Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial

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Summary

Background Levosimendan, a novel calcium sensitiser, improves myocardial contractility without causing an increase in myocardial oxygen demand. We compared the effects of levosimendan and dobutamine on haemodynamic performance and clinical outcome in patients with low-output heart failure.

Methods Patients were recruited into a multicentre, randomised, double-blind, double-dummy, parallel-group trial. Under continuous haemodynamic monitoring, an initial loading dose of levosimendan of 24 μg/kg was infused over 10 min, followed by a continuous infusion of 0.1 μg kg⁻¹ min⁻¹ for 24 h. Dobutamine was infused for 24 h at an initial dose of 5 μg kg⁻¹ min⁻¹ without a loading dose. The infusion rate was doubled if the response was inadequate at 2 h. The primary endpoint was the proportion of patients with haemodynamic improvement (defined as an increase of 30% or more in cardiac output and a decrease of 25% or more in pulmonary-capillary wedge pressure) at 24 h. Analyses were by intention to treat.

Findings 103 patients were assigned levosimendan and 100 dobutamine. The primary haemodynamic endpoint was achieved in 29 (28%) levosimendan-group patients and 15 (15%) in the dobutamine group (hazard ratio 1.9 [95% CI 1.1–3.3]; p=0.022). At 180 days, 27 (26%) levosimendan-group patients had died, compared with 38 (38%) in the dobutamine group (0.57 [0.34–0.95]; p=0.029).

Interpretation In patients with severe, low-output heart failure, levosimendan improved haemodynamic performance more effectively than dobutamine. This benefit was accompanied by lower mortality in the levosimendan group than in the dobutamine group for up to 180 days.

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Introduction

Heart failure is a common and growing problem associated with frequent admissions to hospital and a poor prognosis. It is the one most frequent reason for hospital admissions in people aged over 65 years,1 and about 5000 hospital admissions per million population per year are attributable to or complicated by heart failure.2 Many of these hospital stays are long; 5% or more of medical beds could be occupied by patients with heart failure, accounting for more than 50 000 hospital bed-days per million population per year.2,3 About 40% of patients die within a year of an acute exacerbation of severe heart failure.4

Management of an exacerbation of heart failure varies according to its cause and presentation. Recognition and treatment of precipitating factors such as rapid atrial fibrillation, myocardial ischaemia, and infection are of key importance. Acute cardiogenic pulmonary oedema is frequently treated with intravenous diuretics and oxygen alone, but opioids and nitrates probably have a valuable role,5 although no substantial studies have been done. When exacerbation of heart failure is accompanied by hypotension, oliguria, or other evidence of a low cardiac output, inotropic agents may be considered. However, there is little evidence that intravenous inotropic therapy with β-agonists or phosphodiesterase inhibitors improves outcome.5,7 A meta-analysis of trials of intravenous inotropic agents suggested a non-significant trend towards increased mortality,6 and studies of oral compounds have consistently shown excess mortality.5,10

Levosimendan is a novel agent with a dual mechanism of action developed for the treatment of decompensated heart failure. This agent sensitises troponin C to calcium in a manner dependent on calcium concentration, thereby increasing the effects of calcium on cardiac myofilaments during systole and improving contraction at low energy cost.11,12 Calcium concentration, and therefore sensitisation, declines or is lost during diastole, allowing normal or improved diastolic relaxation. Unlike agents that act through adrenergic pathways, levosimendan does not cause diastolic calcium overload, which can impair myocardial relaxation, increase energy expenditure, or both.12,16 Effects that could result in the adverse effects of the latter classes of inotropic agents. Levosimendan also leads to vasodilatation through the opening of ATP-sensitive potassium channels.7 By these inotropic and vasodilatory actions, levosimendan increases cardiac output without increasing myocardial oxygen demand.12,13,17–19

Dose-ranging studies, with infusion times from 6 h to 24 h, have already shown that levosimendan improves cardiac haemodynamics and offers symptomatic benefit in patients with severe heart failure.20,21 Although placebo-controlled studies of dobutamine have shown that this drug improves haemodynamic variables, outcome data are few.6,22 We compared the effects of dobutamine and levosimendan on haemodynamics over 24 h and then prospectively followed up clinical outcome over the next 31 days. Furthermore, at the request of the regulatory
1 month of study enrolment, an actual cardiac index of less than 0.35 as shown by two-dimensional echocardiography of the left ventricle. In addition, patients had to have a left-ventricular ejection fraction of less than 0.5 and a left-ventricular ejection fraction of less than 0.35 as shown by two-dimensional echocardiography of the left ventricle. This was due to a cardiac or non-cardiac disorder of recent onset.

