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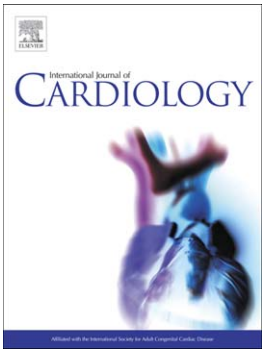

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Preoperative and perioperative use of levosimendan in cardiac surgery: European expert opinion

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Running title: Levosimendan in cardiac surgery

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Abstract

In cardiac surgery, postoperative low cardiac output has been shown to correlate with increased rates of organ failure and mortality. Catecholamines have been the standard therapy for many years, although they carry substantial risk for adverse cardiac and systemic effects, and have been reported to be associated with increased mortality. On the other hand, the calcium sensitiser and potassium channel opener levosimendan has been shown to improve cardiac function with no imbalance in oxygen consumption, and to have protective effects in other organs. Numerous clinical trials have indicated favourable cardiac and non-cardiac effects of preoperative and perioperative administration of levosimendan. A panel of 27 experts from 18 countries has now reviewed the literature on the use of levosimendan in on-pump and off-pump coronary artery bypass grafting and in heart valve surgery. This panel discussed the published evidence in these various settings, and agreed to vote on a set of questions related to the cardioprotective effects of levosimendan when administered preoperatively, with the purpose of reaching a consensus on which patients could benefit from the preoperative use of levosimendan and in which kind of procedures, and at which doses and timing should levosimendan be administered. Here, we present a systematic review of the literature to report on the completed and ongoing studies on levosimendan, including the newly commenced LEVO-CTS phase III study (NCT02025621), and on the consensus reached on the recommendations proposed for the use of preoperative levosimendan.

Keywords: cardiac surgery; CABG; valve surgery; low cardiac output syndrome; inodilator; cardioprotective

1. Introduction

In patients undergoing cardiac surgery, low cardiac output syndrome (LCOS) is a disastrous event that can result in life-threatening complications [1,2]. With LCOS, the mortality rate of these patients can be as high as 16.9% (*versus* 0.9% without LCOS) [2]. Preoperative reduced left ventricular function has been recognised as the main risk factor for LCOS [3,4].

Cardiac surgery is also usually accompanied by multi-faceted effects, which include sympathetic activation, inflammation, and haemodynamic changes, and is thus likely to promote organ dysfunction. Of note, acute kidney injury is frequently observed after cardiac surgery, and this is associated with increased long-term mortality after cardiothoracic surgery [5]. Postoperative acute kidney injury can be part of cardiorenal syndrome, which is a classic example of organ dysfunction that can arise due to hypoperfusion, which triggers a sympathoadrenergic response, hyperglycaemia and inflammation [6].

Inotropic support is frequently initiated in the perioperative period to improve post-bypass ventricular function. However, inotropes include the potential risk of increased myocardial oxygen consumption, which can result in cardiac ischaemia, with subsequent damage to hibernating but viable myocardium, and arrhythmias. This has prompted an ongoing debate on the potential harm associated with inotropic therapy in cardiac surgery. Indeed, the use of perioperative and postoperative inotropes has recently been found to be associated with increased mortality and major postoperative morbidity [7].

Administration of the calcium sensitiser levosimendan, which has been approved for management of acutely decompensated heart failure, might offer a solution to this unmet need. The effects of levosimendan as an inodilator are based on a triple mechanism of action [8] that provides positive inotropy with a neutral effect on oxygen consumption [9], and with preconditioning [10], cardioprotective [11], anti-stunning [12] and anti-ischaemic effects [13].

In a recent meta-analysis of clinical trials, Harrison and colleagues evaluated the effects of levosimendan in cardiac surgery patients with and without preoperative systolic dysfunction [14]. Here, they showed that mortality and other adverse outcomes, such as postoperative renal failure requiring dialysis, postoperative atrial fibrillation, and myocardial injury, were reduced with levosimendan treatment. These benefits were greatest for the patients with diminished left ventricular ejection fraction (LVEF).

The characteristics of the cardiac surgery setting differ from the conditions in the context of levosimendan use in patients with acute heart failure. Factors that apply to cardiology patients are frequently not the same as those that apply perioperatively. Suspension of standard therapy in the perioperative period, use of cardiopulmonary bypass (CPB), blood loss, rapid intravascular and extravascular fluid shifts, and systemic inflammatory response syndrome can affect the impact of levosimendan treatment. This indicated the need for specific handling of levosimendan in cardiac surgery patients with respect to the definition of indications, modality of administration, and management of side effects.

Therefore, 27 experts from 18 countries convened to review the literature and to agree upon a series of recommendations. The panellists are all recognized specialists in the fields of cardiothoracic anaesthesiology, cardiothoracic surgery, cardiology, cardiovascular pharmacology, and intensive care medicine. They extensively discussed the preoperative use of levosimendan, and formulated a list of questions. Thereafter, the panellists received a questionnaire and responded through internet voting. The results are presented here, together with the evidence of the pharmacology of levosimendan, and a discussion of the available clinical data.

2. Pharmacology of the cardioprotective effects of levosimendan

Levosimendan is characterised by a triple mechanism of action [8]; i.e., it acts via calcium-dependent binding to cardiac troponin C, and opens the K_{ATP} channels on smooth muscle cells in the vasculature, and in cardiac mitochondria. This binding of levosimendan to troponin C and the opening of the of K_{ATP} channels on smooth muscle cells in the vessels results in its inotropic and vasodilatory effects, respectively, while the opening of K_{ATP} channels in cardiac mitochondria is believed to be a cardioprotective pathway [15]. The definition of cardioprotection, however, is very broad, and it can be divided into at least two categories of effects: short-term and long-term cardioprotection. Short-term cardioprotection encompasses effects such as preconditioning, postconditioning, and anti-stunning, as well as anti-ischaemic effects. Long-term cardioprotection, on the other hand, is often referred to as having anti-remodelling, anti-apoptotic and anti-inflammatory effects.

2.1. Preconditioning effects of levosimendan

The opening of K_{ATP} channels in the mitochondria has a predominant role in the protection of the myocardium from ischaemia and reperfusion injury [16]. By attenuation of calcium accumulation in the mitochondria and stabilisation of the mitochondrial inner membrane permeability, K_{ATP} channel opening results in a reduction in myocardial cell necrosis and apoptosis induced by ischaemia–reperfusion injury. Therefore, treatment with the K_{ATP} channel opener levosimendan prior to myocardial ischaemia will mimic ischaemic preconditioning. According to *ex-vivo* data obtained by Toit and colleagues, levosimendan preconditioning can reduce infarct size by 90% [11]. Also, when compared with milrinone in an animal model setting, there was less mortality with levosimendan: after occlusion and reperfusion of the coronary vessels, 70% of dogs treated with levosimendan before

ischaemia–reperfusion survived, as compared to 20% of those treated with milrinone [17]. In another model, the lactate/ pyruvate ratio in the ischaemic areas was reduced with levosimendan treatment prior to induction of ischaemia [18]. Finally, Kersten and co-workers also showed that levosimendan has protective effects against myocardial ischaemia in a dog model: with levosimendan treatment, infarct size was decreased by 50% [19].

2.2. Anti-stunning effects of levosimendan

Myocardial stunning occurs when acute myocardial ischaemia leads to a transient impairment of the contractile function. In patients with coronary artery disease, repeated episodes of demand ischaemia can lead to cumulative stunning, which has been suggested to be a factor in the development of chronic post-ischaemic left ventricular dysfunction [20].

Sonntag and co-workers demonstrated the anti-stunning effects of levosimendan in 24 patients with acute coronary syndrome, whereby as compared to placebo, the total number of hypokinetic segments was significantly decreased with levosimendan treatment [21]. In 30 patients with acute myocardial infarction who experienced myocardial stunning after emergency percutaneous coronary intervention, continuous infusion of levosimendan 0.1 μg/kg/min for 24 h significantly improved myocardial function, as compared to placebo [22]. In a recent randomised, double-blind clinical trial with 61 patients who developed clinical signs of heart failure within 48 h of primary percutaneous-coronary-intervention–treated STEMI (including cardiogenic shock), 25-h treatment with levosimendan showed significantly greater improvement in their wall motion score index from baseline to day 5, as compared to placebo [23].

2.3. Anti-ischaemic effects of levosimendan

In a rodent model of healed myocardial infarction, Levijoki and co-workers showed that treatment with levosimendan correlated with decreased mortality [13]. These preclinical data were confirmed more recently in another study [24].

3. Pharmacokinetic and pharmacodynamic considerations

Levosimendan has a half-life for elimination of about 1 h. Without a loading dose, a steady-state concentration can be achieved approximately 4 h after the start of continuous levosimendan infusion. After the infusion, the levosimendan serum concentrations decrease relatively rapidly. Levosimendan, however, has an active circulating metabolite known as OR-1896, which has a half-life for elimination of approximately 80 h [25]. In patients with heart failure, OR-1896 reaches its peak level approximately 2 days after the end of a 24-h infusion of levosimendan, and is removed from the circulation over the following 2 weeks [25]. Lilleberg and colleagues showed that levosimendan treatment of patients with heart failure for 24 h improves cardiac output and reduces pulmonary capillary wedge pressure (PCWP) for at least 1 week [26]. A reduction in the N-terminal-pro-atrial natriuretic peptide levels was observed for at least 2 weeks.

