Drug therapy for heart failure with reduced ejection fraction: what is the ‘right’ dose?

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New guidelines have emphasized the primacy of starting the four key life-saving therapies for patients with heart failure and reduced ejection fraction as quickly as possible, with titration to ‘target dose’ of these, as secondary consideration. In this article, we examine the reasons for this change in emphasis and revisit the evidence regarding the dosing of pharmacological therapy in heart failure. We demonstrate the early benefits obtained with even low doses of most of the foundational therapies for heart failure and reduced ejection fraction. We also clarify that the ‘target dose’ of those therapies requiring titration was a goal based on tolerability and often not reached in trials, i.e. the proven benefits of our foundational therapies were demonstrated with an average dose that was less than target and many patients in these trials were treated with sub-target doses.

Keywords
Heart failure with reduced ejection fraction • Drug therapy

In the past few years, two new therapies have received a class I recommendation in guidelines for the treatment of patients with heart failure and reduced ejection fraction (HFrEF), and four agents—a renin–angiotensin system blocker or sacubitril/valsartan, a beta-blocker, a mineralocorticoid receptor antagonist (MRA) and a sodium–glucose cotransporter 2 (SGLT2) inhibitor—are advised for most patients, in addition to a diuretic, as needed. Collectively, recent guidance documents on the treatment of HFrEF have suggested a prioritization of early introduction of all key pharmacological treatments over the up-titration of the dose of these therapies.1–7 This change in emphasis has surprised many prescribers aware of the focus of previous guidelines on attaining the ‘target dose’ of each of the evidence-based drugs for HFrEF. Although up-titration of dose, guided by patient tolerability, remains important, introduction of each guideline-recommended therapy may be the more important first step, with dose titration the second, recognizing the trade-offs between the benefits of initiating a new therapy and up-titrating the dose of current therapy. Here we revisit the evidence regarding the dosing of pharmacological therapy in heart failure and the background to the changed emphasis in recent guidance.

What does ‘target dose’ mean and what is it based on?

A fundamental principle of evidence-based prescribing in heart failure is that the drug and dose of the drug used in clinical practice should mimic that used in the randomized controlled trial or trials that demonstrated the value of the treatment in question.1–3 Except for SGLT2 inhibitors,8,9 the key ‘disease-modifying’ treatments for heart failure were started at a low dose and the dose was then increased in steps over several weeks to a ‘target dose’ if each dose increment was tolerated as determined by patient symptoms, blood pressure, heart rate, kidney function, or potassium level, depending on the agent used.

When thinking about the application of this approach to clinical practice, there are three crucially important considerations. First, some key trials had an active run-in period to test the tolerability of therapy before patients were randomized (Tables 1–3). Second, patients enrolled in trials were selected based on specific inclusion and exclusion criteria, so higher doses of certain treatments may not be as well tolerated in clinical practice because some patients have lower blood pressure, heart rate and glomerular filtration...
Table 1  Dosing of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in randomized clinical trials in patients with heart failure with reduced ejection fraction

