JACC: Heart Failure
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 1, No. 2, 2013
ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2012.12.004

CLINICAL RESEARCH

Effect of Levosimendan on the Short-Term Clinical Course of Patients With Acutely Decompensated Heart Failure

Milton Packer, MD,* Wilson Colucci, MD,† Lloyd Fisher, PhD,‡ Barry M. Massie, MD,§ John R. Teerlink, MD,§ James Young, MD,‖ Robert J. Padley, MD,¶ Roopal Thakkar, MD,¶ Leticia Delgado-Herrera, RPh,¶ Jeffrey Salon, MD,¶ Chris Garratt, MB, ChB,# Bidan Huang, PhD,¶ Toni Sarapohja, MSc,# for the REVIVE Heart Failure Study Group

Dallas, Texas; Boston, Massachusetts; Seattle, Washington; San Francisco, California; Cleveland, Ohio; Abbott Park, Illinois; and Espoo, Finland

Background This study evaluated the efficacy and safety of levosimendan, a positive inotropic drug with vasodilator effects, given intravenously to patients with acutely decompensated heart failure (ADHF).

Methods We performed 2 sequential trials, the first to develop a new measure of efficacy in 100 patients, and the second to use this measure to evaluate levosimendan in an additional 600 patients. Patients admitted with ADHF received placebo or intravenous levosimendan for 24 h in addition to standard treatment. The primary endpoint was a composite that evaluated changes in clinical status during the first 5 days after randomization.

Results In the 600-patient trial, more levosimendan than placebo patients (58 vs. 44) were improved at all 3 pre-specified time points (6 h, 24 h, and 5 days), whereas fewer levosimendan patients (58 vs. 82) experienced clinical worsening ($p = 0.015$ for the difference between the groups). These differences were apparent, despite more frequent intensification of adjunctive therapy in the placebo group (79 vs. 45 patients). Improvements in patient self-assessment and declines in B-type natriuretic peptide levels with levosimendan persisted for 5 days and were associated with reduced length of stay ($p = 0.009$). Similar findings were present in the 100-patient pilot trial. Levosimendan was associated with more frequent hypotension and cardiac arrhythmias during the infusion period and a numerically higher risk of death across the 2 trials (49 of 350 on a regimen of levosimendan vs. 40 of 350 on a regimen of placebo at 90 days, $p = 0.29$).

Conclusions In patients with ADHF, intravenous levosimendan provided rapid and durable symptomatic relief. As dosed in this trial, levosimendan was associated with an increased risk of adverse cardiovascular events. (Evaluation of Intravenous Levosimendan Efficacy in the Short Term Treatment of Decompensated Chronic Heart Failure; NCT00048425) (J Am Coll Cardiol HF 2013;1:103–11) © 2013 by the American College of Cardiology Foundation

More than 1 million people are hospitalized in the United States for the treatment of acutely decompensated heart failure (ADHF) each year (1), but the optimal management of these patients has not been defined. Patients generally receive immediate intravenous treatment with 1 or more drugs, including diuretics, peripheral vasodilators, and/or positive inotropes, which can produce rapid improvement in hemodynamic variables (2,3). However, it is not clear that these hemodynamic effects translate into clinical benefits (3,4). Many drugs that increase cardiac output and decrease cardiac filling pressures have not been shown to produce symptomatic benefits or improved outcomes (4–6).

See page 112

This apparent dissociation between the hemodynamic and symptomatic effects of intravenous drugs might partly reflect the difficulties inherent in designing, performing, and analyzing clinical trials in these acutely ill patients (7,8). Symptoms in ADHF are difficult to quantify and cannot be

From the *Department of Clinical Sciences, University of Texas Medical Center at Dallas, Dallas, Texas; †Department of Medicine, Boston University School of Medicine, Boston, Massachusetts; ‡Department of Biostatistics, University of Washington, Seattle, Washington; §Department of Medicine, University of California at San Francisco and VA Medical Center, San Francisco, California; ‖Department of Medicine, Cleveland Clinic, Cleveland, Ohio; ¶Abbott Laboratories, Abbott Park, Illinois; and the #Orion Corporation, Orion Pharma, Espoo, Finland. Abbott and Orion Pharma funded the REVIVE program. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 5, 2012; revised manuscript received December 21, 2012, accepted December 28, 2012.

JACC: Heart Failure Vol. 1, No. 2, 2013
April 2013:103–11

Abbreviations and Acronyms

ADHF = acutely decompensated heart failure

BNP = B-type natriuretic peptide

NYHA = New York Heart Association

readily assessed in a standardized fashion. Clinical trials have used a variety of instruments to assess dyspnea, with disappointing or conflicting results (4,6,9). To complicate matters further, nearly 80% of patients with ADHF improve after intensified standard treatment (6–8). Such intensification of background therapy (especially if applied differently across treatment groups) can make it difficult to discern the benefits of any new treatment. Finally, any acute improvement might not be sustained, and the clinical status of many patients might destabilize in the days and weeks after initial symptom relief (3,9,10). However, most trials have focused primarily on the response to drug interventions at a fixed point in time and have not determined the influence of the drug on the clinical course of patients (5,6,11).

