

Inotropic therapy in patients with advanced heart failure. A clinical consensus statement from the Heart Failure Association of the European Society of Cardiology

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This clinical consensus statement reviews the use of inotropic support in patients with advanced heart failure. The current guidelines only support use of inotropes in the setting of acute decompensated heart failure with evidence of organ malperfusion or shock. However, inotropic support may be reasonable in other patients with advanced heart failure without acute severe decompensation. The clinical evidence supporting use of inotropes in these situations is reviewed. Particularly, patients with persistent congestion, systemic hypoperfusion, or advanced heart failure with need for palliation, and specific situations relevant to implantation of left ventricular assist devices or heart transplantation are discussed. Traditional and novel drugs with inotropic effects are discussed and use of guideline-directed therapy during inotropic support is reviewed. Finally, home inotropic therapy is described, and palliative care and end-of-life aspects are reviewed in relation to management of ongoing inotropic support (including guidance for maintenance and weaning of chronic inotropic therapy support).

Keywords

Inotrope • Advanced heart failure • Cardiorenal syndrome • Mechanical circulatory support • Palliation

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Introduction

Inotropic agents are currently recommended in patients in the inpatient setting presenting with acute heart failure (AHF) with low cardiac output and hypotension (systolic blood pressure [SBP] <90 mmHg).¹ This restricted recommendation is provided because of lack of quality evidence supporting other indications for use of inotropes for the majority of patients with AHF or in many other heart failure (HF) clinical settings. However, a group of patients with advanced stages of chronic HF exists, whose symptoms cannot be well managed with current guideline-directed medical therapy and in whom inotropic support may be appropriate in selected instances. Generally, these patients will have advanced HF with severely reduced ejection fraction. The clinical scenarios where inotropes may be considered in this setting have not been well described, nor has the choice of inotropic agent or subsequent clinical management of such patients. The aim of this scientific consensus statement is to provide a review of the literature related to inotropic therapy in patients with advanced chronic HF with reduced ejection fraction (HFrEF) and to describe a strategy for inotrope use in the care of this population.

Advanced chronic heart failure – definitions and clinical scenarios

A list of definitions related to inotropic therapy in patients with chronic HF is given in online supplementary Table S1.^{1–8} Some scenarios of advanced HF outside the setting of cardiogenic shock where inotropic support could be considered are described below (Figure 1). The clinical conditions are dynamic and can be overlapping in some instances. Also, they may incorporate patients recovered from cardiogenic shock, where inotropes may have already been used. Patients with temporary mechanical circulatory support (MCS) are not covered in this scientific consensus report statement.

The clinical conditions are:

- Persistent congestion refractory to loop or combinational diuretic therapy
- Evaluation of reversibility of end-organ dysfunction prior to a decision about durable left ventricular assist device (LVAD) implantation or heart transplant listing
- Inotropic support to stabilize clinical condition prior to heart transplantation (HTx) or LVAD implantation
- Palliative or supportive therapy for advanced HF in patients not eligible for HTx or LVAD implantation

Pharmacology of β -adrenergic drugs (dobutamine, epinephrine, norepinephrine, dopamine)

Dobutamine, epinephrine, norepinephrine and dopamine are sympathomimetic agents that act directly through different adrenoceptors: the α_1 , β_1 and β_2 receptor.⁹ Activation of the

α_1 receptors, that are located in the vascular wall, results in vasoconstriction. Stimulation of the myocardial β_1 (and to some extent β_2) receptors increases inotropy and chronotropy, whereas stimulation of vascular β_2 receptors results in vasodilatation. The stimulation of β_1 adrenergic receptors results in increased intracellular level of cyclic adenosine monophosphate (cAMP), changing calcium handling pathways including increased influx of calcium into the cardiomyocyte. This induces improved contractility, however, at the cost of increased oxygen consumption and arrhythmogenicity.

When addressing the clinical and haemodynamic effects of the different adrenergic drugs, it should be kept in mind that: (i) one drug may act on several different receptors, (ii) the drugs have different affinities for different receptors, and (iii) adrenergic drugs can act both directly on the different receptors and may induce reflex reactions by the autonomic nervous system (e.g. reflex vasodilatation after β_1 stimulation).

The clinical and haemodynamic effects of the different sympathomimetic drugs are summarized in Table 1.

Dobutamine

Dobutamine is a synthetic catecholamine that acts primarily as a β_1 agonist, resulting in increased inotropy and chronotropy and reduction in left ventricular filling pressures. The additional β_2 receptor effect and the reflex vasodilatation due to increased cardiac output may result in a decrease in blood pressure especially with lower doses.

Dopamine

Dopamine is an endogenous precursor of norepinephrine. At moderate to higher dose (>3–5 $\mu\text{g}/\text{kg}/\text{min}$) dopamine has β_1 adrenergic effects, as well as α_1 adrenergic effects, the latter resulting in vasoconstriction. At lower dose (1–3 $\mu\text{g}/\text{kg}/\text{min}$), dopamine acts predominantly through dopamine receptors, resulting in selective vasodilatation (e.g. in the renal beds).

Norepinephrine (also called noradrenaline)

Norepinephrine is an endogenous catecholamine that acts on both α_1 and β_1 receptors, resulting mainly in vasoconstriction and a modest increase in cardiac output. Therefore, its use is limited for the management of significantly reduced blood pressure, and only rarely in chronic HF patients.

Epinephrine (also called adrenaline)

Epinephrine is a potent α_1 , β_1 and β_2 receptor agonist. At low doses, it results in an increase in cardiac output because of the predominant β_1 agonist effect (increase in inotropy and chronotropy), whereas at higher doses, the α_1 receptor agonist effect results in vasoconstriction.

A large proportion of advanced HF patients in whom inotropic support is considered, are on chronic β -blocker therapy. For example, in the LION-HEART study up to 81% of the patients

