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A pragmatic approach to the use of inotropes for the management of acute and advanced heart failure: An expert panel consensus

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ABSTRACT

Inotropes aim at increasing cardiac output by enhancing cardiac contractility. They constitute the third pharmacological pillar in the treatment of patients with decompensated heart failure, the other two being diuretics and vasodilators. Three classes of parenterally administered inotropes are currently indicated for decompensated heart failure, (i) the beta adrenergic agonists, including dopamine and dobutamine and also the catecholamines epinephrine and norepinephrine, (ii) the phosphodiesterase III inhibitor milrinone and (iii) the calcium sensitizer levosimendan. These three families of drugs share some pharmacologic traits, but differ profoundly in many of their pleiotropic effects. Identifying the patients in need of inotropic support and selecting the proper inotrope in each case remain challenging. The present consensus, derived by a panel meeting of experts from 21 countries, aims at addressing this very issue in the setting of both acute and advanced heart failure.

1. Introduction

Inotropes aim at increasing cardiac output by enhancing cardiac contractility. They constitute the third pharmacological pillar in the treatment of patients with decompensated heart failure (HF), the other two being diuretics and vasodilators [1]. Decompensated HF patients who need inotropic support belong to two distinct, though partly overlapping, subpopulations, namely acutely decompensated or acute HF (AHF) and advanced HF (AdvHF, Fig. 1). Acute HF is characterized by a rapidly or gradually evolving hemodynamic derangement, characterized usually by congestion and less commonly by low cardiac output [1]. Advanced HF, on the other hand, represents a severe, sometimes end-stage, form of the syndrome, characterized usually by low cardiac output, with or without congestion [2]. In either conditions, treatment with inotropes may be needed to manage low cardiac output that results in end-organ hypoperfusion, with or without hypotension, despite adequate or even elevated filling pressures. Besides symptomatic improvement, however, there is no compelling evidence suggesting a survival benefit of inotropes by a series of clinical studies [3,4]. In contrast, some inotropes have even been associated with increased short and long-term mortality in clinical trials [5,6] and propensity score-matched analyses of registries [7,8]. The negative effect on survival has been attributed to a series of inherited detrimental effects of inotropes, including myocardial ischemia, hypotension, tachycardia, and arrhythmogenesis [9]. On the other hand, adverse inotrope outcomes may also be related to the fact that their use is sometimes inappropriate. Registry data show that inotropes are often administered in patients with normal or even increased systolic blood pressure, including 14% of patients with systolic blood pressure (SBP) higher than 120 mmHg (OPTIMIZE registry), 13% of those with SBP >160 mmHg (ALARM-HF registry) and 4% of those with SBP >180 mmHg (European Heart Failure Survey II), as well as in 8%–10% of patients with HF with preserved ejection fraction (ADHERE registry) [10–13]. Therefore, there is a clear need to improve both the identification of patients who really need inotropic support, and the selection of the proper inotrope in each case [14].

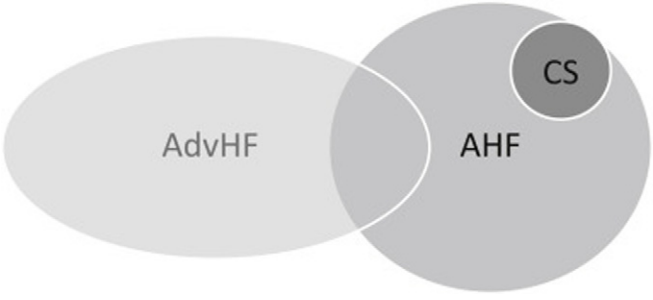

Fig. 1. Clinical entities in which inotropes are used. Acute heart failure (AHF) often overlaps with advanced heart failure (AdvHF), as the vast majority of patients AHF suffer from acute decompensation of the chronic form of the syndrome. Cardiogenic shock (CS) represents a subset of AHF patients.

