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Pharmaco-economics of levosimendan in cardiology: A European perspective

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ABSTRACT

Introduction: Heart failure places a significant economic burden on health care. Acute heart failure requires hospitalization and often frequent re-hospitalization in expensive wards where vasoactive rescue therapy is often added on top of standard medications.
In these lean times, there is a growing need for cost-effective therapeutic options that supply superior support and in addition shorten the length of stay in hospital and reduce re-hospitalization rates. The inodilator levosimendan represents the latest addition to the vasoactive treatments of acute heart failure patients, and it appears to meet these expectations.
Our aim was to answer the question whether the treatment efficacy of levosimendan – when selected as therapy for patients hospitalized for acute heart failure – brings savings to hospitals in various European countries representing different economies.
Methods and results: We took a conservative approach and selected some *a fortiori* arguments to simplify the calculations. We selected seven European countries to represent different economies: Italy, Spain, Greece, Germany, Sweden, Finland and Israel. Data on the costs of medications and on the cost per day were collected and fed in a simple algorithm to detect savings. These saving varied from country to country, from a minimum of €0.50 in Germany to a maximum of €354.64 in Sweden.
Conclusions: The use of levosimendan as a therapy for patients hospitalized for acute heart failure provides a net saving to hospitals driven by a reduction in the length of hospital stay. This finding is true in each of the countries considered in this study.

1. Introduction

Heart failure places a significant economic burden on society and health care system. In Western countries, direct medical costs of heart failure comprise 1% to 2% of overall health expenditure [1]. Two thirds of these disbursals are attributable to frequent and repetitive hospitalization due to episodes of cardiac decompensation [2,3]. This implies the need for cost-effective therapeutic options that shorten the length of hospital stay, and reduce re-hospitalization rates and in-hospital mortality.

The inodilator levosimendan appears to meet these expectations [4]. Its pharmacological effects include increased cardiac contractility, achieved without increased oxygen consumption, combined with vasodilation [5], which is often considered a suitable pharmacological strategy in acute heart failure when patients are 'wet and cold' [6]. In addition to these haemodynamic clinical improvements [7], levosimendan also enhances renal function [8,9] and was shown to have positive effects on survival [10–14]. Furthermore, a greater proportion of days spent alive and outside hospital [11] and shorter hospital stay [14–16] is achieved for levosimendan-treated patients compared to those who receive dobutamine or placebo.

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The pharmaco-economic aspects of levosimendan therapy have been previously addressed in studies that have described both cost-effectiveness and cost-reduction, using different well-established pharmaco-economic methods [4,16–20]. One of these was an evaluation by Lucioni et al. [4] that was based on a retrospective study conducted in patients with acute HF, who had been treated with either levosimendan (n = 147) or dobutamine (n = 145) at a teaching hospital in Rome. Compared to dobutamine, the administration of levosimendan significantly reduced the mean length of hospital stay (LOS) by 1.5 days, decreased the re-hospitalization rate by 6.7%, and the 1-month mortality rate by 4.8%. These data are in keeping with the data obtained in clinical trials on levosimendan [10,11,15,21,22], as well as in a meta-analysis [14].

Lucioni et al. [4] assessed the comparative hospital costs and savings of alternative treatments from the perspective of the payer, and compared the cost difference between the use of levosimendan and dobutamine with the analogous savings difference. The authors reasoned that hospitals might not be inclined to choose levosimendan because of its relatively high acquisition cost, but if the additional expense was offset by savings due to superior efficacy over other treatments, the situation might be different. The authors concluded that levosimendan appears to be a competitive alternative compared with dobutamine for the treatment of acute heart failure in the Italian hospital setting. The costs of hospitalization, however, vary from country to country.

A meeting of experts was held in Seville, Spain, on May 25, 2015, aimed at assessing the European perspective beyond the scope of the data of Lucioni et al. [4]. The panel set out to compare the results previously obtained in Italy, with similar data obtained in six other European countries: Spain, Greece, Germany, Sweden, Finland and Israel. The aim was to shed light on the overall pharmaco-economic consequences arising from the use of levosimendan for patients with acute heart failure and advanced heart failure with frequent hospitalization.