To address these deficiencies, we carried out 2 sequential trials (REVIVE [Randomized EValuation of Intravenous LeVosimendan Efficacy] I and II), which first sought to develop a new measure of efficacy in patients with ADHF and then used this measure to evaluate the efficacy and safety of intravenous levosimendan. Levosimendan possesses positive inotropic and vasodilator properties (12), and in controlled trials in patients with ADHF, it has been reported to produce favorable effects on cardiac performance, symptoms, hospital stays, and survival (13–16). The hemodynamic effects of levosimendan persist for many days after a 24-h infusion, due to a long-lived active metabolite (17).

Methods

The REVIVE I and II trials were carried out in 103 centers in the United States, Australia, and Israel between December 2001 and December 2004 under the direction of an independent Steering Committee, which was responsible for the scientific aspects of the studies. An independent Data Monitoring Committee, comprising 4 cardiologists and a statistician, periodically reviewed (in an unblinded manner) the interim results and was empowered to recommend early termination of the program if a safety concern emerged during the studies. The studies were approved by the local ethics committees of each institution and were conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent before participation in the studies.

Study patients. The REVIVE I and II trials enrolled patients who were hospitalized for the treatment of ADHF and remained dyspneic at rest despite treatment with intravenous diuretics. At randomization, patients might have also received intravenous vasodilators and/or positive inotropic drugs (except amrinone and milrinone), but the infusion rates of these drugs must have remained constant for at least 2 h before entry into the study. All patients had left ventricular dysfunction, evidenced by a left ventricular ejection fraction $\leq$35% within the prior 12 months.

Patients were excluded if intubated or otherwise unable to communicate; had a systolic blood pressure $\leq$90 mm Hg or a heart rate $\geq$120 beats/min; had experienced angina within 6 h or cardioversion within 4 h (or were expected to undergo cardioversion within 5 days); had significant uncorrected valvular obstruction, undergone a cardiac resynchronization procedure within 30 days, or had a stroke or transient ischemic attack or were expected to undergo cardiac revascularization or surgical procedures within 3 months; or had severe hepatic impairment (liver enzymes $>5\times$ the upper limit of normal), severe renal insufficiency (serum creatinine $>$5 mg/dl), severe obstructive pulmonary disease (carbon dioxide retention or ongoing use of steroids), acute bleeding or severe anemia (hemoglobin $<$10 g/l), active infection, serum potassium concentration $<$3.5 or $>$5.4 mmol/l, or a history of torsade de pointes.

Study plan. After initial evaluation, patients were randomly assigned (double-blind) to treatment with placebo or levosimendan, which was added to their existing management for ADHF. Randomization was stratified by the baseline use of positive inotropic and/or vasodilator agents. Treatment with the study medication (levosimendan or placebo) was initiated with an intravenous bolus of 12 μg/kg over 10 min (6 μg/kg if the patient was receiving concurrent intravenous vasodilator or positive inotropic agent) followed by a continuous intravenous infusion of 0.1 μg/kg/min. If tolerated, the infusion was increased after 50 min to 0.2 μg/kg/min and was maintained for 23 additional hours. If not tolerated, the infusion rate could be reduced to 0.05 to 0.1 μg/kg/min or treatment with the study drug could be discontinued. Patients were not aware of changes in hemodynamic variables (including blood pressure or heart rate), on the basis of concerns that knowledge of these might influence the assessment of their symptoms or clinical status.

After randomization, physicians could use any clinically indicated interventions, including initiation of new treatments or adjustment of concomitant medications. However, physicians carefully recorded the reasons for any use of medications or interventions and documented whether such use represented: 1) continuation of an existing strategy to maintain clinical improvement (referred to as "maintenance therapy"); or 2) intensification of treatment in a patient who was deteriorating clinically or failing to improve by 24 h on a regimen of conventional therapy (referred to as "rescue therapy"). Milrinone or amrinone were not permitted within 24 h of randomization.

At 6 and 24 h and after 2, 3, and 5 days after randomization, patients were asked to evaluate changes in overall clinical status (the patient global assessment) and in dyspnea. These changes were characterized as markedly, moderately, or mildly improved; unchanged; or mildly, moderately, or markedly worse. To do so, patients made a self-directed mark on the case report form, without assistance or prompting from study staff. In parallel, physicians independently rated the changes in the overall clinical status of patients. In addition, circulating levels of B-type natriuretic peptide (BNP) were

measured at randomization and after 24 h, 5 days, and 31 days; the New York Heart Association (NYHA) functional status was assessed at 5, 14, 31, 60, and 90 days; and the occurrence of hospital stay and death was evaluated continuously for the first 90 days after randomization.

Study endpoints. The primary endpoint of the study was a composite of clinically relevant measures that was modeled after a similar approach that has been used in the evaluation of drugs for chronic heart failure (18). In contrast to earlier studies that focused on a single measure at a single point in time (11), the composite approach uses a combination of measures to characterize the clinical course of patients over several days. The plan was to evaluate an untested set of criteria as the primary endpoint in the first 100 patients (REVIVE I), evaluate and modify the endpoint on the basis of this initial experience, and then prospectively test the refined endpoint in a definitive trial in an additional 600 patients (REVIVE II).

