

## A Comparison of Haemodynamic Effects and Safety between Domestic Levosimendan versus Dobutamine for Hospitalized Patients with Acute Decompensated Heart Failure

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### Abstract

**Aims:** This study was a phase II trial of efficacy and safety of intravenous treatment with domestic levosimendan versus dobutamine in hospitalized patients with acute decompensated heart failure (ADHF).

**Methods and results:** This was a multicentre, positive-controlled, prospective randomized open-label blinded study. A total of 228 ADHF patients from 8 medical centres were received 24 h intravenous domestic levosimendan (n=114) or dobutamine (n=114) therapy. SWAN-GANZ catheter was applied for patients with Pulmonary Capillary Wedge Pressure (PCWP)  $\geq$  15 mmHg and Cardiac Index (CI)  $\leq$  2.5 L/min/m<sup>2</sup> (n=39 each). Compared with baseline level, left ventricular ejection fraction (LVEF) increased at 24 h in both groups (31.56% versus 28.44%, P<0.01). The change rate of LVEF at 24 h was similar between two groups (10.9% versus 12.7%, P>0.05). The change rate of PCWP at 24 h was remarkably greater in levosimendan group than in dobutamine group (-38.7% versus -23.9%, P<0.05). The change rate of NT-proBNP level at 3 days was also more remarkable in levosimendan group than in dobutamine group (-22.4% versus -8.6%, P<0.01). The incidences of adverse reactions and events were similar between two groups.

**Conclusion:** In patients with ADHF, domestic levosimendan improved haemodynamic performance and NT-proBNP effectively than dobutamine. LVEF improvement was similar between domestic levosimendan and dobutamine. Tolerability and safety were similar between domestic levosimendan and dobutamine.

**Keywords:** Levosimendan, Dobutamine; Acute decompensated heart failure; Haemodynamic effect

**Abbreviations:** ADHF: Acute Decompensated Heart Failure; NYHA: New York Heart Association; CI: Cardiac Index; PCWP: Pulmonary Capillary Wedge Pressure; SBP: Systolic Blood Pressure; DLEs: Dose-Limiting Events; BNP: B-type natriuretic peptide; CO: Cardiac Output; PAWP: Pulmonary Average Mean Pressure; SV: Stroke Volume; SVR: Systemic Vascular Resistance; LVESD: Left Ventricular End-Systolic Diameter; LVEDD: Left Ventricular End-Diastolic Diameter; cAMP: Cyclic Adenosine Monophosphate

### Introduction

Levosimendan is a new inotropic agent and calcium sensitizer which has been found to increase myocardial contractility via a sensitization of cardiac troponin C to calcium, to produce vasodilatation and cardioprotection by opening sarcolemmal and mitochondrial ATP-sensitive potassium channels in vascular smooth muscle cells respectively and to inhibit phosphodiesterase type III [1]. Now, levosimendan has been approved to treat Acute Decompensated Heart Failure (ADHF) in guidelines and widely used in clinical practice for the treatment of heart failure in different settings since year 2000. This is a phase II trial of efficacy and safety of intravenous treatment with domestic levosimendan produced by Chengdu Shengnuo Biopharm

CO. Ltd. versus dobutamine in acute decompensated HF patients.

### Methods

#### Study population

228 patients between 18-75 years old with ADHF of ischemic or non-ischemic origin, in New York Heart Association (NYHA) class III-IV, with left ventricular ejection fraction (LVEF)  $\leq$  40%, were enrolled in 8 medical centers in China including Fuwai Hospital. This study complied with the Declaration of Helsinki, the research protocol had approved by locally appointed ethics committee and that informed consents had

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**Received** April 25, 2016; **Accepted** June 18, 2016; **Published** June 23, 2016

**Citation:** Gan T, Zhao X, Huang Y, Zhang Y, Qing E, et al. (2016) A Comparison of Haemodynamic Effects and Safety between Domestic Levosimendan versus Dobutamine for Hospitalized Patients with Acute Decompensated Heart Failure. Cardiovasc Pharm Open Access 5: 186. doi:[10.4172/2329-6607.1000186](https://doi.org/10.4172/2329-6607.1000186)

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been obtained from the subjects (or their guardians) from April 2007 to June 2009. All patients were randomized into levosimendan group (114 patients) and dobutamine group (114 patients), among them 78 patients were tested by Swan-Ganz catheterization with a Cardiac Index (CI)  $\leq 2.5$  L/min/m and pulmonary capillary wedge pressure (PCWP)  $\geq 15$  mmHg and 39 patients with Swan-Ganz catheterization test in each group.

