CHFS SCIC

Canadian Heart Failure Society
Société canadienne d'insuffisance cardiaque

Inotropes for HF_REF
Heart stimulation: Classifying the "tropes" of heart failure

He who wants a mule without fault, must walk on foot

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Disclosure of Potential Conflicts of Interest

- Research grant :
  - Amgen , Novartis , Sanofi
- Lecture fees
  - Novartis , Servier , Astra Zeneca , Bohringer Ingenheim , Bayer
- Ad Boards
  - Alnylam , Servier , Novartis , Bayer

Theoretical clinical characteristics of an ideal positive inotropic agent

- Easy titration for rapid on/off effect
- Myocardial oxygen supply/demand balance
- Steady effect in time (no tachyphylaxis)
- Direct positive inotropic effect
- β-independent positive inotropic stimulation
- Few or no arrhythmogenic effect
- No intracellular calcium overload
- Maintenance of the coronary perfusion pressure
- Beneficial effects on regional vascular beds
- Reasonable benefit/risk balance

Question 1

- Low cardiac output is usualy associated with all these clinical features except one
  - 1: confusion
  - 2: hypotension
  - 3: hepatic congestion
  - 4: oliguria
  - 5: $SvO2 < 65\%$

Question 1

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Symptoms and signs of low perfusion vs. congestion in heart failure patients

Low Perfusion	Congestion
Fatigue	Fatigue
Confusion	Tachycardia
Agitation	Raised jugular venous pressure
Low level of consciousness	Breathlessness and hypoxemia
Cold peripheries	Pulmonary oedema
Delayed capillary refill time	Lowe extremities oedema
Thready pulse	Hepatic congestion
Hypotension	
Tachycardia	
Oliguria or anuria	
Metabolic acidosis	
$SvO_2 < 65\%$	