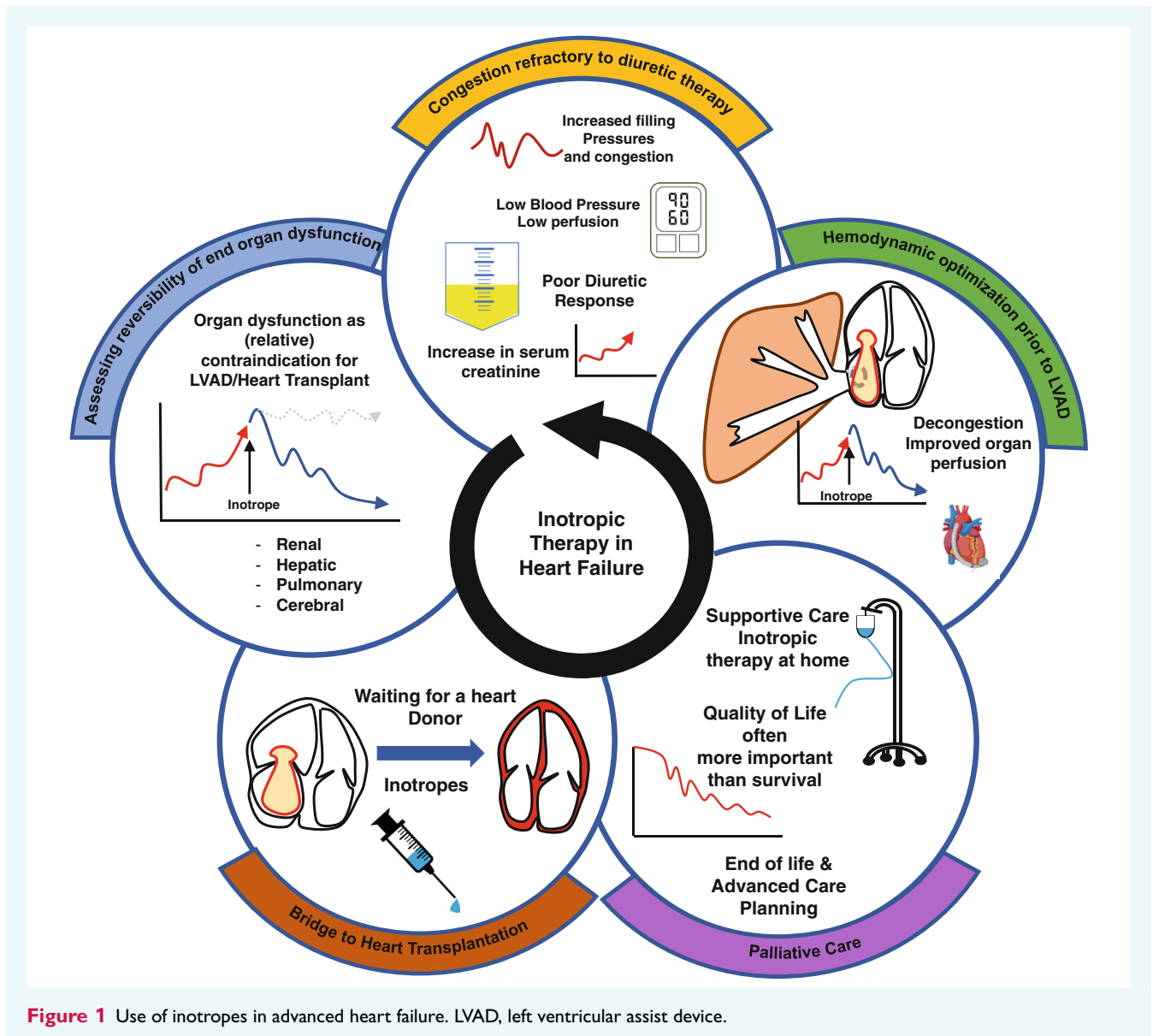


Figure 1 Use of inotropes in advanced heart failure. LVAD, left ventricular assist device.

received β -blockers at baseline, although this was a study using levosimendan.¹⁰ The use of β -blockers (in particular carvedilol, bisoprolol, and to a lesser extent metoprolol) may inhibit the favourable haemodynamic effects of dobutamine.^{11,12} As β -blockers may not influence the haemodynamic effects of phosphodiesterase (PDE) inhibitors (e.g. milrinone) or calcium sensitizers (e.g. levosimendan), these drugs may be preferred over β -adrenergic drugs in patients treated with and tolerating (high-dose) β -blockers.^{12,13}

Pharmacology of phosphodiesterase III inhibitors

The 3', 5' cyclic nucleotide PDEs are a major class of enzymes that play a vital part of this intracellular signalling mechanism. They degrade cAMP or cyclic guanosine monophosphate (cGMP) to their respective 5' nucleotides, thereby providing a key brake

on cyclic nucleotide signalling.¹³ Within the cardiovascular system, numerous functional PDEs have been identified including PDE1–5, PDE8 and PDE9. PDE3 was identified in the cardiovascular system several decades ago. PDE3 inhibitors, most notably including milrinone which was developed in the 1980s, have been consistently demonstrated to exert positive inotropic, vasodilator and positive lusitropic properties in both animal studies and patients with HF. These physiologic actions result in dose-dependent, clinically meaningful improvements in cardiac output, filling pressures and pulmonary arterial pressures. Plasma levels are not usually monitored in clinical practice. It is recommended that dose adjustments should be considered in the setting of an estimated glomerular filtration rate <50 ml/min/1.73 m² as milrinone is renally cleared, although studies suggest that the exposure remains within the therapeutic range in most cases.¹⁴ Adverse effects of milrinone are well recognized including systemic hypotension and arrhythmia.

Table 1 Beta-adrenergic drugs: pharmacology and clinical effects

Drug	Main mode of action	Main clinical effect	Bolus	Infusion rate	Elimination $t_{1/2}$
Dobutamine	β_1 (β_2)	Inotropy Chronotropy Vasodilatation	–	2–20 $\mu\text{g}/\text{kg}/\text{min}$	± 2 min
Epinephrine/ adrenaline	A-1 B-1 B-2	Inotropy Chronotropy Vasoconstriction	+	0.05–0.5 $\mu\text{g}/\text{kg}/\text{min}$	± 2.5 min
Norepinephrine/ noradrenaline	A-1 (B-1)	Vasoconstriction	–	0.2–1.0 $\mu\text{g}/\text{kg}/\text{min}$	± 1 –2 min
Dopamine	Low dose: Dopamine receptors High dose: B-1 and A-1	Low dose: selective vasodilatation High dose: vasoconstriction and inotropy	–	Low dose: <3 $\mu\text{g}/\text{kg}/\text{min}$ High dose: >5 $\mu\text{g}/\text{kg}/\text{min}$	± 2 min

Haemodynamic and functional studies showed that orally administered milrinone improved cardiac index and reduced pulmonary capillary wedge pressure, however these effects were relatively transient given its pharmacokinetic profile. Based on experience with long-term use of lower dose intravenous milrinone therapy in a bridge to transplant patient cohort,¹⁵ an extended release milrinone formulation that yields a stable plasma milrinone profile with twice daily dosing has been developed. In preliminary open-label studies in patients with advanced HFrEF, evidence of improved functional capacity without evidence of increased arrhythmia has been demonstrated¹⁶ and the drug has also shown promise in advanced HF with preserved ejection fraction (HFpEF).¹⁷ Larger trials are required to establish the potential for the selected use of oral PDE3 inhibitors in advanced HF.

Pharmacology of calcium sensitizers

Calcium sensitizers such as levosimendan enhance the sensitivity of cardiac myofilaments to calcium, without influencing intracellular calcium transients. Levosimendan acts through two main mechanisms: (i) calcium sensitization by binding troponin C, changing the conformation of troponin I and reducing its inhibition on actin–myosin bridges formation; and (ii) opening of adenosine triphosphate (ATP)-dependent potassium channels in vascular smooth muscle cells, favouring coronary, pulmonary and systemic vasodilatation and in mitochondria, with cardioprotective effects in ischaemic settings. Levosimendan also holds PDE3 inhibitory effects and increases intracellular cAMP.⁹

Despite levosimendan's short half-life of 1 h, its effect can last for weeks due to the longer (70–90 h) half-life of its active metabolite (OR-1896).¹⁸ This makes levosimendan an option for periodic administrations. Its high oral bioavailability (85%) has stimulated trials on an oral formulation, so far without favourable results. Levosimendan reduces pulmonary artery wedge pressure and

increases cardiac output compared to placebo or dobutamine.¹⁹ The use of bolus should be avoided, as studies where bolus was used reported more initial hypotension²⁰ than studies without bolus use.^{10,21} The dose of 0.1 $\mu\text{g}/\text{kg}/\text{min}$ could be respectively modified to 0.05 or 0.2 $\mu\text{g}/\text{kg}/\text{min}$ based on blood pressure and clinical response.

Istaroxime

Istaroxime inhibits Na/Ca exchange at the sarcolemmal level and activates sarcoplasmic reticulum calcium ATPase. It can be administered intravenously.

Myotropic drugs

Omecamtiv mecarbil is the first oral drug in this class.²² It is a direct cardiac myosin activator, improving cardiac function through an increase in actin–myosin interaction without affecting calcium transients. The drug increases stroke volume and ejection time in healthy volunteers²³ and HF patients²⁴ dependent on plasma concentration. The drug can be administered orally.

New and emerging inotropic therapies

Novel developments in biotechnology hold great promise for future inotropic HF therapies (online supplementary Table S2).^{22,25–43} Technical novelties that are now available have inspired whole new areas of research, including next-level gene therapies and cell reprogramming. Translational research is more important than ever, and basic scientists work together with translational and clinical scientists to identify the most promising therapeutic targets, now that delivery and modification are so much more feasible than before.

Inotropes in advanced chronic heart failure – evidence from clinical trials

Inotropic agents have been tested in several clinical trials that included patients with varying degree of circulatory failure. The main trials are briefly presented below.

