Levosimendan Treatment for Heart Failure: A Systematic Review and Meta-Analysis

Bojun Gong, MD, Zicheng Li, PhD, and Philip Ching Yat Wong, PhD

Objective: **Emerging studies suggest that administration of levosimendan therapy may be better than dobutamine or placebo in decompensated heart failure. The authors performed an updated meta-analysis of trials to obtain the best estimates of the efficacy and safety of levosimendan for the initial treatment of decompensated heart failure.**

Design: **A meta-analysis.**

Setting: **Hospitals.**

Participants: **A total of 5,349 patients from 25 randomized controlled studies were included in the analysis.**

Interventions: **None.**

Measurements and Main Results: **The authors performed a meta-analysis of trials comparing levosimendan therapy with dobutamine or placebo in patients with decompensated heart failure. Twenty-five trials, involving 5,349 patients, were included. Two reviewers performed independent article review and study quality assessment. Data on overall mortality, early-term mortality, midterm mortality, long-term mortality, efficacy outcomes, and adverse events were collected. Mortality outcomes were according to follow-up duration: early term ($\leq$30-day), midterm (30-day to $\leq$6-month), and long term ($>$6-month). Levosimendan was compared with dobutamine or placebo, calculating pooled relatives risk (RRs) and associated 95% confidence intervals (CIs). A random-effects model was selected for meta-analysis if there was significant heterogeneity. Levosimendan significantly reduced total mortality (17.1% versus 20.8%; RR, 0.84; 95% CI, 0.75-0.94). Compared with dobutamine, levosimendan was associated with significant reduction in mortality at final follow-up (RR, 0.86; 95% CI, 0.76-0.97; $I^2 = 7\%$; $p = 0.02$).Compared with placebo, levosimendan was associated with a nonsignificant trend in favor of placebo in mortality at final follow-up (11.6% versus 16.2%, RR, 0.75; 95% CI, 0.56-1.01; $p = 0.06$), but it was associated with a significant reduction in long-term mortality (RR, 0.34; 95%CI, 0.15-0.76; $p = 0.009$). Compared with dobutamine or placebo, levosimendan therapy was associated with improvements in hemodynamically- and echocardiographically-derived cardiac parameters. Levosimendan therapy increased the risks of extrasystoles (RR, 1.88; 95% CI, 1.26-2.81), hypotension (RR, 1.33; 95% CI, 1.15-1.53), and headache or migraine (RR, 1.94; 95% CI, 1.54-2.43) when compared with control therapy.**

Conclusions: **As compared to placebo or dobutamine, levosimendan in patients with heart failure seemed to have hemodynamic and cardiac benefits. It reduced total mortality and was associated with an increased risk of cardiovascular adverse events.**

KEY WORDS: heart failure, meta-analysis, levosimendan, mortality, dobutamine, complications, outcomes

ADVANCED DECOMPENSATED chronic heart failure (CHF) has emerged as a complex clinical condition associated with release of oxygen-derived free radicals that promote progressive left ventricular dysfunction. It is the most frequent reason for hospital admission among patients older than 65,[1] and about 5,000 hospital admissions per million population per year are attributable to heart failure.[2]

Intravenous levosimendan, a vasodilator and inotropic agent for the treatment of acutely decompensated heart failure, improves myocardial contractility and enhances the sensitivity of myofilaments to calcium, thereby causing an increase in myocardial oxygen consumption.[3] It has been found to have phosphodiesterase type-III inhibitory properties at high concentrations,[4] and to produce vasodilatation by opening the ATP-sensitive potassium channels in vascular smooth muscle cells.[5]

When properly applied, meta-analysis can increase the statistical power of primary endpoints, clarify disagreement among studies, and estimate effect sizes to quantify outcomes from a set of individual studies.[6] In early clinical studies in patients with heart failure, levosimendan had favorable effects on cardiac symptoms, hospitalization, and risk of death.[7–9] To better assess the clinical benefit, the authors carried out a meta-analysis of efficacy and safety of levosimendan therapy on clinical outcome and survival in patients with heart failure.

METHODS

Data Sources and Searches

The authors attempted to identify all relevant published randomized trials comparing levosimendan with dobutamine or placebo for the initial treatment of decompensated heart failure. The authors searched MEDLINE (1950-Aug, 2014), EMBASE (1980-Aug, 2014), and the Cochrane Library (2014) for English-language randomized controlled trials using the terms "heart failure," "levosimendan," "dobutamine," "placebo," "controlled clinical trial," "randomized controlled trial," and "random." They also performed a manual search of references from original articles and pertinent reviews. Searches were restricted to completed trials in human beings with abstracts or full texts published in English.

Study Selection

Two investigators (B.J.G., Z.C.L.) independently evaluated studies for inclusion, and any disagreements were resolved by discussion. Criteria for inclusion were (1) proper randomization, (2) inclusion of patients with objectively diagnosed heart failure, (3) comparison of levosimendan with dobutamine or placebo and dobutamine versus placebo for the initial treatment of heart failure, and (4) use of objective methods to assess 1 or more clinical outcomes.

From the Department of Cardiology, First Affiliated Hospital of Jinan University, Guangzhou, China.

