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Review

The role of levosimendan in acute heart failure complicating acute coronary syndrome: A review and expert consensus opinion

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ABSTRACT

Acute heart failure and/or cardiogenic shock are frequently triggered by ischemic coronary events. Yet, there is a paucity of randomized data on the management of patients with heart failure complicating acute coronary syndrome, as acute coronary syndrome and cardiogenic shock have frequently been defined as exclusion criteria in trials and registries. As a consequence, guideline recommendations are mostly driven by observational studies,

Abbreviations: ACS, acute coronary syndrome; HF, heart failure; AHF, acute heart failure; CS, cardiogenic shock; AMI, acute myocardial infarction; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; LVEF, left-ventricular ejection fraction; CI, cardiac index; ECMO, extracorporeal membrane oxygenation; LVAD, left-ventricular assist devices; CO, cardiac output; PCI, percutaneous coronary intervention; ECG, electrocardiography; SaO_2, oxygen saturation; IABP, intra-aortic balloon pump; BNP, brain natriuretic peptide.

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even though these patients have a particularly poor prognosis compared to heart failure patients without signs of coronary artery disease.
In acute heart failure, and especially in cardiogenic shock related to ischemic conditions, vasopressors and inotropes are used. However, both pathophysiological considerations and available clinical data suggest that these treatments may have disadvantageous effects. The inodilator levosimendan offers potential benefits due to a range of distinct effects including positive inotropy, restoration of ventriculo-arterial coupling, increases in tissue perfusion, and anti-stunning and anti-inflammatory effects. In clinical trials levosimendan improves symptoms, cardiac function, hemodynamics, and end-organ function. Adverse effects are generally less common than with other inotropic and vasoactive therapies, with the notable exception of hypotension. The decision to use levosimendan, in terms of timing and dosing, is influenced by the presence of pulmonary congestion, and blood pressure measurements. Levosimendan should be preferred over adrenergic inotropes as a first line therapy for all ACS-AHF patients who are under beta-blockade and/or when urinary output is insufficient after diuretics. Levosimendan can be used alone or in combination with other inotropic or vasopressor agents, but requires monitoring due to the risk of hypotension.

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1. Introduction

Acute coronary syndrome (ACS) is one of the main precipitating factors of acute heart failure (AHF) [1], usually in the context of extensive myocardial ischemia, myocardial dysfunction and injury, and arrhythmia. It can lead to the development of de novo AHF or worsening of chronic heart failure [2]. AHF, in turn, can deteriorate into cardiogenic shock (CS). It has been estimated that 15–28% of patients with ACS experience signs and symptoms of AHF. Cardiogenic shock complicating acute myocardial infarction (AMI) occurs in 5–15% [3].

Levosimendan is a calcium sensitizer and ATP-dependent potassium channel opener [4], developed for the treatment of acute decompensated heart failure [5], with a solid evidence of efficacy and safety [6]. This inodilator, used in clinical practice since year 2000, has been tested in the early phases of development in a randomized, placebo-controlled, double-blind safety and efficacy study in patients with left ventricular failure due to an AMI [7]. In the last 15 years some additional evidence has been collected on the use of levosimendan in AHF and CS complicating ACS. In this review and opinion paper the authors analyze the existing data and clinical experience, and give some recommendations on the use of levosimendan in AHF and CS related to ischemic conditions.

2. Methods

A panel of 34 experts in the field of cardiology, intensive care medicine, internal medicine, and cardiovascular pharmacology from 20 European countries (Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Norway, Poland, Portugal, Russia, Slovenia, Spain, Sweden, the United Kingdom, and Ukraine) convened in Munich on January 22nd, 2016 to review systematically the existing data on the use of levosimendan in AHF and CS complicating ACS. Pertinent studies were independently searched in BioMedCentral, PubMed, and Embase (updated January 7, 2016) by three trained investigators. The full search strategy was aimed to include any randomized study ever performed with levosimendan in the relevant clinical setting. The retrieved literature was available for consultation by all the meeting invitees for two weeks before the meeting. During the meeting the group discussed and reached a consensus on the epidemiology and outcome of AHF and CS complicating ACS, and – in general – on the pathophysiology of myocardial ischemia. Furthermore, the panel reached a consensus on some recommendations regarding the use of levosimendan, based on existing literature and clinical experience. The objectives of this opinion paper, in line with the overall vision of the European Society of Cardiology on guidelines [8], are to enhance the appropriateness of practice, and improve quality of cardiovascular care and patient outcomes.