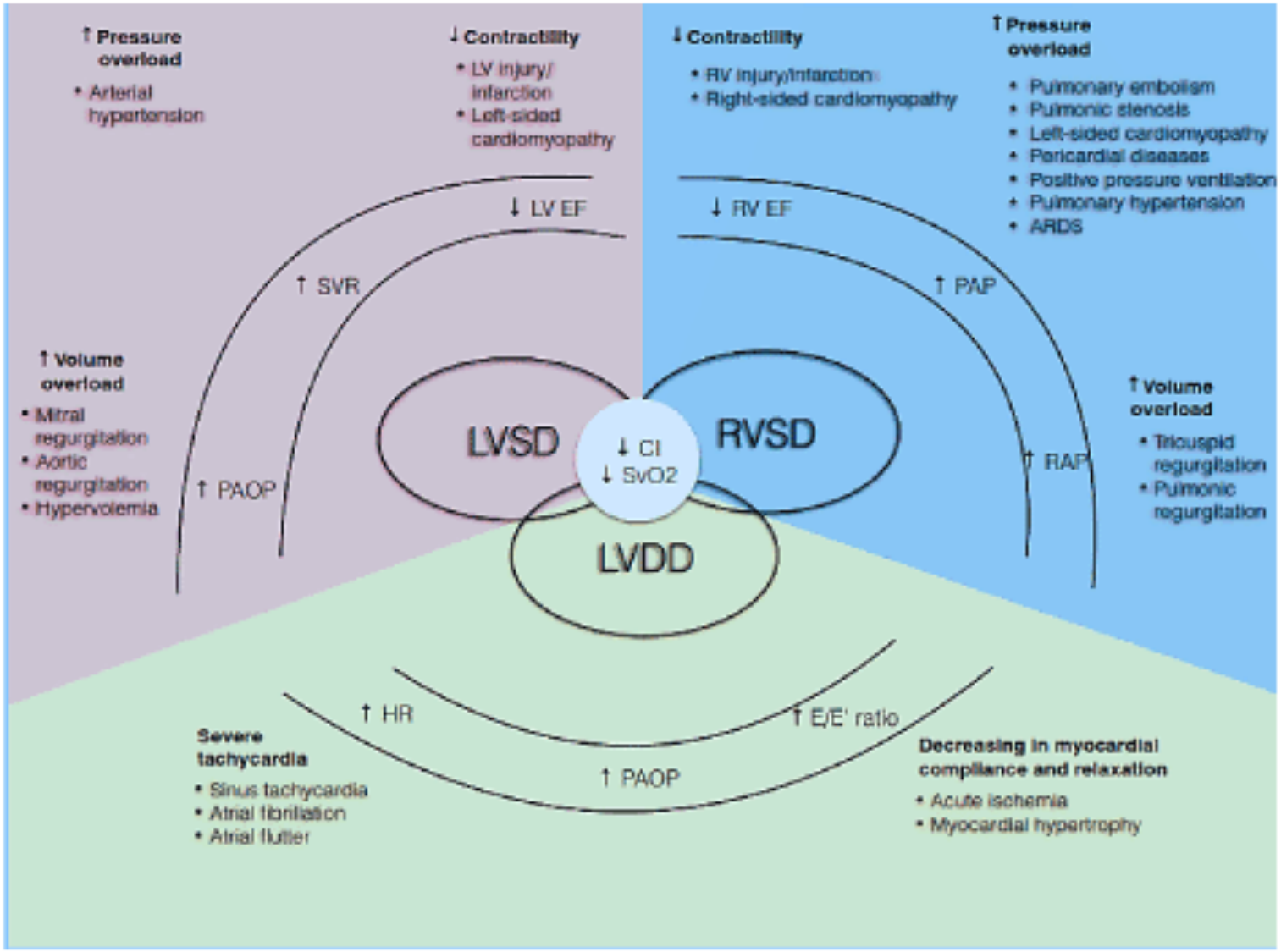
Question 2

- Low cardiac output is usually a sign of decreased left ventricular systolic function
  - 1: True
  - 2: False

Question 2

- Low cardiac output is usualy a sign of decrease left ventricular systolic function
