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RESEARCH ARTICLE

Similar clinical benefits from below-target and target dose enalapril in patients with heart failure in the SOLVD Treatment trial

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Aims To examine associations of below-target and target dose of enalapril, an angiotensin-converting enzyme (ACE) inhibitor, with outcomes in patients with heart failure and reduced ejection fraction (HFrEF) in the Studies of Left Ventricular Dysfunction (SOLVD) Treatment trial.

Methods and results Two thousand five hundred and sixty-nine patients with HFrEF (ejection fraction ≤35%) were randomized to below-target (5–10 mg/day) dose placebo (n = 1284) or enalapril (n = 1285). One month post-randomization, blind up-titration to target (20 mg/day) dose was attempted for both study drugs in 2458 patients. Among the 1444 patients who achieved dose up-titration (placebo, n = 748; enalapril, n = 696; mean dose for both groups, 20.0 mg/day), target dose enalapril (vs. target dose placebo) was associated with a 9% absolute lower risk of the combined endpoint of heart failure hospitalization or all-cause mortality [adjusted hazard ratio (HR) 0.70; 95% confidence interval (CI) 0.60–0.81; $P < 0.001$] during 4 years of follow-up. Among the 1014 patients who could not achieve target dose (placebo, n = 486; enalapril, n = 528; mean dose for both groups, 8.8 mg/day), below-target dose enalapril (vs. below-target dose placebo) was associated with a 12% absolute lower risk of the combined endpoint of heart failure hospitalization or all-cause mortality (adjusted HR 0.68; 95% CI 0.57–0.81; $P < 0.001$). Among the 1224 patients receiving enalapril, target (vs. below-target) dose had no association with the combined endpoint of heart failure hospitalization or all-cause mortality (adjusted HR 1.04; 95% CI 0.87–1.23; $P = 0.695$).

Conclusion In patients with HFrEF, the clinical benefits of ACE inhibitors appear to be similar at both below-target and target doses.

Keywords ACE inhibitors • Target dose • Enalapril • Placebo • Heart failure

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Correction added on 26 October 2017, after first online publication: On page 6, line 3, right column, references "[9,10]" were corrected to "[9,11]".

Introduction

Heart failure (HF) is a chronic condition and a major source of mortality and morbidity.[1−4] Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce the risk of death and hospital admission in patients with HF and reduced ejection fraction (HFrEF). Major HF guidelines recommend initial low-dose ACE inhibitor therapy followed by higher target doses as tolerated.[5,6] This recommendation is based in part on the findings from the Treatment arm of the double-blind Studies of Left Ventricular Dysfunction (SOLVD) trial, in which patients were randomized to receive 2.5−20 mg daily doses of either placebo or enalapril, an ACE inhibitor.[7] Although SOLVD was designed to use study drugs at higher target (20 mg/day) doses, the final mean daily dose of either study drug was 11 mg and at the final visit, 49% of patients in either treatment group were receiving target doses.[7] Thus, the beneficial effects of enalapril in SOLVD may not be attributed to the use of higher target doses. To the best of our knowledge, comparative associations of the two doses of enalapril used in the SOLVD trial have never been published. The objective of the current analysis is to examine associations of target and below-target dose enalapril with outcomes in the SOLVD Treatment trial.

Methods

Data source and study population

The current study is based on the public-use copy of the SOLVD Treatment trial obtained from the National Heart, Lung, and Blood Institute (NHLBI), which also sponsored the trial. The details of the design, methods, and results of the SOLVD trial have been reported previously.[7] Briefly, 2569 patients with HFrEF [ejection fraction (EF) ≤35%], mostly with NYHA class II or III symptoms, who tolerated a pre-randomization stabilization phase with single-blinded enalapril of 5 mg/day for a week were randomized to receive either placebo (n = 1284) or enalapril (n = 1285) at an initial dose of 5−10 mg/day in a double-blind fashion.

During the month following randomization, following a protocol-driven up-titration process, study investigators double-blindly up-titrated the dose of both study drugs to a target dose of 20 mg/day if patients did not have symptomatic hypotension or worsening renal function.[7,8] The current analysis is restricted to 2458 of the 2569 patients who underwent the dose up-titration process. Overall, 61% (748 of 1234) of patients in the placebo group and 57% (696 of 1224) of patients in the enalapril group received the target (20 mg daily) dose (*Figure 1*). Overall, 58.7% (1444 of 2458) of patients received the target dose of the study drugs.

Study outcomes

The primary outcome for the current analysis was all-cause mortality during 4.6 years (average, 2.7 years) of follow-up, which was also the primary outcome in the SOLVD trial.[7] Secondary outcomes included cardiovascular and HF mortality, all-cause, cardiovascular, and HF hospitalizations, and the combined endpoint of HF hospitalization or all-cause mortality. All endpoints were classified by study investigators at each centre on the basis of blinded chart reviews and interviews of family members.

Statistical analysis

Baseline characteristics of study participants receiving below-target and target doses of the study drugs were compared separately within the placebo and enalapril groups using Pearson's χ^2 test and Student's t-test as appropriate. Because doses of both enalapril and placebo were up-titrated double-blindly, we used two separate approaches to examine the dose response in the SOLVD trial. First, we examined the association of enalapril with outcomes separately in the target and below-target groups. This was done first by comparing target dose enalapril with target dose placebo and then by comparing below-target dose enalapril with below-target dose placebo. Second, we examined the association of target dose with outcomes separately in the enalapril and the placebo groups. This was done by comparing target dose enalapril with below-target dose enalapril and then by comparing target dose placebo with below-target dose placebo.

