Treatment of chronic heart failure: a comparison between the major guidelines

John McMurray1* and Karl Swedberg2,3

1 Department of Cardiology, Western Infirmary, Dumbarton Road, Glasgow G11 6NT, Scotland, UK; 2 Department of Emergency and Cardiovascular Medicine, Sahlgrenska Academy, Göteborg University, Göteborg, Sweden; and 3 Department of Medicine, Sahlgrenska University Hospital/Östra, 416 45 Göteborg, Sweden

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Because of rapid advances in the treatment of chronic heart failure, four important guidelines, including those from the European Society of Cardiology, have recently been updated. This review compares and contrasts the levels of evidence and classes of recommendation given to each of the key pharmacological and device therapies advocated by these guidelines. Possible explanations for discrepancies between the guidelines are discussed. Future approaches that might clarify the grade of evidence allocated and class of recommendation made are also described.

KEYWORDS
Heart failure; Guidelines; ACE inhibitor; Beta-blocker; Angiotensin receptor blocker; Aldosterone antagonist

Introduction

There have been several recent and important advances in the use of drugs and devices to further reduce morbidity and mortality in patients with heart failure and a low left ventricular ejection fraction (LVEF) (hereafter referred to as heart failure). These new developments led to the updating of four major guidelines.1–4 The objective of this review was to compare the updated guidelines from the European Society of Cardiology (ESC)1 with those from the American College of Cardiology/American Heart Association (ACC/AHA),2 the Canadian Cardiovascular Society (CCS),3 and the Heart Failure Society of America (HFSA).4 We wished to identify and explain discrepancies and examine their implications for patient’s management. Not all treatment recommendations could be compared in the space available, so we have focused on the most important pharmacological and device treatments, as well as coronary revascularization and multidisciplinary ‘disease management programmes’.

Overview and structure of the guidelines

The ESC, ACC/AHA, and HFSA guidelines are published as longer (‘full’) and shorter (‘summary’) versions—the electronic summary versions are 26 (171 references), 30 (174), and 29 (105) pages long and the CCS one is 23 pages in length (171). The shorter versions are the focus of our review. An erratum has been published to the ACC/AHA guideline.2 Although relatively similar in length, the breadth of the content varies substantially, with some covering acute as well as chronic heart failure. Although the ESC, HFSA, and CCS guidelines discuss treatments according to the functional limitation, quantified by the NYHA classification, the ACC/AHA guideline uses a four-stage classification ranging from patients at risk of heart failure, without structural heart disease, to those with structural disease and refractory heart failure. All use a similar grading of the level of evidence (Table 1), but instead of using classes of recommendation, the HFSA committee uses ‘is recommended’, ‘should be considered’, or ‘may be considered’ (which we have equated to class I, IIa, and IIb, respectively).

Pharmacological therapy

ACE-inhibitors

There is clear agreement that an ACE-inhibitor and beta-blocker form the cornerstone of the treatment for heart failure—both are assigned an evidence level of A and a class I recommendation (Table 2). The ESC and CCS guidelines recommend the use of particular ACE-inhibitors and doses shown to be effective in randomized, controlled, outcome trials. The ACC/AHA guideline advocates a wider range of drugs, and the HFSA guideline does not specify drugs or doses.

Beta-blockers

For beta-blockers, all except the HFSA guideline specify bisoprolol, carvedilol, and metoprolol succinate CR/XL (and the ESC guideline also recommends nebivolol).
Aldosterone antagonists

The guidelines show slightly less agreement when it comes to the use of aldosterone antagonists in the treatment of severely symptomatic patients. The HFSA guideline assigns a level of evidence of A, whereas the other three guidelines assign a level B. Why the difference here? The difference between an A and a B level of evidence reflects multiplicity of trials (or meta-analysis) (Table 1). There is only one randomized trial with spironolactone, RALES, specifically in patients with severe chronic heart failure. Therefore, the disagreement is presumably about whether to take account of a ‘positive’ study, EPHESUS, with another drug in the same class, eplerenone, in patients with a low EF and heart failure or diabetes after acute myocardial infarction. Although it seems that the evidence from this trial in myocardial infarction was not taken into account here, by three of the four committees, evidence from trials in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Classification of recommendations</th>
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<tr>
<td>Class I Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful, and/or effective</td>
<td></td>
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<tr>
<td>Class II Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure/therapy</td>
<td></td>
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<tr>
<td>IIa Weight of evidence/opinion is in favour of usefulness/efficacy</td>
<td></td>
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<tr>
<td>IIb Usefulness/efficacy is less well established by evidence/opinion</td>
<td></td>
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<tr>
<td>Level of evidence</td>
<td></td>
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<tr>
<td>Level of evidence A Data are derived from multiple randomized clinical trials or meta-analyses</td>
<td></td>
</tr>
<tr>
<td>Level of evidence B Data are derived from a single randomized trial or non-randomized studies</td>
<td></td>
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<tr>
<td>Level of evidence C Only consensus opinion of experts, case studies, or standard of care</td>
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Angiotensin receptor blockers

