Adv Ther (2012) 29(12):1037–50.
DOI 10.1007/s12325-012-0070-4

ORIGINAL RESEARCH

Economic Evaluation of Levosimendan Versus Dobutamine for the Treatment of Acute Heart Failure in Italy

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Received: October 18, 2012 / Published online: December 6, 2012

ABSTRACT

Introduction: Inodilators are the first-choice class of drugs for the treatment of acute heart failure (AHF). Levosimendan is a relatively recent inodilatory agent, presenting superior outcomes in comparison with traditional inotropes.

Methods: An economic evaluation of levosimendan for the treatment of AHF in Italy was performed. In a retrospective study conducted on patients with AHF admitted to a teaching hospital in Rome, two groups were derived from an observational registry: 147 patients treated with levosimendan and 145 treated with dobutamine. Follow-up was at 1 year after treatment. In the reference study looked at in this paper, treatment with levosimendan reduced mean length of stay (LOS) by 1.5 days ($P < 0.05$). Reduction in the rehospitalization rate was 6.7% ($P < 0.05$). Mortality rate at 1 month was reduced by 4.8% ($P < 0.05$).

Results: Based on the reference study, a cost analysis from the hospital perspective was carried out. The incremental cost of treatment with levosimendan (€697) was equivalent to the incremental savings (€694), the latter being obtained from the reduction in LOS (€508) and rehospitalization rate (€186).

Conclusion: Despite the limitations of this study, and even neglecting all nonmonetary health gains as additional outcomes, levosimendan appears to be a competitive alternative compared with dobutamine for the treatment of AHF in the Italian hospital setting.

Keywords: Acute heart failure; Cardiology; Cost analysis; Heart failure; Inodilators; Italy; Length of stay; Levosimendan; Rehospitalization rate

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INTRODUCTION

Among cardiovascular diseases, heart failure (HF) is sometimes referred to as a "final stage" condition. The prognosis is poor, with a mortality rate of approximately 50% within the first 5 years following diagnosis [1]. HF is a complex clinical syndrome that can result from any structural or functional cardiac or noncardiac disorder, which leaves the heart unable to pump blood to match the bodies requirements. Acute HF (AHF) may be either de novo HF or worsening (decompensation) of chronic HF, both requiring urgent care [2].

The incidence and prevalence of HF increases with age, affecting more women than men (higher incidence in women may be due to men dying earlier, typically from myocardial infarction). Therefore, with the ongoing aging of the population, the disease is more and more widespread, notably in the industrialized world [3]. In the USA in 2006, the prevalence of HF in the general population was approximately 2%, with hospitalizations amounting to 1.1 million (0.4%) [1].

Due to a lack of more specific data, the number of hospitalizations can be taken as an order of magnitude of the incidence of HF in Italy. A simplified but reliable indicator of the overall hospitalization activity for HF in Italy is the number of admissions in regular wards (including intensive care units [ICUs]/cardiac care units [CCUs], and excluding day hospitals), which are identified by the diagnosis-related group (DRG) code 127 (HF and shock). Data provided by this indicator for the years 2001 to 2003 amounted to approximately 90% of total HF hospitalizations estimated in an ad-hoc study, with more refined methods for the same years in Italy [4]. This number increased from 170,765 in 2000 to 198,614 in 2005 (+16.4%), and consequently to 203,885 in 2010 (+2.7%) [5], suggesting a possible trend slowdown as has already occurred elsewhere [6, 7]. Since 2002, DRG 127 has been second in the ranking of the top 10 DRGs by number of admissions; yearly admissions corresponding to DRG 127 amounted to 0.3% of the Italian population [8] and 2.6% of all hospitalizations of acute patients in regular wards [5].

The financial burden of HF is high. Direct medical costs (of which two-thirds are due to hospitalizations) are 1–2% of the overall health expenditure in developed countries [9]. In the USA, the estimated hospitalization costs in 2008 amounted to $18.8 billion, corresponding to 0.9% of the overall health expenditure [1]. With regard to Italy in 2008, the tariff of DRG 127 was multiplied by the respective number of hospitalizations, and a cost value was obtained (€618 million), corresponding to 1.2% of the total hospital public expenditure [5, 8]. The tariff chosen for this estimate was the mean value of the regional DRG tariffs in Italy, weighted with the corresponding number of admissions [10].