For the primary endpoint in both trials, the clinical course of each patient during the first 5 days was characterized as "improved," "unchanged," or "worse." In the definitive REVIVE II trial, patients were classified as "improved" if they considered themselves moderately or markedly improved at all pre-specified time points (6 h, 24 h, and 5 days) and showed no evidence of clinical deterioration during this period. Patients were classified as "worse" if (during the 5 days) they died; experienced persistent or unresponsive symptoms of heart failure after the first 24 h of randomized therapy or worsening heart failure at any time during the first 5 days, which required a rescue intervention specifically to relieve such symptoms; or considered themselves to have moderately or markedly worsened on global assessment at 6 h, 24 h, or 5 days. The period of 5 days was selected because it corresponds to the average duration of hospital stay for a patient with ADHF in the United States and to the time of persistence of the active metabolite of levosimendan (17). The working definition of the clinical composite in the REVIVE I trial was very similar, except that changes in the patient global assessment were not assessed at 6 h; patients with worsening global assessment were not classified as worse; and the use of intravenous diuretics during the first 72 h was not classified as rescue therapy.

The secondary endpoints in both the REVIVE I and REVIVE II trials included: 1) changes in plasma BNP at 24 h; 2) changes in the patient global assessment at 6 h; 3) changes in patient perception of dyspnea at 6 h; 4) number of days alive and out of hospital during the first 14 days after randomization; 5) time to death or worsening heart failure during 31 days; 6) NYHA functional classification at day 5; and 7) all-cause mortality during the first 90 days. Both trials also pre-specified an analysis of the duration of initial hospital stay for ADHF (19).

Statistical analyses. The sample size for the REVIVE II trial was estimated on the basis of the following assumptions: the proportion of patients considered improved during the first 5 days would be 50% greater in the levosimendan group than in the placebo group; the proportion of patients considered worse during the first 5 days would be 33% lower in the levosimendan group than in the placebo group; the expected rates of improvement and deterioration in the placebo group would both be 25%; and the study would have >90% power to detect a treatment difference ($\alpha = 0.05$).

All efficacy analyses included all randomized patients according to the intention-to-treat principle. For the analysis of the primary endpoint, the distribution of patient outcomes was compared across the groups with the Cochran-Mantel-Haenszel test controlling for variables used for stratification at the time of randomization. A similar approach was used for the analysis of the secondary endpoints. The risk of death for the first 90 days was compared with the Cox proportional hazards model with treatment as a covariate and stratified by randomization strata. Changes in BNP were analyzed with the Kruskal-Wallis test. In addition, a generalized linear model for repeated measures of the patient global assessment and dyspnea at 6, 24, 48, 72, and 120 h was performed with effects of treatment, time, and treatment × time interaction. All statistical analyses were performed in SAS (version 8.2, SAS Institute, Inc., Cary, North Carolina).

Results

The REVIVE I trial enrolled 100 patients, of whom 49 were assigned to placebo and 51 were assigned to levosimendan. The REVIVE II trial enrolled 600 patients, of whom 301 were assigned to placebo and 299 were assigned to levosimendan (Fig. 1). Enrollment took place between December 2001 and September 2004.

In both trials, the treatment groups were similar with respect to all pre-treatment characteristics, which were also similar across the 2 studies (Table 1). Most patients had fluid retention, as evidenced by the high proportion of patients with pulmonary rales and peripheral edema, and most were receiving treatment for chronic heart failure (e.g., digoxin, angiotensin-converting enzyme inhibitors, and beta-blockers). Before enrollment, all had received intravenous diuretics, and approximately one-fourth were receiving intravenous infusions of peripheral vasodilators or positive inotropic agents.

In both trials, >90% of the patients in the levosimendan group received the target infusion rate of 0.2 μg/kg/min at 2 h, and 70% to 85% of the group continued to receive this dose at 24 h. Approximately 12% of the levosimendan group and 7% of the placebo group discontinued the study medication before 24 h in the REVIVE II trial; 1 patient in each group discontinued the drug before 24 h in the REVIVE I trial (Fig. 1).

Primary endpoint. In the REVIVE I trial, 24 patients in the levosimendan group but only 15 patients in the placebo group were improved at both 24 h and at 5 days, whereas 13 patients in the placebo group and 10 patients in the levosimendan group were worse ($p = 0.134$ for the overall

JACC: Heart Failure Vol. 1, No. 2, 2013
April 2013:103–11

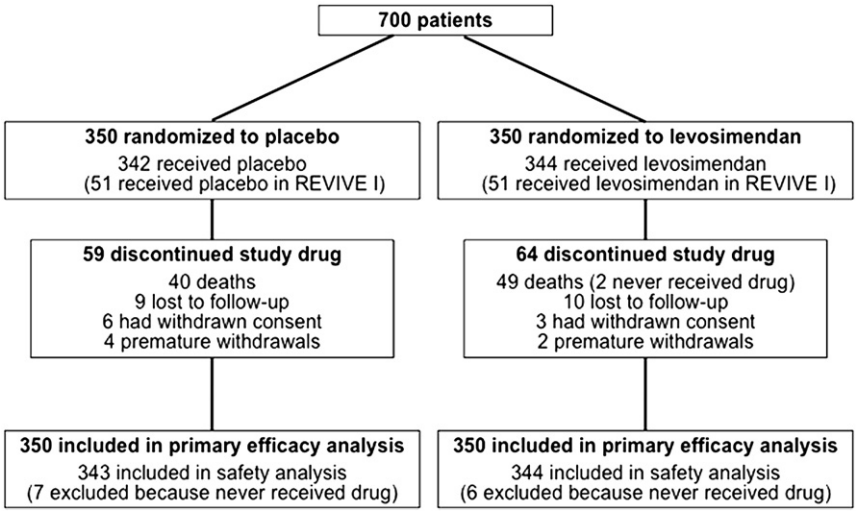

Figure 1 Participant Flow Through the REVIVE Clinical Trials

REVIVE = Randomized EValuation of Intravenous LeVosimendan Efficacy.

difference between the groups). When the criteria were made more stringent by additionally requiring moderate or marked improvement at 6 h to be classified as improved and to allow a patient to be classified as worse if they received intravenous diuretics for worsening within the first 72 h, 17 patients in the levosimendan group but only 7 patients in the placebo group were improved, whereas 18 patients in the placebo group and 12 patients in the levosimendan group were worse ($p = 0.029$ for the overall difference between groups).

