The management of chronic heart failure: part one

Chronic heart failure (CHF) is a common syndrome, and its symptoms include exercise intolerance due to breathlessness and fatigue with cardiac dysfunction. As a group, patients with CHF suffer ongoing symptoms, recurrent hospitalisations and a high mortality rate, but modern medical therapy can reduce each of these features. Many patients can, therefore, be managed appropriately in primary care. Part one of this article reviews diagnostic tools and medical therapy used in the management of CHF.

Gordon A Begg Core Medical Trainee, Leeds General Infirmary, Great George Street, Leeds LS1 3EX
Klaus K Witte* Honorary Cardiovascular Consultant, Division of Cardiovascular Medicine and Diabetes Research, LIGHT laboratories, University of Leeds, LS3 9JT
*email k.k.witte@leeds.ac.uk

Chronic heart failure (CHF) is common, affecting up to 900,000 people in the UK. Despite advances in medical and device therapies, patients with CHF are still associated with a high mortality rate (30% at one year, and 60–70% after 5 years) and are associated with morbidity with frequent readmissions to hospital (20% of patients needing two or more admissions per year).[1]

Of all UK hospital admissions, 5% (120,000 per year) are primarily due to heart failure. Patients with heart failure are also more likely to be admitted for other reasons, such as chest pain, arrhythmias and stroke,[2,3] than patients without the condition. As a result, CHF costs the NHS almost £1 billion (>1·8% of health expenditure).

Most patients with CHF are over 70 years of age,[4] and more than 10% of people over the age of 80 years will have the condition.[5,2] Unlike most chronic conditions, the incidence of CHF is increasing.[6] Mortality and morbidity in CHF are directly related to age,[7,8] with older patients less likely to survive hospitalisation with heart failure than younger individuals.[7] Older patients are also much more likely to be readmitted in the subsequent six months after the first admission.[9]

Although the mean age of participants in almost all randomised studies of CHF is around 60 years, subgroup analysis suggests that the relative reduction in mortality from aggressive treatment in older patients is similar to that seen in younger subjects. Additionally, because of older patients' higher absolute risk, the number needed to treat to extend life or prevent hospital admission is much lower. Despite this, elderly patients with CHF are less likely to be prescribed an angiotensin converting enzyme (ACE) inhibitor or a β-blocker,[10,11] and are less likely to be taking the optimal dose.[10]

Diagnosis

The presenting symptoms of CHF are frequently non-specific, but most commonly include breathlessness or fatigue. For a diagnosis of CHF to be made, there must be evidence of cardiac dysfunction.[12]

Patients presenting with possible heart failure should have a full physical examination. The following signs are suggestive of heart failure: evidence of fluid overload, cardiac murmurs and extra sounds on auscultation, and arrhythmia. Baseline investigations should include a 12-lead electrocardiogram (ECG), blood tests and spirometry. A completely normal ECG makes significant heart failure unlikely.[13] However, conduction disease such as left bundle branch block (LBBB), atrial fibrillation, ischaemia, previous infarction and left ventricular hypertrophy (LVH) imply underlying structural heart disease. Blood tests should

be performed to exclude anaemia, renal failure and thyroid disease. Spirometry can identify patients with chronic obstructive pulmonary disease (COPD).

Plasma N-terminal B-type natriuretic peptide (NTproBNP), is a neuropeptide released by cardiomyocytes in response to stretch. In patients with CHF, it can be used for monitoring the condition and to assess prognosis. The most frequent application of the test, however, is to aid the diagnosis. Although high levels are non-specific and are also found in patients with renal failure, high blood pressure, acute infections and COPD, in the presence of a normal ECG, a normal NTproBNP is a cost-effective way to exclude heart failure.[14]

Most patients with symptoms of CHF should have an ECG. This should be performed and interpreted by an experienced technician or physician. Echocardiography is a repeatable and non-invasive method of establishing the presence of left ventricular dysfunction, identifying clinically relevant valvular disease, and guiding therapy of the breathless patient.

