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# Levosimendan vs. dobutamine: outcomes for acute heart failure patients on β-blockers in SURVIVE†

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**Aims** Many chronic heart failure (CHF) patients take β-blockers. When such patients are hospitalized for decompensation, it remains unclear how ongoing β-blocker treatment will affect outcomes of acute inotrope therapy. We aimed to assess outcomes of SURVIVE patients who were on β-blocker therapy before receiving a single intravenous infusion of levosimendan or dobutamine.

**Methods and results** Cox proportional hazard regression revealed all-cause mortality benefits of levosimendan treatment over dobutamine when the SURVIVE population was stratified according to baseline presence/absence of CHF history and use/non-use of β-blocker treatment at baseline. All-cause mortality was lower in the CHF/levosimendan group than in the CHF/dobutamine group, showing treatment differences by hazard ratio (HR) at days 5 (3.4 vs. 5.8%; HR, 0.58, CI 0.33–1.01, $P = 0.05$) and 14 (7.0 vs. 10.3%; HR, 0.67, CI 0.45–0.99, $P = 0.045$). For patients who used β-blockers ($n = 669$), mortality was significantly lower for levosimendan than dobutamine at day 5 (1.5 vs. 5.1% deaths; HR, 0.29; CI 0.11–0.78, $P = 0.01$).

**Conclusion** Levosimendan may be better than dobutamine for treating patients with a history of CHF or those on β-blocker therapy when they are hospitalized with acute decompensations. These findings are preliminary but important for planning future studies.

**Keywords** Levosimendan • Dobutamine • Heart failure, congestive • Cardiac output, low • β-blockers, adrenergic

## Introduction

For patients with chronic heart failure (CHF), β-blocker therapy is an evidence-based strategy that can enhance survival, lower risk for morbidity, and reduce rates of hospitalization.[1–4] Guidelines recommend β-blocker therapy as a vital component of the treatment regimen for most individuals with CHF.[5–8] However, when a CHF patient receiving β-blocker therapy is hospitalized with an episode of decompensation, the response to treatment with a positive inotrope such as dobutamine can be blunted or unpredictable.[9–11]

A recent large-scale trial, Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE), showed no statistically significant benefit of the calcium-sensitizer levosimendan over the beta-agonist dobutamine on all-cause mortality at 31 days or at 180 days.[12] However, pre-specified analysis showed that levosimendan-treated patients with a history of CHF actually did better for 31 days survival than did

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those treated with dobutamine (HR = 0.73, CI 0.52–1.03; *P*-value for CHF x treatment interaction = 0.05) in a SURVIVE subgroup analysis.[12] We further noted, in a previous study comparing the effect of levosimendan and dobutamine in acute decompensated heart failure, the LIDO study, that patients on β-blockers had a better haemodynamic profile and also had significantly greater survival during the first 5 days after levosimendan infusion (compared with dobutamine), with trending differences through day 14.

We hypothesized that levosimendan therapy may be more beneficial than dobutamine in specific subgroups of patients in the SURVIVE trial—especially those on β-blocker therapy. It is plausible that the pharmacodynamic actions of the β-agonist dobutamine and β-receptor blocking agents antagonize each other, whereas levosimendan's haemodynamic benefits may add additional value to the cardioprotective actions of β-blocker therapy thereby leading to survival advantages. Based on the observation that the active metabolite of levosimendan circulates for about 2 weeks (half-life ~80 h), we further deduced that levosimendan survival benefits in this patient population may be best evidenced early in the course of recovery after treatment for acute decompensation.[12,13]

Accordingly, our present report addresses treatment responses of SURVIVE patients who were on β-blocker therapy before the single intravenous infusion of levosimendan or dobutamine was given. In these analyses, we focus on the initial 31 days after the initiation of therapy.

# Methods

## Study design

The SURVIVE study was a randomized, blinded, double-dummy, multi-centre study of patients hospitalized with acute heart failure ($n = 1{,}327$).[12] Enrolled patients had a need for intravenous (i.v.) inotropic support, as evidenced by an insufficient response to i.v. diuretics or vasodilators (nitroglycerin and nitroprusside) and at least one of the following at screening: oliguria (urine output $<30$ mL/h for at least 6 h) not as a result of hypovolaemia; dyspnoea at rest or need for mechanical ventilation for HF; or haemodynamic impairment in those patients with Swan–Ganz catheter (pulmonary capillary wedge pressure $\geq 18$ mmHg and/or cardiac index $\leq 2.2$ L/min/m$^2$).