3. Epidemiology and outcome

3.1. Acute heart failure complicating ACS

AHF is frequently complicating ACS especially when large infarction, extensive ischemic area with stunning or mitral regurgitation, and arrhythmias are present [9]. In the EHFS II study, 42% of the de novo AHF was due to ACS [9]. In a recent prospective multicenter study, CS and pulmonary edema were found to be more common in ACS–AHF patients than in AHF patients without concomitant ACS [10]. Accordingly, the ACS–AHF patients were found to have markedly higher short-term mortality rates, with an almost two-fold 30-day mortality (13% vs. 8%; $p = 0.03$). ACS was shown to be an independent predictor of 30-day mortality in the HF population. Interestingly, however, the 5-year mortality rates did not differ (59% vs. 61%; $p = 0.80$). In addition, ACS–AHF prolongs hospitalization and requires more costly treatment in intensive care.

Overall, the incidence of AHF as a complication of ACS, as well as the corresponding mortality, has been decreasing over the last years. Based on the data derived from the SWEDEHEART registry that included 199,851 patients admitted with myocardial infarction between 1996 and 2008 [11], the incidence of HF declined from 46% to 28% ($p < 0.001$). This decrease was more pronounced in patients with ST-segment elevation myocardial infarction (STEMI) than in those with non-ST-segment elevation myocardial infarction (NSTEMI). The decrease in HF can probably be explained by more frequent use of primary PCI, which secures early reperfusion in patients with STEMI and, thereby, salvages jeopardized myocardium. Also, an increased use of evidence based pharmacological treatment preventing remodeling may contribute. Finally, the more frequent detection of minor AMI with high-sensitivity troponin testing may lower the estimated HF risk, since the precipitation of AHF depends on the size of injury or ischemic area.

At all events, HF is still a significant complication that affects a substantial proportion of patients and worsens outcomes. Risk factors for the development of AHF during a hospital stay due to ACS, according to multivariate analysis based on the data obtained in SWEDEHEART, include advanced age, female gender, history of AMI, diabetes mellitus, hypertension, and history of chronic HF.

3.2. Cardiogenic shock complicating ACS

The CardShock Study identified ischemic causes as the principal etiology of CS (81%) [12]. As opposed to AHF, the incidence of CS upon admission has remained fairly stable over time, although the incidence during hospital stay has decreased [13]. While CS has become less common in STEMI, this is not the case for patients with non-ST-segment elevation ACS [13]. Although the prognosis of CS has been

slowly improving over the past few decades [14,15], the mortality is still high, and remains between 40% and 50% despite advances in early revascularization and the implementation of new drugs [3]. Patients developing CS due to ischemic heart disease show significantly worse outcomes than those with non-ischemic causes [12]. Among patients with ischemic CS, more than 70% present with multi-vessel disease and this group faces an increased risk of mortality as compared to those with single-vessel disease [3]. Other factors associated with high mortality in CS are advanced age, history of previous myocardial infarction or coronary artery bypass grafting, anoxic brain damage or confusion, decreases in left-ventricular ejection fraction (LVEF), cardiac index (CI) cardiac output and systolic blood pressure, need for vasopressor support, deterioration in renal function, and elevated serum lactate levels [12]. Prior CPR is also an important factor.

A patient who presents with CS should be triaged to a fast track or urgent care setting, with the aim of either maintaining perfusion to prevent organ dysfunction, or trying to retain organ dysfunction in a reversible state [16]. It should be immediately ascertained whether the patient is hemodynamically stable or unstable. In a non-responding patient, the use of mechanical circulatory support system or extracorporeal membrane oxygenation (ECMO) should be considered if it becomes obvious that the patient is not going to be stable under medication alone. The management of patients who develop CS in the course of their hospital stay is even more challenging than that of patients presenting with CS already at admission, and they must not be overlooked. In fact, there has been no major breakthrough in the management of CS since the 1990s. There is still a need to improve understanding, risk stratification, and management of CS.

