Levosimendan: current status and future prospects
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Purpose of review
While patients with acute heart failure typically receive diuretics and vasodilators, contractile dysfunction and peripheral hypoperfusion also leads to a widespread use of inotropic agents despite the lack of evidence for efficacy or safety. Levosimendan, a calcium sensitizer and vasodilator, has been proposed to be superior to standard inotropes. In addition, further possible indications for levosimendan have been described, such as perioperative use, cardioprotection, cardiogenic shock, sepsis, and right ventricular dysfunction.

Recent findings
The mortality benefit of levosimendan has not been confirmed in two recent trials but the substance improves symptoms, decreases brain natriuretic peptide and is effective during β-blocker treatment. The use of levosimendan as an add-on therapy in acute heart failure has been encouraged as well as its perioperative use. Levosimendan may also be useful during right ventricular dysfunction and septic shock due to its favorable effects on splanchnic perfusion.

Summary
Levosimendan is an established substance in the treatment of acute heart failure in several countries despite disappointing findings concerning a possible survival benefit in two recent clinical trials. Owing to its alternative mechanisms of action as compared with traditional cardiotonic agents, several promising clinical applications have arisen. Available evidence for the use of levosimendan in settings other than decompensated heart failure is currently limited.

Keywords
calcium-sensitizer, cardiac surgery, heart failure, levosimendan, myocardial ischemia, perioperative

Introduction
The common clinical syndrome of heart failure, encountered during the final stages of various cardiovascular disorders, is associated with impaired quality of life, high morbidity and mortality and frequent hospitalization, causing a substantial economic burden on the healthcare system [1]. Heart failure is the leading cause of hospitalization in patients over 65 years of age [2] and is a progressive disorder with a poor prognosis. In patients hospitalized with acute heart failure (AHF) the 60-day mortality rate is approximately 10% [3]. Owing to epidemiological changes and advances in treatment the number of patients with heart failure is increasing and consequently also the number of patients with heart failure presenting for surgery. The prognostic importance of perioperative heart failure is underlined by the fact that the 30-day mortality and readmission to hospital rate in patients with coronary artery disease but without the presence of heart failure is similar to that of the general population [4].

Management of acute heart failure
Patients with AHF are generally treated with oxygen, diuretics and vasodilators. The most commonly used vasodilators in the treatment of AHF are nitroglycerin, nitroprusside and nesiritide. The potent hypotensive effect of nitroprusside and the rapid onset of tachyphylaxis to nitroglycerin, however, limit their use in clinical practice. Nesiritide, a form of recombinant human B-type natriuretic peptide, improves hemodynamics effectively and has fewer adverse effects than nitroglycerin. The results of recent meta-analyses, however, suggest that nesiritide may also be useful during right ventricular dysfunction and septic shock due to its favorable effects on splanchnic perfusion.
perfusion to vital organs. Achievement and maintenance of a proper perfusion pressure is a primary target of the treatment of AHF and is generally assumed appropriate if mean arterial blood pressure is equal to or above 65 mmHg. The association of low blood pressure and negative outcome in patients with AHF has also been confirmed in recent trials [7**,8].

**Positive inotropic drugs**

The currently available positive inotropic agents are catecholamines such as dobutamine, phosphodiesterase III inhibitors (PDEIs) such as milrinone, and in some countries calcium-sensitizing agents such as levosimendan.

Beta1-adrenoceptor agonists and PDEIs effectively enhance contractility and improve symptoms, whether used in patients with acute decompensation of chronic heart failure (CHF), contractile dysfunction after myocardial infarction, or stunning after cardiac surgery. These traditional drugs, however, have substantial limitations in the treatment of myocardial contractile dysfunction [9] because they enhance myocardial contractility, but also myocardial oxygen demand and the incidence of arrhythmias [10]. These side-effects are particularly detrimental in the presence of comitant ischemia, as for example in patients with ischemic cardiomyopathy [11]. A possible explanation for the poor safety record of the traditional inotropic agents is that, despite different primary sites of action, all of these drugs eventually enhance myocardial contractility by increasing intracellular levels of cyclic adenosine monophosphate, either generated by an increased rate of synthesis (β1-adrenoceptor agonists) or by a decreased rate of degradation (PDEIs), which ultimately results in an augmentation of free calcium in the cytosol [12].

In contrast, calcium-sensitizers increase the calcium sensitivity of contractile regulatory proteins, causing an increase in myocardial contractility. These agents are free from the risk of calcium overload and do not require an increase in activation energy. Thus, they could improve hemodynamic parameters with a minimum increase in energy expenditure and a low risk of arrhythmias, even under pathological conditions, such as acidosis and stunned myocardium. In addition, due to its site of action, no antagonistic effects are observed when β-adrenergic antagonists are used in parallel.

