Hospital costs for treatment of acute heart failure: economic analysis of the REVIVE II study

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Abstract

Background Acute heart failure (AHF) is the leading cause of hospital admission among older Americans. The Randomized Evaluation of Intravenous Levosimendan Efficacy (REVIVE II) trial compared patients randomly assigned to a single infusion of levosimendan (levo) or placebo (SOC), each in addition to local standard treatments for AHF. We report an economic analysis of REVIVE II from the hospital perspective.

Methods REVIVE II enrolled patients ($N = 600$) hospitalized for treatment of acute decompensated heart failure (ADHF) who remained dyspneic at rest despite treatment with intravenous diuretics. Case report forms documented index hospital treatment (drug administration, procedures, days of treatment by care unit), as well as subsequent hospital and emergency department admissions during follow-up ending 90 days from date of randomization. These data were used to impute cost of admission based on an econometric cost function derived from >100,000 ADHF hospital billing records selected per REVIVE II inclusion criteria.

Results Index admission mean length of stay (LOS) was shorter for the levo group compared with standard of care (SOC) (7.03 vs 8.96 days, $P = 0.008$) although intensive care unit (ICU)/cardiac care unit (CCU) days were similar (levo 2.88, SOC 3.22, $P = 0.63$). Excluding cost for levo, predicted mean (median) cost for the index admission was levo US \$13,590 (9,458), SOC \$19,021 (10,692) with a difference of \$5,431 (1,234) favoring levo ($P = 0.04$). During follow-up through end of study day 90, no significant differences were observed in numbers of hospital admissions ($P = 0.67$), inpatient days ($P = 0.81$) or emergency department visits ($P = 0.41$). Cost-effectiveness was performed with a REVIVE-II sub-set conforming to current labeling, which excluded patients with low baseline blood pressure. Assuming an average price for levo in countries where currently approved, there was better than 50% likelihood that levo was both cost-saving and improved survival. Likelihood that levo would be cost-effective for willingness-to-pay below \$50,000 per year of life gained was about 65%. **Conclusions** In the REVIVE II trial, patients treated with levo had shorter LOS and lower cost for the initial hospital admission relative to patients treated with SOC. Based on sub-group analysis of patients administered per the current label, levo appears cost-effective relative to SOC.

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Abbreviations

ADHF Acute decompensated heart failure
CCU Cardiac care unit

COPERNICUS	Carvedilol prospective randomized cumulative survival trial
CRFs	Case report forms
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study trial
ICU	Intensive care unit
ITT	Intent-to-treat
levo	Levosimendan
REVIVE II	Randomized Evaluation of Intravenous leVosimendan Efficacy trial
SOC	Standard of care

Fig. 1 Hospital admission cost estimation procedure

90 days post-randomization; and (2) determine the incremental cost-effectiveness of levo relative to SOC (Fig. 1).

Introduction

Acute decompensated heart failure (ADHF) is a potentially life-threatening condition and represents one of the leading causes of hospital admission among the elderly in Western nations. In the United States, the annual cost of heart failure exceeds US \$30 billion [1]. The Randomized, multicenter Evaluation of Intravenous leVosimendan Efficacy versus placebo in the short-term treatment of decompensated chronic heart failure (REVIVE) study was conducted to evaluate the efficacy of a single randomized 24-h infusion of levosimendan (levo) compared to placebo, each in addition to standard of care (SOC) in the treatment of acute decompensated chronic heart failure. For patients in need of inotropic support, dobutamine is currently the standard of care, but its efficacy may be compromised by interaction with the beta blockers that are a standard treatment for CHF, and its safety reduced by the effect on arrhythmogenicity and possible adverse effects on survival [2]. Levosimendan is a new treatment option for ADHF now available in a number of countries around the world. Unlike conventional agents, it has been shown to improve symptoms, not just hemodynamics, in patients with heart failure [3, 4].