Table 1 Baseline Characteristics in the REVIVE I and REVIVE II Trials

	REVIVE I		REVIVE II	
	Levosimendan (n = 51)	Placebo (n = 49)	Levosimendan (n = 299)	Placebo (n = 301)
Age (yrs)	59 ± 15	58 ± 15	64 ± 15	63 ± 15
Men	80%	73%	73%	72%
Caucasian	57%	63%	61%	68%
African American	29%	29%	28%	20%
Prior myocardial infarction	49%	47%	55%	52%
LV ejection fraction	0.20 ± 0.06	0.20 ± 0.07	0.23 ± 0.07	0.24 ± 0.07
Pulmonary rales				
Basal only	53%	47%	47%	47%
>1/3 lung fields	14%	12%	23%	23%
>2/3 lung fields	6%	2%	6%	5%
Peripheral edema				
Legs only	59%	61%	57%	59%
Sacral and/or lumbar	2%	8%	11%	8%
Systolic BP (mm Hg)	115 ± 17	115 ± 19	115 ± 17	116 ± 20
Diastolic BP (mm Hg)	69 ± 12	69 ± 14	68 ± 12	69 ± 14
Heart rate (beats/min)	84 ± 15	83 ± 15	82 ± 15	81 ± 15
Digoxin	55%	61%	53%	51%
ACE inhibitor/ARB	67%	80%	78%	76%
Beta-blocker	41%	47%	68%	69%
Spironolactone	35%	35%	37%	37%
IV vasodilator	8%	6%	13%	13%
IV inotropic drug	20%	20%	11%	10%
Both IV vasodilator and inotrope	2%	2%	2%	2%

Values are mean ± SEM or %.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; LV = left ventricular; REVIVE = Randomized EValuation of Intravenous LeVosimendan Efficacy trials.

In the REVIVE II trial, which prospectively used the more stringent criteria for the primary endpoint, 58 patients in the levosimendan but only 44 patients in the placebo group were improved at 6 and 24 h and at 5 days. By contrast, 82 patients in the placebo but only 58 patients in the levosimendan group were worse ($p = 0.015$ for the overall difference between groups). Of note, if the clinical course of patients in the REVIVE II trial were classified with the original definition for the REVIVE I trial, 135 patients in the levosimendan but only 87 patients in the placebo group were improved at 24 h and at 5 days, whereas 64 patients in the placebo but only 41 patients in the levosimendan group experienced clinical worsening ($p < 0.001$ for the difference between groups).

The clinical features and management of worsening in the patients who deteriorated are summarized in Table 2. Overall in the REVIVE II trial, 26% (n = 79) of patients in the placebo but only 15% (n = 45) of patients in the levosimendan group required intravenous rescue therapy for worsening heart failure. Most experienced worsening dyspnea (13% placebo, 7% levosimendan); increased pulmonary edema (6% placebo, and 3% levosimendan); and persistent or unresponsive symptoms (11% placebo and 6% levosimendan). These treatment intensifications included intravenous furosemide (placebo 47, levosimendan 23); nesiritide (placebo 24, levosimendan 17); dobutamine (placebo 19, levosimendan 12); and milrinone (placebo 18, levosimendan 12).

Secondary endpoints and analyses. In the REVIVE II trial, both at 24 h and at 5 days, plasma levels of BNP declined substantially in the levosimendan group compared with the placebo group (both $p < 0.001$); this effect was no longer apparent after 31 days of follow-up (Fig. 2). A similar pattern of effects was seen in the REVIVE I trial.

In the REVIVE II trial, with respect to the patient global assessment at 6 h, a greater proportion of patients reported moderate and marked improvement in the levosimendan group as compared with placebo ($p = 0.081$). This shift in favor of levosimendan persisted after 24 h ($p = 0.027$), 48 h ($p = 0.053$), 3 days ($p = 0.133$), and 5 days ($p = 0.002$), even though patients in the levosimendan group were no longer receiving the study medication, and there was greater intensification of background treatment in the placebo group than in the levosimendan group. An analysis over the entire 5 days indicated a significant difference in favor of levosimendan ($p < 0.002$). A similar pattern was seen with respect to the patient dyspnea assessment, which showed greater improvement in the levosimendan group at 6 h ($p = 0.078$), 24 h ($p = 0.018$), 48 h ($p = 0.102$), 3 days ($p = 0.035$), and 5 days ($p = 0.102$). An analysis over the entire 5 days indicated a significant difference in favor of levosimendan ($p = 0.018$). Similar effects were seen in the REVIVE I trial.