**Levosimendan**

The calcium-sensitizer and vasodilator levosimendan is the most promising agent of this drug group to date. The drug causes dose-dependent increases in stroke volume and cardiac index, and dose-dependent decreases in pulmonary capillary wedge pressure and pulmonary arterial pressure [13,14]. Importantly, levosimendan increases contractile force without impairment of ventricular relaxation in experimental settings [15] and also in patients with cardiomyopathy [16**]. In addition to these positive inotropic and lusitropic effects levosimendan also produces vasodilation by opening of ATP-sensitive potassium channels in vascular smooth muscle [17]. This effect reduces cardiac preload and afterload, improves oxygen supply to the myocardium, increases coronary blood flow [18] and also enhances renal blood flow [19,20]. These effects may account for the reductions in myocardial ischemia [21], as well as the improved function of stunned myocardium [22] observed during the treatment with levosimendan. When compared with dobutamine, Duygu et al. [23*] demonstrated through echocardiographic evidence that levosimendan reduces cardiac filling pressures more effectively in patients with acute systolic left heart failure of ischemic origin. This prospective, randomized, patient-blinded study included 62 patients and the E/E ratio was used as an index to assess left ventricular filling pressure. In addition to its positive inotropic, lusitropic and vasodilatory effects, levosimendan possibly exerts additional anti-inflammatory and antiapoptotic effects. Such effects have been suggested in patients with severe heart failure [24,25] because of reductions of proinflammatory cytokine and TNF-α receptor expression and decreases of serum levels of the apoptotic marker soluble FAS (sFAS) immediately after infusion. These effects were sustained for at least 7 days [26]. These prolonged effects of levosimendan may be related to its metabolism. While the parent drug has an elimination half-life of approximately 1 h, OR-1896, an active metabolite with a similar pharmacological profile to the parent compound, has a half-life of 70–80 h [27]. Peak concentrations of OR-1896 are reached at 1–4 days (mean 2 days) following the cessation of a 24-h infusion of levosimendan [28]. Lilleberg et al. [29*] showed that the maximal hemodynamic and neurohormonal effect of a 24-h levosimendan infusion occurs within 1–3 days after starting the infusion and is sustained for at least 1 week.

**Dosage**

While administration of a 6–24 μg/kg loading dose delivered in 10 min followed by a 24-h infusion at 0.05–0.2 μg/kg/min was considered the optimal dosing regimen [14], the results of recent clinical studies and the experience of many users suggest omission of the loading dose, especially in case of a low blood pressure before start of the infusion [7**,30]. Also, the dose should be reduced in patients with severe renal insufficiency, as the half-life of the levosimendan metabolites was prolonged 1.5-fold in patients with severe chronic renal failure and in patients with end-stage renal disease undergoing hemodialysis [31**].
Safety
At present, there are more controlled clinical data available on levosimendan than on any other intravenous inotropic drug. Levosimendan is generally well tolerated in patients with moderate-to-severe heart failure, with an overall frequency of adverse events of 17–29%, which is similar to that of placebo (17–20%) [13,14,32]. The most common adverse events reported in randomized placebo or dobutamine-controlled clinical trials were hypertension, headache, ventricular tachycardia and atrial fibrillation [7**,32–34]. In the SURVIVE study, levosimendan was associated with a higher incidence of hypotension than was dobutamine (16 versus 14%) [7**]. In most clinical trials, no serious interactions with other routine heart failure drugs including angiotensin-converting enzyme (ACE) inhibitors, β-blockers, digoxin, furosemide and spironolactone have been reported [7**,34].

Clinical application of levosimendan
Levosimendan is well established in the treatment of AHF with or without concomitant ischemia. There are also encouraging preliminary results with levosimendan in patients undergoing cardiac surgery.

Acute decompensation of chronic heart failure
The guidelines of the European Society of Cardiology recommend levosimendan as a second-line therapy for patients with AHF, if the initial therapy with continuous positive airway pressure, loop diuretics and vasodilators has not been successful and the patient has adequate blood pressure (systolic blood pressure between 85 and 100 mm Hg) (class of recommendation IIa, level of evidence B) [3]. Even though the drug has been on the market in several countries in Europe and South America for several years, it has not yet been approved in the USA and a number of European countries.