Cost is increasingly a consideration in hospital formulary decisions and this is certainly the case for heart failure medications where mainstays of treatment, such as dobutamine, are often inexpensive generic products. We report an economic analysis of REVIVE II that was conducted from the hospital perspective because inpatient medications are typically a cost to the hospital not directly reimbursed by third-party payers or national health plans. Formulary committees and other decision-makers are often faced with the task of balancing the additional cost of a new drug versus potential improvement in patient outcomes and changes to other hospital costs. Objectives for the REVIVE II economic analysis were to (1) estimate direct medical costs from the hospital perspective for the index hospital admission and follow-up period through

Methods

Design of the REVIVE II study

The REVIVE program was conducted as two sequential trials at 103 centers in the United States, Australia and Israel. Both trials were double-blind, placebo-controlled, parallel group studies enrolling male and female patients over 18 years age who were hospitalized with a primary or secondary diagnosis of ADHF within 48 h prior to start of study drug infusion. Left ventricular ejection fraction was required to be less than 35% as measured within the previous 12 months. Dyspnea, as assessed by the patient, was to be present at both the screening and baseline evaluation.

REVIVE I ($N = 100$) piloted a measure of efficacy based on a composite of clinical and patient-reported outcomes. That measure was utilized to evaluate the efficacy of levo in REVIVE II, which enrolled a total of 600 patients (levo plus SOC $n = 299$, SOC only $n = 299$). Results of the economic analysis as reported here are based on REVIVE II.

The primary endpoint evaluated the distribution of patients characterized as “Improved,” “Unchanged,” or “Worse” during the first 5 days following randomization. Classification was based on a composite of patient self-reported global assessment at each of three time points (6 h, 24 h and 5 days) without evidence of clinical deterioration during the period of observation. Patients were classified as “Worse” if, during the first 5 days; they died; experienced worsening heart failure (according to prespecified criteria); self-reported moderately or markedly worse symptoms on global assessment at any one of the three time points; or experienced persistent or unresponsive symptoms of heart failure after the first 24 h of treatment. Categorization as

“Improved” required that the self-reported global assessment of heart failure was recorded as “moderately improved” or “markedly improved” at all of the following time points: 6 h, 24 h, 5 days while none of the criteria for worsening heart failure were met during this period. The remaining patients were classified as “Unchanged.” Secondary endpoints included time to death or worsening of heart failure symptoms during the first 31 days after start of study drug infusion and all-cause mortality at 90 days [4].

Cost estimation

Hospital resource utilization was documented in the REVIVE II study by means of clinical case report forms (CRFs). As no actual billing records were obtained during the trial, it was necessary to estimate treatment costs as a function of resource utilization [5].

REVIVE II CRFs were reviewed to characterize each hospital admission in terms of number of days in the intensive care unit (ICU) or cardiac care unit (CCU), number of routine care days, study medication administration, performance of interventional procedures or other special care, and discharge status. Also documented in CRFs were emergency department admissions and hospital outpatient visits where these included the administration of intravenous cardiac medication. Records were created for all study patients summarizing each hospital admission.

A file of detailed hospital billing records was obtained from the Premier Hospital Network, an association of nearly 600 community not-for-profit acute care hospitals (Premier HealthCare Informatics, Charlotte, NC). Premier member hospitals account for nearly 1 in 5 hospital discharges in the United States (US) and are broadly representative of all US acute care general hospitals in terms of patient demographics, teaching status, and urban-rural location. More than 90% of member hospitals pool all of their detailed discharge records in a central database as part of a benchmarking program.

Some 5 million admission records were available in the 2005 Premier Healthcare Informatics database. Each record included patient demographic information, ICD-9-CM diagnostic codes including admission diagnosis and principal discharge diagnosis, ICD-9-CM procedure codes, and detailed lists of the services and supplies received by patients during the admission. Each service or supply item included a cost derived from the particular hospital’s internal cost accounting system. We restricted our analysis to hospitals that used activity-based accounting systems, which offer a more precise measure for the true cost of an item than cost-to-charge-ratio or step-down methods [6]. Application of selection parameters replicating the REVIVE II clinical trial inclusion-exclusion criteria yielded a file of 155,000 records for patients similar to those

enrolled in the trial. For example, heart failure was recorded as the admission diagnosis for all patients and all cases received an intravenous vasodilator or intravenous inotrope during the initial 24-h period. Editing procedures to eliminate records with missing or anomalous utilization or cost data resulted in a final analysis file of 112,000 hospital admission records.