CHF is most frequently taken to imply a condition associated with impairment of ventricular systolic function. However, a significant subset of patients with apparent heart failure (more commonly older women) do not have systolic dysfunction. This situation is sometimes labelled as "diastolic heart failure" (DHF), or "heart failure with preserved ejection fraction" (HFPEF). One theory is that such patients might have "stiff" hearts in which in-flow of blood rather than output is limited.

But, the management of patients with breathlessness and preserved systolic ventricular function is much less clear than the management of those with systolic dysfunction. This is because patients with breathlessness often have other contributing causes for the symptom, such as lung disease, detraining and obesity. Although some of these patients will undoubtedly have abnormalities of the numerous echocardiographic measures of diastolic left ventricular function, these features are also found in elderly patients without symptoms of CHF.[15] Reassuringly, although they do suffer persistent symptoms and a similar hospitalisation rate as those with left ventricular systolic dysfunction, the mortality of patients with DHF is better. This article will focus on the management of CHF due to left ventricular systolic dysfunction.

Treatment

Effective treatment of CHF requires an accurate diagnosis, usually based on some form of imaging. Therefore, most patients with possible heart failure should be seen initially in secondary care. However, once the diagnosis has been confirmed and therapy initiated, many patients, particularly those at lower risk, can be managed and monitored in primary care. To facilitate this, the UK now has an extensive network of community specialist nurses and GPs with a specialist interest in cardiology.

Education

The term "heart failure" can cause significant anxiety to patients and their families. Education about the condition and its treatment not only provides reassurance but can improve compliance with medical therapies. In addition, patients and their carers can be taught to recognise signs of deterioration such as weight gain, ankle oedema or reduced exercise tolerance. Patients should be advised to stop smoking. In the absence of a formal rehabilitation or exercise training programme, regular exercise should be encouraged. Fluid restriction can be useful in hospitalised patients and those with hyponatraemia, but there are few data demonstrating that this has any positive impact upon the condition. It does, however, lead to considerable impairment of quality of life. Patients should also be advised to reduce salt intake.

Medical therapy

Over the last two decades, the treatment of CHF has shifted from being purely centred on the relief of symptoms by the management of fluid overload to treatments that address the underlying chronic neurohormonal activation. An abundance of well-conducted randomised controlled trials has led to clear and evidence-based guidelines for treatment of patients with CHF.[16]

Diuretics

Diuretics are useful in the management of fluid overload, and can be administered orally or intravenously. Despite loop diurectics having a pivotal role in relieving congestion, there has never been a randomised controlled trial of loop diuretics in this area.

High-dose loop diuretic therapy causes rebound salt and water retention, due to renin-angiotensin system activation and intravascular

depletion, contributing to renal impairment. Hence the lowest dose of loop diuretic necessary to control symptoms should be used.[17] Of the two commonly used loop diuretics, furosemide has variable oral bioavailability, particularly in patients with peripheral oedema (as a result of gut oedema), whereas bumetanide has more predictable kinetics (40mg furosemide = 1mg bumetanide). Patients with resistant peripheral oedema often respond to a combination of loop and thiazide diuretics. This can lead to a profound diuresis with hypotension and renal impairment, and patients requiring this combination should be monitored closely. Patients with chronic fluid overload and renal dysfunction are usually best managed as inpatients with intravenous diuretic therapy. This should be an infusion rather than intermittent boluses. Intravenous bumetanide has no benefit over furosemide, but is more expensive.

Gout is a common complication of diuretic therapy. Colchicine is helpful in managing an acute attack and avoids the fluid retaining properties of NSAIDs. Allopurinol is helpful in reducing recurrence.