In the management of AHF, an ideal strategy is to increase myocardial contractility without increasing oxygen consumption due to increased aortic pressure. This dual goal is pursued by inodilators, a class of drugs that increase contractility and cause vasodilatation [11]. Inodilators are the first-choice class of drugs for the treatment of AHF. Levosimendan is a relatively recent inodilatory agent combining positive inotropic and vasodilating actions through its calcium-sensitizing and potassium-channel opening effects. The mechanism for such an accomplishment is novel [12, 13].

A number of studies have been published on the safety and efficacy of levosimendan, administered as initial treatment to hospitalized patients. Indeed, the body of evidence is one of the largest ever produced regarding a new agent for the treatment

Table 1 Major studies on levosimendan

Study[a]	Sample size, *N*	Control	Follow-up (months)	Results (for levosimendan)	Reference
LIDO	203	Dobutamine	6	Better hemodynamic performance and lower mortality	[15]
RUSSLAN	504	Placebo	6	Reduced risk of worsening heart failure and death	[16]
CASINO	199	Dobutamine, placebo	6	Improved survival	[17]
REVIVE II	600	Placebo	3	Improved clinical status	[18]
SURVIVE	1,327	Dobutamine	6	No significant reduction in all-cause mortality	[19]

CASINO Calcium Sensitizer or Inotrope or None in Low-Output Heart Failure Study, *LIDO* Levosimendan Infusion versus Dobutamine study, *PERSIST* Oral levosimendan in patients with severe chronic heart failure, *REVIVE* Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy Versus Placebo in the Short-Term Treatment of Decompensated Heart Failure, *RUSSLAN* 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, *SURVIVE* Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support Study

[a] Levosimendan was administered intravenously (bolus or continuous infusion) similar to most published trials. The PERSIST study [20] is not included here because levosimendan was administered orally

of AHF [14]. The main studies are summarized in chronological order in Table 1 [15–20].

In a recent literature review of intravenous levosimendan, all 45 randomized clinical trials published on levosimendan and reporting mortality data were selected (which included 5,480 patients), and an in-depth meta-analysis was performed (the most comprehensive and statistically robust to date) [14]. The most frequent comparators were dobutamine or placebo, and other comparators were other inodilators (milrinone, enoximone), prostaglandin E1, or no comparator. The findings showed, both overall and in different subgroups, survival gains in patients receiving levosimendan and a reduction in length of stay (LOS) in patients treated for AHF.

Despite these gains, when compared with dobutamine, levosimendan is perceived as an expensive alternative. The objective of the present study was to perform an economic evaluation of levosimendan for the treatment of AHF in Italy.

METHODS

The Reference Study

The present analysis uses Italian clinical data. It is based on a retrospective study conducted on patients with AHF who had been admitted to a major teaching hospital located in Rome (the Department of Cardiovascular, Respiratory, Nephrologic and Geriatric Sciences, "La Sapienza" University of Rome, Policlinico "Umberto I") [21]. Between July 2006 and April 2009, the clinic treated 908 patients with AHF. A total of 147 consecutive patients treated with an infusion of levosimendan were derived from the observational registry, with a

follow-up of 1 year after treatment. As a control group, 145 patients with well-matched baseline characteristics [21] who had been treated with dobutamine in the same unit and over the same period of time were identified a posteriori. The use of established therapies, such as angiotensin-converting enzyme inhibitors, diuretics, and beta-blockers, was permitted in both groups. The assignment of each patient to the initial treatment (levosimendan or dobutamine) had been made with no randomization process and on the judgement of the attending cardiologist.

The mean LOS was significantly ($P < 0.05$) shorter in the levosimendan group (12.1 days) than in the dobutamine group (13.6 days), with a reduction of 1.5 days ($P < 0.05$). Favorable outcomes in the former group were also achieved with regard to the mortality rate at 1 month (2.1% vs. 6.9%; $P < 0.05$; rate reduction: 4.8%) and the readmission rate at 12 months (7.6% vs. 14.3%; $P < 0.05$; rate reduction: 6.7%).

The Economic Analysis

The present evaluation was conducted as a cost analysis (though not as a cost-minimization analysis, since efficacy is not equal between the competing treatments considered here). In this approach, the comparative costs and savings of alternative treatments were analyzed from the perspective of the payer [22]. This analysis did not take into account the above-mentioned benefits of levosimendan in improving symptoms and reducing mortality versus dobutamine. Instead, its approach allowed the payer to assess the economic impact of levosimendan treatment and to make a rational choice among alternatives.