The study was approved by the local ethics committees of each institution and conducted according to the principles of the Declaration of Helsinki.[14] All patients provided written, informed consent before participation.

During the treatment period, patients hospitalized with acute heart failure were randomized to receive a single infusion of levosimendan or dobutamine in a blinded, double-dummy fashion. Levosimendan was initiated with 12 mcg/kg loading dose administered over 10 min, followed by a continuous infusion at 0.1 mcg/kg/min for 50 min. If tolerated, the infusion rate was increased to 0.2 mcg/kg/min for an additional 23 h. Dobutamine was administered at a minimum infusion rate of 5 mcg/kg/min, and the dose was increased to achieve clinical goals, up to 40 mcg/kg/min. The infusion was maintained as long as deemed clinically appropriate (minimum 24 h) and was tapered slowly and in accordance with each patient's clinical status.

The primary endpoint for SURVIVE was all-cause mortality over 180 days following the initial treatment with levosimendan or dobutamine. All-cause mortality at 31 days was pre-specified as a secondary endpoint. *Post hoc* mortality analyses were completed for the 5 and 14 days post-infusion periods. Pre-specified baseline characteristics to be recorded were sex, age, history of CHF, prior use of β-blockers, prior use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, acute myocardial infarction as a cause of hospitalization, dyspnoea at rest, heart rate, and systolic blood pressure. Prior use of β-blockers, i.e. taking a β-blocker at baseline, was defined as having a dose of drug within 24 h prior to initiation of the study drug infusion.

## Statistical analyses

Categorical baseline characteristics and demographics were expressed as number and percentage of patients, and continuous variables were expressed as mean values with standard deviation. Chi-square tests were used to test for the difference between treatment groups for categorical variables and ANOVA was used for continuous variables. Comparisons between β-blocker users and non-users for baseline characteristic/demographic variables were performed similarly.

Numbers, percentages, and hazard ratios [HRs; with 95% confidence intervals (CI)] were reported for all-cause mortality and for mortality by history of CHF or by baseline β-blocker use. Survival differences between the treatment groups were tested for significance by the Cox proportional hazard (CPH) regression model with treatment as the only covariate in all intent-to-treat patients. Interactions were considered significant for *P*-values $\leq 0.10$. The CPH regression model was then used within subgroups of patients, with and without baseline β-blocker use, or with and without a history of CHF, with significant differences at $P < 0.05$. Comparative incidence of adverse events between treatment groups was analysed using a Fisher's exact test.

Summary statistics for mean changes from baseline in daily vital signs (heart rate, systolic blood pressure, and diastolic blood pressure) were calculated by subgroups with and without β-blocker use through day 5. Statistical analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA), and significance was reported at a *P*-value of 0.05 or less.

# Results

## Demographic and other characteristics of patients

In the SURVIVE study population ($n = 1327$), 1171 patients (88%) had previous CHF and 669 (50%) had received β-blockers within 24 h prior to study drug infusion (*Table 1*). The most commonly used β-blockers in the overall population were: carvedilol (21%), metoprolol (15%), and bisoprolol (12%). Of note, 51% of the patients with a history of CHF (602/1171) were receiving β-blocker treatment at baseline.

There were no differences in the mean duration or dose of levosimendan infusion when β-blocker users and non-users were compared, nor were there differences for dobutamine treatment by group. In patients receiving β-blockers at baseline, levosimendan was administered for a mean of $24 \pm 2.6$ h with a mean continuous infusion dose of $0.2 \pm 0.02$ mcg/kg/min, compared to $23 \pm 3.2$ h with a mean continuous infusion dose of $0.2 \pm 0.02$ mcg/kg/min in those patients not receiving β-blocker therapy. For patients receiving dobutamine infusions, the mean duration of treatment was $37 \pm 44.6$ h at a rate of $6.0 \pm 2.8$ mcg/kg/min in patients on β-blocker therapy, compared to a mean of $42 \pm 44.0$ h at a mean infusion rate of $5.8 \pm 2.3$ mcg/kg/min in patients with no

