

Practical recommendations for the use of ACE inhibitors, beta-blockers, aldosterone antagonists and angiotensin receptor blockers in heart failure: Putting guidelines into practice

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Abstract

Surveys of prescribing patterns in both hospitals and primary care have usually shown delays in translating the evidence from clinical trials of pharmacological agents into clinical practice, thereby denying patients with heart failure (HF) the benefits of drug treatments proven to improve well-being and prolong life. This may be due to unfamiliarity with the evidence-base for these therapies, the clinical guidelines recommending the use of these treatments or both, as well as concerns regarding adverse events. ACE inhibitors have long been the cornerstone of therapy for systolic HF irrespective of aetiology. Recent trials have now shown that treatment with beta-blockers, aldosterone antagonists and angiotensin receptor blockers also leads to substantial improvements in outcome. In order to accelerate the safe uptake of these treatments and to ensure that all eligible patients receive the most appropriate medications, a clear and concise set of clinical recommendations has been prepared by a group of clinicians with practical expertise in the management of HF. The objective of these recommendations is to provide practical guidance for non-specialists, in order to increase the use of evidenced based therapy for HF. These practical recommendations are meant to serve as a supplement to, rather than replacement of, existing HF guidelines.

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1. Introduction

Evidence-based medicine is an accepted goal to which doctors should aspire in their clinical practice.[1] Over the last three decades, a remarkable number of large, double-

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blind, controlled trials have been conducted in patients with chronic heart failure (HF) [2–20]. These trials have used clinically important outcome measures, including death or composites of death and relevant non-fatal events (e.g., hospital admissions). Often these trials also measured the effect of treatment on one or more of: symptoms, functional capacity and quality of life [2–20]. The aforementioned trials were also designed with adequate patient numbers and length of follow-up to provide the statistical power for unequivocal interpretation of the results. Consequently, there is now evidence for the efficacy and safety of a considerable number of pharmacological treatments for HF, irrespective of aetiology. With this recent increase in number of effective treatments available, the pharmacological management of HF, in generally elderly patients with often multiple co-morbidities, has become complex.

The uptake of these evidence-based treatments in clinical practice has been variable, despite publication of the trials in prominent journals and their summation in authoritative guidelines [21–31]. In some cases (e.g., ACE inhibitors and beta-blockers), uptake was slow and patients were thus denied the benefits of proven treatments shown to increase quality and quantity of life [32–35].

In contrast, very rapid uptake of the aldosterone antagonist, spironolactone, has been documented [36,37]. Unfortunately, that sudden change in practice was associated with inappropriate use of the drug and an unacceptably high rate of serious adverse effects related to hyperkalaemia.

These contrasting experiences emphasise the need for practical guidance on the appropriate and safe use of treatments of proven benefit in the setting of HF.

2. Need for practical guidance

ACE inhibitors were the first “new” treatment introduced for HF.[2,3] In spite of a number of trials showing significant improvements in survival and reductions in hospital admissions for patients with HF, irrespective of aetiology, who received ACE inhibitors (Table 1), many

clinical surveys conducted in different countries revealed that a substantial proportion of patients who should have been treated with an ACE inhibitor were not receiving that treatment, both in primary care [38,39] and in hospital practice (although, in hospital practice, the rate of use of ACE inhibitors in patients with systolic dysfunction seems to have improved recently) [40–43]. Furthermore, the doses of ACE inhibitors used in clinical practice were (and remain) lower than the doses shown to have survival and other benefits in the clinical trials [34,35,44–49]. Both under-treatment and under-dosing may be more common in women and the elderly [34,35,44–53]. Recent studies have showed that this situation is improving but treatment remains suboptimal [34,35,44–53]. Why doctors were reluctant to prescribe ACE inhibitors is still not entirely clear. Initially there seems to have been undue concern about possible adverse effects, such as hypotension and renal insufficiency [38,54,55]. The experience with ACE inhibitors illustrates why, detailed guidance spelling out the benefits of treatment, appropriate selection of patients for treatment (and identification of those not suitable), dosing strategies and what adverse effects to anticipate (as well as how to deal with these) are important.

The second treatment shown to be convincingly beneficial in HF was a low dose of the aldosterone antagonist, spironolactone (Table 1) [8]. In patients with severe HF, already receiving a diuretic and ACE inhibitor, spironolactone improved survival and reduced hospital admissions, compared to placebo, irrespective of aetiology. A recent report suggested that publication of this trial (RALES) led to a rapid increase in use of spironolactone in the Canadian province of Ontario [36]. Unfortunately, however, this increase in use also seemed to be associated with an increase in hospital admissions and deaths related to hyperkalaemia. The Canadian and Danish experience (and that of other investigators) suggests that many of the problems encountered were due to misuse of spironolactone i.e., prescription in inappropriate patients, use of unnecessarily high doses of the drug and failure to closely monitor blood chemistry [37,56–58]. Paradoxically, physicians

Table 1
Benefits of evidence-based pharmacological treatment in patients with heart failure and a low left ventricular ejection fraction

Events avoided per 1000 patients treated	ACEI (1)	Beta-blocker (2)	Aldosterone blocker (3)	ARB (4)
Death	45	36	113	29
Patients hospitalised for HF	96	46	95	60
Death or HF hospitalisation	108	63	–	48

(1) Based on the treatment arm of the SOLVD Ref. [3] average follow-up 3.5 years.

(2) Based on the MERIT-HF study Refs. [7,9] — average follow-up 1 year.

(3) Based on the RALES trial Ref. [8] — average follow-up 2 years.

(4) Based on CHARM low LVEF trials Ref. [17] — average follow-up 3.3 years.

NOTE: a) shorter follow-up tends to exaggerate benefit b) absolute benefit is a function of absolute risk — RALES recruited much higher risk patients (NYHA Class III/IV) than the other trials (mainly NYHA Class II/III c) beta-blockers and spironolactone have largely been evaluated *in addition* to ACE inhibitors; ARBs have been evaluated in addition to ACE inhibitors *and beta-blockers*.

seem not to have been concerned about the possible adverse effects of an “old” drug and perhaps one thought easier to initiate without the blood pressure (and heart rate) lowering effects of an ACE inhibitor (or beta-blocker). As a generic drug, the usual educational programmes related to the launch of a new indication for a patented drug did not accompany the use of spironolactone in severe HF. Whatever their explanation, the findings from Ontario emphasise that encouragement of evidence-based treatment also carries with it the responsibility of ensuring the safe use of these drugs. We believe that the experience with spironolactone is another illustration of why detailed and practical guidance of the type presented here is important.