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatments (n)</th>
<th>Median trial duration (months)</th>
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<th>Proportion reaching half target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS</td>
<td>Enalapril (127) Placebo (126)</td>
<td>6.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
<td>2.5 mg qd 3–4 days/2.5 mg bid 3–4 days/5 mg bid 1 wk/10 mg bid increasing to 20 mg bid depending on response&lt;sup&gt;c&lt;/sup&gt;</td>
<td>40 mg</td>
<td>18.4 mg (E) 27.3 mg (P)</td>
<td>22% (E) 45% (P)</td>
<td>–</td>
</tr>
<tr>
<td>SOLVD-T</td>
<td>Enalapril (1285) Placebo (1284)</td>
<td>41.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>2.5 mg bid 2–7 days run-in/2.5 mg bid 1 wk or 5 mg bid/5 mg bid 2 wk /10 mg bid (if 5 mg bid tolerated)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>20 mg</td>
<td>16.6 mg (E) 18.0 mg (P)</td>
<td>49% (E)&lt;sup&gt;d&lt;/sup&gt; 49% (P)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>59% (E)&lt;sup&gt;d&lt;/sup&gt; 55% (P)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>SOLVD-P</td>
<td>Enalapril (2111) Placebo (2117)</td>
<td>37.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yes</td>
<td>No</td>
<td>2.5 mg bid 2–7 days run-in/2.5 mg bid 1 wk or 5 mg bid/5 mg bid 2 wk /10 mg bid</td>
<td>20 mg</td>
<td>16.9 mg (E)&lt;sup&gt;e&lt;/sup&gt; 18.2 mg (P)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>57% (E)&lt;sup&gt;e&lt;/sup&gt; 62% (P)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>67% (E)&lt;sup&gt;e&lt;/sup&gt; 68% (P)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>V-HeFT II</td>
<td>Enalapril (403) [H-ISDN] (401)</td>
<td>30&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>Yes</td>
<td>5 mg bid 2 wk/10 mg bid</td>
<td>20 mg</td>
<td>15 mg (E)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>OVERTURE</td>
<td>Enalapril (2884) Omapatrilat (2886)</td>
<td>14.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>Yes</td>
<td>2.5 mg bid 3–14 days/5 mg bid 3–14 days/10 mg bid</td>
<td>20 mg</td>
<td>17.7 mg (E)</td>
<td>86% (E)</td>
<td>–</td>
</tr>
<tr>
<td>CIBIS-3</td>
<td>Enalapril (505)&lt;sup&gt;f&lt;/sup&gt; [Bisoprolol] (505)</td>
<td>14.6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>No</td>
<td>2.5 mg bid 2 wk/5 mg bid 2 wk/10 mg bid</td>
<td>20 mg</td>
<td>17.2 mg (E in E 1st group) 15.8 mg (E in B 1st group)</td>
<td>77% (E in E 1st)&lt;sup&gt;f&lt;/sup&gt; 67% (E in B 1st)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>90% (E in E 1st)&lt;sup&gt;f&lt;/sup&gt; 82% (E in B 1st)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>CARMEN</td>
<td>Enalapril (190 + 191)&lt;sup&gt;f&lt;/sup&gt; [Carvedilol] (191)</td>
<td>22</td>
<td>No</td>
<td>Yes</td>
<td>2.5 mg bid/5 mg bid/10 mg bid</td>
<td>20 mg</td>
<td>16.8 mg (E in E only) 14.9 mg (E in E only + CL group)</td>
<td>96% (E in E only)&lt;sup&gt;f&lt;/sup&gt; 96% (E in E + CL)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>96% (E in E only)&lt;sup&gt;f&lt;/sup&gt; 95% (E in E + CL)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>NETWORK</td>
<td>Enalapril - low (506) Enalapril - medium (510) Enalapril – high (516)</td>
<td>Fixed 6</td>
<td>Yes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
<td>2.5 mg qd days 1–3/2.5 mg bid days 4–7/5 mg bid 1 wk/10 mg bid&lt;sup&gt;h&lt;/sup&gt;</td>
<td>5 mg 10 mg 20 mg</td>
<td>5.0 mg (E) 9.7 mg (E) 16.7 mg (E)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>100% (E) 96% (E) 85% (E)&lt;sup&gt;h&lt;/sup&gt;</td>
<td>100% (E) 99% (E) 95% (E)&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nanas</td>
<td>Enalapril – standard (207) Enalapril – high (207)</td>
<td>Fixed 12</td>
<td>No</td>
<td>Yes</td>
<td>2.5 mg bid to 10 mg bid in 5 wk&lt;sup&gt;i&lt;/sup&gt; 2.5 mg bid to 30 mg bid in 9 wk</td>
<td>20 mg 60 mg</td>
<td>17.9 mg (E standard dose)&lt;sup&gt;i&lt;/sup&gt; 42.5 mg (E high dose)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>72.5% (E standard dose)&lt;sup&gt;i&lt;/sup&gt; 32.5% (E high dose)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>–</td>
</tr>
</tbody>
</table>
Table