2. Methods

2.1. Type of economic analysis

This evaluation was conducted as a cost–benefit analysis (rather than a cost-minimization analysis, as the competing treatments considered here do not have the same efficacy). In this approach, the comparative costs and benefits (in terms of savings) of alternative treatments were analyzed from the perspective of the payer [23]. This analysis did not take into account the benefits of levosimendan for the improvement of patients symptoms and for the reduction of patient mortality versus the comparators, as those data are described elsewhere (for review, see Nieminen et al. [6]). Instead, the approach used here allows the payer to assess the cost impact of levosimendan treatment. The economic evaluation was performed from the hospital perspective, through a comparison of the hospital costs for the use of levosimendan versus other treatments in the cardiology setting.

2.2. Selected countries

Seven European countries were selected to represent different European economies: Italy, Spain, Greece, Germany, Sweden, Finland and Israel. Data were collected on the costs per day for the hospital wards and on the costs of therapies in those countries.

2.3. Cost savings for hospitals

Considering the drug costs only, a hospital might not be inclined to choose levosimendan, because of its relatively high acquisition cost. However, the situation might be different if proven that the incremental drug cost is offset by the savings from the improved treatment effectiveness of the drug compared to other treatments, particularly relating to the shorter hospitalization. Such savings would thus be in the form of cost reduction from length of stay (LOS) reductions.

In reimbursement systems based on diagnosis-related groups (DRGs), the reimbursement to the hospital is fixed (up to a point), and includes also costs for the patient ward care length, calculated from an average LOS. In case the patient is discharged in advance compared to the reference LOS, the system generates a gain for the hospital, while prolonged hospitalization makes a net loss. This is however not true with regard to some costs, such as the hospital overheads and medical staff, as these are not directly linked to the LOS.

Ideally, savings on the variable costs due to a LOS reduction should be measured on the basis of the average variable cost per day of a hospital stay (including drugs, subsidiary procedures, diagnostic tests, etc.), here with reference to a Cardiology Department. For the sake of precision, it should be noted 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 [18].

2.4. The assumptions

To simplify the model, we make some assumptions that are intended to be *a fortiori* arguments i.e. from yet stronger reasons. For example we set the effect of levosimendan on re-hospitalization rate as null, the effect of levosimendan on co-morbidities affecting hospital costs as null, and the effect of levosimendan on mortality as null. We intend to demonstrate in the following paragraphs that these assumptions can be used as arguments *a fortiori* as they are all conservative and exceeded by the data in the literature.

2.4.1. Cost of comparator treatment

We assume that the costs of the comparators (usually dobutamine, but in some case milrinone, enoximone, etc.) are as low as €30 per treatment. This sum was obtained by finding the lowest retail discounted price for an inotropic support treatment with the cheapest generic (dobutamine) within the seven countries considered in this study. As, in reality, these treatments do have a higher cost in all the other countries and in the majority of the hospitals, this is a valid *a fortiori* argument in the model. As a comparison, Cleland et al. [17] calculated – on the basis of the clinical trial LIDO and on the average prices in Denmark, Finland, France, Germany, The Netherlands, Norway, Sweden and the UK in year 2000 – that the cost of 24 hour treatment with dobutamine was €41.30 (i.e. 700 mg × 0.059 €/mg).

2.4.2. Overall cost of drugs

In the literature, it has been reported that the use of levosimendan in cardiology settings is associated with less use of rescue pharmacological treatments [15]. Again, for the sake of simplicity, in our model we assume that the overall difference in costs of the drugs (apart from levosimendan) for patients treated with levosimendan versus the comparator is null. This assumption is valid more so in cases when levosimendan is used on top of standard of care. For all of these reasons above we consider also this a valid *a fortiori* argument.

2.4.3. Re-hospitalization rate

Data obtained from the literature show that the use of levosimendan is associated with a reduction in re-hospitalization rates [11,20]. Thus, further savings might be derived in the heart failure patient care chain from this improved effectiveness of levosimendan, as shown by Lucioni et al. [4] However, this postulate remains fully valid only as far as a full occupancy assumption can be made for the beds in a Cardiology Department, whereas without a full bed occupancy situation, new admissions would not need to compete for beds. In the absence of a national average value of bed occupancy in the cardiology setting for acute heart failure hospitalization, we believe that considering the effect of levosimendan treatment on re-hospitalization as null is a useful and justified *a fortiori* argument.

