EDITORIAL

ESC-CHF: guidelines for the aspirational and the practical

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The recently published guidelines by the European Society of Cardiology on the diagnosis and treatment of chronic heart failure are well worth reading, include important new recommendations and are reviewed here

The 2005 European Society of Cardiology chronic heart failure (ESC-CHF) guidelines,¹ recently published in the *European Heart Journal*, provide a thorough and timely update to the existing UK guidance, the NICE (National Institute for Health and Clinical Excellence) guidelines of 2003² and the slightly older SIGN (Scottish Intercollegiate Guidelines Network) guidelines of 2001.³ The ESC guidelines are well worth reading in their entirety. This editorial summarises the progress made by the ESC in implementing evidence from the new clinical trials of drug and device therapy, with data available up to March 2005. Also new is the ESC-CHF strategy for escalation of drug treatment, which takes a novel and slightly different approach to the current UK recommendations.

ADVANCES IN DRUG THERAPY FOR CHF

Major new studies available to the ESC reviewers since NICE and SIGN included: BEST (bucindolol)⁴; CAPRICORN (carvedilol)⁵; the three CHARM trials (candesartan)⁶; COMET (carvedilol and metoprolol)⁷; EPHEsus (eplerenone)⁸; EUROPA (perindopril)⁹; SENIORS (nebivolol)¹⁰; and VALIANT (valsartan).¹¹

DIURETICS

Loop diuretics are recommended for relief of symptoms of fluid retention or if pulmonary congestion is present. Thiazides can be added if the glomerular filtration rate is < 30 ml/min. One new addition is the suggestion to discontinue diuretics in class I heart failure and only to use in New York Heart Association (NYHA) functional II if symptoms indicate and fluid overload is present. Use in NYHA III or IV is recommended. So far, so good.

β BLOCKERS

Like NICE, ESC-CHF recommends β blockers for the treatment of all patients (in NYHA functional class II–IV) with stable, mild, moderate and severe heart failure from ischaemic or non-ischaemic cardiomyopathies and reduced left ventricular ejection fraction (LVEF) on standard treatment including diuretics and angiotensin converting enzyme (ACE) inhibitors, unless there is a contraindication. ESC-CHF emphasises that β blockers are the only heart failure drugs that induce a significant improvement of LVEF.

The guideline does remind us that the improved left ventricular systolic function does not always result in better exercise capacity. ESC-CHF also recommends β blockers for all patients post-myocardial infarction (MI) regardless of NYHA class.

NICE recommended bucindolol, carvedilol and metoprolol for symptomatic heart failure. This recommendation is now superseded. COMET showed that carvedilol is superior to metoprolol tartrate, bisoprolol has important benefits over placebo (CIBIS studies), and importantly, bucindolol (from the BEST trial) has no benefit. Accordingly, only four drugs, namely bisoprolol, carvedilol, metoprolol succinate and nebivolol can be recommended for patients with CHF. In the UK, only carvedilol and bisoprolol are licensed for use in heart failure at the time of writing. It is expected that nebivolol will be granted a licence for use in elderly CHF patients in the near future.

ESC-CHF does not provide clear guidance on what to do about a patient already treated with a non-recommended β blocker. NICE section 1.2.2.8 suggests leaving a patient already established on a non-tested β blocker—for example, propranolol. ESC-CHF does not say that such a β blocker should be discontinued, but favours replacement with carvedilol, bisoprolol, metoprolol succinate or nebivolol. We believe that the best interpretation of the data and what ESC-CHF really means is only to use the four approved β blockers for patients with heart failure, if necessary switching patients from non-approved agents.