<table>
<thead>
<tr>
<th>Trial</th>
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</tr>
</thead>
<tbody>
<tr>
<td>CHARM</td>
<td>Candesartan (2289)</td>
<td>40</td>
<td>No</td>
<td>Yes</td>
<td>4 or 8 mg qd 2 wk/dose doubled every 2 wk until 32 mg qd 2 wk/dose doubled every 2 wk until 160 mg bid</td>
<td>32 mg</td>
<td>24 mg (CN)</td>
<td>60% (CN)</td>
<td>78% (C)</td>
</tr>
<tr>
<td></td>
<td>Placebo (2287)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>27 mg (P)</td>
<td>60% (CN)</td>
<td>73% (P)</td>
<td>85% (P)</td>
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<tr>
<td>Val-HeFT</td>
<td>Valsartan (25 11)k</td>
<td>23b</td>
<td>No</td>
<td>Yesk</td>
<td>40 mg bid 2 wk/dose doubled every 2 wk until 250 mg bid</td>
<td>320 mg</td>
<td>254 mg (V)k</td>
<td>84% (V)</td>
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<tr>
<td></td>
<td>Placebo (2499)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>283 mg (P)k</td>
<td>93% (P)</td>
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</tbody>
</table>

B, bisoprolol; bid, twice daily; CL, carvedilol; CN, candesartan; E, enalapril; P, placebo; H, hydralazine; H-ISDN, combination of hydralazine and isosorbide dinitrate; qd, once daily; V, valsartan; wk, week.

[...] Treatment not considered in the table.

a CONSENSUS and NETWORK did not require measurement of left ventricular ejection fraction; the table does not include trials in patients with myocardial infarction or other cardiovascular disease risk factors.

b Mean.

c Because of hypotension, the protocol was revised after 67 patients were enrolled to reduce initial dose from 5 mg bid to 2.5 mg qd for 3 to 4 days increasing to 2.5 mg bid for the remainder of the first week and then to 5 mg bid.

d From protocol – usual starting dose enalapril 5 mg bid but if considered high risk, could receive 2.5 mg bid for 1 week, increasing thereafter to 5 mg bid for 2 weeks. Among all randomized patients, final mean daily dose was 11.2 mg (among patients taking enalapril it was 16.6 mg). At the final visit, 1.8% were taking 2.5 mg daily, 6.7% 5 mg daily, 9.5% 10 mg daily, 49.3% 20 mg daily in the enalapril group, and 0.6% 2.5 mg daily, 3.2% 5 mg daily, 5.0% 10 mg daily, 49.1% 20 mg daily in the placebo group. By the end of the trial, 32.5% had discontinued enalapril and 41.4% had discontinued placebo.

e Patients could not have overt heart failure or be treated for heart failure with a diuretic/digoxin/vasodilator. Doses/proportions shown were obtained from prescription at the last visit. By the end of the trial, 24% had discontinued enalapril and 27% had discontinued placebo.

f Patients randomized to enalapril (n = 505) or bisoprolol (n = 505) first and the second drug added after 6 months (i.e. combination therapy for 6–24 months). Proportions shown are among patients continuing to receive treatment.

g Patients randomized to enalapril only (n = 190), carvedilol only (n = 191), or both drugs (n = 191). Proportions shown are at the maintenance phase.

h All patients had to tolerate a 2.5 mg test dose of enalapril. Only 10 mg bid arm analysed. At the final visit: 5 mg daily 11.2%, 10 mg daily 15.3%, 20 mg daily 71.1%, and non-protocol dose 2.3%. Doses shown were calculated excluding non-protocol doses.

i The precise dosing regimens are not reported. Doses/proportions shown are at 3 months. By the end of the first year, 79.6% of standard dose and 45.5% of high-dose patients reached their target enalapril doses.

j Two trials, one of which included patients receiving background angiotensin-converting enzyme inhibitor treatment (55.7% of patients). Doses shown are at 6 months. The dose achieved in CHARM-Alternative was 23 mg (59% at 32 mg target) and in CHARM-Added was 24 mg (61% at target) in the candesartan group.