3.3. Pathophysiology following myocardial ischemia

Within hours, ischemia of the myocardium may induce AHF due to increased wall stiffness, stunning and mechanical complications of infarction and reduced contractility (Fig. 1) [17]. The subsequent changes in hemodynamics occur within the first 24–48 h. Recovery is delayed in stunning or hibernating myocardium (2–4 d). Due to the rapid development of HF, the pulmonary vasculature is frequently not able to adapt promptly. While the right ventricle might function normally, impaired left ventricular function and hemodynamic overload results in backward failure with pulmonary congestion/edema. Mitochondrial dysfunction may contribute to the progression of cardiac ischemic injury, especially at the onset of reperfusion, because defective oxidative phosphorylation in the presence of an excessive energy demand is likely to trigger irreversible damage of cardiomyocytes [18]. Therefore, recovery is greatly accelerated if the worsening condition is treated without delay. According to the Forrester classification [19], the most challenging HF patients are those who show both congestion and hypoperfusion ("wet and cold").

In terms of pathophysiology, profound depression of myocardial contractility leads to CS, resulting in a vicious spiral of reduced cardiac output (CO), low blood pressure, impaired coronary perfusion, and further concomitant reductions in contractility and CO. Also, an acute deterioration in the diastolic function may contribute to further derangement of ventricular function and congestion. The classical paradigm predicts that compensatory systemic vasoconstriction occurs in response to this, i.e. over activation of adrenergic and RAAS reflex-mechanisms causing increases in vascular resistance, but this is not always the case [20]. Impaired hemodynamic capability is also due to changes in ventricular and arterial elastance [21]. Under normal conditions ventricular and arterial elastances show approximately equal slopes, providing hemodynamic equilibrium to occur at the lowest energy cost [22]. In a failing condition, however, reductions in the contractility and/or increases in the arterial elastance lead to ventriculo-arterial uncoupling and increased myocardial oxygen consumption. The administration of vasopressors worsen this problem by enhancing peripheral vasoconstriction and, thereby, further worsening ventriculo-arterial coupling. Overtime inflammation induced vasodilation will decrease organ perfusion and will result in multiorgan dysfunction.

4. Current practice and evidence-based guidelines

At present, specific consensus and international guidelines on the comprehensive pharmacological and non-pharmacological treatments of ACS patients with HF are not available. HF guidelines commonly exclude ACS patients, while ACS guidelines tend to focus predominantly on invasive therapies. This lack of treatment guidelines can be explained

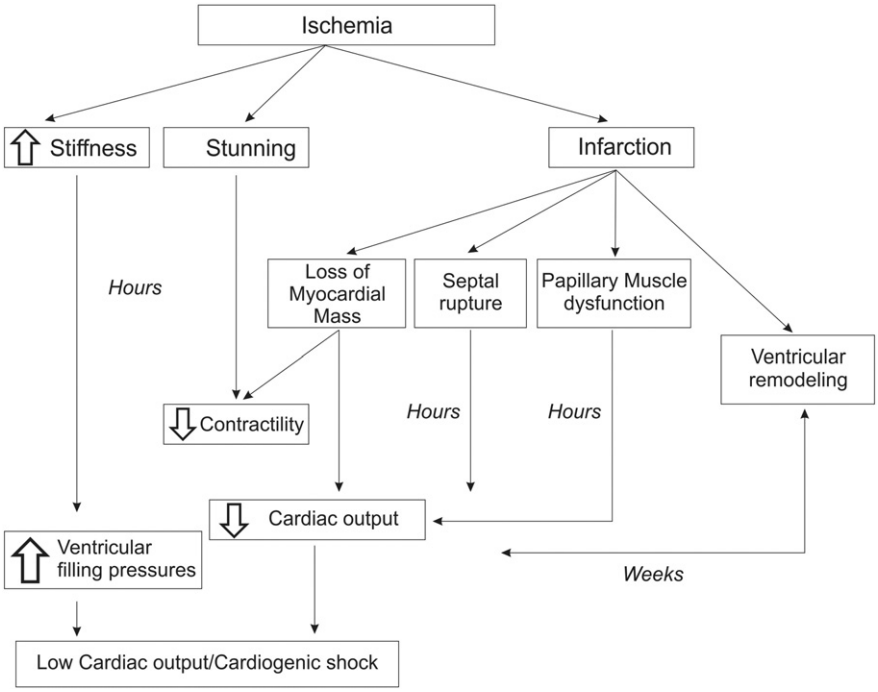

Fig. 1. Factors contributing to heart failure in acute coronary syndromes [17].

the paucity of data, since many clinical trials and even registries have excluded patients with AHF/CS due to ACS. According to the only available guideline in Europe (the German–Austrian S3 Guideline on diagnosis, monitoring and treatment of CS due to myocardial infarction [23]), there is a lack of evidence for all recommended therapeutic strategies.