2.4.4. Effects on co-morbidities that affect hospital costs

Data obtained from the literature show that the use of levosimendan is associated with a reduction in serious adverse events and comorbidities (e.g. cardiac failure [12], and renal complications [9]) that affect hospital costs. Thus, considering the effects of levosimendan treatment on this parameter as null is also a useful and justified *a fortiori* argument.

2.4.5. Variations in the costs of 'a day in hospital'

The costs of a 'day in hospital' vary with the level of the ward, from several thousand euros per day when an acute patient is treated in the intensive settings of a Cardiac Critical Care Unit, to some hundreds of euros per day when the patient is transferred to a cardiac ward at the end of his/her stay. Indeed, levosimendan is used during the acute phase, but many reports fail to show clear distinctions between the days spent in intensive cardiac units (more expensive) and the days spent in the post-acute cardiac wards (less expensive). In our calculation, we thus consider the costs of a 'day in hospital' in the cardiac ward (Table 1) as if all of the LOS benefits would be obtained in the later and less expensive phase of the hospital stay. We consider also this as a valid *a fortiori* argument.

2.5. The calculations

The analysis is an incremental type, with the comparison of the cost differences between two in-hospital therapies (levosimendan and the comparator, respectively) with the respective savings differences. Costs and savings are referred to one patient/treatment case. The outcome of the analysis can then be defined as:

$$NS = (S_L - C_L) \quad (1)$$

where

NS is the net savings
S_L is the benefit (savings) from using levosimendan versus the comparator
C_L is the additional costs for using levosimendan versus the comparator.

Table 1
Costs and savings of levosimendan treatment of patients hospitalized for acute heart failure.

Country	Costs (€)		Net savings (€)
	C_L[a]	Cardiac ward (per day)[b]	By using levosimendan[c]
Italy	648.86	416[d]	−12.58
Spain	598.79	421[e]	−70.60
Greece	487.07	361[f]	−86.92
Germany	715.00	450[g]	−0.50
Sweden	648.65	631[h]	−354.64
Finland	659.18	450[i]	−56.32
Israel	561.57	368[j]	−23.55

[a]Additional drug costs of a levosimendan treatment vs. comparator treatment calculated according to the text; [b]excluding the costs for levosimendan; [c]net savings considering a reduction of 1.59 days of stay in the cardiac ward obtained by levosimendan treatment; [d]calculated from DRG 127 in the ICD9-CM DRG classification [29]; [e]in 2013 according to RECH [30]; [f]calculated from the data by Parissis et al. [24]; [g]data calculated from the Fallpauschalen-Katalog for the relevant DRG codes (InEK 2014) [31]; [h]average cardiac ward cost at 'Akademiska sjukhuset', Uppsala, Sweden; [i]from HUS Palveluhinnasto 2015 [32]; [j]according to the Israeli Ministry of Health [33].

2.5.1. Costs

For the treatment costs, the DRG 127 tariff is considered as a proxy for the costs borne by a hospital for hospitalization of one patient with acute heart failure. This tariff is applicable to all patients, regardless of the treatment that they will receive. As the cost of one vial of levosimendan is not included in the DRG 127 tariff, we thus define C_L as the cost of one vial of levosimendan (which is the average dose for a single treatment) detracted by an assumed price for treatment with comparator (see Section 2.4.1) of €30. The costs for one vial of levosimendan were obtained from the local retailers that supply the hospitals in the countries considered in this study. These prices were an average over the retail prices in year 2014. All exchange rates, if the price was not in Euro, were the one of May 31, 2015.

2.5.2. Benefit (savings)

The savings (S_L) corresponding to each discharge that occurs in advance (i.e. shorter hospitalization) due to the use of levosimendan are evaluated by multiplying the LOS reduction, by the cost on one day in hospital.

$$S_L = \Delta LOS_L \times \text{daily hospital cost.} \quad (2)$$

As already indicated, this additional revenue is not net. Indeed, only a part should be taken into account corresponding to the variable costs, but this operation is particularly demanding since the variable costs in a hospital department are very difficult to estimate. In the fortunate case of Greece we relied on the data presented by Parissis et al. [24] who did calculate an average cost for AHF, an average LOS, and even indicated which percentage of the expenses were generated by fixed and variable costs.

