REVIEW

Challenging the dogma of high target doses in the treatment of heart failure: Is more always better?

Le dogme des hautes doses cibles pour le traitement de l’insuffisance cardiaque : est-il tenable?

Ferenc Follath

University Hospital Zürich, Office HAL 18/D2, Raemistrasse 100, CH 8091 Zürich, Switzerland

Received 3 August 2009; accepted 4 August 2009
Available online 13 November 2009

KEYWORDS
Heart failure; Treatment; Angiotensin-converting enzyme inhibitors; Beta-blockers; Dosage

Summary Current therapeutic guidelines for chronic heart failure (HF) recommend high (if possible, maximum) target doses of angiotensin-converting enzyme (ACE) inhibitors and beta-blockers. This is based on "evidence" from large-scale trials in selected patient populations. In "real life", however, many patients receive doses below defined targets, which is usually classified as "under-treatment". When considering whether everyday practice is suboptimal, an important question arises: is more always better and should dosage recommendations be followed in all patients? The superiority of high vs. low-to-moderate doses of ACE inhibitors and beta-blockers in reducing mortality from chronic HF has not been documented convincingly. In large trials with beta-blockers, the efficacy of below-target doses was not significantly different from that of high doses. With high-dose lisinopril, a reduction in the rate of hospitalizations was achieved at the cost of more adverse events. A combination of ACE inhibitors and angiotensin receptor blockers in chronic HF may also cause more problems than benefits. The risks of high doses of spironolactone, digoxin and diuretics are well-known. Sicker elderly and multimorbid patients often do not tolerate the recommended targets but can still have a good clinical response with an improved outcome at lower doses. Therefore lower-than-target doses may not necessarily be wrong in certain patients and are better than "no doses", for example, failure to prescribe essential heart-failure drugs. Individualized doses of ACE inhibitors and beta-blockers (best in combination) are indicated in most patients with chronic HF. Less rigid application of guideline recommendations may improve their acceptance. © 2009 Elsevier Masson SAS. All rights reserved.
The goals of modern treatment in chronic heart failure (HF) are rapid relief of symptoms and reduction in rates of mortality and hospitalizations. Based on data from large-scale, multicentre trials, European [1] and US [2] guidelines list angiotensin-converting enzyme (ACE) inhibitors and beta-blockers as first-line drugs. It is recommended to up-titrate the doses of these drugs to high target levels as defined in the original trial protocols, assuming a superior efficacy compared with lower doses. Adherence to the guidelines in “real life” is, however, still disappointing, not only by generalists [3] but also cardiologists [4,5]. In particular, beta-blockers are prescribed less frequently than indicated and the average doses of both of these important drugs usually remain below the recommendations. This practice is regarded as an indication of widespread “under-treatment” of chronic HF patients [6] and various measures are suggested to correct the situation. The gap between guideline recommendations and clinical routine is an important issue; suboptimal treatment should be avoided by all physicians involved in the care of patients with chronic HF. There are several arguments against an uncritical and dogmatic enforcement of the guideline recommendations and a disregard of the special characteristics of certain patient sub-populations. The aim of this review is to critically re-examine this question: are low doses of ACE inhibitors and beta-blockers really less effective and is a higher dose of a HF drug always better?

**Argument 1**

The “landmark” trials do not provide a sufficient evidence base for the treatment of elderly patients with comorbidities, who comprise a major part of the chronic HF population. Patients included in the clinical trials were usually men aged less than 70 years with systolic left ventricular dysfunction, coronary artery disease but no renal failure, coexisting chronic lung disease or systolic blood pressure less than 120 mmHg. In contrast, in recent HF epidemiological surveys [7—9], the patients’ mean age was more than 70 years, around 50% were women, and they had a preserved left ventricular ejection fraction and several relevant comorbid conditions (Table 1). Thus, the results of the main studies with ACE inhibitors and beta-blockers, especially the dosage used, cannot be extrapolated to other types of patients.

**Argument 2**

The predefined high target doses were not always reached and maintained, even in the selected trial populations (Table 2) [10—13]. Not surprisingly, in a large proportion of ambulatory and hospital patients, the ACE inhibitor and beta-blocker doses remained below 50% of the defined targets (Table 3) [3,14]. The difficulty in up-titrating the carvedilol dose in a consecutive series of 100 patients has been described well by Mehta et al. [15]. Experience from clinical practice indicates a sometimes unrealistic expectation of HF specialists regarding the practicability of the dosage recommendations in the guidelines. We may have to consider a more flexible and individualized approach to treatment.

