European Heart Journal Supplements (2017) **19** (Supplement C), C15–C21
The Heart of the Matter
doi:10.1093/eurheartj/sux003

The potential of the inodilator levosimendan in maintaining quality of life in advanced heart failure

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KEYWORDS
Levosimendan;
Inodilatation;
Quality of life;
End-of-life;
Advanced heart failure;
Repetitive dosing

Maintaining adequate quality of life (QoL) is an important therapeutic objective for patients with advanced heart failure and, for some patients, may take precedence over prolonging life. Achieving good QoL in this context may involve aspects of patient care that lie outside the familiar limits of heart failure treatment. The inodilator levosimendan may be advantageous in this setting, not least because of its sustained duration of action, ascribed to a long-acting metabolite designated OR-1896. The possibility of using this drug in an outpatient setting is a notable practical advantage that avoids the need for patients to attend a clinic appointment. Intermittent therapy can be integrated into a wider system of outreach and patient monitoring. Practical considerations in the use of levosimendan as part of a palliative or end-of-life regimen focused on preserving QoL include the importance of starting therapy at low doses and avoiding bolus administration unless immediate effects are required and patients have adequate baseline arterial blood pressure.

Introduction

Patients with advancing/worsening chronic heart failure (HF) experience deterioration of health-related quality of life (HRQoL) over time. One recent investigation of this issue found correlations between New York Heart Association (NYHA) class and all HRQoL domains,[1] with particular impact being observed in the domains of sleep and self-reported energy in the acute phase and in the energy domain at 6 months. Strikingly, an improvement in disease severity was not always accompanied by an improvement in HRQoL, suggesting that while decompensation of HF may be the factor that precipitates a decline in HRQoL, haemodynamic or arrhythmia-based influences may contribute to its persistence once established. Neuroendocrine activation including, but not necessarily limited to, the renin–angiotensin–aldosterone system, elevation of sympathetic nervous activity, vasopressin and a range of biomarkers including natriuretic peptides and cystatin-C may be another set of stress-response reasons for this disjunction. Others include depression and social function disability, which may persist even after overt physical symptoms associated with HF-impaired HRQoL have been resolved. These lead to inactivity-acquired weakness. Observations from HF unit patients indicate that this may be persistent and contribute to diminished functional capacity and HRQoL.[2] Data in HF suggest that a similar process may affect diaphragm function and hence respiration and dyspnoea.[3]

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Table 1 Effects of inotropic and vasoactive therapies currently used in clinical practice on outcomes in patients with advanced decompensated HF. Reproduced with permission from Nieminen *et al.*[23]

Therapy	Haemodynamics		Neurohormones	QoL-related parameters				Survival
	Cardiac index	Congestion/ PCWP		Dyspnoea	Rehospitalization rate	Depression	MLHFQ/ KCCQ	
Dobutamine	↑↑	↓	↓	↓	↑	n.d.	n.d.	↓
Milrinone	↑↑	↓↓	—	↓	—	n.d.	n.	↓
Levosimendan	↑↑	↓↓	↓	↓	↓	↓	↓	↑
Nitroprusside	↑	↓↓	↓	↓	—	n.d.	n.	↑
Nesiritide	↑	↓↓	↓	↓	—	n.d.	n.	—

QoL, quality of life; PCWP, pulmonary capillary wedge pressure; MLHFQ, Minnesota Living with Heart Failure Questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire; n.d., not determined; n., neutral.

Features of advanced heart failure

Advanced heart failure (AdHF) is defined by severe symptoms of HF (NYHA class IIIb or IV); episodes of fluid retention and/or peripheral hypoperfusion; objective evidence of severe cardiac dysfunction; severe impairment of functional capacity; history of one or more HF hospitalizations in the past 6 months; and the presence of all of the above features despite attempts to optimize therapy.[4] These features undermine HRQoL; they also lead to more frequent hospitalizations and a more prolonged length of stay which themselves diminish HRQoL and are major contributors to the cost of managing HF.

Targets of medical therapy designed to improve HRQoL in patients with advanced HF with reduced ejection fraction (EF) include:

- Pulmonary capillary wedge pressure (PCWP) <20 mmHg (preferably 16–18 mmHg)
- Cardiac index >2.0
- Systolic blood pressure (SBP) >100 mmHg (although some patients will tolerate a markedly lower mean pressure)
- Resting heart rate (HR) 70–75 beats/min (maximum rate at exercise usually <140 beats/min)
- Mean pulmonary artery pressure <20 mmHg
- Control of symptoms and signs of congestion.

