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Effect of baseline characteristics on mortality in the SURVIVE trial on the effect of levosimendan vs dobutamine in acute heart failure: Sub-analysis of the Finnish patients

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ABSTRACT

Background: In the SURVIVE trial, including 1327 acute heart failure patients, no statistically significant difference between levosimendan and dobutamine in the 180-day all-cause mortality was seen. Country-specific differences in outcome were, however, present. In the Finnish sub-population in fact, mortality was significantly lower in levosimendan treated patients. We aim to understand the reasons for this disparity.
Methods: The risk factors for all-cause mortality were identified in the whole study population using multivariate Cox proportional hazards regression analysis. Those factors were evaluated in the 95 patients of the Finnish sub-population.
Results: The treatment by country interaction for mortality in Finland vs. other countries was significant, $p = 0.029$. Levosimendan treated patients had a lower 180-day mortality compared to dobutamine treated (17% vs. 40%, $p = 0.023$) in the Finnish sub-population. Baseline variables predicting survival in the whole SURVIVE trial population included age, systolic blood pressure, heart rate, myocardial infarction during admission, levels of NT-pro-BNP, glucose, creatinine, and alanine transferase, use of ACE inhibitors and β-blockers, oliguria, time from hospital admission to randomization, history of cardiac arrest, and left ventricular ejection fraction. Finnish patients were more frequently treated with β-blockers (88% vs. 52%, $p < 0.0001$), their study treatment was started earlier (mean ± SD 41 ± 40 h vs. 81 ± 154; $p < 0.0001$), and they had more often acute myocardial infarction at admission (39% vs. 16%, $p < 0.0001$).
Conclusion: The lower mortality in the Finnish patients treated with levosimendan was associated with higher use of β-blockers, higher frequency of myocardial infarction at admission, and shorter delay between randomization and start of treatment.

1. Introduction

Levosimendan is a calcium sensitizer and ATP-dependent potassium channel opener [1], developed for the treatment of acute decompensated heart failure (AHF) [2]. This inodilator has been in clinical use since year 2000 and is currently available in 60 countries.

The earlier clinical study LIDO (Levosimendan Infusion versus Dobutamine) suggested a mortality benefit with levosimendan in comparison with dobutamine in 203 patients with low output heart failure [3]. In the later SURVIVE trial (Levosimendan vs dobutamine for patients with acute decompensated heart failure) including 1327 patients with AHF, no statistically significant difference in 180-day mortality was observed between levosimendan and dobutamine [4]. However, in patients with ongoing beta-blockade, levosimendan outperformed dobutamine [5].

The SURVIVE trial was conducted at 75 centers in 9 countries (Austria, Finland, France, Germany, Israel, Latvia, Poland, Russia, and the United Kingdom). The result as it regards mortality was significantly different among the different participating countries [6,7]. In Finland, mortality was lower in levosimendan treated patients compared to dobutamine treated. In this retrospective analysis of the SURVIVE data, we aimed to find explanations for this difference in order to better understand which kind of patients benefit most of a treatment with levosimendan.

2. Methods

SURVIVE was a randomized, controlled, parallel-group trial to evaluate the efficacy and safety of dobutamine and levosimendan in 1327 adult patients (aged >18 years) hospitalized due to AHF and meeting specified eligibility criteria, including a need for parenteral inotropes.

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In the analyses, we excluded 7 patients who never received the study drug. The primary endpoint was all-cause mortality during the 180 days following randomization. The trial was event rate-driven, requiring 330 deaths. Secondary endpoints included 31-day all-cause mortality and change in brain natriuretic peptide (BNP) level during the first 24 h of treatment [4].

In this retrospective analysis we identified the risk factors for worse outcome in the whole study population by multivariate analysis, and tested those factors in the two treatment arms of the 95 Finnish patients.

2.1. Multivariate analysis

All the demographic and baseline variables captured on the case record form (CRF) of patients in the intent-to-treat (ITT) cohort of SURVIVE were considered as potential explanatory factors for survival (Appendix A).

Variables were classified and evaluated as continuous, categorical (>2 categories) or binary (two categories) as appropriate.