For both approaches, we used multivariable Cox proportional hazard models that were adjusted for all baseline characteristics displayed in *Table 1*. We used the same models to generate adjusted survival curves for target vs. below-target dose patients, separately for the enalapril and the placebo groups. Because systolic blood pressure and serum creatinine were the two key variables used for dose up-titration eligibility, to examine their confounding effect on the association between dose and primary outcome, we performed additional analysis adjusting for these two variables. We also compared the total number of all-cause, cardiovascular, and HF hospitalizations, and tested for statistical significance as appropriate using Student's t-test or the Wilcoxon rank sum test. All statistical tests were two-tailed with 95% confidence intervals (CIs) and a P-value <0.05 was considered significant. IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA) was used for all data analysis.

Results

Baseline characteristics

Overall, the 2458 patients included in the current analysis had a mean age (± standard deviation) of 60 (±10) years, a mean EF of 25 (±7)%, 20% were women, and 15% were African American. Baseline characteristics between patients receiving below-target and target dose of the study drugs are presented in *Table 1* separately for patients in the placebo and enalapril groups. Mean systolic blood pressure was higher and mean serum creatinine was lower among patients receiving target dose of both placebo and enalapril, reflecting blind dose up-titration (*Table 1*). Other baseline characteristics are displayed in *Table 1*.

Overall, the mean dose of the study drugs for patients in the placebo and enalapril groups was 15.6 and 15.2 mg/day, respectively (P = 0.077). The mean dose of the study drugs for patients in the below-target and target dose groups was 8.8 and 20.0 mg/day, respectively, which was similar for both placebo and enalapril groups (*Table 1*). All patients in the target dose group received a 20 mg/day dose. The vast majority of the patients in the below-target group received 10 mg/day (n = 774); 76% and 77% of patients in the placebo and enalapril groups, respectively, received this dose. Other below-target doses were: 2.5 mg/day (n = 23), 5 mg/day (n = 215), 7.5 mg/day (n = 1), 15 mg/day (n = 1).

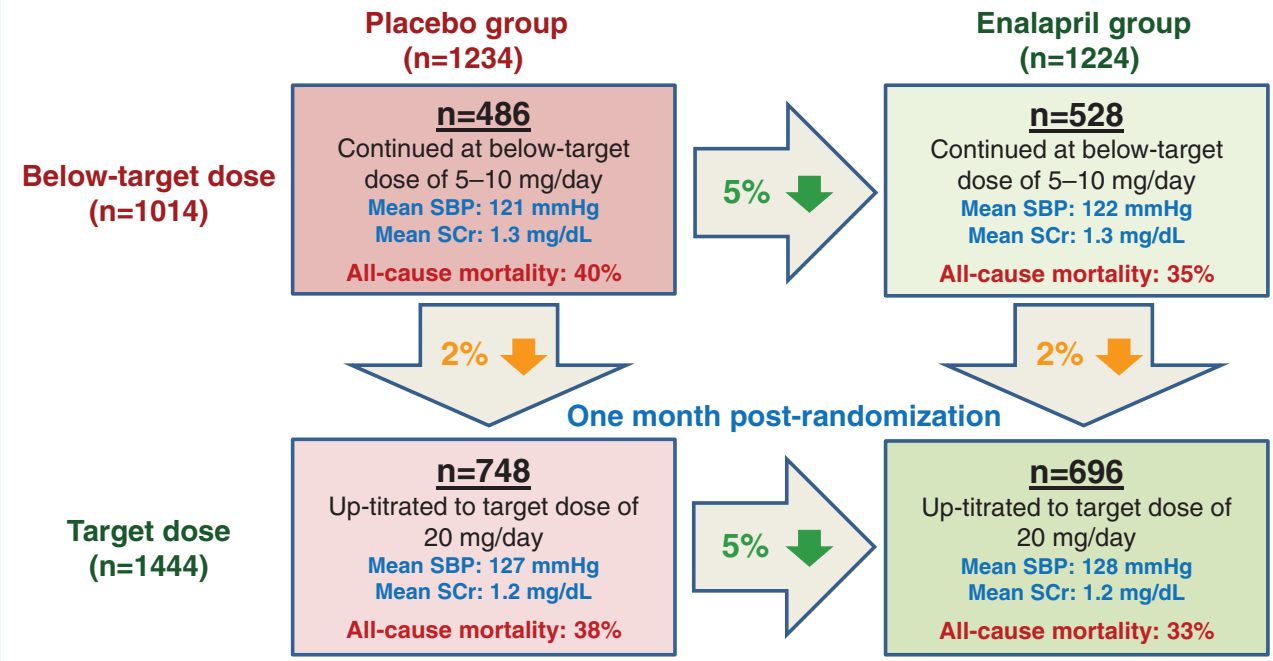

Figure 1 Flow chart for study cohort assembly for the current analysis. In the SOLVD Treatment trial, 2569 patients with heart failure and left ventricular ejection fraction ≤35% were randomized to below-target (5–10 mg/day) dose enalapril or matching placebo at baseline. One month post-randomization, double-blind up-titration to target (20 mg/day) dose was attempted per protocol for both study drugs in 2458 patients, based primarily on systolic blood pressure (SBP) and serum creatinine (SCr). Dose up-titration was achieved in 1444 patients and 1014 patients continued on below-target dose. Baseline SBP and SCr and all-cause mortality during 4.6 (average, 2.7) years of follow-up for each group are displayed in their respective cells.

Enalapril and all-cause mortality in the original SOLVD cohort

As previously reported, among the 2569 patients enrolled in the SOLVD trial, the primary endpoint of all-cause mortality occurred in 40% and 35% of patients in the placebo and the enalapril groups, respectively [hazard ratio (HR) when enalapril was compared with placebo, 0.84; 95% CI 0.74–0.96; $P = 0.008$).[7]

Enalapril and all-cause mortality in the dose up-titration cohort

Among the 2458 patients included in the current analysis, all-cause mortality occurred in 39% and 34% of patients receiving placebo and enalapril, respectively (HR associated with enalapril use, 0.83; 95% CI 0.73–0.95; $P = 0.005$).