Eligible patients were those admitted to hospital with low-output heart failure who were judged to require haemodynamic monitoring and treatment with an intravenous inotropic agent. Patients in one or more of the following clinical categories could be included: deterioration of severe chronic heart failure despite optimum oral therapy with vasodilators and diuretics, including those awaiting cardiac transplantation; severe heart failure after cardiac surgery; or acute heart failure related to a cardiac or non-cardiac disorder of recent onset. In addition, patients had to have a left-ventricular ejection fraction of less than 0.35 as shown by two-dimensional echocardiography or radionuclide ventriculography within 1 month of study enrolment, an actual cardiac index of less than 2.5 L min⁻¹ m⁻², and a mean pulmonary-capillary wedge pressure of more than 15 mm Hg.

Exclusion criteria were: age younger than 21 years; child-bearing potential; heart failure due to restrictive or hypertrophic cardiomyopathy or to uncorrected stenotic valvular disease; chest pain at the time of randomisation; sustained ventricular tachycardia or ventricular fibrillation within the previous 2 weeks; atrioventricular block of second or third degree; heart rate more than 120 beats/min at rest; systolic blood pressure below 85 mm Hg; severe renal failure (serum creatinine >450 μmol/L); hepatic failure; cardiac tamponade; adult respiratory distress syndrome; and septic shock. The protocol prohibited intravenous β-adrenergic agonists within 30 min before baseline haemodynamic measurements, intravenous vasodilators within 2 h, intravenous milrinone or enoximone within 12 h, and intravenous amrinone within 2 days. The timing of other cardiovascular drugs (such as digoxin, diuretics, angiotensin-converting-enzyme inhibitors, and other vasodilators) was standardised to minimise any effect on haemodynamic measurements. These drugs had to be given at least 6 h before baseline measurements, between 4 h and 18 h of the study period, or after the end of the study drug infusion. In general, the dose of these concomitant medications was held constant, unless urgent modifications were required on clinical or haemodynamic grounds. Written informed consent was obtained at the time of initial screening before any haemodynamic assessments.

Protocol
To maintain masking, each patient received two simultaneous infusions, one active and one placebo. The placebo infusion regimen was identical to its respective active counterpart. Patients were enrolled by the study investigators and assigned randomly to the levosimendan group or the dobutamine group in blocks of four according to a computer-generated code created by Orion Pharma for each centre. Treatment allocation and size of the randomisation blocks were concealed from the investigators. The recruiting investigator received a sealed envelope for each patient, containing the details of the treatment to which that patient had been allocated in case of emergency. All but four envelopes were returned unopened after the end of the study.

Treatments with levosimendan was started with a loading dose given as an infusion of 24 μg/kg over 10 min, followed by a continuous infusion of 0.1 μg kg⁻¹ min⁻¹. Treatment with dobutamine was started with a continuous infusion of 5 μg kg⁻¹ min⁻¹ without a loading dose. If an adequate response (defined as an increase in cardiac index of at least 30%) was not achieved after 2 h, the rate of infusion of the study-assigned drug was doubled. The infusions were maintained at a constant rate for 24 h, unless dose-limiting events occurred or the patient had a major cardiovascular event, had a serious adverse reaction, or needed rescue intravenous inotropic or vasodilator therapy. If the following dose-limiting events occurred, the infusion of either study drug was stopped for 30–60 min or until the dose-limiting event had resolved: symptomatic hypotension; systolic blood pressure below 80 mm Hg; and tachycardia (heart rate >140/min at least 10 min or increased by >25 beats/min). The infusion was then restarted at half the rate being received at the time of the dose-limiting event. If a dose-limiting event was noted at the lower infusion rate, the rate of the infusion could be halved twice or infusion discontinued. Infusion of either study drug was discontinued immediately if the patient had a major cardiovascular event or a serious adverse reaction that was thought to be related to the infusion of the study drug, or if he or she needed more than two reductions in the infusion rate because of recurrent dose-limiting events. Under these circumstances, haemodynamic measurements and other study procedures were done as scheduled.