k Overall, 93% of patients taking an angiotensin-converting enzyme inhibitor at baseline.
<table>
<thead>
<tr>
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<th>Mean daily dose achieved</th>
<th>Proportion reaching target dose</th>
<th>Proportion reaching half target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia/New Zealand</td>
<td>Carvedilol (207)</td>
<td>19</td>
<td>Yes</td>
<td>No</td>
<td>6.25 mg bid 2–3 wk run-in/6.25 mg bid 1 wk/12.5 mg bid 1 wk/25 mg bid</td>
<td>50 mg</td>
<td>41 mg (C)</td>
<td>48% (C)</td>
<td>6% (C)</td>
</tr>
<tr>
<td></td>
<td>Placebo (208)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45 mg (P)</td>
<td>– (P)</td>
<td>– (P)</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>Carvedilol (696)</td>
<td>6.5</td>
<td>Yes</td>
<td>No</td>
<td>Varied</td>
<td>50 mg ≤85 kg</td>
<td>45 mg (C)</td>
<td>80% (C)</td>
<td></td>
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<tr>
<td></td>
<td>Placebo (398)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60 mg (P)</td>
<td>– (P)</td>
<td>– (P)</td>
<td></td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>Carvedilol (1116)</td>
<td>9.7</td>
<td>(10.4)b</td>
<td>No</td>
<td>3.125 mg bid 2 wk/6.25 mg bid 2 wk/12.5 mg bid 2 wk/25 mg bid</td>
<td>50 mg</td>
<td>37 mg (C)e</td>
<td>65% (C)e</td>
<td>76% (C)e</td>
</tr>
<tr>
<td></td>
<td>Placebo (1133)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>41 mg (P)e</td>
<td>78% (P)e</td>
<td>84% (P)e</td>
<td></td>
</tr>
<tr>
<td>COMET</td>
<td>Carvedilol (1511)</td>
<td>58h</td>
<td>No</td>
<td>No</td>
<td>3.125 mg bid 2 wk/6.25 mg bid 2 wk/12.5 mg bid 2 wk/25 mg bid</td>
<td>50 mg</td>
<td>42 mg (C)f</td>
<td>75% (C)f</td>
<td>87% (C)f</td>
</tr>
<tr>
<td></td>
<td>Metoprolol-S</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85 mg (M-T)f</td>
<td>78% (M-T)f</td>
<td>87% (M-T)f</td>
<td></td>
</tr>
<tr>
<td>CARMEN</td>
<td>Carvedilol (191 + 191)</td>
<td>22</td>
<td>No</td>
<td>Yes</td>
<td>3.125 mg bid 2 wk/6.25 mg bid 2 wk/12.5 mg bid 2 wk/25 mg bid</td>
<td>50 mg</td>
<td>48 mg (C in C only)</td>
<td>94% (C in C only)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[Enalapril] (190)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>49 mg (C in C + E group)</td>
<td>95% (C in C + E)</td>
<td>95% (C in C + E)</td>
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<tr>
<td>CIBIS-ELD</td>
<td>Carvedilol (445)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50 mg &lt;85 kg</td>
<td>24 mg ≤85 kg (C)</td>
<td>32% (C)f</td>
<td>57% (C)f</td>
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<tr>
<td>CIBIS-ELD</td>
<td>Bisoprolol (413)</td>
<td>Fixed 3</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>10 mg</td>
<td>5 mg (B)</td>
<td>31% (B)f</td>
<td>54% (B)f</td>
</tr>
<tr>
<td>CIBIS II</td>
<td>Bisoprolol (1327)</td>
<td>15.6h</td>
<td>No</td>
<td>No</td>
<td></td>
<td>1.25 mg qd 2 wk/2.5 mg qd 2 wk/5 mg qd 2 wk/10 mg qd</td>
<td>10 mg</td>
<td>6.2 mg (B)</td>
<td>48% (B)</td>
</tr>
<tr>
<td>CIBIS III</td>
<td>Bisoprolol (505)</td>
<td>14.6h</td>
<td>No</td>
<td>No</td>
<td></td>
<td>10 mg</td>
<td>7.3 mg (P)</td>
<td>65% (B)</td>
<td>85% (B)</td>
</tr>
<tr>
<td>RESOLVD</td>
<td>Metoprolol-S (214)</td>
<td>Fixed 6</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>10 mg</td>
<td>8.1 mg (B)</td>
<td>65% (B)</td>
<td>86% (B)</td>
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<tr>
<td>MERIT-HF</td>
<td>Metoprolol-S (1990)</td>
<td>12h</td>
<td>No</td>
<td>No</td>
<td></td>
<td>10 mg</td>
<td>7.1 mg (B in E 1st)</td>
<td>54% (B in E 1st)</td>
<td>72% (B in E 1st)</td>
</tr>
<tr>
<td></td>
<td>Placebo (212)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>156 mg (M-S)f</td>
<td>81% (M-S)f</td>
<td>– (P)f</td>
<td></td>
</tr>
</tbody>
</table>