The present consensus document sought to address the issue of inotrope use in the setting of both AHF and AdvHF. The paper summarizes the key messages derived by an expert panel meeting, organized by the Heart Failure Unit of the Second Department of Cardiology, Attikon University Hospital, National and Kapodistrian University of Athens, Greece, held in Athens in September 2018 and attended by experts from 21 countries (Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Israel, Italy, Poland, Russia, Slovenia, Spain, Sweden, Switzerland, and Turkey).

2. Current inotropes

Based on the main mechanism of action, there are three classes of parenterally administered inotropes currently indicated for the treatment of decompensated HF, (i) the beta adrenergic agonists, including primarily dopamine and dobutamine and also the catecholamines epinephrine and norepinephrine, (ii) the phosphodiesterase III inhibitor (PDEi) milrinone and enoximone and (iii) the calcium sensitizer levosimendan (Table 1) [14].

2.1. Beta agonists

β-agonists stimulate the sarcolemmal beta-1 adrenergic receptor of cardiomyocytes, leading to increased activation of intracellular adenyl cyclase, increased synthesis of cyclic adenosine monophosphate (cAMP), increased release of Ca^{2+} from sarcoplasmic reticulum and thus enhanced actin-myosin interaction and ultimately increased contractility, by means that also increase myocardial oxygen demand [15]. The different beta agonists bear diverse pharmacologic properties because of their diverse affinity for the beta-1 receptors and their action on other receptors.

Dopamine is an endogenous molecule. At low doses (0.5 to 2.5 μg/kg/min), it causes renal and splanchnic vasodilation and increase in renal blood flow, independently of cardiac output, through the activation of dopaminergic receptors 1 and 2. At moderate doses (3 to 5 μg/kg/min), it exerts mainly inotropic and chronotropic effects through beta-1 receptors, while at higher doses (>5 μg/kg/min), it causes vasoconstriction by stimulating alpha-1 adrenergic receptors [16].

Dobutamine is a synthetic analogue of dopamine with mainly inotropic and less chronotropic properties. At low doses (<5 μg/kg/min), it induces inotropic and mild vasodilatory effects that may cause hypotension, while at higher doses (>10 μg/kg/min), it exerts inotropic, chronotropic, and mild vasoconstrictive actions.

Table 1
Inotropic agents in current use for the treatment of heart failure (modified from Bistola V & Chioncel O [31]).

	Adrenergic receptors agonists				Calcium sensitizer	PDE III inhibitor
Agents	Dopamine	Dobutamine	Nor-epinephrine	Epinephrine	Levosimendan	Milrinone
Mechanism of action	D > β; HD, α	β1 > β2 > α	α > β1 > β2	β1 = β2 > α	Calcium sensitization; HD, PDE III inhibition	PDE III inhibition
Inotropic effect	↑↑	↑↑	(↑)	↑↑	↑	↑
Arterial vasodilatation	↑↑ (renal, LD)	↑	0	↑	↑↑	↑↑↑
Vasoconstriction	↑↑ (HD)	↑ (HD)	↑↑	↑ (HD)	0	0
Pulmonary vasodilatation		↑ or 0	↓ or 0 (at high PVR)	↓ or 0 (at high PVR)	↑↑	↑↑
Elimination $t_{½}$	2 min	2.4 min	3 min	2 min	1,3 h (active metabolite, 80 h)	2,5 h
Infusion dose	<3 μg/kg/min: renal vasodilation; 3–5 μg/kg/min: inotropic; >5 μg/kg/min vasoconstrictor	1–20 μg/kg/min	0.02–10 μg/kg/min	0.05–0.5 μg/kg/min	0.05–0.2 μg/kg/min	0.375–0.75 μg/kg/min
Bolus dose	No	No	No	1 mg during resuscitation every 3–5 min	6–12 μg/kg over 10 min (optional, only in euvolemic and eukalemic state)	25–75 μg/kg over 10–20 min

PDE: phospodiestarase; D: dopaminergic receptors; HD: high dose; LD: low dose; PVR: pulmonary vascular resistances; CS: cardiogenic shock.