Treatment was discontinued if patients withdrew consent, rescue therapy with intravenous positive inotropic or vasodilator drugs other than the study drug was given, or the investigator believed that withdrawal from the study was in the best interests of the patient.

The study protocol was reviewed and approved by local ethics committees and done according to the principles of the Declaration of Helsinki 1975 and subsequent amendments.

Assessments
A medical history was taken, the patient underwent a physical examination, and blood was taken for measurement of standard laboratory variables. Thereafter, a flow-directed pulmonary-artery thermodilution catheter was inserted, and repeated baseline measurements of cardiac output and pulmonary-capillary wedge pressure were done until the results were stable (values within 10% of each other). Cardiac output, pulmonary-capillary wedge pressure, mean right atrial pressure, pulmonary-artery pressures, systolic and diastolic blood pressure (by cuff or from an arterial cannula), and heart rate (electrocardiogram [ECG]) were measured 10 min, 1 h, 2 h, 2.5 h, 4 h, 8 h, 23.5 h, and 24 h after the start of the infusion and 6 h after the end of infusion (30 h after the start of treatment). Cardiac index, stroke volume, and systemic vascular resistance were derived from the haemodynamic measurements. If pulmonary-capillary wedge pressures could not be obtained, the pulmonary-artery diastolic pressure was used. Patients were also monitored by continuous ECG recording for supraventricular and ventricular arrhythmias.

The prospectively defined primary endpoint was the proportion of patients with haemodynamic improvement at the end of the 24 h infusion period. Haemodynamic improvement was defined as a 30% or greater increase in...
cardiac output and a 25% or greater (at least 4 mm Hg) decrease in pulmonary-capillary wedge pressure at 24 h. Patients who needed and received rescue therapy with intravenous positive inotropic or vasodilator drugs during the double-blind study period were classified as showing no haemodynamic improvement, irrespective of the magnitude of the haemodynamic benefit seen after 24 h. Prospectively defined secondary endpoints were: changes from baseline in haemodynamic variables other than cardiac output and pulmonary-capillary wedge pressure (eg, cardiac index, stroke volume, diastolic pulmonary-artery pressure, mean right atrial pressure, systolic and diastolic blood pressure, heart rate, and total peripheral resistance) at 24 h; changes from baseline to 24 h in symptoms of heart failure (dyspnoea and fatigue) on a four-grade scale (much better, slightly better, no change, worse); proportion of patients needing intravenous rescue therapy with positive inotropic drugs, vasodilators, or diuretics during the infusion of study drug; number of days alive and out of hospital and not receiving intravenous drugs during the first month; and time to development of worsening heart failure or death.

Safety endpoints were spontaneous reports of adverse reactions, laboratory safety tests (blood and urine), and all-cause mortality at 31 days and 180 days after randomisation. The original protocol and its amendments specified an analysis of all-cause mortality at 31 days. The analysis of mortality at 180 days was done after the code had been broken at the request of the Swedish regulatory authority. The endpoint of days alive and out of hospital was also retrospectively followed up for 180 days.

Statistical analysis

On the basis of the definition of haemodynamic improvement, an estimated 164 patients were needed for a three-fold difference in response rates between the treatment groups to be detected with a two-sided 0·05 and 90% power. Given the possibility of dropouts and other protocol violations, the trial was designed to enrol at least 200 patients.

All analyses were done by intention to treat. The primary endpoint was analysed with the Mantel-Haenszel test and control for centre effects. The Mantel-Haenszel risk ratio (and associated 95% CI) was calculated, and homogeneity of the risk ratios across centres was tested.

Changes in haemodynamic and clinical variables from baseline to 24 h were calculated for each patient who had a baseline measurement and a value at 23–5–24 h. These values were then ranked. Patients who had stopped the study drug and therefore had missing haemodynamic or clinical variables at 23–5–24 h because they had received intravenous positive inotropic drugs (other than the study drugs) or were withdrawn owing to lack of efficacy, worsening clinical condition, or death, were assigned worst rank. Patients without paired data (at baseline or at 23–5–24 h) for technical or administrative reasons were also excluded from this analysis. The distribution of the ranks was then compared between the two treatment groups by the Cochran-Mantel-Haenszel test with control for centres via standardised midranks. However, to test for a possible interaction between treatment and the use and non-use of β-blockers at baseline on change in cardiac output and pulmonary-capillary wedge pressure at 24 h, ANCOVA methods were applied to the variable in question, with information from all patients who had complete data at baseline and at 23–5–24 h. Changes in symptoms from baseline to 24 h were analysed by a similar approach.