We identified a set of data elements from the REVIVE II hospital admission file to serve as explanatory variables in a multivariate model of the cost of a Premier admission. The general form of the model was:

$$\text{COST}_{\text{Premier}} = f(\text{Age, Gender, ICU, Routine Procedure, Died})$$

Where

$\text{COST}_{\text{Premier}}$ = cost of the admission as recorded in the Premier record

Age = patient age in years

Gender = patient sex

ICU = days in the intensive care or cardiac care unit

Routine = days in a routine care unit

Procedure = set of indicator variables designating that the patient underwent a specific procedure or a specified combination of procedures¹

Died = patient expired during the admission

Because the cost data were highly skewed, the cost function was estimated using gamma regression with a log link [7]. This procedure yielded a set of parameter estimates that could be applied to corresponding variables from the REVIVE II hospital admission file to impute a cost for each admission.

Descriptive statistical analysis

We tabulated resource utilization (e.g., days in ICU, days in routine care) and costs of hospital admission for the initial hospital stay where patients were randomized to treatment, for the period following discharge from initial hospitalization through end of study (day 90 after randomization, and for the complete episode of treatment. Mean and median values were calculated by study group as well as difference for the levo group relative to SOC. Magnitude of difference between the two groups was assessed via the Kruskal–Wallis statistic, a non-parametric

¹ Arterial or venous central line catheter, Cardiac ablation, Cardiac biopsy, Cardiac (Pulmonary artery; Swan-Ganz) catheter, Cardiac defibrillation, Cardio-pulmonary resuscitation, Continuous positive airway pressure, Coronary artery bypass graft (CABG), Electrophysiology study, Heart transplant, Hemodialysis, Implantable cardiac defibrillator, Intra-aortic balloon pump, Left ventricular assist device, Percutaneous transluminal cardiac angioplasty (PTCA), Permanent pacemaker, Temporary pacemaker, Thoracentesis, Ventilator support.

test for equality of medians, as well as bootstrapped confidence intervals for the difference in means [8].

Cost-effectiveness analysis

Cost-effectiveness was measured as the incremental cost per life-year gained for patients randomized to levo relative to SOC. Duration of patient follow up in REVIVE II was relatively short (90 days) and most patients were alive at study termination. Calculating cost-effectiveness based only on the observed survival during the period of the trial could underestimate treatment benefit. Therefore, lifetime survival for patients alive at day 90 was projected based on data from the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial where mean survival in the treatment group was 2.14 years [9]. This approach has been used in a previous economic analysis of levo [10]. As a sensitivity analysis, the survival projection was performed using survival results from the more recent Carvedilol Prospective Randomized Cumulative Survival COPERNICUS trial where projected mean treatment group survival was 7.3 years [11].

Incremental cost-effectiveness was calculated via a bootstrapping procedure where the patient-level cost and survival outcome for each study group was resampled 1,000 times with mean cost and mean survival calculated for each iteration.

Results

Clinical trial results

For the REVIVE II primary endpoint, 58 patients in the levo group recorded improvement versus 44 in the SOC group, while 82 patients in the SOC group but only 58 levo patients experienced worsening ($P = 0.015$). Survival was somewhat lower in the levo group than for SOC with 45 (15.1%) deaths in the levo group and 35 (11.6%) in the SOC group during the 90-day study period (hazard ratio 1.33, $P = 0.21$). Characteristics of the study population are shown in Table 1. Further details on the trial design and results are provided in the REVIVE II Final Study Report which is available on the internet.²