In the cardiac surgery setting, OR-1896 can be found in the plasma, but compared to heart failure patients, its formation occurs at a slower pace [27]. Peak levels are observed 5 days to 6 days after the discontinuation of levosimendan infusion. This is probably due to preoperative fasting and to the use of broad-spectrum antibiotics in cardiac surgery. Clinical data obtained in patients with low preoperative LVEF (≤30%) scheduled for elective cardiac surgery indicated a prolonged effect of levosimendan on the stroke volume index [28]. The patients received either levosimendan 0.1 μg/kg/min infusion for 19 h or milrinone 0.5

μg/kg/min infusion for 83 h. Within the first few hours, the effects on stroke volume index were comparable in both groups, but a more pronounced effect was seen with levosimendan during the follow-up period for up to 48 h, even though levosimendan treatment had already been discontinued (**Figure 1**).

By overviewing the pharmacodynamic and pharmacokinetic properties of levosimendan, it becomes clear that its preoperative, or alternatively perioperative, use might have effects that are very different. Indeed, in the preoperative settings, the cardioprotective effects of levosimendan would have a major role along with its haemodynamic effects (inotropic and vasodilatory), and levosimendan might be further differentiated from other inodilatory, haemodynamically active or vasoactive drugs.

4. Published data on the preoperative and perioperative use of levosimendan

In the systematic analysis of the literature, the data sources used were PubMed, Index Medicus, Excerpta Medica, Reference Update, BIOSIS, and Science Citation Index. The pertinent studies were independently identified by two trained investigators (updated March 27, 2014). The papers and abstracts found by searching ([levosimendan OR Simdax] AND [surgery OR bypass OR valve OR CABG OR anest*]) were selected according to the PRISMA search and the inclusion strategy described in **Figure 2**, and grouped according to the timing of the use of levosimendan and the type of intervention, as in the following sections.

4.1. Preoperative use in on-pump cardiac surgery

4.1.1. Coronary artery bypass grafting surgery

In a randomised, double-blind, placebo-controlled trial by Tritapepe and coworkers, levosimendan 24 μg/kg infusion for 10 min before initiation of coronary artery bypass grafting (CABG) led to significant reductions in tracheal intubation time, length of Intensive Care Unit (ICU) stay ($P < 0.01$ for both), and the proportion of patients requiring inotropic support for >12 h (3.8% vs. 18.0% for placebo; $P = 0.021$) [29]. As compared to placebo, levosimendan-treated patients had significantly lower postoperative troponin I levels **(Figure 3)** and a significantly higher cardiac index ($P < 0.0001$ each).

The preoperative use of levosimendan in high-risk patients with severe left ventricular dysfunction (LVEF <25%) scheduled for CABG was assessed in a randomised, placebo-controlled trial [30]. Levosimendan was started 24 h before surgery, with a loading dose of 10 μg/kg infusion for 1 h that was followed by continuous infusion of 0.1 μg/kg/min infusion for 23 h. Overall, 252 patients participated in the study. Levosimendan reduced mortality compared to placebo (3.9% vs. 12.8%; $P < 0.05$), and decreased the incidence of LCOS (7.1% vs. 20.8%; $P < 0.05$) and of complicated weaning from CPB (2.4% vs. 9.6%; $P < 0.05$). The levosimendan-treated group also showed lower requirement for other inotropes compared to placebo (7.9% vs. 58.4%; $P < 0.05$), and for vasopressors (14.2% vs. 45.6%; $P < 0.05$), and lower use of an intra-aortic balloon pump (6.3% vs. 30.4%; $P < 0.05$).

4.1.2. CABG and aortic valve surgery

In 24 patients undergoing combined aortic valve and CABG surgery, preoperative levosimendan 12 μg/kg infusion for 10 min followed by a continuous infusion of levosimendan 0.2 μg/kg/min infusion for 24 h significantly improved cardiac index and stroke volume index throughout the 4-day postoperative period ($P < 0.05$) [31]. The LVEF was maintained in the levosimendan group, whereas it decreased in the control group.

4.2. Perioperative use in on-pump cardiac surgery

4.2.1. CABG surgery

A randomised, double-blind trial assessed the effects of levosimendan on haemodynamics, coronary blood flow, and myocardial substrate use early after CABG [32]. Two dose schedules (levosimendan 8 μg/kg or 24 μg/kg as 5-min infusions after CABG) were compared with placebo. Although levosimendan improved cardiac performance by increasing cardiac output and coronary sinus blood flow, it did not increase myocardial oxygen consumption or change myocardial substrate use.

De Hert and co-workers conducted a randomised study with 30 patients scheduled for CABG with preoperative LVEF ≤30% [28]. In addition to dobutamine, the patients received either milrinone 0.5 μg/kg/min infusion or levosimendan 0.1 μg/kg/min infusion immediately after the release of the aortic crossclamp. These infusions were continued until weaning from inotropic support. The stroke volume index declined 12 h after surgery in the milrinone group, but not in the levosimendan group ($P < 0.05$) despite similar filling pressures. Total dose, duration of inotropic drug administration, and norepinephrine doses were significantly lower with levosimendan ($P < 0.05$). Moreover, the duration of tracheal intubation was shorter in the levosimendan-treated group ($P = 0.008$).

Levin and colleagues compared levosimendan (10 μg/kg as 1 h infusion followed by 0.1 μg/kg/min infusion for 24 h) and dobutamine (starting dose, 5 μg/kg/min infusion) in a randomised trial with 137 patients with LCOS after surgery [33]. Patients treated with levosimendan experienced significant benefits in the postoperative period, with improvements in haemodynamic parameters with levosimendan that were greater and occurred earlier than with dobutamine. Postoperative mortality was lower in the levosimendan group compared to

dobutamine (8.7% vs. 25%; P <0.05), as was the need for vasopressors, second or third inotropes, and intraaortic balloon pump (IABP) use **(Figure 4)**.

In the randomised, double-blind LEWE study, levosimendan facilitated weaning from CPB and reduced the need for additional inotropic or mechanical circulatory support in patients with impaired LVEF (≤50%) undergoing CABG [34]. Sixty patients received either levosimendan as a 12 µg/kg bolus followed by 0.2 µg/kg/min infusion, or placebo, started immediately after the induction of anaesthesia. Levosimendan significantly facilitated primary weaning from CPB as compared with placebo (P = 0.002; **Figure 5**). Four patients in the placebo group even failed the second weaning and had to be supported by IABP, as compared with none in the levosimendan group (P = 0.112).

4.2.2. CABG and valve surgery

In a randomised, placebo-controlled trial, Lahtinen and colleagues demonstrated that levosimendan treatment diminished the incidence of heart failure after heart valve or combined heart valve and CABG surgery [35]. Levosimendan 24 µg/kg over 30 min of infusion followed by 0.2µg/kg/min infusion for 24 h, or placebo, were administered after induction of anaesthesia. Fifteen percent of patients in the levosimendan group and 58% in the placebo group experienced postoperative heart failure (P <0.001). Accordingly, the use of rescue inotropes and IABP was significantly less in the interventional arm (P = 0.005 and P = 0.018, respectively). The level of the myocardial fraction of creatine kinase, which is indicative of myocardial damage, was lower in the levosimendan group on the first postoperative day, compared to placebo (P = 0.011). In contrast, the use of vasopressors was significantly higher in the levosimendan arm due to arterial hypotension (P <0.001). Hospital mortality rates and 6-month mortality rates were similar in both groups.

4.2.3. Aortic valve surgery

Twenty-four patients with severe aortic stenosis and left ventricular hypertrophy undergoing aortic valve surgery were included in a randomised, double-blind trial by Järvelä and co-workers [36]. In patients receiving a 24-h infusion of levosimendan 0.2 μg/kg/min starting after the induction of anaesthesia, LVEF was maintained, while it dropped in the placebo-treated group. This difference was not significant, however.

Jörgensen and others found that in addition to its inotropic effects, levosimendan can have a positive lusitropic effect in patients with left ventricular hypertrophy, as it shortened isovolumic relaxation time and improved left ventricular filling [37]. This randomised, blinded study compared two dose schedules (0.1 μg/kg/min and 0.2 μg/kg/min infusions for 20 min, after initial loading dose of 12 μg/kg infusion for 10 min) with placebo in 23 patients after aortic valve replacement for aortic stenosis. Levosimendan treatment showed a dose-dependent increase in cardiac output (+28%; P <0.001) and stroke volume (+26%; P <0.001), and a decrease in systemic vascular resistance (-22%; P <0.001). There was a trend towards an increase in LVEF (12%; P = 0.058). After the administration of levosimendan, as compared to placebo, isovolumic relaxation time decreased (-3%; P <0.001), as did the deceleration slope of early diastolic filling (-45%; P <0.01). Both peak early diastolic filling velocity (16%, P <0.01) and peak late diastolic filling velocity (15%; P <0.001) increased significantly.

4.2.4. CABG and mitral valve surgery

A case-matched study compared levosimendan with the use of an IABP in heart failure patients undergoing elective CABG without or with concomitant mitral valve surgery [38]. Eleven patients received levosimendan infusion at a dose of 0.1 μg/kg/min for 24 h, while another 11 patients received preoperative IABP. The length of stay at the ICU was

significantly reduced in the levosimendan-treated group, compared to IAPB use (2.5 vs. 5 days; P = 0.01).