The main exclusion criteria were systolic blood pressure (SBP)  $>180$  mmHg or  $<90$  mmHg, malignant arrhythmia, valvular heart disease, hypertrophic and restrictive cardiomyopathy, acute coronary syndrome during 1 week before baseline, severe liver or renal dysfunction, severe pulmonary disease and participating in other clinical trials during 3 months before baseline. During the trial, 3 patients (1.3%) were eliminated, 1 patient (0.4%) in levosimendan group and 2 patients (0.8%) in dobutamine group. 12 patients (5.3%) were omitted, 5 patients (2.2%) in levosimendan group and 7 patients (3.1%) in dobutamine group. The main causes were patients lost to follow or cannot meet the inclusion criteria.

### Study design

All patients received optimized conventional treatment for HF. Levosimendan group: Levosimendan (Chengdu Shengnuo Biopharm CO. Ltd. 12.5 mg/5 mL. Lot number: 061201) was firstly administered as an initial loading dose of 12  $\mu$ g/kg delivered over 10 min and then followed by a continuous intravenous infusion of 0.1  $\mu$ g/kg/min for 2 hours. The levosimendan infusion rate was increased to 0.2  $\mu$ g/kg/min for further 22 hours if no Dose-Limiting Events (DLEs) occurred. Dobutamine group: Dobutamine (Shanghai No.1 Biochemical & Pharmaceutical Co. Ltd. 20 mg/2 mL, Lot number: 070402) was administered as a continuous infusion without a loading dose, beginning at a rate of 2  $\mu$ g/kg/min for 2 hours, and then increased to 4  $\mu$ g/kg/min for further 22 hours. After the therapy, patients received observation for 5-7 days in hospital. During this period, echocardiography was tested with Simpson's method. Dyspnea and systemic HF symptoms, and NYHA class was assessed. B-type Natriuretic Peptide (BNP) plasma levels were tested. Haemodynamic variables were measured at baseline and at 1, 2, 3, 4, 6, and 24 h in patients received Swan-Ganz catheterization test at baseline. Measurements included PCWP, CI, Cardiac Output (CO), Pulmonary Average Mean Pressure (PAWP), Stroke Volume (SV) and Systemic Vascular Resistance (SVR). Also lab tests and safety assessment were assessed.

### Statistical methods

Full Analysis Sets (FAS) and Per-Protocol Sets (PPS) were all used in efficacy analyses. Paired-t-test was used to compare the data in the group with normal distribution. Wilcoxon signed rank test was used to compare the data in the group with non-normal distribution. Analysis of covariance adjusted center effects and baseline effects was used to compare the data between groups after test of homogeneity of variance. Cochran mantel-haenszel  $\chi^2$  test adjusted center effect was used to compare count data between groups. All statistical analyses were performed using SAS<sup>®</sup> 9.1.3 (SAS Institute, Cary, NC, USA), testing significant resistance levels with bilateral  $\alpha=0.05$ . All authors made the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the data and analyses.

## Results

### Patient baseline characteristics

In patients with or without Swan-Ganz catheterization test, the differences of demographic characteristics including age and gender, and baseline HF characteristics including blood pressure, heart rate (Table 1) and treatment of heart failure medication (including  $\beta$  blockers, angiotensin converting enzyme inhibitors or angiotensin receptor antagonists, aldosterone antagonists, diuretics, vasodilators and inotropic agents) between levosimendan group and dobutamine group were not statistically significant. The etiology of heart failure (including ischemic cardiomyopathy, dilated cardiomyopathy and valvular heart disease after surgery) was also no remarkable difference between the two groups.