B, bisoprolol bid, twice daily; C, carvedilol; E, enalapril; M-S, metoprolol succinate (long-acting); M-T, metoprolol tartrate (short-acting); P, placebo; qd, once daily; wk, week.

[a] The table does not include trials in patients with myocardial infarction.

[b] Mean.

[c] The actual doses at the end of follow-up were: 12.5 mg daily 7%, 25 mg daily 16%, and 50 mg daily 48%.

[d] Stratification in the US carvedilol programme was stratified into one of four trials based on 6-min walk distance. The allocation to carvedilol vs placebo was one-to-one in the moderate-heart-failure, and two-to-one in the mild- and severe-heart-failure trials (initial dose 12.5 mg increasing to 25 mg bid in people weighing <85 kg and to 50 mg bid in those ≥85 kg). In the dose-ranging trial, patients were randomly assigned to one of 4 groups: placebo or 6.25, 12.5, or 25 mg of carvedilol bid.

[e] From clinical study report; daily dose in surviving patients at 120 days; 65% 30 mg; 25 mg; 9% 12.5 mg; 6.25 mg; 9% 0 mg in carvedilol group, 78% 30 mg; 6% 25 mg; 4% 12.5 mg; 2% 6.25 mg; 10% 0 mg in the placebo group.

[f] Patients randomized to enalapril only (n = 190), carvedilol only (n = 191), or both drugs (n = 191). Proportions shown are at maintenance phase.

[g] The Food and Drug Administration review 154 mg and 69% mean time to maximum titration was 93 days for the metoprolol group.

[h] Proportions shown are at the end of study.

[i] Proportions shown are maximum dose reaching during the study period.

[j] Proportions shown are maximum dose reaching during the study period.

[k] Patients randomized to bisoprolol (n = 505) or enalapril first (n = 505) and second drug added after 6 months (i.e., combination therapy for 6–24 months). Proportions shown are among patients continuing to receive treatment.
Table 3 Dosing of mineralocorticoid receptor antagonists in randomized clinical trials in patients with heart failure with reduced ejection fraction

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatments (n)</th>
<th>Median trial duration (months)</th>
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</thead>
<tbody>
<tr>
<td>RALES</td>
<td>Spironolactone (822) Placebo (841)</td>
<td>24b</td>
<td>No</td>
<td>No</td>
<td>25 mg qd 8 week/50 mg qd (could be reduced to 25 mg alt. days) eGFR 50 ml/min/1.73 m²: 25 mg qd 4 wk/50 mg qd eGFR 30–49 ml/min/1.73 m²: 25 mg alt. Days 4 week/25 mg qd</td>
<td>50 mg</td>
<td>26 mg (S)c</td>
<td>12% (S)c</td>
<td>80% (S)c</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>Eplerenone (1364) Placebo (1373)</td>
<td>21</td>
<td>No</td>
<td>No</td>
<td>50 mg 25 mg</td>
<td>4244 mg (Ep/P in high eGFR group)²</td>
<td>85%/81% (Ep/P in high eGFR group)²</td>
<td>99%/100% (Ep/P in high eGFR group)²</td>
<td>99%/99% (Ep/P in low eGFR group)²</td>
</tr>
</tbody>
</table>

a, alternative; bid, twice daily; Ep, eplerenone; eGFR, estimated glomerular filtration rate; P, placebo; qd, once daily; S, spironolactone; wk, week.