Enalapril and outcomes within the target dose group

Among patients in the target dose group ($n = 1444$), all-cause mortality occurred in 38% and 33% of patients receiving target dose placebo and target dose enalapril, respectively (HR associated with target dose enalapril, 0.91; 95% CI 0.83–0.99; $P = 0.029$; *Table 2* and *Figure 2*). This association remained unchanged after multivariable risk adjustment (adjusted HR 0.90; 95% CI 0.82–0.98; $P = 0.017$; *Table 2*). Target dose enalapril was also associated with a lower risk of HF hospitalization (adjusted HR 0.75; 95% CI 0.68–0.83; $P < 0.001$), and consequently a lower risk of the combined endpoint of HF hospitalization or all-cause mortality (adjusted HR 0.70; 95% CI 0.60–0.81; $P < 0.001$; *Table 2*). Associations of target dose enalapril (vs. target dose placebo) with other outcomes are displayed in *Table 2*.

Enalapril and outcomes within the below-target dose group

Among patients in the relatively smaller below-target dose group ($n = 1014$), all-cause mortality occurred in 40% and 35% of patients receiving below-target dose placebo and below-target dose enalapril, respectively (HR associated with below-target dose enalapril, 0.91; 95% CI 0.82–1.01; $P = 0.068$; *Table 2* and *Figure 2*). This association remained unchanged after multivariable risk adjustment (adjusted HR 0.90; 95% CI 0.81–1.00; $P = 0.057$; *Table 2*). Below-target dose enalapril was also associated with a lower risk of HF hospitalization (adjusted HR 0.79; 95% CI 0.71–0.89; $P < 0.001$) as well as the combined endpoint of HF hospitalization or all-cause mortality (HR 0.68; 95% CI 0.57–0.81; $P < 0.001$; *Table 2*). Associations of below-target dose enalapril (vs. below-target dose placebo) with other outcomes are displayed in *Table 2*.

Table 1 Baseline characteristics of patients receiving below-target doses vs. target doses of the study drugs in the SOLVD Treatment trial, for the placebo and enalapril groups separately

	Placebo (n = 1234)			Enalapril (n = 1224)		
	Below-target dose (n = 486)	Target dose (n = 748)	P-value	Below-target dose (n = 528)	Target dose (n = 696)	P-value
Age (years)	61 (±10)	60 (±9)	0.061	60 (±11)	60 (±10)	0.662
Female*	128 (26)	119 (16)	<0.001	102 (19)	127 (18)	0.634
African American	91 (19)	86 (12)	<0.001	95 (18)	100 (14)	0.086
Dose of study drugs (mg/day)	8.8 (±2.3)	20.0 (±0.0)	<0.001	8.8 (±2.2)	20.0 (±0.0)	<0.001
Current smoker*	87 (18)	178 (24)	0.014	127 (24)	155 (22)	0.463
New York Heart Association class						
I	60 (12)	113 (15)	<0.001	63 (12)	110 (16)	0.083
II	252 (52)	428 (57)		275 (52)	374 (54)	
III	152 (31)	200 (27)		181 (34)	205 (30)	
IV	22 (5)	7 (1)		9 (2)	7 (1)	
Past medical history						
Chronic heart failure aetiology						
Ischaemic causes	337 (69)	556 (74)	0.118	384 (73)	479 (69)	0.095
Other causes	54 (11)	62 (8)		59 (11)	71 (10)	
Unknown causes	95 (20)	130 (17)		85 (16)	146 (21)	
Acute myocardial infarction	310 (64)	492 (66)	0.474	362 (69)	451 (65)	0.168
Hypertension	203 (42)	307 (41)	0.800	204 (39)	314 (45)	0.023
Diabetes mellitus*	135 (28)	195 (26)	0.508	118 (22)	177 (25)	0.212
Angina pectoris	188 (39)	295 (39)	0.791	199 (38)	247 (36)	0.428
Atrial fibrillation†	36 (7)	46 (6)	0.386	46 (9)	62 (9)	0.905
Cardiothoracic ratio >0.5	284 (58)	410 (55)	0.210	307 (58)	402 (58)	0.892
Clinical findings						
Pulse (beats/min)	81 (±14)	79 (±13)	0.018	80 (±14)	80 (±13)	0.579
Systolic blood pressure (mmHg)	121 (±18)	127 (±16)	<0.001	122 (±18)	128 (±17)	<0.001
Diastolic blood pressure (mmHg)	75 (±10)	77 (±10)	<0.001	76 (±10)	78 (±10)	<0.001
Weight (kg)	76 (±10)	77 (±9)	0.003	76 (±9)	77 (±8)	0.049
Laboratory data						
Serum sodium (mEq/L)	140 (±3)	140 (±3)	0.413	140 (±3)	140 (±3)	0.195
Serum potassium (mEq/L)	4.3 (±0.47)	4.3 (±0.45)	0.688	4.2 (±0.44)	4.3 (±0.46)	0.334
Serum creatinine (mEq/L)	1.3 (±0.32)	1.2 (±0.29)	0.002	1.3 (±0.32)	1.2 (±0.29)	0.033
Ejection fraction (%)	25 (±7)	25 (±7)	0.608	25 (±7)	25 (±7)	0.714
Medications						
Beta-blockers	26 (5)	62 (8)	0.050	41 (8)	59 (9)	0.652
Digitalis†	305 (63)	541 (72)	<0.001	339 (64)	464 (67)	0.369
Diuretics	3399 (82)	650 (87)	0.021	444 (84)	598 (86)	0.373
Potassium-sparing diuretics	39 (8)	76 (10)	0.207	46 (9)	68 (10)	0.528
Calcium channel blockers*	158 (33)	243 (33)	0.993	141 (27)	223 (32)	0.043
Nitrates†	226 (47)	312 (42)	0.097	228 (43)	255 (37)	0.020
Anti-arrhythmics	111 (23)	145 (19)	0.144	116 (22)	160 (23)	0.673
Potassium supplements	233 (48)	369 (49)	0.633	262 (50)	360 (52)	0.466
Anti-coagulants	93 (19)	110 (15)	0.040	87 (17)	106 (15)	0.553
Anti-platelets	189 (39)	230 (31)	0.003	203 (38)	203 (29)	0.001

Values are mean (±SD) or numbers and proportion of patients (%).
*P-value <0.05, when patients in the below-target dose enalapril group were compared with those in the below-target dose placebo group.
†P-value <0.05, when patients in the target dose enalapril group were compared with those in the target dose placebo group.