**Table 1 Baseline demographic profiles and characteristics of patients stratified according to use of β-blockers**

| Variable[a] | β-blocker users ($n = 669$) | | β-blocker non-users ($n = 658$) | |
|---|---|---|---|---|
| | Levosimendan ($n = 336$) | Dobutamine ($n = 333$) | Levosimendan ($n = 328$) | Dobutamine ($n = 330$) |
| Male | 261 (78%) | 239 (72%) | 232 (71%) | 224 (68%) |
| Age, years [mean (SD)] | 66 (12) | 64 (12) | 69 (12) | 68 (11) |
| Weight, kg [mean (SD)] | 80 (17) | 81 (16) | 78 (18) | 78 (16) |
| Height, cm [mean (SD)] | 170 (8) | 170 (9) | 169 (9) | 168 (8) |
| White race | 318 (95%) | 314 (94%) | 309 (94%) | 311 (94%) |
| Left ventricular ejection fraction, mean (SD) | 24 (5) | 24 (5) | 24 (6) | 24 (5) |
| Main reason for hospitalization | | | | |
| Worsening HF | 262 (78%) | 257 (77%) | 268 (82%) | 261 (79%) |
| Myocardial infarction | 50 (15%) | 47 (14%) | 33 (10%) | 48 (15%) |
| Aetiology of heart disease | | | | |
| Ischaemic | 241 (72%) | 236 (71%) | 262 (80%) | 266 (81%) |
| Non-ischaemic | 74 (22%) | 78 (23%) | 40 (12%) | 43 (13%) |
| Hypertension | 15 (5%) | 15 (5%) | 16 (5) | 14 (4%) |
| Cardiovascular history | | | | |
| History of heart failure | 304 (90%) | 298 (89%) | 282 (86%) | 286 (87%) |
| Atrial fibrillation/flutter | 160 (48%) | 144 (43%) | 164 (50%) | 164 (50%) |
| Ventricular tachycardia | 49 (15%) | 46 (14%) | 32 (10%) | 32 (10%) |
| Ventricular fibrillation | 14 (4%) | 10 (3%) | 12 (4%) | 12 (4%) |
| History of hypertension | 199 (59%) | 217 (65%) | 206 (63%) | 212 (64%) |
| Type 2 diabetes | 103 (31%) | 115 (35%) | 102 (31%) | 108 (33%) |
| Cardiovascular medications prior (24 h) to infusion | | | | |
| ACE-inhibitors or ARBs | 269 (80%) | 262 (79%) | 194 (59%) | 189 (57%) |
| Aldosterone antagonists | 188 (56%) | 210 (63%) | 148 (45%) | 156 (47%) |

Use of β-blockers was defined as taking a β-blocker within 24 h prior to the start of levosimendan or dobutamine infusion. Data are shown for the intent-to-treat population.
ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker.
[a]*n* (%) unless indicated otherwise.

β-blocker use. There was no significant difference in cumulative dobutamine exposure between the β-blocker use and non-use subgroups: 1095 ± 1799 vs. 1208 ± 1881 mg, respectively.

## All-cause mortality analyses

For the intent-to-treat SURVIVE population, there were numerical differences in all-cause mortality through 31 days, albeit not statistically significant (*Figure 1A*). However, stratifying the SURVIVE population according to the presence or absence of a history of CHF at baseline, treatment-by-subgroup interaction was significant at day 14 ($P = 0.01$) and at day 31 ($P = 0.05$) as shown in *Figure 1B*. Based on these findings, additional exploratory analyses examined treatment differences for all-cause mortality among the 1171 patients (586 levosimendan and 585 dobutamine) with previous CHF. All-cause mortality was lower in the levosimendan group compared with the dobutamine group with a significant treatment difference at day 14 (7.0 vs. 10.3%; HR, 0.67, CI 0.45–0.99, $P = 0.045$) and differences at 5 and 31 days that trended toward significance (3.4 vs. 5.8%, HR, 0.58, CI 0.33–1.01, $P = 0.05$; and 10.1 vs. 13.3%, HR, 0.73, CI 0.52–1.03, $P = 0.07$, respectively; *Figure 1B*).