β -agonists

Dobutamine's safety and efficacy were extrapolated from a subgroup analysis of the Flolan International Randomized Survival Trial (FIRST) that randomized 471 patients with New York Heart Association (NYHA) class IIIb–IV symptoms to epoprostenol (prostacyclin) infusion versus standard care with unfavourable results in the epoprostenol group. A post-hoc analysis of this study showed that dobutamine use was associated with a higher 6-month mortality rate. The dobutamine group, however, included a sicker population, which may have influenced the results.⁴⁴ A trend to excess mortality with intermittent dobutamine therapy was also observed in a meta-regression analysis along with trends to improved symptoms.⁴⁵

Similarly, the addition of low-dose dopamine infusion to low-dose furosemide in the Efficacy and safety of high dose versus low dose furosemide with or without dopamine infusion: the Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) and Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF) trials failed to show a favourable effect on renal function and diuresis and any beneficial effects in the in-hospital and post-discharge outcomes.^{46,47} In some studies dopamine has been associated with an increased risk of tachycardia or atrial arrhythmias.^{47,48} Lack of improvement in renal function with dopamine was also recently reported in patients with HFpEF.⁴⁹

Phosphodiesterase III inhibitors

Phosphodiesterase inhibitors in two landmark studies failed to offer additional benefit in patients with severe or acutely decompensated HF (ADHF). In the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial, oral milrinone therapy was not only associated with more frequent hospitalizations, and more hypotensive and syncopal episodes, but also with a significant increase in mortality.⁵⁰ In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial, where 951 patients with acute exacerbations of chronic HF were randomized to either milrinone (0.375–0.75 $\mu\text{g}/\text{kg}/\text{min}$) or saline placebo, the PDE inhibitor offered no benefit on either mortality or readmission endpoints. Those randomized to milrinone experienced more clinically relevant hypotension (possibly related to the loading dose) and atrial arrhythmias and patients with ischaemic heart disease had significantly greater in-hospital mortality with milrinone. In contrast, outcomes in non-ischaemic patients tended to be improved in terms of the primary endpoint (number of

days hospitalized due to cardiovascular causes within 60 days) and the composite of death or rehospitalization implying a rather bidirectional effect based on aetiology in decompensated HF.⁵¹

Low-dose oral enoximone, compared with placebo, in 1854 patients with advanced HF had neutral effects on the combined endpoint of all-cause or cardiovascular hospitalization and did not change exercise capacity, assessed by the 6 min walking distance.⁵²

Calcium sensitizers

Levosimendan has been tested in several trials including patients with advanced HF, both in the acute and more chronic settings. Despite the favourable haemodynamic results of the phase II Levosimendan Infusion versus Dobutamine (LIDO) trial,¹⁹ levosimendan in the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) randomized trial offered no advantage in 6-month mortality when compared to dobutamine in patients with acute decompensated HF.⁵³ Similar findings were reported from two US trials comparing levosimendan to placebo in AHF.²⁰ Several smaller prospective, randomized trials have evaluated the effect of repeated doses of levosimendan in the setting of advanced chronic HF (LevoRep, LAICA and LION-HEART). Levosimendan was used repetitively with cycles every 2–4 weeks in similar patient populations with different dose schedules. In the LevoRep study the primary endpoint comprised improvement in 6-min walking distance and quality of life assessed by Kansas City Cardiomyopathy Questionnaire, which were not significantly improved with levosimendan.^{21,54} In the Levosimendan® Intermittent administration in Outpatients: effects on Natriuretic peptides in advanced chronic HEART failure (LION-HEART) study, the primary endpoint of change in N-terminal pro-B-type natriuretic peptide was significantly improved with levosimendan treatment. A significant reduction in combined incidence of all-cause mortality and hospitalization for patients receiving levosimendan was observed, but importantly the study was small and not powered to assess effect on hard outcomes.¹⁰ In the Long-Term Intermittent Administration of Levosimendan in Patients with Advanced Heart Failure (LAICA) study, efficacy and safety of long-term intermittent use of levosimendan to reduce the incidence of hospital admissions was evaluated, however the study was stopped prematurely for lack of funding and slow patient recruitment. Although the reduction in the incidence of hospital readmissions for ADHF did not reach statistical significance, there was a significantly lower cumulative incidence of ADHF and mortality during short (1 and 3 months) and long-term (1 year) levosimendan treatment.⁵⁵ Results from a larger randomized study in patients with advanced HF symptoms after an admission for ADHF are underway but the study has been terminated early because of slow recruitment related to the COVID-19 pandemic.⁵⁶ In all, despite clear haemodynamic effects, no adequately powered study on levosimendan has demonstrated effect on mortality or hospitalization in chronic advanced HF.

Myotropic drugs

In a large placebo-controlled trial conducted in patients with HFrEF in NYHA class II–IV enrolled either during a hospitalization for HF (inpatients, 25.3%) or as outpatients with a HF event in the previous year (outpatients), omecamtiv mecarbil reduced the primary endpoint of cardiovascular mortality or HF hospitalization.²⁶ Its beneficial effects on the risk of cardiovascular death and HF hospitalizations were greater in the patients with the lower left ventricular ejection fraction (LVEF) or lower blood pressure as well as in the subgroup ($n = 2258$) with advanced HF according to the Heart Failure Association (HFA) criteria.^{57,58} In another trial it did not increase exercise capacity compared with placebo.⁵⁹ Currently, this drug is undergoing evaluation by the regulatory agencies.

Selection of patients for inotropic support: clinical scenarios

Inotropes may be an appropriate therapy for patients with chronic HF who present with volume overload resistant to diuretic therapy or with organ malperfusion. Their use should be limited to the lowest clinically effective dose administered for the shortest period of time.

Clinical condition 1: Congestion refractory to diuretic therapy

Congestion resistant to diuretic therapy frequently accompanies advanced HF, and patients, while not in cardiogenic shock, but with persistent congestion despite several days of aggressive diuretic therapy may be candidates for short-term inotropic support. Haemodynamically these patients are characterized by elevated filling pressures, and cardiac index may be low or normal. SBP is often low but may be >90 mmHg. Often renal function is compromised due to reduced renal perfusion and venous congestion or by concomitant kidney disease. These advanced HF patients are often diuretic resistant due to their haemodynamic profile, tubular hypertrophy due to long-term use of loop diuretics and renal congestion. Diuretic resistance further deteriorates persistent congestion, which will detrimentally impact left- and right-sided filling pressures and reduce cardiac output and renal perfusion. In parallel, high right-sided filling pressures, increased congestion and preload to the right ventricle can also lead to worsening tricuspid regurgitation, all of which are associated with deteriorating renal function.^{60–62}

Short-term inotropic support may be useful to overcome this vicious circle of low perfusion, persistent congestion and diuretic resistance. As discussed above, dopamine, which has previously been used often in this setting, has no role in treating these patients considering neutral results of randomized controlled trials^{46,47} Milrinone has been shown to increase renal blood flow in a small study of postoperative HF.⁶³ Levosimendan increased estimated glomerular filtration rate and urine output in a small randomized study in 21 patients with advanced HF⁶⁴ likely by improving

intrarenal haemodynamics.⁶⁵ After decongestion, inotropic support should be discontinued and guideline-directed medical therapy resumed.^{1,8} Need for inotropic support to overcome diuretic resistance in congested patients should always prompt considerations for referral of the patient to an advanced HF centre for advanced HF therapies such as LVAD implantation or HTx.³

Clinical condition 2: Evaluation of reversibility of end-organ dysfunction prior to decision on durable LVAD implantation or heart transplant listing (renal, hepatic, pulmonary)

Severe, irreversible renal or hepatic dysfunction is a contraindication to LVAD implantation and HTx.^{1,66} However, commonly, end-organ dysfunction is a consequence of worsening HF, either due to congestion or inadequate perfusion, rather than an intrinsic organ disease *per se*.^{60,67,68} A period of haemodynamic optimization using inotropic support may in some instances revert end-organ dysfunction (cardio-renal, cardio-hepatic syndrome or elevated pulmonary pressures), proving that the dysfunction was caused by HF and enabling listing for transplantation or LVAD implantation. Although elevated pulmonary vascular resistance is a contraindication to HTx,⁶⁹ a challenge using inotropic support is generally recommended if pulmonary vascular resistance remains fixed after inhalation of nitric oxide or acute vasodilator infusion. Hence, inotropic support could occasionally be used as 'bridge to candidacy' either for LVAD or HTx, where it may then be continued as described under 'Clinical condition 3'.