4.2.5. Mitral valve surgery

Gandham and co-workers compared the use of levosimendan 0.1 μg/kg/min infusion with dobutamine 5 μg/kg/min infusion for weaning from CPB in 60 patients who were undergoing mitral valve repair or replacement for severe mitral stenosis [39]. The patients who received levosimendan showed greater reductions in systemic vascular resistance index, central venous pressure, and mean arterial pressure, compared to dobutamine. The requirement of inotropes and vasoconstrictors was increased in the levosimendan-treated group. Compared to dobutamine, there was a statistically significant increase in cardiac index with levosimendan, even 12 h after discontinuation.

4.3. Off-pump cardiac surgery

Several studies have tested the hypothesis that levosimendan treatment is associated with beneficial haemodynamic effects during and after off-pump CABG in patients with good preoperative left ventricular function. A randomised, four-times–masked, controlled study investigated levosimendan at two dose schedules: low dose (12 μg/kg) and high dose (24 μg/kg) as 10 min infusions [40]. These treatments were administrated 20 min before the start of the surgery. Compared to placebo, significant increases in cardiac output and LVEF occurred after both the high-dose (P <0.001 and P = 0.006, respectively) and the low-dose (P = 0.001 and P = 0.002, respectively) treatments. Both levosimendan doses produced significant increases in stroke volume and decreases in systemic vascular resistance.

In a double-blind randomised trial, 24 patients received either placebo or levosimendan at a dose of 12 μg/kg as an infusion for 15 min before CABG [41]. At 10 min

and 60 min post-infusion, the cardiac index and the LVEF were significantly higher with levosimendan than with placebo (P = 0.018 each). The stroke volume index was significantly higher for levosimendan at 10 min (P = 0.018), but not at 60 min (P = 0.063).

Kodalli and colleagues compared levosimendan 0.1 μg/kg/min infusion and placebo after induction of general anaesthesia in a double-blind manner [42]. In patients receiving levosimendan, compared to placebo, the cardiac index was significantly higher and the systemic vascular resistance index was significantly lower at 6, 12, 18 and 24 h after CABG. No improvements were noted in terms of duration of ventilation or ICU length of stay.

The double-blind, randomised trial by Shah and colleagues tested preoperatively administered levosimendan 200 μg/kg infusion for 24 h against placebo for off-pump CABG in 50 patients with left ventricular dysfunction (LVEF <30%) [43]. As compared to the control group, the levosimendan-treated patients had higher cardiac index and PCWP during the operative and early postoperative period. Also, requirements for inotropes, IABP and CPB support were lower for levosimendan, and both ICU and hospital length of stay were reduced.

4.4. Effects of levosimendan on kidney function

As renal dysfunction is an important complication of cardiac surgery, several trials have investigated the potential renal benefits mediated by levosimendan. In a randomised, placebo-controlled study, levosimendan significantly improved renal parameters after cardiac surgery with CPB [44]. Levosimendan was applied as a 0.1 μg/kg/min infusion for 1 h after a loading dose of a 12 μg/kg infusion. When compared to placebo, this treatment caused a significant 12% increase in renal blood flow, and a significant 21% increase in glomerular filtration rate, whereas renal vascular resistance decreased significantly by 18%. There were no significant changes in filtration fraction, renal oxygen consumption, or renal oxygen extraction. These

effects clearly differed from those of dopamine, which also increased renal blood flow, but did not increase the glomerular filtration rate.

Baysal and co-workers compared levosimendan (6 μg/kg infusion after removal of the aortic cross-clamp, followed by 24-h infusion of 0.1 μg/kg/min) with placebo in addition to standard inotropic therapy [45]. The cohort consisted of 128 patients with LVEF ≤45% who were undergoing mitral valve surgery. Compared with the group of patients who received only standard inotropic therapy, the addition of levosimendan improved postoperative renal clearance on days 1 and 3. At these time points, serum creatinine levels were lower and the estimated glomerular filtration rates were higher than in the control arm. There was a trend in favour of levosimendan regarding the need for renal replacement therapy.

A meta-analysis by Harrison and colleagues also highlighted the beneficial effects of perioperative levosimendan on renal function, as it showed significant reductions in the need for dialysis in levosimendan-treated patients (P = 0.003) [14]. A consensus paper on the overall renal effects of levosimendan appeared also recently in the literature [46].

4.5. Effects of levosimendan on hepatic function

Liver dysfunction due to low cardiac output after cardiac surgery is associated with poor prognosis. A randomised controlled study by Alvarez and colleagues compared the effects of dobutamine and levosimendan on hepatic blood flow in patients with low cardiac output after cardiac surgery [47]. A total of 25 patients were randomised to receive either levosimendan 12 μg/kg infusion for 15 min followed by 0.2 μg/kg/min infusion for 24 h, or dobutamine 7.5 μg/kg/min infusion for 24 h. As compared to dobutamine, levosimendan improved systemic and hepatic haemodynamics (cardiac index, portal vein flow, pulsatility index) at 24 h and 48 h. They also noted that levosimendan can be considered as a liver vasodilator that improves

hepatic blood flow through both the hepatic artery and the portal venous system. In contrast, dobutamine treatment only affected portal venous blood flow.

4.6. Effects of levosimendan on right heart function

The efficacy of levosimendan in increasing right ventricular contractility and reducing right ventricular afterload has been demonstrated in heart failure, cardiogenic shock related to acute myocardial infarction, and septic shock (for review, see Nieminen et al. 2013 [48]). Levosimendan also proved to be beneficial in patients with preoperative right ventricular dysfunction who were undergoing implantation of a left ventricular assist device [49]. Similarly, in a small retrospective study, Theiss and co-workers showed superior twelve-month survival compared to INTERMACS registry data in patients with right ventricular dysfunction treated with levosimendan before left ventricular assist device implantation [50]. Finally, in a pilot study in patients with low-cardiac-output heart failure after cardiac surgery, Labriola and co-workers administered levosimendan and observed improved cardiac index and PCWP. At the same time, the mean pulmonary artery pressure and right arterial pressure decreased by 13% ($P < 0.001$) and 25% ($P < 0.001$), respectively [51].

5. Pharmaco-economic considerations

Health- and pharmaco-economic analyses on the use of levosimendan in acute decompensated heart failure have shown that its use is cost-effective [52-54]. We did not find in the literature, however, systematic health economic studies on the use of levosimendan in cardiac surgery. From an analysis of the available data, it appeared to us that levosimendan positively affects the major elements which are likely to increase the costs of treatment in cardiac surgery: (1) the ICU stay has been reported to be shorter in several levosimendan studies [29,30]; (2) there

is less need for IABP (both the actual number of the patients and the duration)[28, 30, 33, 35, 55]; and (3) there is less need for renal replacement therapy in levosimendan treated patients [14, 30, 33, 45]. As it regard the concomitant use of other vasoactive drug, a higher need for vasopressors when using levosimendan is compensated by a lower need of inotropes. Overall, the expectation is that levosimendan treatment in cardiac surgery would be cost-effective [56], despite its higher cost compared to dobutamine.

6. Ongoing trials

A number of European trials are currently assessing the perioperative use of levosimendan (see Table 3). The LICORN study is investigating the efficacy of preoperative levosimendan in patients with LVEF ≤40% undergoing CABG with or without valve replacement under CPB (study number P110138, France). The primary endpoint of this placebo-controlled study is a composite that includes the use of inotropic agents beyond 24 h after the end of study drug infusion, or the need of postoperative mechanical assist devices (IABP or others), or the impossibility to wean the patients from circulatory support if they were already in use preoperatively, or the need for renal replacement therapy. Secondary endpoints include mortality at days 28 and 180, each item of the primary endpoint separately, and length of ICU and hospital stays. Levosimendan is being administered as a 0.1 µg/kg/min infusion for 24 h and is started at the time of anaesthesia induction, without bolus application. The study population will include 340 patients.

A recently completed (but not yet published) double-blind study by Argyriadou and co-workers was aimed at confirmation of the benefits of preoperative levosimendan in patients with left ventricular dysfunction (LVEF ≤40%) routinely scheduled for CABG (NCT01318460). Thirty-two patients were randomised to either levosimendan 0.1 µg/kg/min

infusion for 24 h before surgery, or placebo. A preliminary analysis of the data favoured levosimendan treatment to a significant degree: while the placebo group showed no significant difference between preoperative and postoperative LVEF, LVEF increased significantly in the levosimendan group on the 7th postoperative day. Moreover, cardiac index, tissue perfusion, and PCWP were significantly improved in the experimental arm.

In North America, a randomised, placebo-controlled, phase III pivotal trial in high-risk patients undergoing CABG (LVEF ≤25%) and/or mitral or aortic valve surgery (LVEF ≤35%) started in the third quarter of 2014 (NCT02025621). A total of 760 patients in 50 cardiac surgery centres across North America will receive either levosimendan 0.2 µg/kg/min infusion for 1 h followed by 0.1 µg/kg/min infusion for 23 h, or placebo. Infusion will be started before surgery. Co-primary endpoints comprise death, use of mechanical assist devices (IABP, left ventricular assist device), myocardial infarction, and dialysis. Secondary endpoints include postoperative duration of stay at the ICU or coronary care unit, and incidence of LCOS. The safety endpoint is the all-cause mortality by day 90.

Finally, the study of levosimendan in high-risk patients undergoing cardiac surgery (HSR-LEVO) is comparing levosimendan to placebo on mortality and morbidity in 1000 patients at risk of LCOS, and this is currently recruiting (NCT00994825). An interim analysis of the data is planned after the first 250 patients.

