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 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 2569 patients with HFrEF (EF d35%) 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, 748; enalapril, 696; mean dose for both groups, 20.0 mg/day), target dose enalapril (versus target dose placebo) was associated with a 9% absolute lower risk of the combined end point of HF 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, 486; enalapril, 528; mean dose for both groups, 8.8 mg/day), below-target dose enalapril (versus below-target dose placebo) was associated with a 12% absolute lower risk of the combined end point of HF 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 (versus below-target) dose had no association with the combined end point of HF hospitalization or all-cause mortality (adjusted HR, 1.04; 95% CI, 0.87–1.23; p=0.695).

Conclusion In patients with HF and reduced EF, clinical benefit of ACE inhibitor appear to be similar at both below-target and target doses.

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Introduction

Heart failure (HF) is a chronic condition and is 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 to 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 a 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 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 (EF d35%), 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 to 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 target dose of the study drugs.

Study outcomes

The primary end point 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 combined end point of HF hospitalization or all-cause mortality. All end points were classified by study investigators at each center 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 Chi-square 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 characteristic displayed in Table 1. We used the same models to generate adjusted survival curves for target versus 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 Wilcoxon rank sum test. All statistical tests were two-tailed with 95% confidence levels {CI} and a p-value <0.05 was considered significant. IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.) was used for all data analysis.

Results

Baseline characteristics

Overall, the 2458 patients included in the current analysis had a mean age of 60 (±10) years, mean EF of 25 (±7) percent, 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 were 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 were 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 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).

Enalapril and all-cause mortality in the original SOLVD cohort

As previously reported, among the 2569 patients enrolled in the SOLVD trial, the primary end point 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 end point 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 (versus 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 end point 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 (versus below-target dose placebo) with other outcomes are displayed in **Table 2**.

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 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 end point 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 (versus 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**). 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 (versus 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 versus 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 (versus 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 end point 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.[9,10] 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 (versus 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 (versus 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 prior RCTs comparing target (versus 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 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 benefit of target dose, if present, is 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 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 (versus 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 trials, enalapril had a strong and significant effect on HF hospitalization.[7] We observed that enalapril (versus 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 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 (versus low) doses of ACE inhibitors or ARBs found any mortality benefit.[9-11] Two of these RCTs reported reduction of mortality or HF hospitalization,[9,10] 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 (versus 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, hyperkalemia and elevation of serum creatinine.[9,15,16] The use of 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 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 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 (versus target dose placebo) and below-target dose enalapril (versus below-target dose

placebo) was associated with a similar lower risk of death, HF hospitalization or the combined end point of HF hospitalization or death. We also observed that the use of target dose enalapril (versus 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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Figure Legend:

Figure 1. All-cause mortality by study drug and dose in the SOLVD-Treatment trial (SBP = systolic blood pressure, SCr = serum creatinine)

Figure 2. Kaplan-Meier plots for all-cause mortality in patients with heart failure with reduced ejection fraction randomized to receive enalapril or placebo in the SOLVD-Treatment trial, separated by dose of the study drugs (HR = hazard ratio, CI = confidence interval)

Figure 3. Multivariable-adjusted* survival plots for all-cause mortality by target vs. below-target dose of the study drugs in the SOLVD-Treatment trial (HR = hazard ratio, CI = confidence interval)

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