A Cox proportional hazards model with forward stepwise addition of variables was used for multivariate modeling versus all-cause mortality at 180 days. The statistical strength of each variable's contribution to the prediction of outcome was expressed as the χ^2 statistic with one degree of freedom. Step forward process had entry criteria of $p < 0.10$ and variables meeting the criterion of $p < 0.05$ were retained for further evaluation. Clinical variables identified in this way provided the elements of our reference model. The final model included categorized/binary variables for country (Finland vs. other countries), randomized study treatment (levosimendan vs. dobutamine), use of beta-blocking agents, and previous congestive HF (vs. de novo HF).

All demographic variables and baseline characteristics selected in the final model were compared between Finland and other countries, using two-group T-test for continuous and Fisher's exact test for categorical and binary variables. A p value below <0.05 was considered statistically significant.

3. Results

In Finland, levosimendan treated patients had a lower 180-day all-cause mortality: 8/47 (17%) vs. 19/48 (40%), hazard ratio 0.38 [95% confidence interval 0.17, 0.88], $p = 0.023$, whereas no significant differences between levosimendan and dobutamine in mortality were observed in the whole study population or in the rest of the study population (Fig. 1). The treatment by country interaction in 180-day mortality for Finland vs. other countries was significant ($p = 0.029$). (See Fig. 2.)

The baseline characteristics of patients in Finland and in other countries are presented in Table 1. All the baseline variables collected in the case report forms (Appendix A) were examined for their influence on survival at 180 days. Factors significantly associated with 180-day mortality in the total study population are shown in Table 2. In addition, beta-blocker use and previous congestive heart failure were included in the table as earlier analyses suggest that, in those patients, levosimendan outperforms dobutamine [5], and as the use of beta-blockers has been consistently shown to improve outcome in heart failure [8].

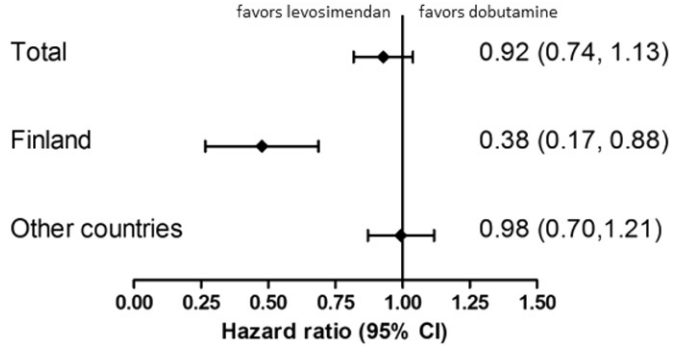

Fig. 1. Hazard ratio for 180-day all-cause mortality (levosimendan:dobutamine) in SURVIVE patients. Treatment by country interaction $p = 0.029$.