In both the REVIVE I and REVIVE II trials, there were no differences between the groups in the number of days alive and out of the hospital over 14 days (levosimendan 7.3 vs. placebo 8.9 days, $p = 0.258$). However, in both trials, patients in the levosimendan group were discharged from the hospital earlier than those in the placebo group. Brief hospital stays (5 days) were more common in the levosimendan group than in the placebo group (46% vs. 37%), whereas long hospital stays (>10 days) were more common in the placebo group than in the levosimendan group (23% vs. 16%, $p = 0.009$). The NYHA functional class at 5 days was not significantly different between treatment groups ($p = 0.196$). Similar trends were seen in the REVIVE I trial.

Safety. In both the REVIVE I and REVIVE II trials, both systolic and diastolic blood pressure decreased significantly during the 24-h infusion of levosimendan (in the REVIVE II trial by 4 mm Hg and by 6 mm Hg, respectively, when compared with placebo); the hypotensive effects of the drug dissipated within 12 h after withdrawal of the drug at the end of the 24-h infusion. By contrast, heart rate increased during the 24-h infusion of levosimendan (in the REVIVE II trial, by 2 to 8 beats/min), and this effect was still statistically significant at the end of 5 days.

Adverse events reported in both the REVIVE I and REVIVE II trials during the first 31 days of the study are listed in Table 3. In the REVIVE II trial, 5 adverse events were seen more frequently in the levosimendan group with nominal $p < 0.05$ (hypotension, 50% vs. 36%; headache, 30% vs. 15%; ventricular tachycardia, 25% vs. 17%; atrial fibrillation, 9% vs. 2%; and ventricular extrasystoles, 8% vs. 2%), whereas 1 adverse event was seen more frequently in the placebo group (rash 4% vs. 1%, nominal $p < 0.05$). An excess

Table 2 Worsening Clinical Status Requiring Rescue Therapy in REVIVE I and REVIVE II

	REVIVE I		REVIVE II	
	Levosimendan (n = 51)	Placebo (n = 49)	Levosimendan (n = 299)	Placebo (n = 301)
Proportion requiring rescue therapy	16%	29%	15%	26%
Worsening dyspnea or tachypnea	10%	12%	7%	13%
Increased pulmonary edema	0%	2%	3%	6%
Diaphoresis	0%	2%	1%	1%
Cool extremities and cyanosis	2%	2%	0%	2%
Worsening renal function	6%	2%	3%	5%
Decreased mental status	0%	0%	1%	2%
Persistent/unresponsive symptoms	10%	18%	6%	11%

Values are %. Patients could report multiple symptoms.
REVIVE = Randomized EValuation of Intravenous LeVosimendan Efficacy trials.

JACC: Heart Failure Vol. 1, No. 2, 2013
April 2013:103–11

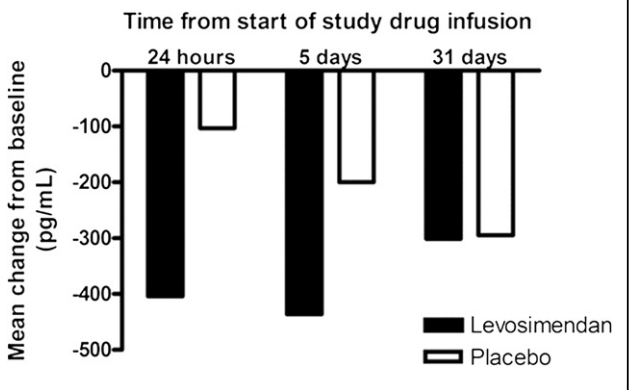

Figure 2 Change in Plasma B-Type Natriuretic Peptide During and After Infusion of Levosimendan in REVIVE II

REVIVE = Randomized EValuation of Intravenous LeVosimendan Efficacy.

of these adverse events was apparent both during the first 24 h and from 24 h to 5 days, except for hypotension, whose occurrence was increased only within the first 24 h. The most common adverse event leading to discontinuation of treatment was hypotension, which was the cause of withdrawal in 8.1% of the levosimendan group and 2.3% of the placebo group. Other adverse events leading to withdrawal were infrequent and similar in the 2 treatment groups.

By the protocol-specified time point of 90 days, 5 patients in the placebo group and 4 in the levosimendan group had died in the REVIVE I trial, and 35 patients in the placebo group and 45 in the levosimendan group had died in the REVIVE II trial. The hazard ratio for all-cause mortality was 1.33 (95% confidence interval: 0.85 to 2.06) for the REVIVE II trial alone ($p = 0.21$) and was 1.26 (95% confidence interval: 0.83 to 1.91) for the REVIVE I and REVIVE II trials combined ($p = 0.29$) (Fig. 3). An excess risk of death in the levosimendan group (vs. placebo) was apparent as early as 5 days; was nominally significant at 14 days; and was largely seen in subgroups at highest risk of death before entry into the study (e.g., patients with systolic blood pressure <100 mm Hg). After 14 days, we observed an inverse relation between baseline systolic pressure and the magnitude and direction of the treatment-related difference in the risk of death, with an excess hazard in the levosimendan group when the baseline systolic pressure was <100 to 110 mm Hg (Fig. 4). After 90 days, the relative risk of death (levosimendan/placebo) was 1.9 in patients with a pre-treatment systolic blood pressure <100 mm Hg but was 1.1 in patients with a systolic blood pressure ≥100 mm Hg.

