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REVIEW

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.[1,2] 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

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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[a]

Trial	Treatments (*n*)	Median trial duration (months)	Active run-in	Prior exposure to trial therapy	Dose titration schedule (starting, dose steps and duration of steps)	Target daily dose	Mean daily dose achieved	Proportion reaching target dose	Proportion reaching half target dose
CONSENSUS	Enalapril (127) Placebo (126)	6.3[b]	No	No	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[c]	40 mg	18.4 mg (E) 27.3 mg (P)	22% (E) 45% (P)	–
SOLVD-T	Enalapril (1285) Placebo (1284)	41.4[b]	Yes	No	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)[d]	20 mg	16.6 mg (E) 18.0 mg (P)	49% (E)[d] 49% (P)[d]	59% (E)[d] 55% (P)[d]
SOLVD-P	Enalapril (2111) Placebo (2117)	37.4[b]	Yes	No	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	20 mg	16.9 mg (E)[e] 18.2 mg (P)[e]	57% (E)[e] 62% (P)[e]	67% (E)[e] 68% (P)[e]
V-HeFT II	Enalapril (403) [H-ISDN] (401)	30[b]	No	Yes	5 mg bid 2 wk/10 mg bid	20 mg	15 mg (E)	–	–
OVERTURE	Enalapril (2884) [Omapatrilat] (2886)	14.5[b]	No	Yes	2.5 mg bid 3–14 days/5 mg bid 3–14 days/10 mg bid	20 mg	17.7 mg (E)	86% (E)	–
CIBIS-3	Enalapril (505)[f] [Bisoprolol] (505)	14.6[b]	No	No	2.5 mg bid 2 wk/5 mg bid 2 wk/10 mg bid	20 mg	17.2 mg (E in E 1st group) 15.8 mg (E in B 1st group)	77% (E in E 1st)[f] 67% (E in B 1st)[f]	90% (E in E 1st)[f] 82% (E in B 1st)[f]
CARMEN	Enalapril (190 + 191)[g] [Carvedilol] (191)	22	No	Yes	2.5 mg bid/5 mg bid/10 mg bid – duration of each not described	20 mg	16.8 mg (E in E only group) 14.9 mg (E in E + CL group)	96% (E in E only)[g] 96% (E in E + CL)[g]	–
NETWORK	Enalapril - low (506) Enalapril - medium (510) Enalapril – high (516)	Fixed 6	Yes[h]	No	2.5 mg qd days 1–3/2.5 mg bid days 4–7/5 mg bid 1 wk/10 mg bid[h]	5 mg 10 mg 20 mg	5.0 mg (E) 9.7 mg (E) 16.7 mg (E)[h]	100% (E) 96% (E) 85% (E)[h]	100% (E) 99% (E) 95% (E)[h]
Nanas	Enalapril – standard (207) Enalapril - high (207)	Fixed 12	No	Yes	2.5 mg bid to 10 mg bid in 5 wk[i] 2.5 mg bid to 30 mg bid in 9 wk	20 mg 60 mg	17.9 mg (E standard dose)[i] 42.5 mg (E high dose)[i]	72.5% (E standard)[i] 32.5% (E high)[i]	–

Table 1 (Continued)

Trial	Treatments (*n*)	Median trial duration (months)	Active run-in	Prior exposure to trial therapy	Dose titration schedule (starting, dose steps and duration of steps)	Target daily dose	Mean daily dose achieved	Proportion reaching target dose	Proportion reaching half target dose
CHARM	Candesartan (2289)[j] Placebo (2287)	40	No	Yes[j]	4 or 8 mg qd 2 wk/dose doubled every 2 wk until 32 mg qd	32 mg	24 mg (CN)[j] 27 mg (P)[j]	60% (CN) 73% (P)	78% (C) 85% (P)
Val-HeFT	Valsartan (2511)[k] Placebo (2499)	23[b]	No	Yes[k]	40 mg bid 2 wk/dose doubled every 2 wk until 160 mg bid	320 mg	254 mg (V)[k] 283 mg (P)[k]	84% (V) 93% (P)	–