7. Composition of the panel and mode of agreement on the recommendations

The panellists were 27 experts from 18 countries (Austria, Belgium, Croatia, Czech Republic, Finland, France, Germany, Greece, Hungary, Israel, Italy, Russia, Slovenia, Spain, Sweden, Switzerland, the U.K., and the U.S.A.), all of whom were recognized specialists in the fields of cardiothoracic anaesthesiology, cardiothoracic surgery, cardiology, cardiovascular

pharmacology, and intensive care medicine. They were invited to join the panel by the chairmen (WT, MH, FG), on the basis of their experience with preoperative and perioperative use of levosimendan documented in the literature.

After discussing the available evidence on preoperative and intraoperative use of levosimendan, the panel found that the rationale for preoperative use of levosimendan is profoundly different from that for its perioperative (or intraoperative) use. Indeed, intraoperatively, levosimendan is primarily used for its inodilatory effects, which can be achieved without any negative impact on myocardial oxygen balance. In contrast, in the preoperative setting, levosimendan is used also in an attempt to provide patient benefit through its cardioprotective properties that come into effect later during the intraoperative period.

For the sake of clarity, the panel decided to discuss these two applications of levosimendan separately. The panel recognized that the use of levosimendan in the perioperative setting had already been reviewed and discussed by Toller et al. [66]. The recommendations of Toller et al. [66] on the operative use of levosimendan were embraced by the present panel of experts.

The panel thus decided to limit the present consensus to the preoperative use of levosimendan. The panel agreed on a series of questions and took a vote on the following questions: (1) which patients could benefit from the preoperative use of levosimendan and in which kind of procedures, (2) at which doses and timing should levosimendan be administered, and finally (3) which potential side effects of a preoperative use of levosimendan have to be taken into account and how to best prevent and treat them. These were answered electronically and anonymously by 24 respondents (all of the authors, with the exception of PP and MK, to avoid any conflict of interest, and of RHM, because the use of levosimendan in U.S.A. has not yet been approved), on the basis of (i) their experience with

levosimendan, and (ii) the knowledge in the available literature. The answers were disclosed to the group and a second round of opinion was allowed to agree on some recommendations (see votes by the experts in Table 2).

8. Conclusions of the panel

Clinical studies show that levosimendan effectively improves general and pulmonary haemodynamics in patients undergoing cardiac surgery, thereby reducing the need for inotropic agents and mechanical circulatory support, and additionally optimising renal and hepatic function. In general, the length of stay on the ICU and in the hospital is shortened. Overall, levosimendan treatment is considered as a kind of "safety net" in the surgical setting. The unique inotropic and cardioprotective properties of levosimendan can provide sustained effects for several days and can thus help to reduce complications in the postoperative period. On the other hand, vasodilation occurs with this treatment, which can necessitate the administration of vasopressors.

The panellists recommended preoperative use of levosimendan in patients with generally compromised myocardial function, including right ventricular dysfunction. They advised against a bolus injection when used outside the operation room. The day prior to surgery was suggested as the optimal time point for initiation of a preoperative therapy with levosimendan. The recommended dose of levosimendan agreed upon was 0.1 µg/kg/min infusion for 24 h, or to the end of the vial. When levosimendan infusion is started during or after induction of anaesthesia, the addition of a bolus is considered to be a feasible option.

Levosimendan can be administered in any hospital setting, provided that haemodynamic monitoring is guaranteed. In fact, as levosimendan produces significant dose-dependent increases in stroke volume and cardiac output, and decreases in pulmonary

capillary wedge pressure, mean blood pressure, mean pulmonary artery pressure, mean right atrial pressure, and total peripheral resistance [48], it should be administered in a safe and adequately monitored environment, ready to prevent and treat side effects. If vasodilation occurs, the experts suggest the combination of levosimendan with norepinephrine or vasopressin. If additional inotropic support becomes necessary in a levosimendan-treated patient, dobutamine should be the preferred inotrope.

In general, the data so far collected are promising, but it was noted that only some of the clinical studies are robust, as many trials were conducted in relatively few patients, thus the scientific evidence for use of levosimendan is yet to be further expanded. Since all of the meta-analyses on operative use of levosimendan to date [14, 67-70] show positive benefits from levosimendan, there is a strong rationale for further expansion of the data pool. Clinical trials currently ongoing in Europe and the USA are expected to contribute significantly, and to possibly support further the existing data. In the phase of revision of this manuscript a Bayesian network meta-analysis on the effect of inodilatory agents on mortality was published [71] in which it was shown that levosimendan has 90% probability to be the best in improving survival in cardiac surgery when compared with PDE inhibitors, dobutamine, and placebo.

Author contributions

Three of the authors (FG, MK, PP) independently performed the preliminary search for the relevant publications. All of the authors contributed substantially to discussions of the existing literature and to the text of the recommendations, and reviewed the manuscript before submission.

Declaration of interest

This project did not receive any financial support, apart from logistic expenses related to the organisation of the consensus meeting in Munich on 28 March, 2014, which were covered by unrestricted grants from Orion Pharma (Finland), Tenax Therapeutic (U.S.A.), Medis d.o.o. (Slovenia) and Biomed JR Ltd. (Israel). The attendees did not receive any honoraria. PP and MK are employees of Orion Pharma.

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Table 1: Studies on preoperative and perioperative use of levosimendan (from PubMed).

First author	Title	Type of study/ comparator	Number of patients	Levosimendan dosing/ timing of dose	Results
ON-PUMP PREOPERATIVE					
CABG					
Tritapepe 2009 [29]	Levosimendan pre-treatment improves outcomes in patients undergoing CABG	Randomised, double-blind / vs. placebo	106 (2× 53)	24 μg/kg for 10 min infusion before the initiation of bypass	Significant reductions in tracheal intubation time, length of ICU stay and number of patients requiring inotropic support for >12 h with levosimendan. Significantly lower postoperative troponin I concentrations and higher cardiac index
Levin 2012 [30]	Preoperative levosimendan decreases mortality and the development of low cardiac output in high-risk patients with severe left ventricular dysfunction undergoing CABG with cardiopulmonary bypass (EF<25%)	Randomised / vs. placebo	253 (127 vs. 125)	Loading dose (10 μg/kg), 23 h infusion (0.1 μg/kg/ min)	Levosimendan group had a lower incidence of complicated weaning from CPB (2.4% vs. 9.6%;P <0.05), decreased mortality (3.9% vs. 12.8%; P <0.05) and a lower incidence of LCOS (7.1% vs. 20.8%; P <0.05) compared with the control group, lower requirement for inotropes (7.9% vs. 58.4%; P <0.05), vasopressors (14.2% vs. 45.6%; P <0.05) and intra-aortic balloon pumps (6.3% vs. 30.4%; P <0.05)
Dogan 2013 [57]	Levosimendan use decreases atrial fibrillation in patients after CABG: a pilot study	Prospective, randomised / vs. placebo	200 (2× 100)	Levosimendan started 6 h before operation. In the operating room, levosimendan continued at 24 μg/kg as a slow drip through the central venous catheter and stopped before the initiation of CPB. During the rewarming period, levosimendan was started again via the central vein with the same dose.	Postoperative AF in levosimendan group was reduced in patients with poor left ventricle function after CABG operations. C-reactive protein was higher postoperatively in the control
Eris 2014 [56]	Preoperative uses of levosimendan in patients undergoing CABG (LVEF<30%)	Retrospective / levosimendan infusion applied 12 h before operation (G1), after induction of anaesthesia (G2), during the pump removal (G3) and non-LS control (G4).	40 (4× 10)	(0.2 μg/kg/min infusion)	Increase of LVEF; infusion of levosimendan 12 h before surgery produced less myocardial damage
CABG+AORTIC VALVE					
Leppikangas 2011 [31]	Preoperative levosimendan infusion in combined aortic valve and coronary bypass surgery	Randomised / vs. placebo	24 (2× 12)	12 μg bolus for 10 min followed by 0.2 μg/kg/min infusion for 24 h; treatment was started on the day before surgery	Higher cardiac index and stroke volume index with levosimendan for the 4-day postoperative period (P <0.05). LVEF maintained (the control group showed a decrease)
ON-PUMP PERIOPERATIVE					
CABG					
Lilleberg 1998 [32]	Effects of levosimendan on	Randomised,	23 (8, 8, 7)	Two dose schedules: 8 μg/kg or 24	Heart rate increased significantly after the higher dose; cardiac