The economic evaluation was performed from the hospital perspective, comparing hospital costs with levosimendan versus dobutamine treatment. The cost of levosimendan is not reimbursed by the Italian National Health Service (NHS) to hospitals where the drug is administered to patients with AHF. In strict budgetary terms, it would then make no difference to the NHS whether levosimendan is used as an alternative to other inodilators or not, as no incremental payment would, in any case, be borne by the NHS. Accordingly, the economic perspective of the analysis cannot be that of the NHS; it has to be shifted to the hospital – the real decision-maker and payer for the use of levosimendan (levosimendan has been approved in Italy for hospital use only).

Possible Cost Savings for Hospitals from Better Effectiveness of Levosimendan

Considering drug costs only, a hospital might not be inclined to choose levosimendan because of its relatively high (and not reimbursed) acquisition cost. However, the situation might be different if the incremental drug cost was offset by the savings coming from the superior effectiveness of the drug compared to other treatments; such savings would either be in the form of cost reduction (from LOS reduction) or in the form of more revenues (from reduced rehospitalization rate).

Savings from LOS Reduction

A DRG tariff is constant (up to a point), and a hospital is paid even when variable costs for the patient's care cease following discharge. Such "undue" coverage (arising when the patient is discharged in advance compared to a LOS taken as reference) corresponds to a gain for the hospital. This is not true with regard to fixed costs, such as overheads and medical staff, which are not linked to individual hospitalizations; in this case, the coverage of such costs by the DRG tariff is justified regardless of the actual LOS.

Ideally, savings in the variable costs due to LOS reduction should be measured on the basis of the average variable cost per day of a patients stay (including drugs, subsidiaries, diagnostic tests and procedures, and hotel costs), with reference to a cardiology department. However, as these types of specific data are generally unavailable in Italy (or ad-hoc research would be required), they were evaluated in the present study using the above-mentioned gain as a proxy. For the sake of precision, it should be pointed out that an average value would overestimate the correct value, due to the right-skewed distribution of the variable cost as a function of the in-patient stay time [22]. However, a precise estimate could not be attained in the present study.

Savings from a Reduction in Rehospitalization Rate

As far as a full occupancy assumption can be made of beds in a cardiology department, further savings might be derived from the superior effectiveness of levosimendan. The reduction of the rehospitalization rate means that fewer admissions for AHF (i.e., classified with DRG 127) will occur in the department. If the beds released are then occupied by patients with a higher (on average) DRG tariff, there would be revenue for the hospital. The point is then to compare the DRG 127 tariff with the average tariff calculated on the DRG mix in the department.

In contrast, without a full bed occupancy situation, that is in a context with lesser demand for hospitalizations, new admissions would not need to compete for beds. In this sense, the reduced rehospitalization rate of admissions classified with DRG 127 would provide no additional revenue to the hospital.

A numerical example might be useful to grasp this issue. As a start, the authors assume that a cardiology department is equipped with 100 beds and works at 100% occupancy. In this case, a 10% reduction in the rehospitalization rate when patients are treated with levosimendan means that 10 beds will be released and will most likely be occupied by other patients, with an expected disease distribution according to the activity mix of the department. Whereas, if the 100 beds occupancy is at 90%, by definition the 10 beds left free will remain redundant. If the occupancy is at 95%, 95 beds will be occupied and five will remain unoccupied. On these grounds, the necessary condition for additional revenue from the discussed reduction in rehospitalization rate could be formulated as: occupancy rate >100% – reduced rehospitalization rate. If the reduction in rehospitalization rate is ≤0 then the condition cannot be satisfied and there is no revenue. Otherwise, if the condition is satisfied, if occupancy rate = 100% then the revenue is full; if occupancy rate <100% then the revenue can only be partial.

However, the situation is not exactly like this in practice. The reason is that the department activity involved with DRG 127 (that is, where the reduction in rehospitalization rates occurs) is generally only a subset of the whole activity of the department, which has a mix of DRGs. Therefore, a rate reduction of 10% does not mean 10 beds are left free; fewer beds will be free because that rate does not refer to the 100 beds of the whole department, but only to the subset with DRG 127. The number of beds actually released will ultimately depend on the proportion of the number of admissions for AHF divided by the total number of admissions included in the mix of the department.