Clinical condition 3: Haemodynamic optimization of patients prior to LVAD implantation

Pulmonary congestion and high central venous pressures increase the risk of early right ventricular failure post-LVAD implantation. Further, hepatic congestion or hypoperfusion is associated with coagulopathy and increased bleeding risk. Consequently, pre-LVAD optimization of congestion and organ perfusion is often pursued using inotropic support. If inotropes are administered for extended periods and attempts to wean have resulted in recurrence of end-organ dysfunction, the patient is designated inotrope-dependent. A new definition of inotrope dependency with specific criteria and taking into consideration non-continuous inotropic support is given in *Table 2*. In Europe, approximately 40% of LVAD implantations are performed in this group of patients (referred to as INTERMACS level 3).⁷⁰ Few studies have described strategies for haemodynamic optimization, but improved outcomes, compared with registry data after initiating systematic preoperative inotrope management in non-inotrope-dependent patients have been demonstrated.⁷¹ Compliance during a period of intermittent intravenous inotropic therapy may also suggest acceptance of long-term LVAD therapy. Efficacy and safety of a strategy of intravenous inotropic therapy before either as 'destination therapy'

Table 2 Inotrope dependence (proposed European Society of Cardiology Heart Failure Association definition)

FAILURE to wean intravenous inotropic support^a within 72 h^b WITHOUT:

- 1) Development of symptomatic arterial hypotension OR
- 2) Worsening renal or hepatic function defined as eGFR decrease >30% or clinically important elevation in liver enzymes or INR OR
- 3) Worsening congestion leading to or upholding NYHA class IV symptoms.^c

The diagnosis of inotrope dependence should not be made during simultaneous introduction or up-titration of β -blockers or RAS inhibitors.

eGFR, estimated glomerular filtration rate; INR, international normalized ratio; NYHA, New York Heart Association; RAS, renin–angiotensin system.

^aEpinephrine, norepinephrine, dopamine, dobutamine, milrinone.

^bIf the patient has received continuous intravenous inotropic support >7 days, inotrope dependence is defined as failure to reduce infusion rate at 72 h after each attempt to reduce. In the case of levosimendan infusion, dependence is defined as need for new infusion <10 days after the former.

^cIn the absence of reduction in loop diuretic dose.

or as ‘bridge to LVAD’ both require final data through randomized trials.

Clinical condition 4: Inotropic support as bridge to heart transplantation

In the most recent International Society for Heart and Lung Transplantation registry analysis, 36% of patients undergoing HTx were treated with inotropic support⁷² and in some series a substantial proportion of patients bridged with inotropic support can reach transplantation.⁷³ This proportion has decreased in parallel to an increased use of MCS as bridge to HTx. If sufficient, inotropic support is often preferred over MCS in heart transplant candidates with anticipated short waiting time and always preferred where LVADs are likely ineffective, such as patients with severe or isolated right ventricular failure. In a large transplant registry analysis, inotropic support was not associated with inferior outcomes after HTx.⁷²

Clinical condition 5: Palliative therapy for advanced heart failure in patients not candidates for heart transplantation or LVAD implantation

Patients with advanced HF not eligible for HTx or LVAD implantation may be treated with extended inotropic support either as *continuous* intravenous infusion of dobutamine or milrinone or *intermittent* infusions of dobutamine or levosimendan. Years of inotropic support can occasionally be relevant. Treatment may also be offered in the home setting in some countries. Clear indications and protocols should be followed even if they may vary from

institution to institution, and treatment goals should be set with plans for re-evaluation at regular intervals. If adverse events occur or the treatment is no longer effective, as per the pre-defined goals, it should be terminated. The palliative use of inotropes in end-of-life care is discussed below.

Management of guideline-directed therapy and diuretics during inotropic support

There is only scarce evidence on the safety and efficacy of guideline-directed therapy in chronic HF patients already on inotropic support, as these patients have routinely been excluded from randomized clinical trials. Often, such patients are unable to tolerate neurohormonal-directed therapy due to circulatory insufficiency or co-existing end-organ dysfunction such as chronic kidney disease not caused by cardiac failure. In the recent LCZ696 in Advanced Heart Failure (LIFE) study in patients with advanced HFrEF where 20% used ambulatory inotropic support, sacubitril/valsartan therapy did not impact on the clinical composite endpoint.⁷⁴ In a subsequent analysis, these investigators identified reasons for intolerance to sacubitril/valsartan therapy and noted that a lower mean arterial pressure, lower serum chloride, moderate or greater mitral regurgitation, were factors associated with inability to tolerate the drug, among other factors.⁷⁵ In the chronic outpatient setting, the use of guideline-directed therapy should remain the cornerstone of HF treatment even if the patient is on inotropic support. However, tolerability of these therapies is more challenging, especially those that impact blood pressure which is often lower in advanced HF patients. It may therefore sometimes be necessary to down-titrate or even (temporarily) discontinue these therapies to be able to initiate or continue inotropic support. In patients treated with repeated levosimendan infusion interruption of β -blockade is seldom necessary and β -blockade may even enhance the effect of levosimendan.⁷⁶

In the clinical setting of low cardiac output and elevated filling pressure, combination of inotropic support and diuretic treatment is often required. The focus in these patients should be adequate decongestion by whatever means necessary. After decongestion inotropes should be weaned and guideline-directed therapy reinitiated. As these patients are often haemodynamically fragile, it is often advisable to restart standard therapy while still in hospital with subsequent outpatient up-titration. In some cases it may be possible to initiate low-dose guideline-directed therapy while the patient is still on inotropes, followed by down-titration and discontinuation of inotropic therapy if possible.⁷⁷

Oral inotropic agents for the long-term treatment of patients with advanced heart failure

Safe and effective oral inotropes would be highly attractive for the treatment of advanced HF, but at this time no oral drugs have

been approved for this indication. Digoxin has inotropic effect and may be helpful in patients with atrial fibrillation but likely has little effect in advanced HF in the presence of sinus rhythm. Omecamtiv mecarbil reduced the primary endpoint of cardiovascular death and HF hospitalizations in the Global Approach to Lowering Adverse Cardiac Outcomes Through Improving Contractility in Heart Failure (GALACTIC-HF) trial enrolling 8256 patients with HFrEF (hazard ratio [HR] 0.92; 95% confidence interval [CI] 0.86–0.99; $p = 0.03$).²⁶ The effects were larger in the patients with lower LVEF as well as in those with criteria for severe HF.⁵⁸ Amongst the pre-specified subgroups, LVEF was the strongest modifier of the treatment effect of omecamtiv mecarbil on the primary outcomes.⁷⁸ In addition, omecamtiv mecarbil was well tolerated, with no significant changes in blood pressure or kidney function. In another subgroup analysis, omecamtiv mecarbil, compared with placebo, appeared to be more effective in reducing the primary composite endpoint in patients with SBP ≤ 100 mmHg (HR 0.81; 95% CI 0.70–0.94) compared with those with SBP > 100 mmHg (HR 0.95; 95% CI 0.88–1.03; p -value for interaction = 0.051).⁵⁷ Thus, if approved by regulatory bodies, omecamtiv mecarbil will be a treatment option that may be considered in patients with advanced HF.^{1,79}