Norepinephrine is a vasoconstrictor rather than an inotropic agent through its action on alpha-1 receptors and, in the case of HF, is usually used in combination with classical inotropes in cardiogenic shock to restore blood pressure or in association with dobutamine or inodilators to avoid hypotension. Epinephrine causes vasodilation at low doses (<0.01 μg/kg/min) and inotropy along with vasoconstriction at higher doses (0.05–0.5 μg/kg/min). It is used primarily in the setting of cardiac arrest. Epinephrine may result in lactic acidosis while its use in cardiogenic shock has been associated with increased mortality and should be avoided [17].

2.2. The phosphodiesterase III inhibitors

Phosphodiesterase III inhibitors include milrinone and enoximone, although the latter is not currently available or in use in many countries. Phosphodiesterase III inhibitors increase intracellular cAMP levels in cardiomyocytes by inhibiting its breakdown by the sarcoplasmic reticulum-associated phosphodiesterase III, thus increasing intracellular Ca^{2+}. Besides their inotropic effect, they also cause peripheral and pulmonary vasodilatation and thus a drop in systemic and pulmonary pressure and resistance through an effect on vascular smooth muscle cells. On the other hand, due to their pharmacokinetic and pharmacodynamic characteristics, they induce tolerance [18] as well an increase in vascular resistance in end-organs [19].

2.3. The calcium sensitizer levosimendan

Levosimendan exerts its inotropic effects through sensitization of cardiac troponin C to Ca^{2+}, without increasing the intracellular Ca^{2+} concentration, thus without disturbing relaxation or myocardial oxygen consumption/supply balance. Levosimendan also causes vasodilation by activation of the ATP-sensitive K^+ channels in vascular smooth muscle cells, while at higher doses, it also acts as a PDEi. In addition to its hemodynamic effects, levosimendan has further been shown to bear pleiotropic properties beyond HF and the heart, including protection of myocardial, renal, hepatic and neural cells from ischemia/reperfusion injury, and further anti-inflammatory and anti-oxidative effects [20]. These properties seem to be primarily related to the activation of ATP-sensitive K^+ channels in mitochondria [21]. Another particular feature of the drug is the prolonged action, compared to other inotropes, that lasts several days after discontinuation of the infusion, which is provided by the long elimination half-life of the active metabolite OR-1896 of approximately 80 h. In patients with severe renal dysfunction, the elimination half-life may be extended up to 1.5 fold, prolonging further the action of the drug. In a review of different meta-analyses, levosimendan was consistently associated with lower mortality that reached statistical significance in most of the studies [22].

2.4. Comparing the properties of inotropes

It has been shown that all of the above inotropic agents, besides increasing cardiac contractility, also bear vasoactive properties, causing either vasoconstriction, as in the case of norepinephrine, epinephrine and high-dose dopamine or vasodilation, as in the case of PDEi, levosimendan and low-dose dobutamine. These properties should be taken under consideration when choosing among the different inotropes. Due to their combined inotropic and vasodilating effects, PDEi and levosimendan are often referred to as inodilators.

Inotropes bear a non-negligible risk of important adverse events. Dopamine may induce tachyarrhythmias, particularly at high doses [16]. Dobutamine, apart from tachyarrhythmias, also causes hypotension at low doses due to vasodilation. Norepinephrine may indirectly induce arrhythmias by unbalancing myocardial oxygen supply-demand and increasing systemic vascular resistance. Epinephrine has several adverse effects including tachyarrhythmias, myocardial ischemia and systemic or pulmonary hypertension. Milrinone causes tachyarrhythmias and profound arterial hypotension, while it should be used with caution in patients with impaired or deteriorating renal function. Levosimendan may cause arrhythmias and hypotension. The most commonly encountered form of arrhythmia is atrial fibrillation, while the arrhythmogenic effect of the drug is less pronounced compared to other inotropes due to the avoidance of cardiomyocyte calcium overload [20,23]. Furthermore, limited data shows that the hypotensive effect of levosimendan may not require an excessive increase in vasopressors in cardiogenic shock [24] as in the case of PDEi [25]. Both adverse events may be avoided or restricted if no loading dose is administered [20].