ACE INHIBITORS

ACE inhibitors remain initial treatment in all patients with LV systolic dysfunction, with or without symptoms. Achieving the doses used in clinical trials is emphasised. ESC-CHF reminds us that early intervention with ACE inhibitors or angiotensin receptor blockers (ARBs) reduces significantly the occurrence of heart failure in high cardiovascular risk populations such as patients with previous cardiovascular disease, diabetes, alone or with nephropathy and hypertension. The new guideline does not go as far as

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Abbreviations: ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CHF, chronic heart failure; CRT, cardiac resynchronisation therapy; ESC, European Society of Cardiology; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NICE, National Institute for Health and Clinical Excellence; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SIGN, Scottish Intercollegiate Guidelines Network

recommending ACE inhibitors (or ARBs) for every patient with coronary disease, hypertension or diabetes. This might disappoint proponents of renin–angiotensin blockers for all patients at cardiovascular risk, but this is outside the remit of the ESC-CHF guideline. It is left up to the individual physician to decide how far to implement the results of EUROPA⁹ and HOPE.¹² We will have to wait and see whether the impressive results from ASCOT¹³ influence a more widespread recommendation for such drugs.

ALDOSTERONE ANTAGONISTS

Aldosterone receptor antagonists are more contentious. Aldosterone antagonists are recommended in addition to ACE inhibitors, β blockers and diuretics in advanced heart failure (NYHA III–IV) to improve survival and morbidity. No change there. However, aldosterone antagonists are now recommended by ESC-CHF, in addition to ACE inhibition and β blockade, as combination therapy for patients post-MI with left ventricular systolic dysfunction and signs of heart failure, to reduce mortality and morbidity. Based on the results from EPHESUS⁸ and RALES,¹⁴ this moves eplerenone and spironolactone into much greater prominence than their current use reflects. While we applaud implementation of important trials, it is our own belief that caution and vigilance, especially with spironolactone, is crucial. Juurlink and others¹⁵ have pointed out the considerable increase in hyperkalaemia following implementation of the RALES results. ESC-CHF recommends measuring serum creatinine and potassium every 5–7 days after initiation of treatment until the values are stable. Thereafter, measurements can be made every 3–6 months. This would be a minimum requirement. ESC-CHF does point out that aldosterone antagonists are still unproven in patients with class II heart failure or asymptomatic left ventricular dysfunction.

ANGIOTENSIN RECEPTOR BLOCKERS

The CHARM trials and VALIANT have provided much new material for the ESC guideline writers and they have been forward looking with their recommendations. ARBs are confirmed as alternative first line treatment in heart failure, or in the post-MI patient with signs of heart failure or left ventricular dysfunction, if patients are ACE intolerant. This is uncontroversial and already in practice, although only slowly being fully implemented. ESC-CHF goes further, and implements CHARM-added, suggesting the addition of an ARB to patients who remain symptomatic (that is, NYHA class II or worse) despite ACE inhibitor and β blocker therapy. This is quite a step for prescribing in the UK, where ACE inhibitors are only reaching about half of the appropriate patients at the moment. But there is nothing wrong in guidelines being aspirational, pointing the way to best available treatment. Implementation in our current practice is another question. Importantly, ESC-CHF emphasises that the perceived negative interaction between ARBs and β blockers (based on ValHeFT¹⁶) was a statistical quirk, and that they offer important benefits together. ESC-CHF also points out the increased risk of hypotension, renal impairment or hyperkalaemia with the combination of ACE inhibitor and ARB, and indicates the need for careful monitoring in such patients.

Thus a patient with a prior MI and symptoms of heart failure should, according to ESC-CHF, be considered for an ACE inhibitor, an appropriate β blocker and spironolactone, with a loop diuretic if needed, and also an antiplatelet agent and a statin. An ARB can be added.

OTHER DRUGS

Digoxin is rightly consigned to be used only in patients with heart failure and atrial fibrillation (AF), and should be

combined with a β blocker. Regarding vasodilators, the hydralazine–isosorbide dinitrate combination (tested in the 1980s in VeHFT-I)¹⁷ remains for individuals truly intolerant to ACE inhibitors or ARBs. α Blockers are finally discarded, although undergraduate textbooks of medicine *still* recommend them! The calcium channel blockers amlodipine and felodipine are permissible for treatment of concomitant angina or hypertension if required; they have a neutral effect on survival. Other vasodilators are rejected; in particular diltiazem and verapamil were noted to be contraindicated in LV systolic dysfunction.