### Echocardiography and haemodynamic assessments between two groups after 24 h

**Echocardiographic assessments:** After 24 h of treatment, LVEF was significantly increased and Left Ventricular End-Systolic Diameter (LVESD) was significantly decreased ( $P<0.01$ ) in both groups compared with baselines. SV was significantly increased in levosimendan group ( $P=0.03$ ). Left Ventricular End-Diastolic Diameter (LVEDD) was significantly decreased in dobutamine group. Comparing with levosimendan and dobutamine groups, the change rate of LVESD and SV from baselines showed no statistically significant difference between the two groups ( $P>0.05$ ) (Figure 1).

**Haemodynamic assessments:** After 24 h of treatment, PCWP, CI, CO, PAMP, and SV showed statistically significant differences compared with baselines in both groups (all  $P<0.05$  or  $<0.01$ ). The SVR had statistically significant difference compared with baseline only in levosimendan group ( $P<0.01$ ). Comparing with levosimendan and dobutamine groups, the change rate of PCWP, CI, SVR and CO from baselines showed statistically significant difference between the two groups ( $P=0.04$ ,  $P=0.01$ ,  $P=0.01$ ,  $P=0.01$ ) (Figure 2).

### NT-proBNP assessment between two groups after 72 h

NT-proBNP levels were significantly decreased when compared with baselines in both groups. The change rate of NT-proBNP from baseline in levosimendan group [ $(-22.36 \pm 38.98)\%$ ] was significantly greater than which in dobutamine group [ $(-8.56 \pm 42.42)\%$ ] ( $P<0.01$ ).

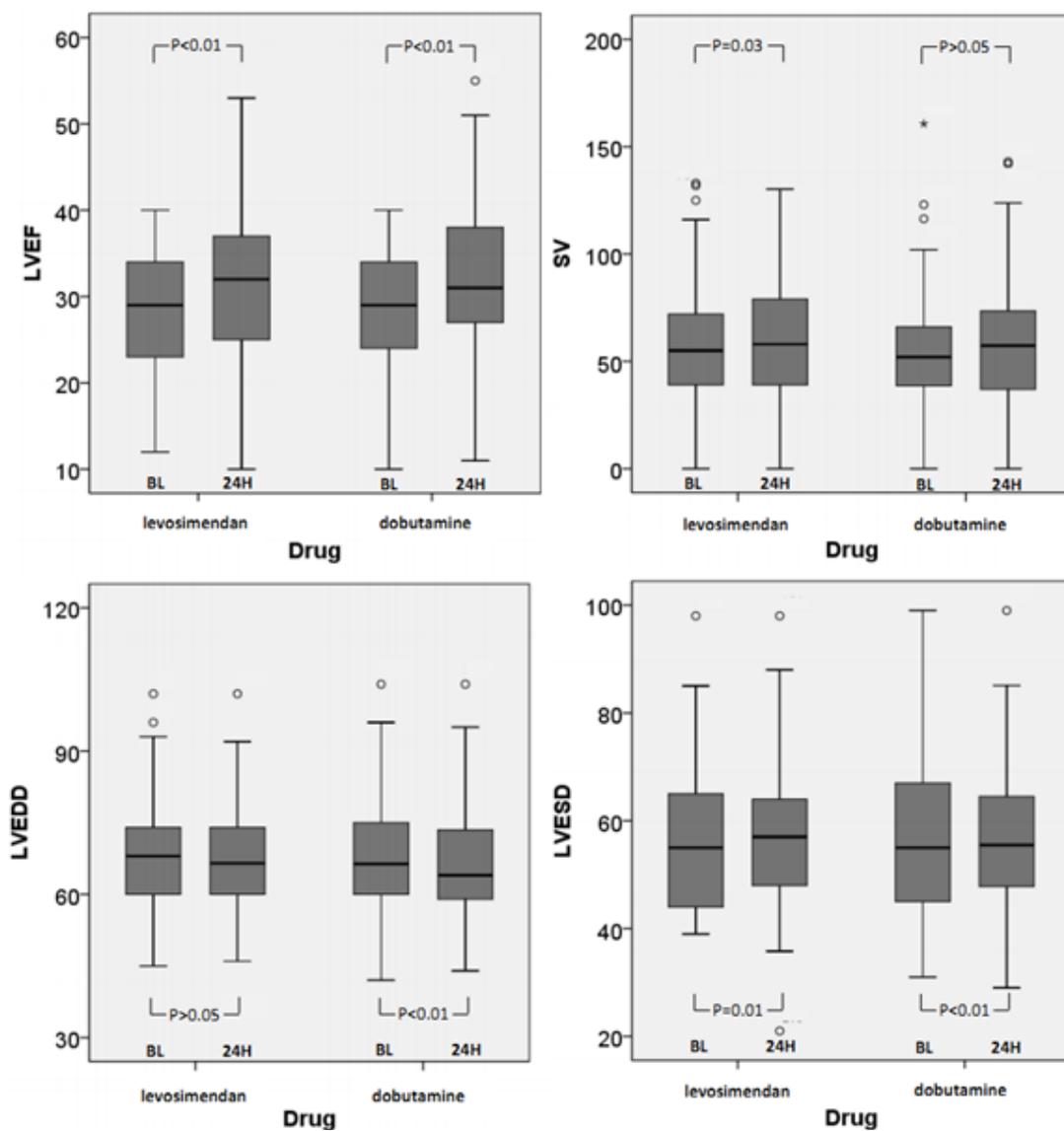
### Clinical conditions assessments after treatment