Likewise, in their review of pharmacologic therapies for acute CS, Nativi-Nicolau et al. [24] found that reliable information regarding comparative efficacy of individual agents is insufficient. Moreover, mortality data are not available or uncertain. The authors concluded that the use of inotropes and vasopressors and diuretics should be limited to the bridging of patients to recovery, mechanical circulatory support or heart transplantation. A Cochrane analysis on inotropic agents and vasodilator strategies for AMI complicated by shock or low-cardiac-output syndrome [25] states that there is no robust or convincing data to support a specific inotropic or vasodilatory therapy as a superior strategy to other therapies used to reduce mortality in hemodynamically unstable patients.

Guidelines recommend the administration of adrenergic agents if necessary for maintaining adequate circulation, but recommend also that these drugs should be given at as low dose and for as short duration as possible to prevent side effects.

4.1. Inotropes in patients with ACS and CS

Inotropic drugs are indeed used as first-line treatment, without or with vasopressors in patients with CS related to ACS [26]. The administration of these drugs requires continuous monitoring of hemodynamic parameters and, in a state of hypoperfusion, fluid compensation under invasive measurement of blood pressure and possibly CO. Inotropic agents should be given for a limited period of time, and it is advisable to define criteria for planned weaning at the time of initiation of treatment. As soon as a stable condition has been achieved, weaning off should be considered. Mechanical circulatory support should be considered as soon it becomes clear that hemodynamic stability with preserved end organ function cannot be maintained with medication alone.

4.2. Vasoconstrictors/inopressors in patients with ACS and CS

Vasopressors and inotropes are a mainstay of treatment of patients with CS. Vasopressors are frequently used alone in an attempt to restore blood pressure. Several studies suggest, however, that this approach is not advisable since it may inflict harm. An analysis combining three data bases [27] showed that the mortality was higher in patients treated with vasopressors alone than in those receiving combinations of vasopressors and inotropes. This effect was independent of the underlying disease and the database used.

These results are echoed in other studies, such as an analysis of approximately 5000 patients with AHF including CS in the ALARM database [28]. In this study, the use of epinephrine and norepinephrine predicted the poorest outcomes.

Overall, these data are a strong signal indicating that monotherapy with vasopressors and/or inopressors should be avoided in the treatment of the failing heart, as the associated increase in LV afterload imposes a burden on the ischemic myocardium. In contrast, these pathophysiological considerations render the use of an inodilator more suitable.

Of course, mechanical circulatory support is an important part of the treatment of CS. Choices have to be made between the available options, and the treatment should be implemented as quickly as possible. Also, the prevention or management of potential complications related to the devices should be considered. As for patient selection, the combination of NT-proBNP levels >3.500 ng/L and/or levels of the cardiac biomarker ST2 > 350 μg/mL is predictive of high mortality rates, reaching 70%–80% during the first 24 h and can help to identify patients with the highest likelihood to benefit from assist devices [12].

5. Data on levosimendan

5.1. Pharmacologic rationale for the use of levosimendan

The inodilator levosimendan offers potential benefits in the setting of AHF/CS complicating ACS. Levosimendan has been developed for the treatment of AHF and other cardiac conditions where the use of an inodilator is considered appropriate. At least three major pharmacological actions have been identified [4], i.e. (i) the selective binding to Ca^{2+}-saturated cardiac troponin C, (ii) the opening of ATP-sensitive potassium (K_{ATP}) channels in the vasculature, and (iii) the opening of K_{ATP} channels in the mitochondria. The pharmacology of levosimendan includes positive inotropy with energy-sparing effects, positive effects on ventriculo-arterial coupling, peripheral vasodilation and increasing tissue perfusion, anti-stunning effects and anti-inflammatory effects [4].