The 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic HF[5] provide a comprehensive discussion of all aspects of optimal medical therapy. Optimization of background medical therapy is important for the attainment of the goals identified above. Diuretics are usually required in all patients; a combination of neuro-hormonal antagonists—angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), beta-blockers (BB) and spironolactone [or an equivalent mineralocorticoid antagonist (MCA)]—is indicated for most patients unless there are specific contrary circumstances. It should be noted that whereas ACE inhibitors, ARBs, BB and MCAs are used on the basis of their proven effects on mortality and morbidity, the use of diuretics rests on their capacity to improve symptoms and exercise capacity in patients with signs and symptoms of congestion.[5]

Ivabradine is recommended to prevent readmissions in symptomatic patients who have EF <35% in sinus rhythm and HR >70 beats/min.

Digoxin is no longer suited to general use but retains a role for rate control in atrial fibrillation or to enhance symptoms and signs and reduce hospitalization of advanced HF patients already on optimized medical therapy (OMT).

Pacemakers should be considered for bradycardia and resynchronization therapy should be used in order to improve symptoms and reduce morbidity and mortality in patients with reduced left ventricular ejection fraction (LVEF ≤35%), left bundle-branch block, and a QRS duration ≥130 ms who remain symptomatic after at least 3 months of OMT; an implantable cardioverter-defibrillator (ICD) is indicated in order to reduce mortality (including sudden death) in symptomatic HF patients with LVEF ≤35% (despite at least 3 months of OMT). However, there is no indication for an ICD within 40 days of a myocardial infarction because implantation at this time does not improve prognosis.[5]

Advanced HF (NYHA class IV) with <1 year of life expectancy is a contraindication to an ICD, unless the patient is eligible for a transplant or a left ventricular assist device (LVAD).[5]

Inodilator uses in AdHF

Patients who are hospitalized due to a severe decompensation of AHF often have their medical therapy supplemented with inotropes, inodilators, or vasodilators. These agents have been used as palliative interventions or as part of a 'bridge to transplant' approach. Their effects on endpoints related to HRQoL have also been described, although to date incompletely (*Table 1*).

Other drugs that merit attention in this context include nesiritide,[6,7] carperitide,[8] the vasoactive peptide hormone serelaxin,[9,10] and ularitide, a synthetic natriuretic peptide hormone.[11] At present, however, experience with all these drugs is limited. Liraglutide would appear to have no role in this situation.[12]

Levosimendan emerges from this preliminary comparison with an attractive profile in the context of HRQoL (*Table 1*). In contrast to chronic or repeated use of dobutamine[13] or milrinone,[14] use of levosimendan as intermittent or repeated therapy is not associated with

increased mortality and may indeed be associated with improved survival;[15] levosimendan has a long duration of action (exerted via its long-acting active metabolite OR-1896[16]), which may be a practical advantage, and unlike dobutamine is not associated with the development of tachyphylaxis.

Levosimendan has at least three mechanisms of action relevant to its haemodynamic and cardiovascular effects:[16]

(1) Enhancement of the calcium sensitivity of the myofilament by binding to troponin C.
(2) Opening of adenosine triphosphate-sensitive potassium (K_{ATP}) channels in vasculature smooth muscle.
(3) Opening of mitochondrial K_{ATP} channels.

Levosimendan augments cardiac index, stroke volume and coronary blood flow and reduces PCWP.[17]

Levosimendan was developed in the 1990s as a therapy for acute decompensated chronic HF. However, due to the recurring nature of acute decompensation and the associated frequency of rehospitalization in the late phase of the chronic HF syndrome (AdHF), levosimendan started to be used more than once during the patient journey. This stimulated interest in the potential benefits of repetitive or intermittent doses of levosimendan as a means of preventing lapses into acute decompensation. In one early long-term (6 months) investigation of intermittent use, levosimendan was associated with significant reductions in ventricular volumes and the severity of mitral regurgitation, whilst having no adverse effects on the incidence of ventricular arrhythmias.[18] Levosimendan has also been shown to confer positive effects on renal function.[19,20]

Patients who could benefit from levosimendan treatment

According to a panel of experts,[21] indications for repetitive use of levosimendan in chronic AdHF include:

- Severe systolic dysfunction (LVEF $<$35%)
- and/or NYHA IIIb–IV and/or INTERMACS levels 4–6
- and/or repeated hospitalization or emergency department visits ($\geq$2 in the past year)
- All of the above despite optimal treatment for HF.