INOTROPES

ESC-CHF recommends against repeated or prolonged treatment with oral inotropic agents, drugs which increase mortality. Brief use of intravenous inotropes is unchanged. The one new recommendation is to consider the new oral calcium sensitiser levosimendan in patients with symptomatic low cardiac output secondary to cardiac systolic dysfunction without severe hypotension.¹⁸

ANTITHROMBOTIC DRUGS

The new guideline opens this interesting section with, “There is little evidence to show that anti-thrombotic therapy modifies the risk of death or vascular events in patients with heart failure”. ESC-CHF recommends warfarin for patients with heart failure and AF, mural thrombus, or a previous thromboembolic event. The guideline recommends antiplatelet agents for individuals with coronary heart disease. The major new addition is the recommendation to discontinue or avoid aspirin in patients with recurrent hospitalisation with worsening heart failure. Intriguingly, this point is not expanded upon. Is this such common knowledge that no reference was needed? Presumably the authors are quoting the WASH trial, which showed an excess of heart failure admissions in CHF patients on aspirin.¹⁹

ANTIARRHYTHMIC DRUGS

β Blockers and amiodarone remain the only recommended drugs for supraventricular and ventricular arrhythmias (alone or in combination) for CHF patients; digoxin remains for AF (see above).

SURGERY AND DEVICES

Indications for conventional cardiac surgery are really unchanged. Revascularisation, whether coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), is not routinely recommended for CHF patients with coronary heart disease, although exceptions (for example, left main stem stenosis) may be considered. There are no trial data available. ESC-CHF points out the substantially increased risk of CABG and poor LV function. Mitral valve surgery is occasionally indicated. Aortic valve replacement is not mentioned but our own experience is that selected individuals with CHF and severe aortic stenosis may undergo remarkable improvement following surgery. Ventricular tachycardia in the postoperative period is worth watching for. Apart from aneurysmectomy, other radical LV remodelling is not recommended.

Device therapy is where things really warm up. The rate at which new data are becoming available has forced the authors of ESC-CHF to provide general guidelines only.

CARDIAC RESYNCHRONISATION THERAPY

The authors point out firstly that conventional right ventricular pacing has no established role in the treatment of heart failure except for conventional bradycardia indication, when atrioventricular synchronous pacing should be used.

Resynchronisation therapy using biventricular pacing can be considered in patients with reduced ejection fraction and ventricular dyssynchrony (QRS width ≥ 120 ms) and who remain symptomatic (NYHA III–IV) despite optimal medical treatment to improve symptoms. Biventricular pacing improves symptoms, exercise capacity and reduces hospitalisations, and we now know from CARE-HF that all cause mortality is improved by 36%.²⁰ Cleland and co-authors in their paper go further than ESC-CHF and suggest, “The implantation of a cardiac-resynchronization device should routinely be considered in such patients”. Well, yes, but health boards will need persuading. Nevertheless, since guidelines provide aspirational best practice ESC-CHF certainly points the way for the future. Some thought is needed because of the large difference in the actual ejection fraction and QRS width of patients recruited into COMPANION and CARE-HF compared to the inclusion criteria. The results, therefore, should apply to patients whose characteristics match those of patients in the trial, not the inclusion criteria.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

ESC-CHF makes three recommendations for implantable cardioverter-defibrillators (ICDs):

- Implantation of an ICD in combination with biventricular pacing can be considered in patients who remain symptomatic with severe heart failure NYHA class III–IV with LVEF $\leq 35\%$ and QRS duration > 120 ms to improve mortality or morbidity.
- ICD therapy is recommended to improve survival in patients who have survived cardiac arrest or who have sustained ventricular tachycardia, which is either poorly tolerated or associated with reduced systolic left ventricular function.
- ICD implantation may be considered in selected patients with LVEF $< 35\%$ on optimal background therapy including ACE inhibitor, ARB, β blocker and an aldosterone antagonist, where appropriate, to reduce sudden death.