Table 1: Baseline demographics, clinical characteristics, and concomitant drugs

<table>
<thead>
<tr>
<th>Concomitant drugs‡</th>
<th>Dobutamine (n=100)</th>
<th>Levosimendan (n=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin†</td>
<td>75 (75%)</td>
<td>78 (76%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>90 (90%)</td>
<td>98 (95%)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>88 (88%)</td>
<td>92 (89%)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>39 (39%)</td>
<td>38 (37%)</td>
</tr>
<tr>
<td>Organic nitrates</td>
<td>50 (50%)</td>
<td>33 (32%)</td>
</tr>
<tr>
<td>Antiaggregants</td>
<td>42 (42%)</td>
<td>45 (44%)</td>
</tr>
<tr>
<td>Class III antiarrhythm agents</td>
<td>13 (13%)</td>
<td>16 (16%)</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>4 (4%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

ACE=angiotensin-converting enzyme. Data are number of participants (%) unless otherwise indicated. † Some patients had deterioration of chronic heart failure and were awaiting heart transplant. ‡ Concomitant drugs were not recorded in four patients who did not receive their assigned study drug.
The study was supported by a grant from Orion Pharma, Espoo, Finland. The sponsor was involved in the study design, planning and running of the statistical analyses, and preparation of the trial report. The study was managed and data obtained by Quintiles/Innovex (Biodesign, Freiburg, Germany), Orion Pharma (Espoo, Finland), and Ercopharma (Kvistgaard, Denmark).

### Results

#### Characteristics of study groups

203 patients were enrolled between Jan 2, 1997, and Nov 3, 1998: 103 were assigned treatment with levosimendan and 100 dobutamine (figure 1). Baseline characteristics of the two groups are summarised in table 1. Four patients (one assigned levosimendan, three dobutamine) did not receive an infusion of the study drug (catheter insertion failed or consent was withdrawn during catheter insertion) and did not undergo any haemodynamic measurements. These patients were included in all efficacy and safety analyses in accordance with the intention-to-treat principle and were classified as non-responders for the analysis of the primary endpoint. They were also included in the haemodynamic analyses and assigned worst rank, and for the analyses of death and worsening heart failure they were included as if they had received the study drug.

Five patients in the levosimendan group and six in the dobutamine group had dose-limiting events leading to temporary discontinuation of study medications (figure 1). 16 patients did not receive study drugs for the planned duration of treatment (ten dobutamine, six levosimendan).

#### Median changes in haemodynamic variables from baseline to 24 h

Table 2: Median changes in haemodynamic variables from baseline to 24 h

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mediation change</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output, L/min</td>
<td>0.80</td>
<td>1.09</td>
</tr>
<tr>
<td>Pulmonary-wedge pressure (mm Hg)</td>
<td>–3</td>
<td>–7</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Pulmonary-artery diastolic pressure (mm Hg)</td>
<td>–3</td>
<td>–6</td>
</tr>
<tr>
<td>Systemic vascular resistance (mmHg L^-1 min^-1)</td>
<td>–4.6</td>
<td>–5.8</td>
</tr>
</tbody>
</table>

*Mantel-Haenszel test was used to control via standardised midranks.

#### Interaction test p values based on ANCOVA with effects for treatment, subgroup, treatment subgroup interaction, and baseline value as covariate.

![Figure 2: Effect of concomitant β-blockade on cardiac output and pulmonary-capillary wedge pressure](image)

Interaction test p values based on ANCOVA with effects for treatment, subgroup, treatment subgroup interaction, and baseline value as covariate.

#### Role of the funding source

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![Figure 3: Change in cardiac output and pulmonary-capillary wedge pressure from baseline to 30 h](image)

Error bars indicate standard error of mean.
Haemodynamic effects

A significantly greater proportion of patients in the levosimendan group than in the dobutamine group achieved the primary endpoint; at 24 h, haemodynamic performance had improved in 29 (28%) versus 15 (15%) patients (hazard ratio 1·9 [95% CI 1·1–3·3]; p=0·022).