As opposed to other inotropic drugs used in HF treatment, levosimendan does not raise intracellular calcium levels [29]. This implies that less energy is utilized by the cardiomyocytes, because re-internalization of calcium increases ATP expenditure and accounts for 30% of the energy consumed by the cardiomyocyte during the contraction–relaxation cycle. A comparison of levosimendan and milrinone [30] shows that both molecules intensify cardiac contraction, but while milrinone increases oxygen consumption, levosimendan does not. In clinical settings, levosimendan was also shown to be superior to dobutamine as it regards myocardial efficiency [31,32].

Levosimendan-mediated opening of K_{ATP} channels on smooth muscle cells in the vasculature has been demonstrated in many different vessels. According to another comparison of levosimendan and milrinone [33], levosimendan improves the microcirculation in the splanchnic vessels, whereas milrinone has a neutral effect, even though both drugs have a similar influence on systemic blood pressure. Further, levosimendan improved long-term renal function in patients with advanced chronic HF awaiting cardiac transplantation [34], possibly via enhanced renal blood flow. Both creatinine levels and creatinine clearance were improved as compared to controls.

In another study, Bragadottir et al. [35] showed that levosimendan had positive effects on renal blood flow, glomerular filtration rate, renal oxygen consumption and oxygenation. The authors found a remarkable difference between levosimendan and dopamine regarding glomerular filtration rates [36]. A possible explanation for this is that levosimendan has differential effects on afferent and efferent vessels in the kidney, whereas the effects of dopamine are independent of the vessel type [37].

Opening of K_{ATP} channels in the cardiac mitochondria is assumed to exert cardioprotective effects [38]. Du Toit et al. [39] showed that in a guinea pig model, preconditioning with levosimendan decreased the extent of hypoxic myocardial injury from 100% to 10%. Also, post-conditioning activity of levosimendan was demonstrated by Hönisch et al. [40]. The use of levosimendan after an ischemic event can diminish stunning. According to Sonntag et al. [41], patients with ACS treated with levosimendan experienced a decrease in the total number of hypokinetic segments as compared to placebo. Levosimendan reduces myocardial infarct size and increases left-ventricular function after acute coronary occlusion [42]. Additionally, in animal models levosimendan showed anti-ischemic [43], anti-remodeling [44] and anti-apoptotic effects [45]. As it regards effects on neurohormones, in the SURVIVE study levosimendan was superior to dobutamine for a sustained decrease of BNP [46].

5.2. Levosimendan in the treatment of AHF complicating ACS

In the placebo-controlled RUSSLAN trial [7], 6-h infusions of levosimendan at different doses were shown to be safe in 504 patients, who developed HF within 5 days after AMI and required inotropic therapy due to symptomatic HF despite conventional therapy. Levosimendan decreased the incidence of worsening heart failure and reduced both short-term and long-term mortality (Fig. 2). Hypotension, as a side effect

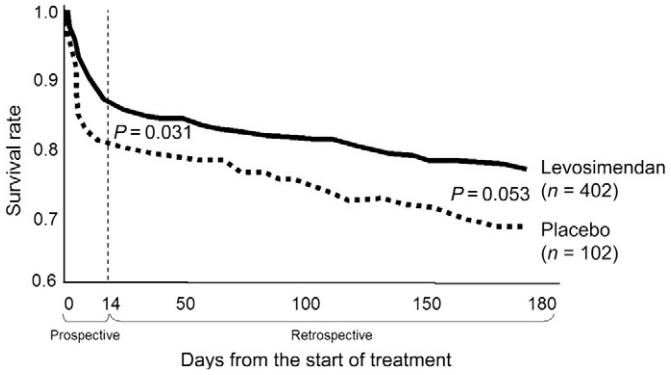

Fig. 2. RUSSLAN trial: overall survival during 180 days after infusion of levosimendan or placebo. Adapted from Moiseyev et al. [7].

of levosimendan, occurred in 4%–10% of patients, depending on the dose and use of a bolus. Other adverse events, such as episodes of ischemia, ventricular extra-systoles, and sinus tachycardia, occurred mainly or exclusively at higher doses. The lower levosimendan doses of 0.1 μg/kg/min and 0.2 μg/kg/min were accompanied by a low risk of adverse events.

In their placebo-controlled trial, Sonntag et al. [41] evaluated 24 patients with ACS. Levosimendan was administered as a bolus (24 μg/kg) for 10 min after PCI. This treatment induced reductions in the number of hypokinetic segments in the left ventricle and increased LVEF, suggesting that levosimendan may counteract post-ischemic stunning. In addition, pulmonary arterial pressure decreased in the levosimendan group, but not in the placebo group.