The Model

The present analysis was of an incremental type, confronting the cost difference between the two in-hospital therapies (levosimendan and

dobutamine, respectively) with the analogous savings difference. Costs and savings are referred to one patient/treatment case. The outcome of the analysis can then be defined as:

$$NS = (S_L - S_D) - (C_L - C_D)$$

The definitions in the model are: net savings (NS); savings from using levosimendan (S_L); savings from using dobutamine (S_D); cost for using levosimendan (C_L); cost for using dobutamine (C_D).

Costs

With regard to treatment costs, in the present study the DRG 127 tariff is considered as a proxy of the costs borne by a hospital for the hospitalization of one patient with AHF. As such, we have:

$$C_L = T_{127} + V_L$$
$$C_D = T_{127}$$

The definitions in the model are: DRG 127 tariff (T_{127}); cost of one vial of levosimendan, not included in the DRG 127 tariff (V_L).

Savings

With regard to the savings, the DRG 127 tariff (defined in the model as T_{127}) is to be considered as the revenue a hospital receives for the hospitalization of a patient with AHF. This kind of revenue is common to both therapies.

Furthermore, there are two possible savings (for levosimendan therapy only) stemming from its higher effectiveness.

Savings from LOS Reduction

The savings corresponding to each discharge occurring in advance due to levosimendan are evaluated in two steps. First, a nominal "daily" DRG tariff is calculated by dividing the DRG 127 tariff by the average LOS. Second, the result is multiplied by the LOS reduction; i.e., by the number of days for which the hospital is reimbursed after the patient has been discharged (1.5 days in the reference study [21]). The definition used in the model is: savings from LOS reduction due to levosimendan (S_{LOS}).

As already pointed out, such additional revenue is not net revenue. Actually, only a quota should be taken into account corresponding to the variable costs, but this operation is hardly feasible as, as already stressed, variable costs in a hospital department are very difficult to estimate. Consequently, the savings are overestimated.

Savings from a Reduction in Rehospitalization Rate

Clearly, the additional revenue for each treatment with levosimendan (instead of dobutamine) is not the entire difference between the average tariff of the DRG mix in the cardiology department and the DRG 127 tariff. It would only be so when any treatment with dobutamine was followed by a rehospitalization and any treatment with levosimendan was followed by no rehospitalization (i.e., if the reduced rehospitalization rate due to levosimendan was 100%). Instead, the amount will be proportional to the actual reduction assessed in the rehospitalization rate (6.7% in the reference study [21]). Such amount is defined in the model below (savings from rehospitalization rate reduction due to levosimendan [S_{RRR}]).

Total savings:

$$S_L = T_{127} + S_{LOS} + S_{RRR}$$
$$S_D = T_{127}$$

Net savings:

$$NS = (S_L - S_D) - (C_L - C_D)$$
$$NS = [(T_{127} + S_{LOS} + S_{RRR}) - T_{127}] - [(T_{127} + V_L) - T_{127}]$$
$$NS = S_{LOS} + S_{RRR} - V_L$$

Further Data

In order to evaluate the magnitude and the plausibility of the above mentioned savings, the authors obtained further administrative data (Table 2) from the cardiology department of the "Umberto I" hospital.

These data were preliminarily processed for analysis. Average annual values were calculated between the 2 years reported (in order to simplify the analysis from cumbersome yearly details) and between the two settings (regular ward and ICU) to enable linking with the outcomes from the reference study (which are at the whole department level). The number of admitted patients was used for weighting LOS and bed occupancy rate data from the respective settings, and the number of discharged patients for weighting revenue data.

From the same source, the number of patients treated for AHF between 2006 and 2009 was obtained.

Unit Costs

The cost for one vial of levosimendan (€697) was taken from the reference study [21].

Following devolution of healthcare management from a national to a regional base, variation can be found among the local tariffs of a given DRG. With regards to DRG 127, an average data for Italy (€3,079) was calculated on the 2008 regional tariff values [8], weighted with the corresponding number of admissions [5]. The national average LOS (9.1 days), which was used to estimate a nominal "daily" DRG tariff, was also drawn from the same source [5]. In particular, the average revenue per discharged patient (based on data in Table 2) was adopted as a proxy for the average tariff of the DRG mix in the cardiology department (€5,885).

Sensitivity Analysis

The impact of possible variations in the estimated inputs of the model was tested with a one-way deterministic analysis. With regard to the reduction of LOS due to levosimendan, the low and high values of its 95% confidence intervals (CI) were respectively assumed. A similar approach was adopted for the reduction of the rehospitalization rate.