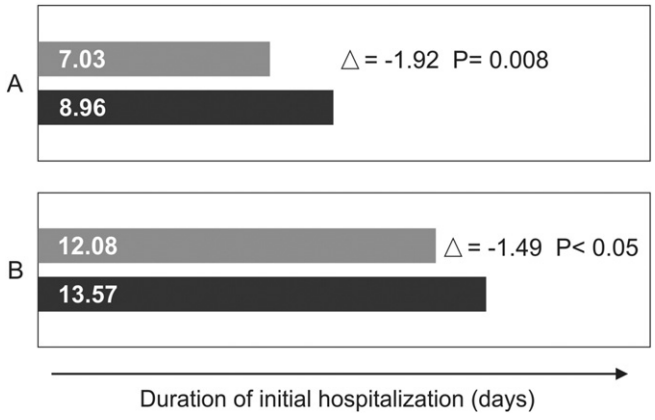

Fig. 1. Levosimendan, on top of standard of care, shortened the hospital stay for patients with acute heart failure in a phase III study vs. placebo (panel A, from de Lissavoy [16]), and in a single center large registry study vs. dobutamine (panel B, from Fedele [20]). Levosimendan (gray), dobutamine (black).

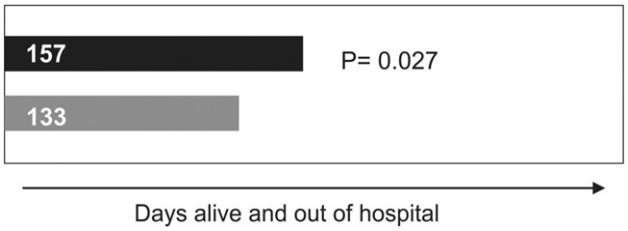

Fig. 2. The composite parameter 'days alive and out of hospital' in a phase III regulatory study of levosimendan vs. dobutamine (from Follath [11]). Levosimendan (gray), dobutamine (black).

2.6. The benefits in length of hospital stay

Levosimendan, on top of standard of care, shortens hospital stays for patients with acute heart failure. These data have been shown both in a phase III study (vs. placebo) [16] and in a single center large registry study (vs. dobutamine) [20] (see Fig. 1).

An earlier phase III regulatory study corroborates these conclusions by showing that the composite parameter 'days alive and out of hospital' was significantly in favor of levosimendan over dobutamine [11] (Fig. 2).

Finally, in a meta-analysis of the eight studies in which levosimendan was used in cardiology settings which reported LOS data, the LOS was decreased by 1.59 days for the levosimendan-treated patients in addition to a significant reduction in mortality [14] (Fig. 3).

For the sake of the present exercise we thus considered that levosimendan, when used in cardiology settings, shortens LOS by 1.59 days.

3. Results

We performed the calculations based on the algorithm and conservative assumptions described above, and obtained the level of net savings for the selected countries and for the ward environment considered (Table 1). In all cases, the choice of levosimendan was shown to be dominant over comparators; i.e. there is a net saving from the hospital perspective.

This saving varies from country to country, from a minimum of €0.50 in Germany to a maximum of €354.64 in Sweden.

4. Discussion

The model which we used here is a very simple approximation of a cost analysis. We intended to answer the question whether levosimendan, sold at the current price, consistently brings savings to hospitals in selected European countries when it is used as therapy for patients hospitalized for acute heart failure. We did not aim to quantify these savings, and therefore we used *a fortiori* arguments which by definition simplify the calculations at the price of losing the real value of the savings. Parameters such as the positive effects of levosimendan on the costs of additional drugs, on re-hospitalization, and on co-morbidity – which were neglected in our calculations – might have increased the savings figures. Similarly, we assumed that the reduction in LOS associated with the use of levosimendan was not due to less days spent in intensive cardiac units (more expensive) but to less days spent in the post-acute cardiac wards (less expensive). Indeed, a sign that levosimendan reduces also the LOS in intensive cardiac unit was seen in the regulatory Phase III study REVIVE [16]: in the levosimendan study arm the patients left the ICU 0.348 days earlier ($p = 0.63$) than in the control group (placebo on top of standard of care). Since the cost of one day in ICU varies between €1000 and €2500 in the European countries under scrutiny in this paper, this would lead to a much positive calculation of hospital savings of several hundred euros. In fact, according to the pharmaco-economic analysis of the REVIVE study (performed in the U.S.A. between 2003 and 2005 [15,16]), the cost differential favoring levosimendan was about $1800 ($P = 0.01$) for the sub-set corresponding to current labeling (patients with SBP ≥ 100 mm Hg).