Discussion

The REVIVE studies demonstrate that a continuous intravenous infusion of levosimendan for 24 h, when added to existing treatments, has a favorable symptomatic effect on the short-term clinical course of patients with ADHF. Patients who received levosimendan on top of standard of care were more likely to experience an improvement in symptoms and less likely to experience a worsening of symptoms than those who received standard therapy alone. Moreover, levosimendan-treated patients experienced fewer episodes of and required fewer pharmacological interventions for worsening heart failure and had fewer prolonged hospital stays. These benefits of levosimendan were apparent as early as 6 h and persisted for at least 5 days, even though the drug was infused for only 24 h. The difference in symptoms in favor of levosimendan could be discerned, even though background treatment was intensified to a greater degree in the placebo group—an imbalance that would generally have been expected to have diminished the ability of our study to detect a favorable effect of active treatment (7–9).

The clinical composite endpoint used in these studies was designed to address many of the limitations of measures previously used to assess the effects of new drugs in patients with ADHF. This composite included a clinically important change in a patient-reported assessment of overall clinical status as well as the occurrence of adverse cardiovascular events sufficiently severe to warrant the use of additional intravenous medications for heart failure. Therefore the endpoint was devised to ensure that no unbiased, clinically meaningful information was excluded; that clinically important events (which frequently lead to the early withdrawal of a patient from the study and their exclusion from an efficacy analysis) would be included; and that the duration of observation would represent a meaningful length of time (e.g., the average duration of a hospital stay for ADHF). A similar approach has been used successfully to assess the effects of new drugs and new devices for the treatment of chronic heart failure (18). We tested our new endpoint initially in a pilot trial (REVIVE I), modified it, and then used it prospectively to evaluate the effects of levosimendan (in REVIVE II). Of note, our results did not depend on the specific definition used in either trial (i.e., levosimendan benefits could be demonstrated, whether we used our original REVIVE I definition or our modified [and more stringent] REVIVE II definition for the clinical composite endpoint).

The benefits of levosimendan seen in the current trials are consistent with its known pharmacological properties. Levosimendan exerts direct positive inotropic effects by enhancing calcium sensitivity of the cardiac contractile elements and exerts direct peripheral vasodilator effects by blocking adenosine triphosphate–dependent potassium channels in vascular smooth muscle (12). Both actions result in an increased cardiac output and reduced cardiac filling pressures in patients with ADHF (13–16). In contrast to some other positive inotropic agents, these effects are not attenuated by concomitant treatment with beta-blockers (16,20,21) and are sustained beyond the duration of the drug infusion, because levosimendan has an active metabolite with a long half-life (70 to 80 h) (17,22,23).

The infusion of levosimendan in the REVIVE I and REVIVE II trials was associated with important adverse

Table 3 Adverse Events Occurring With a Frequency ≥5% in REVIVE I and REVIVE II

	REVIVE I		REVIVE II	
	Levosimendan (n = 51)	Placebo (n = 48)	Levosimendan (n = 293)	Placebo (n = 294)
Hypotension	28 (54.9%)	23 (47.9%)	147 (50.2%)	107 (36.4%)
Headache	23 (45.1%)	13 (27.1%)	88 (30.0%)	44 (15.0%)
Cardiac failure	14 (27.5%)	13 (27.1%)	98 (33.5%)	108 (36.7%)
Ventricular tachycardia	12 (23.5%)	10 (20.8%)	72 (24.6%)	51 (17.3%)
Nausea	17 (33.3%)	11 (22.9%)	53 (18.1%)	46 (15.6%)
Dizziness	13 (25.5%)	4 (8.3%)	38 (13.0%)	35 (11.9%)
Hypokalemia	7 (13.7%)	8 (16.7%)	35 (11.9%)	36 (12.2%)
Renal failure	4 (7.8%)	1 (2.1%)	36 (12.3%)	40 (13.6%)
Insomnia	9 (17.6%)	7 (14.6%)	32 (10.9%)	37 (12.6%)
Constipation	5 (9.8%)	3 (6.3%)	34 (11.6%)	35 (11.9%)
Vomiting	4 (7.8%)	6 (12.5%)	27 (9.2%)	22 (7.5%)
Hyperkalemia	5 (9.8%)	5 (10.4%)	21 (7.2%)	19 (6.5%)
Diarrhea	4 (7.8%)	1 (2.1%)	21 (7.2%)	20 (6.8%)
Back pain	6 (11.8%)	5 (10.4%)	13 (4.4%)	20 (6.8%)
Urinary tract infection	1 (2.0%)	1 (2.1%)	20 (6.8%)	21 (7.1%)
Muscle cramp	6 (11.8%)	3 (6.3%)	20 (6.8%)	11 (3.7%)
Anxiety	1 (2.0%)	1 (2.1%)	17 (5.8%)	18 (6.1%)
Pain in extremity	1 (2.0%)	4 (8.3%)	14 (4.8%)	18 (6.1%)
Anemia	2 (3.9%)	3 (6.3%)	16 (5.5%)	15 (5.1%)
Angina pectoris	—	—	18 (6.1%)	18 (6.1%)
Atrial fibrillation	4 (7.8%)	1 (2.1%)	25 (8.5%)	6 (2.0%)
Pyrexia	—	2 (4.2%)	16 (5.5%)	18 (6.1%)
Cough	2 (3.9%)	4 (8.3%)	13 (4.4%)	15 (5.1%)
Ventricular extrasystoles	3 (5.9%)	2 (4.2%)	22 (7.5%)	6 (2.0%)
Dyspnea exacerbated	3 (5.9%)	3 (6.3%)	10 (3.4%)	15 (5.1%)
Hypoglycemia	1 (2.0%)	3 (6.3%)	15 (5.1%)	8 (2.7%)