Target dose and outcomes within the enalapril group

Among patients in the enalapril group (n = 1224), all-cause mortality occurred in 35% and 33% of patients receiving below-target dose enalapril and target dose enalapril, respectively (HR associated with target dose enalapril, 0.89; 95% CI 0.74–1.09; P = 0.26, *Table 3*). Multivariable-adjusted HR for this association was 1.01 (95% CI 0.82–1.24; P = 0.95; *Table 3* and *Figure 3*). HR adjusted for baseline systolic blood pressure and serum creatinine, the

Table 2 Outcomes by randomization to placebo vs. enalapril in the SOLVD Treatment trial, separately in the target and below-target dose groups

	Target dose (n = 1444)					
	Events (%)			Hazard ratio (95% CI); P-value		
	Placebo (n = 748)	Enalapril (n = 696)	ARD[a]	Unadjusted	Age, sex, race adjusted	Multivariable adjusted[b]
Mortality						
All-cause	287 (38%)	233 (33%)	−5%	0.91 (0.83–0.99); P = 0.029	0.91 (0.83–0.99); P = 0.033	0.90 (0.82–0.98); P = 0.017
Cardiovascular	257 (34%)	207 (30%)	−4%	0.91 (0.83–0.99); P = 0.032	0.91 (0.83–0.99); P = 0.034	0.90 (0.81–0.98); P = 0.020
Heart failure	97 (13%)	82 (12%)	−1%	0.92 (0.80–1.07); P = 0.286	0.93 (0.80–1.07); P = 0.296	0.91 (0.78–1.06); P = 0.236
Hospitalization						
All-cause	556 (74%)	474 (68%)	−6%	0.88 (0.83–0.93); P < 0.001	0.88 (0.83–0.93); P < 0.001	0.87 (0.82–0.93); P < 0.001
Cardiovascular	470 (63%)	386 (56%)	−7%	0.88 (0.82–0.94); P < 0.001	0.88 (0.82–0.94); P < 0.001	0.87 (0.81–0.93); P < 0.001
Heart failure	270 (36%)	172 (25%)	−11%	0.78 (0.71–0.86); P < 0.001	0.77 (0.70–0.85); P < 0.001	0.75 (0.68–0.83); P < 0.001
Combined endpoint of heart failure hospitalization or all-cause mortality	415 (55%)	322 (46%)	−9%	0.74 (0.64–0.85); P < 0.001	0.73 (0.63–0.85); P < 0.001	0.70 (0.60–0.81); P < 0.001
	Below-target dose (n = 1014)					
	Events (%)			Hazard ratio (95% CI); P-value		
	Placebo (n = 486)	Enalapril (n = 528)	ARD[a]	Unadjusted	Age, sex, race adjusted	Multivariable adjusted[b]
Mortality						
All-cause	196 (40%)	185 (35%)	−5%	0.91 (0.82–1.01); P = 0.068	0.92 (0.83–1.01); P = 0.091	0.90 (0.81–1.00); P = 0.057
Cardiovascular	178 (37%)	163 (31%)	−6%	0.90 (0.81–1.00); P = 0.047	0.90 (0.81–1.01); P = 0.064	0.89 (0.80–0.99); P = 0.039
Heart failure	66 (14%)	59 (11%)	−3%	0.89 (0.75–1.06); P = 0.183	0.91 (0.76–1.09); P = 0.301	0.91 (0.75–1.10); P = 0.310
Hospitalization						
All-cause	365 (75%)	375 (71%)	−4%	0.92 (0.86–0.99); P = 0.022	0.92 (0.86–0.99); P = 0.024	0.93 (0.86–1.00); P = 0.054
Cardiovascular	308 (63%)	302 (57%)	−6%	0.90 (0.83–0.98); P = 0.011	0.90 (0.83–0.97); P = 0.009	0.89 (0.82–0.97); P = 0.008
Heart failure	181 (37%)	140 (27%)	−10%	0.79 (0.71–0.89); P < 0.001	0.80 (0.72–0.90); P < 0.001	0.79 (0.71–0.89); P < 0.001
Combined endpoint of heart failure hospitalization or all-cause mortality	285 (59%)	249 (47%)	−12%	0.71 (0.60–0.84); P < 0.001	0.71 (0.60–0.85); P < 0.001	0.68 (0.57–0.81); P < 0.001

ARD, absolute risk difference; CI, confidence interval.
[a]Estimated by subtracting event rates in the enalapril group from those in the placebo group.
[b]Adjusted for all variables included in *Table 1*.

two characteristics that were used to determine blind up-titration suitability, was 0.97 (95% CI 0.80–1.18; P = 0.76). Target dose enalapril was not associated with the combined endpoint of HF hospitalization or all-cause mortality (HR 1.04; 95% CI 0.87–1.23; P = 0.70; *Table 3*). Associations of target dose enalapril (vs. below-target dose enalapril) with other outcomes are displayed in *Table 3*.

Target dose and outcomes within the placebo group

Among patients in the placebo group (n = 1234), all-cause mortality occurred in 40% and 38% of patients receiving below-target dose placebo and target dose placebo, respectively (HR associated with target dose placebo, 0.91; 95% CI 0.76–1.09; P = 0.28; *Table 3*).