The first substantial disagreement between the guidelines arises in connection with angiotensin receptor blockers (ARBs). Here, the recommendations are more complex. The patient intolerant of an ACE-inhibitor is easy to deal with. The ESC guideline gives an evidence level of B, whereas the other three guidelines give an evidence level of A (all make a class I recommendation). The ESC guidelines committee took the position that there is only one specific trial in the patients intolerant of ACE-inhibitors i.e. CHARM-Alternative trial. The North American guidelines appear to have accepted the separate publication of a retrospective subgroup analysis of the effect of valsartan on ACE-inhibitor untreated (as opposed to specifically intolerant) patients as equivalent to a prospective randomized trial. We do not think, however, that this inconsistency, should have a major impact on the management of patients.

The level of evidence and the grade of recommendation given to the addition of an ARB in patients who remain symptomatic despite treatment with an ACE-inhibitor and beta-blocker are more complicated. Here, the ESC guideline introduces a new approach, grading the evidence for particular outcomes—specifically hospital admission for worsening heart failure and, separately, death. As the first of these was reduced in two large prospective randomized trials i.e. CHARM-Added and Val-HeFT, the level of evidence allocated is A (with a class I recommendation). The level and recommendation given for reduction in death are B and IIa, respectively, reflecting the inconsistent findings of Val-HeFT and CHARM-Added. The CCS committee gives a level A, class I recommendation, with the explanatory text implying that this refers to the effect of ARBs in reducing hospital admissions. The two US guidelines do not
differentiate between outcomes. The HFSA guideline assigns an evidence level of A for this combination (under 'poly-pharmacy' and not in the section on ARBs) and says this combination ‘should be considered’ i.e. equating to a class IIa recommendation. Therefore, the ESC, CCS, and HFSA guidelines are relatively consistent in giving the ‘add on’ ARB treatment a level A or B and class I or IIa recommendations.

The ACC/AHA guideline, however, gives a level B, class IIb, recommendation. This disagreement between guidelines is potentially important from a patient’s management perspective. Physicians will probably be encouraged by health services and providers to implement class I and IIa recommendations, especially if based upon level A or B evidence. This is less likely to be so for a class IIb recommendation. Understanding this discrepancy is, therefore, important. It probably reflects the difficulty in interpreting clinical trials that do not give entirely consistent results, undue prominence afforded to subgroup analyses, and the difference between the findings of a large post-infarction study (VALIANT) and those of Val-HeFT and CHARM-Added.

Digoxin
The disagreement in the grade of evidence given to the use of digoxin in patients in sinus rhythm is less notable. The ESC and CCS guidelines allocate an evidence level of A to this indication, whereas the ACC/AHA guideline assigns a level of B. Both the ESC and ACC/AHA guidelines give a class IIa recommendation, whereas the CCS guideline gives a class I recommendation. The HFSA guideline allocates level A (class IIa) for patients in NYHA classes II and III and level B (class IIa) for those in NYHA class IV. It is easy to consider the discrepancy in the grading of the level of evidence. There are several meta-analyses of randomized trials of digoxin supporting a level A grading, although, of course, the data used in these are overwhelmingly derived from the DIG trial. Perhaps, the ACC/AHA guideline committee did not consider any meta-analysis more informative than the single large randomized outcome trial with this drug.