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, 5.5% 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 2 Dosing of beta-blockers in randomized clinical trials in patients with heart failure with reduced ejection fraction[a]

Trial	Treatments (*n*)	Median trial duration (months)	Active run-in	Prior exposure to trial therapy	Dose titration schedule (starting, dose steps and duration of steps)	Target daily dose	Mean daily dose achieved	Proportion reaching target dose	Proportion reaching half target dose
Australia/New Zealand Carvedilol	Carvedilol (207) Placebo (208)	19[b]	Yes	No	6.25 mg bid 2–3 wk run-in/6.25 mg bid 1 wk/12.5 mg bid 1 wk/25 mg bid	50 mg	41 mg (C) 45 mg (P)	48% (C)[c] – (P)[c]	64% (C)[c] – (P)
US Carvedilol	Carvedilol (696) Placebo (398)	6.5	Yes	No	Varied[d]	50 mg ≤85 kg 100 mg >85 kg	45 mg (C) 60 mg (P)	80% (C) – (P)	–
COPERNICUS	Carvedilol (1156) Placebo (1133)	9.7 (10.4[b])	No	No	3.125 mg bid 2 wk/6.25 mg bid 2 wk/12.5 mg bid 2 wk/25 mg bid	50 mg	37 mg (C)[e] 41 mg (P)[e]	65% (C)[e] 78% (P)[e]	76% (C)[e] 84% (P)[e]
COMET	Carvedilol (1511) [Metoprolol-T] (1518)	58[b]	No	No	3.125 mg bid 2 wk/6.25 mg bid 2 wk/12.5 mg bid 2 wk/25 mg bid	50 mg	42 mg (C)[f] 85 mg (M-T)[f]	75% (C)[f] 78% (M-T)[f]	87% (C)[f] 87% (M-T)[f]
CARMEN[g]	Carvedilol (191 + 191) [Enalapril] (190)	22	No	Yes	3.125 mg bid 2 wk/6.25 mg bid 2 wk/12.5 mg bid 2 wk/25 mg bid	50 mg	48 mg (C in C only group) 49 mg (C in C + E group)	94% (C in C only)[g] 95% (C in C + E)[g]	–
CIBIS-ELD	Carvedilol (445)				3.125 mg bid 2 wk/6.25 mg bid 2 wk/12.5 mg bid 2 wk/25 mg bid 2 wk/>85 kg 50 mg bid 3 wk	50 mg ≤85 kg 100 mg >85 kg	24 mg ≤85 kg (C) 48 mg >85 kg (C)	32% (C)[h]	57% (C)[h]
CIBIS-ELD	Bisoprolol (431)	Fixed 3	No	Yes	1.25 mg qd 2 wk/2.5 mg qd 2 wk/5 mg qd 2 wk/10 mg qd	10 mg	5 mg (B)	31% (B)[h]	54% (B)[h]
CIBIS II	Bisoprolol (1327) Placebo (1320)	15.6[b]	No	No	1.25 mg qd 1 wk/2.5 mg qd 1 wk/3.75 mg qd 1 wk/5 mg qd 4 wk/7.5 mg qd 4 wk/10 mg qd	10 mg	6.2 mg (B) 7.3 mg (P)	48% (B)[i] 65% (B)[i]	72% (B)[i] 85% (B)[i]
CIBIS III[j]	Bisoprolol (505) [Enalapril] (505)	14.6[b]	No	No	1.25 mg qd 2 wk/2.5 mg qd 2 wk/3.75 mg qd 2 wk/5 mg qd 2 wk/7.5 mg qd 2 wk/10 mg qd	10 mg	8.1 mg (B in B 1st group) 7.1 mg (B in E 1st group)	65% (B in B 1st)[i] 54% (B in E 1st)[i]	86% (B in B 1st)[i] 72% (B in E 1st)[i]
RESOLVD	Metoprolol-S (214) Placebo (212)	Fixed 6	Yes	No	12.5 mg qd 1 wk run-in/25 mg qd 2 wk/50 mg qd 2 wk/75 mg qd 2 wk/100 mg qd 2 wk/200 mg qd	200 mg	156 mg (M-S)[k] – (P)[k]	81% (M-S)[k] – (P)[k]	–
MERIT-HF	Metoprolol-S (1990) Placebo (2001)	12[b]	No	No	12.5–25 mg qd 2 wk/50 mg qd 2 wk/100 mg qd 2 wk/200 mg qd	200 mg	159 mg (M-S) 179 mg (P)	64% (M-S)[l] 82% (P)[l]	87% (M-S)[l] 91% (P)[l]