The nominal "daily" DRG 127 tariff overestimates the real savings from LOS reduction, because it includes a fixed-costs quota,

Table 2 "Umberto I" hospital: activity indicators for the cardiology department

Indicators[a]	Regular ward		ICU	
	2009	2010	2009	2010
Admitted patients, *n*	851	815	223	226
Discharged patients, *n*	1,032	976	97	108
LOS, days	7.0	7.7	13.2	11.4
Bed occupancy rate, %	100.7	99.1	97.1	100.6
Average revenue per discharged patient, €	5,615	5,562	8,094	8,810

ICU intensive care unit, *LOS* length of stay

[a] The discrepancies within each setting between admitted and discharged patients are chiefly explained by considering that many patients who are admitted to the ICU are later transferred to the regular ward, from which they are eventually discharged. Other inter-hospital transfers, as well as stays extending from 1 year to the following year, can account for the residual explanation

which cannot be considered additional revenue. As the real amount of such quota could not easily be known, the value inputted in the base case model was halved, as an approximate adjustment, in the sensitivity analysis.

The impact of a full occupancy assumption on savings due to the reduction in rehospitalization rate was tested conjecturing that in the narrow interval of a 100% occupancy the attenuation of the assumption might imply that the savings specifically due to the reduction in rehospitalization rates would linearly decrease from their full amount (corresponding to 100% occupancy) to zero (with occupancy outside the neighbourhood region). The neighborhood region was indicatively set between 100% and 100% minus 1.5%. The ratio between the number of hospitalizations with DRG 127 and the total number of hospitalizations with all DRGs related to cardiocirculatory diseases was

Table 3 Costs and savings (per one patient/treatment)

	Levosimendan	Dobutamine	Incremental values
Costs for treatment			
DRG 127 tariff (proxy for one hospitalization cost with standard care), €	3,079	3,079	0
Cost for one vial of levosimendan, €	697	0	697
Total costs, €	**3,776**	**3,079**	**697**
Savings from treatment			
DRG 127 tariff (revenue from one hospitalization cost with standard care), €	3,079	3,079	0
Savings from LOS reduction			
Average LOS, days	9.1		
Nominal "daily" tariff (of DRG 127), €	338		
LOS reduction due to levosimendan, days	1.5		
Additional revenue from LOS reduction due to levosimendan, €	508	0	508
Savings from rehospitalization rate reduction			
Average revenue per discharged patient (proxy for average tariff of DRG mix), €	5,885		
Difference between DRG mix and DRG 127 tariffs, €	2,776		
Reduction in rehospitalization rate due to levosimendan, %	6.7		
Additional revenue from reduced rehospitalization rate due to levosimendan, €	186	0	186
Total savings, €	**3,773**	**3,079**	**694**
Net savings, €	**−3**	**0**	**−3**

DRG 127 diagnosis-related group code 127 (heart failure and shock), *LOS* length of stay

about one-fifth in Italy in 2009 [10]. Assuming this ratio could approximately represent the analogous activity proportion in a cardiology department, it was used to weigh the reduction in rehospitalization rates (6.7%), obtaining approximately 1.5%.

The net savings of levosimendan versus dobutamine were then calculated for three scenarios:

1. 100% bed occupancy, corresponding to full savings from reduced rehospitalization rate due to levosimendan (base case)
2. 99.25% occupancy, corresponding to half savings
3. 98.5% (or less) occupancy, corresponding to no savings.

RESULTS

Base Case

The incremental cost of the treatment with levosimendan (€697; i.e., the cost for one vial) is in balance with the incremental treatment savings (€694) (Table 3). This benefit is the sum of two addends: the major addend (€508) stems from the LOS reduction (1.5 days), the other addend (€186) from the reduction in rehospitalization rate (6.7%).

Sensitivity Analysis

The outcomes from the sensitivity analysis are reported by decreasing order of impact magnitude in Table 4.

In the base case, the net savings value is approximately zero; as such, net savings resulting from the sensitivity analysis may sometimes take opposite values (positive/negative with respect to zero). More generally, in unfavorable conditions the cost of levosimendan is only partially balanced by savings.

Economic results appear to be most sensitive to LOS reduction (1.5 days). When such reduction was set at the highest value reasonably assumable (corresponding to the 95% CI higher limit), the treatment net benefit would increase to €470; whereas at the lowest value the loss would be as big, in absolute value. Of course, these values represent only the two extremes in the distribution of the likely net benefit values as a function of LOS reduction.