Additional large-scale studies have recently been carried out to verify the symptomatic efficacy of the drug in patients with decompensated heart failure (Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy; REVIVE) [30] and to compare its efficacy and safety with dobutamine (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support; SURVIVE) [7**], which is the most frequently used intravenous inotropic drug in this setting. Owing to the results of several moderate-size randomly controlled multicenter trials [32,33] speculations were made that this drug might improve survival of patients with decompensated heart failure although these trials were not adequately powered to assess mortality.

The much larger REVIVE-2 (600 patients) and SURVIVE (1327 patients) trials subsequently demonstrated that levosimendan improves symptoms of heart failure, decreases brain natriuretic peptide (BNP) levels but overall does not improve survival [7**,30]. The SURVIVE study was the first prospective, randomized trial to monitor long-term survival in patients with AHF. Despite a marked initial decrease in plasma BNP level in patients in the levosimendan group, the results revealed no significant difference between levosimendan and dobutamine in all-cause mortality at 31 and 180 days after study drug infusion. There are several possible explanations, apart from the greater number of patients included, for the differences between the results of earlier trials and the REVIVE-2 and SURVIVE studies. First, the volume status of the patients in this study might have been different from earlier trials. While the initial studies with levosimendan included only ‘wet’ patients according to the hemodynamic classification of patients with heart failure [35], the REVIVE-2 and SURVIVE protocols also allowed ‘dry’ patients to be included. Moreover, the patients in REVIVE-2 and SURVIVE were not invasively monitored. Second, levosimendan and dobutamine may differ in their survival effects only in a subgroup of AHF patients. Especially in patients receiving β-adrenergic antagonists levosimendan outperformed dobutamine in earlier studies and in a subanalysis of the new SURVIVE trial [36]. Similarly, treatment differences in favor of levosimendan were more apparent in patients with a history of heart failure than in those with a recent onset of heart failure [37]. The individualized dosing strategy adopted for dobutamine in the SURVIVE trial may offer a third explanation for the lack of differences between dobutamine and levosimendan. While patients received an average low dose of 6 μg/kg/min dobutamine, a high dosing regime of levosimendan was mandated suggesting comparison of a low-dose dobutamine group with a high-dose levosimendan group of patients. Finally, major differences between countries in patient survival suggest that variable treatment practices may have influenced patient outcomes [34].

Combination with catecholamines
Although there are no clinical data evaluating specific combinations of positive inotropic drugs, numerous reports suggest the use of levosimendan in combination with dobutamine in patients with decompensated heart failure that is refractory to dobutamine alone [38,39**,40].

Myocardial ischemia and cardioprotection
In contrast to other inotropic agents, the safety of levosimendan was studied in patients with left ventricular failure after acute myocardial infarction. In the RUSSLAN study various doses of levosimendan were investigated for safety, efficacy, and effects on mortality. A 6-h infusion of levosimendan at doses from 0.1 to 0.2 μg/kg/min did not induce hypotension or ischemia and reduced the risk of worsening heart failure and death in patients with left
ventricular failure complicating acute myocardial infarction [32]. An important limitation of the study, however, is that it was not prospectively designed and not adequately powered to show a difference in mortality as an end-point.

In addition to these beneficial effects in patients with acute myocardial infarction, a direct cardioprotective effect was suggested from earlier experimental studies due to opening of myocardial ATP-sensitive potassium channels by levosimendan. Accordingly, in a recent clinical study in cardiac surgery levosimendan-treated patients had lower postoperative troponin I concentrations than control patients without production of adverse effects [41*]. Similarly, several reports of a successful use of levosimendan in the setting of myocardial stunning [42–44] suggest an important role of this drug especially in the setting of myocardial ischemia. This is also underlined by the fact that levosimendan improves ventriculo-arterial coupling and cardiovascular performance in coronary patients with left ventricular dysfunction both by enhancing myocardial contractility and by reducing arterial elastance [45].

Cardiogenic shock
Despite its vasodilatory effects, successful and effective administration of levosimendan has been frequently reported, both as a single substance and especially in combination with other catecholamines [43,44,46–49] during cardiogenic shock. These findings suggest an important role of the different mechanism of action as compared with other inotropes in this setting.

Perioperative administration of levosimendan
The clinical data on the perioperative administration of levosimendan are not as extensive as in the treatment of heart failure and are primarily restricted to cardiac surgery [50**], but its efficacy during states of ischemia, myocardial stunning and postoperative low-output states suggest that levosimendan in general might be a useful drug before, during and after surgery.