The table does not include trials in patients with myocardial infarction.
bMean.
cDoses shown are among patients continuing to receive treatment after 24 months of follow-up. Proportion shown are maximum achieved doses after 24 months of follow-up among patients continuing to receive treatment.
dDoses shown are at month 5 visit (overall mean dose 39 mg). Proportion shown are maximum achieved doses during study period.

1. What was the rate of ‘target dose’ achievement in trials?

Table 1-3 show the proportion of patients achieving the ‘target dose’ of treatment in trials, with all the caveats described above. As can be seen in trials using an ACE inhibitor or ARB, on average approximately 50%–70% of patients achieved the ‘target dose’. Although the placebo-controlled trials showed that the proportion of patients attaining the target dose in the placebo group was not statistically significant, this was minimal. This design requirement renders understanding the efficacy of a given therapy difficult. The design requirement over the established control treatment (e.g., placebo) is based on the treatment arm of the Studies of Left Ventricular Dysfunction (SOLVD). This ‘target dose’ approach was used in the original placebo-controlled landmark trials using an ACE inhibitor (enalapril) or an ARB (candesartan). As in these trials, all participants were taking the target dose at the time of randomization. This was to either the mean dose of enalapril given in SOLVD (control therapy) or to either continue the specific angiotensin- or aldosterone antagonist (enalapril) alone. This design requirement renders understanding the efficacy of a given therapy difficult.

2. Why was the ‘target dose’ approach used in the original placebo-controlled landmark trials using an ACE inhibitor (enalapril) or an ARB (candesartan)?

The design requirement was to achieve the mean dose of enalapril given in SOLVD (control therapy) or to either continue the specific angiotensin- or aldosterone antagonist (enalapril) alone. This design requirement renders understanding the efficacy of a given therapy difficult.

3. What was the rate of ‘target dose’ achievement in the trials?

As can be seen in trials using an ACE inhibitor or ARB, on average approximately 50%–70% of patients achieved the ‘target dose’. Although the placebo-controlled trials showed that the proportion of patients attaining the target dose in the placebo group was not statistically significant, this was minimal. This design requirement renders understanding the efficacy of a given therapy difficult.

4. What does the ‘target dose’ approach reflect?

The ‘target dose’ approach reflects the requirement of achieving the mean dose of enalapril given in SOLVD (control therapy) or to either continue the specific angiotensin- or aldosterone antagonist (enalapril) alone. This design requirement renders understanding the efficacy of a given therapy difficult.
Indeed, in CONSENSUS, the trial that included patients with the most advanced heart failure, only 45% of patients in the placebo group were titrated to the target dose, indicating that failure to successfully up-titrate therapy is often because of the patient’s underlying condition, and changes in condition over time, or physician perception, independent of the effect of treatment. The data for beta-blockers are generally similar with the exception of CIBIS-ELD, a trial designed to compare target dose attainment and tolerability of bisoprolol and carvedilol. It is not clear why only 31% of patients reached the target dose, although all participants were aged 65 years or older. Importantly, the low rate of target dose attainment was despite the prescription of a beta-blocker in 60% of patients before trial entry (Table 2). Similarly, the achievement of target dose appears to differ greatly between RALES and EMPHASIS-HF. However, target dose achievement with MRAs is particularly hard to assess given the protocol mandated reasons not to increase dose and the higher rate of target dose achievement in EMPHASIS-HF likely reflected the stratification of dose by estimated glomerular filtration rate (eGFR) at baseline in that trial.