Beta blockers were the next class of agent shown to be of benefit in HF. Four large clinical trials, published between 1999 and 2001, showed that the addition of a beta blocker to standard treatment with a diuretic and ACE-inhibitor, led to a significant increase in survival, reduction in hospital admissions and improvement in symptoms and well-being, irrespective of aetiology (Table 1) [4,6,7,9,10,13]. Though both the efficacy and safety of beta blockers in HF was convincingly demonstrated in these trials, there was considerable concern about whether these drugs could be used safely in ordinary clinical practice. Regulatory labelling in many countries even restricted the use of beta blockers in HF to hospital-based specialists. Nowhere has the need for detailed practical guidance been more critical than with beta-blockers.

Angiotensin receptor blockers (ARBs) are the most recent class of drug to be shown to be of benefit in HF. Two large trials have shown morbidity and mortality benefits in patients with mild-moderately severe HF already treated with an ACE inhibitor, beta blocker and, in a minority of cases, spironolactone, irrespective of aetiology (Table 1) [11,12,15–18]. The prospect of using at least three neurohumoral antagonists (an ACE inhibitor, a beta blocker and an ARB or an aldosterone antagonist) and two or even three inhibitors of the renin–angiotensin–aldosterone system (an ACE inhibitor and an ARB or an aldosterone antagonist or both) has led us to update the earlier version of this guidance (see below) [59]. We also see the present guidance as a companion document to the European Society of Cardiology guidelines on the diagnosis and treatment of HF which have also recently been updated [31].

3. Development of recommendations

On the assumption that the previously demonstrated reluctance of doctors to prescribe ACE inhibitors [34,35,38–50,60] and beta-blockers [34,35,44,46–48,61–67] reflected, in part, a lack of practical, easy-to-follow advice on dosing, (both initiation and maintenance) and identification of potential problems, with clear recommendations on how to handle these if they should arise, a group of clinicians with expertise in the diagnosis and management

of HF met on one occasion (meeting sponsored by AstraZeneca) [50,68,69]. The output of that original meeting was a step-wise, concise set of clinical recommendations for each of beta-blockers, ACE inhibitors and spironolactone, based on the questions which a physician is likely to ask when considering treatment options; why should the treatment be given, in whom and when, where (in which setting), which agent and what dose, how to use, advice to patient, and problem solving [59]. The group did recognise, however, that even easy to follow practical recommendations are only valuable if widely disseminated to their target audience, and read and acted upon by that audience.

We were therefore pleased to discover that the original version of this guidance was also reproduced in the NICE guidelines for the treatment of HF which were distributed to all doctors in the UK [29].

However our practical recommendations were not (and are not) meant to replace existing guidelines but rather to complement them and offer a simple tool to facilitate their implementation [21–31].

Following the presentation and publication of the ARB trials in HF, the same committee met again in order to update the original guidance [11,12,15–18]. The opportunity was also taken to revise and update the prior guidance on spironolactone in light of the aforementioned findings from Ontario and elsewhere [36,56–58], as well as the publication of an important trial in patients with HF after myocardial infarction which used another aldosterone antagonist [70]. Similarly, the section on beta-blockers was updated to take account of a trial comparing two beta blockers [14], and a new trial with a further beta-blocker in very elderly patients with HF [20].

4. Practical recommendations

The recommendations start from on the assumption that the physician has made a clinical diagnosis of HF and may have initiated a diuretic to treat the symptoms and signs of sodium and water retention. Unfortunately, there is no good evidence-base for the use of diuretics, but the reader may wish to consult some examples of recommended practice [71,72].

Step 1 requires that the presence of left ventricular systolic dysfunction (typically defined as an ejection fraction <0.40) is confirmed using echocardiography, radionuclide ventriculography, radiological left ventricular angiography or cardiac magnetic resonance imaging. The use of one of these investigations is regarded as representing the minimum standard of care [21–31].

Step 2 requires the initiation of first-line therapy which, for all patients with HF due to LVSD, consists of both an ACE inhibitor and a beta-blocker, unless these are contraindicated. It is important that contra-indications and cautions are observed. It is recommended that the ACE inhibitor is initiated first, *quickly* followed by the beta-blocker. The

Table 2

Practical guidance on the use of ACE inhibitors in patients with HF due to left ventricular systolic dysfunction

Why? Two major randomised trials (CONSENSUS I and SOLVD-T) and a meta-analysis of smaller trials have conclusively shown that ACE inhibitors increase survival, reduce hospital admissions and improve NYHA Class and quality of life in patients with *all* grades of symptomatic HF. Other major randomised trials in patients with systolic dysfunction or HF after acute myocardial infarction (SAVE, AIRE, TRACE) have shown that ACE inhibitors increase survival. In patients with heart failure (ATLAS), the composite end-point of death or hospital admission was reduced by higher doses of ACE inhibitor compared to lower doses. ACE inhibitors have also been shown to delay or prevent the development of symptomatic HF in patients with *asymptomatic* left ventricular systolic dysfunction (LVSD).

In whom and when?

Indications:

- Potentially *all* patients with HF
- 1st line treatment (along with beta-blockers) in patients with NYHA Class II–IV HF; start as early as possible in course of disease. ACE inhibitors are also of benefit in patients with asymptomatic LVSD (NYHA Class I).

Contraindications:

- History of angioneurotic oedema
- Known bilateral renal artery stenosis

Cautions/seek specialist advice:

- Significant hyperkalaemia ($K^+ > 5.0$ mmol/L)
- Significant renal dysfunction (creatinine > 221 μ mol/L or > 2.5 mg/dL)
- Symptomatic or severe asymptomatic hypotension (systolic BP < 90 mmHg)

Drug interactions to look out for:

- K^+ supplements/ K^+ sparing diuretics e.g., amiloride and triamterene (beware combination preparations with furosemide).
- Aldosterone antagonists (spironolactone, eplerenone), angiotensin receptor blockers, NSAIDs*
- “Low salt” substitutes with a high K^+ content

Where?

- In the community for most patients
- Exceptions — see Cautions/specialist advice above

Which ACE inhibitor and what dose?

	Starting dose (mg)	Target dose (mg)
•Captopril	6.25 thrice daily	50 thrice daily
•Enalapril	2.5 Twice daily	10–20 twice daily
•Lisinopril	2.5–5 once daily	20–35 once daily
•Ramipril	2.5 once daily	5 twice daily or 10 once daily
•Trandolapril	0.5 once daily	4 once daily

How to use?