**Improvement of dyspnea:** After 24 h of administration of levosimendan, the proportions of patients with markedly improved dyspnea symptom, improved dyspnea symptom and no improved dyspnea symptom were separately 15.3%, 28.8% and 55.8%. After 24 h of administration of dobutamine, the proportions of patients with

|                                     | Levosimendan group (n=114) | Dobutamine group (n=114) | P value |
|-------------------------------------|----------------------------|--------------------------|---------|
| Age (years), mean (SD)              | 54.2 (12.5)                | 54.5 (12.9)              | 0.85    |
| Gender male, n (%)                  | 88 (77.2)                  | 86 (75.4)                | 0.76    |
| BMI (kg/m <sup>2</sup> ), mean (SD) | 23.7 (3.5)                 | 23.7 (3.4)               | 0.97    |
| LVEF (%), mean (SD)                 | 28.4 (7.1)                 | 28.6 (7.5)               | 0.84    |
| SBP (mmHg), mean (SD)               | 113.5 (16.7)               | 116.9 (20.0)             | 0.16    |
| DBP (mmHg), mean (SD)               | 72.6 (11.0)                | 74.1 (12.9)              | 0.35    |
| HR (beats per minutes), mean (SD)   | 78.7 (13.7)                | 78.7 (14.4)              | 0.99    |
| Breath (per minutes), mean (SD)     | 18.7 (3.2)                 | 18.9 (3.4)               | 0.54    |

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate

Table 1: Characteristics of the study patients (n=228).



BL: Baselines; 24H: 24 hours

Figure 1: Absolute changes in echocardiographic assessments in levosimendan group and dobutamine group.

markedly improved dyspnea symptom, improved dyspnea symptom and no improved dyspnea symptom were separately 7.21%, 15.3% and 69.3%. There was significant difference between two groups ( $P=0.04$ ).

**NYHA class assessments:** After 24 h and 5-7 days of administration, there was no significant difference on improvement of NYHA class between levosimendan group and dobutamine group (all  $P>0.05$ ).