Levosimendan has vasodilatory effects in addition to its inotropic actions. Post-hoc analyses identified systolic blood pressure <100 mmHg or diastolic blood pressure <60 mmHg at baseline as a factor increasing mortality risk. In patients with low blood pressure at baseline,

mortality was 26.6% for levo versus 16.3% for SOC. Conversely, in patients with higher blood pressure at baseline (systolic BP ≥ 100 and diastolic BP ≥ 60), mortality was 8.4% for levo and 9.1% with standard of care (hazard ratio 0.92, $P = 0.81$; REVIVE II Final Study Report). Levosimendan product labeling now advises cautious use in patients with low baseline systolic or diastolic blood pressure [12]. For this reason, we present descriptive results of economic analysis for both the full (intent-to-treat; ITT) REVIVE II study population ($n = 600$), and for a patient subset identified in post-hoc analysis ($n = 388$) corresponding to current labeling that advises that the drug "...should be used with caution" in patients with low baseline systolic (<100 mm/Hg) or diastolic (<60 mm/Hg) blood pressure.

Hospital resource utilization

Use of hospital inpatient and emergency department services is described for both the REVIVE II ITT population and for a subset of patients corresponding to current labeling in Table 2. In the full study group, the overall length of stay (LOS) during REVIVE II, index admission was on average shorter by 1.9 days for levo patients relative to standard of care ($P = 0.008$). LOS in routine care unit was shorter on average by 1.2 days ($P = 0.02$) while LOS in the ICU/CCU was not statistically different ($P = 0.63$). For the subset of patients who did not have low blood pressure at baseline, days in routine care were similar to the full study cohort; however, average duration of ICU stay was lower by about 0.5 days ($P = 0.21$). As a result, overall length of stay was somewhat shorter in both study groups and favored levo by 1.4 days ($P = 0.01$).

Relatively shorter LOS in the levo group could be attributable to differential mortality. As a sensitivity analysis we compared LOS for patients surviving the index hospital admission. For the ITT population, mean length of stay was 6.87 for levo versus 8.77 for standard of care ($P = 0.01$), while in the subset not having low blood pressure, LOS was 6.58 versus 7.83 days ($P = 0.2$).

During ITT group follow-up through 90 days after date of randomization, there was a non-significant trend to slightly greater use of hospital services in the levo group (ITT group; Table 2). Number of hospital readmissions was slightly greater (levo 0.73, SOC 0.67, $P = 0.67$) as was the total number of inpatient days (levo 5.14, SOC 4.36, $P = 0.81$). Similar patterns were seen in the subset typical of current labeling group.

Hospital treatment costs

Hospital costs incurred by patients during the index admission and the follow-up period are presented in

² http://www.clinicalstudyresults.org/drugdetails/?drug_name_id=694&study_name=REVIVE&sort=c.company_name&page=1&drug_id=3455

Table 1 REVIVE II patient characteristics and outcomes. *levo* Levosimendan, *SOC* standard of care

Patient characteristics and trial outcomes	All REVIVE II (ITT)		Sub-set corresponding to current labeling	
	levo <i>n</i> = 299	SOC <i>n</i> = 301	levo <i>n</i> = 190	SOC <i>n</i> = 197
Gender (<i>n</i> , %)				
Male	219 (73.2%)	216 (71.8%)	145 (76.3%)	139 (70.6%)
Female	80 (26.8%)	85 (28.2%)	45 (23.7%)	58 (29.4%)
Age years				
Mean, SD	63.8 (14.8)	63.3 (14.8)	62.0 (14.1)	61.6 (14.7)
Range	20–93	22–90	24–93	24–90
Ejection fraction				
Mean, SD	22.8 (7.0)	23.5 (7.4)	22.6 (6.6)	23.7 (7.5)
Range	10–37	7–35	10–35	7–35
Prior history of myocardial infarction (<i>n</i> , %)				
No	136 (45.5%)	146 (48.5%)	97 (51.0%)	109 (55.3%)
Yes	163 (54.5%)	155 (51.5%)	93 (49.0%)	88 (44.7%)
Primary study outcome (<i>n</i> , %)				
Improved	58 (19.4%)	44 (14.6%)	39 (20.5%)	29 (14.7%)
Unchanged	183 (61.2%)	175 (58.1%)	118 (62.1%)	119 (60.4%)
Worse	58 (19.4%)	82 (27.2%)	33 (17.4%)	49 (24.9%)
Secondary study outcome (<i>n</i> , %)				
Death during index admission	15 (5.0%)	6 (2.0%)	3 (1.6%)	5 (2.5%)
Death during follow-up	29 (9.7%)	29 (9.6%)	12 (6.3%)	13 (6.6%)
Total deaths	44 (14.7%)	35 (11.6%)	15 (7.9%)	18 (9.1%)