- Start with a low dose (see above)
- Double dose slowly at *not less than* 2 weekly intervals+
- Aim for target dose (see above) or, failing that, the highest tolerated dose
- Remember *some* ACE inhibitor is better than no ACE inhibitor
- Monitor blood pressure and blood chemistry (urea/BUN, creatinine, K^+)
- Check blood chemistry 1–2 weeks after initiation and 1–2 weeks after final dose titration
- When to stop up-titration/reduce dose/stop treatment— see *Problem solving*
- A specialist HF nurse may assist with patient education, follow-up (in person/by telephone), biochemical monitoring and dose up-titration

Advice to patient?

- Explain expected benefits (see *Why?*)
- Treatment is given to improve symptoms, to prevent worsening of HF leading to hospital admission and to increase survival
- Symptoms improve within a few weeks to a few months of starting treatment
- Advise patients to report principal adverse effects i.e., dizziness/symptomatic hypotension, cough—see *Problem solving*
- Advise patients to avoid NSAIDs* not prescribed by a physician (self-purchased “over the counter”) and salt substitutes high in K^+

Problem solving

Asymptomatic low blood pressure:

- Does not usually require any change in therapy

Symptomatic hypotension:

- If dizziness, light-headedness and/or confusion and a low blood pressure reconsider need for nitrates, calcium channel blockers** and other vasodilators
- If no signs/symptoms of congestion consider reducing diuretic dose
- If these measures do not solve problem seek specialist advice

Cough:

- Cough is common in patients with heart failure, many of whom have smoking related lung disease, including cancer
- Cough is also a symptom of pulmonary oedema which should be excluded when a new or worsening cough develops

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Table 2 (continued)

*Problem solving (continued)**Cough (continued):*

- ACE inhibitor induced cough rarely requires treatment discontinuation
- When a very troublesome cough does develop (e.g., one stopping the patient sleeping) and can be proven to be due to ACE inhibition (i.e., recurs after ACE inhibitor withdrawal and rechallenge) substitution of an angiotensin receptor blocker can be considered inhibition withdrawal and rechallenge) substitution of an angiotensin receptor blocker should be made (see Table 4)

Worsening renal function

- Some rise in urea (blood urea nitrogen), creatinine and potassium is to be expected after initiation of an ACE inhibitor; if an increase is small and asymptomatic no action is necessary
- An increase in creatinine of up to 50% above baseline, or 266 $\mu\text{mol/L}$ (3 mg/dL), *which ever is the smaller*, is acceptable
- An increase in potassium to ≤ 5.5 mmol/L is acceptable
- If urea, creatinine or potassium do rise excessively consider stopping concomitant nephrotoxic drugs (e.g., NSAIDs*), other potassium supplements/retaining agents (triamterene, amiloride, spironolactone/eprenone***) and, if no signs of congestion, reducing the dose of diuretic
- If greater rises in creatinine or potassium than those outlined above persist despite adjustment of concomitant medications, the dose of the ACE inhibitor should be halved and blood chemistry rechecked within 1 – 2 weeks; if there is still an unsatisfactory response specialist advice should be sought
- If potassium rises to >5.5 mmol/L or creatinine increases by $>100\%$ or to above 310 $\mu\text{mol/L}$ (3.5 mg/dL) the ACE inhibitor should be stopped and specialist advice sought
- Blood chemistry should be monitored frequently and serially until potassium and creatinine have plateaued

NB: it is very rarely necessary to stop an ACE inhibitor and clinical deterioration is likely if treatment is withdrawn — ideally, specialist advice should be sought before treatment discontinuation.

* Avoid unless essential.

** Calcium channel blockers should be discontinued unless absolutely essential (e.g., for angina or hypertension).

*** The safety and efficacy of an ACE inhibitor used with an ARB and spironolactone (as well as beta-blocker) is uncertain and the use of all 3 inhibitors of the renin–angiotensin–aldosterone system together is not recommended.

[†]Health care professionals with experience in the use of ACE inhibitors may wish to up-titrate the dose of ACE inhibitor more rapidly, taking account of the risk of adverse effects and the need for close monitoring of toleration and blood chemistry.

ACE inhibitor should initially be introduced at a low dose, up-titrated slowly and titrated to the target dose used in the clinical trials, checking tolerability and blood chemistry. Precisely the same approach should be adopted with the beta-blocker. These steps are detailed in Tables 2 and 3 In patients with severe HF (NYHA Class IV), beta-blockers should be initiated under expert supervision and only in those patients who are not currently decompensated.

The objective is to treat all patients with both an ACE inhibitor and a beta-blocker, both, ideally at the target doses used in the large randomised trials. There is now good evidence that this goal can be achieved in the majority of patients if a determined and concerted effort is made in hospital, at outpatient clinics and in the community [61,66,73–77]. It was, however, the panel's view that lower doses of both treatments were still likely to be of value and should be used if larger doses are not tolerated. These recommendations are set out in more detail in Table 2 for ACE inhibitors and Table 3 for beta-blockers.

ACE inhibitors are also of benefit in patients with *asymptomatic* left ventricular systolic dysfunction (i.e., in NYHA class I).

There is also new evidence since the publication of the first version of this guidance that an ARB should be used in place of an ACE inhibitor if the latter drug is not tolerated [12,16]. This is especially true if intolerance is due to cough (as ARBs do not cause cough). ARBs are as likely as an ACE inhibitor to cause hypotension and renal dysfunction but are probably less likely to cause angioedema.

Step 3 requires the prescription of *additional* therapy for those patients in whom there are persisting signs and symptoms of HF. The prior guidance recommended spironolactone in patients with severe symptoms (NYHA Class III/IV) and this has not changed. However, the experience from Ontario emphasises the importance of appropriate patient selection, the need to check baseline renal function and blood chemistry, to monitor these measures after the introduction of treatment and to use only low doses of this treatment. The newer, more selective aldosterone antagonist, eplerenone, may be substituted if spironolactone causes unpleasant anti-androgenic side effects such as painful gynaecomastia in men.

There is new evidence since the publication of the first version of this guidance that an ARB should be added in patients with persisting symptoms (NYHA Class II–IV). This treatment should be added after optimisation of ACE inhibitor and beta-blocker therapy.