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.
[...] Treatment not considered in the table.
[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]Enrolment 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 mg). 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% 50 mg,11% 25 mg, 9% 12.5 mg, 6% 6.25 mg, 9% 0 mg in carvedilol group, 78% 50 mg, 6% 25 mg, 4% 12.5 mg, 2% 6.25 mg, 10% 0 mg in the placebo group).
[f]At entry into the maintenance phase; the titration phase could take up to 14 weeks from randomization.
[g]Patients randomized to enalapril only ($n = 190$), carvedilol only ($n = 191$), or both drugs ($n = 191$). Proportions shown are at maintenance phase.
[h]Proportions shown are at the end of study.
[i]Proportions shown are maximum dose reaching during the study period.
[j]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.
[k]Food and Drug Administration review 154 mg and 69%; mean time to maximum titration was 93 days for the metoprolol group.
[l]Proportions shown are at the end of study.

Table 3 Dosing of mineralocorticoid receptor antagonists in randomized clinical trials in patients with heart failure with reduced ejection fraction[a]

Trial	Treatments (*n*)	Median trial duration (months)	Active run-in	Prior exposure to trial therapy	Dose titration schedule (starting, dose steps and duration of steps)	Target daily dose	Mean daily dose achieved	Proportion reaching target dose	Proportion reaching half target dose
RALES	Spironolactone (822) Placebo (841)	24[b]	No	No	25 mg qd 8 week/50 mg qd (could be reduced to 25 mg alt. days)	50 mg	26 mg (S)[c] 31 mg (P)[c]	12% (S)[c] 27% (P)[c]	80% (S)[c] 95% (P)[c]
EMPHASIS-HF	Eplerenone (1364) Placebo (1373)	21	No	No	eGFR 50 ml/min/1.73 m^2: 25 mg qd 4 wk/50 mg qd eGFR 30–49 ml/min/1.73 m^2: 25 mg alt. Days 4 week/25 mg qd	50 mg 25 mg	42/44 mg (Ep/P in high eGFR group)[d] 25/27 mg (Ep/P in low eGFR group)[d]	85%/81% (Ep/P in high eGFR group)[d] 71%/76% (Ep/P in low eGFR group)[d]	99%/100% (Ep/P in high eGFR group)[d] 99%/99% (Ep/P in low eGFR group)[d]

alt., alternative; bid, twice daily; Ep, eplerenone; eGFR, estimated glomerular filtration rate; P, placebo; qd, once daily; S, spironolactone; wk, week.
[a]The table does not include trials in patients with myocardial infarction.
[b]Mean.
[c]Doses 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.
[d]Doses shown are at month 5 visit (overall mean dose 39 mg). Proportion shown are maximum achieved doses during study period.

rate than permitted in the trials. Third, and most importantly, not all patients were able to reach the 'target dose' in the trials, despite run-in periods and specific inclusion and exclusion criteria (*Tables 1–3*). So, although the proportion of patients reaching the 'target dose' is often used as a measure of good prescribing, this approach provides a limited and perhaps flawed assessment of the adequacy of treatment (see below). In addition, the reporting of dosing data varies widely in terms of the denominator, i.e. whether all patients or just patients taking therapy (this is even less clear in 'real-world' cohorts) and timing (at a fixed time point during follow-up or at the end of the trial – and trial duration varied considerably). This is further complicated by a diverging denominator if active therapy improves survival compared to placebo (and the characteristics of patients in each treatment group differ with increasing follow-up).