Table 4 Sensitivity analysis

	Variation range	Net savings at lower limit, €	Net savings at upper limit, €	Difference (impact magnitude), €
LOS reduction	95% CI	−474	470	944
Reduction in rehospitalization rate	95% CI	−187	180	367
"Daily" average tariff (DRG 127) adjustment	Halved amount (base case: full amount)	−257	−3	254
Full occupancy assumption attenuation	98.5% occupancy (base case: 100%)	−189	−3	186
Full occupancy assumption attenuation	99.25% occupancy (base case: 100%)	−96	−3	93

CI confidence interval, *DRG 127* diagnosis-related group code 127 (heart failure and shock), *LOS* length of stay

Relaxing the assumption of full occupancy in a cardiology department (i.e., considering an occupancy rate ≤98.5%), the net savings would be negative (–€189).

DISCUSSION

The present cost analysis was performed in order to evaluate the economic impact of levosimendan versus dobutamine for the treatment of AHF, from the perspective of an Italian hospital. This perspective was chosen on consideration that the cost of levosimendan is not reimbursed to hospitals by the Italian NHS, so an analysis from the perspective of the NHS would not be realistic. Actually, levosimendan is not a new treatment, which is not currently reimbursed but is expected to become so. In this instance, it would make sense conducting an analysis from the NHS perspective by including the cost of the drug as the requested reimbursement price. On the contrary, levosimendan's life in the market has already reached the maturity phase, which makes it unlikely that a change in its reimbursement profile will happen.

This analysis exploits the real hospitalization outcomes from an Italian retrospective study [21]. As far as comparison is possible, such outcomes appear to be in line with those which are reported in published clinical trials of levosimendan [15–19] and in a comprehensive meta-analysis [14], in particular with regards to shortened LOS; the gain of 1.5 days reported by Fedele et al. [21] is the same as that reported by Landoni et al. [14]. In other words, all these clinical findings appear to be confirmed by a "real-life" clinical experience in Italy. A similar appraisal can be formulated about the consistency between the present analysis results and the conclusions of various economic evaluations of levosimendan [23–26].

Some limitations are present in the current analysis, mainly regarding the generalizability of its results. In fact, the sample size is reduced to one center, though of primary importance. Also, the plausibility of a full occupancy assumption in a cardiology department, introduced in the analysis to estimate savings from reduced rehospitalization rates, is confirmed only in the hospital where the reference study was conducted. On the other hand, for more general information no useful statistical sources were found. Ad-hoc questionnaires should otherwise have been administered to a sample of hospitals. In any case, the results of the present analysis can be correctly applied in a given cardiology department only after having tested its occupancy level.

Again, with regard to the study sample, the fact that the assignment of each patient to the initial treatment was made on the judgement of the attending cardiologist might have created a bias. Confounding by indication is a bias frequently encountered in observational epidemiologic studies of drug effects. Because the allocation of treatment in observational studies is not randomized and the indication for treatment may be related to the risk of future health outcomes, the resulting imbalance in the underlying risk profile between treated and comparison groups can generate biased results [27]. However, the consideration could be made that an expensive drug, like levosimendan, is given to the sicker patients, which would represent a "conservative" bias.

With regard to savings from LOS reduction, resulting data is to some degree overestimated since the calculation method which, for lack of specific information, had to be adopted bypasses the problem that the cost distribution is not uniform in time, but shifted to higher values in the first days. Due to this flaw, and to the

modest proportion of the number of days saved compared to the whole LOS, savings may have a lower impact.

Another limitation relates to unit cost data, which were preferably adopted at the national level (because this was more appropriate for the generalizability of results). There is, however, a lack of homogeneity between the tariff value adopted for the DRG 127 (a value at the national level) and the average revenue per discharged patient (a value assessed in the "Umberto I" hospital). The latter value was taken as a proxy of an average tariff of the DRG mix in an Italian cardiology department due to the difficulty of achieving a realistic estimate.

Using the reimbursement DRG tariffs as proxies of the true hospital costs is an approach that, though largely adopted at least in Italian research, is not recommendable as a method. However, it should be considered that true cost data were unavailable at the reference hospital, as is generally the case at most Italian sites. Moreover, this approach might be appreciated as far as true hospital costs vary from hospital to hospital; namely, faced with such variation, using the DRG tariff as a proxy could be accepted as a generalization, allowing a broader perspective in the analysis than the mere hospital where the study was performed.