It is *important* to note, however, that there is insufficient evidence as to whether *both* an ARB and spironolactone should be used in addition to an ACE inhibitor and little experience with this triple treatment. There is no definite evidence of benefit but renal dysfunction and hyperkalaemia are definitely more likely to occur. Use of these three agents together is, therefore, *not* recommended and if all three are used, very careful monitoring of blood chemistry, especially potassium and creatinine, is essential.

One or other of an ARB or an aldosterone antagonist *should* be used in a patient who remains symptomatic despite treatment with an ACE inhibitor, beta-blocker or,

Table 3

Practical guidance on the use of beta-blockers in patients with HF due to left ventricular systolic dysfunction

Why? Several major randomised controlled trials (i.e., USCP, CIBIS II, MERIT-HF, COPERNICUS) have shown, conclusively, that certain beta-blockers increase survival, reduce hospital admissions and improve NYHA Class and quality of life when added to standard therapy (diuretics, digoxin and ACE inhibitors) in patients with *stable* mild and moderate HF and in some patients with severe HF. In the SENIORS trial which differed substantially in design from the aforementioned studies (older patients, some patients with preserved left ventricular systolic function, longer follow-up), nebivolol appeared to have a smaller treatment effect, though direct comparison is difficult. One other trial (BEST) [32] did not show a reduction in all cause mortality but did report a reduction in cardiovascular mortality and is otherwise broadly consistent with the aforementioned studies. The COMET trial showed that carvedilol was substantially more effective than short-acting metoprolol tartrate* (long acting metoprolol succinate was used in MERIT-HF).

In whom and when?

Indications:

- Potentially *all* patients with *stable* mild and moderate HF; patients with severe HF should be referred for specialist advice
- 1st line treatment (along with ACE inhibitors) in patients with *stable* NYHA Class II–III HF; start as early as possible in course of disease

Contraindications:

- Asthma

Cautions/seek specialist advice:

- Severe (NYHA Class IV) HF
- Current or recent (<4 weeks) exacerbation of HF e.g., hospital admission with worsening HF
- Heart block or heart rate <60/min
- Persisting signs of congestion, hypotension/low blood pressure (systolic <90 mmHg), raised jugular venous pressure, ascites, marked peripheral oedema

Drug interactions to look out for:

- Verapamil/diltiazem (should be discontinued)**
- Digoxin, amiodarone

Where?

- In the community in stable patients (NYHA Class IV/severe HF patients should be referred for specialist advice)
- Not in unstable patients hospitalised with worsening HF
- Other exceptions – see *Cautions/seek specialist advice*

Which beta-blocker and what dose?

	Starting dose (mg)	Target dose (mg)
•Bisoprolol	1.25 once daily	10 once daily
•Carvedilol	3.125 twice daily	25–50 twice daily
•Metoprolol CR/XL	12.5–25 once daily	200 once daily*
•Nebivolol	1.25 once daily	10 mg once daily

How to use?

- Start with a low dose (see above)
- Double dose at *not less than* 2 weekly intervals
- Aim for target dose (see above) or, failing that, the highest tolerated dose
- Remember *some* beta-blocker is better than no beta-blocker
- Monitor HR, BP, clinical status (symptoms, signs — especially signs of congestion, body weight)
- Check blood chemistry 1–2 weeks after initiation and 1–2 weeks after final dose titration
- When to stop up-titration/reduce dose/stop treatment— see *Problem solving*
- A specialist HF nurse may assist with patient education, follow-up (in person/by telephone), biochemical monitoring and dose up-titration

Advice to patient?

- Explain expected benefits (see *Why?*)
- Treatment is given to improve symptoms, prevent worsening of HF leading to hospital admission and to increase survival
- Symptomatic improvement may develop slowly after starting treatment, taking 3–6 months or longer
- Temporary* symptomatic deterioration *may* occur during initiation/up-titration phase; in long-term beta blockers improve well-being
- Advise patient to report deterioration (see *Problem solving*) and that deterioration (tiredness, fatigue, breathlessness) can usually be easily managed by adjustment of other medication; patients should be advised not to stop beta-blocker therapy without consulting their physician
- To detect and treat deterioration early, patients should be encouraged to weigh themselves daily (after waking, before dressing, after voiding, before eating) and to increase their diuretic dose should their weight increase, persistently (>2 days), by >1.5–2.0 kg.***

Problem solving

Worsening symptoms/signs (e.g., increasing dyspnoea, fatigue, oedema, weight gain):

- If increasing congestion increase dose of diuretic and/or halve dose of beta-blocker (if increasing diuretic doesn't work)
- If marked fatigue (and/or bradycardia—see below) halve dose of beta-blocker (rarely necessary)
- Review patient in 1–2 weeks; if not improved seek specialist advice
- If serious deterioration halve dose of beta-blocker or stop this treatment (rarely necessary); seek specialist advice

Low heart rate:

- If <50 beats/min and worsening symptoms — halve dose beta-blocker or, if severe deterioration, stop beta-blocker (rarely necessary)
- Review need for other heart rate slowing drugs e.g., digoxin, amiodarone, diltiazem/verapamil**

(continued on next page)

Table 3 (continued)

Problem solving

Low heart rate (continued):

- Arrange ECG to exclude heart block
- Seek specialist advice

Asymptomatic low blood pressure:

- Does not usually require any change in therapy

Symptomatic hypotension:

- If dizziness, light-headedness and/or confusion and a low blood pressure reconsider need for nitrates, calcium channel blockers** and other vasodilators
- If no signs/symptoms of congestion consider reducing diuretic dose or ACE inhibitor
- If these measures do not solve problem seek specialist advice

NB: beta-blockers should not be stopped suddenly unless absolutely necessary (there is a risk of a “rebound” increase in myocardial ischaemia/infarction and arrhythmias) — ideally specialist advice should be sought before treatment discontinuation.

* Metoprolol tartrate should not be used in preference to an evidence-based beta-blocker in HF.

** Calcium channel blockers should be discontinued unless absolutely necessary and diltiazem and verapamil are generally contraindicated in HF.