Monitoring of patients on inotropic support and practical aspects of administration (ward/intensive care unit)

The monitoring needs of patients receiving inotropic support vary depending on several factors including the inotrope used, the patient's clinical status and medical history, the aim of inotropic support as well as local protocols and care level at different ward types. This is reflected by the fact that some patients receiving inotropes are treated in the intensive care unit (ICU) while others are managed at home (see below). Patients treated with multiple inotropes or requiring norepinephrine or epinephrine need admission to an ICU/cardiac care unit and placement of a pulmonary artery catheter will likely be helpful in most cases.⁸⁰ Patients treated with inodilators or low-dose dopamine may in many instances be treated in the cardiology/internal medicine ward. Thresholds to accept non-ICU administration of inotropes may be higher in patients where a clear palliative strategy has been decided upon and in patients with an implantable cardioverter-defibrillator (ICD). In recent years, levosimendan in particular, has been used in non-ICU settings. Levosimendan can be administered in hospital, in the ward or in a day hospital (for 6 h infusions) with electrocardiogram and non-invasive blood pressure monitoring during the drug infusion. Electrolyte monitoring is advisable.^{81,82} Patients with severe hypotension (SBP < 90 mmHg) should be admitted to the ICU for the levosimendan infusion to enable vasopressor support if needed. In some centres low-dose dobutamine, dopamine or milrinone is also used outside the ICU setting with precautions as described above.

Administration of inotropes in the ambulatory setting ('home inotropes')

Among the growing population of patients refractory to conventional HF therapy, only a minority are candidates for HTx or MCS¹ whereas the majority of this group, either due to advanced biological age, various comorbidities or psychosocial factors, is not. The latter patients require palliative care mainly for improvement in quality of life.^{3,83} Advanced HF patients referred to specialized HF centres are commonly hospitalized, optimally treated and re-assessed for their potential eligibility for HTx or MCS. Frequently, candidates for those two procedures require long-term inotropic support. The HTx or MCS un-eligible patients may also benefit from inotropic therapy, in terms of quality of life.^{84,85} The safety concerns of inotropes described above are based on studies mostly published before the ICD era and the broad use of β -blockers and were largely disproved by more contemporary studies.^{85,86} This has opened a possibility for longer-term home treatment with inotropes. This practice has been extensively used in the United States, potentially reflecting prior organ heart transplant allocation rules, but until recently less frequently in Europe.

When home inotropic support is considered indicated, several factors including different pharmacological properties of the inotropic agents used affect the decision between which of the different agents to be used. Dobutamine is less expensive than milrinone but there are no head-to-head studies comparing the safety and efficacy of those two agents in the home setting. Compared with dobutamine, more patients treated in their home with milrinone eventually underwent HTx or LVAD implantation (30% vs. 10%) suggesting more frequent use of milrinone in the HTx or MCS eligible population and dobutamine use in the non HTx or MCS eligible palliative care population.²²

Because of a very high risk of phlebitis,⁸⁷ longer-term administration of dobutamine and milrinone requires an indwelling catheter such as peripherally inserted central catheter and bears the potential for various adverse events including arrhythmias and line infections.⁸⁵ The doses used, mandated by the safety concerns, are lower than those used in the monitored setting and are typically in the range 0.125–0.325 $\mu\text{g}/\text{kg}$ body weight/min of milrinone and 1–5 $\mu\text{g}/\text{kg}$ body weight/min of dobutamine.⁸⁸ Because of the long half-life of its pharmacodynamically active metabolite, levosimendan administered intermittently in hospital or in an outpatient setting will also have pharmacological effects after the patient is sent home but is not considered a 'home inotrope'. The tolerability and safety of the repetitive use of this agent was discussed above. There are no head-to-head studies comparing the safety and efficacy of levosimendan and milrinone in the home inotrope setting.

It appears rational to apply home inotropic support in a hierarchical order: start and continue with dobutamine if still effective (because of lowest cost). In cases of reduced inotropic effectiveness of dobutamine, switch to milrinone. When prolonged support is expected or if the patient is intolerant to insertion of an indwelling venous catheter, consider switching to levosimendan if available in the geo-region. Repeated doses of levosimendan may be the first

choice in those patients with history of positive clinical response to this agent.

As a rule, monitor for adverse effects and avoid hypokalaemia: keep potassium levels above 4.0 mmol/L. Consider modifying the diuretic dose and guideline-directed medical therapy, and in the palliative group, discuss with the patient turning off the shock therapy if the patient has an ICD or a cardiac resynchronization therapy-defibrillator device. In patients treated with home inotropes with a non-palliative target, appropriate measures (typically an implantable defibrillator) to avoid sudden arrhythmic death must be taken.

Use of home inotropic support with dobutamine, milrinone and levosimendan as bridge to advanced HF therapy or, in selected cases, as palliative therapy is a viable option. Repetitive home infusions of levosimendan in advanced HF seem to be feasible and a more practical approach although systematic studies are lacking. Evidence-based protocols for continuous intravenous inotropic support are needed.

End-of-life considerations for patients with advanced chronic heart failure on inotropic support

American and European guidelines suggest inotropes may prove effective as a palliative therapy for symptomatic relief in patients with advanced HF who have no further treatment options.^{1,89} Patients with advanced HF can experience multiple symptoms, including physical, psychological or social in nature. Several studies illustrate the beneficial outcome of inotropic therapy in terms of improving functional class for this group of patients.⁹⁰ The impetus and understanding to integrate palliative care early into HF management would support the consideration of inotropic therapy for symptomatic relief,⁸ however with the caveat that its initiation follows open communication and an informed decision shared with the patient and close family members. When death is imminent, cessation of inotropic therapy, like deactivation of ICD should be discussed.

For most patients, their preferred place of care is home. The provision of ambulatory or home-based inotropic therapy is appealing, however this is frequently determined by healthcare organizational factors, socio-demographic characteristics, the patient's level of social support and living arrangements.⁹¹ A small study ($n = 21$) conducted in Belgium found that when intravenous inotropic support was provided at home to patients recently discharged with advanced HF, there was an improved quality of life and 75% (9 out of 12 patients) of the patients died in their preferred place of care – that being at home.⁸⁴ Results from this study are supported by a previous report from the US showing that patients ($n = 217$) who received inotropic support at home were more likely to die at home, as compared to national sample of patients with HF.⁹² This choice and control regarding place of death is an important factor in what patients perceive as a 'good death'.⁹³ However, this should not be the only factor, rather the patient's clinical status including intravenous access, as well as the treatment expectations and concerns expressed by the patient and family members. Such

should be carefully considered to ensure adverse effects associated with current therapy do not outweigh its benefits. A pilot of a cardiac home hospice programme has shown promising results within the United States, however transferability to other countries and healthcare systems may be limited.⁹⁴

All too often patients with complex HF symptoms do not or are unable to avail themselves of hospice services. Increased education on how to best manage complex patients with HF at the end of life is recognized as an essential missing component within the HF specialist training curricula for both cardiologists, nurses as well as that of the hospice staff.^{8,95} Since the first palliative care position paper published by the HFA over a decade ago,⁹⁶ there is greater awareness of the need for sensitive discussions and advanced planning concerning complex therapies such as ICDs and LVADs. For the successful instigation of the use of inotropes in advanced HF, informing the patient that cessation of the treatment may be warranted as the disease progresses, is vital.

Gaps in evidence and directions for future research

As evident from the discussion above, there are several gaps in our knowledge about how to use inotropic support in chronic HF. First, although progress has been made with respect to the documentation of safety of long-term use of inotropes, evidence for efficacy in terms of improved survival is lacking. Unfortunately, existing trials have not been adequately powered and recently an ongoing trial has been stopped due to slow inclusion.⁵⁶ This leaves uncertainty regarding the use of these drugs even in situations where they appear necessary including in the scenarios described above. New drugs affecting cardiac function offer promise for long-term use in patients with advanced HF, but we are still awaiting evidence from clinical trials. More knowledge about the integration of new and conventional inotropes with guideline-directed medical therapy for chronic HF is clearly needed. As the prognosis in non-advanced chronic HF has improved tremendously with the development of modern drug therapy, better tools and a better understanding of how to treat advanced HF in patients not eligible for MCS or HTx are clearly needed to improve overall well-being and survival of the entire HF population.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: none declared.