3. Inotropes in acute heart failure

Acute HF is defined as the new onset of or change in symptoms and signs of HF that requires medical intervention and usually leads to hospitalization [14]. Acute HF encompasses a wide spectrum of clinical conditions, ranging from mild and gradually developing central and peripheral congestion in the presence of chronic HF, to abrupt congestion with acute pulmonary edema caused by an acute hemodynamic derangement, such as a hypertensive peak, to low output syndromes and to cardiogenic shock [26]. Prognosis varies accordingly,

with in-hospital mortality ranging between 2% and 40% at the two ends of the spectrum, respectively [27,28].

No pharmacologic therapies, including either classical drugs or novel and investigational agents, have hitherto been shown to improve outcomes in AHF in terms of hard endpoints (Supplementary Table 1). As a result, recommendations for the management of AHF include etiological treatment, when a specific treatable cause or precipitant is identified, such as acute coronary syndromes, along with the alleviation of symptoms caused by congestion and the restoration of cardiac output in the case of low output states.

In AHF, inotropes are required for the treatment of the subset of patients with low cardiac output, resulting in persistent symptomatic hypotension and/or end-organ hypoperfusion, despite adequate intravascular volume. In the ESC-Heart Failure Long-Term Registry, inotropes were used in 12% of patients admitted with AHF [8]. Epidemiological evidence shows that patients with low cardiac output and peripheral hypoperfusion comprise <10% of the AHF population, but this particular subpopulation bears the worst prognosis with the highest mortality rates [29]. In these patients, current guidelines recommend the use of any of the aforementioned inotropic agents with a class IIb recommendation [14]. It should be stressed that the use of inotropes should be limited to the lowest dose and the shortest possible period of time.

Identifying the patients with true end-organ hypoperfusion can be challenging. Symptoms, signs and laboratory findings that can be used as criteria to decide the presence of peripheral hypoperfusion include persistent hypotension, cold and wet extremities, mottled skin, altered mental status, oliguria, low cardiac index, elevated serum lactate, elevated serum transaminases or low venous oxygen saturation [14]. These criteria should be used in combination and it is important to remember that peripheral hypoperfusion may occur even in the absence of significant hypotension, due to sympathetic activation causing a profound peripheral vasoconstriction [30]. At the same time, hypovolaemia should always be excluded based on signs and tests of adequate intravascular volume, such as presence of normal or elevated central venous pressure, lack of inferior vena cava distensibility, negative fluid challenge or negative passive leg raising test.

Treatable causes of AHF, such as acute coronary syndrome, pulmonary embolism, mechanical complications of myocardial infarction, tachyarrhythmias or valvular disorders should be timely diagnosed and managed accordingly [14]. In the latter case, inotropes may still be needed in combination with or as a bridge to the treatment of the relevant etiology. Furthermore, viable alternatives to inotropes, such as mechanical circulatory support with temporary ventricular assist devices or extracorporeal membrane oxygenation (ECMO), should also be explored, particularly in patients not adequately responding to inotropes.

Once inotropes are deemed necessary, the choice of the proper agent should be based on patient's profile as determined by medical history, background medications, hemodynamic status and comorbid conditions [31]. In patients with decompensated ischemic HF without true hypoperfusion, milrinone showed a deleterious effect [32], while levosimendan has been associated with a trend towards survival improvement in different meta-analyses [22]. Thus, it has been proposed that levosimendan or dobutamine are more preferable options, despite the absence of direct head-to-head comparisons [33]. In patients with right ventricular failure and/or pulmonary hypertension, milrinone and levosimendan are preferred due to their vasodilatory effects on pulmonary vasculature. In terms of background medication, patients on beta blockers theoretically respond better to levosimendan or milrinone, as these drugs act independently of the β-adrenergic receptors; the same is true in the case of beta-1 receptor down-regulation that has been noticed in HF [34]. Concerning the hemodynamic status, in the presence of persistent hypotension, besides adequate volume status, norepinephrine is the vasopressor of choice and can be used in combination with vasodilating inotropes such as dobutamine and levosimendan in an effort to enhance cardiac contractility while maintaining adequate blood pressure for tissue perfusion; vasopressor may subsequently be withdrawn with the amelioration of cardiac performance [35]. The combination of two different classes of inotropes, in contrast, does not seem to provide additional benefit. With respect to comorbidities, in patients with primary renal failure, one should consider the long half-lives of milrinone and levosimendan (Table 1). In patients with cardiorenal syndrome in the context of AHF, levosimendan may be the proper option. In a small study in AHF, levosimendan improved glomerular filtration rate along with increasing renal blood flow and renal artery diameter [36], while the drug has further been shown to bear reno-protective effects in experimental and clinical studies [21,37]. Finally, in AHF-associated cardio-hepatic dysfunction, levosimendan seems to be superior to dobutamine [38].