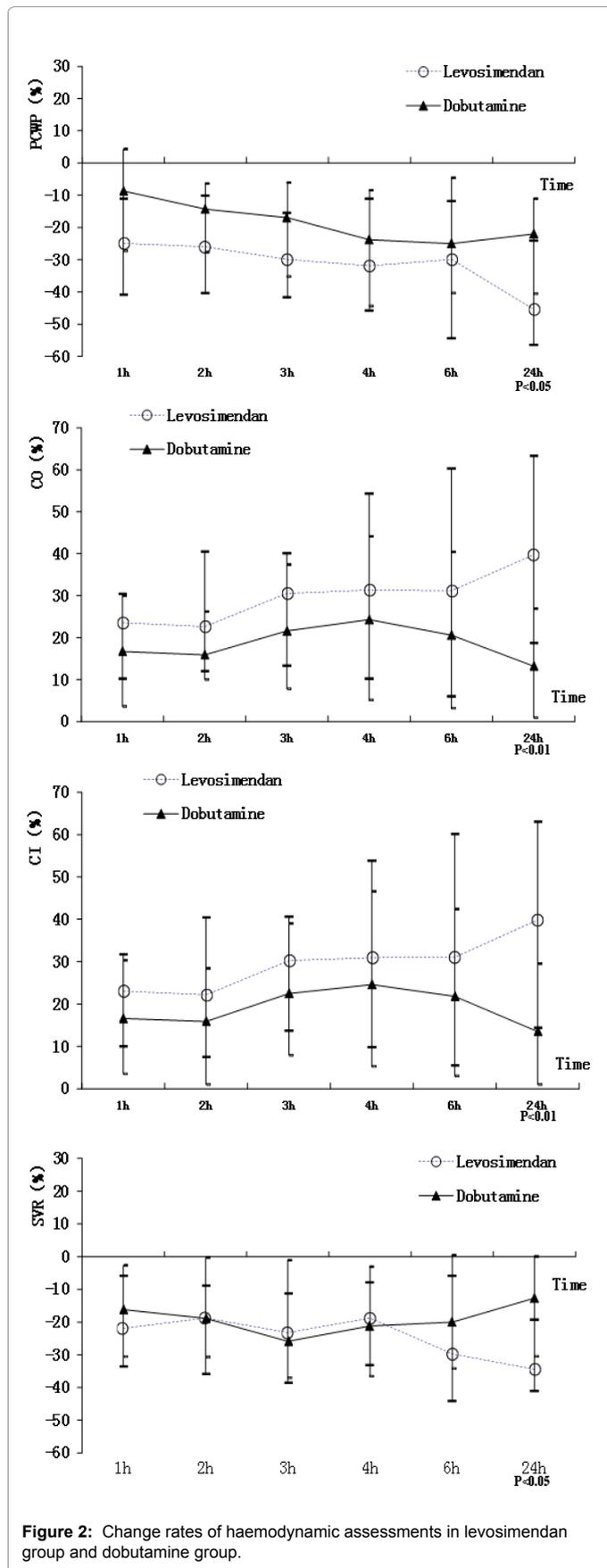
**Other assessments:** After 24 h of administration, the changes of edema, hepatomegaly, jugular vein distention, lung rales and urine volume of 24 h from baselines were no significant difference between two groups (all  $P>0.05$ ).

#### Safety assessments

Changes in vital signs before and after administration: the systolic and diastolic blood pressure in levosimendan group were significantly

lower compared with dobutamine group after 1, 2, 3, 4, 6 and 24 h of administration (all  $P<0.05$  or  $<0.01$ ). The systolic and diastolic blood pressure had no significant difference between two groups on baseline and after 5-7 days of administration. Safety assessments including change of heart rate, arrhythmia, liver and renal function showed no difference before and after administration, and also no difference between two groups (all  $P>0.05$ ).

**Adverse events:** the incidences of adverse events were 28.07% in levosimendan group and 38.60% in dobutamine group. The incidences of side effects were 7.02% in levosimendan group and 8.77% in dobutamine group. The incidences of severe adverse events were 1.75% in levosimendan group and 3.51% in dobutamine group. The incidences of severe side effects were 0.88% in levosimendan group and 1.75% in dobutamine group. There was no significant difference in all these between two groups.



## Discussion

Levosimendan is a novel calcium sensitizer, which has inotropic effect by increasing sensitivity of  $Ca^{2+}$  in the contraction site. Levosimendan could improve myocardial contractility without increasing intracellular cyclic Adenosine Monophosphate (cAMP) or  $Ca^{2+}$  concentration. But levosimendan does not affect heart rate and increase myocardial oxygen consumption. In addition, the inotropic effect of levosimendan is not affected by  $\beta$  blockers, so that levosimendan could be used accompanied by  $\beta$  blockers [2]. The LIDO study showed that levosimendan may improve the hemodynamic of acute heart failure and 180-day survival rate more effectively [3]. García-González et al. founded that levosimendan can improve haemodynamic parameters in critically ill patients with reduce LVEF [4].