When the SURVIVE population was stratified according to the use or non-use of β-blockers at baseline, treatment-by-subgroup interaction was significant at day 5 ($P = 0.03$) but not at days 14 ($P = 0.16$) or 31 ($P = 0.55$) (*Figure 1C*). Additional exploratory analysis examined treatment differences for all-cause mortality among the 669 patients (336 levosimendan and 333 dobutamine) who used β-blockers. All-cause mortality during the 5, 14, and 31 days following the start of the study drug infusion was numerically lower in the levosimendan group compared with the dobutamine group: the HRs (with 95% CI values) at days 5, 14, and 31, respectively, were 0.29 (CI 0.11–0.78, $P = 0.01$), 0.58 (CI 0.31–1.10, $P = 0.1$), and 0.75 (CI 0.44–1.27, $P = 0.29$). Further, in the levosimendan-treated group, all cause mortality was much lower in patients with both previous CHF and β-blocker treatment, compared to patients with previous CHF alone, use of β-blockers alone, or neither CHF nor β-blocker use (*Table 2*). Such results suggest an additive survival benefit of previous CHF status and the use of β-blockers at baseline in patients treated with levosimendan. Indeed, the mortality of patients with previous CHF who are β-blocker users is the lowest at each time point.

### Safety and tolerability according to prior use or non-use of β-blockers and according to treatment

Prior use or non-use of β-blockers did not affect the heart rate, systolic, or diastolic blood pressure responses to either

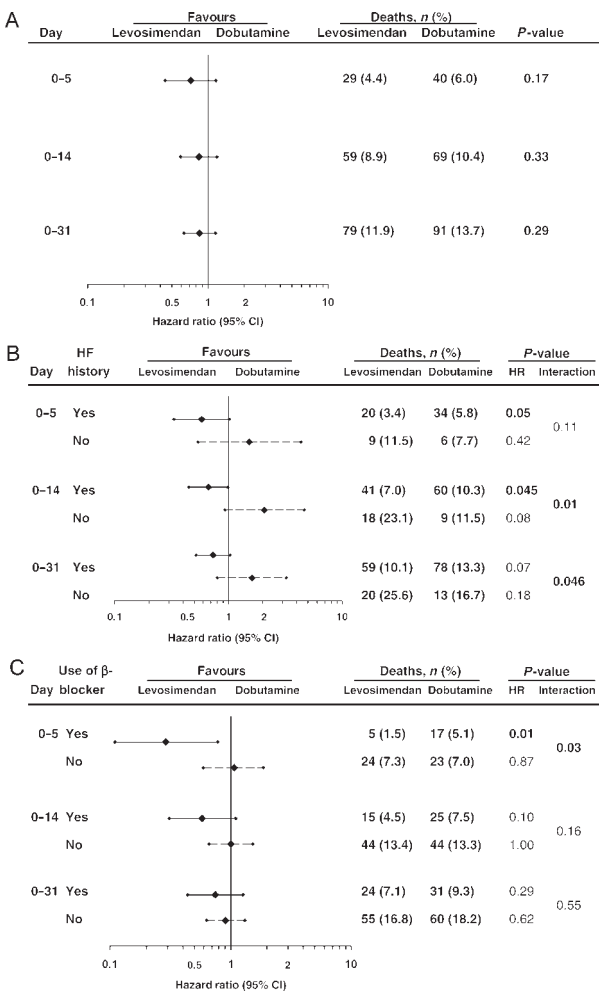


**Figure 1** (*A*) Hazard ratios for all-cause mortality up to 31 days in all acute heart failure patients who were treated with levosimendan ($n = 663$) or dobutamine ($n = 664$) in the SURVIVE trial. These data include patients with acute decompensation of chronic heart failure as well as those with acute *de novo* heart failure. *P*-values shown were derived by the Cox proportional hazards model with effect for treatment only. Data represent the intent-to-treat population. (*B*) Hazard ratios for all-cause mortality up to 31 days in the SURVIVE trial with stratification according to whether or not patients had a history of chronic heart failure (HF). This analysis included patients who were treated with levosimendan ($n = 586$ with history of HF; $n = 78$ without history of HF) or dobutamine ($n = 585$ with history of HF; $n = 78$ without history of HF). *P*-values shown were derived by the Cox model with effect for treatment only. *P*-values for treatment × subgroup interactions were 0.10, 0.01, and 0.046 at days 5, 14, and 31, respectively. (*C*) Hazard ratios for all-cause mortality up to 31 days in the SURVIVE trial with stratification according to β-blocker status at the start of the trial. The analysis included acute heart failure patients who were treated with levosimendan ($n = 336$ β-blocker users; $n = 328$ β-blocker non-users) or dobutamine ($n = 333$ β-blocker users; $n = 330$ β-blocker non-users).