3.1. Inotropes in cardiogenic shock

Cardiogenic shock (CS) is a particular form of AHF with ominous prognosis and increased mortality [39]. It is defined as the presence of SBP <90 mmHg for >30 min (or need of catecholamines to maintain SBP >90 mmHg), associated with clinical signs of pulmonary congestion as well as impaired organ perfusion with at least one of the following: (i) altered mental status, (ii) cold and clammy skin and extremities, (iii) serum lactate >2.0 mmol/L, (iv) oliguria with urine output <30 mL/h (<0.5 ml/kg/min), caused by a cardiac condition [40]. It is associated with significant derangement of tissue perfusion, resulting in a vicious circle of progressive interrelated multi-organ dysfunction that is lethal unless proper and timely interventions are applied.

The management of CS consists of treating the etiology - as in the case of acute coronary syndromes that represents a major cause of CS - along with the hemodynamic support with inotropes and vasopressors to increase cardiac output and blood pressure in order to restore tissue perfusion. Mechanical circulatory support, with temporary ventricular assist devices or ECMO, may be needed when the patient is not responding to initial therapy or as a bridge to etiological treatment, durable mechanical circulatory support or heart transplantation. In CS, norepinephrine provides a survival advantage over dopamine, according to a sub-analysis of the SOAP-II trial [16], and over epinephrine, according to the OPTIMA-CC trial, in which epinephrine induced excessive refractory HF [17]. The association of epinephrine with increased short and medium-term mortality compared to other inotropes and vasopressors may be related to the greater neurohormonal activation and myocardial and renal injury [41]. As an example for the differential effects of inotropes, it has been shown that patients in cardiogenic shock after cardiac surgery requiring temporary extracorporeal life support and inotrope support for weaning may benefit from levosimendan, without an increase in norepinephrine requirements, when compared to milrinone [42]. Furthermore, a Cochrane systematic review, showed that levosimendan may be superior to dobutamine in terms of short-term survival; however, this finding did not translate into a significant long-term survival benefit, while some studies included in the analysis were considered as low-quality evidence [43].

A propensity score-matched analysis by the GREAT network showed that combining vasopressors (epinephrine, norepinephrine, or dopamine) with vasodilating inotropes (dobutamine, levosimendan or PDE inhibitors) leads to better survival than vasopressors alone [35].

4. Inotropes in advanced heart failure

Patients with AdvHF represent 1–10% of all HF patients, a prevalence that is expected to increase because of the growing HF population and its improving survival [2]. In 2018, the Heart Failure Association of the European Society of Cardiology updated its definition of AdvHF [2]; this new definition is provided in Supplementary Table 2.

Patients with AdvHF suffer from severe and persistent symptoms, often unresponsive to drug therapy, poor performance status with marked limitation in exercise capacity, significantly impaired quality of life (QoL), progressive deterioration of multiple organ function such as renal and hepatic functions, intolerance to disease-modifying therapies and repeated hospitalizations [30]. A proposed classification of AdvHF that identifies the involvement of other organs besides the heart allows to distinguish AdvHF from end-stage cardiac patients [44].