A further underappreciated consideration is the influence of concomitant therapy on the dosing of an added treatment. This can be best seen in two trials (CIBIS III and CARMEN) comparing initiation of treatment with an angiotensin-converting enzyme (ACE) inhibitor (enalapril) or a beta-blocker (bisoprolol or carvedilol) first and adding the alternative second.[10–13] When enalapril was used first, the dose achieved was larger than when it was used second, i.e. added to a beta-blocker rather than used before a beta-blocker (*Table 1*). Of course, in the trial on which our target dose of enalapril is based on (the treatment arm of the Studies of Left Ventricular Dysfunction, SOLVD-T) the use of a beta-blocker was minimal.[14]

This 'target dose' approach used in the original placebo-controlled landmark trials using renin–angiotensin system blockers also influenced the design of subsequent trials comparing and adding alternative agents such as the neprilysin inhibitor/angiotensin receptor blocker (ARB) combination sacubitril/valsartan and the direct renin inhibitor aliskiren.[15,16] In these trials, all participants were required to demonstrate toleration of the target dose of enalapril (control therapy) before randomization to either the experimental therapy or control therapy. This was because the achievement of at least the mean dose of enalapril shown to be effective in SOLVD-T was considered a prerequisite for demonstration of non-inferiority or superiority of the experimental therapy over the established control treatment (enalapril).[16] This design requirement renders understanding the dosing of sacubitril/valsartan particularly difficult as all patients were taking the target dose at the time of randomization (to either continue sacubitril/valsartan 97/103 mg twice daily or to enalapril 10 mg twice daily) – see below.

What was the rate of 'target dose' achievement in trials?

Tables 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 a target dose, although the placebo-controlled trials showed that the proportion of patients attaining the target dose in the placebo group was not

100% (*Table 1*). 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.[17] 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 participants 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?

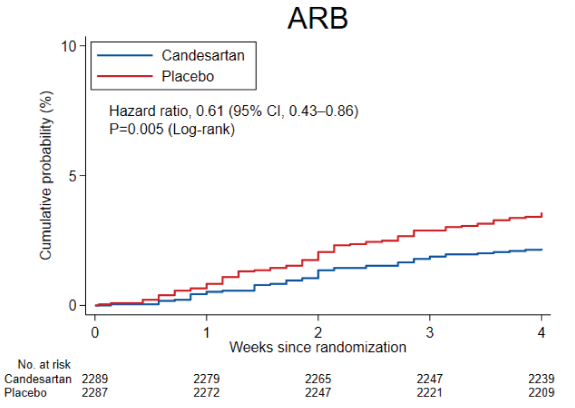
For one evidence-based drug, enalapril, there is evidence about the success rate in achieving different target doses. Here, an indirect comparison of the CONSENSUS and SOLVD-T trials is instructive (*Table 1*).[14,18] In CONSENSUS, only 22% of patients randomized to enalapril were titrated to the target 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.[19] 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.[1]

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.[20]

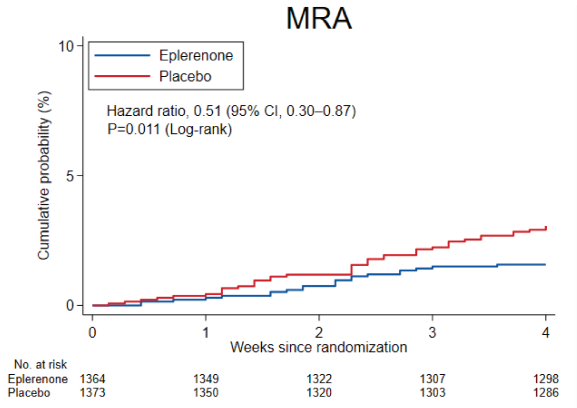
Unfortunately, similar data do not exist for beta-blockers.