	haemodynamics, coronary blood flow, and myocardial substrate use early after CABG	double-blind / vs. placebo		µg/kg infusions after CABP	output increased significantly after both doses, while systemic and pulmonary vascular resistance decreased significantly. Coronary sinus blood flow increased after both doses
Nijhawan 1999 [58]	Levosimendan enhances cardiac performance after cardiopulmonary bypass: a prospective, randomised placebo-controlled trial	Prospective, randomised, double-blind / vs. placebo	18 (3× 6)	Two dose schedules: 18 (low dose) or 36 (high dose) µg/kg bolus and 0.2 (low dose) or 0.3 (high dose) µg/kg/min infusion. Administration started before separation from CPB and was continued for 6 h after CPB	Placebo patients experienced significant increases in heart rate and decreases in systemic vascular resistance 15 min after CPB, as well as later increases in mean arterial pressure and cardiac output and decreases in stroke volume and pulmonary vascular resistance. Heart rate was greater in patients receiving high-dose but not low-dose levosimendan *versus* placebo immediately after CPB. Mean arterial pressure also was lower in patients treated with either levosimendan dose compared with placebo after CPB. Levosimendan increased cardiac output and decreased systemic vascular resistance.
Alvarez 2005 [59]	Hemodynamic effects of levosimendan following cardiac surgery	Randomised / vs. dobutamine	30 (2× 15)	Loading dose 18 µg/kg in 15-20 min infusion followed by 24-h infusion of 0.2 µg/kg/ min	Heart rate and cardiac index increased in the levosimendan group only (P <0.05). MAP, systemic and pulmonary vascular resistance decreased significantly in the levosimendan group (P <0.05) only.
Alvarez 2006 [60]	Hemodynamic effects of levosimendan compared with dobutamine in patients with low cardiac output after cardiac surgery	Randomised / vs. dobutamine	41 (20 vs. 21)	Loading dose 12 µg/kg infusion followed by 24-h infusion of 0.2 µg/kg/min	Levosimendan improved cardiac index more than dobutamine (2.4 [0.2] vs. 2.9 [0.3] l/min/m^2, respectively, at 24 h; P <0.05) and reduces systemic and pulmonary vascular resistance, decreases systemic arterial, pulmonary arterial, pulmonary capillary wedge, and central venous pressure
Al-Shawaf 2006 [61]	Levosimendan or milrinone in the type 2 diabetic patient with low LVEF undergoing elective coronary artery surgery	Randomised / vs milrinone 50 µg/kg for 10 min followed by 0.3 to 0.5 µg/kg/min infusion for 24 h	30 (14 vs. 16)	12 µg/kg bolus for 10 min followed by 0.1 to 0.2 µg/kg/min infusion for 24 h	Significantly higher cardiac index and mixed venous oxygen saturation with levosimendan; significantly lower pulmonary capillary wedge pressure, systemic vascular resistance and oxygen extraction ratios
Akgul 2006 [55]	Levosimendan for weaning from cardiopulmonary bypass after CABG	Prospective	15	12-24 µg/kg loading dose for 10 min infusion followed by 0.1-0.2 µg/kg/min infusion for 24 h	All patients showed evidence of hemodynamic improvement with the start of LS infusion, and 93.3% were successfully weaned from CPB. 53.3% experienced significant increases in cardiac index and blood pressure, leading to a lessening of the need for catecholamine support
De Hert 2007 [28]	The effects of levosimendan in cardiac surgery patients with poor left ventricular function	Randomised / vs. milrinone 0.5mg/kg/min infusion	30 (2× 15)	0.1 mg/kg/min infusion started immediately after the release of the aortic crossclamp, continued until weaning from inotropic support	Stroke volume declined 12 h after surgery in the milrinone group but not in the LS group (P <0.05) despite similar filling pressures. Total dose, duration of inotropic drug administration and norepinephrine dose were lower with levosimendan (P <0.05). The duration of tracheal intubation was shorter with levosimendan (P = 0008). Three patients in the milrinone group but none in the levosimendan group died within 30 days of surgery
Levin 2008 [33]	Levosimendan gives superior results to dobutamine in postoperative low cardiac output syndrome	Randomised /vs. dobutamine 5 µg/kg/min infusion	137 (69 vs. 68)	10 µg/kg loading dose followed by 0.1 µg/kg/min infusion for 24 h	Improvement of hemodynamic parameters was greater with levosimendan and occurred earlier. Postoperative mortality was lower (8.7% vs. 25%; P <0.05), as were major postoperative complications. The need for additional inotropic drug treatment, vasopressor therapy or balloon counterpulsation was lower. Levosimendan-treated patients experienced shorter ICU stay
Eriksson 2009 [27]	Levosimendan facilitates weaning from cardiopulmonary bypass in patients	Prospective, randomised,	60 (2× 30)	12 µg/kg bolus for 10 min followed by 0.2 µg/kg/min infusion	Levosimendan significantly enhanced primary weaning from CPB compared with placebo (P = 0.002). Four patients in the

	undergoing CABG with impaired left ventricular function	double-blind / vs. placebo		for 24 h; administration was started immediately after induction of anaesthesia	placebo group failed the second weaning and underwent IABP compared with none in the levosimendan group (P = 0.112).
Lomivorotov 2011 [62]	Levosimendan *versus* intra-aortic balloon pump in high-risk cardiac surgery	Randomised / vs. preoperative IABP	40 (2× 20)	12 μg bolus for 10 min followed by 0.2 μg/kg/min infusion for 24 h; treatment was started after induction of anaesthesia	Significantly lower levels of troponin I at 6 h after surgery with levosimendan, significantly shorter intensive care unit stay
Lomivorotov 2012 [63]	Levosimendan *versus* an intra-aortic balloon pump in high-risk cardiac patients.		90 (3× 30)		Levosimendan caused significantly increased cardiac index 5 min after CPB, at the end of the operation, and 2 h and 4 h after perfusion. Significantly lower level of troponin I 6 h after surgery, significantly shorter stay at the intensive care unit
CABG+VALVE					
Tasouli 2007 [64]	Efficacy and safety of perioperative infusion of levosimendan in patients with compromised cardiac function undergoing open-heart surgery: importance of early use	Randomised: during or after open-heart surgery	45	0.1 μg/kg min without loading dose for 24-48 h	ICU stay and hospital stay were significantly decreased when levosimendan was started in the operating theatre already rather than at the ICU
Lahtinen 2011 [35]	Levosimendan reduces heart failure after cardiac surgery: a prospective, randomised, placebo-controlled trial	Prospective, randomised /vs. placebo	200 (99 vs. 101)	24 μg/kg bolus over 30 min followed by 0.2 μg/kg/min infusion for 24 h	Levosimendan led to a reduced incidence of heart failure, but was associated with arterial hypotension and increased requirement of vasopressor agents postoperatively
Järvelä 2008 [36]	Levosimendan in aortic valve surgery: cardiac performance and recovery	Prospective, randomised, double-blind /vs. placebo	24 (2× 12)	0.2 μg/kg/min infusion for 24 h beginning after the induction of anaesthesia	LVEF was maintained with levosimendan but dropped with placebo (n.s.)
Jörgensen 2008 [37]	Effects of levosimendan on left ventricular relaxation and early filling at maintained preload and afterload conditions after aortic valve replacement for aortic stenosis	Prospective, randomised, blinded /vs. placebo	23 (12 vs. 11)	Two dose schedules: 0.1 or 0.2 μg/kg/min infusion for 20 min after initial loading doses of 12 μg/kg infusion for 10 min	Levosimendan gave rise to dose-dependent increases in cardiac output (28%; P <0.001) and stroke volume (26%; P <0.001) as well as decreases in systemic vascular resistance (-22%; P <0.001). Trend for an increase in LVEF. Decreases in isovolumic relaxation time and deceleration slope of early diastolic filling; increased peak early diastolic filling velocity and peak late diastolic filling velocity
CABG + MITRAL					
Severi 2011 [38]	Levosimendan *versus* intra-aortic balloon pump in high-risk cardiac surgery patients	Case-matched / vs. preoperative IABP	22 (2× 11)	0.1 μg/kg/min infusion for 24 h	Shorter duration of ICU stay with levosimendan (2.5 vs. 5 days; P = 0.01)
MITRAL					
Gandham 2013 [39]	A comparison of hemodynamic effects of levosimendan and dobutamine in patients undergoing mitral valve repair / replacement for severe mitral stenosis	Randomised / vs. dobutamine 5 μg/kg/min infusion	60 (2× 30)	0.1 μg/kg/min infusion while weaning off CPB	Increased vasodilation and lesser inotropic activity with levosimendan, statistically significant increase in cardiac index even after 12 h of discontinuation. Increased requirement of inotropes and vasoconstrictors
OFF-PUMP					
Barisin 2004 [40]	Levosimendan in off-pump coronary artery bypass: a four-times masked controlled study	Randomised, four-times masked /vs. placebo	31 (11, 10, 10)	Two dose schedules: low dose (12 μg/kg), high dose (24 μg/kg) over 10 min; treatment was given 20 min before start of surgery	Significant increases in cardiac output and LVEF occurred after high-dose (P <0.001; P = 0.006) and low-dose levosimendan (P = 0.001; P = 0.002). Both levosimendan doses produced significant increased stroke volume and decreased systemic vascular resistance.
Husedzinović 2005 [41]	Levosimendan as a new strategy during off-pump CABG: double-blind randomised placebo-controlled trial	Randomised, double-blind /vs. placebo	24 (2× 12)	12 μg/kg bolus for 15 min before surgery	Cardiac index and LVEF were significantly higher 10 min and 60 min (P = 0.018 for all) after levosimendan administration. After 60 min, cardiac index increased from 2.18 to 2.84 l/min/m^2.