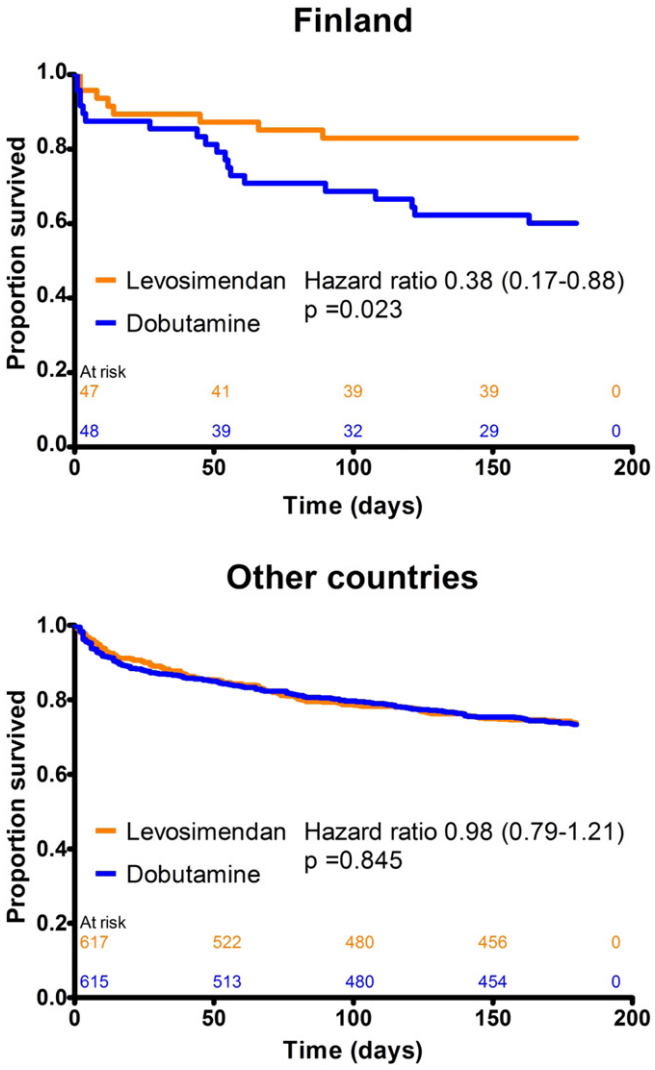

Fig. 2. Kaplan–Meier curves for mortality in Finland and other countries (combined).

Of these factors, beta-blocker use (88% vs 52% in Finland and other countries, respectively), previous congestive heart failure (77% vs 89%), acute myocardial infarction (AMI) during current admission (39% vs. 16%), time from hospital admission until decision of entry to the study (41 h vs. 81 h), use of loop diuretics (99% vs. 94%), ascites (5.3% vs. 20.3%) and peripheral oedema (42% vs. 70%) were significantly different in Finland compared to other countries (Table 2).

There were no statistically significant differences in dosing of levosimendan or dobutamine between Finland and other countries (Table 3). Also, there were no meaningful differences in adverse events of special interest (Table 4).

4. Discussion

The SURVIVE study evaluated whether there is a significant difference in 180-day mortality between levosimendan and dobutamine in patients with AHF and in need of inotropic support. In the whole study population, there was no significant difference in the outcome between

Table 1
Baseline characteristics.

Variable	Finland			Other countries		
	Levo (n = 47)	Dobu (n = 48)	Total (n = 95)	Levo (n = 617)	Dobu (n = 615)	Total (n = 1232)
Age; years mean (SD)	69 (12)	68 (11)	68 (12)	67 (12)	66 (12)	66 (12)
Male gender (%)	19%	25%	22%	26%	31%	28%
BMI; kg/m^2 mean (SD)	27 (5)	28 (5)	28 (5)	28 (6)	28 (5)	28 (5)
Systolic BP; mm Hg mean (SD)	113 (15)	113 (19)	113 (17)	116 (18)	116 (19)	116 (19)
Diastolic BP; mm Hg mean (SD)	63 (14)	63 (11)	63 (12)	71 (11)	71 (11)	71 (11)[a]
Heart rate; bpm mean (SD)	80 (15)	82 (16)	81 (16)	84 (18)	83 (17)	83 (17)
LVEF; % mean (SD)	23 (4)	23 (5)	23 (5)	24 (5)	24 (5)	24 (5)
Etiology of heart disease[a]						
Ischemic; %	68%	60%	64%	76%	77%	77%
Hypertension; %	9%	13%	11%	4%	4%	4%
Other; %	23%	27%	25%	19%	19%	19%
Cardiovascular history, %						
Pre-existing heart failure	72%	81%	77%	89%	89%	89%[a]
History of hypertension	47%	56%	52%	62%	65%	64%[a]
Chronic arrhythmias	60%	69%	64%	57%	54%	56%
Diabetes mellitus	38%	42%	40%	32%	37%[b]	34%
AMI at index hospitalization	47%	31%	39%	14%	17%	16%[a]
Selected concomitant medications; %						
Beta-blocker	94%	83%	88%	51%	53%	52%[a]
ACEi/ARB	77%	60%	68%	72%	73%	73%
Aldosterone-antagonist	11%	40%[b]	25%	55%	58%	56%[a]
Selected laboratory variables; mean (SD)						
B-Hemoglobin; g/dL	12.7 (1.4)	12.5 (1.8)	12.6 (1.6)	13.3 (1.8)	13.4 (1.8)	13.4 (1.8)[a]
P-Creatinine; μmol/L	110 (41)	125 (47)	118 (44)	125 (56)	124 (62)	125 (59)
P-NT-pro-BNP; ng/L	24,286 (27,764)	28,185 (26,840)	26,256 (27,226)	23,116 (21,049)	24,676 (35,256)	23,895 (31,027)
B-WBC; $\times 10^9$/L	9.27 (2.79)	9.30 (3.27)	9.28 (3.02)	8.85 (4.17)	8.52 (3.14)	8.69 (3.69)
P-Glucose; mmol/L	7.6 (2.3)	8.3 (3.9)	7.9 (3.2)	7.7 (3.2)	7.9 (3.4)	7.8 (3.3)
Signs and symptoms of heart failure; %						
Shortness of breath at rest	100%	100%	100%	95%	95%	95%[a]
Oliguria	2%	10%	6%	8%	8%	8%
Time to study drug administration; hours mean (SD)	36 (30)	45 (48)	41 (40)	77 (68)	84 (70)	81 (154)[a]