Values are n (%). Versions of Medical Dictionary for Regulatory Activities + differed slightly between studies.
REVIVE = Randomized EValuation of Intravenous LeVosimendan Efficacy trials.

cardiovascular effects. As with other agents that dilate arterial and venous blood vessels (11,24), levosimendan lowered blood pressure, and its use was associated with both headache and hypotension. Similarly, as with other agents that increase cardiac contractility (5,24), levosimendan increased heart rate, and its use was associated with an increased frequency of both atrial and ventricular rhythm disturbances. Both types of adverse events have been reported in earlier studies with levosimendan (13–16), but in these earlier studies, the risk of hypotension and arrhythmias

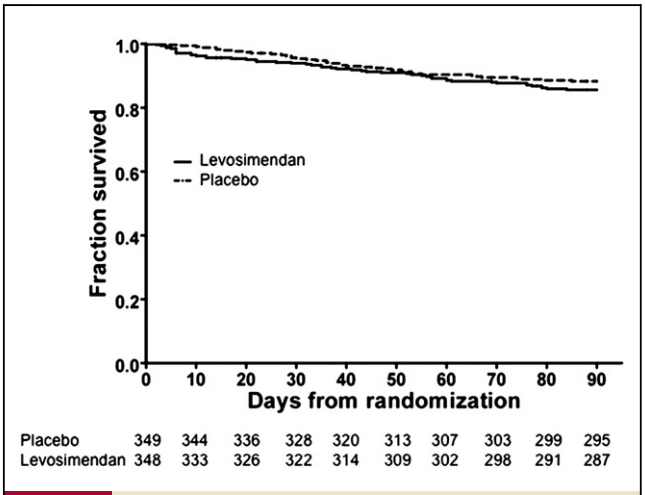

Figure 3 Time to Death for Any Reason During First 90 Days After Randomization

The REVIVE I and II trials combined.

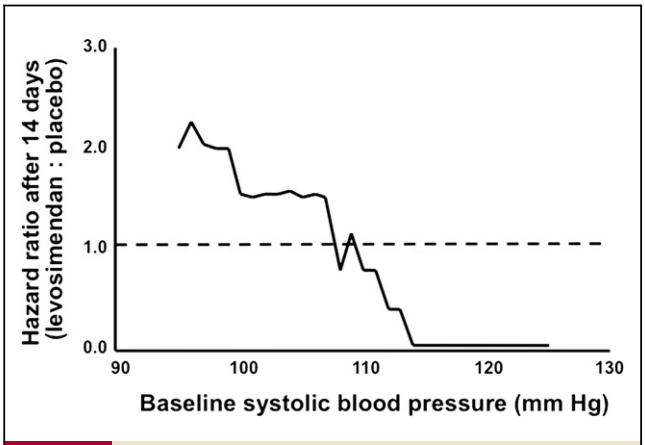

Figure 4 Hazard Ratio for All-Cause Mortality

Hazard ratio for all-cause mortality (levosimendan/placebo) at 14 days as a function of the systolic blood pressure at randomization.

was not translated into an increased frequency of major adverse cardiovascular events.

In experimental studies and in several controlled trials, the use of levosimendan has been reported to be associated with a reduction in the risk of death, when compared with placebo or with other positive inotropic agents (15,16). However, in the REVIVE II trial, the risk of death was numerically greater in levosimendan-treated patients than in those who were assigned to placebo. Given the small number of events, it is possible that this observation represents the play of chance. Indeed, a meta-analysis of 23 trials with levosimendan used in cardiology settings—which included both the REVIVE I and REVIVE II trials but was based on a much larger number of events—reported a significant reduction in the risk of all-cause mortality in levosimendan-treated patients (25). Alternatively, levosimendan might increase the risk of death under certain circumstances, particularly in patients with low pre-treatment blood pressures. In contrast with earlier studies with levosimendan (13–16), the REVIVE trials allowed the administration of levosimendan to patients receiving other drugs, such as dobutamine, nitroglycerin, and nesiritide (with milrinone permitted after 24 h). These drugs exert their own positive inotropic and/or vasodilatory effects, and some have been individually associated with an increased risk of death (5,26–28). Therefore the mortality findings in the REVIVE trials might have been related to excessive cardiocirculatory responses, which were triggered by pharmacological interactions among agents with potentially synergistic effects in patients with a low systolic blood pressure before treatment. The likelihood of such interactions might have been increased by the use of a loading dose of levosimendan, an approach that is no longer commonly used in clinical practice (29,30).

Conclusions

Despite the challenges inherent in the evaluation of acutely ill patients with ADHF who are receiving rapidly changing background treatments, the current study demonstrates that levosimendan can produce meaningful symptomatic benefits, which might (in the doses used) be counterbalanced by an increased risk of serious adverse events.

Acknowledgments

The authors thank the investigators, staff, and participants of the REVIVE studies for their valuable contributions.