ACE inhibitors and ARBs

Heart failure, and the diuretics used to treat congestion, leads to renin angiotensin-aldosterone system (RAAS) activation. Consequently, this leads to sodium and water retention, vasoconstriction and sympathetic activation. ACE inhibitors block the breakdown of bradykinin and also the conversion of angiotensin I to angiotensin II thereby leading to venous and arterial dilatation, a fall in arterial pressure, and an increase in renal blood flow. ACE inhibitors improve symptoms; slow the progression of ventricular dysfunction;[18–21] reduce mortality,[22,23] hospitalisation rates[24–27] and days in hospital;[18,21] and increase average life expectancy by 6–36 months.[20,28,29] Higher doses appear more effective in reducing morbidity,[27,30] and there is no difference in benefit from ACE inhibitors between older and younger patients.[24] The accumulation of bradykinin as a result of ACE inhibition, can in some patients lead to cough or angioedema.

Agents specifically blocking the angiotensin receptor (angiotensin receptor blockers or ARBs) do not lead to increased bradykinin levels but are likely to be as effective as ACE inhibitors and are an alternative.[31] Adding an ARB to the combination of ACE inhibitors and β-blockers seems to lead to additional reductions in morbidity and mortality in CHF,[32] despite one study suggesting adverse effects.[33] The relative reduction in mortality from both ACE inhibitors and ARBs is the same in older as in younger patients.[31,32] Hence, since older patients have more events, the number needed to treat to "save" a life is lower in the elderly cohort.

The most frequent concern when starting an ACE inhibitor or ARB is that of inducing renal failure. Although renal artery stenosis (RAS) is relatively common in patients with ischaemic heart disease,[34] ACE inhibitor-induced renal failure is rare.

A 10% increase in creatinine is common and tolerable. Patients taking high doses of diuretics are more likely to experience a worsening of renal function, and a reduction in diuretic dose can reduce this risk.

β-blockers

Sympathetic nervous system activation is a cardinal feature of CHF, and contributes to vasoconstriction and adverse remodelling of the left ventricle; provokes arrhythmias; causes cardiac myocyte apoptosis; and enhances RAS activation and hypokalaemia. Inhibiting the effect of the sympathetic activation has had dramatic effects on survival, and β-blocker therapy should be considered for all patients with chronic heart failure.

β-blockers probably do not improve symptoms in the short term and they may make them worse.[35] In the long term, however, they improve symptoms of breathlessness in many patients[36] and stop or slow deterioration in many more.[37] β-blockers reduce the risk of hospitalisation (mainly by reducing the risk of worsening heart failure),[38–41] they reduce the overall amount of time that the patient spends in hospital,[38–41] and they may increase average life expectancy by 12–24 months[37,39–42] in addition to the benefits offered by ACE inhibitor therapy.

No study has examined the use of β-blockers in elderly patients with CHF specifically due to left ventricular systolic dysfunction. Nevertheless, most of the trials have included older patients, such that more patients aged >65 years have been randomised into studies of β-blockers than other agents used for heart failure therapy. Each of the large studies and subsequent meta-analyses[8] confirmed that an elderly cohort of randomised patients gained the same mortality benefit as their younger counterparts, even in patients with severe heart failure on otherwise optimal therapy.[37,40,43,44] Older patients seem also to gain similar reductions in hospital admissions[11] and increases in left ventricular ejection fraction.[45]

There is no upper age limit of benefit from β-blocker therapy;[46] precipitating admission or decompensation with initiation of β-blockade is rare; and patients admitted with a decompensation should not have their β-blocker discontinued.[47] Traditionally, ACE inhibitors are the first-line agents in such patients, although β-blockers can be initiated as first line safely in patients with stable symptoms.[48] Higher doses of β-blockers are associated with a greater reduction in mortality. Nevertheless, the starting dose should be low and increased at intervals. A typical schedule would be to start with carvedilol 3·125mg twice daily, and then increasing by doubling the dose at two weekly intervals. The target should be the highest tolerated dose, or the dose shown to be of benefit in clinical trials, whichever is the lower.