[a] $p < 0.05$ between Finland and other countries, using T-test for continuous variables and χ^2 test for categorical and binary variables.
[b] $p < 0.05$ between levosimendan and dobutamine within country stratum, using T-test for continuous variables and χ^2 test for categorical and binary variables.

the two treatments [4]. According to our analyses, there were, however, significant country-specific differences in mortality. In Finland alone, the survival significantly favored levosimendan.

We identified predictors of worse outcome in the whole study population. These are in line with earlier findings in other publications. Age, higher baseline heart rate, lower systolic blood pressure and left ventricular ejection fraction and renal impairment are well known predictors of worse outcome in acute heart failure [9–11]. Higher NT-pro-BNP, white blood cell, glucose and alanineaminotransferase levels have also been related to increased mortality [10,12,13]. The use of ACE inhibitors/angiotensin receptor blockers and beta-blockers has shown to improve outcome in these patients [14,15].

Most of the predictors of poor outcome showed similar frequency patients in Finland and other countries. However, beta-blocker use, prevalence of AMI during current admission, ascites and peripheral oedema, time from hospital admission to study drug treatment, and left ventricular ejection fraction were significantly different.

Ascites and peripheral oedema were less prevalent in the Finnish population. However, there were no prespecified criteria for the diagnosis of ascites in the study protocol (e.g. ultrasonography) and it may well be that the differences are not exactly representing real differences between the populations. Therefore, it is difficult to draw conclusions on the effect, if any, of these baseline variations. The difference in left ventricular ejection fraction values between Finland and other countries at baseline should also be interpreted with caution.

Although mean ejection fraction was statistically lower in Finnish patients, the numerical difference was very small and probably had no clinical significance.

Remarkably, the mean time to study drug administration was almost twice as long in other countries compared to Finland. As a matter of fact, by analyzing the data-set of the SURVIVE trial, we found some outlier data collected for patients who received the treatment (either levosimendan or placebo) only 25 days after randomization. In this regard, it has been shown that a shorter delay between the hospitalization and the start of an effective treatment has significantly improved outcome [16]. The importance of early randomization in acute heart failure trials was recently highlighted [17,18].

In the SURVIVE trial, Finnish patients also had significantly more often AMI infarction during the current admission. Levosimendan has been shown to exert beneficial effects in this subgroup in earlier studies. In the RUSSLAN study, levosimendan showed significantly lower mortality compared to placebo in 504 patients with AMI and signs of left ventricular dysfunction [19]. In addition, in several smaller-scale placebo-controlled studies in PCI-treated patients with acute coronary syndrome levosimendan improved myocardial stunning [20], coronary flow and hemodynamics [21], and left ventricular wall motion [22]. Indeed several meta-analyses, now based on a population of over 6000 patients in randomized clinical trials, provide the general understanding of significant benefits for levosimendan in terms of patient mortality [23]. On the contrary, an overall worse prognosis in the mid-term to

Table 2
Baseline factors associated with increased mortality in the SURVIVE study, and difference in them between Finland and other countries.