**Do we have any other trial evidence about toleration of evidence-based therapy?**

For one evidence-based drug, enalapril, there is evidence about the success rate in achieving different target doses. Here, an indirect comparison of the CONSENSUS and SOLVD-T trials is instructive (Table 1). In CONSENSUS, only 22% of patients randomized to enalapril were titrated to the target dose of 20 mg twice daily, compared with the 49% reaching the target dose of 10 mg twice daily in SOLVD-T. A better comparison is provided by a trial in which patients were randomized to enalapril 20 or 60 mg/day. In that trial, Nanas and colleagues reported that 72.5% and 32.5% of the patients, respectively, reached their target enalapril doses by the end of 3 months of follow-up, and 79.6% and 45.5% by the end of the first year. Although patient characteristics may influence the likelihood of attaining the target dose, collectively, these data suggest that the current target dose of at least enalapril (i.e. 10 mg twice daily) has been chosen appropriately.

A unique analysis of EMPHASIS-HF discussed in the next section also shows that the target dose of an MRA (eplerenone) may be smaller in some participants than others, depending on patient characteristics, and yet be highly effective.

Unfortunately, similar data do not exist for beta-blockers.

**Can we learn anything more about dose and outcome from the landmark trials?**

The focus on achievement of target dose, or of at least half the target dose, in many analyses of patient cohorts has implied that smaller doses are ineffective. This is not correct. Figure 1 shows an analysis of the first 30 days of follow-up of the CHARM HFrEF trials. Treatment with candesartan led to a significant reduction in the composite of death or heart failure hospitalization within

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**Figure 1** Kaplan–Meier analysis for the composite of all-cause death or hospitalization for heart failure up to 4 weeks in trials using an angiotensin receptor blocker (ARB) (CHARM-HFrEF trials) and a mineralocorticoid receptor antagonist (MRA) (EMPHASIS-HF). CI, confidence interval.

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As can be seen from Figure 2A, the benefit of candesartan was apparent from 15 days after starting treatment, yet mean daily dose of candesartan was only 24.8 (SD 10.5) mg and 27.6 (SD 12.3) mg, respectively. At 2 and 4 weeks, the mean daily dose of eplerenone was only 23.7 (5.7) mg and 27.6 (10.8) mg, respectively.

Of note, the absolute risk difference was 1.4% in both trials (CHARM HFrEF and EMPHASIS-HF), so the effect size was not small even after this short period of treatment.

Interestingly, the picture with beta-blockers is different. Another, perhaps overlooked, analysis of EMPHASIS-HF also illustrated that lower than target doses are highly effective in reducing adverse clinical outcomes (Table 3).20,23 In this trial, the target dose of eplerenone/placebo was stratified at randomization according to eGFR; the target was 50 mg daily in people with an eGFR ≥50 ml/min/1.73 m² and up to 25 mg daily if the eGFR was 30–49 ml/min/1.73 m². Because of stratification at randomization, EMPHASIS-HF was, effectively, ‘two trials within a trial’, comparing low-dose eplerenone to placebo and high-dose eplerenone to placebo in different patient cohorts defined by their eGFR at baseline. The effect of treatment on the primary composite endpoint (cardiovascular death or heart failure hospitalization) was identical with a HR of 0.62 (95% CI 0.49–0.78) in the low-dose stratum and 0.58 (0.45–0.74) in the high-dose stratum (p-interaction = 0.89). At 5 months, the mean daily dose of eplerenone in the low eGFR/low-dose stratum was 24.8 ± 10.8 mg, and in the high eGFR/high-dose stratum it was 42.0 ± 12.3 mg.

Unlike renin–angiotensin system blockers and MRAs, the early benefit of beta-blockers is less clear. After initiation, beta-blockers may cause worsening of heart failure. Indeed, careful scrutiny of the Kaplan–Meier curves in the placebo-controlled trials and comparison of the first 6 months of treatment with either enalapril or bisoprolol in CIBIS III demonstrates an early excess of heart failure hospitalizations following initiation of a beta-blocker, although there is no indication of an increase in risk of death.11,24–28 Indeed, it is clear that the risk of death is reduced relatively early after starting treatment with a beta-blocker, for example in combined analysis of the trials in the US carvedilol programme.27

Understanding the importance of dose with sacubitril/valsartan is more difficult because of the design of the PARADIGM-HF trial, as mentioned above.14 In this trial, outcomes were compared in patients having either their dose of either sacubitril/valsartan (42% of randomized participants) or enalapril (43%) reduced compared to those who remained on the starting (target) doses or each treatment.29 The treatment benefit of sacubitril/valsartan over enalapril following a dose reduction was similar (HR 0.80, 95% CI 0.70–0.93, p < 0.001) to that seen in patients who did not have any dose reduction (HR 0.79, 95% CI 0.71–0.88, p < 0.001) and consistent whether the reduction was to 50%–100% of target or to <50% of target dose.29

What other dosing and dose–response information do we have?