  - 1: True
  - 2: False

Pathophysiologic mechanisms of low-output heart failure

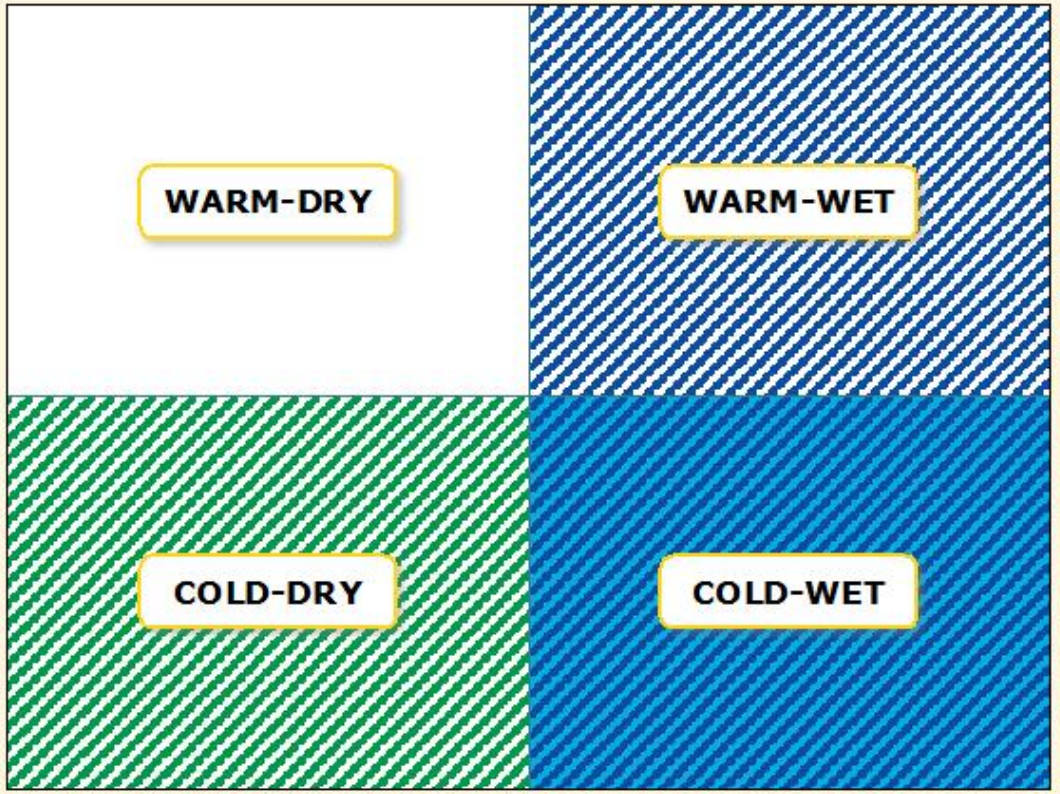


Clinical profiles of patients with acute heart failure based on the presence/absence of congestion and/or hypoperfusion