Table 3 for both the (REVIVE II ITT population and the subset of patients who correspond to current labeling. For patients in the *levo* group, cost of the index admission was substantially lower than for SOC. In the ITT analysis, the cost differential favoring *levo* exceeded \$5,000 ($P = 0.04$) while for the sub-set corresponding to current labeling, the difference was about \$1,800 ($P = 0.01$). Corresponding to the somewhat greater use of hospital resources during follow-up, costs incurred during this period were somewhat greater for the *levo* group by \$2,400 ($P = 0.82$) for the ITT group and \$1,800 ($P = 0.16$) in the sub-set. For the complete episode of care (index admission plus follow-up), total cost was somewhat lower in the *levo* group, although differences were not significant. Lower costs for the *levo* group during the index hospital admission were offset by somewhat higher costs during the follow-up period.

Cost and cost differentials as described in the preceding section do not include the price of *levo*, which is now marketed in many nations. Figure 2 shows the impact on the difference in cost of the index admission for *levo* relative to SOC with the cost for *levo* ranging from \$0 to \$800 per course of treatment. The cost differential reflects the subset of patients who correspond to current labeling as reported in Table 3. At a cost of \$700 for *levo*, predicted cost for the index admission was about \$1,347 less for patients treated with *levo* relative to SOC (90% confidence interval $-\$3,836$ to $+\$1,003$).

Cost-effectiveness

Calculation of cost-effectiveness for the REVIVE-II ITT population was not warranted because mortality was somewhat greater in the levosimendan group relative to SOC. Cost-effectiveness of *levo* relative to SOC for the patient sub-set that would most likely be treated in accordance with current guidelines is shown graphically in Fig. 3. Here cost is based on the complete episode of care (Table 3), while survival reflects extrapolation to lifetime survival based on the CONSENSUS treatment group. Each point on the graph represents the incremental survival (horizontal axis) and incremental cost (vertical axis) of *levo* relative to SOC for one bootstrap replication of the cost-effectiveness analysis; a total of 1,000 points are shown. Dispersion of the points demonstrates substantial variability across the cost-effectiveness estimates. The upper-right quadrant includes points where both incremental cost and incremental survival are greater for *levo* relative to SOC; 12.6% (126/1,000) of points appear in this quadrant. Points in the lower-right quadrant depict relatively lower incremental cost and greater incremental survival for the levosimendan group; 59.6% (596/1,000) of points appear here. The upper-left and lower-right quadrants represent points with lower incremental survival and included 27.8% (278/1,000) of points.

Table 2 REVIVE II hospital resource utilization

Hospital resource	Study group mean		Difference			
	levo	SOC	Mean	90% confidence interval		P-value
				Lower	Upper	
Intent to treat						
Index admission						
ICU days	2.88	3.22	-0.348	-0.85	+0.19	0.63
Routine care days	4.15	5.74	-1.196	-1.88	-0.57	0.021
Total length of stay	7.03	8.96	-1.920	-2.87	-1.04	0.008
Follow-up						
Emergency department visits	0.23	0.18	0.06	-0.02	+0.13	0.41
Hospital admissions	0.73	0.67	0.05	-0.08	+0.18	0.67
Inpatient days	5.14	4.36	0.83	-0.50	+2.11	0.81
Total inpatient days	11.89	12.68	-0.79	-2.58	0.96	0.38
Subset typical of current labeling ^a						
Index admission						
ICU days	2.39	2.75	-0.34	-0.97	+0.33	0.21
Routine care days	4.32	5.22	-0.92	-1.70	-0.17	0.18
Total length of stay	6.73	8.15	-1.43	-2.46	-0.47	0.01
Follow-up						
Emergency department visits	0.22	0.15	0.07	-0.02	+0.15	0.38
Hospital admissions	0.69	0.57	0.11	-0.04	+0.27	0.32
Inpatient days	4.31	3.50	0.82	-0.57	+2.18	0.19
Total inpatient days	10.89	11.37	-0.48	-2.33	1.45	0.63