Due to the fact that AdvHF is a persistent condition, that usually worsens over time, and may demand permanent solutions including durable mechanical circulatory support and cardiac transplantation, inotropes may be required repeatedly. Neutral results on overall long-term survival are shown when pooling the data of all studies on intermittent inotrope administration in AdvHF, irrespectively of the drug [45,46]. In this setting, levosimendan may have an advantage over the other inotropes due to the long-lasting effect of its active metabolite OR-1896 [47]. Indeed, a number of clinical trials have provided encouraging evidence on the use of repetitive levosimendan infusions in AdvHF, showing improvement in functional status, QoL, hemodynamic outcomes, and neurohormonal and inflammatory markers [48–51]. A meta-analysis of 7 randomized trials including 438 patients followed for 8 months in average showed that levosimendan led to a significant reduction in mortality and 3-month hospitalizations by 46% and 60%, respectively, compared to dobutamine or placebo [52]. However, the multicenter randomized trial LevoRep (n = 120) showed no effect on the primary endpoint of improvement in functional capacity (6-min walked distance, 6MWD, increase by 20% or more) and QoL (Kansas City Cardiomyopathy Questionnaire, KCCQ, improvement by 15% or more), despite a reduction in the composite of death, heart transplantation, and acute heart failure rates [53]. In contrast, the LION-HEART study (n = 69) met its primary endpoint of NT-proBNP reduction, and it further showed a significant decline in the rate of all-cause death or HF hospitalization [54]. A meta-analysis of all available clinical trials, confirmed the effect of levosimendan on re-hospitalization in AdvHF [55]. The ongoing LeoDOR trial tests the hypothesis that repetitive levodimendan infusions will improve outcomes in AdvHF patients when applied during the vulnerable post-discharge period, when a significant proportion of readmissions occur [56].

Patients with AdvHF are inherently unstable and begin to decompensate well before being hospitalized [2,57]. As illustrated in Fig. 2, there is often a crucial interval during which the timely recognition of signs and symptoms of decompensation can avoid unplanned hospitalization due to haemodynamic derangement, which seems to be followed by loss of myocardial tissue. Preventing re-hospitalization in this window of opportunity represents therefore and important target in this population. The effect of this preemptive strategy based on repeated inodilators, such as levosimendan, remains to be proven [56,58].

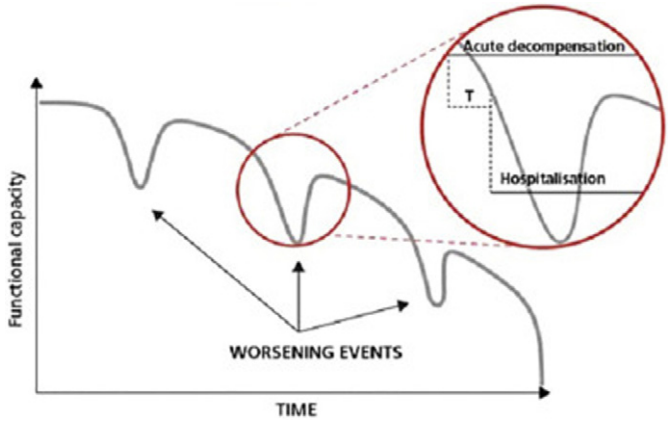

Fig. 2. The variable course of decompensation in advanced heart failure. It could be possible in many instances to identify intervals (T) during which the timely recognition of the signs and symptoms of decompensation permit interventions that can avert unplanned hospitalizations due to hemodynamic deterioration (modified from Oliva et al. [65]).

5. Inotropes and patient reported outcomes

Randomized trials have generally failed to provide compelling evidence that inotropes improve survival endpoints in patients with HF. Still, inotropes are indispensable in the setting of both AHF and AdvHF as they do improve patients' symptoms. In addition, treatment of AdvHF patients is often primarily palliative, and HF patients seem to attach more weight to QoL rather than to longevity [59]. Therefore, evaluation of the effects of inotropes on patient reported outcomes (PRO) is important. Incorporating the patient perspective through the evaluation of PRO is becoming increasingly essential in clinical trials. However, large randomized trials have not sufficiently addressed the effects of inotropes on PRO.