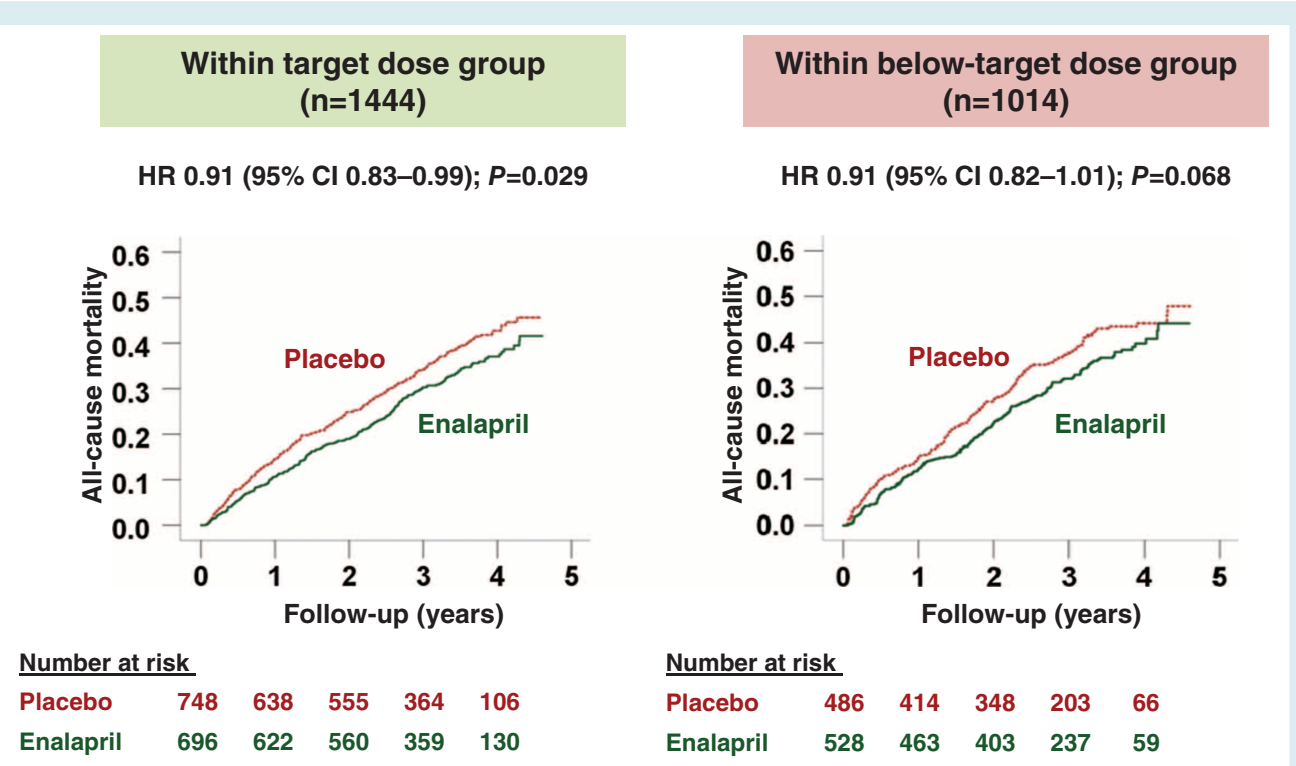

Figure 2 Kaplan–Meier plots for all-cause mortality in patients with heart failure and left ventricular ejection fraction ≤35% in the SOLVD Treatment trial, by randomization to enalapril or placebo, separately within the below-target and target dose groups. HR, hazard ratio; CI, confidence interval.

Multivariable-adjusted HR for this association was 0.96 (95% CI 0.79–1.16; $P = 0.67$; *Table 3* and *Figure 3*). As observed in the enalapril group, HR adjusted for baseline systolic blood pressure and serum creatinine was similar to that observed after multivariable adjustment (HR 0.98; 95% CI 0.81–1.18; $P = 0.79$). Associations of target dose placebo (vs. below-target dose placebo) with other outcomes are displayed in *Table 3*.

Associations with total number of hospitalizations

Among the 2458 patients included in the current analysis, patients in the enalapril group had 32% fewer HF hospitalizations (634 vs. 931 in the placebo group; $P < 0.001$; *Table 4*). There was no difference in total number of hospitalizations between the two dose groups receiving enalapril or placebo (*Table 4*).

Target dose and outcomes in SOLVD, ATLAS, NETWORK, and HEAAL

The design, name and dose of study drugs, demographics, and key outcomes data of the current study and the randomized controlled trials (RCTs) of higher (vs. lower) doses of ACE inhibitors or angiotensin II receptor blockers (ARBs) are presented in *Table 5*. In none of these RCTs did high dose reduce the risk of death (*Table 5*).[9–11] The composite endpoint of mortality or HF hospitalization was significantly reduced in two of these trials and both were driven by a reduction in the risk of HF hospitalization.[9,11] The point estimate for risk reduction for HF hospitalization in the ATLAS trial was not provided,[9] and in the HEAAL trial there was a significant but modest 1% reduction in HF hospitalization per 100 patient-years of follow-up in the high-dose losartan group.[11]

Discussion

Findings from this post hoc analysis of the SOLVD data demonstrate that enalapril (vs. placebo) use was associated with a similar lower risk of mortality separately in the below-target and target dose groups, and that the magnitude of the absolute risk reduction in these two dose groups was similar to that observed in the main trial.[7] When we examined the association of target (vs. below-target) dose with mortality, we found similar modest non-significant unadjusted associations in both placebo and enalapril groups reflecting selection bias and blind up-titration of the study drugs. This lack of evidence of greater mortality benefit from higher target dose observed in our study is generally consistent with findings from previous RCTs comparing target (vs. below-target) dose of ACE inhibitors or ARBs.[9–11] The lower risk of combined endpoints observed in some of these trials was driven primarily by a modest reduction in HF hospitalization. Taken

Table 3 Outcomes by below-target vs. target doses of the study drugs in the SOLVD Treatment trial, separately in the enalapril and placebo groups