*** This is generally good advice for all patients with HF.

ideally, both. It is important that contra-indications and cautions are observed. Whichever is used, it should be

Table 4

Practical guidance on the use of ARBs in patients with HF due to left ventricular systolic dysfunction

Why? When added to standard therapy, including an ACE inhibitor, in patients with all grades of symptomatic HF, the ARBs valsartan and candesartan have been shown, in two major randomised trials (Val-HeFT and CHARM), to reduce HF hospital admissions, improve NYHA class and maintain quality of life. The two CHARM low LVEF trials (CHARM Alternative and CHARM-Added) also showed that candesartan reduced all-cause mortality. In patients previously intolerant of an ACE inhibitor, candesartan has been shown to reduce the risk of the composite outcome of cardiovascular death or HF hospitalisation, the risk of HF hospital admission and to improve NYHA class. These findings in HF are supported by another randomised trial in patients with left ventricular systolic dysfunction, heart failure or both complicating acute myocardial infarction (VALIANT) in which valsartan was as effective as the ACE inhibitor captopril in reducing mortality and cardiovascular morbidity.

In whom and when?

Indications:

- Potentially *all* patients with HF
- 1st line treatment (along with beta-blockers) in patients with NYHA Class II–IV HF intolerant of an ACE inhibitor
- 2nd line treatment (after optimisation of ACE inhibitor and beta-blocker*) in patients with NYHA Class II–IV HF

Contraindications:

- Known bilateral renal artery stenosis

Cautions/seek specialist advice:

- Significant hyperkalaemia ($K^+ > 5.0$ mmol/L)
- Significant renal dysfunction (creatinine > 221 μ mol/L or > 2.5 mg/dL)
- Symptomatic or severe asymptomatic hypotension (systolic BP < 90 mmHg)

Drug interactions to look out for:

- K^+ supplements/ K^+ sparing diuretics e.g., amiloride and triamterene (beware combination preparations with furosemide). Aldosterone antagonists (spironolactone, eplerenone), ACE inhibitors, NSAIDS**
- “Low salt” substitutes with a high K^+ content

Where?

- In the community for most patients
- Exceptions – see *Cautions/specialist advice* above

Which ARB and what dose?

	Starting dose (mg)	Target dose (mg)
• Candesartan	4 or 8 mg once daily	32 mg once daily
• Valsartan	40 mg twice daily	160 mg twice daily

How to use?

- Start with a low dose (see above)
- Double dose at *not less than 2* weekly intervals
- Aim for target dose (see above) or, failing that, the highest tolerated dose
- Remember *some* ARB is better than no ARB
- Monitor blood pressure and blood chemistry (urea/BUN, creatinine, K^+)
- Check blood chemistry 1–2 weeks after initiation and 1–2 weeks after final dose titration
- When to stop up-titration/reduce dose/stop treatment— see *Problem solving*
- A specialist HF nurse may assist with patient education, follow-up (in person/by telephone), biochemical monitoring and dose up-titration

Table 4 (continued)

Advice to patient?

- Explain expected benefits (see *Why?*)
- Treatment is given to improve symptoms, prevent worsening of HF leading to hospital admission and to increase survival
- Symptoms improve within a few weeks to a few months of starting treatment
- Advise patients to principal adverse effect i.e., report dizziness/symptomatic hypotension
- Advise patients to avoid NSAIDs** not prescribed by a physician (self-purchased “over the counter”) and salt substitutes high in K⁺

Problem solving

Asymptomatic low blood pressure:

- Does not usually require any change in therapy

Symptomatic hypotension:

- If dizziness, light-headedness and/or confusion and a low blood pressure reconsider need for nitrates, calcium channel blockers*** and other vasodilators
- If no signs/symptoms of congestion consider reducing diuretic dose
- If these measures do not solve problem seek specialist advice

Worsening renal function:

- Some rise in urea (blood urea nitrogen), creatinine and potassium is to be expected after initiation of an ARB; if the increase is small and asymptomatic no action is necessary
- An increase in creatinine of up to 50% above baseline, or 266 μmol/L (3 mg/dL), *which ever is the smaller*, is acceptable
- An increase in potassium to ≤5.5 mmol/L is acceptable
- If urea, creatinine or potassium do rise excessively consider stopping concomitant nephrotoxic drugs (e.g., NSAIDs**), other potassium supplements/retaining agents (triamterene, amiloride, spironolactone/eplerenone*) and, if no signs of congestion, reducing the dose of diuretic
- If greater rises in creatinine or potassium than those outlined above persist despite adjustment of concomitant medications, the dose of the ARB should be halved and blood chemistry rechecked within 1–2 weeks; if there is still an unsatisfactory response specialist advice should be sought
- If potassium rises to >5.5 mmol/L or creatinine increases by >100% or to above 310 μmol/L (3.5 mg/dL) the ARB should be stopped and specialist advice sought
- Blood chemistry should be monitored frequently and serially until potassium and creatinine have plateaued

NB: it is very rarely necessary to stop an ARB and clinical deterioration is likely if treatment is withdrawn — ideally, specialist advice should be sought before treatment discontinuation.

* The safety and efficacy of an ARB used with an ACE inhibitor *and* spironolactone (as well as beta-blocker) is uncertain and the use of all 3 inhibitors of the renin–angiotensin–aldosterone system together is not recommended.

** Avoid unless essential.

*** Calcium channel blockers should be discontinued unless absolutely essential (e.g., for angina or hypertension).

initiated at a low dose and then up-titrated checking tolerability and blood chemistry. The recommendations for an ARB are set out in Table 4 and aldosterone antagonists in Table 5.

In many hospital centres and in primary care, specially trained HF nurses successfully assist in the initiation, up titration and monitoring (including adjustment of dose as necessary) of all of the aforementioned evidence-based treatments [73,77–79].

Digoxin has not been included in this revised summary, though one large trial showed that it reduced the need for hospital admission, particularly for worsening HF, though this treatment had no effect on survival, either positive or negative.⁵ It is also important to note that the trial was conducted at a time when the role of beta-blockers, aldosterone antagonists and ARBs in the treatment of heart failure had not been established. Digoxin may still have a special role in the patient with atrial fibrillation when rapid control of the ventricular rate is needed (which cannot be achieved with cautious introduction and up-titration of a beta-blocker). This initial treatment with digoxin should not preclude subsequent introduction of a beta-blocker. Digoxin can be withdrawn if an excessive bradycardia develops during combined digoxin beta-blocker treatment.

In another recent study (A-HeFT), the combination of hydralazine (initiated at a dose of 37.5 mg and titrated to a

target of 75 mg tid) and isosorbide dinitrate (initiated at a dose of 20 mg and titrated to a dose of 40 mg tid), given in a combined medication formulation, improved survival and additional outcomes when added to other evidence-based treatments in African-Americans with NYHA class III or IV HF [19]. This combination had been shown previously to reduce mortality in patients with heart failure in the “pre-ACE inhibitor era”. Subsequently, in a head to head comparison, the combination proved inferior to enalapril. The A-HeFT trial now suggests that hydralazine and isosorbide dinitrate is of benefit when *added* to an ACE inhibitor (and beta-blocker and spironolactone), at least in black Americans. At present the place of hydralazine and isosorbide dinitrate in other patients with HF is as an alternative when neither an ACE inhibitor nor ARB is tolerated [80,81].