CONGESTION (−)

CONGESTION (+)
- Pulmonary congestion
- Orthopnoea/paroxysmal nocturnal dyspnoea
- Peripheral (bilateral) oedema
- Jugular venous dilatation
- Congested hepatomegaly
- Gut congestion, ascites
- Hepatojugular reflux

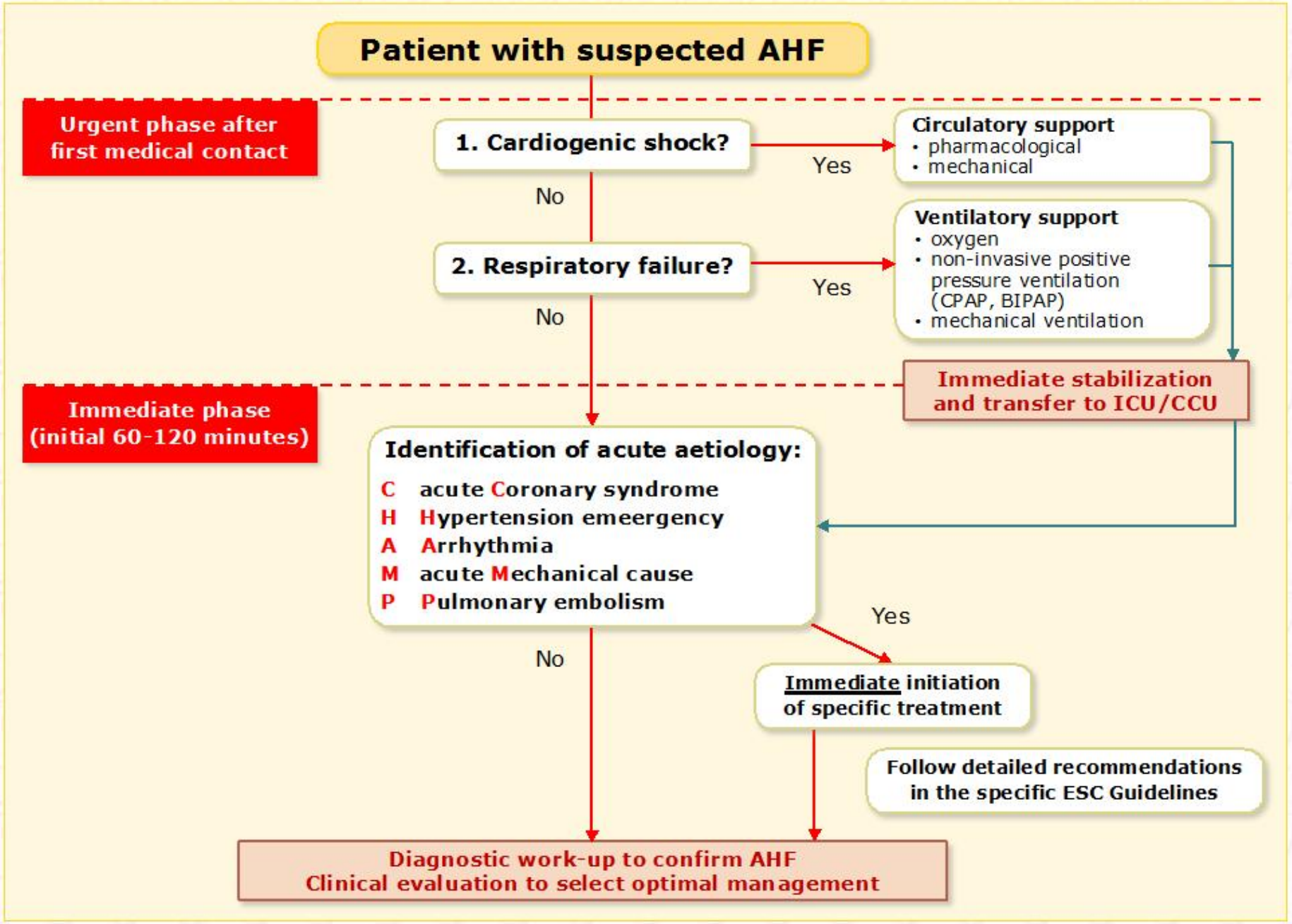
HYPOPERFUSION (−)