**Table 2 Mortality at days 5, 14, and 31 in patients treated with levosimendan according to the use or non-use of β-blockers and the existence of previous chronic heart failure**

| | | Mortality at day 5 | | Mortality at day 14 | | Mortality at day 31 | |
|---|---|---|---|---|---|---|---|
| | | β-blocker users | β-blocker non-users | β-blocker users | β-blocker non-users | β-blocker users | β-blocker non-users |
| Previous CHF | Yes, *n* (%) | 4/304 (1.3) | 6/282 (5.7) | 12/304 (3.9) | 29/282 (10.2) | 20/304 (6.6) | 39/282 (13.8) |
| | No, *n* (%) | 3/32 (9.3) | 3/46 (6.5) | 3/32 (9.3) | 15/46 (32.6) | 4/32 (12.5) | 16/46 (34.8) |

CHF; chronic heart failure.

randomized agent, as previously described,[12] and as shown for each treatment group (*Figures 2A–C*). Although the two randomized treatment groups experienced different vital sign responses, patients receiving β-blockers at baseline were less likely to experience cardiovascular adverse events that are commonly observed in a heart failure population, independent of treatment group (*Table 3*). Cardiac arrest, sudden death, cardiac failure, pulmonary oedema, cardiogenic shock, tachycardia, ventricular extra-systole, renal failure, and hypotension occurred with consistently lower incidence in patients receiving β-blockers, although the differences were not necessarily statistically significant. *Table 3* further shows that the previously described increased incidence in atrial fibrillation with levosimendan was seen in both β-blocker users and non-users, whereas the increased incidence of ventricular extra-systole with levosimendan was reduced in β-blocker users.

# Discussion

Our results suggest an advantage of levosimendan treatment over dobutamine for lowering all-cause mortality during the first weeks following treatment, as shown in patients admitted with acute decompensated heart failure and with a known history of CHF and/or currently being treated with oral β-blockers. These findings can be put into perspective with related studies. In the LIDO trial (Levosimendan Infusion vs. Dobutamine), patients hospitalized for an acute decompensation of CHF were treated with infusions of levosimendan or dobutamine.[15] Results showed that haemodynamic responses among patients on β-blockers were enhanced for those treated with levosimendan but blunted for those who received dobutamine.[15] This was confirmed by the prospectively designed BEAT-CHF study.[16] LIDO results further suggested a 180 day survival advantage after initial infusion of levosimendan, in comparison with dobutamine.[15] Results of the SURVIVE trial, specifically designed to compare mortality outcomes in patients hospitalized for acute heart failure, showed numerically fewer deaths among individuals given levosimendan infusions compared with dobutamine, but the differences were not statistically significant at 31 and 180 day endpoints.[12]

Half of the CHF patients in our current analyses were receiving β-blocker treatment at baseline. To explore CHF status or use of