Address reprint requests to Bojun Gong, MD, Department of Cardiology, First Affiliated Hospital of Jinan University, Guangzhou, China. E-mail: bojungong@hotmail.com

1053-0770/2601-0001$36.00/0

http://dx.doi.org/10.1053/j.jvca.2015.03.023

Outcomes

Study outcomes were analyzed comparing the results from trials with levosimendan versus dobutamine, the results from trials with levosimendan versus placebo, and the results from trials with dobutamine versus placebo.

The hemodynamic and cardiac parameters of levosimendan were measured by the mean arterial pressure (MAP), pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), cardiac index (CI), stroke volume (SV), left ventricular ejection fraction (LVEF), left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic dimension (LVEDD), and ratio of E-wave and A-wave peak velocities of the mitral flow profile (E/A).

The safety outcomes were adverse events, such as ventricular tachycardia, extrasystoles, hypotension, constipation, diarrhea, hypokalemia, nausea, vomiting, urinary tract infection, dizziness, headache or migraine, angina pectoris, chest pain or myocardial ischemia, and mortality. Mortality outcomes were according to their follow-up duration: early term ($\leq$30 days), midterm (30 days to $\leq$6 months), and long term (>6 months).

Statistical Analyses

The authors determined pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) for mortality in heart failure patients who received levosimendan or treatment with dobutamine or placebo. Furthermore, the pooled RR of any adverse event was calculated. Data were pooled by use of a fixed-effects model (Mantel–Haenszel method).[10] Results obtained with a fixed-effects model also were compared with those obtained with a random-effects model. Heterogeneity was assessed by visual inspection of the forest plots and by the Q-statistic. All analyses were performed using Review Manager software 5.1.

RESULTS

Study Selection and Characteristics

There were 25 studies[11–35] (as shown in Fig 1) with 5,349 patients in the present meta-analysis (study characteristics are listed in Table 1), among which seven[11–14,22,23,25] were double-blind, three[26,27,31] were single-blind, eight[19,20,24,28–30,34,35] were intention-to-treat, and seven[15–18,21,32,33] had concealed allocation. The dose of levosimendan varied between 0 and 24 μg/kg (as an intravenous bolus) or between 0.05 and 0.6 μg/kg/min (as a continuous infusion). Follow-up durations were $\leq$30 days in 12 trials,[14–16,21,24–29,31,33,34] 1 month in 2 trials,[22,23] 3 months in 2 trials,[13,28] 4 months in 1 trial,[32] 5 months in 1 trial,[30] 6 months in 6 trials,[11,12,17,18,20,35] and 12 months in 1 trial.[19]

Methodologic Quality

The authors summarized the methodologic quality of Jadad scores of the reported studies in Table 1. The bias assessments were shown in Figures 2–10 according to the risk of bias.

Meta-Analysis

Mortality Outcomes

Death occurred in 407 of 2,380 patients (17.1%) treated with levosimendan and in 502 of 2,411 patients (20.8%) treated with controls. Use of levosimendan was associated with a

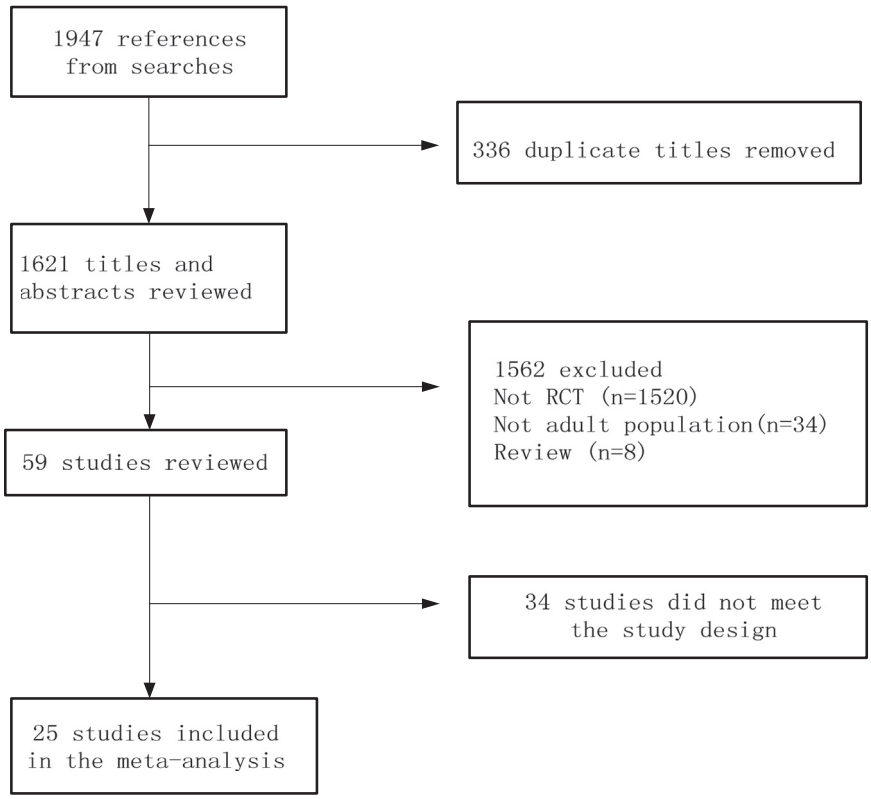

Fig 1. PRISMA flow diagram for study selection.