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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].

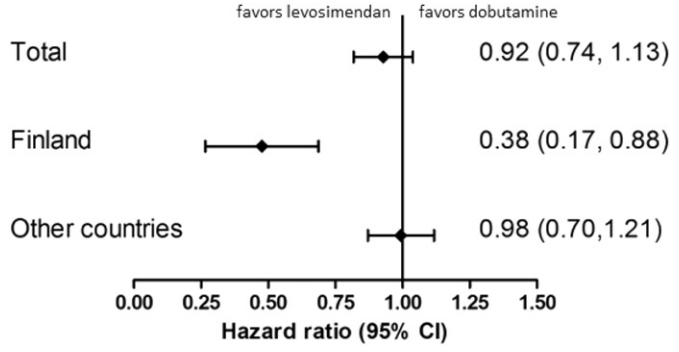

Fig. 1. Hazard ratio for 180-day all-cause mortality (levosimendan:dobutamine) in SURVIVE patients. Treatment by country interaction $p = 0.029$.

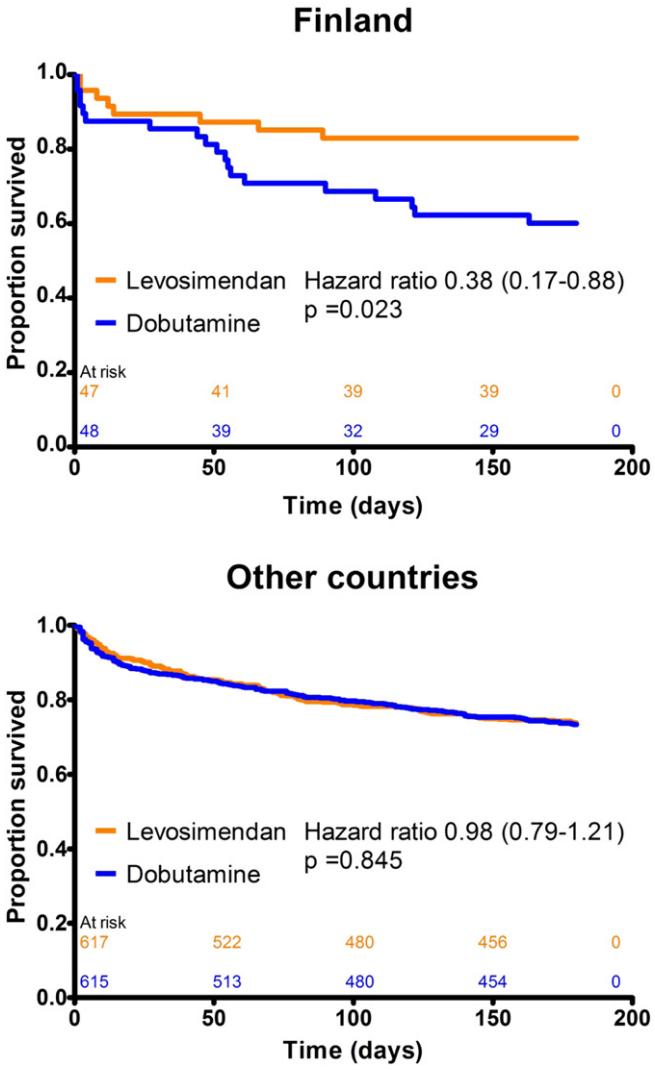

Fig. 2. Kaplan–Meier curves for mortality in Finland and other countries (combined).

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