As an example, suitable patients who may be candidates for intermittent levosimendan therapy include those who are listed for heart transplantation or implantation of a LVAD, and those with similar characteristics who are not eligible for those procedures. In the first instance, levosimendan is one element of a 'bridge to definitive intervention' strategy: in that situation, the treatment goal is preservation of organ function. In the second category of patients, the priority is the stabilization and well-being of the patients and the avoidance of rehospitalization. This latter use may be thought of and spoken of as 'palliative' but the term 'end-of-life care' is to be preferred because, in contrast to oncology, the length of the end-of-life phase of HF is variable and hard to predict. The emergence of a new staging system for HF is a welcome innovation in this regard[22] but is only one part of an evolution of approaches to care that still has a way to go.

Practicalities of intermittent levosimendan

The feasibility and general safety of intermittent levosimendan treatment in the management of patients with AdHF have been established in studies such as that of Mavrogeni *et al.*[18] and Levo-Rep[23] and further evaluation is underway in studies such as LION-HEART (ClinicalTrials.gov identifier: NCT01536132). Some general principles for use have been proposed,[21] framed by the recognition that patient characteristics and responses to treatment vary considerably:

(1) Doses in the range 0.05–0.2 μg/kg/min for 6–24 h every 2–4 weeks should be used.
(2) Treatment can be started at a low dose, which can be increased stepwise during the treatment phase.
(3) The maintenance infusion rate may be down-titrated if adverse events occur.
(4) Bolus dosing should be administered only if immediate effects are required and if SBP exceeds 100 mmHg. Exclusion of routine bolus dosing can be expected to minimize the risks of hypotension and arrhythmias, as were reported from the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support[24] and Randomized EValuation of Intravenous Levosimendan Efficacy[25] studies.
(5) Hypokalaemia and hypovolaemia should be avoided before and during treatment.

Some additional considerations in the use of intermittent levosimendan are set out in *Table 2*. The fact that this drug can be administered in an outpatient setting in a hospital clinic is a substantial practical advantage and may in itself represent a contribution to QoL as it spares patients the need to be hospitalized. Intermittent therapy can be integrated into a wider system of outreach and patient monitoring, bearing in mind that deterioration to the point where hospitalization is necessary represents a failure both of QoL and quality of care. The value of cardiac rehabilitation[26] and training[27] as part of a comprehensive programme is acknowledged, as is the impact of telemedicine:[28,29] this last is an area poised for rapid and not wholly predictable development as advances in digital technology raise the possibility of taking patient monitoring to unprecedented levels. Whether this change will be evolutionary—enabling existing programmes to be delivered with more immediacy, lower cost, and more precise tailoring to the circumstances of individual patients—or paradigm-changing, remains to be seen.

Endpoints for QoL

There is growing recognition that the patient experience of illness may be characterized by functional limitations and impairments in HRQoL that are not captured by hard clinical endpoints, i.e. hospitalizations and mortality. A Cardiovascular Roundtable initiative of the ESC has emphasized the need for 'meaningful characterization of the burden of disease for patients' as an essential component of composite endpoints for HF clinical trials.[30] Both this initiative and an earlier, related contribution[31] acknowledge

Table 2 Considerations in the use of an intermittent levosimendan infusion in patients with advanced or end-of-life HF. See text for further discussion. Reproduced with permission from Nieminen *et al.*[23]

For safety purposes, the monitoring of blood pressure, heart rate, body weight and serum sodium, potassium, and creatinine levels is recommended when intravenous levosimendan is administered.
A systolic blood pressure of 85–100 mmHg does not rule out treatment with repetitive use of levosimendan, although there should be close monitoring according to the patient profile.
In the case of hypovolaemia, fluid substitution during infusion might be needed or temporarily reduced and/or a vasopressor added (e.g. noradrenaline). Intense diuresis might be seen in some patients: reduction of the regular diuretic should be considered and additional fluid given as needed.
For therapy in an outpatient setting it is recommended that the first administration(s) of levosimendan are performed in hospital (ideally a day hospital), with monitoring of blood pressure and heart rate.
The agenda and intervals of monitoring visits should be determined according to the individual patient risk assessment.
Other guidance measures include counselling on diet and exercise/daily activity/rest, as well as quality-of-life evaluation. Ideally, trained HF nurses can perform these tasks in global HF management programme settings, according to standardized protocols. The exact frequency of levosimendan dosing (2–4 weeks) should be guided by the increasing symptoms of the patient.