Patients with preserved blood pressure or hypertensive patients tolerate initiation of a β-blocker and uptitration well. In those in whom there is a concern about hypotension, the loop diuretic dose can be reduced, or even omitted, on the first day. Alternatively, the dose of the ARB or ACE inhibitor can be slightly reduced.

Concerns over the consequences of the haemodynamic changes are frequently not realised even in those with systolic blood pressure around 100mmHg. Symptoms of postural hypotension often recur early at each titration stage, but settle once the patient is established on the increased dose. It is generally accepted that patients should be on a low dose of both β-blocker and ACE inhibitor/ARB rather than a full dose of one or the other. Best practice in patients with symptomatic hypotension on starting β-blockers, is to persist by reducing the ACE inhibitor/ARB dose and start again with the β-blocker. For patients for whom an increase in only one agent (β-blocker or ACE inhibitor) is possible, you should keep in mind that the remodelling effects of β-blockers are dose dependent. Therefore, a policy of increasing the β-blocker over the ACE inhibitor leads to a better response in terms of LV function.[49]

One reason for the under-prescribing of β-blockers in CHF patients is fear of inducing deterioration in lung function. However, most patients with COPD do not have reactive bronchospasm, and β-blockers are well tolerated in CHF[50] patients with COPD. At worst, they may have a small, asymptomatic reduction in FEV_1.[50,51] Therefore, patients with this disease and little wheeze should not be excluded from using β-blockers.[51]

Although β-blockers are often anecdotally reported to worsen diabetic control, carvedilol is as well tolerated in diabetics as in non-diabetics;[52] it leads to a decrease in insulin resistance[53] and no increase in glycosylated haemoglobin (HbA1c). Metoprolol, on the other hand, is associated with an increase in HbA1c.[54] Diabetics with heart failure have a similar reduction in mortality with carvedilol as their non-diabetic counterparts.[55]

Peripheral vascular disease is also often thought to be a contraindication to β-blockade, but worsening of claudication or peripheral perfusion has not been reported in trials of patients with heart failure.[56] Carvedilol seems

not to have an adverse affect on cognitive function or functional capacity in elderly patients.[57]

Spironolactone

Aldosterone is increased in CHF due to RAAS activation and leads to potassium loss; stimulates myocardial and vascular collagen synthesis; and contributes to hyperparathyroidism, cellular calcium loading, inflammatory activation and bone demineralisation. Spironolactone is an aldosterone antagonist and reduces mortality and hospitalisation rates in patients with more severe CHF.[58] It is also recommended in patients with current or previous hospitalisations for CHF, and is useful in patients with fluid overload as an adjunct to loop diuretics.

The major side-effect of spironolactone is hyperkalaemia.[59] Patients more likely to develop dangerous hyperkalaemia include those with more severe renal impairment, diabetes and those already taking high dose ACE inhibitors or ARBs. Other side effects include gynaecomastia and an alternative agent, eplerenone, is available for patients with this side effect.[60] Elderly patients seem to benefit from aldosterone antagonists to the same extent as younger patients.[60,61]

Digoxin

Digoxin is a mild positive inotrope and diuretic, and it slows atrioventricular conduction. In patients in sinus rhythm, digoxin appears to improve symptoms.[62] But the only large randomised placebo-controlled trial of digoxin demonstrated no mortality benefit when it was added to an ACE inhibitor.[63] There was a reduction in heart failure death matched by an increase in death due to arrhythmia.

Digoxin can also be used as an adjunct to β-blockers for rate control in CHF patients with atrial fibrillation, but care must be taken in those patients on high dose loop diuretics since the risk of arrhythmia is greatest in the presence of hypokalaemia.