5. Conclusions

Under-prescribing and under-dosing of some treatments which reduce both mortality and morbidity in patients with HF in controlled clinical trials is a persisting problem. This under-treatment has denied patients the benefits of these treatments; it may also have had an adverse effect on health services (in terms of avoidable hospital admissions).

Table 5

Practical guidance on the use of aldosterone antagonists in patients with HF due to left ventricular systolic dysfunction

Why? The RALES study showed that low dose spironolactone increased survival, reduced hospital admissions and improved NYHA Class when added to standard therapy (diuretic, digoxin, ACE inhibitor and, in a minority of cases, a beta-blocker) in patients with severe (NYHA Class III or IV) HF. These findings in HF are supported by another randomised trial in patients with left ventricular systolic dysfunction and heart failure (or diabetes) complicating acute myocardial infarction (EPHESUS) in which another aldosterone antagonist, eplerenone, increased survival and reduced hospital admissions for cardiac causes.

In whom and when?

Indications:

- Potentially all patients with symptomatically moderately severe or severe HF (Class III/IV NYHA)
- Second line therapy (after ACE inhibitors and beta-blockers*) in patients with NYHA Class III–IV HF; there is no evidence of benefit in patients with milder HF

Cautions/seek specialist advice:

- Significant hyperkalaemia ($K^+ > 5.0$ mmol/L)**
- Significant renal dysfunction (creatinine > 221 μ mol/L or 2.5 mg/dL)**

Drug interactions to look out for:

- K^+ supplements/ K^+ sparing diuretics e.g., amiloride and triamterene (beware combination preparations with furosemide). ACE inhibitors, ARBs, NSAIDs***
- “Low salt” substitutes with a high K^+ content

Where?

- In the community or in hospital
- Exceptions — see Cautions/seek specialist advice

*Which dose? ***

	Starting dose (mg)	Target dose (mg)
• Spironolactone	25 once daily or on alternate days	25–50mg once daily
• Eplerenone	25 once daily	50 once daily

How to use?

- Start with a low dose (see above)
- Check blood chemistry at 1, 4, 8 and 12 weeks; 6, 9 and 12 months; 6 monthly thereafter
- If K^+ rises above 5.5 mmol/L or creatinine rises to 221 μ mol/L (2.5 mg/dL) reduce dose to 25 mg on alternate days and monitor blood chemistry closely
- If K^+ rises to ≥ 6.0 mmol/L or creatinine to > 310 μ mol/L (3.5 mg/dL) stop spironolactone immediately and seek specialist advice
- A specialist HF nurse may assist with patient education, follow-up (in person/by telephone), biochemical monitoring and dose up-titration

Advice to patient?

- Explain expected benefits (see *Why?*)
- Treatment is given to improve symptoms, prevent worsening of HF leading to hospital admission and to increase survival
- Symptom improvement occurs within a few weeks to a few months of starting treatment
- Avoid NSAIDs** *not prescribed by a physician (self-purchased “over the counter”) and salt substitutes high in K^+
- If diarrhoea and/or vomiting occurs patients should stop spironolactone and contact their physician

Problem solving

Worsening renal function/hyperkalaemia:

• See *How to use?* section

- Major concern is hyperkalaemia (≥ 6.0 mmol/L); although this was uncommon in RALES it has been seen more commonly in clinical practice; conversely, a high normal potassium may be desirable in HF patients, especially if taking digoxin
- It is important to avoid other K^+ retaining drugs (e.g., K^+ sparing diuretics such as amiloride and triamterene) and nephrotoxic agents (e.g., NSAIDs***)
- The risk of hyperkalaemia and renal dysfunction when an aldosterone antagonist is given to patients already taking an ACE inhibitor and ARB is higher than when an aldosterone is added to just an ACE inhibitor or ARB given singly; close and careful monitoring is mandatory*
- Some “low salt” substitutes have a high K^+ content
- Male patients treated with spironolactone may develop breast discomfort and/or gynaecomastia (these problems are significantly less common with eplerenone)

* The safety and efficacy of spironolactone used with an ACE inhibitor and an ARB (as well as beta-blocker) is uncertain and the use of all 3 inhibitors of the renin–angiotensin–aldosterone system together is not recommended.

** It is extremely important that these cautions and doses are adhered to in the light of recent evidence of serious hyperkalaemia with spironolactone in usual clinical practice in Ontario [36].

*** Avoid unless essential.

Conversely, inappropriate use of spironolactone appears to have led to an unacceptably high risk of serious hyperkalaemia-related hospitalisations and death. The preparation of these concise and practical clinical recommendations for

the prescribing of proven pharmacological treatments should provide doctors with the confidence to practise evidence-based medicine in their patients with HF whilst avoiding unnecessary toxicity. This should improve not only

the outcomes for the individual patient but also reduce the burden of HF on health care systems [82].