^a Excluding patients with low blood pressure at study entry

Cost-effectiveness results as depicted in Fig. 3 are summarized in the form of the acceptability curves shown in Fig. 4. An acceptability curve indicates the likelihood (vertical axis) that the incremental cost per year of life gained is equal to or less than a specified upper limit on willingness to pay (WTP) per life-year gained (horizontal axis). Here the cost of levo is set at \$700 per vial and the analysis is again based on the patient subset conforming to current treatment guidelines. Lines on the graph represent actual survival as observed in the REVIVE II study (lower line) and extrapolation of survival based on CONSENSUS (middle line) and COPERNICUS (upper line) treatment groups. The curves indicate that there is better than 50% likelihood that levo is cost-effective relative to SOC at near-zero WTP per year of life gained. This reflects the results shown in Fig. 3, where more than 50% of the incremental cost-effectiveness estimates were situated in quadrant 4 (lower cost and better survival). The likelihood that levo would be considered cost-effective for WTP less

Table 3 Cost of treatment (US\$)

Component of cost	Study group		Difference			
	levo	SOC	Mean	90% confidence interval		<i>P</i> -value
				Lower	Upper	
Full REVIVE II study population (intent-to-treat)						
Index admission						
Mean	13,590	19,021	−5,431	−10,161	−1,299	0.043
Median	9,458	10,692				
Follow-up						
Mean	9,483	7,047	+2,436	−116	5,238	0.82
Median	0	0				
Total episode						
Mean	23,073	26,068	−2,995	−8,423	2,088	0.44
Median	14,774	15,317				
Subset typical of current labeling						
Index admission						
Mean	12,485	14,532	−2,047	−4,536	+303	0.01
Median	9,034	10,039				
Follow-up						
Mean	7,513	5,679	1,834	−328	+3,936	0.16
Median	0	0				
Total episode						
Mean	19,998	20,211	−213	−3,495	+3,053	0.66
Median	13,046	13,960				

than or equal to \$50,000 per life-year gained is less than 68%, due primarily to the 28% of incremental cost-effectiveness estimates located in quadrants 2 and 3, where survival for levo is lower relative to SOC.

Discussion

REVIVE II compared levo and standard therapy with placebo and standard therapy for treatment of ADHF. Standard treatment consisted of physician-selected therapies used in treating AHF, such as diuretics, vasodilators, and inotropes. Our economic analysis of the REVIVE II trial demonstrates that the improved patient outcome for patients treated with levos as measured by the primary study endpoint was achieved at no increase in cost of treatment, and a trend to lower costs (Table 3). In the REVIVE II study subset corresponding to current labeling, there was better than 50% likelihood that levo was both cost-saving and offered improved survival relative to SOC.

Our cost-effectiveness results are contingent on the robustness of estimates for both the cost of treatment and long-term survival in the two study groups. While we

Fig. 2 Projected difference in cost of index hospital admission for patients treated with levosimendan (levo) relative to standard of care (SOC); sub-group of patients meeting current labeling (excludes patients presenting with systolic blood pressure <100 or diastolic blood pressure <60)

Fig. 3 Incremental survival and cost for levo relative to SOC with levo price \$700 per vial and survival based on CONSENSUS treatment group; results of bootstrapped cost-effectiveness analysis for the sub-group of patients meeting current labeling

lacked actual billing records, we employed a rigorous and complex procedure for estimating hospital costs, with data derived from a file of more than 100,000 similar heart failure patients, and state-of-the-art statistical methods.