Anticoagulation

Patients with CHF are at high risk of thromboembolic events. Many will have underlying coronary artery disease. Most are therefore prescribed aspirin. However, aspirin is at best neutral in terms of prognosis, and may in fact be harmful because it may counter some of the beneficial effects of ACE inhibitors and increase the risk of gastrointestinal haemorrhage. By contrast, formal anticoagulation with warfarin is associated with a reduction in CHF hospitalisations and a trend to reduced mortality compared with aspirin.[64] Aspirin should be stopped in patients with "resistant" fluid retention or deteriorating renal function. Patients with heart failure and atrial arrhythmias should be offered anticoagulation in the absence of contraindications. Whether clopidogrel offers appropriate antiplatelet activity without the side-effects of aspirin is under investigation.

Conclusion

Chronic heart failure is a common and serious disease that consumes a large part of the NHS budget. There have been dramatic advances in treatments for CHF in recent years, and optimal management of patients can lead to important reductions in mortality and hospitalisations, and improvements in quality of life. However, many patients are still receiving sub-optimal therapy, leading to unnecessary early deaths and hospital admissions. Since much follow-up and monitoring of patients with CHF is now appropriately performed in primary care, primary care physicians and community heart failure nurses need to be confident at initiating and uptitrating medical therapy to the doses recommended in clinical trials.

We have no conflict of interest

1. McMurray J, McDonagh T, Morrison CE, Dargie HJ. Trends in hospitalisation for heart failure in Scotland 1980-1990. *Eur Heart J* 1993; **14**:1158–62
2. Brown A, Cleland JGF. Influence of concomitant disease on patterns of hospitalisations in patients with heart failure from Scottish hospitals in 1995. *Eur Heart J* 1998; **19**: 1063–9
3. Khand AU, Gemmell I, Rankin AC, Cleland JGF. Clinical events leading to the progression of heart failure: insights from a national database of hospital discharges. *Eur Heart J* 2001; **22**: 153–64
4. Witte KK, Clark AL. Carvedilol in the treatment of elderly patients with chronic heart failure. *Clin Interv Aging* 2008; **3**: 55–70
5. Cowie MR, Wood DA, Coats AJ, et al. Incidence and aetiology of heart failure: a population-based study. *Eur Heart J* 1999; **20**: 421–8
6. Bonneux L, Barendregt JJ, Meeter K. Estimating clinical morbidity due to ischaemic heart disease and congestive heart failure: the future rise of heart failure. *Am J Public Health* 1994; **84**: 20–8
7. Cleland JG, Gemmell I, Khand A, Boddy A. Is the prognosis of heart failure improving? *Eur J Heart Fail* 1999; **1**: 229-41
8. Dulin BR, Haas SJ, Abraham WT, Krum H. Do elderly systolic heart failure patients benefit from beta blockers to the same extent as