We did an additional per-protocol analysis on all randomised patients who received their study drug for at least 18 h and had at least two baseline and 24 h haemodynamic measurements (n=94 for levosimendan, n=88 for dobutamine). Patients who received no study drug, those who did not receive the drug for at least 18 h (figure 1), and those for whom baseline measurements were missing (two levosimendan, one dobutamine) were excluded from this analysis (nine levosimendan, 12 dobutamine). One patient who received a 22·6 h infusion of dobutamine was included in the per-protocol analysis but was also classified as a permanent withdrawal; another patient who received a 24 h infusion of dobutamine but withdrew consent at this time was also included in the per-protocol analysis. 29 (31%) of 94 patients in the levosimendan group and 13 (15%) of 88 in the dobutamine group achieved the primary endpoint at 24 h (hazard ratio 2·09 [1·6–3·7]; p=0·021).

Levosimendan treatment had a consistently better effect than dobutamine on the individual haemodynamic variables at the end of the 24 h treatment period (table 2). Both levosimendan and dobutamine increased heart rate by a modest and similar amount (5·7 [SD 12·1] vs 4·0 [9·8] beats/min). Serum creatinine concentration and markers of liver dysfunction declined in the levosimendan group compared with the dobutamine group, possibly reflecting a superior effect on organ perfusion.

Clinical symptoms of dyspnoea and fatigue tended to improve to a greater extent with levosimendan than with dobutamine, but these differences were not significant. Dyspnoea improved in 52 (68%) of 76 and 44 (59%) of 74 patients with baseline symptoms in the levosimendan and dobutamine groups, respectively (p=0·865); fatigue improved in 50 (63%) of 79 and 37 (47%) of 79 (p=0·159).

The use of β-blockers had significant effects on the increase in cardiac output and the decrease in pulmonary-capillary wedge pressure (p=0·01 and p=0·03, respectively; figure 2). β-blockade attenuated the effect of dobutamine on cardiac output and pulmonary-wedge pressure, but did not reduce the effects of levosimendan. On the basis of a post-hoc Breslow-Day analysis for homogeneity of the odds ratios, β-blockade did not significantly affect the primary endpoint (p=0·46). The haemodynamic advantage of levosimendan over dobutamine was apparently accentuated in the presence of β-blockade. However, of the patients who were not receiving a β-blocker, the primary endpoint was reached by 19 of 70 in the levosimendan group and 11 of 71 in the dobutamine group (hazard ratio 1·75 [95% CI 0·91–3·40]; p=0·092). Of patients receiving β-blockers, haemodynamic improvement was seen in ten of 33 in the levosimendan group and three of 29 in the dobutamine group (2·93 [0·97–8·88]; p=0·056).

Termination of the infusion led to rapid (<6 h) loss of the effects of dobutamine, but not those of levosimendan (figure 3).

Morbidity and mortality

The median number of days alive and out of hospital during the first 180 days was 157 (range 101–173) in the levosimendan group and 133 (43–169) in the dobutamine group (p=0·027). Eight (8%) of 103 patients in the levosimendan group died within 31 days compared with 17 (17%) of 100 assigned dobutamine (hazard ratio 0·43 [95% CI 0·18–1·00]; p=0·049). The results of the per-protocol analysis were similar (eight of 102 vs 17 of 97; 0·44 [0·19–1·05]; p=0·063). After 180 days, there had been 27 (26%) deaths in the levosimendan group and 38 (38%) in the dobutamine group (0·57 [0·34–0·95]; p=0·029; figure 4). The findings of the per-protocol analysis were again similar (27 of 102 vs 37 of 97; hazard ratio 0·59 [0·35–0·99]; p=0·046).

Figure 4: Kaplan-Meier estimates (analysis of time to first event) of risk of death during first 180 days after randomisation (based on the intention-to-treat analysis)
Leucocytes (10^9/L) 91 96 0·51 (1·83) –0·14 (2·34) 0·11