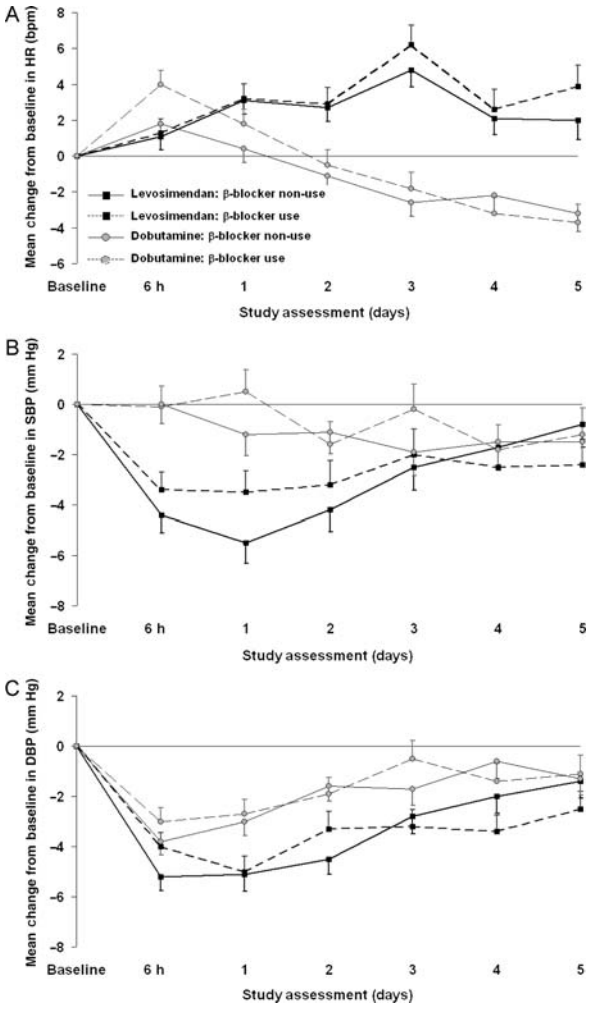


**Figure 2** Haemodynamic parameters according to prior use or non-use of β-blockers and to treatment. (*A*)–(*C*), respectively, are heart rate, systolic and diastolic blood pressure, shown as mean changes from baseline (±standard error) during 5 days after the start of treatment.

**Table 3 Incidence of adverse events by prior use of β-blockers and by treatment**

| | β-blocker users | | β-blocker non-users | |
|---|---|---|---|---|
| | Levosimendan ($n$ = 333), $n$ (%) | Dobutamine ($n$ = 333), $n$ (%) | Levosimendan ($n$ = 327), $n$ (%) | Dobutamine ($n$ = 327), $n$ (%) |
| Blood system disorders | | | | |
| Anaemia | 9 (2.7) | 9 (2.7) | 6 (1.8) | 8 (2.4) |
| Cardiac disorders | | | | |
| Angina pectoris | 5 (1.5) | 12 (3.6) | 7 (2.1) | 6 (1.8) |
| Atrial fibrillation | 27 (8.1) | 18 (5.4) | 33 (10.1) | 22 (6.7) |
| Cardiac arrest | 6 (1.8) | 11 (3.3) | 14 (4.3) | 15 (4.6) |
| Sudden death | 3 (0.9) | 2 (0.6) | 7 (2.1) | 4 (1.2) |
| Cardiac failure as acute, congestive, or general | 46 (13.8) | 45 (13.5) | 62 (19.0) | 87 (26.6) |
| Pulmonary oedema | 7 (2.1) | 7 (2.1) | 13 (4.0) | 11 (3.4) |
| Cardiogenic shock | 2 (0.6) | 7 (2.1) | 13 (4.0) | 16 (4.9) |
| Tachycardia | 10 (3.0) | 7 (2.1) | 23 (7.0) | 27 (8.3) |
| Ventricular extra systole | 14 (4.2) | 11 (3.3) | 26 (8.0) | 13 (4.0) |
| Ventricular tachycardia | 25 (7.5) | 23 (6.9) | 27 (8.3) | 25 (7.6) |
| Vascular disorders | | | | |
| Hypotension | 43 (12.9) | 35 (10.5) | 59 (18.0) | 57 (17.4) |
| Gastrointestinal disorders | | | | |
| Constipation | 11 (3.3) | 9 (2.7) | 15 (4.6) | 19 (5.8) |
| Diarrhoea | 12 (3.6) | 9 (2.7) | 18 (5.5) | 12 (3.7) |
| Nausea | 18 (5.4) | 18 (5.4) | 27 (8.3) | 31 (9.5) |
| Vomiting | 6 (1.8) | 8 (2.4) | 16 (4.9) | 16 (4.9) |
| General disorders | | | | |
| Chest pain | 15 (4.5) | 21 (6.3) | 17 (5.2) | 26 (8.0) |
| Pyrexia | 9 (2.7) | 7 (2.1) | 13 (3.9) | 12 (3.7) |
| Infections | | | | |
| Acute bronchitis | 8 (2.4) | 8 (2.4) | 3 (0.9) | 4 (1.2) |
| Pneumonia | 14 (4.2) | 7 (2.1) | 16 (4.9) | 17 (5.2) |
| Urinary tract infection | 8 (2.4) | 13 (3.9) | 13 (4.0) | 17 (5.2) |
| Metabolism and nutrition disorders | | | | |
| Hypokalaemia | 27 (8.1) | 19 (5.7) | 35 (10.7) | 20 (6.1) |
| Nervous system disorders | | | | |
| Dizziness | 6 (1.8) | 8 (2.4) | 13 (4.0) | 8 (2.4) |
| Headache | 21 (6.3) | 21 (6.3) | 34 (10.4) | 10 (3.1) |
| Renal disorders | | | | |
| Renal failure or impairment | 18 (5.4) | 14 (4.2) | 26 (8.0) | 25 (7.6) |

Table lists treatment-emergent events with incidence ≥2% in any subgroup. Data are shown for safety population.