De Luca et al. [47] investigated levosimendan as compared to placebo in 26 patients with STEMI and left-ventricular dysfunction (EF <40%). Levosimendan was applied at a bolus dose of 12 μg/kg 10 min after PCI, followed by an infusion at 0.1 μg/kg/min for 24 h. As compared with placebo, levosimendan was associated with improved coronary flow reserve, reduced pulmonary capillary wedge pressure, and increased CI. Another study by the same group [48] was conducted in 52 patients with anterior STEMI. Again, they were treated with levosimendan at a bolus dose of 12 μg/kg for10 min after PCI, followed by an infusion at 0.1 μg/kg/min for 24 h. Levosimendan improved isovolumetric relaxation as compared to placebo, and reduced the ratio of peak early to late diastolic flow velocities, indicating decreased filling pressure.

Sixty-one patients who developed clinical signs of HF (including CS) within 48 h after primary PCI-treated STEMI were included in the trial by Husebye et al. [49]. The treatment consisted of levosimendan at a dose of 0.2 μg/kg/min for 60 min followed by 0.1 μg/kg/min for 24 h, or placebo. The infusions were started approximately 24 h after PCI. Evaluation of the primary endpoint, which was defined as the change in wall motion score index after 5 days, by echocardiography, showed that levosimendan improved contractility in post-ischemic myocardium compared to placebo ($p = 0.031$). Numerically fewer patients died or were re-hospitalized for HF, even though this difference was not statistically significant. Hypotension occurred more frequently with levosimendan (67% vs. 36%; $p = 0.029$).

In the randomized, placebo-controlled, open-label study by Wu et al. [50], 30 patients with severe HF (NYHA III–IV) and LVEF <40% after PCI-treated AMI received either levosimendan as an infusion at 0.1 μg/kg/min for 24 h, or placebo. Low-dose dobutamine echocardiography showed significantly less stunned and infarcted segments in levosimendan group than with placebo.

Another randomized, placebo-controlled trial [51] enrolled 160 patients with HF due to AMI, who were treated with or without revascularization. Levosimendan was administered as a bolus at a dose of 24 μg/kg in 10 min followed by an infusion at 0.1 μg/kg/min for 24 h. As compared to placebo, this treatment induced significant improvement in the primary endpoint, which was a composite outcome including death and worsening heart failure at six months (43.7% vs. 62.5%; HR, 0.636; $p = 0.041$).

Indeed the largest head to head comparison of levosimendan vs. dobutamine in AHF related to AMI remains the SURVIVE clinical trial. This randomized, double-blind trial compared the efficacy and safety of intravenous levosimendan or dobutamine in 1327 patients hospitalized with acute decompensated heart failure who required inotropic support [52]. A relevant number of patients were hospitalized with AMI (178, or 13.4%) and the data of mortality were stratified also for this parameter. The 31-day mortality in the AHF-AMI subgroup was 23/83 (28%) and 30/95 (32%) in the levosimendan and dobutamine arms respectively (RR 0.83 [0.48–1.43]). As a comparison, the 31-day mortality in the non-AHF-AMI subgroup was 56/581 (10%) and 61/568 (11%) in the levosimendan and dobutamine arms respectively (RR 0.89 [0.62–1.28]).

Two independent meta-analyses by Landoni et al. [53] and Koster et al. [54], considering 45 and 48 randomized studies respectively, focused also on the adverse effects of levosimendan vs. comparator arms (active drugs or placebo on top of standard of care). With the exception of hypotension, no other signs for increase of adverse events by levosimendan were reported in either meta-analyses.

5.3. Levosimendan in the treatment of CS complicating ACS

In their randomized, prospective, single-center, open-label trial, Fuhrmann et al. [55] found that levosimendan appeared superior to enoximone as an add-on therapy in refractory CS complicating AMI. Thirty-two patients received levosimendan (a bolus at 12 μg/kg/10 min followed by an infusion at 0.1 μg/kg/min for 50 min and 0.2 μg/kg/min for 23 h) or enoximone on top of the current treatment (PCI, vasopressors, etc.). Both drugs had similar hemodynamic effects, but the survival at 30 days was significantly in favor of levosimendan (69% vs. 37%; $p = 0.023$). Death from multiple organ failure occurred only in the enoximone group. The levosimendan-treated arm tended to require less additive dobutamine and norepinephrine treatment than the enoximone group to maintain tissue perfusion.