On the other hand, our estimates of post-trial survival are somewhat speculative as they are grounded in data from rather small studies based on somewhat different patient

selection criteria, where outcomes reflect medical practice some 10–20 years in the past. Today's SOC includes not only angiotension-converting enzyme inhibitors (the study treatment for CONSENSUS) and beta-blockers (the study treatment for COPERNICUS), but also angiotensin receptor blockers, aldosterone antagonists, implantable cardioverter devices and cardiac resynchronization therapy. All of these

Fig. 4 Cost-effectiveness acceptability curve for the incremental cost-effectiveness (ICER) of levo relative to SOC; cost of levo \$700 per vial; subgroup of patients meeting current labeling

interventions tend to prolong survival, and longer duration of survival accentuates the absolute difference across treatment groups in number of patients alive at the end of the trial. Therefore the survival assumptions in our analysis are conservative.

One critical question is whether the current recommendation for cautious use of levo among patients who present with low blood pressure will confer the level of survival benefit as seen in our analysis of a REVIVE II subset that excluded these patients. Previous levosimendan trials such as LIDO [3], RUSSLAN [13], and SURVIVE [14] have all demonstrated some survival benefit. New trials or registry studies will be necessary to clearly address this issue of optimal patient selection. Higher mortality rates among patients with lower baseline BP have been observed in other clinical trials and registries of AHF [15–17].

In addition to informing clinicians and health care policy makers about the relative cost-effectiveness of levo, data from the REVIVE II study SOC group ($N = 301$) offers new information on current treatment patterns for ADHF. Seventy-five percent of patients had an index

admission length of stay of 10 days or less, with 5 or fewer days spent in the ICU/CCU (Fig. 5a); cost of the admission was \$15,000 or less (Fig. 5b). Costs for the most expensive 5% of cases in the SOC group spanned an extremely wide range from \$45,000 to \$527,000. Among the six cases where cost of admission exceeded \$100,000, three patients underwent heart transplants and three received left-ventricular assist devices (LVAD); one of these patients experienced both LVAD placement and heart transplant. Although the majority of SOC patients had relatively short and inexpensive hospital stays, these were in general very sick patients as more than half had been readmitted to hospital by the end of the 90-day study period.

Conclusions

In the REVIVE II trial, patients treated with levo had shorter length of stay and lower cost for the initial hospital admission relative to patients treated with SOC. The economic analysis presented here suggests that, when

Fig. 5 **a** Distribution of index hospital admission length of stay [total and intensive care unit (ICU)/coronary care unit (CCU)] in the REVIVE II intent-to-treat (ITT) SOC group. **b** Distribution of index hospital admission cost in the REVIVE II ITT SOC group

administered per the current label, levosimendan is efficacious and cost-effective relative to SOC. While levo represents an important new addition to the spectrum of treatments for ADHF, ongoing studies are needed to fully characterize this innovative compound and further refine its optimal place in therapy. Overall results of the REVIVE II trial underscore the enormous challenges clinicians face in the management of heart failure, and the urgent need for advances in both acute care of the patient in crisis, and continuing care for patients at high risk of rehospitalization.