The rationale of preoperative administration of levosimendan is related to both possible preconditioning effects [41*,51] and the preparation of high-risk cardiomyopathic patients to the frequent hemodynamic derangements during surgery both in patients with preoperative low-output syndrome [52] and in those with low-gradient low-output aortic stenosis [53,54]. Although these effects have not been investigated in a large number of patients, this concept appears very attractive and promising; because outcome of such patients is known to be poor, strategies for therapy lacking and administration of levosimendan are performed without the necessity of a loading dose. At our institution, such patients are transferred to the post-anesthesia intensive care unit 4–12 h preoperatively and receive levosimendan 0.1 μg/kg/min without a loading dose. Standard monitoring including ECG, pulsoxymetry and noninvasive blood pressure measurement are performed and electrolytes including potassium and magnesium corrected. Using this strategy, so far no serious adverse events have occurred.

Although levosimendan is also of benefit when started intraoperatively [39**,50**,55,56] administration during this time is more challenging and requires some experience of the clinician with the use of this drug because of its pharmacological profile. As intraoperatively the requirement for a positive inotropic drug is mostly urgent and the effects are needed within a few minutes, levosimendan typically has to be administered with a loading dose. While rapid positive inotropic effects can be achieved by such a strategy, the concomitant vasodilative effects can produce hypotension in this situation due to additional anesthesia-related vasodilation and possibly relative hypovolemia. As a consequence parallel administration of a vasoconstrictor, such as norepinephrine, is frequently necessary in this situation. Despite the fact that levosimendan is sometimes started intraoperatively at our institution, in our opinion more easily titratable positive inotropic drugs with a short elimination half-life like dobutamine or epinephrine are preferable in this situation.

In contrast, most evidence regarding the perioperative use of levosimendan relates to the postoperative period including treatment of postcardiomyotomy low-cardiac output [50**,57–62], acute graft failure after heart transplantation [63], weaning from postcardiomyotomy mechanical assist device [64] or intraaortic balloon counterpulsation [65]. Compared with the intraoperative period, hemodynamic derangements, blood losses and the effects of anesthesia are substantially lower in the postoperative period and therefore suggest a prudent and safe administration of levosimendan in this setting both as an addition to or replacement of other positive inotropic therapy. In our institution, we postoperatively administer levosimendan early without a loading dose in the situation of anticipated duration of standard catecholamine therapy for more than 3 days or existing combination of several catecholamines and phosphodiesterase inhibitors. Administration of levosimendan in this setting is always a supplement to the existing positive inotropic therapy with a subsequent weaning and removal of other inotropic therapy. If, in rare cases of insufficient inotropic support by levosimendan alone, another drug has to be added, a combination of levosimendan with dobutamine is more effective than a combination of milrinone with dobutamine [39**].

Potential future indications
Experience with levosimendan in several other clinical settings is encouraging due to its unique mechanisms of
action that considerably differ from those of the traditional inotropes.

**Right ventricular dysfunction**

In addition to the beneficial effects on left-sided hemodynamics, levosimendan improved right ventricular performance and pulmonary hemodynamics in several experimental and clinical studies [66–68]. Compared with dobutamine, levosimendan was superior in patients with depressed right ventricular function and elevated pulmonary arterial pressures because of similar inotropic effects, but additional pulmonary vasodilatory action [68].

In a clinically relevant porcine model of ischemia–reperfusion induced right ventricular dysfunction, Missant et al. [69**] demonstrated that levosimendan optimized right ventriculoarterial coupling by moderately increasing right ventricular systolic output. Importantly, levosimendan did not affect normal pulmonary vascular tone while effectively counteracting pulmonary vasoconstriction during pathologic conditions. In the perioperative period, several small studies reported beneficial effects of levosimendan on severe right ventricular dysfunction following mitral valve replacement [70] or heart transplantation [63,71].

**Septic shock**

Based on the pathophysiology of myocardial contractile dysfunction during sepsis – desensitization of myocardial myofilaments – administration of levosimendan theoretically may be an excellent alternative for hemodynamic optimization and improvement of splanchnic perfusion in septic shock. Accordingly, in a rabbit model of abnormal cardiac function in human sepsis, levosimendan but not milrinone or dobutamine improved both systolic and diastolic cardiac function [72*]. Similarly, in a model of endotoxic shock, both levosimendan and dobutamine increased cardiac output and maintained whole body oxygen delivery, but only levosimendan prevented a decrease in mesenteric oxygen delivery [73*]. Superiority of levosimendan over milrinone and dobutamine in increasing gastric mucosal oxygenation in dogs [74] indicates redistribution of perfusion towards splanchnic organs by this drug. Therefore, in the future levosimendan may become a prophylactic or therapeutic option to support the integrity of the gastrointestinal mucosa and to preserve or restore its barrier function with a subsequent attenuation of the onset or severity of organ failure.