					Stroke volume index was significantly higher at 10 min (P = 0.018), but not at 60 min (P = 0.063)
Kodalli 2013 [42]	Effect of levosimendan on hemodynamic changes in patients undergoing off-pump CABG: a randomised controlled study	Randomised /vs. placebo	30 (2× 15)	0.1 μg/kg/min infusion during surgery	Significant increase of cardiac index and significant decrease of vascular resistance index with levosimendan at 6, 12, 18 and 24 h after surgery. No outcome benefit in terms of duration of ventilation or ICU stay
Shah 2014 [43]	Levosimendan during off-pump CABG in patients with LV dysfunction	Randomised double-blind /vs. placebo	50 (2× 25)	200 μg/kg infusion in 24 h	Levosimendan increased cardiac index during operative and early operative period. Levosimendan-treated patients had less requirement for inotropes, IABP, CPN, ICU stay and hospital stay.
MAINLY DESCRIBING RENAL FUNCTION					
Ristikankare 2012 [65]	Effects of levosimendan on renal function in patients undergoing coronary artery surgery	Prospective, randomised, double-blind substudy /vs. placebo	60 (2× 30)	12 μg/kg bolus for 10 minutes followed by 0.2 μg/kg/min infusion for the next 23 h and 50 min	No significant changes in plasma creatinine, serum cystatin C, and urine NAG at any of the measuring points
Bragadottir 2013 [44]	Effects of levosimendan on glomerular filtration rate, renal blood flow, and renal oxygenation after cardiac surgery with cardiopulmonary bypass: a randomised placebo-controlled study	Prospective, randomised /vs. placebo	30 (2× 15)	0.1 μg/kg/min infusion for 1 h after a loading dose of 12 μg/kg	Increases in cardiac index (22%), stroke volume index (15%) and heart rate (7%) with levosimendan over placebo, decreased systemic vascular resistance index (21%). Significant increases in renal blood flow (12%, P <0.05) and glomerular filtration rate (21%, P <0.05), decreased renal vascular resistance (18%, P <0.05).
Baysal 2014 [45]	Levosimendan improves renal outcome in cardiac surgery: a randomised trial	Randomised /vs. placebo on top of standard inotropic therapy.	280 (2× 64)	Loading dose (6 μg/kg) after removal aortic cross-clamp, 24 h infusion (0.1 μg/kg/min) in addition to standard inotropic therapy.	Valve surgery improved immediate postoperative renal function (eGFR) and reduced need for renal replacement therapy
MAINLY DESCRIBING LIVER FUNCTION					
Alvarez 2013 [47]	A comparison of dobutamine and levosimendan on hepatic blood flow in patients with a low cardiac output state after cardiac surgery: a randomised controlled study	Randomised /vs. dobutamine 7.5 μg/kg/min infusion for 24 h	25	Levosimendan (12 μg/kg infusion) over 15 min + infusion of 0.2 μg/kg/min for 24 h	The systemic and hepatic haemodynamics at 24 h and 48 h were all better after levosimendan than dobutamine. Levosimendan is selective liver vasodilator and improves hepatic blood flow through both the hepatic artery and portal venous system.
MAINLY DESCRIBING RIGHT HEART FUNCTION					
Sponga 2012 [49]	Preoperative treatment with levosimendan in candidates for mechanical circulatory support.	Consecutive	21	Levosimendan 0.1 to 0.2 mg/kg/min infusion for a maximum of 48 h without bolus.	Levosimendan improves preoperative hemodynamic conditions in LVAD candidates with borderline right ventricular function.
Labriola 2004 [51]	Haemodynamic effects of levosimendan in patients with low-output heart failure after cardiac surgery.	Consecutive	11	Levosimendan 12 μg/kg over 10 minutes, followed by a continuous infusion of 0.1 μg/kg/min for 12 h	Levosimendan improves cardiac index, and reduces PCWP, mean pulmonary artery pressure and right arterial pressure
Theiss 2004 [50]	Preconditioning with levosimendan before implantation of left ventricular assist devices.	Retrospective, consecutive	9	Levosimendan continuous infusion of 0.1 μg/kg/min for 24 h	Levosimendan improved clinical outcome and survival when used as pretreatment in patients with right heart insufficiency prior to LVAD implantation

Table 2: Opinions of the 24 European experts on the preoperative use of levosimendan in cardiac surgery.

1. Type of patient

Which type of cardiac surgical patients would you suggest to give preoperative levosimendan?	*Definitely yes*	*Neutral opinion/ no direct experience/no answer*	*Definitely no*
CABG with low LVEF	100%	0%	0%
CABG plus mitral valve surgery	71%	29%	0%
Mitral valve replacement plus aortic valve replacement	29%	71%	0%
Mitral valve replacement	33%	67%	0%
Aortic stenosis with low LVEF	50%	33%	17%
Aortic regurgitation with low LVEF	54%	38%	8%
Type of cardiac surgical patients who was shown in literature to benefit from preoperative levosimendan.	*Convincing evidence*	*Some evidence*	*Scarce/no evidence*
CABG with low LVEF	92%	8%	0%
CABG plus mitral valve surgery	50%	29%	21%
Mitral valve replacement plus aortic valve replacement	17%	50%	33%
Mitral valve replacement	17%	58%	25%
Aortic stenosis with low LVEF	21%	54%	25%
Aortic regurgitation with low LVEF	17%	46%	38%
Would you suggest giving preoperative levosimendan in generally compromised myocardial function, including right ventricular dysfunction?	100% YES		
Would you suggest giving preoperative levosimendan in high-risk surgery (recent myocardial infarction, age, forecasted long ischaemic period) independently of LVEF, EuroSCORE or cardiac score?	67% YES		
Would you suggest preoperative administration of dobutamine in high-risk cases (see above questions)?	92% NO		
Would you suggest giving levosimendan before left ventricular assist device implantation to support the right ventricle?	96% YES		
Would you suggest to give preoperative levosimendan in pulmonary hypertension and right ventricle failure (e.g. during cardiac transplantation)?	92% YES		
Would you suggest preoperative levosimendan in patients undergoing Mitraclip procedure for functional/ischaemic mitral regurgitation?	75% YES		
Would you suggest preoperative levosimendan in patients undergoing transcatheter aortic valve implantation when LVEF is <35%?	63% NO		

2. Modality of administration

Where would you suggest preoperative levosimendan to be given? (multiple answers are allowed)	On surgical ward 3/24		In ICU 5/24		Any place BUT under hemodynamic monitoring and clinical control 21/24
Which dose regimen would you recommend for preoperative levosimendan to be given on the day prior to surgery? (multiple answers are allowed)	Bolus +infusion 0/24		Bolus alone 0/24		Infusion without bolus 24/24
Which dose regimen would you recommend for preoperative levosimendan to be given on induction of anaesthesia? (multiple answers are allowed)	Bolus +infusion 7/24		Bolus alone 0/24		Infusion without bolus 19/24
In case of bolus administration, which dose would you suggest?	6 µg/kg 67%		12 µg/kg 29%		24 µg/kg 4%
What dose of levosimendan would you suggest for continuous infusion?	0.1 µg/kg/min 83%		0.2 µg/kg/min 17%		0.3 µg/kg/min or higher 0%
How long shall the infusion last after surgery?	24h 44%		eventually less than 24h (to the end of the vial) 50%		more than 24h 4%
Would you suggest a second dose in a patient in whom a first dose had no effect?	63% NO				
When would you suggest a second dose to be given in a patient in whom a first dose worked well?	After 3-4 days 92%		Just following the first dose 8%		
If acute inotropic effect is needed, what would you suggest?	Increase levosimendan dose 17%		Add another inotrope 83%		
If – after adequate reperfusion time – weaning from CPB cannot be easily accomplished in a patient pretreated with levosimendan (24 h before surgery or for a sufficient time and with a sufficient dose), what would do next? (multiple answers are allowed)	IABP plus second inotrope 7/24	Add a second inotrope 10/24	Urge the surgeon to insert an IABP (if no contraindications) 10/24	Proceed with weaning anyway and delay decisions for some h, awaiting the sometimes prolonged effect of levosimendan in the further course 2/24	
Would you suggest combining levosimendan and phosphodiesterase inhibitors?	83% NO				
Alternatively: Which inotrope do you recommend as a first-line agent, if additional inotropic support becomes necessary in a patient treated with levosimendan? (multiple answers are allowed)	Dobutamine 14/24	PDEI 4/24	Epinephrine 8/24	Dopamine 2/24	Others 1/24
Would you suggest combining levosimendan and norepinephrine or vasopressin if vascular tone needs to be handled?	100% YES				
If yes, which vasopressor approach do you suggest?	The vast majority (23/24) suggests first-line norepinephrine and vasopressin only for severe hypotension				

In a patient under beta blocker treatment requiring preoperative inotropic therapy, which drug would you suggest? (multiple answers are allowed)	All the respondents (24/24) favour levosimendan. Phosphodiestherase inhibitors were suggested by 4/24, while dobutamine and dopamine were not supported at all.		
Would you suggest the use of levosimendan plus IABP in a patient with overt LCOS?	88% YES		
Would you urge the surgeon to implant an IABP in a patient preoperatively treated with a full dose of levosimendan, if post-induction TOE still shows severely depressed myocardial function?	YES 50%	NO 17%	It depends (i.e. more likely in a patient with MV and/or TV regurgitation than in a single CABG case) 33%

3. Management of side effects

In order to avoid arrhythmias during levosimendan infusion, what potassium target corridor would you suggest?	Maintaining potassium levels of >4.0mmol/L 92%	Maintaining potassium levels of >3.5mmol/L 8%	
In order to avoid hypotension during levosimendan infusion, what would you suggest to do? (multiple answers are allowed)	Optimising volume status before starting the drug administration 19/24	Combining a vasoactive drug 16/24	Combining a beta agonist drug 0/24
In order to avoid hypotension during levosimendan infusion, would you suggest to stop ACE inhibitor therapy before operation?	63% YES		

Table 3: Ongoing clinical trials on the use of levosimendan in cardiac surgery.