Twenty-two STEMI patients with CS after PCI were enrolled in a randomized, prospective, single-center, open-label trial [56] comparing levosimendan (a bolus dose of 24 μg/kg over 10 min followed by an infusion at 0.1 μg/kg/min/24 h) and dobutamine (5 $\mu g\ kg^{-1}\ min^{-1}$, without loading dose) in addition to current standard therapy. Treatment effects on CI and cardiac power index were consistently better with levosimendan than with dobutamine. Significant reductions in isovolumetric relaxation time and increases in the early diastolic/late diastolic flow ratio occurred in the levosimendan group at 24 h [57], and the LVEF was significantly improved ($p = 0.003$) [58]. No difference was seen regarding long-term survival.

In their observational study, Russ et al. [59] treated 56 patients with myocardial infarction and persisting CS 24 h after percutaneous revascularization with levosimendan 12 μg/kg for 10 min followed by 0.05–0.2 μg/kg/min for 24 h. Norepinephrine and dobutamine therapy only resulted in marginal improvements in CI and mean arterial pressure, while levosimendan produced significant increases in CI ($p < 0.01$) and cardiac power index ($p < 0.01$). At the same time, systemic vascular resistance decreased significantly ($p < 0.01$).

A non-randomized trial [60] compared supplementary levosimendan treatment with intra-aortic balloon pump placement in patients with AMI and refractory CS following preliminary hemodynamic support (dobutamine with or without norepinephrine) and primary PCI. Infusion of levosimendan resulted in early and sustained hemodynamic improvement. CI and cardiac power index rose more rapidly in the levosimendan arm, and systemic vascular resistance showed a more pronounced initial decrease. For mean arterial pressure, there were no differences between the two treatments. This also applied to the use of supplementary drugs (dobutamine and norepinephrine).

Data from 94 consecutive patients with CS due to STEMI [61] that were obtained prospectively in two Swedish registries suggest that

the use of levosimendan neither increases nor decreases mortality. Moreover, there were no differences in adverse events or length of hospital stay between patients who received levosimendan and those who did not.

Another potential indication of levosimendan therapy is transient left ventricular apical ballooning syndrome (Takotsubo cardiomyopathy). In an animal model mimicking Takotsubo syndrome [62], levosimendan was shown to reverse adrenaline-induced apical dysfunction. In a case series comprising 13 consecutive patients with Takotsubo cardiomyopathy, Santoro et al. [63] found that the use of levosimendan was associated with significantly improved left-ventricular function. The introduction of levosimendan rapidly provided relief of signs and symptoms of HF. Similarly, in isolated RV cardiogenic shock patients levosimendan showed profound hemodynamic improvement [64].

Overall, the existing studies on levosimendan in AHF and CS are not adequately powered for reaching conclusions on the effect of the treatment on survival. As reviewed, however, the existing data on the beneficial activity of levosimendan treatment can justify its use in certain AHF settings and in CS also when related to ACS.

6. Panel's recommendations on the use of levosimendan in AHF/CS complicating ACS

6.1. Indication

Based on the available evidence, levosimendan should be considered in the setting of AHF/CS complicating ACS according to the clinical manifestations. The four Killip classes were considered as a starting point for the discussion, but class I was omitted since it includes individuals with no clinical signs of heart failure. The patients in the remaining three classes were further segmented in four types (see Table 1). The table details the suggested drug treatment in each of these types after initial therapy, including recommendations on the use of levosimendan. Overall, while levosimendan could convey benefits in patients with SBP > 110 only when β-blocker is used, and urinary output is insufficient after diuretics, it is a rationale option when SBP is between 85 and 110 mm Hg, and should be a drug of choice in CS, usually combined with norepinephrine.

Levosimendan can either replace other inotropic drugs, or can be used in combination with other inotropic and vasopressor agents. Once the patient's cardiac function improves, weaning off the co-medication is possible. Finally, it is also important to prefer levosimendan over adrenergic inotropes as a first line therapy for all ACS-AHF patients who are taking beta-receptor blockers chronically and/or when urinary output is insufficient after diuretics.