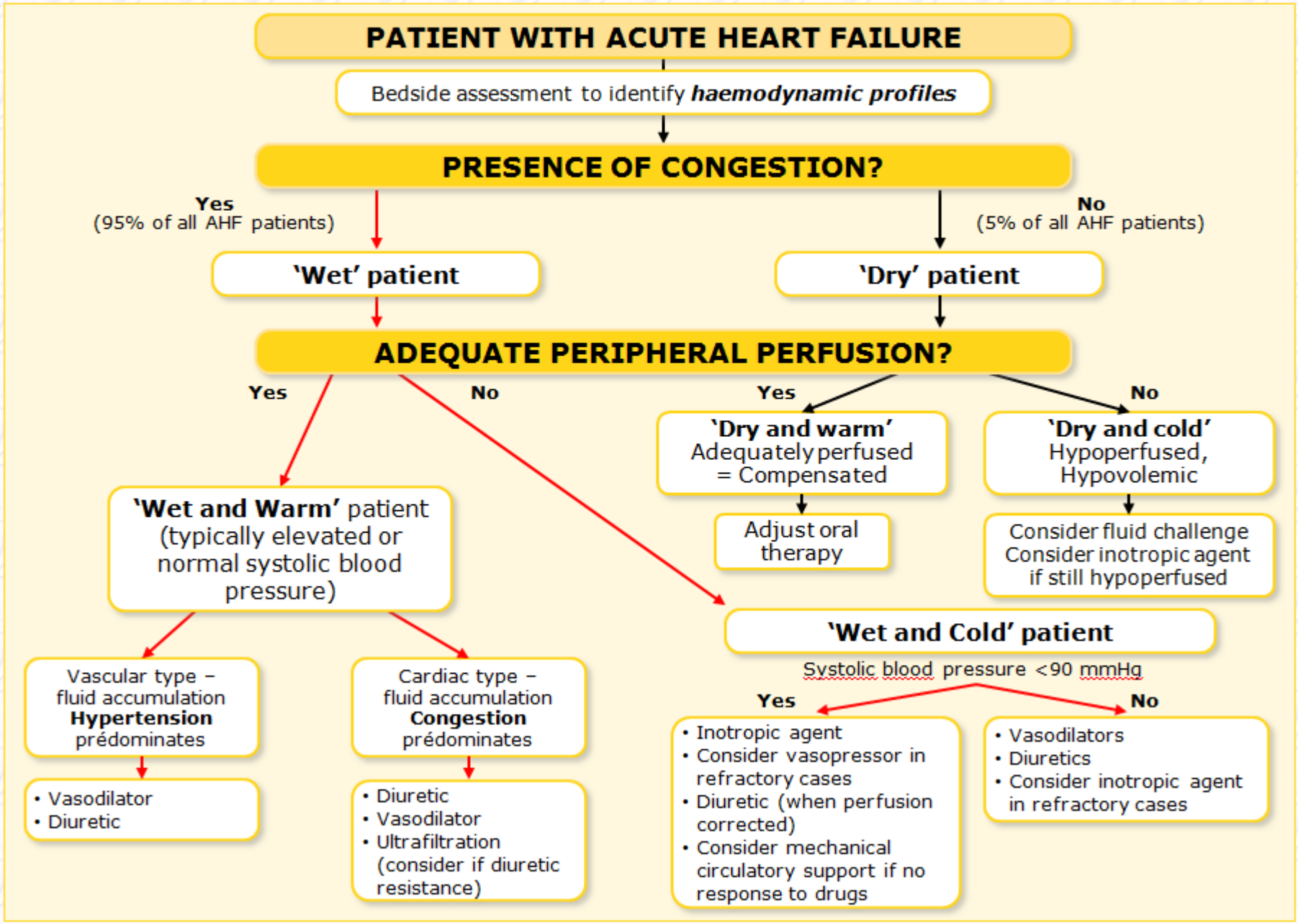
HYPOPERFUSION (+)
- Cold sweated extremities
- Oliguria
- Mental confusion
- Dizziness
- Narrow pulse pressure