Data from COMPANION were available.²¹ COMPANION compared combination cardiac resynchronisation therapy (CRT)-ICD therapy with medical treatment. All cause mortality was reduced by 36%, remarkably similar to CARE-HF. Whether ICD added to CRT alone adds much more has not yet been tested. Intuitively additional ICD therapy should, but at substantially greater cost. We await these trials with expectancy, since ICDs save many lives.

ASYMPTOMATIC SYSTOLIC LEFT VENTRICULAR DYSFUNCTION

Treatment with an ACE inhibitor is recommended in patients with reduced systolic function if indicated by a substantial reduction in LVEF. β Blockers should be added to the treatment in patients with asymptomatic LV dysfunction following an acute MI.

MANAGEMENT OF HEART FAILURE CAUSED BY DIASTOLIC DYSFUNCTION

There is quite a long section about the management of patients with symptoms of heart failure yet with preserved systolic function. ESC-CHF admits its general principles are mostly speculative, apart from the long term data which exist, coming from the CHARM Preserved study and the SENIORS trial. Five suggestions are made:

- ACE inhibitors may improve relaxation and cardiac distensibility directly and may have long term effects

through their antihypertensive effects and regression of hypertrophy.

- Diuretics may be necessary when episodes with fluid overload are present, but should be used cautiously so as not to lower preload excessively and thereby reduce stroke volume and cardiac output.
- β Blockade could be instituted to lower heart rate and increase the diastolic period.
- Verapamil-type calcium antagonists may be used for the same reason. Some studies with verapamil have shown a functional improvement in patients with hypertrophic cardiomyopathy
- A high dose of an ARB may reduce hospitalisations.

The CHARM-Preserved trial just hinted at some benefit and the interpretation of SENIORS is complicated by the inclusion of a broad selection of patients.

HEART FAILURE TREATMENT IN THE ELDERLY

The section on treatment of older patients is full of good common sense although no specific new data. Important recommendations include reminders that older persons are more sensitive to digoxin. For AF with heart failure, ESC-CHF inclines toward rate control with digoxin first, plus a β blocker if needed. Warfarin is strongly recommended.

CARE AND FOLLOW-UP

A good section is devoted to structured care plans and nurse-led community teams, although not all studies have shown benefit. Exercise training is discussed in detail with tables of suggested protocols which are useful. There are several tables of plans to achieve the highest tolerated doses of ACE inhibitors, ARBs, β blockers, diuretics and aldosterone antagonists, with recommendations for commencing treatment, titration and monitoring. There are further sections about more severe heart failure and transplantation which are good if not new.

ALGORITHM OF PHARMACOLOGICAL TREATMENT

This is new. ESC-CHF takes the view that since most patients present with symptoms—that is, at least NYHA class II—the algorithm should begin there, as shown in fig 1. It is noteworthy that diuretics are indicated only if fluid retention is present, an important departure from the traditional view of diuretics first, other drugs next. The algorithm is based on neurohumoral blockade with compelling ACE inhibitor/ARB and β blocker use early on, plus aldosterone blockers early if post-MI, and later if NYHA III or IV. Routine dual treatment of ACE inhibitor + ARB for NYHA III is quite clear. Digoxin can be added in class III or IV.

WHAT DOES ESC-CHF LEAVE OUT?

Well, very little. The authors tacitly acknowledge that device therapy is moving so fast that only general recommendations can be made (see above). The writers give no recommendation either way for statin treatment. We will have to wait for CORONA (an ongoing study comparing rosuvastatin or placebo in heart failure) and other trials to report.

ESC-CHF concentrates (rightly) on symptomatic heart failure, but a stronger view of the place of ACE inhibitors in CHD patients would have been welcome. There have been suggestions from many respected physicians that more widespread use is indicated. Perhaps we will have to wait for the next ESC-CHF guideline for this.