Study indicators: title, acronym, NCT number and main investigator (when available)	Patient population	Patient number	Levosimendan dose and time	Comparator	Endpoints
LICORN (P110138) B. Cholley	Patients with LVEF ≤40% undergoing CABG with or without valve replacement under CPB	340	0.1 µg/kg/min infusion for 24 h, started at the time of anaesthesia induction, without bolus application.	Placebo	Composite primary endpoint including use of inotropic agents beyond 24 h after end of study drug infusion, or need for postoperative mechanical assist devices (IABP or others), or impossibility to wean patients from them if they were already in use preoperatively, or the need for renal replacement therapy. Secondary endpoints comprise mortality at days 28 and 180, each item of the primary endpoint separately, and length of intensive care unit and hospital stays.
Intracoronary administration of levosimendan in cardiac surgery patients, (NCT01500785) K. Järvelä	Patients undergoing aortic valve and CABG surgery	50	Intracoronary 12 µg/kg infusion, initiated at the induction of cardioplegia	Placebo	Primary endpoint of change in cardiac output 15 min after separation from CPB, compared to baseline. Secondary endpoints include change in LVEF between baseline and 5 min after sternal closure, and cTnT/CK-MB levels of first postoperative morning
LEVO-CTS (NCT02025621) R. H. Mehta	Patients undergoing CABG (LVEF ≤25%) and/or mitral valve surgery (LVEF ≤35%)	760	0.2 µg/kg/min infusion for 1 h followed by 0.1 µg/kg/min infusion for 23 h, started before surgery.	Placebo	Two co-primary endpoints: • All-cause death at 30 days or use of mechanical assist device to day 5 • All-cause death at 30 days, or perioperative non-fatal myocardial infarction to day 5, or need for renal dialysis to day 30, or use of mechanical assist device to day 5 Secondary endpoints: • Length of intensive care unit/ coronary care unit stay • Incidence of post-operative low cardiac output syndrome • Postoperative use of secondary inotrope
Aristotle University of Thessaloniki, Greece K. Anastasiadis	Patients with left ventricular dysfunction (LVEF ≤40%) scheduled for CABG	32	0.1 µg/kg/min infusion for 24 h before surgery	Placebo	Primary endpoint of assessment of left ventricular function by transthoracic echocardiography on 7th postoperative day. Secondary endpoints of cardiac index, tissue perfusion, and PCWP.
HSR-LEVO (NCT00994825) G. Landoni	High risk patients undergoing cardiac surgery with perioperative myocardial dysfunction	1000	24-48 h infusion (varying doses)	Placebo	Primary endpoint of 30-day mortality

Figure legends

Figure 1. Stroke volume (SVI) at the start of surgery (Base), 15 min after the end of cardiopulmonary bypass (post-CPB), at the end of the operation (End surgery), at arrival in the intensive care unit (T0), and 6 (T6), 12 (T12), 24 (T24), and 48 (T48) h later. Levosimendan (□) and Milrinone (▲). Data are mean ±standard deviation. *, Statistically significant difference between groups for P <0.05. (data from de Hert et al. [28])

Figure 2. PRISMA flow diagram [72] for search and inclusion of scientific information into systematic reviews applied to the search ((levosimendan OR Simdax) AND (surgery OR bypass OR valve OR CABG OR anest*)) updated March 27, 2014

Figure 3. Cardiac troponin I concentrations (mean ±95% confidence intervals) in the levosimendan (□) and placebo (▲) groups before surgery (baseline), on arrival in the intensive care unit (0), and after 6, 24, and 48 h. (data from Tritapepe et al. [29])

Figure 4. Need for additional inotropic support in patients with LCOS after cardiac surgery in the study by Levin and colleagues [33], with treatment with levosimendan (white bars) and dobutamine (black bars). *, Statistically significant difference between groups for P <0.05.

Figure 5. Weaning from cardiopulmonary bypass (CPB). First weaning attempt with levosimendan (white bars) and placebo (black bars). Epinephrine added to second weaning attempt. *, Weaning failure led to use of intra-aortic balloon pump (data from Eriksson et al. [27]).