Hypoperfusion is not synonymous with hypotension, but often hypoperfusion is accompanied by hypotension

Initial management of a patient with acute heart failure



Management of patients with acute heart failure based on clinical profile during an early phase

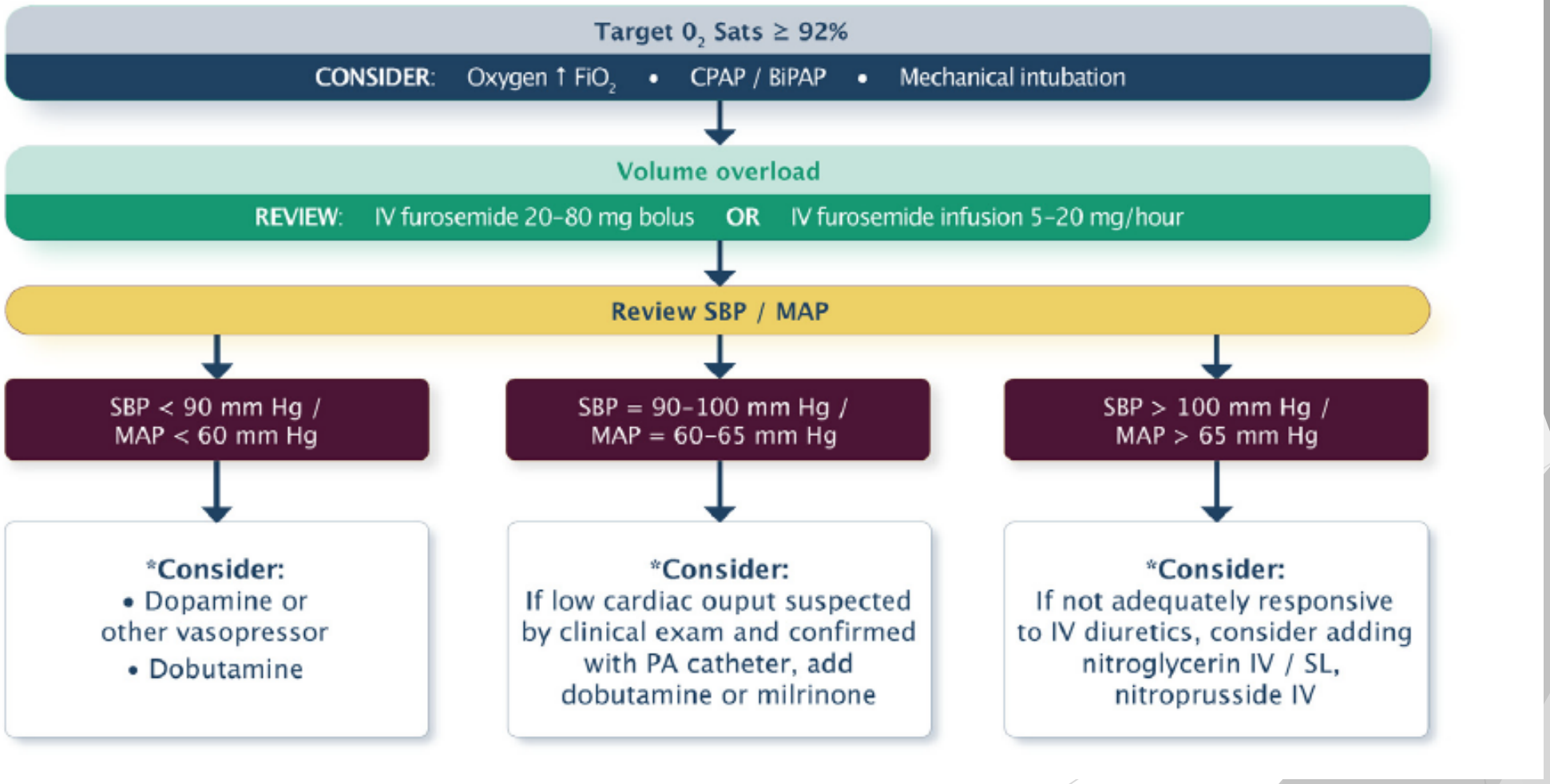


CCS guidelines

- 2012: Inotropic agents have not been shown to improve patient outcomes.
  - OPTIME-HF No statistically significant benefit was found from the use of milrinone in terms of mortality or hospitalizations, whereas milrinone was linked to increased risk of prolonged hypotensive episodes and arrhythmias.23 In a subgroup analysis, milrinone was associated with increased mortality rates in patients with HF of ischaemic aetiology
- 2017: Consider Advanced HF management strategies for pts NYHA 3 or 4 with more then one of

- **LVEF < 25% and, if measured, peak exercise oxygen consumption < 14 mL/kg/min (or less than 50% predicted).**
- **Evidence of progressive end organ dysfunction due to reduced perfusion and not to inadequate ventricular filling pressures.**
- **Recurrent HF hospitalizations (2 in 12 months) not due to a clearly reversible cause.**
- **Need to progressively reduce or eliminate evidence based HF therapies such as ACEis, MRAs, or b-blockers,**
  - **because of circulatory-renal limitations such as renal insufficiency or symptomatic hypotension.**
- **Diuretic refractoriness associated with worsening renal function.**
- **Requirement for inotropic support for symptomatic relief or to maintain end organ function.**
- **Worsening right HF (RHF) and secondary pulmonary hypertension.**
- **Six-minute walk distance < 300 m.**
- **Increased 1-year mortality (eg, > 20%-25%) predicted by HF risk scores**
- **Progressive renal or hepatic end organ dysfunction.**
- **Persistent hyponatremia (serum sodium < 134 mEq/L).**
- **Cardiac cachexia.**
- **Inability to perform activities of daily living.**

CCS guidelines 2017



ESC HF guidelines

Inotropic agents – dobutamine, dopamine, levosimendan, phosphodiesterase III (PDE III) inhibitors		
Short-term, i.v. infusion of inotropic agents may be considered in patients with hypotension (SBP <90 mmHg) and/or signs/symptoms of hypoperfusion despite adequate filling status, to increase cardiac, increase blood pressure, improve peripheral perfusion and maintain end-organ function.	**IIb**	**C**
An intravenous infusion of levosimendan or a PDE III inhibitor may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypotension with subsequenthypoperfusion.	**IIb**	**C**
Inotropic agents are not recommended unless the patient is symptomatically hypotensive or hypoperfused because of safety concern.	**III**	**A**
Vasopressors		
A vasopressor (norepinephrine preferably) may be considered in patients who have cardiogenic shock, despite treatment with another inotrope, to increase blood pressure and vital organ perfusion.	**IIb**	**B**
It is recommended to monitor ECG and blood pressure when using inotropic agents and vasopressors, as they can cause arrhythmia, myocardial ischaemia, and in the case of levosimendan and PDE III inhibitors also hypotension	**I**	**C**
In such cases intra-arterial blood pressure measurement may be considered.	**IIb**	**C**