Clinical chemistry

Table 4: Changes in haemological and biochemical variables

<table>
<thead>
<tr>
<th></th>
<th>Number with data</th>
<th>Change in variable</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dobutamine</td>
<td>Levosimendan</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>91</td>
<td>96</td>
<td>0·5</td>
</tr>
<tr>
<td></td>
<td>–0·4 (0·9)</td>
<td>–0·8 (1·1)</td>
<td>0·005</td>
</tr>
<tr>
<td>Erythrocytes (10^12/L)</td>
<td>80</td>
<td>87</td>
<td>0·13</td>
</tr>
<tr>
<td></td>
<td>–0·13 (0·33)</td>
<td>–0·27 (0·42)</td>
<td>0·05</td>
</tr>
<tr>
<td>Leucocytes (10^9/L)</td>
<td>91</td>
<td>96</td>
<td>0·51</td>
</tr>
<tr>
<td></td>
<td>0·14 (2·34)</td>
<td>0·11 (1·83)</td>
<td>0·11</td>
</tr>
<tr>
<td>Platelets (10^9/L)</td>
<td>91</td>
<td>96</td>
<td>0·46</td>
</tr>
<tr>
<td></td>
<td>21·8 (34·3)</td>
<td>26·5 (29·3)</td>
<td>0·46</td>
</tr>
</tbody>
</table>

Serum alkaline phosphatase (U/L) 77 84 –3 (-14 to 7) –6 (–13 to 0) 0·22

Serum aspartate aminotransferase (U/L) 86 92 –2 (-6 to 1) –2·5 (-8 to -1) 0·03

Serum glutamyltranspeptidase (U/L) 78 84 –3 (-15 to 1) –6 (–13 to 0) 0·22

Values are mean (SD) and p values are calculated by ANCOVA. | Values are median (IQR) and p values are calculated by Mann-Whitney sum of ranks test.

Intravenous drugs for heart failure

18 (18%) dobutamine-group patients and 22 (21%) in the levosimendan group received other intravenous drugs for heart failure, mainly diuretic therapy, during the study (p=0·6).

Safety

Overall, 48 (47%) levosimendan-group patients and 42 (42%) in the dobutamine group had an adverse event. 13 serious adverse events occurred in five patients in the dobutamine group and two serious adverse events arose in one patient in the levosimendan group. Three patients in the dobutamine group died during the 24 h of infusion, but there were no deaths in the levosimendan group. Treatment was withdrawn because of adverse events in six levosimendan-group patients and ten in the dobutamine group. The most frequent adverse events are shown in table 3. Angina pectoris, chest pain, or myocardial ischaemia were reported in more dobutamine-group than levosimendan-group patients, and there was a higher proportion of patients with rate and rhythm disorders in the dobutamine group. There was a trend towards a higher frequency of headache or migraine in the levosimendan group. Decreases in packed-cell volume, serum creatinine, and mean serum potassium over 24 h were reported in the levosimendan group (table 4). The former could reflect haemodilution resulting from vasodilatation.
could have had a direct long-lasting protective effect on the myocardium. By contrast to catecholamines, levosimendan in therapeutic doses does not increase intracellular concentrations of cyclic AMP and calcium ions.22,23 Levosimendan also had an antistunning effect in experimental models,24,25 and it does not increase myocardial oxygen requirements in patients.26 Improvement of myocardial perfusion as a result of vasodilatation could also have contributed. Furthermore, levosimendan has no proarrhythmic effects.27 The long-term benefit could also be due to the presence of a pharmaco logically active metabolite with a long elimination half-life, leading to persisting haemodynamic effects for hours or days after the infusion.28 There are several limitations to our study in addition to the absence of a placebo control and its size. The study provided no information on the duration of infusion of levosimendan needed for optimum benefit or on how often it may be repeated in patients who do not respond initially or who relapse after an initial response. Also, patients with cardiogenic shock were excluded. Whether levosimendan is beneficial or harmful in such patients is not known, but care should be taken in view of the risk of hypotension through the vasodilatory action. A larger-scale clinical trial will be needed to confirm the longer-term clinical advantages of levosimendan.

Our results are encouraging and suggest that levosimendan could be, for several reasons, a better choice than dobutamine as inotropic therapy for patients with decompensated heart failure.

Contributors
F Follath, J G Y Papp, H Just, and H Schultz were responsible for the design, preparation, and conduct of the study; L A Lehtonen was involved in the study design, and M Abdalla was responsible for the statistical analyses. F Follath, J G Cleland, and E-P Sandell prepared the draft report and all the investigators contributed to its revision. K Peukurainen, V P Harjola, and V Mitrovic were lead investigators. The sponsors reviewed the report for the accuracy of data.

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Conflict of interest statement
E-P Sandell is employed by Orion Pharma. L Lehtonen has been employed by Orion Pharma.

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References

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