the non-elderly? Meta-analysis of >12,000 patients in large-scale clinical trials. *Am J Cardiol* 2005; **95**: 896-8
9. Cleland JG, Clark A. Has the survival of the heart failure population changed? Lessons from trials. *Am J Cardiol* 1999; **83**: 112D-119D
10. Komajda M, Follath F, Swedberg K, et al. Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Euroheart Failure Survey Programme—a survey on the quality of care among patients with heart failure in Europe: Part 2. Treatment. *Eur Heart J* 2003; **24**: 464–74
11. Sin DD, McAlister FA. The effects of beta-blockers on morbidity and mortality in a population-based cohort of 11942 elderly patients with heart failure. *Am J Med* 2002; **113**: 650–6
12. Witte KK, Clark AL. Why does chronic heart failure cause breathlessness and fatigue. Prog *Cardiovasc Dis* 2007; **5**: 366–84
13. Khan NK, Goode KM, Cleland JG, et al. EuroHeart Failure Survey Investigators. Prevalence of ECG abnormalities in an international survey of patients with suspected or confirmed heart failure at death or discharge. *Eur J Heart Fail* 2007; 9: 491–501
14. The National Institute for Health and Clinical Excellence. Chronic Heart Failure: management of chronic heart failure in primary and secondary care 2003. http://tiny.cc/GS8F7 (accessed 18 February 2010)
15. Witte KK, Nikitin NP, Cleland JG, Clark AL. Excessive breathlessness in patients with diastolic heart failure. *Heart* 2006; **92**: 1425–9
16. European Society of Cardiology (ESC); Heart Failure Association (HFA) of the ESC; European Society of Intensive Care Medicine (ESICM). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. *Eur J Heart Fail* 2008;**10**: 933–89
17. Cleland JG, Coletta A, Witte K. Practical applications of intravenous diuretic therapy in decompensated heart failure. *Am J Med* 2006; **119**(12 Suppl 1): S26–36
18. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *New Engl J Med* 1991; **326**: 293–302
19. Yusuf S, Nicklas JM, Timmis G, et al. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *New Engl J Med* 1992; **327**: 685–91
20. Yusuf S, Sleight P, Pogue J, et al. Effects of the angiotensin converting enzyme inhibitor, ramipril, on cardiovascular events in high risk patients. The Heart Outcomes Prevention Evaluation study investigators. *New Engl J Med* 2000; **342**: 145–53
21. Jong P, Yusuf S, Rousseau MF, et al. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. *Lancet* 2003; **361**: 1843–8
22. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987; **316**: 1429–35
23. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *New Engl J Med* 1991; **325**: 303–10
24. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. *JAMA* 1995; **273**: 1450–6
25. Yusuf S, Pepine CJ, Garces C, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992; **340**: 1173–8
26. Torp-Pedersen C, Kober L. Effect of ACE inhibitor trandolapril on life expectancy of patients with reduced left ventricular fundtion after acute myocardial infarction. TRACE study group. *Lancet* 1999; **354**: 9–12
27. Packer M, Poole Wilson PA, Armstrong PW, et al on behalf of the ATLAS investigators. 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**: 2312–8
28. Swedberg K, Kjekshus J, Snapinn S, and CONSENSUS investigators. Long-term survival in severe heart failure in patients treated with enalapril; ten year follow-up of CONSENSUS I. *Eur Heart J* 1999; **20**: 136–139
29. Cleland JGF, Thygesen K, Uretsky BF, et al. Cardiovascular critical event pathways for the progression of heart failure. A report from the ATLAS study. *Eur Heart J* 2001; **22**: 1601–12
30. The NETWORK Investigators. Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison. *Eur Heart J* 1998; **19**: 481-9
31. Granger CB, McMurray JJV, Yusuf S, et al, for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; **362**: 772–76
32. McMurray JJV, Östergren J, Swedberg K, et al, for the CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; **362**: 767–71
33. Cohn JN, Tognoni G, for the Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker Valsartan in chronic heart failure. *N Engl J Med* 2001; **345**: 1667–75
34. de Silva R, Loh H, Rigby AS, et al. Epidemiology, associated factors, and prognostic outcomes of renal artery stenosis in chronic heart failure assessed by magnetic resonance angiography. *Am J Cardiol* 2007; **100**: 273–9
35. MacMahon S, Sharpe N, Doughty R, et al. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet* 1997; **349**: 375–80
36. Witte KK, Thackray S, Nikitin NP, Cleland JG, Clark AL. The effects of long-term beta-blockade on the ventilatory responses to exercise in chronic heart failure. *Eur J Heart Fail* 2005; **7**: 612–7
37. Packer M, Fowler MB, Roecker EB, et al. Carvedilol Prospective