Finally, experimental evidence suggests that levosimendan may become a possible renal protective agent in sepsis syndrome because of a substantial protection against endotoxemic acute renal failure in a rodent model [75*].

**Uptitration of β-adrenoceptor blockade**

The neutral effects of concomitant β-adrenergic blockade on the actions of levosimendan as compared with dobutamine [33,36] suggest an interesting and important role during uptitration of β-adrenergic blockade in patients with severe contractile dysfunction. In a prospective, randomized, open, parallel group trial of monthly 24-h infusions with levosimendan and chronic infusion with prostaglandin E1, both facilitated uptitration of β-blocker therapy in previously intolerant advanced CHF patients. Prostaglandin E1 treatment, however, allowed uptitration in more patients and resulted in a better clinical outcome than levosimendan [76]. Whether shorter time intervals between levosimendan infusions might be more effective remains to be elucidated.

**Conclusion**

Although there seems to be no ideal inotropic agent at present, the differing mechanisms of action of levosimendan in comparison with other cardiotonic drugs provide a new approach in the management of cardiac failure. In decompensated heart failure, levosimendan may outperform dobutamine and be the superior choice either in patients with ischemic heart disease or in the presence of long-term maintenance therapy with β-blockers. The available evidence about the use of levosimendan in settings other than decompensated heart failure is rather limited.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 91).

7. Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA 2007; 297:1883–1891. In this large, randomized, double-blind trial comparing the efficacy and safety of intravenous levosimendan or dobutamine in 1327 patients hospitalized with acute decompensated heart failure, levosimendan did not significantly reduce all-cause mortality at 180 days or affect any secondary clinical outcomes.
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8. This study demonstrated that the positive inotropic and lusitropic effects of levosimendan in humans with left ventricular dysfunction: alteration of the force-frequency or relaxation-frequency relationship.


16. Levosimendan caused a greater reduction of E/E’ ratio, a noninvasive, pulse-wave and tissue Doppler echocardiographic indicator of left ventricular filling pressure, than dobutamine in acute systolic left heart failure.


23. In this double-blind, parallel group study in 22 patients with NYHA II to IV heart failure, left-ventricular ejection fraction under 26% and pulmonary capillary wedge pressure (PCWP) under 12 mmHg, a 24-h levosimendan infusion produced sustained hemodynamic effects and decreases of NT-proBNP for up to at least 1 week with maximal effects occurring after 1–3 days.


29. In cardiac surgery patients with a low preoperative ejection fraction, stroke volume and tissue Doppler echocardiographic indicator of left ventricular filling pressure, than dobutamine in acute systolic left heart failure.


31. This small but very interesting study demonstrated that a short infusion of levosimendan before coronary artery bypass grafting resulted in less myocardial injury and neurohormonal and immune activation in patients with advanced heart failure and those with end-stage renal disease undergoing hemodialysis. The authors therefore suggest that the dose of levosimendan should be reduced in patients with severe renal insufficiency.


36. In cardiac surgery patients with a low preoperative ejection fraction, stroke volume was better maintained with the combination of dobutamine with levosimendan started immediately after the release of the aortic crossclamp than with the combination of dobutamine with milrinone. Total dose, duration of inotropic drug administration and norepinephrine dose were lower in the levosimendan group than in the milrinone group.


39. This small but very interesting study demonstrated that a short infusion of levosimendan before coronary artery bypass grafting resulted in less myocardial damage, suggestive of a preconditioning effect. Levosimendan-treated patients had lower postoperative troponin I concentrations and a higher cardiac index than the control group.


**Cardiovascular anaesthesia**


70. In an experimental pig model of acute postischemic right ventricular dysfunction levosimendan improved global hemodynamics and optimized right ventriculoarterial coupling via a moderate increase in right ventricular contractility and a mild reduction of right ventricular afterload.


74. In an experimental rabbit model treatment with levosimendan improved both systolic and diastolic functions, while milrinone or dobutamine improved only systolic function.


76. In an ovine model of endotoxic shock both levosimendan and dobutamine increased cardiac output and prevented the decrease in whole body oxygen delivery, but only levosimendan was able to prevent the decrease in mesenteric oxygen delivery.


79. This study demonstrated a substantial protection of levosimendan-treated rodents against endotoxemic acute renal failure without apparent reduction in lipopolysaccharide-induced inflammatory response. The authors suggest an important role of kATP channel opening by levosimendan in the mediation of these beneficial effects.