Explanatory variable	Factors associated with increased mortality in the SURVIVE study			Difference between Finland and other countries; mean (SD) where applicable		
	χ^2 score	p-Value	Hazard ratio	Finland (n = 95)	Other countries (n = 1232)	p-Value
Systolic blood pressure; mm Hg	55.3	<0.0001	0.97	113 (17)	116 (19)	0.1234[b]
NT-pro-BNP; ng/L	39.2	<0.0001	1.00	26,256 (27,226)	23,895 (31,027)	0.4713[b]
White blood cell count; $\times 10^9$/L	32.6	<0.0001	1.05	9.3 (3.0)	8.7 (3.7)	0.0712[b]
Myocardial infarction during current admission; no vs. yes	24.4	<0.0001	0.49	39%	16%	<**0.0001**[c]
Creatinine; μmol/L	24.3	<0.0001	1.00	118 (44)	125 (59)	0.1531[b]
Use of ACE inhibitors or ARBs; yes vs. no	17.5	<0.0001	0.61	68%	73%	0.3419[c]
Heart rate; bpm	12.2	0.0005	1.01	81 (16)	83 (17)	0.1985[b]
Oliguria; no vs. yes	12.1	0.0005	0.57	6%	8%	0.8402[c]
Age; years	9.8	0.0017	1.02	68 (12)	66 (12)	0.1489[b]
Time from hospital admission to randomization; hours	8.4	0.0038	1.00	41 (40)	81 (154)	<**0.0001**[b]
Ascites; no vs. yes	8.1	0.0044	0.67	5%	20%	**0.0001**[c]
Glucose; mmol/L	7.1	0.0079	1.04	7.9 (3.2)	7.8 (3.3)	0.7230[b]
Alanine transaminase; IU/L	6.9	0.0084	1.00	92 (260)	66 (243)	0.3060[b]
Cardiopulmonary arrest; no vs. yes	5.2	0.0221	0.51	1%	2%	>0.999[c]
Peripheral oedema; no vs. yes	5.1	0.0234	0.75	42%	70%	<**0.0001**[c]
Use of loop diuretics; yes vs. no	4.6	0.0319	1.74	99%	94%	**0.0382**[c]
Coronary artery disease; no vs. yes	4.4	0.0355	0.72	72%	77%	0.2056[c]
Use of beta blockers[a]; yes vs. no	2.4	0.1241	0.83	88%	52%	<**0.0001**[c]
Previous congestive heart failure[a]; yes vs. no	0.0	0.9659	1.01	77%	89%	**0.0014**[c]

The bold emphasis is for the significant values ($p < 0.05$). and appears self evident
[a] Fixed terms in Cox proportional hazards stepwise selection model.
[b] T-test.
[c] Fisher's.

long-term has indeed been associated with the use of dobutamine in a meta-analyses by Tacon et al. [24].

In the SURVIVE trial, almost 90% of the Finnish patients were treated with beta-blockers at baseline, whereas only about half of the patients in other countries were receiving beta-blockade. In the LIDO study, the hemodynamic effect of levosimendan on cardiac output and pulmonary capillary wedge pressure was more pronounced in beta-blocked patients, whereas the opposite was seen with dobutamine [3], which is expected as it is a beta-agonist. In the whole SURVIVE study population, levosimendan showed superior survival effect over dobutamine in beta-blocked patients within five days after randomization [5].

The study drugs were dosed similarly, with no difference in total dose or infusion duration, in Finland and other countries. The adverse event profile showed no difference either.

A play of chance for the different outcome in Finland cannot be ruled out since the number of patients in the Finnish cohorts was rather small. However, the most striking differences in baseline characteristics were the frequencies of beta-blocker users and patients with AMI, and levosimendan has been earlier shown to benefit these particular patient populations. The limitations of our study are the relatively small sample size in each participating country, and the retrospective nature of the analyses.

5. Conclusions

There were country-specific differences in the outcome in the SURVIVE trial. In Finland alone, levosimendan showed significantly lower mortality when compared to dobutamine. This may be related to different baseline characteristics. Beta-blocker usage and AMI at admission were more frequent and the time to study drug treatment shorter in Finland; levosimendan may be superior to dobutamine in these patients and conditions.

Author contributions

PP and MK independently performed the preliminary searches for relevant available data. TS performed the statistical analyses. All of the authors contributed substantially to discussions of the results, and reviewed the manuscript before submission.

Declaration of interest

This project did not receive any financial support. PP, TS, and MK are employees of Orion Pharma. V-PH and MSN received honoraria for educational lectures and research grants from Orion Pharma.