Randomized Cumulative Survival (COPERNICUS) Study Group. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002; **106**: 2194–9
38. CIBIS-II Investigators and Committee. The Cardiac insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; **353**: 9–13
39. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; **333**: 2001-7
40. Packer M, Coats AJ, Fowler MB, et al; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; **344**: 1651–8
41. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalization, and well-being in patients with heart failure: the metoprolol CR-XL randomized intervention trial in congestive heart failure (MERIT-HF). *JAMA* 2000; **283**: 1295–1302
42. Packer M, Bristow MR, Cohn JN, et al, for the US carvedilol study group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *New Engl J/ Med* 1996; **334**: 1349–55
43. Krum H, Roecker EB, Mohacsi P, et al. Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. *JAMA* 2003; **289**: 712–8
44. Krum H, Mohacsi P, Katus HA, et al. Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study Group. Are beta-blockers needed in patients receiving spironolactone for severe chronic heart failure? An analysis of the COPERNICUS study. *Am Heart J* 2006; **151**: 55–61
45. Krum H, Hill J, Fruhwald F, Sharpe C, et al. Tolerability of beta-blockers in elderly patients with chronic heart failure: the COLA II study. *Eur J Heart Fail* 2006; **8**: 302–7
46. Witte KK, Clark AL. Carvedilol in the treatment of elderly patients with chronic heart failure. *Clin Intervent Ageing* 2008; **3**: 1–16
47. Jondeau G, Neuder Y, Eicher JC, et al; for the B-CONVINCED Investigators. B-CONVINCED: Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode. *Eur Heart J* 2009 e-pub ahead of print
48. Willenheimer R, van Veldhuisen DJ, Silke B, et al. CIBIS III Investigators. Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril, as compared with the opposite sequence: results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. *Circulation* 2005; **112**: 2426–35
49. Sliwa K, Norton GR, Kone N, et al. Impact of initiating carvedilol before angiotensin-converting enzyme inhibitor therapy on cardiac function in newly diagnosed heart failure. *J Am Coll Cardiol* 2004; **44**: 1825–30
50. Shelton RJ, Rigby AS, Cleland JG, Clark AL. Effect of a community heart failure clinic on uptake of beta blockers by patients with obstructive airways disease and heart failure. *Heart* 2006; **92**: 331–6
51. Witte KK, Clark AL. Beta-blockers and inspiratory pulmonary function in chronic heart failure. *J Card Fail* 2005; **11**: 112–6
52. Nodari S, Metra M, Dei Cas A, Dei Cas L. Efficacy and tolerability of the long-term administration of carvedilol in patients with chronic heart failure with and without concomitant diabetes mellitus. *Eur J Heart Fail* 2003; **5**: 803–9
53. Ferrua S, Bobbio M, Catalano E, et al. Does carvedilol impair insulin sensitivity in heart failure patients without diabetes? *J Card Fail* 2005; **11**: 590–4
54. Bakris GL, Fonseca V, Katholi RE, et al; GEMINI Investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA* 2004; **292**: 2227–36
55. Bell DS, Lukas MA, Holdbrook FK, Fowler MB. The effect of carvedilol on mortality risk in heart failure patients with diabetes: results of a meta-analysis. *Curr Med Res Opin* 2006; **22**: 287-96
56. Hiatt WR, Stoll S, Nies AS. Effect of beta-adrenergic blockers on the peripheral circulation in patients with peripheral vascular disease. *Circulation* 1985; **72**: 1226–31
57. Leonetti Luparini R, Celli V, et al. Carvedilol in elderly patients with chronic heart failure, a 12 weeks randomized, placebo controlled open trial. *Arch Gerontol Geriatr* 1999; **29**: 275–82
58. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; **341**: 709–17
59. The RALES Investigators. Effectiveness of spironolactone added to an angiotensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (the Randomized Aldactone Evaluation Study [RALES]. *Am J Cardiol* 1996; **78**: 902-7
60. Pitt B, Remme W, Zannad F, Neaton J, et al. 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. *N Engl J Med* 2003; **348**: 1309–21
61. Pitt B, White H, Nicolau J, et al; EPHESUS Investigators. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *J Am Coll Cardio* 2005; **46**: 425–31
62. Packer M, Gheorghiade M, Young JB, et al for the RADIANCE study. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. *New Engl J Med* 1993; **329**: 1–7
63. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *New Engl J Med* 1997; **336**: 525–33
64. Massie BM, Collins JF, Ammon SE, et al. WATCH Trial Investigators. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation* 2009; **119**(12): 1616–24