	Enalapril (n = 1224)					
	Events (%)			Hazard ratio (95% CI); P-value		
	Below-target dose (n = 528)	Target dose (n = 696)	ARD[a]	Unadjusted	Age, sex, race adjusted	Multivariable adjusted[b]
Mortality						
All-cause	185 (35%)	233 (33%)	−2%	0.89 (0.74–1.09); P = 0.257	0.91 (0.75–1.10); P = 0.325	1.01 (0.82–1.24); P = 0.947
Cardiovascular	163 (31%)	207 (30%)	−1%	0.90 (0.74–1.11); P = 0.326	0.92 (0.75–1.13); P = 0.403	1.02 (0.83–1.27); P = 0.827
Heart failure	59 (11%)	82 (12%)	+1%	0.97 (0.69–1.35); P = 0.838	0.98 (0.70–1.37); P = 0.916	1.22 (0.85–1.74); P = 0.286
Hospitalization						
All-cause	375 (71%)	474 (68%)	−3%	0.87 (0.76–0.99); P = 0.037	0.87 (0.76–1.00); P = 0.048	0.91 (0.78–1.05); P = 0.173
Cardiovascular	302 (57%)	386 (56%)	−1%	0.90 (0.78–1.05); P = 0.175	0.90 (0.78–1.05); P = 0.191	0.94 (0.81–1.11); P = 0.478
Heart failure	140 (27%)	172 (25%)	−2%	0.88 (0.70–1.10); P = 0.264	0.90 (0.72–1.12); P = 0.348	0.99 (0.78–1.25); P = 0.899
Combined endpoint of heart failure hospitalization or all-cause mortality	249 (47%)	322 (46%)	−1%	0.92 (0.78–1.09); P = 0.346	0.94 (0.80–1.11); P = 0.485	1.04 (0.87–1.23); P = 0.695
	Placebo (n = 1234)					
	Events (%)			Hazard ratio (95% CI); P-value		
	Below-target dose (n = 486)	Target dose (n = 748)	ARD[a]	Unadjusted	Age, sex, race adjusted	Multivariable adjusted[b]
Mortality						
All-cause	196 (40%)	287 (38%)	−2%	0.91 (0.76–1.09); P = 0.284	0.92 (0.76–1.10); P = 0.349	0.96 (0.79–1.16); P = 0.666
Cardiovascular	178 (37%)	257 (34%)	−3%	0.89 (0.74–1.08); P = 0.250	0.91 (0.75–1.11); P = 0.347	0.94 (0.77–1.16); P = 0.579
Heart failure	66 (14%)	97 (13%)	−1%	0.91 (0.66–1.24); P = 0.530	0.95 (0.69–1.30); P = 0.732	1.17 (0.82–1.66); P = 0.381
Hospitalization						
All-cause	365 (75%)	556 (74%)	−1%	0.95 (0.83–1.08); P = 0.425	0.95 (0.83–1.09); P = 0.447	1.00 (0.86–1.15); P = 0.947
Cardiovascular	308 (63%)	470 (63%)	0%	0.95 (0.82–1.10); P = 0.481	0.94 (0.81–1.09); P = 0.399	0.99 (0.84–1.15); P = 0.845
Heart failure	181 (37%)	270 (36%)	−1%	0.92 (0.76–1.11); P = 0.357	0.93 (0.77–1.13); P = 0.454	1.03 (0.84–1.26); P = 0.772
Combined endpoint of heart failure hospitalization or all-cause mortality	285 (59%)	415 (56%)	−3%	0.89 (0.77–1.04); P = 0.129	0.89 (0.77–1.04); P = 0.143	0.93 (0.79–1.09); P = 0.374

ARD, absolute risk difference; CI, confidence interval.
[a]Estimated by subtracting event rates in the below-target group from those in the target group.
[b]Adjusted for all variables included in *Table 1*.

together, these findings suggest that target dose ACE inhibitor is not associated with incremental mortality benefit beyond that achieved at below-target dose and that other clinical benefits of target dose, if present, are modest.

By protocol, the blind up-titration of enalapril and placebo in the SOLVD trial was based on patients' conditions, specifically the absence of symptomatic hypotension and/or impaired kidney function—a process that may have selected patients with a better prognosis in the target dose group. As a result, patients receiving both target dose enalapril and target dose placebo had significantly higher mean systolic blood pressure and lower mean serum creatinine levels at baseline (*Table 1*), characteristics that have been