The cost of dobutamine was not taken into account due to its relatively weak impact (treatment with the generic drug would only cost approximately €4.5 per patient) and assuming that, unlike levosimendan, it is reimbursed to hospitals through the DRG 127 tariff. Ultimately, costs were substantially balanced with savings in the present analysis.

A further benefit from the reduction in rehospitalization rate might be considered. The authors consider the preservation of the quality of life when a hospitalization (or, more specifically, the emergency that causes it) is avoided as an advantage for the patient and for the hospital. The considerations which follow have no pretension to extrapolate the results of this analysis to cost-effectiveness decisions; they are only aimed at giving some more, indicative elements of evaluation.

A quality-adjusted life year (QALY), 1 year of life in full health, can be given different monetary values [22]. The value conservatively considered in the present study corresponds to the lower limit of the range (€25,000–40,000 per QALY gained) indicated by Associazione Italiana di Economia Sanitaria (AIES) guidelines [28] as a threshold for the acceptability of a new health technology. AIES guidelines refer to threshold values implicitly or explicitly used in health systems comparable to the Italian NHS [29]. One-tenth of such amount (i.e., €2,500) could then be assumed as a rough measure of the value of a 10% change in a subject's quality of life.

No elicitation was performed in the reference study [21] on health state utility values in AHF, so data from other sources, which shall be reported here, have a purely orientative value.

In a study conducted from 1977 to 1997 in the UK, 5,102 patients with newly diagnosed type 2 diabetes were recruited [30]. For those patients who had experienced no diabetes-related complications, the mean tariff value (based on EuroQol Group [EQ]-5D utilities) for quality of life was 0.785. For a patient with a history of HF, the impact on such value was –0.108, corresponding to a loss in quality of life of about 14%.

A recent original research conducted in Italy presented that moving from a general health condition (mean tariff: 0.906) to a postinfarction condition (mean tariff: 0.727) resulted in a loss of approximately 20% of a patients quality of life. Moreover, it takes at least 1 year to make up for this loss [31].

Also in this latter study, the limitations in comparability are strong; the quality of life of a patient with AHF is lower than the general populations, and the AHF condition is different from a myocardial infarction. But in light of the study, as a first approximation, avoiding a hospitalization due to AHF might reasonably be worth €2,500 (as this amount was assumed to correspond to a 10% change in quality of life, which is smaller than a 20% loss due to a cardiovascular event) [31].

Following one treatment with levosimendan, rehospitalization is reduced by 6.7% (compared with dobutamine [21]). In these terms, a €2,500 × 6.7% = €165 additional gain could be deemed to correspond to that treatment. Of course, such benefit would be outside the hospital's strictly economic perspective (for this reason, it has been discussed but not included in the core of the evaluation). On the other hand, it should not be completely neglected by a decision maker who, like a hospital manager, is committed to patients' health and their health-related quality of life.

In accordance with this kind of argument, the reduction in the mortality rate at 1 month as a result of the treatment with levosimendan (2.1% vs. 6.9% [21]) should be appreciated too. Considering that in 2010 approximately 200,000 hospitalizations occurred with DRG 127 [5], almost 10,000 patients could be saved from death (at least at 1 month) every year. Notably, the survival benefits observed in the Italian study match those in the recent comprehensive meta-analysis [14].

CONCLUSION

For all the limitations discussed in this analysis, levosimendan appears to be a competitive alternative to dobutamine for the treatment of AHF in an Italian hospital setting.

ACKNOWLEDGMENTS

The study and article processing charges were funded by a grant from Orion Pharma Srl. The sponsor played no part in the study design or conduct; collection, analysis, interpretation of data; writing of the report; or in the decision to submit the paper to Advances in Therapy. The authors' work was independent of the funding provider.

All authors contributed to the design, analysis, and interpretation of data, had full access to all of the data, and were involved in drafting the article. All authors revised the article and provided final approval of the version to be published. Dr. Lucioni is the guarantor for this article, and takes responsibility for the integrity of the work as a whole. Native English editing was provided by Mary Hines, of inScience Communications, Springer Healthcare.

Conflict of Interest. Piero Pollesello and Marjo Apajasalo are employees of Orion Pharma. The remaining authors have no conflicts of interest to declare.

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