6.2. Dosing

In the setting of AHF/CS, we recommend doses of 0.05–0.1 μg/kg/min for 24 h. If a faster onset of action is needed, an infusion of 0.2 μg/kg/min could be used during the first 60 min. Risk–benefit profile with 0.2 μg/kg/min dose is shown to be favorable with up to 6-h infusion. Application of a bolus dose should be avoided due to the risk of hypotension.

6.3. Monitoring

Hypotension, a well-known side effect of levosimendan, is of particular concern in patients with ACS. Therefore, continuous hemodynamic monitoring is of major importance. This includes ECG, blood pressure, SaO_2, heart rate, urinary output, potassium levels, and clinical signs. End-organ function (liver, kidney, mental status) should be evaluated. Central venous and arterial catheter measurements are required in CS. Furthermore, a pulmonary artery catheter offers a complete hemodynamic assessment and monitoring of mixed venous saturation reflects general tissue oxygenation in complicated cases, and is recommended to be used in cardiogenic shock to monitor filling pressures and output. Also, CO can be assessed non-invasively using echocardiography.

As a general rule, we feel that the use of levosimendan should preferable reside with experienced physicians.

7. Conclusions

On the basis of the existing literature and the direct clinical experience, the members of the panel agree that (i) the inodilator levosimendan offers potential benefits in treatment of acute heart failure and/or cardiogenic shock complicating ACS due to a range of distinct effects including positive inotropy, restauration of ventriculo-arterial coupling, increases in tissue perfusion, and anti-stunning and anti-inflammatory effects; (ii) clinical trials investigating levosimendan in acute heart failure and cardiogenic shock suggest improvements in cardiac function, hemodynamics, and end-organ function. Re-hospitalization rates are decreased, (iii) adverse effects are generally less common with levosimendan than with other inotropes, inodilators or inoconstrictors, (iv) the indication of levosimendan depends on the presence of congestion, levels of

Table 1
Medical treatment options in patients with AHF/CS and ACS after initial therapies[a].

Killip class	II, rales, pulmonary congestion		III, acute pulmonary oedema	IV, hypotension or CS
AHF/CS, segmentation by SBP	SBP > 110 mm Hg	85 < SBP < 110 mm Hg, worsening of HF	85 < SBP < 110 mm Hg, decreasing	SBP <; 85 mm Hg, evidence of peripheral vasoconstriction
Loop diuretic (e.g. furosemide i.v.)	+	+	+	+
β-blocker	maintain	reduce or withdraw according to patient status[b]	withdraw[b]	withdraw
Vasodilator (e.g. nitrate)	+	+ initially	+ initially	−
Inotrope i.v. (e.g. dobutamine)	−	+ initially	+ in case of poor response to standard therapy	+ initially
Vasopressor i.v. (e.g. norepinephrine)	−	− not initially	− not initially	+ (aiming for SBP > 90 mm Hg, with inotrope or inodilator)
Inodilator i.v. levosimendan	−/+ (when β-blocker is used and urinary output is insufficient after diuretics)	−/+ (when β-blocker is used and urinary output is insufficient after diuretics)	+ (when SBP > 90 mm Hg, if hypotensive response, consider filling or combining vasopressor)	+ (with vasopressor)
ECMO, LVAD, (IABP[c])	−	−	−	+ (with CI < 1.8 L/min and not responding to medical treatment)

AHF, acute heart failure; CS, cardiogenic shock; ACS, acute coronary syndrome; SBP, systolic blood pressure; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; CI, cardiac index.

[a] Monitoring, fluid challenge, arrhythmia care, cardiac catheter including angiography/Percutaneous Coronary Intervention (PCI).

[b] Some patients in this class need beta-blockade despite hemodynamic impairment, to manage ventricular arrhythmias, or to rate control AF.

[c] IABP is indeed not recommended by the most recent STEMI ESC guidelines but in case of mechanical complication.

blood pressure and heart rate, and the extent of cardiac ischemia, (v) levosimendan can be used alone or in combination with other agents, but (vi) it requires continuous monitoring due to the risk of hypotension. Finally, the panel agrees on the practical recommendations on indication, dosing, and monitoring as described in chapter 6 of this article.

Author contributions

Three of the authors (M.S.N., M.K., and P.P.) 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

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