This was a multi-center, randomized, blinded, phase II clinical trial comparing efficacy and safety of domestic levosimendan with dobutamine. Levosimendan showed a significantly greater improvement in LVEF and a significantly greater decrease in LVESD compared with dobutamine. The data from patient with Swan-Ganz catheterization showed levosimendan had significantly greater decreases in PCWP and SVR, and significantly greater increases in CO and CI after 24 h treatment of levosimendan compared with dobutamine. In general, levosimendan could do better in improving hemodynamics in ADHF patients, improving cardiac output while reducing pulmonary congestion, and reducing the circulation resistance. Previous study had shown that levosimendan also could improve hemodynamics in patients with chronic heart failure, increase cardiac contractility and dilate blood vessels [5].

After 72 h treatment of levosimendan, NT-proBNP level was significantly reduced. This reduction occurred after 3 days of treatment, which may related to the peak time of bioactive metabolite of levosimendan on the third day. The significant reduction of NT-proBNP level may partially reflect the treatment effect on acute heart failure. The value and rate of change of NT-proBNP level after 3 day treatment of levosimendan from baseline were significantly greater than which in dobutamine group, indicating that levosimendan had better effect on relieving acute heart failure than dobutamine. The SURVIVE study [6] enrolled 1327 cases of acute heart failure patients, and the results showed that levosimendan had significantly greater decrease in BNP level after administration of 24 hours than dobutamine. Research by Parissis [7] showed that levosimendan significantly reduced NT-proBNP level and tumor necrosis factor- $\alpha$  level, but no such changing in dobutamine group before and after treatment.

In the aspect of clinical symptoms, levosimendan group had significantly greater improvement of dyspnea than dobutamine group, which also because of their rapidly reduction of PCWP and increasing of CO. There were also some improvements in NYHA class and rales, however there was no significant difference between levosimendan and dobutamine.

In the safety evaluation, after administration of levosimendan, systolic and diastolic blood pressure of patients were significantly reduced on 1, 2, 3, 4 and 24 hours compared with dobutamine. But the lowest average blood pressure was 106.9 mmHg over 66.21 mmHg, in the safe level of absence of any clinical complaints. The haemodynamic monitoring also showed SVR reduced after treatment of levosimendan, which meant levosimendan could dilate blood vessels while decreasing PCWP and increasing CO, thereby reducing afterload in acute heart failure patients. The pharmacological effect is that levosimendan could

activate the ATP-dependent potassium channel. Safety evaluation including heart rate, liver and renal function have no significant difference before and after treatment. There was no statistically remarkable difference in the incidence of overall adverse events between the two groups. However, dobutamine group has significantly higher incidence of arrhythmias than levosimendan group, which may be linked with increased myocardial oxygen consumption caused by activation of dopamine receptor and increasing of calcium influx. Levosimendan does not increase the incidence of malignant arrhythmia.

In summary, the results of this study revealed that the domestic levosimendan had better effects on reducing PCWP, increasing CO and reducing SVR than dobutamine. Also, levosimendan could lower NT-proBNP level and improve dyspnea with good tolerability and safety.

#### Funding

This study was supported by grants from the Key Projects in the National Science & Technology Pillar Program of the 12th Five-year Plan Period (No.2011BA111B02), project for heart failure, Beijing, China.

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**Citation:** Gan T, Zhao X, Huang Y, Zhang Y, Qing E, et al. (2016) A Comparison of Haemodynamic Effects and Safety between Domestic Levosimendan versus Dobutamine for Hospitalized Patients with Acute Decompensated Heart Failure. *Cardiovasc Pharm Open Access* 5: 186. doi:[10.4172/2329-6607.1000186](https://doi.org/10.4172/2329-6607.1000186)

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