β-blockers in combination with levosimendan therapy, we used *post hoc* analyses at early time-points (during the first 31 days after the start of study drug) and a focused examination of specific subgroups of SURVIVE patients. We noted that patients with a history of CHF, like those in the LIDO study, had significantly higher survival at day 14 after levosimendan infusion than did patients after dobutamine.[15] We further noted that patients on β-blockers also had significantly greater survival during the first 5 days after levosimendan infusion (compared with dobutamine), with trending differences through day 14. The difference in mortality between levosimendan and dobutamine groups in the initial 14 days after drug infusion coincides with the expected pharmacokinetic behaviour of the drugs. The active metabolite of levosimendan peaks approximately 3 days after the start of study drug infusion and has a half-life of approximately 80 h, thus the metabolite is expected to be present during the initial 2 weeks period.[13] Conversely, dobutamine has a relatively short serum half-life and has no known metabolite that might extend the activity of the parent compound.[17]

As the population ages and survival after acute cardiac events improves, the number of patients with CHF has increased steadily, as have hospitalizations for episodes of decompensation.[18,19] Trial results show that the majority of patients who present with acutely decompensated heart failure (if acute coronary syndromes are excluded) have a history of CHF—up to 80% or more.[12,20–22] Because treatment guidelines recommend use of β-blockers to

improve long-term survival in patients with CHF, an increasing proportion of patients with acute decompensation can be expected to receive these agents chronically.[5–7] Accordingly, when a patient is hospitalized with acute cardiac decompensation, a key question is how the patient's status with regard to CHF and customary β-blockade therapy will affect his or her response to in-hospital treatment. Results of our present *post hoc* analyses suggest that levosimendan, rather than dobutamine, may be considered as a treatment for acute decompensated heart failure in patients who are receiving chronic oral β-blockade therapy.

## Limitations of our study

There are limitations to our study design and conclusions, generally related to the *post hoc* nature of the subgroup analyses. Patients were not randomized into the study according to β-blocker status at baseline—even though the number of participants was evenly distributed between users and non-users. In addition, the day 5 and 14 time-points were not pre-specified, while day 31 was a time-point for secondary outcomes. Our study findings suggested benefits for use of levosimendan over dobutamine in patients taking β-blockers or in patients with a prior history of CHF; however, there was considerable overlap between these groups. It will be necessary to conduct a full-scale prospective study to pinpoint how these baseline characteristics are related to the patients' responses to levosimendan.

Additional design limitations are possible confounders. Patients unable to tolerate β-blockers are known to have higher mortality, thus non-β-blocker use in this study may have characterized a refractory subgroup of patients. Furthermore, the initiation or adjustment of patients' β-blocker treatment was not monitored after discharge from the index hospitalization. When rehospitalizations were needed (data not shown), patients were not required to receive infusions matching their original randomized treatment assignments, so crossover therapy may have blunted all-cause mortality differences during intervals beyond the index hospitalization. Other factors may also have confounded the outcome interpretations, for example non-ischaemic aetiology was more frequent in β-blocker users, as was treatment with ACE inhibitors.

## Summary

In summary, results of our analyses suggest a possible advantage of levosimendan treatment over dobutamine for lowering all-cause mortality during the first weeks following treatment, as shown in patients admitted with acute decompensated heart failure and with a known history of CHF and/or currently being treated with oral β-blockers. This observation should be confirmed by a prospective study that is adequately powered to measure such differences.

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**Conflict of interest:** A.M., M.S.N., G.S.F., and A.C.-S. served as members of the Steering Committee for the SURVIVE Trial, which was funded by a grant from Abbott Laboratories. J.G.C. served on the SURVIVE Data Safety Monitoring Committee. J.E.S., R.T., and R.J.P. are Abbott employees who participated in the design of the SURVIVE trial; other Abbott employees are Leticia Herrera, who worked on manuscript preparation, and B.H., who conducted statistical analyses for *post hoc* and subgroup analyses.

ClinicalTrials.gov number: NCT00348504.

# Appendix

# SURVIVE trial Investigators

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