References

- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2022;**24**:4–131.
- Desjardin JT, Teerlink JR. Inotropic therapies in heart failure and cardiogenic shock: an educational review. *Eur Heart J Acute Cardiovasc Care.* 2021;**10**:676–86.

3. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2018;**20**:1505–35.
4. Stewart GC, Ambardekar AV, Kittleson MM. Defining ambulatory advanced heart failure: MedaMACS and beyond. *Curr Heart Fail Rep.* 2017;**14**:498–506.
5. Chioncel O, Parissis J, Mebazaa A, Thiele H, Desch S, Bauersachs J, et al. Epidemiology, pathophysiology and contemporary management of cardiogenic shock – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2020;**22**:1315–41.
6. Cholley B, Levy B, Fellahi JL, Longrois D, Amour J, Ouattara A, et al. Levosimendan in the light of the results of the recent randomized controlled trials: an expert opinion paper. *Crit Care.* 2019;**23**:385.
7. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, et al. The use of diuretics in heart failure with congestion - a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2019;**21**:137–55.
8. Hill L, Prager Geller T, Baruah R, Beattie JM, Boyne J, de Stoutz N, et al. Integration of a palliative approach into heart failure care: a European Society of Cardiology Heart Failure Association position paper. *Eur J Heart Fail.* 2020;**22**:2327–39.
9. Maack C, Eschenhagen T, Hamdani N, Heinzel FR, Lyon AR, Manstein DJ, et al. Treatments targeting inotropy. *Eur Heart J.* 2019;**40**:3626–44.
10. Comin-Colet J, Manito N, Segovia-Cubero J, Delgado J, García Pinilla JM, Almenar L, et al.; LION-HEART Study Investigators. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial. *Eur J Heart Fail.* 2018;**20**:1128–36.
11. Metra M, Nodari S, D'Aloia A, Muneretto C, Robertson AD, Bristow MR, et al. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. *J Am Coll Cardiol.* 2002;**40**:1248–58.
12. Kindermann M, Maack C, Schaller S, Finkler N, Schmidt KI, Lär S, et al. Carvedilol but not metoprolol reduces beta-adrenergic responsiveness after complete elimination from plasma in vivo. *Circulation.* 2004;**109**:3182–90.
13. Maurice DH, Ke H, Ahmad F, Wang Y, Chung J, Manganiello VC. Advances in targeting cyclic nucleotide phosphodiesterases. *Nat Rev Drug Discov.* 2014;**13**:290–314.
14. Woolfrey SG, Hegbrant J, Thysell H, Fox PA, Lendrem DW, Lockwood GF, et al. Dose regimen adjustment for milrinone in congestive heart failure patients with moderate and severe renal failure. *J Pharm Pharmacol.* 1995;**47**:651–5.
15. Lee EC, McNitt S, Martens J, Bruckel JT, Chen L, Alexis JD, et al. Long-term milrinone therapy as a bridge to heart transplantation: safety, efficacy, and predictors of failure. *Int J Cardiol.* 2020;**313**:83–8.
16. Nanayakkara S, Mak V, Crannitch K, Byrne M, Kaye DM. Extended release oral milrinone, CRD-102, for advanced heart failure. *Am J Cardiol.* 2018;**122**:1017–20.
17. Nanayakkara S, Byrne M, Mak V, Carter K, Dean E, Kaye DM. Extended-release oral milrinone for the treatment of heart failure with preserved ejection fraction. *J Am Heart Assoc.* 2020;**9**:e015026.
18. Puttonen J, Laine T, Ramela M, Häkkinen S, Zhang W, Pradhan R, et al. Pharmacokinetics and excretion balance of OR-1896, a pharmacologically active metabolite of levosimendan, in healthy men. *Eur J Pharm Sci.* 2007;**32**:271–7.
19. Follath F, Cleland JGF, Just H, Papp JGY, Scholz H, Peuhkurinen K; Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) study. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet.* 2002;**360**:196–202.
20. Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J, et al.; REVIVE Heart Failure Study Group. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. *JACC. Heart Fail.* 2013;**1**:103–11.
21. Altenberger J, Parissis JT, Costard-Jaeckle A, Winter A, Ebner C, Karavidas A, et al. Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial. *Eur J Heart Fail.* 2014;**16**:898–906.
22. Psotka MA, Gottlieb SS, Francis GS, Allen LA, Teerlink JR, Adams KF, et al. Cardiac calcitropes, myotropes, and mitotropes: JACC review topic of the week. *J Am Coll Cardiol.* 2019;**73**:2345–53.
23. Teerlink JR, Clarke CP, Saikali KG, Lee JH, Chen MM, Escandon RD, et al. Dose-dependent augmentation of cardiac systolic function with the selective cardiac myosin activator, omecamtiv mecarbil: a first-in-man study. *Lancet.* 2011;**378**:667–75.
24. Cleland JGF, Teerlink JR, Senior R, Nifontov EM, McMurray JVV, Lang CC, et al. The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial. *Lancet.* 2011;**378**:676–83.
25. Carubelli V, Zhang Y, Metra M, Lombardi C, Felker GM, Filippatos G, et al.; Istaroxime ADHF Trial Group. Treatment with 24 hour istaroxime infusion in patients hospitalised for acute heart failure: a randomised, placebo-controlled trial. *Eur J Heart Fail.* 2020;**22**:1684–93.
26. Teerlink JR, Diaz R, Felker GM, McMurray JVV, Metra M, Solomon SD, et al.; GALACTIC-HF Investigators. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med.* 2021;**384**:105–16.
27. Abraham WT, Kuck KH, Goldsmith RL, Lindenfeld J, Reddy VY, Carson PE, et al. A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation. *JACC Heart Fail.* 2018;**6**:874–83.
28. Madonna R, Van Laake LW, Davidson SM, Engel FB, Hausenloy DJ, Lecour S, et al. Position paper of the European Society of Cardiology Working Group Cellular Biology of the Heart: cell-based therapies for myocardial repair and regeneration in ischemic heart disease and heart failure. *Eur Heart J.* 2016;**37**:1789–98.
29. Madonna R, Van Laake LW, Botker HE, Davidson SM, De Caterina R, Engel FB, et al. ESC Working Group on Cellular Biology of the Heart: position paper for cardiovascular research: tissue engineering strategies combined with cell therapies for cardiac repair in ischaemic heart disease and heart failure. *Cardiovasc Res.* 2019;**115**:488–500.
30. Menasché P, Vanneaux V, Hagege A, Bel A, Cholley B, Parouchev A, et al. Transplantation of human embryonic stem cell-derived cardiovascular progenitors for severe ischemic left ventricular dysfunction. *J Am Coll Cardiol.* 2018;**71**:429–38.
31. Liu B, Lee BW, Nakanishi K, Villasante A, Williamson R, Metz J, et al. Cardiac recovery via extended cell-free delivery of extracellular vesicles secreted by cardiomyocytes derived from induced pluripotent stem cells. *Nat Biomed Eng.* 2018;**2**:293–303.
32. Gabisonia K, Prosdocimo G, Aquaro GD, Carlucci L, Zentilin L, Secco I, et al. MicroRNA therapy stimulates uncontrolled cardiac repair after myocardial infarction in pigs. *Nature.* 2019;**569**:418–22.
33. Lenihan DJ, Anderson SA, Lenneman CG, Brittain E, Muldowney JAS, Mendes L, et al. A phase I, single ascending dose study of cimaglermin alfa (neuregulin 1β3) in patients with systolic dysfunction and heart failure. *JACC Basic Transl Sci.* 2016;**1**:576–86.
34. Tzahor E, Poss KD. Cardiac regeneration strategies: staying young at heart. *Science.* 2017;**356**:1035–9.
35. Reichart B, Längin M, Radan J, Mokelke M, Buttgereit I, Ying J, et al. Pig-to-non-human primate heart transplantation: the final step toward clinical xenotransplantation? *J Heart Lung Transplant.* 2020;**39**:751–7.
36. Griffith BP, Goerlich CE, Singh AK, Rothblatt M, Lau CL, Shah A, et al. Genetically modified porcine-to-human cardiac xenotransplantation. *N Engl J Med.* 2022;**387**:35–44.
37. Garry DJ, Garry MG. Interspecies chimeras and the generation of humanized organs. *Circ Res.* 2019;**124**:23–5.
38. Greenberg B, Butler J, Felker GM, Ponikowski P, Voors AA, Desai AS, et al. Calcium upregulation by percutaneous administration of gene therapy in patients with cardiac disease (CUPID 2): a randomised, multinational, double-blind, placebo-controlled, phase 2b trial. *Lancet.* 2016;**387**:1178–86.
39. Chung ES, Miller L, Patel AN, Anderson RD, Mendelsohn FO, Traverse J, et al. Changes in ventricular remodeling and clinical status during the year following a single administration of stromal cell-derived factor-1 non-viral gene therapy in chronic ischaemic heart failure patients: the STOP-HF randomized phase II trial. *Eur Heart J.* 2015;**36**:2228–38.
40. Hammond HK, Penny WF, Traverse JH, Henry TD, Watkins MW, Yancy CW, et al. Intracoronary gene transfer of adenylyl cyclase 6 in patients with heart failure: a randomized clinical trial. *JAMA Cardiol.* 2016;**1**:163–71.
41. Täubel J, Hauke W, Rump S, Viereck J, Batkai S, Poetsch J, et al. Novel antisense therapy targeting microRNA-132 in patients with heart failure: results of a first-in-human phase 1b randomized, double-blind, placebo-controlled study. *Eur Heart J.* 2021;**42**:178–88.
42. Clemens PR, Rao VK, Connolly AM, Harper AD, Mah JK, Smith EC; CINRG DNHs Investigators. Safety, tolerability, and efficacy of viltolarsen in boys with Duchenne muscular dystrophy amenable to exon 53 skipping: a phase 2 randomized clinical trial. *JAMA Neurol.* 2020;**77**:982–91.
43. Newby GA, Liu DR. In vivo somatic cell base editing and prime editing. *Mol Ther.* 2021;**29**:3107–24.
44. O'Connor CM, Gattis WA, Uretsky BF, Adams KF, McNulty SE, Grossman SH, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). *Am Heart J.* 1999;**138**:78–86.
45. Thackray S, Easthaugh J, Freemantle N, Cleland JGF. The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure – a meta-regression analysis. *Eur J Heart Fail.* 2002;**4**:515–29.
46. Triposkiadis FK, Butler J, Karayannis G, Starling RC, Filippatos G, Wolski K, et al. Efficacy and safety of high dose versus low dose furosemide with or without