The ideal way to compare the effect of different doses of a drug is to randomize patients to those doses and, understandably, this has rarely been done. The only examples examining clinical outcomes used renin–angiotensin system blockers which, unfortunately,
## Table 4 Randomized clinical outcome trials comparing effects of low and high-dose renin–angiotensin system blockers in patients with heart failure and reduced ejection fraction

<table>
<thead>
<tr>
<th>Treatments (n)</th>
<th>Median trial duration (months)</th>
<th>Target dose</th>
<th>Mean daily dose achieved</th>
<th>All-cause mortality or HF hospitalization, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATLAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril-low (1596)</td>
<td>46</td>
<td>2.5–5.0 mg qd</td>
<td>4.5 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.85 (0.78–0.93), p = 0.0002</td>
</tr>
<tr>
<td>Lisinopril-high (1568)</td>
<td>32.5–35 mg qd</td>
<td>33.2 mg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>p = 0.128</td>
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<tr>
<td>HEAAL</td>
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<tr>
<td>Losartan-low (1919)</td>
<td>56.4</td>
<td>50 mg qd</td>
<td>46 mg&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.90 (0.82–0.99), p = 0.027</td>
</tr>
<tr>
<td>Losartan-high (1927)</td>
<td>150 mg qd</td>
<td>129 mg&lt;sup&gt;b&lt;/sup&gt;</td>
<td>p = 0.24</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; HF, heart failure; HR, hazard ratio; qd, once daily; SD, standard deviation.

<sup>a</sup>At the end of dose titration. Over the whole duration of the trial, the mean (SD) daily dose of lisinopril in the high-dose group was 22.5 (15.7) mg compared to 3.2 (2.5) mg in the low-dose group.

<sup>b</sup>From the time of follow-up to the time of a primary endpoint or study end, the mean daily losartan doses administered were 129 mg (SD 39) for the 150 mg group and 46 mg (SD 11) for the 50 mg treatment group. For the composite of cardiovascular death or heart failure hospitalization, the HR was 0.88 (95% CI 0.79–0.97; p = 0.011).

The most correct conclusion from the landmark trials in HFrEF (ATLAS, EMPHASIS-HF) is that the substantial benefits observed were obtained despite a third to a half of patients not achieving the 'target doses', similar to the findings with diuretics and other classes of drugs.

What can we conclude about the dosing of evidence-based pharmacotherapy in heart failure with reduced ejection fraction?
to. However, it is important to reiterate that in all trials it was recognized that every patient would not tolerate the target dose and up-titration towards the target might be limited by intolerance (and indeed for some drugs was limited by the protocol e.g. because of hyperkalemia). The rate of target dose achievement must also be interpreted in the light of the rates achieved in the placebo group. Therefore, the average dose achieved and the proportion attaining the target dose, as compared with the same metrics in the relevant trials, is the best way to assess dosing success in a patient cohort; it is a mistake to assume that 100% of patients should achieve the target dose. More importantly, it must be recognized that the low doses used during the up-titration phase of these drugs also have a substantial effect. It is this evidence – that there is a clear clinical benefit from even low doses and this is demonstrable within a very short time after starting treatment – that supports the change in emphasis in the new guidance.67 Up-titrating the dose of a single agent before starting the next therapy is of secondary importance.38 Initiating a low dose of as many protective therapies as possible as quickly as possible is the priority. This is to avoid delay in obtaining the early and additive benefit from the multiple mechanistically distinct evidence-based therapies available. As argued elsewhere, the order in which these drugs is started does not matter and may be tailored to patient characteristics.39,40 Up-titration of dose, guided by patient tolerability, remains important but can be done later.

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