Table S1. Definitions relevant for considerations for inotropic therapy in chronic advanced heart failure

Inotropes:

A group of drugs that increase the force or the velocity (the strength) of the myocardial fibre contraction. Recently, inotropes have been classified by their mechanism of action into 1) Calcitropes (e.g., Dobutamine, Milrinone) 2) myotropes (e.g., Omecamtiv Mecarbil) 3) mitotropes

Acute Cardiovasc Care 2021; 10: 676-686.

Advanced heart failure:

A patient fulfilling the criteria below. The patient can be an outpatient or admitted to hospital.

1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].

2. Severe cardiac dysfunction defined by a reduced LVEF ≤30%, isolated RV failure (e.g., ARVC) or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities.

3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.

4. Severe impairment of exercise capacity with inability to exercise or low 6MWTD (<300 m) or pVO2(<12–14 mL/kg/min), estimated to be of cardiac origin.

European Journal of Heart Failure 2018; 20: 1505–1535.

Ambulatory advanced heart failure:

Patients fulfilling criteria for advanced HF not currently admitted to hospital. In the INTERMACS classification they would be classified as profile 4-7 (unless on home inotrope therapy and inotrope dependent (see definitions) then=3).

Current Heart Failure Reports 2017; 14: 498-506

Acute heart failure:

Refers to rapid or gradual onset of symptoms and/or signs of HF, severe enough for the patient to seek urgent medical attention, leading to an unplanned hospital admission or and emergency department visit.

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Cardiogenic shock:

A syndrome caused by a primary cardiovascular disorder in which inadequate CO results in a life-threatening state of tissue hypoperfusion associated with impairment of tissue oxygen metabolism and hyperlactatemia which depending on its severity, may result in multi-organ dysfunction and death. European Journal of Heart Failure (2020) 22, 1315–1341

Systemic hypoperfusion:

A presentation including one or more of the following clinical signs: cold sweated extremities, oliguria, mental confusion, dizziness, narrow pulse AND one or more laboratory results signifying tissue hypoxia and altered cellular metabolism: elevated creatinine, metabolic acidosis or elevated lactate. Blood pressure is often but not invariably low.

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Hypotension:

A systolic blood pressure < 90 mmHg. This should be differentiated from symptomatic hypotension, which requires that the patient has symptoms caused by low blood pressure (e.g., dizziness, syncope)

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Repeated inotrope infusions:

A planned strategy of repetitive intravenous infusion of short- or longer acting inotropes with fixed or variable intervals with the purpose of preventing or attenuating end organ dysfunction and reduce the need for unplanned heart failure hospitalizations or bridge for heart transplantation or long term mechanical circulatory support.

Crit Care. 2019 Nov 29;23(1):385.

Diuretic resistance:

Diuretic resistance is defined as an impaired sensitivity to diuretics resulting in the need for higher diuretic doses due to reduced natriuresis and diuresis limiting the possibility to achieve euvolemia.

European Journal of Heart Failure (2019) 21, 137–155

Inotrope dependence (Proposed ESC HFA definition):

FAILURE to wean intravenous inotropic support* within 72 hours**

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 IV symptoms.***

The diagnosis of Inotrope dependence should not be made during simultaneous introduction or up titration of betablockers or RAS inhibitors.

*Epinephrine, norepinephrine, dopamine, dobutamine, milrinone.

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

***In the absence of reduction in loop diuretic dose.

Palliative care:

An approach that improves the quality of life of patients and families through the prevention and relief of suffering, focusing on expert assessment and management of symptoms, evaluation and support of informal caregivers, and the interdisciplinary coordination of continuing care. Palliative treatment is not synonymous with end-of-life care.

European Journal of Heart Failure (2020) 22, 2327–2339

Intensive care unit:

A hospital department with high level of patient monitoring options including as a minimum continuous intraarterial blood pressure, central venous pressure, oxygen saturation, ECG. Mechanical ventilation, mechanical circulatory support and continuous renal replacement therapy may be options offered.

Home inotropic therapy:

Continuous or intermittent intravenous infusion of inotropic drugs in the patient's home or a non-hospital care facility (e.g., nursing home or hospice). Oral treatment with inotropic drugs or hospital-based infusion of long-acting inotropes (i.e., with prolonged effect after discharge) is NOT considered home inotropic therapy.

Supplemental Table 2. New and Emerging Inotropic Therapies

Therapy		**Mechanism of action**	**Application**	**Status**	**Reference**
Mitotropes	Perhexiline, Trimetazidine		Peripartum CMP, non-cardiac surgery	Clinical trials	[16]Psotka et al
Istaroxime		Na+/Ca+ inhibition; activation SERCA2a	Acute decompensated HF	Clinical trial	[78]Carubelli et al
Myotropes	Omecamtiv Mecarbil	Myosin activation	Chronic HFrEF	Reduce HF hospitalization/CV mortality in phase III trial	[45]Teerlink et al
Cardiac Contractility Modulation		Pacemaker-generated electric signal in refractory period to increase calcium influx	Severe chronic HF with LVEF 25-45%, narrow QRS	Clinical trials (increased VO2 max), evidence still considered insufficient	[79]Abraham et al
Stem Cells	First generation (bone marrow, mesenchymal stem cells)	Modification of remodeling, neovascularization, immune response (paracrine)	Chronic HFrEF, acute myocardial infarction	Clinical trials (safe, but very limited efficacy)	[80]Madonna et al
	Second+ generation (pluripotent	Paracrine and direct inotropy (new	Chronic HFrEF	Clinical trials (ongoing)	[81]Madonna et al [82]Menasche

	stem cell-derived cardiomyocytes, tissue engineering)	myocytes)			et al
Cell-Free Stem Cell Based Therapy		Paracrine effects (e.g., via extracellular vesicle contents)	Chronic HFrEF, acute HF?	Pre-clinical studies	[81]Madonna et al [83]Liu et al
Induced Cardiomyocyte Proliferation	Modifiers of YAP – Hippo pathway	Proliferation of resident cardiomyocytes	Acute HF post-myocardial infarction (in future non-genetic chronic HFrEF?)	Pre-clinical studies	[84]Gabisonia et al
	Neuregulin		Chronic HFrEF	Clinical trials	[85]Lenihan et al
Direct Reprogramming	Small molecules, microRNAs, gene transcription factors	Trans differentiation of resident fibroblasts into cardiomyocytes	Chronic HFrEF (non-genetic)	Pre-clinical studies	[86]Tzahor et al
Xeno-transplantation	Total xeno organ	Transplantation of animal (e.g., pig) heart	End-stage HF	Pre-clinical and clinical studies	[87]Reichart et al [88]Griffith
	Chimeras	Transplantation of humanized heart grown in animal	End-stage HF	Pre-clinical studies	[89]Garry et al
Genetic correction therapy	Gene therapy	(Viral) delivery to increase expression	HFrEF	Clinical trials	• [90]Greenberg et al • [91]Chung et al • [92]Ham

					mond et al
	Antisense	Reduce or ablate expression, exon skipping (to avoid mutations)	HFrEF, genetic CMP	Clinical trials (approved therapy for Duchenne neurological outcomes)	• [93]Täubel et al • [94]Clemens et al
	Gene editing	Deletion, correction, up/downregulation (CRISPR-Cas9 base editing, prime editing)	Genetic CMP	Experimental (mainly *in vitro*)	• [95]Newby et al