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.[21] Treatment with candesartan led to a significant reduction in the composite of death or heart failure hospitalization within



	Dose level (mg)	2 weeks Patients (%)	4 weeks Patients (%)
	0	2.6	4.4
	4	81.5	14.9
	8	15.8	67.3
	16	0.1	13.2
	32	-	0.2
Mean daily dose achieved (mg)		4.7±1.5	8.5±3.5



	Dose level (mg)	2 weeks Patients (%)	4 weeks Patients (%)
	0	0.8	0.7
	12.5	14.2	12.3
	25	83.3	70.5
	50	1.7	16.6
Mean daily dose achieved (mg)		23.7±5.6	27.6±10.8

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.

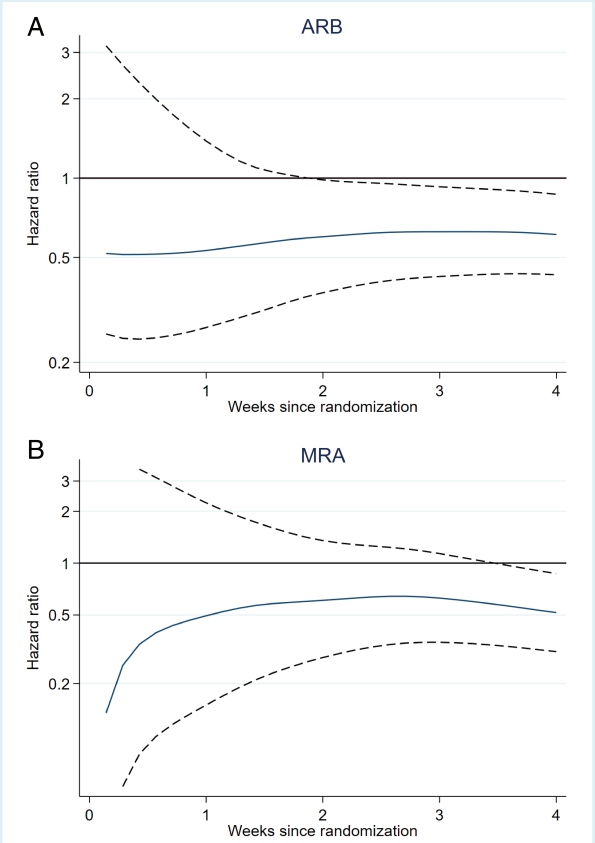


Figure 2 (*A*) Effect of candesartan compared with placebo on the composite of all-cause death or hospitalization for heart failure over the first 4 weeks after randomization. The horizontal blue line shows a continuous hazard ratio and the interrupted lines the 95% confidence interval. The upper 95% confidence interval falls below 1 after 15 days and remains under 1 thereafter. (*B*) Effect of eplerenone compared with placebo on the composite of all-cause death or hospitalization for heart failure over the first 4 weeks after randomization. The horizontal blue line shows a continuous hazard ratio and the interrupted lines the 95% confidence interval. The upper 95% confidence interval falls below 1 after 24 days and remains under 1 thereafter. ARB, angiotensin receptor blocker: MRA, mineralocorticoid receptor antagonist.

28 days of randomization with a hazard ratio (HR) of 0.61 (95% confidence interval [CI] 0.43–0.86). Indeed 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 at 2 and 4 weeks was only 4.7 (SD 1.5) mg and 8.5 (SD 3.5) mg, respectively. In other words, even at 4 weeks when a sustained benefit of candesartan was evident, only 13% had reached half the target dose. Similar data have been published from SOLVD-T.[22]

Figure 1 demonstrates the same finding for an MRA. In the EMPHASIS-HF trial, a significant reduction in the composite endpoint was also observed within 28 days, with a HR of 0.51 (95% CI 0.30–0.87).[20] As can be seen from *Figure 2B*, the benefit of eplerenone was apparent from 24 days after starting treatment, yet 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 m^2 and up to 25 mg daily if the eGFR was 30–49 ml/min/1.73 m^2. 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.[16] 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