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References

- Rosamond, W., Flegal, K., Friday, G., et al.: Heart disease and stroke statistics—2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* **115**, e69–e171 (2007). doi:[10.1161/CIRCULATIONAHA.106.179918](https://doi.org/10.1161/CIRCULATIONAHA.106.179918)
- Bayram, M., De Luca, L., Massie, M.B., Gheorghiade, M.: Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. *Am. J. Cardiol.* **96**, 47G–58G (2005). doi:[10.1016/j.amjcard.2005.07.021](https://doi.org/10.1016/j.amjcard.2005.07.021)
- Follath, F., Cleland, J.G., 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* **360**, 196–202 (2002). doi:[10.1016/S0140-6736\(02\)09455-2](https://doi.org/10.1016/S0140-6736(02)09455-2)
- Packer, M.: REVIVE II: Multicenter Placebo-controlled Trial of Levosimendan on Clinical Status in Acutely Decompensated Heart Failure. In: Program and abstracts from the American Heart Association Scientific Sessions 2005 Dallas (2005)
- de Lissovoy, G., Fraeman, K., Sterz, R., Durtschi, A., Mullahy, J.: Estimating cost of hospital treatment for patients in a randomized clinical trial. In: Presented at the International Health Economics Association's 6th World Congress: Explorations in Health, Copenhagen (2007)
- Emmett, D., Forget, R.: The utilization of activity-based cost accounting in hospitals. *J. Hosp. Mark. Public Relat.* **15**, 79–89 (2005). doi:[10.1300/J375v15n02_06](https://doi.org/10.1300/J375v15n02_06)
- Manning, W.G., Basu, A., Mullahy, J.: Modeling Costs with Generalized Gamma Regression [working paper]. Available at: <http://www.src.uchicago.edu/prc/pdfs/manning02.pdf>. (2007)
- Ramsey, S., Willke, R., Briggs, A., et al.: Good research practices for cost-effectiveness analysis alongside clinical trials: the ISPOR RCT-CEA Task Force report. *Value Health* **8**, 521–533 (2005). doi:[10.1111/j.1524-4733.2005.00045.x](https://doi.org/10.1111/j.1524-4733.2005.00045.x)
- Swedberg, K., Kjeksus, J., Snapinn, S.: Long-term survival in severe heart failure in patients treated with enalapril. Ten year follow-up of CONSENSUS I. *Eur. Heart J.* **20**, 136–139 (1999). doi:[10.1053/ehj.1998.1098](https://doi.org/10.1053/ehj.1998.1098)
- Cleland, J.G., Takala, A., Apajasalo, M., Zethraeus, N., Kobelt, G.: Intravenous levosimendan treatment is cost-effective compared with dobutamine in severe low-output heart failure: an analysis based on the international LIDO trial. *Eur. J. Heart Fail.* **5**, 101–108 (2003). doi:[10.1016/S1388-9842\(02\)00246-5](https://doi.org/10.1016/S1388-9842(02)00246-5)
- Packer, M., Coats, A.J., Fowler, M.B., et al.: Effect of carvedilol on survival in severe chronic heart failure. *N. Engl. J. Med.* **344**, 1651–1658 (2001). doi:[10.1056/NEJM200105313442201](https://doi.org/10.1056/NEJM200105313442201)
- Abbott Laboratories: Update SIMDAX Summary of Product Characteristics (SmPC) (2006). <http://www.abbott.com/>
- Moiseyev, V.S., 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 (RUS-SLAN). *Eur. Heart J.* **23**, 1422–1432 (2002). doi:[10.1053/ehj.2001.3158](https://doi.org/10.1053/ehj.2001.3158)
- Mebazaa, A., Nieminen, M.S., Packer, M., et al.: Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. *JAMA* **297**, 1883–1891 (2007). doi:[10.1001/jama.297.17.1883](https://doi.org/10.1001/jama.297.17.1883)
- Felker, G.M., Leimberger, J.D., Califf, R.M., et al.: Risk stratification after hospitalization for decompensated heart failure. *J. Card. Fail.* **10**, 460–466 (2004). doi:[10.1016/j.cardfail.2004.02.011](https://doi.org/10.1016/j.cardfail.2004.02.011)
- Fonarow, G.C., Adams Jr., K.F., Abraham, W.T., Yancy, C.W., Boscardin, W.J.: Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA* **293**, 572–580 (2005). doi:[10.1001/jama.293.5.572](https://doi.org/10.1001/jama.293.5.572)
- Gheorghiade, M., Abraham, W.T., Albert, N.M., et al.: Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* **296**, 2217–2226 (2006). doi:[10.1001/jama.296.18.2217](https://doi.org/10.1001/jama.296.18.2217)