A key PRO that has been broadly studied in HF is QoL through the use of a series of well-structured and usually self-administered questionnaires and tools [60]. A number of factors affect QoL in patients with AHF or AdvHF, besides symptoms of central and peripheral congestion, including neurohormonal and inflammatory activation, impaired peripheral muscle perfusion and function, comorbid conditions such as anemia or pulmonary disease, wasting and cachexia, deconditioning, psychological impairment and depression as well as social status [61,62]. In turn, QoL seems to be an independent predictor of prognosis in chronic HF and impaired QoL has been associated with reduced survival and increased event rate [63]. In the placebo arm of the SHIFT-HF trial, impaired QoL, as determined by the lower KCCQ tertile, was significantly associated with increased incidence of the primary composite endpoint of cardiovascular death and heart failure hospitalization [63]. However, the prognostic value of QoL questionnaires in AHF is limited.

Studies in refractory AdvHF patients have shown that treatment with intermittent low-dose dobutamine infusions, either in outpatient clinic or at home, improves QoL, without having an effect on survival [45]. Similarly, small studies have shown that repeated levosimendan administration also improves functional capacity and QoL in AdvHF [64,65]. However, as previously stated, the two randomized trials on repeated levosimendan infusions, LevoRep and LION-HEART, provided conflicting evidence.

6. Conclusions

Inotropes increase cardiac output by enhancing cardiac contractility through different mechanisms of action, but they also bear variable vasodilatory or vasoconstrictive effects depending on agent and dosage. They constitute an important tool for the treatment of patients with AHF or AdvHF, as they are often effective in improving hemodynamics and symptoms. However, their administration has been associated with increased short and long-term mortality due to frequent adverse effects, but also due to their improper use. The classes of inotropes currently used in HF are the β-adrenergic receptor agonists including dopamine, dobutamine and the catecholamines norepinephrine and epinephrine, the PDE III inhibitor milrinone and the calcium sensitizer levosimendan.

In AHF, inotropes are indicated with a IIb recommendation by the ESC guidelines only for patients with peripheral hypoperfusion because of low cardiac output. Identifying patients with truly low cardiac output in need of inotropic support can be challenging, while selecting the proper agent according to patients' clinical profile and limiting infusion to the shortest time and lowest dose possible are important to optimize inotrope use. Levosimendan bears some pharmacological and pharmacokinetical advantages in this setting, but its positive clinical evidence is based mainly on observational studies, small randomized