**Argument 3**

The decisive question relates to the assumed superiority of high doses of ACE inhibitors and beta-blockers. Is there convincing evidence to accept the routine application of the proposed targets as a quality standard?
Table 1  Comparison of patient characteristics in randomized trials vs. clinical surveys.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean age (years)</th>
<th>Men/women (%)</th>
<th>CAD (%)</th>
<th>Exclusion for comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trials [ref]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOLVD [10] Enalapril</td>
<td>60.9</td>
<td>81/19</td>
<td>70</td>
<td>RD, PD and any relevant disease</td>
</tr>
<tr>
<td>ATLAS [16] Lisinopril</td>
<td>63.6</td>
<td>79/21</td>
<td>64</td>
<td>RD and any relevant disease</td>
</tr>
<tr>
<td>MERIT-HF [12] Metoprolol</td>
<td>63.9</td>
<td>77/23</td>
<td>65</td>
<td>RD and any relevant disease</td>
</tr>
<tr>
<td><strong>Surveys [ref]</strong></td>
<td></td>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMPROVEMENT [8]</td>
<td>ND</td>
<td>70</td>
<td>55/45</td>
<td>57 RD 19%, PD 31%, TIA 16%, D 20%</td>
</tr>
<tr>
<td>EURO-HF I [7]</td>
<td>ND</td>
<td>71</td>
<td>57/43</td>
<td>68 RD 17%, PD 32%, TIA 10%, D 27%</td>
</tr>
</tbody>
</table>

ATLAS: assessment of treatment with lisinopril and survival; CAD: coronary artery disease; CIBIS II: Cardiac Insufficiency Bisoprolol Study II; COPERNICUS: carvedilol prospective randomized cumulative survival; D: diabetes; LD: liver disease; PD: pulmonary disease; MERIT-HF: Metoprolol CR/XL Randomized Intervention Trial in Heart Failure; ND: not defined; RD: renal disease (elevated serum creatinine); ref: reference; RLD: relevant disease; SOLVD: studies of left ventricular dysfunction; TIA: transient ischemic attack.

Table 2  Mean doses vs. target doses in clinical trials with ACE inhibitors and beta-blockers.

<table>
<thead>
<tr>
<th>Trial [ref]</th>
<th>Drug</th>
<th>Mean dose (mg/day)</th>
<th>Target dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLVD [10]</td>
<td>Enalapril</td>
<td>11.2</td>
<td>20</td>
</tr>
<tr>
<td>COPERNICUS [13]</td>
<td>Carvedilol</td>
<td>37</td>
<td>50</td>
</tr>
</tbody>
</table>

ACE: angiotensin-converting enzyme; CIBIS II: Cardiac Insufficiency Bisoprolol Study II; COPERNICUS: carvedilol prospective randomized cumulative survival; MERIT-HF: Metoprolol CR/XL Randomised Intervention Trial in Heart Failure; SOLVD: studies of left ventricular dysfunction.

The first randomized dose comparison with enalapril was carried out by the NETWORK investigators [16], assessing the outcome in primary care and hospitalized patients with symptomatic chronic HF. During a relatively short follow-up of 24 weeks, there were no significant differences in the risks of death, hospitalization for HF or worsening HF with doses of 2.5 mg, 5 mg and 10 mg enalapril, each given twice daily.

The main reason for recommending a maximized dosage comes from the Assessment of Treatment with Lisinopril and Survival (ATLAS) Trial [17], which compared the outcomes in more than 3000 patients observed for at least three years, who were receiving treatment with low (2.5–5 mg/day) or high (32.5–35 mg/day) doses of lisinopril. At the end of the study, there was no significant difference in all cause or cardiovascular mortality, but a 12% lower relative risk ($p=0.002$) of the composite endpoint of total mortality plus hospitalization for any reason. Hospitalizations for HF were also reduced by 24%. However, these relative advantages of high-dose lisinopril were achieved at the cost of significantly more adverse events, such as hypotension, dizziness and worsening renal function. It should also be noted that patients with poor tolerance of lisinopril during a run-in phase were excluded before randomization. More recently,

Table 3  Drug dosage in the ESC guidelines [13] and the EuroHeart Failure Survey [3,14].