Table 3
Dosing of levosimendan and dobutamine in Finland and other countries.[a]

	Finland		Other countries	
	Levosimendan (n = 46)	Dobutamine (n = 48)	Levosimendan (n = 614)	Dobutamine (n = 612)
Duration; hours mean (SD)	23.1 (3.6)	35.0 (23.6)	23.5 (2.8)	39.7 (45.6)
Cumulative dose; mg mean (SD)	22.1 (6.3)	1440.4 (1193.9)	22.6 (5.9)	1128.4 (1879.7)

[a] No statistically significant differences.

Table 4
Adverse events of special interest in Finland and other countries.

Adverse events of special interest; n (%)	Finland			Other countries		
	Levosimendan (n = 46)	Dobutamine (n = 48)	Total (n = 94)	Levosimendan (n = 614)	Dobutamine (n = 612)	Total (n = 1226)
Atrial arrhythmias	9 (20%)	5 (10%)	14 (15%)	66 (11%)	52 (8%)	118 (10%)
Ventricular arrhythmias	8 (17%)	6 (13%)	14 (15%)	95 (15%)	82 (13%)	177 (14%)
Myocardial ischemia	3 (7%)	5 (10%)	8 (9%)	54 (9%)	66 (11%)	120 (10%)
Hypotension	9 (20%)	9 (19%)	18 (19%)	96 (16%)	84 (14%)	180 (15%)
Renal disorders	3 (7%)	4 (8%)	7 (7%)	40 (7%)	36 (6%)	76 (6%)
Heart failure	9 (20%)	10 (21%)	19 (20%)	119 (19%)	145 (24%)	264 (22%)
Increased blood glucose	3 (7%)	3 (6%)	6 (6%)	26 (4%)	18 (3%)	44 (4%)
Decreased plasma potassium	9 (20%)	6 (13%)	15 (16%)	61 (10%)	36 (6%)	97 (8%)

Appendix A. All the baseline variables collected in the case report forms

A.1. Demographics

- Age
- Sex
- Ethnic origin
- Use of tobacco products
- Current drug abuse
- Country (Finland vs. Others)
- Time from hospital admission to randomization

A.2. Vital signs

- Weight
- Height
- Body mass index
- Heart rate
- Systolic blood pressure
- Diastolic blood pressure

A.3. Baseline central laboratory variables

- Hematocrit
- Hemoglobin
- Platelets
- Red blood cell count
- White blood cell count
- ALT Alanine aminotransferase
- AST Aspartate aminotransferase
- Alkaline phosphatase
- Creatinine
- Glucose
- Potassium
- Sodium
- Brain natriuretic peptide (BNP)
- N-terminal pro brain natriuretic peptide (NT-proBNP)

A.4. Data on initial hospitalization

- Locus from where admitted
- Main reason for hospitalization
- Previous congestive heart failure
- Etiology of congestive heart failure
- Ejection fraction
- Myocardial infarction during current admission
- Thrombolytics administered
- Angioplasty
- Cardiopulmonary arrest
- Swan–Ganz catheter
- Mechanical ventilation for heart failure
- Oliguria

A.5. Signs and symptoms of heart failure on admission

- Shortness of breath
- Orthopnea
- Fatigue
- Pulmonary rales
- Radiographic signs of congestion
- Peripheral edema
- Cold extremities
- Peripheral cyanosis
- Diaphoresis
- Ascites
- Mental slowness/confusion

A.6. ECG findings

- Sinus rhythm, paced rhythm or ECG evidence of atrial fibrillation
- Conduction normal, BBB, AV block or other
- Morphology (abnormal Q waves or T waves, inverted T waves or ST segment depressed or elevated)
- Baseline PR, QRS, QT, QTcB and QTcF interval

A.7. Cardiovascular history

- Coronary artery disease
- Hypertension
- Diabetes mellitus
- Cerebrovascular symptoms
- Arrhythmias
- Hemodynamically relevant valve disorders
- Other cardiovascular symptoms

A.8. Selected baseline concomitant medications

- ACE inhibitors or ARBs
- β-Blocking agents
- Loop diuretics
- Nitroglycerine
- Aldosterone antagonists

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