The discrepancy in the class of evidence awarded is more interesting and, as ARBs, probably illustrates how ‘opinion’, consciously or unconsciously, still plays an important role in weighing ‘evidence’. A class II grading infers that there is no unanimous agreement about the usefulness or effectiveness of the treatment (Table 1). Although there is relatively consistent evidence that digoxin improves symptoms, and decreases the risk of deterioration and hospital admission, that evidence pre-dates the trials demonstrating the value of beta-blockers, aldosterone antagonists, and even, in some studies, ACE-inhibitors. The weighting of evidence is, therefore, more complex than just taking account of the trials in which the drug of interest was used. The background treatment (historical context), the benefits obtained (outcomes or endpoints studied), and the alternatives available (evidence for newer treatments) are all relevant factors. Balancing all of these considerations is difficult, does not always seem logical, and can lead to internal inconsistency in guidelines e.g. the more favourable class of evidence (IIa) is given to digoxin than to ARBs (IIb) in the ACC/AHA guideline. The basis of the class I recommendation from the CCS committee is uncertain. We feel that the inconsistent recommendations for digoxin (level A or B and class I or IIa) are unlikely to affect patient’s management.

Combination of hydralazine and isosorbide dinitrate
The advice on the use of hydralazine and isosorbide dinitrate (HISDN) also differs. For patients unable to take an ACE-inhibitor or ARB, the guidelines vary between an evidence level of B (ESC, ACC/AHA, and CCS) or C (HFSA) and a class IIa (ESC) or IIb (ACC/AHA and CCS) recommendation. The HFSA guideline gives the equivalent of IIa for patients intolerant of an ACE-inhibitor because of renal dysfunction or hyperkalaemia and IIb for other intolerance (preferring an ARB). These discrepancies are relatively large and could affect patient’s management, and it is again interesting to look at why they might have arisen. Strictly speaking, no trial has studied this combination in the patients in question. Two trials, however, suggested that H-ISDN can reduce mortality in heart failure, although one of these randomized only self-defined African Americans (most of which were taking an ACE-inhibitor) and the other was a relatively small trial conducted in the ‘pre-ACE-inhibitor era’, which, on its own, was statistically unconvincing. If one accepts the equivalent of ‘ACE-inhibitor naïve’ and ‘ACE-inhibitor intolerant’, then this treatment combination is probably worthy of at least a level B recommendation. The C level of evidence stated in the ACC/AHA and HFSA guidelines means, presumably, that those committees did not accept that equivalence (yet both committees seem to have done so when evaluating ARBs in these patients). We would argue that the ESC guideline class IIa recommendation (as opposed to the North American class IIb recommendations) is more accurate, as the weight of evidence suggests that H-ISDN is beneficial in patients with heart failure.

Curiously, all the North American guidelines give the combination of HISDN an A level of evidence (and a class I or IIa recommendation) for use in addition to an ACE-inhibitor in African Americans, when there are clearly not two trials (or a meta-analysis) supporting such a therapeutic approach.

Devices
There is also some lack of consensus about the indications for ‘cardiac resynchronization therapy’ (CRT) and the use of an implantable cardioverter defibrillator (ICD) (Table 3).

Cardiac resynchronization therapy
For CRT in selected patients (Table 3), the ESC guideline again grades the evidence for the effect of treatment on symptoms and hospital admission separately from its effect on death. The former gets a level A, class I recommendation, whereas the latter receives a level B, class I recommendation, because there is only one large trial showing a reduction in death with this treatment, although there are meta-analyses supporting a mortality benefit. The North American guidelines do not distinguish between outcomes and each assigns an evidence level of A to CRT (and the ACC/AHA and CCS guidelines make a class I recommendation, or the equivalent of IIa in the case of the HFSA). We feel that a small discrepancy of this type should not usually affect the use of treatment in practice, although, because of the cost of devices, a weaker level or class could encourage some payers to restrict treatment.
Table 3  Guideline recommended device therapy for CHF with LV systolic dysfunction

<table>
<thead>
<tr>
<th>CRT</th>
<th>ESC</th>
<th>ACC/AHA</th>
<th>CCS</th>
<th>HFSA</th>
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<tr>
<td>NYHA class III or IV, LVEF &lt; 0.35 and dysynchrony (QRS ≥ 120 ms)⁶</td>
<td>–</td>
<td>A</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>To improve symptoms/reduce hospitalization</td>
<td>A</td>
<td>I</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>To reduce mortality</td>
<td>B</td>
<td>I</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Primary prevention ICD</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
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</table>

| Non-ischaemic aetiology | A² | I | A | I | A | I | A² | Ila |
| Non-ischaemic aetiology | A² | I | B² | I | B² | Ila | A² | Ila |

⁶ESC guideline does not specify LVEF. HFSA guideline gives a level B recommendation for NYHA class IV. ACC/AHA, CCS, and HFSA guidelines do not distinguish between outcomes.