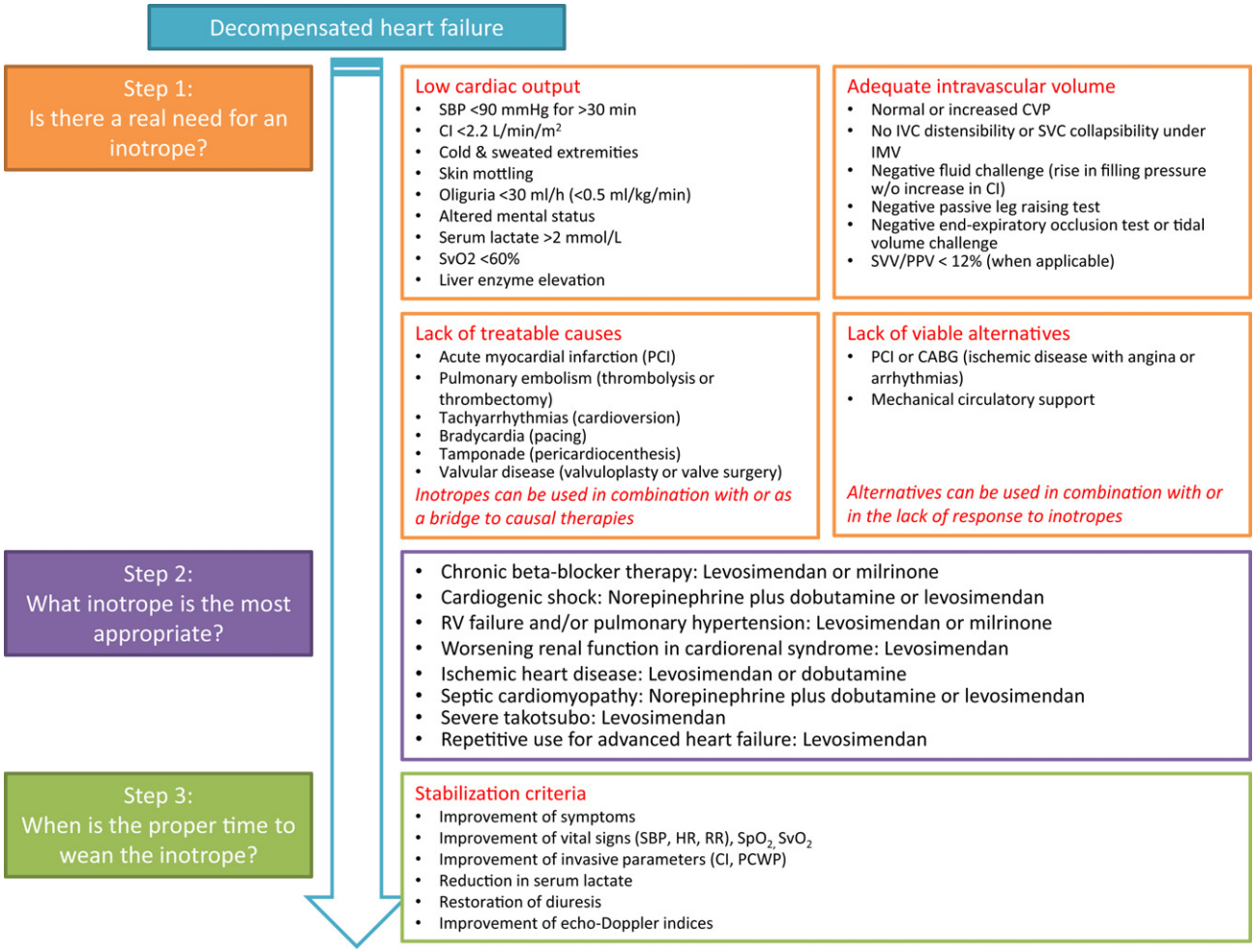

Fig. 3. Practical recommendations for the use of inotropes in acute heart failure. SBP, systolic blood pressure; CVP, central venous pressure; ICV, inferior vena cava; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome; HR, heart rate; RR, respiratory rate; PCWP, pulmonary capillary wedge pressure; CABG, coronary artery bypass surgery; IMV, intermittent mechanical ventilation; SVV, stroke volume variation; PPV, pulse pressure variation; CI, cardiac index.

regulatory trials and meta-analyses as the large randomized trials have hitherto provided neutral results.

In AdvHF, inotropic agents are required for the relief of persistent symptoms and the improvement of quality of life. Day clinic-based or home-based repetitive infusions may reduce hospital admission, which is a key factor in the quality of live and perhaps overall prognosis of the disease. Levosimendan bears an advantage in this setting due to its long-acting active metabolite, but evidence from properly powered randomized trials are awaited.

Fig. 3 provides a practical approach to the three main steps required for the optimal use of inotropes in HF, namely (i) the identification of the right patient, (ii) the choice of the proper inotrope and (iii) the definition of the adequate weaning time.

The effects of inotropes on PRO and QoL in general, remain poorly defined, and more studies on this important and clinically meaningful aspect of AHF and AdvHF patient care are warranted.

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Declaration of competing interest

DF, LB, JC-C, FF, JMG-P, GG, FG, V-PH, AH, KK, JM, AM, GP, CT, DvL, BV, and JP have received lectures honoraria by Orion Pharma, the developer of levosimendan. JC-C, AM, GP, and JP received unrestricted grants for clinical studies from Orion Pharma. PP and MK are employees of Orion Pharma. The other co-authors do not have any conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.09.005.

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