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References

- [1] Whitcomb ME. Why we must teach evidence-based medicine. *Acad Med* 2005;80:1–2.
- [2] 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.
- [3] The Study of Left Ventricular Dysfunction (SOLVD) Investigators. Effects of Enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293–302.
- [4] Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. carvedilol heart failure study group. *N Engl J Med* 1996;334:1349–55.
- [5] The effect of digoxin on mortality and morbidity in patients with heart failure. The digitalis investigation group. *N Engl J Med* 1997;336:525–33.
- [6] The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9–13.
- [7] Effect of metoprolol CR/XL in chronic heart failure: metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). *Lancet* 1999;353:2001–7.
- [8] 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.
- [9] Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;283:1295–302.
- [10] 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.
- [11] Cohn JN, Tognoni G, 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.
- [12] Maggioni AP, Anand I, Gottlieb SO, et al, Val-HeFT Investigators (Valsartan Heart Failure Trial). Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol* 2002;40:1414–21.
- [13] 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.
- [14] 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;362:7–13.
- [15] McMurray JJ, Ostergren J, Swedberg K, et al, 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.
- [16] Granger CB, McMurray JJ, Yusuf S, et al, 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;362:772–6.
- [17] Young JB, Dunlap ME, Pfeffer MA, et al, Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) Investigators and Committees. Mortality and morbidity reduction with Candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. *Circulation* 2004;110:2618–26.
- [18] O'Meara E, Solomon S, McMurray J, et al. Effect of candesartan on New York Heart Association functional class. Results of the Candesartan in Heart failure: assessment of Reduction in Mortality and Morbidity (CHARM) programme. *Eur Heart J* 2004;25:1920–6.
- [19] Taylor AL, Ziesche S, Yancy C, et al, African-American Heart Failure Trial Investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. *N Engl J Med* 2004;351:2049–57.
- [20] Flather MD, Shibata MC, Coats AJ, et al, 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.
- [21] US Department of Health and Human Services. Agency for Health Care Policy and Research. Heart Failure: evaluation and care of patients with left-ventricular systolic dysfunction. Rockville: The Agency; 1994 (Clinical Practice Guideline No. 11). AHCPR Publication No. 94-0612.
- [22] McMurray J, Gyarfas I, Wenger NK, et al. Concise guide to the management of heart failure. *Am J Geriatr Cardiol* 1996;5:13–30.
- [23] New Zealand guidelines for the management of chronic heart failure. The National Heart Foundation of New Zealand Cardiac Society of Australia and New Zealand and the Royal New Zealand College of General Practitioners Working Party. *N Z Med J* 1997;110:99–107.
- [24] Heart Failure Society of America (HFSA). Practice guidelines. HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dysfunction—pharmacological approaches. *J Card Fail* 1999;5:357–82.
- [25] Hoppe UC, Erdmann E, Kommission Klinische Kardiologie. Guidelines for the treatment of chronic heart failure. Issued by the executive committee of the German society of cardiology—heart and circulation research, compiled on behalf of the commission of clinical cardiology in cooperation with pharmaceutical commission of the German physicians' association. *Z Kardiol* 2001;90:218–37.
- [26] Krum H. National heart foundation of Australia and cardiac society of Australia and New Zealand chronic heart failure clinical practice guidelines Writing Panel. Guidelines for management of patients with chronic heart failure in Australia. *Med J Aust* 2001;174:459–66. NOTE: these guidelines are currently under revision (H. Krum, personal communication).
- [27] 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 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2001;38:2101–13.
- [28] Liu P, Arnold JM, Belenkie I, et al, Canadian Cardiovascular Society. The 2002/3 Canadian Cardiovascular Society consensus guideline update for the diagnosis and management of heart failure. *Can J Cardiol* 2003;19:347–56.