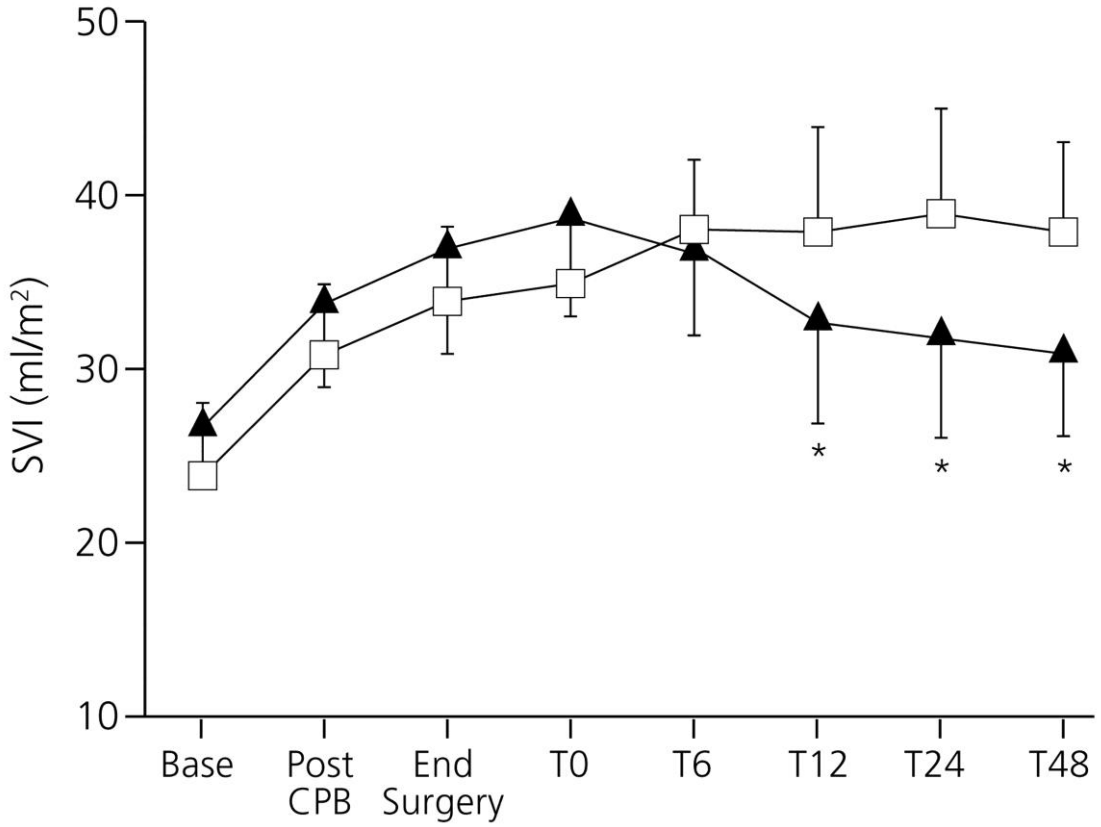

Fig. 1

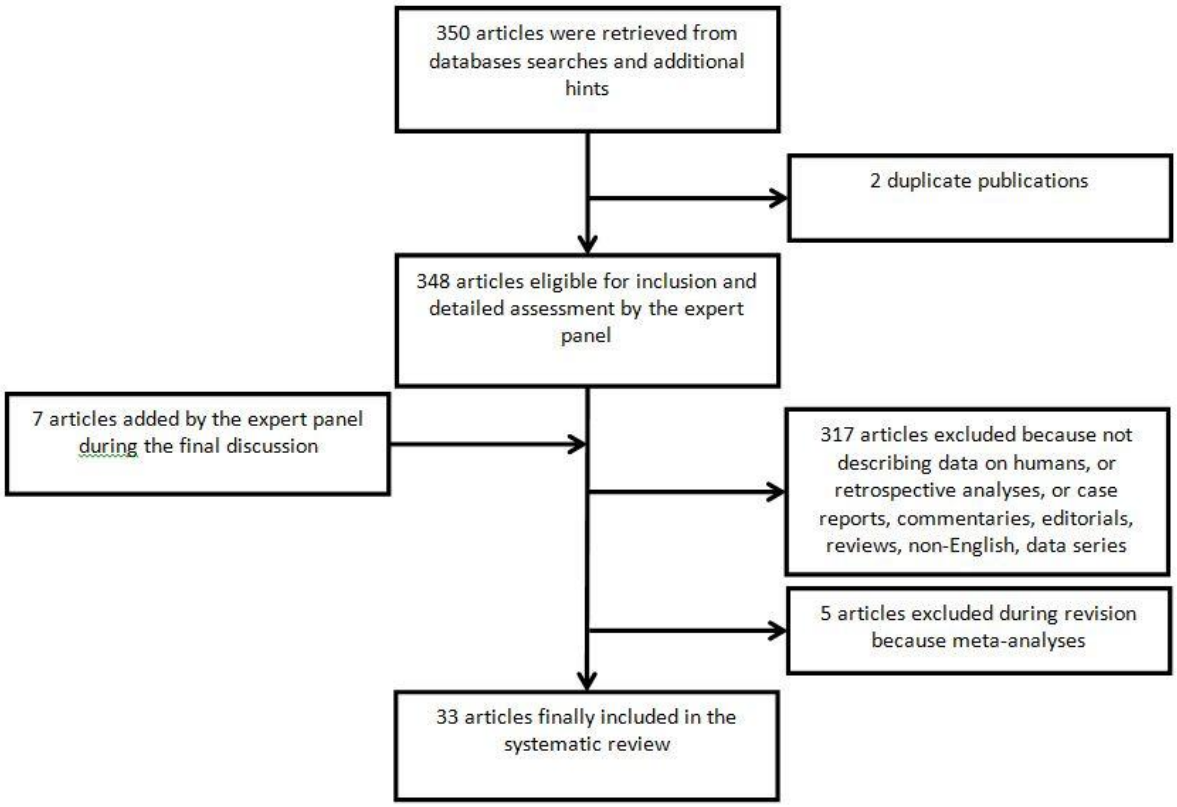

Fig. 2

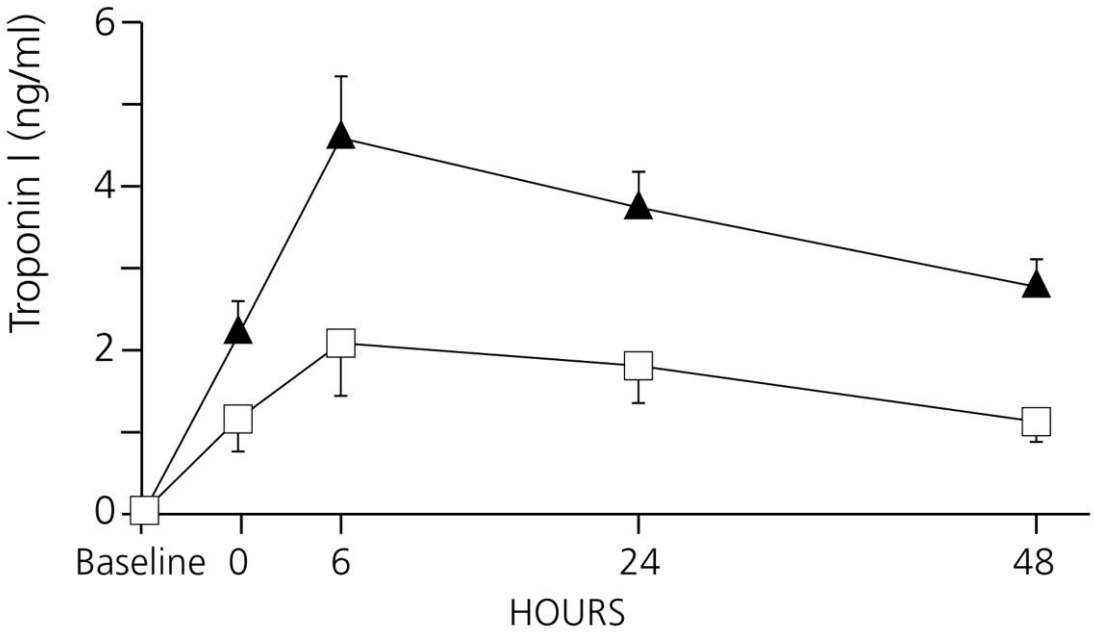

Fig. 3

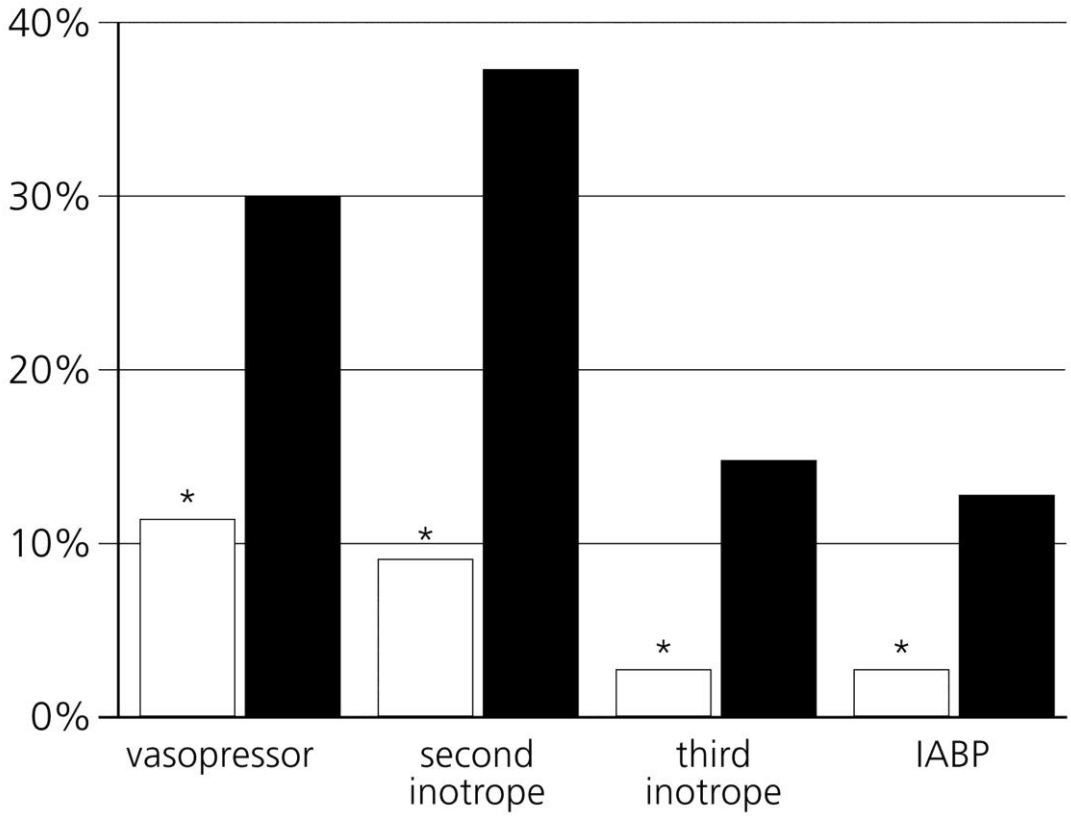

Fig. 4

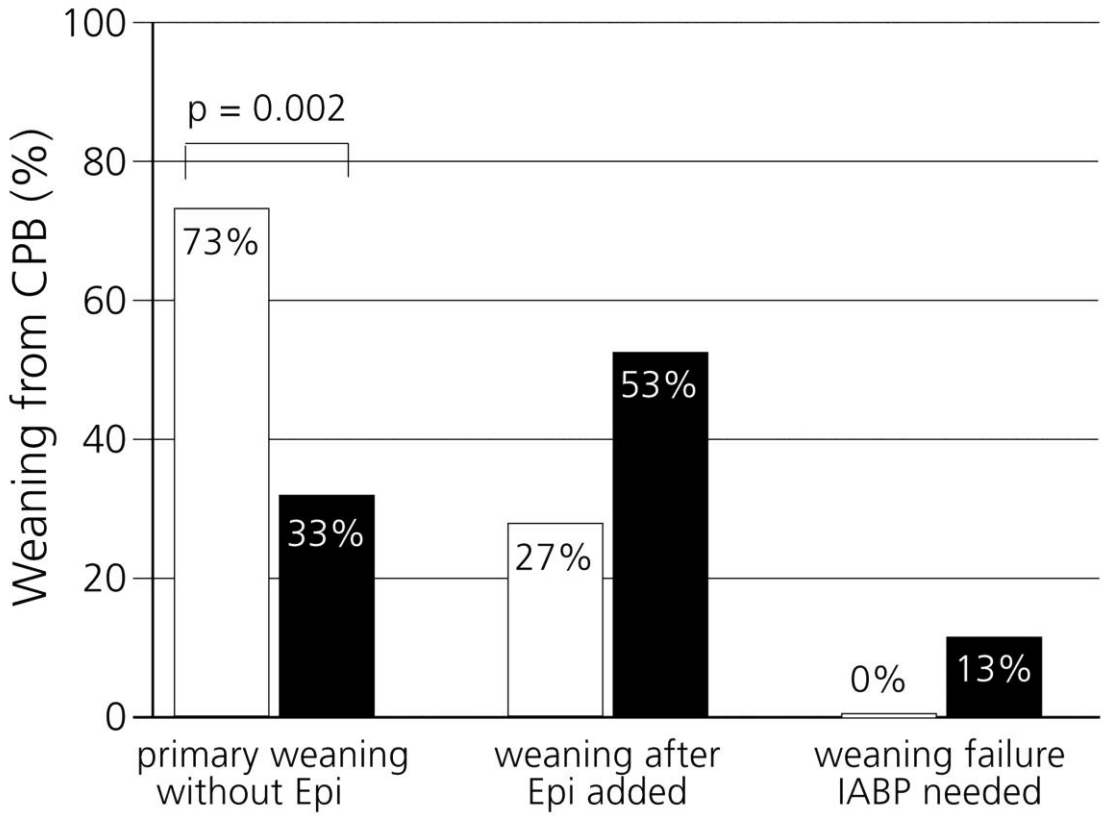

Fig. 5

Highlights

- Review of cardiac and non-cardiac effects of intraoperative levosimendan treatment
- A consensus on the use of levosimendan in the pre-operative settings is presented
- Clear recommendations are proposed.
- The ongoing studies on intraoperative levosimendan are described and commented