²ESC guideline states LVEF < 0.30–0.35. HFSA guideline gives a class IIb recommendation for LVEF 0.31–0.35. See also footnote ‘d’.

²ESC and HFSA guidelines do not distinguish between ischaemic and non-ischaemic aetiology.

²²CCS guideline gives a level C, class IIb recommendation for LVEF 0.31–0.35.

Implantable cardioverter defibrillator

The ESC and two of the North American recommendations for implanting an ICD in patients without severe symptoms also diverge somewhat. Both the ACC/AHA and CCS guidelines differentiate heart failure of ischaemic aetiology from non-ischaemic aetiology and give a lower level of evidence for the use of this type of device in patients with non-ischaemic heart failure (B compared with A in ischaemic patients), whereas the other two do not differentiate on the basis of aetiology. The reasons underlying this discrepancy are unknown. The most important trial that provided evidence that an ICD reduces the risk of premature death in patients with heart failure was the SCD-HeFT in which there was no interaction between aetiology and the effect of ICD treatment.¹⁹ A prior, smaller, study in patients with non-ischaemic, low LVEF, heart failure showed a directionally similar effect, although not one reached a conventional level of statistical significance.²⁰ Strictly speaking, there is, therefore, only one trial showing that an ICD reduces all-cause mortality in symptomatic heart failure (i.e. supporting a B, rather than A, level of evidence). On the contrary, if the post-infarction ICD trials are considered, then there is more evidence, overall, of a mortality benefit of an ICD in patients with a low LVEF and especially in those with coronary heart disease. If this interpretation is correct, it is interesting to note that the ‘bigger picture’ does not seem to have been incorporated in the same way for aldosterone antagonists.

While the ACC/AHA guideline recommends an ICD only in patients with a LVEF 30%, the other guidelines accept that there may also be an indication in patients with a LVEF in the range 30–35%, potentially affecting the treatment of many patients.

Revascularization

The guidelines are harmonious in stating ‘strong’ support (i.e. level A or B, class I or IIa) for confining revascularization only to patients with angina (and not in patients with asymptomatic coronary disease e.g. ‘hibernating myocardium’). They do not recommend revascularization for the improvement of ventricular function or heart failure symptoms.

Disease management programmes

There is also a harmony about disease management programmes, which are given an A level of evidence by each of the committees and a class I recommendation in the ESC (level B, class Ila for reduction in mortality), ACC/AHA, and CCS guidelines and the equivalent of a class Ila recommendation by the HFSA. There was less agreement about the specific outcomes improved by these programmes (only the ESC and CCS guidelines specified reduction in mortality) and, understandably, less certainty about the evidence for the individual components of a programme. All the North American guidelines recommend these programmes, strongly, only for patients at high risk of deterioration or hospital admission (including those recently hospitalized). The ESC guideline is less prescriptive, potentially resulting in this form of management being applied to a much larger proportion of patients.

Conclusions

This review has identified some of the potential difficulties facing guideline committees after 15 years of rapid advances in the treatment of heart failure. These include the necessity of adding each new treatment on top of the proved therapy (making comparison with historical treatments difficult), the growing use of composite morbidity–mortality outcomes (because improving prognosis has made all-cause mortality trials unfeasibly large), the finding of apparently conflicting outcomes from similar trials, and the appropriateness or otherwise of taking account of trials in separate, but related, disease areas. Despite this, there is generally good agreement between the four guidelines reviewed. Our review identified a number of areas where there could be improvement in clarity. We believe that it is advisable to make specific recommendations for specific outcomes. An explicit statement about how conflicting results were resolved would be
helpful. It is also helpful to state, explicitly, where trials in related disease areas are included as part of the evidence used to make recommendations. The precise weight placed on the meta-analysis for a given recommendation should also be stated, especially where only one (or even no) individual trial shows improvement in the outcome of interest or where a single trial contributes most of the information in the meta-analysis. Of course, the greatest remaining question is why we need four guidelines, including three from North America, where one could suffice? While clearly a challenge in the interpretation of evidence in clinical medicine, a single guideline would also be the best testament to that evidence.

Conflict of interest: J.M. and K.S. have received research grants and/or fees for lectures and/or consulting from a number of companies manufacturing and/or marketing the therapeutic products for heart failure described in this review, including AstraZeneca, GlaxoSmithKline, Medtronic, Novartis, Pfizer, Roche and/or Takeda.

References