HF, heart failure.

that instruments to assess patient-reported outcomes 'in order to assess the quality of care in everyday practice and the efficacy of novel therapies and management strategies in clinical trials' are still clinical research in progress for both technical and regulatory reasons. Not the least of the regulatory concerns is the possibility that interventions that improve functional status may nevertheless be associated with worse mortality; there are precedents for such an outcome.[32]

This understandable regulatory conflict with clinical research illustrates some of the tensions and contradictions encountered in discussion of QoL in HF when contrasted with the findings of Kraai *et al.*,[33] who reported that 61 of their 100 patients gave a higher value to QoL than longevity: 9% and 14% of patients were prepared to trade off 6 or 12 months, respectively of an assumed remaining lifespan of 5 years in return for perfect health; 5% of patients were prepared to trade off 4.5 of their nominal 5 remaining years of life to attain the same goal. In multivariate logistic regression, the factors showing a significant association with willingness to trade time for QoL were a higher N-terminal pro-brain natriuretic peptide level ($P = 0.04$) and a lower score on the Euro-Qual 5D questionnaire ($P = 0.03$). Other time trade-off investigations have reached similar conclusions.[34,35]

An additional consideration is that HRQoL is not the entirety of QoL. Particularly for patients who sense that the end of life is imminent, 'quality' relates as much to needs fulfilment, which can embrace a very wide range of priorities, such as satisfaction with either the process of care or its effects on symptoms. As an instance of this, Heo *et al.*[36] reported that, in their convenience sample of 20 patients with HF, the patients' definition of QoL included 'ability to perform physical and social activities; maintaining happiness; engaging in fulfilling relationships'. Other factors included the ability to undertake self-care, economic status, and positive attitude (*Figure 1*). Heo and colleagues also noted that 'Patients' self-evaluation of their QoL was at times contrary to their own definitions of QoL', a state of affairs often explained by patients having a more or less cheerful perspective of their own situation than might be warranted by the medical circumstances.

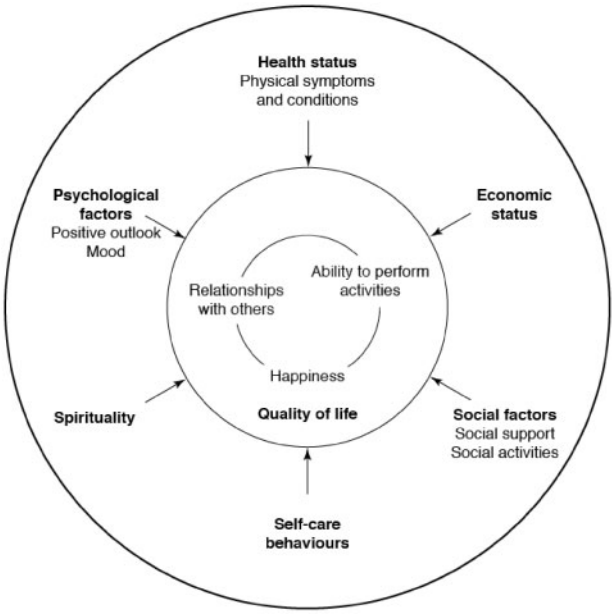

Figure 1 Factors, priorities, and considerations that interface with quality of life in patients with heart failure. From Heo *et al.*[36]

This intimation of a psychological component of QoL is hardly surprising but directs attention towards depression in HF. An association has been reported for QoL by clinical questionnaires in HF[37] and Yu *et al.*[38] have identified depression as a prominent element in one of three distinct symptom clusters that characterize HF patients and are correlated with lower QoL.

Cognitive behavioural therapy and related 'mindfulness' exercises have been reported to improve depressive status in HF patients.[39,40] The effects of antidepressants on prognosis of HF have been the subject of several recent investigations, which have reached divergent conclusions.[41–43] Whether or not antidepressants promote QoL is uncertain and may need to be evaluated separately for individual drugs.

No discussion of depression in HF can be complete without acknowledging the impact of HF on the patient's close

relatives and friends. Bearing in mind that personal relations are a high priority for many patients with late-stage HF, efforts to identify and mitigate depression in spouses, care-givers, and others close to the patient are an important contribution to promoting patient QoL.[44]

Other factors for consideration for promoting QoL in HF include sleep-disordered breathing (SDB) and sexual dysfunction.