Finally, data obtained from the literature show that the use of levosimendan in cardiology settings is associated with both an

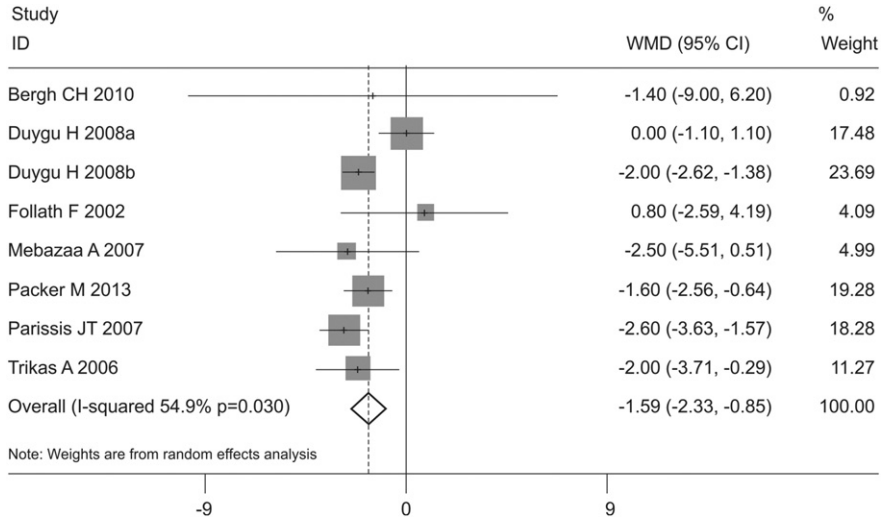

Fig. 3. Length of stay in hospital from a meta-analysis of eight studies of levosimendan in cardiology settings (adapted from Landoni [14]). WMD, weighted mean difference. Weights are from random effect analysis. The studies listed in the Forrest plot refer to the following publications: Berg 2010 [34], Duygu 2008a [35], Duygu 2008b [36], Follath 2002 [11], Mebazaa 2007 [22], Packer 2013 [15], Parissis 2007 [37], Trikas 2006 [38].

improvement in patient Quality of Life [25] and a reduction in patient mortality [14], which provides even stronger support for the rationale of using the drug.

An important limitation of this study is that in the countries selected for this exercise the hospital costs for acute heart failure are not available in the same form; sometimes they include the costs of drugs and diagnosis, sometimes not. A more exact calculation is warranted when such exact data on fixed and variable costs of hospitalization will be available for all countries.

Levosimendan is the 'first in class' of the calcium sensitizer and potassium channel opener family, and its current clinical development aims to take this treatment beyond the field of acute decompensated heart failure. It was demonstrated that levosimendan decreases infarct size in ischemia-reperfusion models [26] and improves survival in healed myocardial infarction models [27], and many clinical trials have followed to test the effects of this drug in cardiac surgery [28]. It should be noticed, however, that the present pharmaco-economic calculations were focused exclusively on the use of levosimendan in cardiac settings and cannot be applied directly to other settings, where both the costs and the effects of levosimendan will be most probably different. A separate analysis in those settings would be of great interest and is warranted.

5. Conclusions

The use of levosimendan for patients hospitalized for acute heart failure brings net savings to hospitals primarily due to the consistent reduction in LOS. Furthermore, these savings are gained in all of the European countries considered in the present study.

Author contributions

Three of the authors (MSN, MK, PP) independently performed the preliminary search for relevant publications. All of the authors contributed substantially to discussions of the existing literature, the costs and benefits, and the validity of the model. All of the authors, moreover, reviewed the manuscript before submission.

Conflict of interest

This project did not receive any financial support. PP and MK are employees of Orion Pharma. The other authors do not declare any conflict of interest.

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