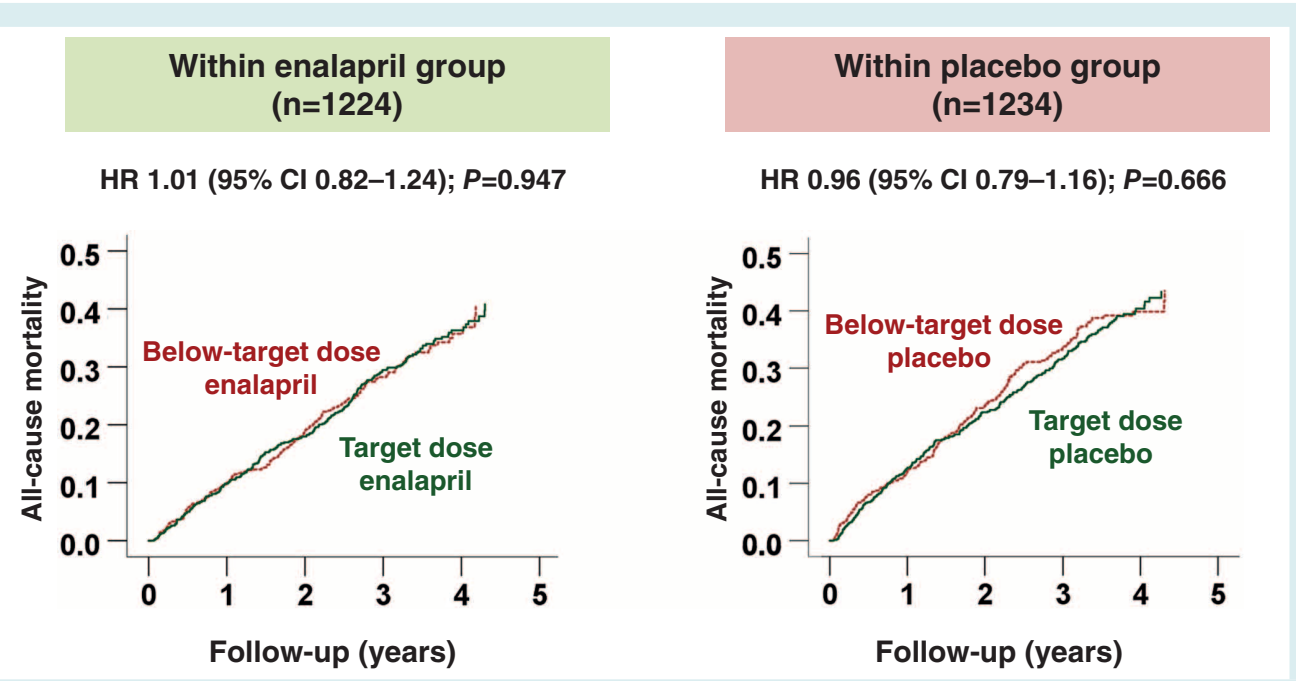

Figure 3 Adjusted survival plots for all-cause mortality in patients with heart failure and left ventricular ejection fraction ≤35% in the SOLVD Treatment trial, by receipt of the below-target vs. the target dose of the study drugs, separately within the enalapril and the placebo groups. Multivariable-adjusted Cox regression model was adjusted for all variables included in *Table 1*. CI, confidence interval; HR, hazard ratio.

Table 4 Total numbers of hospitalizations for any reason, cardiovascular reason, and heart failure in the SOLVD Treatment trial, by below-target vs. target doses of the study drugs, separately in the enalapril and placebo groups

	Hospitalizations for any reason, total (mean/patient)		**Hospitalizations for CV reason, total (mean/patient)**		**Hospitalization for HF, total (mean/patient)**	
	2268 (1.9)[a]		**1562 (1.3)[b]**		**634 (0.5)[c]**	
Enalapril (n = 1224)	Below-target dose (n = 528)	Target dose (n = 696)	Below-target dose (n = 528)	Target dose (n = 696)	Below-target dose (n = 528)	Target dose (n = 696)
	1004 (1.9)[d]	1264 (1.8)[e]	679 (1.3)[f]	883 (1.3)[g]	281 (0.5)[h]	353 (0.5)[i]
	P = 0.465[j]		P = 0.612[j]		P = 0.445[j]	
	Hospitalizations for any reason, total (mean/patient)		**Hospitalizations for CV reason, total (mean/patient)**		**Hospitalization for HF, total (mean/patient)**	
	2738 (2.2)[a]		**1967 (1.6)[b]**		**931 (0.8)[c]**	
Placebo (n = 1234)	Below-target dose (n = 486)	Target dose (n = 748)	Below-target dose (n = 486)	Target dose (n = 748)	Below-target dose (n = 486)	Target dose (n = 748)
	1110 (2.3)[d]	1628 (2.2)[e]	800 (1.7)[f]	1167 (1.6)[g]	398 (0.8)[h]	533 (0.7)[i]
	P = 0.971[j]		P = 0.672[j]		P = 0.682[j]	

CV, cardiovascular; HF, heart failure.
[a,b,c]*P*-values comparing hospitalization for any reason, cardiovascular reason, and heart failure, between placebo and enalapril, overall were derived from Student's *t*-tests and were <0.001 for all three outcomes.
[d–i]*P*-values comparing hospitalization for any reason, cardiovascular reason, and heart failure, between placebo and enalapril, separately within below-target ([d]0.021, [f]0.008, and [h]0.003) and target ([e]0.005, [g]0.005, and [i]0.002) dose groups.
[j]*P*-values comparing hospitalization for any reason, cardiovascular reason, and heart failure, between below-target and target dose groups, were derived from the Wilcoxon rank sum (or Mann–Whitney) tests.

Table 5 Comparison of studies of dose effect of renin–angiotensin system inhibition in patients with heart failure and reduced ejection fraction

Study	Design	Drug (*n*); dose/day (low vs. high); *n* (low vs. high)	Mean age, women, African American	Primary endpoint	Events, low vs. high dose (%); hazard ratio (95% CI); *P*-value				Total number (low vs. high dose); *P*-value
					All-cause mortality	HF hospitalization	Combined endpoint of HF hospitalization or all-cause mortality	Combined endpoint of CV hospitalization or all-cause mortality	HF hospitalizations
SOLVD (*n* = 2458)	Post hoc analysis of RCT	Enalapril (*n* = 1224); <20 vs. 20 mg; 528 vs. 696	60 years 19% 16%	All-cause mortality	35% vs. 33%; 1.01 (0.82–1.24); *P* = 0.947	27% vs. 25%; 0.99 (0.78–1.25); *P* = 0.899	47% vs. 46%; 1.01 (0.82–1.24); *P* = 0.947	69% vs. 67%; 0.95 (0.82–1.01); *P* = 0.488	281 vs. 353; *P* = 0.712
		Placebo (*n* = 1234); <20 vs. 20 mg; 486 vs. 748	61 years 20% 15%		40% vs. 38%; 0.96 (0.79–1.16); *P* = 0.666	37% vs. 36%; 1.01 (0.84–1.26); *P* = 0.772	59% vs. 56%; 0.93 (0.79–1.09); *P* = 0.374	76% vs. 75%; 0.95 (0.83–1.10); *P* = 0.508	398 vs. 533; *P* = 0.229
ATLAS (*n* = 3164)	RCT	Lisinopril 2.5–5 vs. 32.5–35 mg; 1596 vs. 1568	64 years 20% 9%	All-cause mortality	45% vs. 43%; 0.92 (0.82–1.03); *P* = 0.128	Not reported	60% vs. 55%; 0.85 (0.78–0.93); *P* < 0.001	74% vs. 71%; 0.92 (0.84–0.99); *P* = 0.036	1576 vs. 1199; *P* = 0.002
NETWORK (*n* = 1532)	RCT	Enalapril; 5 vs. 10 vs. 20 mg; 506 vs. 510 vs. 516	70 years 35% —	All-cause mortality, worsening HF or HF hospitalization	Not reported	Not reported	Not reported	Not reported	Not reported
HEAAL (*n* = 3846)	RCT	Losartan 50 vs. 150 mg; 1913 vs. 1921	66 years 30% 1%	All-cause mortality or HF hospitalization	35% vs. 33%; 0.94 (0.84–1.04); *P* = 0.24	26% vs. 23%; 0.87 (0.76–0.98); *P* = 0.025	12% vs. 11%; 0.90 (0.82–0.99); *P* = 0.027	17% vs. 16%; 0.92 (0.85–1.01); *P* = 0.068	503 vs. 450; *P* = 0.025