SDB is widely prevalent among the HF population (≈50%)[45,46] and is associated with detrimental effects on both cardiac function and QoL. SDB can be differentiated into obstructive sleep apnoea and central sleep apnoea. The former appears to respond to continuous positive airway pressure, with favourable effects on symptoms, biomarkers, and QoL, though not mortality.[47] The Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure trial reported an improvement in performance of the 6-min walk test, which may be pertinent to QoL,[48] but the SERVE-HF trial did not demonstrate any benefit from adaptive servo-ventilation (ASV) on QoL (except perhaps for sleepiness), HF-related hospitalizations or survival.[49] Further assessment of ASV is ongoing (see, e.g.[50,51]) but this intervention is not recommended in the 2016 ESC guidelines.[5]

The impact of HF on sexual activity is extensive and profound and there are self-evident implications for QoL.[52] This subject is too large to be examined in detail in this essay but a comprehensive treatment may be found in a consensus document from the American Heart Association and the ESC Council on Cardiovascular Nursing and Allied Professions[53] and some salient points may be registered.

(1) Sexual activity is not advised for patients with decompensated or advanced (NYHA class III or IV) HF until their condition is stabilized and/or optimally managed (Class III; Level of Evidence C).
(2) Where possible, drugs with the potential to contribute to sexual dysfunction should be substituted (e.g. eplerenone instead of spironolactone).
(3) Resynchronization therapy may improve libido and erectile function.
(4) Agents such as sildenafil may be effective and safe for erectile dysfunction but should be avoided in high-risk patients.
(5) There is a notable reduction in self-reported satisfaction with sexual life after LVAD implantation, a fact which many patients avoid discussing with their physicians.
(6) Even this summary reveals that addressing sexual dysfunction in AdHF requires an extensive range of skills and resources, some of which fall outside our familiar limits of HF management.

Palliative and terminal end-of-life care

The erratic and often prolonged trajectory of HF makes it inappropriate to think of 'palliative care' as something to be initiated only in the last weeks of life. Rather, palliation should be an integral part of the philosophy and process of care in patients with advanced (NYHA class III–IV) HF when they are in a distinct phase of terminal care, characterized by renal impairment, hypotension, persistent oedema, fatigue, and anorexia despite maximal therapy. All these patient characteristics emerge when death is imminent and require a further revision of priorities.

The Advanced Heart Failure Study Group of the Heart Failure Association of the ESC has examined the issue of palliative care in detail.[54] Advance discussion with the patient and their relatives of what they want and what they expect is a central theme, along with the need to review those wishes and expectations regularly as the situation develops and to provide clear information and assurance. This can include palliative care consultations in preparation for the implantation of an LVAD[55] and discussions regarding when and why to disable an implanted cardiac defibrillator.[54]

Implementation of some of these ideas in the context of late-stage (but not terminal) HF implies a revised model of palliation in which, rather than an abrupt withdrawal of curative care and the equally abrupt introduction of palliative care, both processes proceed in tandem, with their relative contributions varying in response to the trajectory of the case. This in turn creates the possibility of two models of care, which the Study Group characterize as: (i) HF specialist care aligned with end-of-life care consultancy and (ii) HF-oriented palliative care services. The latter is a model in which end-of-life care services assume responsibility for the basic care of the patient and their family and HF specialists serve as consultants for specific issues relating to the treatment of HF.

These are substantial proposals for the evolution of end-of-life care services in HF but are framed in broad terms because the Study Group considered that the variety of health service models in Europe and beyond precludes a single formula for the delivery of these services. Even so, some movement towards these general principles is highly desirable: evidence from a range of countries indicates continuing under-provision of end-of-life care in HF.[55–59]

Conclusions

Advanced HF is associated with high rates of hospitalization, important impacts on QoL and high costs of care.

Levosimendan has a range of qualities that make it potentially beneficial in advanced HF when given as intermittent/repeated infusions. It provides sustained haemodynamic benefits and symptom control and—in short—gives time to patients and healthcare professionals when it is needed most.

Published data, ongoing research and direct experience indicate that this approach is feasible and safe, and leads to relief of symptoms and reduction in the number of hospitalizations.

There is a strong rationale for further evaluation of levosimendan in this application.

Conflict of interest: none declared.

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