- dopamine infusion: the Dopamine in Acute Decompensated Heart Failure II (DAD-HF II) trial. *Int J Cardiol.* 2014;**172**:115–21.
47. Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR; NHLBI Heart Failure Clinical Research Network. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA.* 2013;**310**:2533–43.
 48. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C; SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med.* 2010;**362**:779–89.
 49. Sharma K, Vaishnav J, Kalathiyar R, Hu JR, Miller J, Shah N, et al.; Osler Medical Housestaff. Randomized evaluation of heart failure with preserved ejection fraction patients with acute heart failure and dopamine: the ROPA-DOP trial. *JACC Heart Fail.* 2018;**6**:859–70.
 50. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med.* 1991;**325**:1468–75.
 51. Felker GM, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM; et al.; OPTIME-CHF Investigators. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol.* 2003;**41**:997–1003.
 52. Metra M, Eichhorn E, Abraham WT, Linseman J, Böhm M, Corbalan R, et al.; ESSENTIAL Investigators. Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials. *Eur Heart J.* 2009;**30**:3015–26.
 53. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, et al.; SURVIVE Investigators. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE randomized trial. *JAMA.* 2007;**297**:1883–91.
 54. Altenberger J, Gustafsson F, Harjola VP, Karason K, Kindgen-Milles D, Kivikko M, et al. Levosimendan in acute and advanced heart failure: an appraisal of the clinical database and evaluation of its therapeutic applications. *J Cardiovasc Pharmacol.* 2018;**71**:129–36.
 55. García-González MJ, Aldea Perona A, Lara Padron A, Morales Rull JL, Martínez-Sellés M, de Mora Martín M, et al. Efficacy and safety of intermittent repeated levosimendan infusions in advanced heart failure patients: the LAICA study. *ESC Heart Fail.* 2021;**8**:4820–31.
 56. Pözl G, Allipour Birgani S, Comin-Colet J, Delgado JF, Fedele F, García-González MJ, et al. Repetitive levosimendan infusions for patients with advanced chronic heart failure in the vulnerable post-discharge period. *ESC Heart Fail.* 2019;**6**:174–81.
 57. Metra M, Pagnesi M, Claggett BL, Diaz R, Felker GM, McMurray JVV, et al. Effects of omecamtiv mecarbil in heart failure with reduced ejection fraction according to blood pressure: the GALACTIC-HF trial. *Eur Heart J.* 2022;**43**:5006–16.
 58. Felker GM, Solomon SD, Claggett B, Diaz R, McMurray JVV, Metra M, et al. Assessment of omecamtiv mecarbil for the treatment of patients with severe heart failure: a post hoc analysis of data from the GALACTIC-HF randomized clinical trial. *JAMA Cardiol.* 2022;**7**:26–34.
 59. Lewis GD, Voors AA, Cohen-Solal A, Metra M, Whellan DJ, Ezekowitz JA, et al. Effect of omecamtiv mecarbil on exercise capacity in chronic heart failure with reduced ejection fraction: the METEORIC-HF randomized clinical trial. *JAMA.* 2022;**328**:259–69.
 60. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. *J Am Coll Cardiol.* 2009;**53**:582–8.
 61. Deis T, Balling L, Boesgaard S, Rossing K, Schou M, Oturai P, et al. Relation between invasive hemodynamics and measured glomerular filtration rate by ⁵¹Cr-EDTA clearance in advanced heart failure. *Scand J Clin Lab Invest.* 2019;**79**:194–201.
 62. Agricola E, Marini C, Stella S, Monello A, Fiscarò A, Tufaro V, et al. Effects of functional tricuspid regurgitation on renal function and long-term prognosis in patients with heart failure. *J Cardiovasc Med (Hagerstown).* 2017;**18**:60–8.
 63. Lannemyr L, Bragadottir G, Redfors B, Ricksten SE. Effects of milrinone on renal perfusion, filtration and oxygenation in patients with acute heart failure and low cardiac output early after cardiac surgery. *J Crit Care.* 2020;**57**:225–30.
 64. Fedele F, Bruno N, Brasolin B, Caira C, D'Ambrosi A, Mancone M. Levosimendan improves renal function in acute decompensated heart failure: possible underlying mechanisms. *Eur J Heart Fail.* 2014;**16**:281–8.
 65. Lannemyr L, Ricksten SE, Rundqvist B, Andersson B, Bartfay SE, Ljungman C, et al. Differential effects of levosimendan and dobutamine on glomerular filtration rate in patients with heart failure and renal impairment: a randomized double-blind controlled trial. *J Am Heart Assoc.* 2018;**7**:e008455.
 66. Potapov EV, Antonides C, Crespo-Leiro MG, Combes A, Färber G, Hannan MM, et al. 2019 EACTS expert consensus on long-term mechanical circulatory support. *Eur J Cardiothorac Surg.* 2019;**56**:230–70.
 67. Vishram-Nielsen JKK, Deis T, Balling L, Sabbah M, Boesgaard S, Rossing K, et al. Relationship between invasive hemodynamics and liver function in advanced heart failure. *Scand Cardiovasc J.* 2019;**53**:235–46.
 68. Ter Maaten JM, Dauw J, Martens P, Somers F, Damman K, Metalidis C, et al. The effect of decongestion on intrarenal venous flow patterns in patients with acute heart failure. *J Card Fail.* 2021;**27**:29–34.
 69. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, et al.; International Society for Heart Lung Transplantation (ISHLT) Infectious Diseases, Pediatric and Heart Failure and Transplantation Councils. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant.* 2016;**35**:1–23.
 70. Gustafsson F, Shaw S, Lavee J, Saeed D, Pya Y, Krabatsch T, et al. Six-month outcomes after treatment of advanced heart failure with a full magnetically levitated continuous flow left ventricular assist device: report from the ELEVATE registry. *Eur Heart J.* 2018;**39**:3454–60.
 71. Theiss HD, Grabmaier U, Kreissl N, Hagl C, Steinbeck G, Sodian R, et al. Preconditioning with levosimendan before implantation of left ventricular assist devices. *Artif Organs.* 2014;**38**:231–4.
 72. Khush KK, Hsieh E, Potena L, Cherikh WS, Chambers DC, Harhay MO, et al.; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-eighth adult heart transplantation report - 2021; Focus on recipient characteristics. *J Heart Lung Transplant.* 2021;**40**:1035–49.
 73. Hashim T, Sanam K, Revilla-Martinez M, Morgan CJ, Tallaj JA, Pamboukian SV, et al. Clinical characteristics and outcomes of intravenous inotropic therapy in advanced heart failure. *Circ Heart Fail.* 2015;**8**:880–6.
 74. Mann DL, Givertz MM, Vadar JM, Starling RC, Shah P, McNulty SE, et al.; LIFE Investigators. Effect of treatment with sacubitril/valsartan in patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA Cardiol.* 2022;**7**:17–25.
 75. Vadar JM, Givertz MM, Starling RC, McNulty SE, Anstrom KJ, Desvigne-Nickens P; LIFE Investigators. Tolerability of sacubitril/valsartan in patients with advanced heart failure: analysis of the LIFE trial run-in. *JACC Heart Fail.* 2022;**10**:449–56.
 76. Mebazaa A, Nieminen MS, Filippatos GS, Cleland JG, Salo JE, Thakkar R, et al. Levosimendan vs. dobutamine: outcomes for acute heart failure patients on beta-blockers in SURVIVE. *Eur J Heart Fail.* 2009;**11**:304–11.
 77. Constantinescu AA, Caliskan K, Manintveld OC, van Domburg R, Jewbali L, Balk AHMM. Weaning from inotropic support and concomitant beta-blocker therapy in severely ill heart failure patients: take the time in order to improve prognosis. *Eur J Heart Fail.* 2014;**16**:435–43.
 78. Teerlink JR, Diaz R, Felker GM, McMurray JVV, Metra M, Solomon SD, et al.; GALACTIC-HF Investigators. Effect of ejection fraction on clinical outcomes in patients treated with omecamtiv mecarbil in GALACTIC-HF. *J Am Coll Cardiol.* 2021;**78**:97–108.
 79. Ameri P, Bertero E, Maack C, Teerlink JR, Rosano G, Metra M. Medical treatment of heart failure with reduced ejection fraction: the dawn of a new era of personalized treatment? *Eur Heart J Cardiovasc Pharmacother.* 2021;**7**:539–46.
 80. Hernandez GA, Lemor A, Blumer V, Rueda CA, Zalawadiya S, Stevenson LW, et al. Trends in utilization and outcomes of pulmonary artery catheterization in heart failure with and without cardiogenic shock. *J Card Fail.* 2019;**25**:364–71.
 81. Farmakis D, Agostoni P, Baholli L, Bautin A, Comin-Colet J, Crespo-Leiro MG, et al. A pragmatic approach to the use of inotropes for the management of acute and advanced heart failure: an expert panel consensus. *Int J Cardiol.* 2019;**297**:83–90.
 82. Pözl G, Altenberger J, Baholli L, Beltrán P, Borbély A, Comin-Colet J, et al. Repetitive use of levosimendan in advanced heart failure: need for stronger evidence in a field in dire need of a useful therapy. *Int J Cardiol.* 2017;**243**:389–95.
 83. Girerd N, Mewton N, Tartièrre JM, Guijarro D, Jourdain P, Damy T, et al.; a panel of multidisciplinary experts and the Heart Failure Working Group of the French Society of Cardiology. Practical outpatient management of worsening chronic heart failure. *Eur J Heart Fail.* 2022;**24**:750–61.
 84. Martens P, Vercammen J, Ceysens WV, Jacobs L, Luwel E, Van Aerde H, et al. Effects of intravenous home dobutamine in palliative end-stage heart failure on quality of life, heart failure hospitalization, and cost expenditure. *ESC Heart Fail.* 2018;**5**:562–9.
 85. Assad-Kottner C, Chen D, Jahanyar J, Cordova F, Summers N, Loebe M, et al. The use of continuous milrinone therapy as bridge to transplant is safe in patients with short waiting times. *J Card Fail.* 2008;**14**:839–43.