Overall, ESC-CHF is an excellent guideline with important updates to our own current NICE and SIGN guides. ESC-CHF is current, mostly balanced and very well written. We recommend a thorough study. The British Hypertension

	For survival/morbidity mandatory treatment	For symptoms
NYHA I	Continue ACE inhibitor/ARB if ACE inhibitor intolerant, continue aldosterone antagonist if post-MI. Add β blocker if post-MI	Reduce/stop diuretic
NYHA II	ACE inhibitor as first line treatment/ARB if ACE inhibitor intolerant. Add β blocker and aldosterone antagonist if post-MI	+/- diuretic depending on fluid retention
NYHA III	ACE inhibitor plus ARB or ARB alone if ACE intolerant β blocker Add aldosterone antagonist	+ diuretics + digitalis if still symptomatic
NYHA IV	Continue ACE inhibitor/ARB β blocker Aldosterone antagonist	+ diuretics + digitalis + consider temporary inotropic support

Figure 1 Algorithm for pharmacological treatment of chronic heart failure. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; MI, myocardial infarction; NYHA, New York Heart Association.

Society ABCD hypertension guideline already exists. Whether we can implement and afford the ABCD of heart failure remains to be seen:

- A: angiotensin/aldosterone blockers
- B: β blockers
- C: cardiac resynchronisation therapy
- D: defibrillator implantation.

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REFERENCES

- 1 Swedberg K, Cleland J, Dargie H, *et al*. Guidelines for the diagnosis and treatment of chronic heart failure (update 2005). *Eur Heart J* 2005;**26**:1115–41.
- 2 NICE. Chronic heart failure. Management of chronic heart failure in adults in primary and secondary care. National Institute for Clinical Excellence July, 2003.
- 3 Scottish Intercollegiate Guidelines Network. Diagnosis and treatment of heart failure due to left ventricular systolic dysfunction. Scottish Intercollegiate Guidelines Network 1999;(SIGN).
- 4 Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001;**344**:1659–67.
- 5 The Capricorn Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;**357**:1385–90.
- 6 Pfeffer MA, Swedberg K, Granger CB, *et al*. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;**362**:759–66.
- 7 Poole-Wilson PA, Swedberg K, Cleland JG, *et al*. 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**:7–13.
- 8 Pitt B, Remme W, Zannad F, *et al*. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–21.
- 9 Fox KM. European trial on reduction of cardiac events with perindopril in stable coronary artery disease investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;**362**:782–8.
- 10 Flather MD, Shibata MC, Coats AJ, *et al* for the SENIORS Investigators. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J* 2005;**26**:215–25.
- 11 Pfeffer MA, McMurray JJ, Velazquez EJ, *et al*. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;**349**:1893–906.
- 12 Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;**355**:253–59.
- 13 Dahlöf B, Sever PS, Poulter NR, *et al*. Anglo-Scandinavian cardiac outcomes trial—blood pressure lowering arm (ASCOT-BPLA): a multicentre randomized controlled trial. *Lancet* 2005;**366**:895–906.
- 14 Pitt B, Zannad F, Remme WJ, *et al*. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized aldosterone evaluation study investigators. *N Engl J Med* 1999;**341**:709–17.
- 15 Juurlink DN, Mamdani MM, Lee DS, *et al*. Rates of hyperkalemia after publication of the randomized aldosterone evaluation study. *N Engl J Med* 2004;**351**:543–51.
- 16 Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667–75.
- 17 Cohn JN, Archibald DG, Phil M, *et al*. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a veterans administration cooperation study. *N Engl J Med* 1986;**314**:1547–52.
- 18 Follath F, Cleland JG, Just H, *et al*. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 2002;**360**:196–202.
- 19 Cleland J, Findlay I, Jafri S, *et al*. The warfarin/aspirin study in heart failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004;**148**:157–64.
- 20 Cleland JG, Daubert JC, Erdmann E, *et al* for the Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–49.
- 21 Bristow MR, Saxon LA, Boehmer J, *et al*. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–50.