CI, confidence interval; CV, cardiovascular; HF, heart failure; RCT, randomized controlled trial.

shown to be associated with better outcomes in patients with HF.[12,13] A 2% non-significant absolute reduction in unadjusted mortality in the target dose enalapril (vs. below-target enalapril) group suggests that the risk reduction associated with the higher target dose was at best modest. However, two observations point to another explanation—a potential selection bias. First, the modest association of target dose and mortality disappeared when adjusted for just systolic blood pressure and serum creatinine, and second, similar unadjusted and adjusted associations of target dose and mortality were also observed in the placebo group.

In the SOLVD Treatment trial, enalapril had a strong and significant effect on HF hospitalization.[7] We observed that enalapril (vs. placebo) in both target and below-target dose use was associated with a similar lower risk of HF hospitalization, suggesting that a higher target dose did not provide any incremental benefit for this outcome. The lack of dose effect was also supported by our observation that neither target dose of enalapril nor target dose of placebo had any association with HF hospitalization when compared with their below-target dose counterparts (*Table 3*). However, as explained below, these findings in terms of HF hospitalization are not entirely consistent with findings from some of the RCTs on dosing.[9,11]

As mentioned before, none of the three RCTs that examined the effect of high (vs. low) doses of ACE inhibitors or ARBs found any mortality benefit.[9–11] Two of these RCTs reported a reduction of mortality or HF hospitalization,[9,11] which was driven by a modest reduction in the risk of HF hospitalization. However, neither had a placebo group to demonstrate the effect of low dose compared with placebo. Findings from our study suggest that enalapril use at both below-target and target dose of enalapril was associated with a similar lower risk for HF hospitalizations (*Table 3*). These findings are also consistent with findings from a recent study that observed similar efficacy of sacubitril/valsartan (vs. enalapril) in the below-target dose group (HR 0.80, 95% CI 0.70–0.93, $P < 0.001$) and the target dose group (HR 0.79, 95% CI 0.71–0.88, $P < 0.001$).[14]

Findings from our study have important clinical implications. The use of higher target doses of ACE inhibitors and ARBs is associated with a modest increase in the risk of adverse effects, including hypotension, dizziness, hyperkalaemia, and elevation of serum creatinine.[9,15,16] The use of a higher dose of these drugs may also preclude the initiation or up-titration of beta-blockers and aldosterone antagonists, and switching to an angiotensin receptor–neprilysin inhibitor (ARNI).[6,17] Recent updates in HF guidelines recommend the use of an ARNI, a combination of valsartan and sacubitril, to replace ACE inhibitors in ambulatory patients with mild to moderate chronic HFrEF who tolerate a high target dose of ACE inhibitors.[6,17]

The SOLVD trial was conducted during an earlier era of HF management, which may limit generalization to contemporary HFrEF patients. However, the SOLVD trial remains the cornerstone of the evidence base for the use of ACE inhibitors in patients with HFrEF. Importantly, the use of target dose ACE inhibitors in the SOLVD trial is often cited as a rationale to recommend higher target doses of ACE inhibitors, although data on outcomes in patients receiving below-target and target dose have not been previously published. Thus, the current analysis based on the SOLVD trial is relevant in clarifying current interpretations of the findings from that trial. Because dose in our study was not determined by randomization, confounding due to selection bias is possible. However, this is not a concern as we did not observe any clinical benefit in patients receiving higher target doses who may have had a lower risk due to selection bias. Finally, the similar associations of below-target and target dose enalapril with mortality observed in our study is consistent with the similar effect of below-target and target dose ACE inhibitors or ARBs on mortality observed in the ATLAS, NETWORK, and HEAAL trials.[9–11]

In conclusion, in patients with HFrEF enrolled in the SOLVD trial, the use of target dose enalapril (vs. target dose placebo) and below-target dose enalapril (vs. below-target dose placebo) was associated with a similar lower risk of death, HF hospitalization, or the combined endpoint of HF hospitalization or death. We also observed that the use of target dose enalapril (vs. below-target dose enalapril) was not associated with these outcomes or total number of hospitalizations. Taken together with the findings from the ATLAS, NETWORK, and HEAAL trials, these findings suggest that ACE inhibitor use is associated with clinical benefits for those who can tolerate a higher dose as well as for those who cannot tolerate a higher dose or may not be eligible for such a dose, and that incremental clinical benefits associated with a higher dose, if present, are modest.

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Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott); Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, PLx Pharma, Takeda. J.B. discloses the following relationships - consultant to Amgen, Astra-Zeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, Janssen, Luitpold, Medtronic, Novartis, Relypsa, Vifor, and ZS Pharma. G.S.F. participated in committees of trials and registries sponsored by Vifor, Novartis, Bayer, Servier. G.C.F. discloses the following relationships - consultant to Amgen, Novartis, Medtronic, St. Jude Medical.

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