Reprint requests and correspondence: Dr. Milton Packer, Department of Clinical Sciences, University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, Texas 75225. E-mail: Milton.Packer@UTSouthwestern.edu.

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation 2012;125:e2–220.
2. Fonarow GC. Pharmacologic therapies for acutely decompensated heart failure. Rev Cardiovasc Med 2002;3Suppl 4:S18–27.
3. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol 2006;47:76–84.
4. Shah MR, Hasselblad V, Stinnett SS, et al. Dissociation between hemodynamic changes and symptom improvement in patients with advanced congestive heart failure. Eur J Heart Fail 2002;4:297–304.
5. Cuffe MS, Califf RM, Adams KF Jr., et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002;287:1541–7.
6. O'Connor CM, Gattis WA, Adams KF Jr., et al. Tezosentan in patients with acute heart failure and acute coronary syndromes: results of the Randomized Intravenous TeZosentan Study (RITZ-4). J Am Coll Cardiol 2003;41:1452–7.
7. O'Connor CM, Gattis WA, Teerlink JR, Adams KF Jr., Gheorghiade M. Design considerations and proposed template for clinical trials in hospitalized patients with decompensated chronic heart failure. Am Heart J 2003;145:S47–50.
8. Teerlink JR. Overview of randomized clinical trials in acute heart failure syndromes. Am J Cardiol 2005;96:59G–67G.
9. Teerlink JR. Dyspnea as an end point in clinical trials of therapies for acute decompensated heart failure. Am Heart J 2003;145:S26–33.
10. O'Connor CM, Stough WG, Gallup DS, Hasselblad V, Gheorghiade M. Demographics, clinical characteristics, and outcomes of patients hospitalized for decompensated heart failure: observations from the IMPACT-HF registry. J Card Fail 2005;11:200–5.
11. Publication Committee for the VMAC Investigators (Vasodilatation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA 2002;287:1531–40.
12. Papp Z, Edes I, Fruhwald S, et al. Levosimendan: molecular mechanisms and clinical implications: consensus of experts on the mechanisms of action of levosimendan. Int J Cardiol 2012;159:82–7.
13. Nieminen MS, Akkila J, Hasenfuss G, et al. Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. J Am Coll Cardiol 2000;36:1903–12.
14. Slawsky MT, Colucci WS, Gottlieb SS, et al., on behalf of the Study Investigators. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Circulation 2000;102:2222–7.
15. Moiseyev VS, Poder P, Andrejevs N, et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). Eur Heart J 2002;23:1422–32.
16. Follath F, Cleland JG, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet 2002;360:196–202.
17. Lilleberg J, Laine M, Palkama T, Kivikko M, Pohjanjousi P, Kupari M. Duration of the haemodynamic action of a 24-h infusion of levosimendan in patients with congestive heart failure. Eur J Heart Fail 2007;9:75–82.
18. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. J Card Fail 2001;7:176–82.
19. de Lissovoy G, Fraeman K, Teerlink JR, et al. Hospital costs for treatment of acute heart failure: economic analysis of the REVIVE II study. Eur J Health Econ 2010;11:185–93.
20. Lehtonen L, Sundberg S. The contractility enhancing effect of the calcium sensitiser levosimendan is not attenuated by carvedilol in healthy subjects. Eur J Clin Pharmacol 2002;58:449–52.
21. Mebazaa A, Nieminen MS, Filippatos GS, et al. Levosimendan vs. dobutamine: outcomes for acute heart failure patients on beta-blockers in SURVIVE. Eur J Heart Fail 2009;11:304–11.
22. Kivikko M, Antila S, Eha J, Lehtonen L, Pentikäinen PJ. Pharmacokinetics of levosimendan and its metabolites during and after a 24-hour continuous infusion in patients with severe heart failure. Int J Clin Pharmacol Ther 2002;40:465–71.
23. Kivikko M, Lehtonen L, Colucci WS. Sustained hemodynamic effects of intravenous levosimendan. Circulation 2003;107:81–6.

24. Capomolla S, Febo O, Opasich C, et al. Chronic infusion of dobutamine and nitroprusside in patients with end-stage heart failure awaiting heart transplantation: safety and clinical outcome. Eur J Heart Fail 2001;3:601–10.
25. Landoni G, Biondi-Zoccai G, Greco M, et al. Effects of levosimendan on mortality and hospitalization. A meta-analysis of randomized controlled studies. Crit Care Med 2012;40:634–46.
26. O'Connor CM, Gattis WA, Uretsky BF, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1999;138:78–86.
27. Abraham WT, Adams KF, Fonarow GC, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). J Am Coll Cardiol 2005; 46:57–64.
28. Tacon CL, McCaffrey J, Delaney A. Dobutamine for patients with severe heart failure: a systematic review and meta-analysis of randomised controlled trials. Intensive Care Med 2012;38: 359–67.
29. Archan S, Toller W. Levosimendan: current status and future prospects. Curr Opin Anaesthesiol 2008;21:78–84.
30. Lunghetti S, Palmerini E, Urselli R, et al. Effects of levosimendan without loading dose on systolic and diastolic function in patients with end-stage heart failure. Cardiol J 2011;18:532–7.

Key Words: heart failure ■ inotropic agents ■ trials.

APPENDIX

For a list of the Steering Committee members, Data and Safety Monitoring Board members, and the REVIVE Program Investigators, please see the online version of this article.