective analysis of mortality, based on the cause of heart failure, in patients enrolled in the PRAISE randomised controlled trial. 370 patients died in the placebo group and 362 in the amlodipine group)

4.20f. **Spironolactone**, in addition to standard therapy, substantially reduces the risk of both morbidity and death among patients with **severe heart failure**. The relative risk of death in the spironolactone versus the placebo group was 0.70 (95% CI 0.60-0.82, p<0.001). This 30% reduction was attributed to a lower risk of both death from progressive heart failure and sudden death from cardiac causes. The frequency of hospitalisation for worsening heart failure was 35% lower in the spironolactone group than in the placebo group (relative risk of hospitalisation = 0.65, 95% CI 0.54-0.77; p<0.001). In addition, patients who received spironolactone had a significant improvement in New York Heart Association functional class (p<0.001)[i].

Gynecomastia or breast pain was reported in 10% of men who were treated versus 1% in the placebo group. The incidence of hyperkalemia was minimal in both groups of patients. *These patients were at higher risk than those evaluated in recent studies of beta-blockers and further research is needed to examine both the tolerability and the effectiveness of beta-blockers as well as the effects of the concomitant use of an aldosterone-receptor blocker and a beta-blocker*[i].

i. Pitt B, Zannad F, Remme WJ *et al*; for the Randomized Aldactone Evaluation Study Investigators (RALES). The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *New England Journal of Medicine* 1999; **341(10)**: 709-717

(Type II evidence – randomised double-blind controlled trial with mean follow-up of 24 months. 1,663 patients (mean age 65 years, 73% men, 87% white) with severe heart failure (NYHA Class III or IV, and Class IV within past six months) and left ventricular ejection fraction of ≤ 35%. Patients were allocated to placebo or spironolactone (25 mg/day which could be doubled after 8 weeks on the basis of evidence of worsening coronary heart failure without hyperkalemia, or changed to 25 mg every other day if hyperkalemia occurred. Patients were already being treated with an ACE inhibitor, a loop diuretic and, in most cases, digoxin. An intention-to-treat analysis was used.

Reviewed in: Spironolactone reduced mortality in severe congestive heart failure. *ACP Journal Club* 2000; **132(1)**: 2)

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4.20g. A primary focus of care for **advanced heart failure** is ongoing identification and treatment of the elevated filling pressures that cause disabling symptoms. While angiotensin-converting enzyme inhibitors and beta-adrenergic agents can slow disease progression and prolong survival, titration and tolerability often present challenges. Most patients are not eligible for surgical intervention but do benefit from a medical regimen tailored to individual clinical and hemodynamic profiles and from heart failure management programs that reduce rehospitalisation. Survival ranges from 80% at two years for patients rendered free of congestion to less than 50% at six months for patients with refractory symptoms, in whom end-of-life options may include hospice care and inactivation of implantable defibrillators[i].

i. Nohria A, Lewis E, Stevenson LW. Medical management of advanced heart failure. *Journal of the American Medical Association* 2002; **287(5)**: 628-640
(Type V evidence – expert guidance based on a systematic review of the literature)

4.20h. A trial is underway to examine the utility of the **pulmonary artery catheter** in patients with **advanced heart failure**, independent of various treatment approaches used by individual physicians[i].

i. Shah MR, O'Connor CM, Sopko G *et al*; for the ESCAPE Investigators. Evaluation study of congestive heart failure and pulmonary artery catherterization effectiveness (ESCAPE): Design and rationale. *American Heart Journal* 2001; **141**: 528-535
(Type II evidence – ongoing randomised controlled trial)

4.20i. In end stage heart failure a strategy is urgently needed to ensure a timely progressive move away from invasive treatment towards **supportive terminal care**. Palliative care specialists have developed treatment strategies which effectively control many of the distressing symptoms reported by heart failure patients. The teaching of these techniques and skills should be included in training programmes for prospective cardiologists[i].

Advice on **palliative management** is provided in the NICE guidelines[ii].

i. Ward C. The need for palliative care in the management of heart failure. *Heart* 2002; **87**: 294-298
(Type V evidence – expert opinion)

ii. Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care. London: National Institute for Clinical Excellence, 2003
http://www.nice.org.uk/pdf/Full_HF_Guideline.pdf
[full guideline]

http://www.nice.org.uk/pdf/CG5NICEguideline.pdf
[NICE guideline]

[accessed 22.12.03]
(Evidence based guideline – systematic literature search to 2002 for specific study types based on clinical questions set out by the technical team)

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4.21 Guidelines

4.21a. Evidence-based guidelines are available for the evaluation and management of heart failure[i-iv].

i. Chronic heart failure: Management of chronic heart failure in adults in primary and secondary care. London: National Institute for Clinical Excellence, 2003
http://www.nice.org.uk/pdf/Full_HF_Guideline.pdf
[full guideline]

http://www.nice.org.uk/pdf/CG5NICEguideline.pdf
[NICE guideline]

[accessed 22.12.03]

(Evidence based guideline – systematic literature search to 2002 for specific study types based on clinical questions set out by the technical team)

ii. 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. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). Developed in collaboration with the International Society for Heart and Lung Transplantation. Endorsed by the Heart Failure Society of America. *Circulation* 2001; **104**: 2996-3007

(Evidence based guidelines. Also published in *Journal of Heart and Lung Transplantation* 2002; 21**(2)**: 189-203)

iii. Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. *European Heart Journal* 2001; **22**: 1527-1560

(Expert consensus guidelines)

iv. Scottish Intercollegiate Guidelines Network (SIGN). *Diagnosis and treatment of heart failure due to left ventricular systolic dysfunction*. Guideline No. 35. Edinburgh: Royal College of Physicians, February 1999
http://www.sign.ac.uk/pdf/qrg35.pdf [accessed 22.12.03]

(Evidence based guidelines. Search methodology not provided. The guidelines are due for review in 2003 and the estimated publication date for the update is early 2005)