	Treatments (*n*)	Median trial duration (months)	Target dose	Mean daily dose achieved	All-cause mortality or HF hospitalization, HR (95% CI)	All-cause mortality, HR (95% CI)	Cardiovascular mortality, HR (95% CI)
ATLAS	Lisinopril-low (1596)	46	2.5–5.0 mg qd	4.5 mg[a]	0.85 (0.78–0.93)	0.92 (0.82–1.03)	0.90 (0.81–1.01)
	Lisinopril-high (1568)		32.5–35 mg qd	33.2 mg[a]	$p = 0.002$	$p = 0.128$	$p = 0.073$
HEAAL	Losartan-low (1919)	56.4	50 mg qd	46 mg[b]	0.90 (0.82–0.99)[b]	0.94 (0.84–1.04)	0.92 (0.81–1.05)
	Losartan- high (1927)		150 mg qd	129 mg[b]	$p = 0.027$	$p = 0.24$	$p = 0.20$

CI, confidence interval; HF, heart failure; HR, hazard ratio; qd, once daily; SD, standard deviation.
[a]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.
[b]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; $p = 0.011$).

had not by themselves been shown to be superior to placebo (*Table 4*).[30–32] Consequently, we do not know how to compare either the higher or lower dose of the drugs used to the doses of enalapril or candesartan proven to reduce death and hospital admission.

However, in each of these two dose-comparison trials, the larger dose of treatment resulted in a lower event rate. As can be seen, the incremental benefit was modest and was driven by a reduction in hospitalization for heart failure, as opposed to mortality. In a meta-analysis adding some smaller trials, among a total of 5829 randomized participants, there was still no difference in mortality (HR 0.95, 95% CI 0.88–1.02).[32]

It is also important to consider the actual dose in the treatment arms in the two larger trials – in ATLAS these were 4.5 versus 33.2 mg of lisinopril and in HEAAL 46 versus 129 mg of losartan.[30,31] Here ATLAS is perhaps most striking in suggesting that even a small dose (one-seventh of the higher dose) preserves much of the benefit of a larger dose of an ACE inhibitor. However, we still have the problem of knowing what dose of enalapril or candesartan 4.5 mg of lisinopril is equivalent to. There are no satisfactory comparisons of doses of lisinopril and enalapril, or doses of lisinopril and candesartan, in people with heart failure. However, the data that do exist, and comparisons in hypertension, suggest that the low dose of lisinopril used in ATLAS was probably equivalent to less than 10 mg of enalapril.[33] Of interest, in both HEAAL and ATLAS, the proportion of patients who discontinued study drugs did not differ between the high and low-dose groups. In both trials, hypotension, renal dysfunction and hyperkalaemia occurred more frequently in the higher dose group but there was no significant excess of discontinuation for any of these reasons in the higher dose group in either trial.

Although three trials comparing doses of beta-blockers showed a greater increase in left ventricular ejection fraction with bigger doses, each was small and reported too few deaths and hospital admissions (or reported these incompletely) to draw any meaningful conclusion about a dose-related effect on outcomes.[34–36] Two of these trials compared carvedilol over a wide daily dose range (5 to 50 mg).[34,35] The other trial compared 12.5, 50 and 200 mg bucindolol daily with placebo.[36]

Similarly, there are no formal dose comparisons for MRAs that have examined clinical outcomes, although the stratified analysis of EMPHASIS-HF is discussed above (*Table 3*). The choice of dose of spironolactone for the RALES trial was based on the reduction in N-terminal pro atrial natriuretic peptide level (as a surrogate for efficacy) and increase in potassium (safety assessment).[37]

What can we conclude about the dosing of evidence-based pharmacotherapy in heart failure with reduced ejection fraction?

The most correct conclusion from the landmark trials in HFrEF is that the substantial benefits observed were obtained despite a third to a half of patients not achieving the 'target doses' aspired

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 hyperkalaemia). 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.[6,7] 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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