86. Harhash AA, Cassuto J, Hussein A, Achu E, Zucker MJ, Goldschmidt M, et al. Safety of outpatient milrinone infusion in end-stage heart failure: ICD-level data on atrial fibrillation and ventricular tachyarrhythmias. *Am J Med.* 2020;**133**:857–64.
87. Silva EVC, Ochiai ME, Vieira KRN, Pereira Barretto AC. The use of peripherally inserted central catheter reduced the incidence of phlebitis in heart failure patients: a randomized trial. *J Vasc Access.* 2021. <https://doi.org/10.1177/11297298211059650>
88. Rao A, Anderson KM, Mohammed S, Hofmeyer M, Gholami SS, Sheikh FH, et al. Chronic intravenous inotropic support as palliative therapy and bridge therapy for patients with advanced heart failure: a single-center experience. *J Card Fail.* 2021;**27**:974–80.
89. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2022;**79**:e263–421.
90. Nizamic T, Murad MH, Allen LA, McIlvennan CK, Wordingham SE, Matlock DD, et al. Ambulatory inotropic infusions in advanced heart failure: a systematic review and meta-analysis. *JACC Heart Fail.* 2018;**6**:757–67.
91. Houttekier D, Cohen J, Van den Block L, Bossuyt N, Deliens L. Involvement of palliative care services strongly predicts place of death in Belgium. *J Palliat Med.* 2010;**13**:1461–8.
92. Taitel M, Meaux N, Pegus C, Valerian C, Kirkham H. Place of death among patients with terminal heart failure in a continuous inotropic infusion program. *Am J Hosp Palliat Care.* 2012;**29**:249–53.
93. Smith R. A good death. An important aim for health services and for us all. *BMJ.* 2000;**320**:129–30.
94. Jordan L, Russell D, Baik D, Dooley F, Masterson Creber RM. The development and implementation of a cardiac home hospice program: results of a RE-AIM analysis. *Am J Hosp Palliat Care.* 2020;**37**:925–35.
95. Metzger M, Norton SA, Quinn JR, Gramling R. 'That don't work for me': Patients' and family members' perspectives on palliative care and hospice in late-stage heart failure. *J Hosp Palliat Nurs.* 2013;**15**:177–82.
96. Jaarsma T, Beattie JM, Ryder M, Rutten FH, McDonagh T, Mohacsi P, et al.; Advanced Heart Failure Study Group of the HFA of the ESC. Palliative care in heart failure: a position statement from the palliative care workshop of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2009;**11**:433–43.