- [29] National Institute for Clinical Excellence (NICE). Clinical Guideline 5. Chronic heart failure. Management of chronic heart failure in adults in primary and secondary care. London July 2003. http://www.nice.org.uk/pdf/Full_HF_Guideline.pdf.
- [30] Mosterd WL, Rosier PF. Guideline 'Chronic heart failure'. *Ned Tijdschr Geneesk* 2004;148:609–14.
- [31] Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005 Jun;26(11):1115–40.
- [32] Bungard TJ, McAlister FA, Johnson JA, Tsuyuki RT. Underutilisation of ACE inhibitors in patients with congestive heart failure. *Drugs* 2001;61:2021–33.
- [33] Hobbs FD, Jones MI, Allan TF, et al. European survey of primary care physician perceptions on heart failure diagnosis and management (Euro-HF). *Eur Heart J* 2000;21:1877–87.
- [34] Cleland JGF, Cohen-Solal A, Aguilar JC, et al. Management of heart failure in primary care (the IMPROVEMENT of Heart Failure Programme): an international survey. *Lancet* 2002;360:1631–9.
- [35] 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.
- [36] Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004;351:543–51.
- [37] Svensson M, Gustafsson F, Galatius S, et al. Hyperkalaemia and impaired renal function in patients taking spironolactone for congestive heart failure: retrospective study. *Br Med J* 2003;327:1141–2.
- [38] Mair FS, Crowleu TS, Brundred PE. Prevalence, aetiology and management of heart failure in general practice. *Br J Gen Pract* 1996;46:77–9.
- [39] Houghton A, Cowley A. Why are angiotensin converting enzyme inhibitors underutilized in the treatment of heart failure by general practitioners? *In JK Cardiol* 1997;59:7–10.
- [40] Philbin EF, Andreou C, Rocco TA, et al. Patterns of angiotensin-converting enzyme inhibitors use in congestive heart failure in two community hospitals. *Am J Cardiol* 1996;77:832–8.
- [41] Smith NL, Psaty BM, Pitt B, et al. Temporal patterns in the medical treatment of congestive heart failure with angiotensin-converting enzyme inhibitors in older adults, 1989 through 1995. *Arch Intern Med* 1998;158:1074–80.
- [42] Reis SE, Holubkov R, Edmundosicz D, et al. Treatment of patients admitted to the hospital with congestive heart failure: speciality-related disparities in practice patterns and outcomes. *J Am Coll Cardiol* 1997;30:733–8.
- [43] Lenzen MJ, Scholte OP, Reimer WJ, et al. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. *Eur Heart J* 2004;25:1214–20.
- [44] Boyles PJ, Peterson GM, Bleasel MD, Vial JH. Undertreatment of congestive heart failure in an Australian setting. *J Clin Pharm Ther* 2004;29:15–22.
- [45] Masoudi FA, Rathore SS, Wang Y, et al. National patterns of use and effectiveness of angiotensin-converting enzyme inhibitors in older patients with heart failure and left ventricular systolic dysfunction. *Circulation* 2004;110:724–31.
- [46] Muntwyler J, Cohen-Solal A, Freemantle N, et al. Relation of sex, age and concomitant diseases to drug prescription for heart failure in primary care in Europe. *Eur J Heart Fail* 2004;6:663–8.
- [47] Murphy NF, Simpson CR, McAlister FA, et al. National survey of the prevalence, incidence, primary care burden, and treatment of heart failure in Scotland. *Heart* 2004;90:1129–36.
- [48] Roman-Sanchez P, Conthe P, Garcia-Alegria J, et al. Factors influencing medical treatment of heart failure patients in Spanish internal medicine departments: a national survey. *QJM* 2005;98:127–38.
- [49] Krum H, Tonkin AM, Currie R, Djundjek R, Johnston CI. Chronic heart failure in Australian general practice. The Cardiac Awareness Survey And Evaluation (CASE) Study. *Med J Aust* 2001;174:439–44.
- [50] Kasje WN, Denig P, Stewart RE, et al. Physician, organisational and patient characteristics explaining the use of angiotensin converting enzyme inhibitors in heart failure treatment: a multilevel study. *Eur J Clin Pharmacol* 2005;11 (Electronic publication ahead of print, Mar.).
- [51] Rathore SS, Foody JM, Wang Y, et al. Sex, quality of care, and outcomes of elderly patients hospitalized with heart failure: findings from the National Heart Failure Project. *Am Heart J* 2005;149:121–8.
- [52] Fruhwald FM, Rehak P, Maier R, et al. Austrian survey of treating heart failure—AUSTRIA. *Eur J Heart Fail* 2004;6:947–52.
- [53] Smith NL, Chan JD, Rea TD, et al. Time trends in the use of beta-blockers and other pharmacotherapies in older adults with congestive heart failure. *Am Heart J* 2004;148:710–7.
- [54] McMurray JJ. Failure to practice evidence-based medicine: why do physicians not treat patients with heart failure with angiotensin-converting enzyme inhibitors? *Eur Heart J* 1998;19(Suppl L):L15–21.
- [55] Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000;160:685–93.
- [56] McMurray JJ, O'Meara E. Treatment of heart failure with spironolactone — trial and tribulations. *N Engl J Med* 2004;351:526–8.
- [57] Witham MD, Gillespie ND, Struthers AD. Tolerability of spironolactone in patients with chronic heart failure — a cautionary message. *Br J Clin Pharmacol* 2004;58:554–7.
- [58] Tamirisa KP, Aaronson KD, Koelling TM. Spironolactone-induced renal insufficiency and hyperkalemia in patients with heart failure. *Am Heart J* 2004;148:971–8.
- [59] McMurray J, Cohen-Solal A, Dietz R, et al. Practical recommendations for the use of ACE inhibitors, beta-blockers and spironolactone in heart failure: putting guidelines into practice. *Eur J Heart Fail* 2001;3:495–502.
- [60] Butler J, Arbogast PG, Daugherty J, et al. Outpatient utilization of angiotensin-converting enzyme inhibitors among heart failure patients after hospital discharge. *J Am Coll Cardiol* 2004;43:2036–43.
- [61] Maggioni AP, Sinagra G, Opasich C, et al. Beta blockers in patients with congestive heart failure: guided use in clinical practice Investigators. Treatment of chronic heart failure with beta adrenergic blockade beyond controlled clinical trials: the BRING-UP experience. *Heart* 2003;89:299–305.
- [62] Pont LG, Sturkenboom MC, van Gilst WH, et al. Trends in prescribing for heart failure in Dutch primary care from 1996 to 2000. *Pharmacoepidemiol Drug Saf* 2003;12:327–34.
- [63] Rutten FH, Grobbee DE, Hoes AW. Differences between general practitioners and cardiologists in diagnosis and management of heart failure: a survey in every-day practice. *Eur J Heart Fail* 2003;5:337–44.
- [64] McKee SP, Leslie SJ, LeMaitre JP, et al. Management of chronic heart failure due to systolic left ventricular dysfunction by cardiologist and non-cardiologist physicians. *Eur J Heart Fail* 2003;5:549–55.
- [65] Di Lenarda A, Scherillo M, Maggioni AP, et al, TEMISTOCLE Investigators. Current presentation and management of heart failure in cardiology and internal medicine hospital units: a tale of two worlds—the TEMISTOCLE study. *Am Heart J* 2003;146:E12.
- [66] Franciosa JA, Massie BM, Lukas MA, et al. Beta-blocker therapy for heart failure outside the clinical trial setting: findings of a community-based registry. *Am Heart J* 2004;148:718–26.
- [67] Rywik TM, Rywik SL, Korewicki J, et al. A survey of outpatient management of elderly heart failure patients in Poland—treatment patterns. *Int J Cardiol* 2004;95:177–84.
- [68] Manyemba J, Mangoni AA, Pettingale KW, Jackson SH. Determinants of failure to prescribe target doses of angiotensin-converting enzyme inhibitors for heart failure. *Eur J Heart Fail* 2003;5:693–6.

- [69] Bennett AA, Brien JA, Macdonald PS. Barriers to diagnosing and managing heart failure in primary care. *Med J Aust* 2005;182:309.
- [70] 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.
- [71] Stromberg A, Martensson J, Fridlund B, et al. Nurse-led heart failure clinics improve survival and self-care behaviour in patients with heart failure: results from a prospective, randomised trial. *Eur Heart J* 2003;24:1014–23.
- [72] Blue L, Stewart S. *Improving outcomes in chronic heart failure* second edition. London: Br Med J Books; 2004.
- [73] Ekman I, Fagerberg B, Andersson B, et al. Can treatment with angiotensin-converting enzyme inhibitors in elderly patients with moderate to severe chronic heart failure be improved by a nurse-monitored structured care program? A randomized controlled trial. *Heart Lung* 2003;32:3–9.
- [74] Tandon P, McAlister FA, Tsuyuki RT, et al. The use of beta-blockers in a tertiary care heart failure clinic: dosing, tolerance, and outcomes. *Arch Intern Med* 2004;164:769–74.
- [75] Ansari M, Shlipak MG, Heidenreich PA, et al. Improving guideline adherence: a randomized trial evaluating strategies to increase beta-blocker use in heart failure. *Circulation* 2003;107:2799–804.
- [76] Fonarow GC, Gheorghide M, Abraham WT. Importance of in-hospital initiation of evidence-based medical therapies for heart failure — a review. *Am J Cardiol* 2004;94:1155–60.
- [77] Jain A, Mills P, Nunn LM, et al. Success of a multidisciplinary heart failure clinic for initiation and up-titration of key therapeutic agents. *Eur J Heart Fail* 2005;7:405–10.
- [78] Blue L, McMurray J. How much responsibility should heart failure nurses take? *Eur J Heart Fail* 2005;7:351–61.
- [79] McAlister FA, Stewart S, Ferrua S, McMurray JJ. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: a systematic review of randomized trials. *J Am Coll Cardiol* 2004;44:810–9.
- [80] Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine–isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303–10.
- [81] Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a veterans administration cooperative study. *N Engl J Med* 1986; 314:1547–52.
- [82] Andersson F, Cline C, Ryden-Bergsten T, Erhardt L. Angiotensin converting enzyme (ACE) inhibitors and heart failure. The consequences of underprescribing. *Pharmacoeconomics* 1999;15:535–50.