<table>
<thead>
<tr>
<th>Drug</th>
<th>ESC guidelines</th>
<th>EuroHeart Failure Survey</th>
</tr>
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<tbody>
<tr>
<td><strong>ACE inhibitor</strong></td>
<td></td>
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</tr>
<tr>
<td>Captopril</td>
<td>25–50 mg tid</td>
<td>57.5 ± 37.1 mg/day</td>
</tr>
<tr>
<td>Enalapril</td>
<td>10 mg bid</td>
<td>14.3 ± 9.1 mg/day</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>5–20 mg/day</td>
<td>12.3 ± 7.8 mg/day</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5–5 mg bid</td>
<td>5.1 ± 3.0 mg/day</td>
</tr>
<tr>
<td><strong>Beta-blocker</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>10 mg/day</td>
<td>4.7 ± 2.6 mg/day</td>
</tr>
<tr>
<td>Metoprolol CR</td>
<td>200 mg/day</td>
<td>74.9 ± 43.3 mg/day</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>50 mg/day</td>
<td>17.6 ± 16.6 mg/day</td>
</tr>
</tbody>
</table>

ACE: angiotensin-converting enzyme; bid: twice daily; ESC: European Society of Cardiology; tid: three times daily.
a meta-analysis of HF trials testing the combination of ACE inhibitors plus angiotensin receptor blockers showed no clear clinical advantages of intensified blockade of the renin-angiotensin-aldosterone system, but again confirmed the increased risks of symptomatic hypotension, worsening renal function and hyperkalaemia [18].

The lack of superior efficacy of high vs. moderate-to-low doses of beta-blockers has been well documented in the two major trials with metoprolol and bisoprolol. In the Metoprolol CR/XL Randomized Intervention Trial in MERIT-HF [19], the reduction in total mortality, sudden death and death from worsening HF was in the same range in patients receiving more than 100 mg metoprolol succinate and in those tolerating only less than 100 mg daily (Fig. 1). A most important finding in this trial was a faster and more marked reduction of heart rate ≤ 70 beats/min in the low-dose subgroup, indicating a greater sensitivity to the beta-blocking effects (Fig. 2). A similar outcome was reported in a secondary analysis of the Cardiac Insufficiency Bisoprolol Study II (CIBIS II) [20], showing significant and similar relative reductions in mortality by low (< 5 mg), moderate (5–7.5 mg) and high (10 mg) daily doses of bisoprolol vs. the corresponding randomized placebo groups.

In addition to the ACE inhibitor and beta-blocker trials mentioned above, there are also well-known data documenting increased risks with higher doses of digoxin [21], diuretics [22] and spironolactone [23]. Hence, it can be concluded that more is not always better in the drug treatment of patients with HF.

**Argument 4**

Could it be that an apparently better survival trend in patients who tolerate the higher targets is not due directly to the dose levels achieved but to the selection of patients with a lower overall risk and a better prognosis? There are several observations suggesting that this theory may be true. A reduced dose tolerance of bisoprolol in CIBIS II [20] was associated with more advanced HF, older age, lower systolic and diastolic blood pressures, severe arrhythmias and left bundle branch block, all of which are predictors of a worse outcome. Similar reasons for intolerance of metoprolol doses greater than 100 mg were found in the low-dose subgroup of patients in the MERIT-HF trial [19]. Such patient characteristics could also explain some of the differences between rates of prescription of the main HF drugs by cardiologists and general internists. Cardiologists prescribe more ACE inhibitors and beta-blockers and use higher doses than generalists, but the patient populations managed by the two groups of specialists belong to quite different risk groups [24].

Advanced age is probably the most important limiting factor for dose titration to higher levels. In the recently published Trial of Intensified vs. Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) Trial [25], a treatment selected according to brain natriuretic peptide levels was compared with standard management in patients aged less than 75 years and more than 75 years. A higher average dose of ACE inhibitors and beta-blockers achieved in the brain natriuretic peptide-guided subgroup did not improve the clinical outcome and was associated with a poorer quality of life in the older age group (more than 75 years).

**Conclusions**

A guideline-recommended choice of drugs remains the scientifically validated basis for treatment in all patients with chronic HF. Beta-blockers and ACE inhibitors can improve prognosis and reduce rates of hospitalization even in the...
elderly. The additive therapeutic effects of these agents are, therefore, usually beneficial, regardless of age and comorbid conditions. However, instead of insisting on high target doses, the dose should be adapted individually, considering renal function, blood pressure, concomitant treatments and other conditions. Very low initial doses and slower up-titration will improve the tolerance and acceptance of HF drugs by elderly patients. Close observation of patients, with repeated careful clinical examinations to detect early signs of adverse reactions, will allow therapeutic goals to be reached, even if doses lower than the recommended targets are used. A dogmatic approach to treatment regimens does not always produce a general advantage in all types of chronic HF patients.

Conflict of interest

None.

References