Medication	Usual Infusion Dose	Receptor Binding				Hemodynamic Effects
		α_1	β_1	β_2	Dopamine	
Vasopressor/inotropes						
Dopamine	0.5–2 μg·kg^{-1}·min^{-1}	–	+	–	+++	↑CO
	5–10 μg·kg^{-1}·min^{-1}	+	+++	+	++	↑↑CO, ↑SVR
	10–20 μg·kg^{-1}·min^{-1}	+++	++	–	++	↑↑SVR, ↑CO
Norepinephrine	0.05–0.4 μg·kg^{-1}·min^{-1}	++++	++	+	–	↑↑SVR, ↑CO
Epinephrine	0.01–0.5 μg·kg^{-1}·min^{-1}	++++	++++	+++	–	↑↑CO, ↑↑SVR
Phenylephrine	0.1–10 μg·kg^{-1}·min^{-1}	+++	–	–	–	↑↑SVR
Vasopressin	0.02–0.04 U/min	Stimulates V_1 receptors in vascular smooth muscle				↑↑SVR, ↔PVR
Inodilators						
Dobutamine	2.5–20 μg·kg^{-1}·min^{-1}	+	++++	++	–	↑↑CO, ↓SVR, ↓PVR
Isoproterenol	2.0–20 μg/min	–	++++	+++	–	↑↑CO, ↓SVR, ↓PVR
Milrinone	0.125–0.75 μg·kg^{-1}·min^{-1}	PD-3 inhibitor				↑CO, ↓SVR, ↓PVR
Enoximone	2–10 μg·kg^{-1}·min^{-1}	PD-3 inhibitor				↑CO, ↓SVR, ↓PVR
Levosimendan	0.05–0.2 μg·kg^{-1}·min^{-1}	Myofilament Ca^{2+} sensitizer, PD-3 inhibitor				↑CO, ↓SVR, ↓PVR

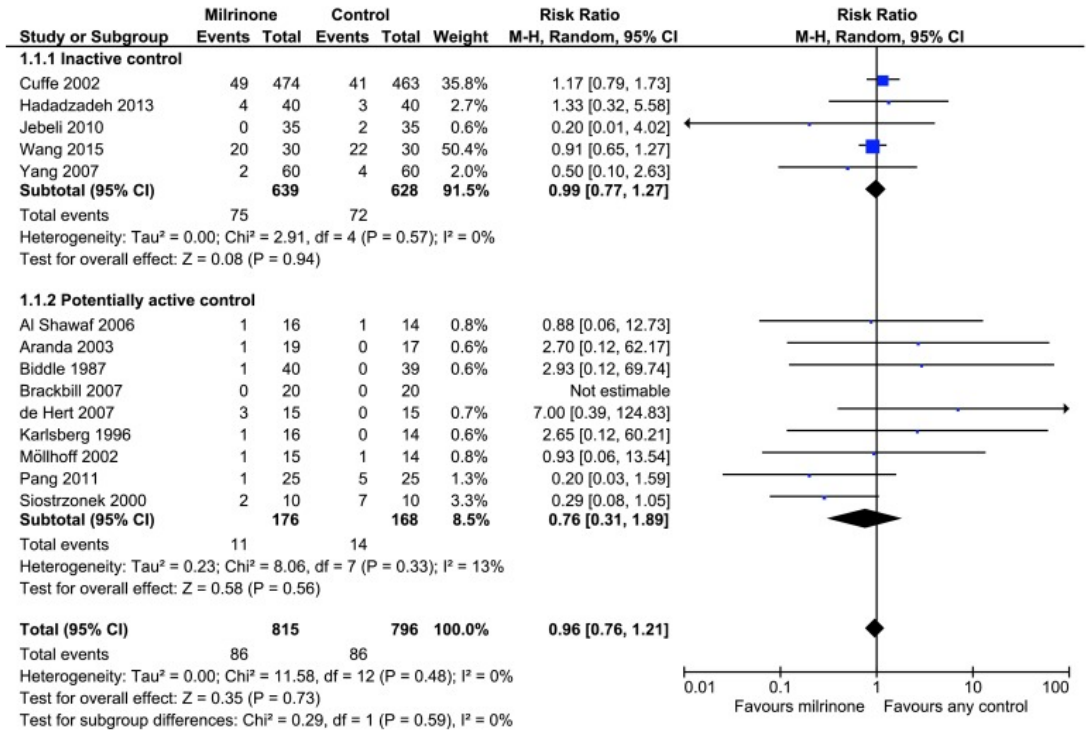
CO indicates cardiac output; CS, cardiogenic shock; PD-3, phosphodiesterase-3; PVR, pulmonary vascular resistance; and SVR, systemic vascular resistance.

Positive inotropes and/or vasopressors used to treat acute heart failure

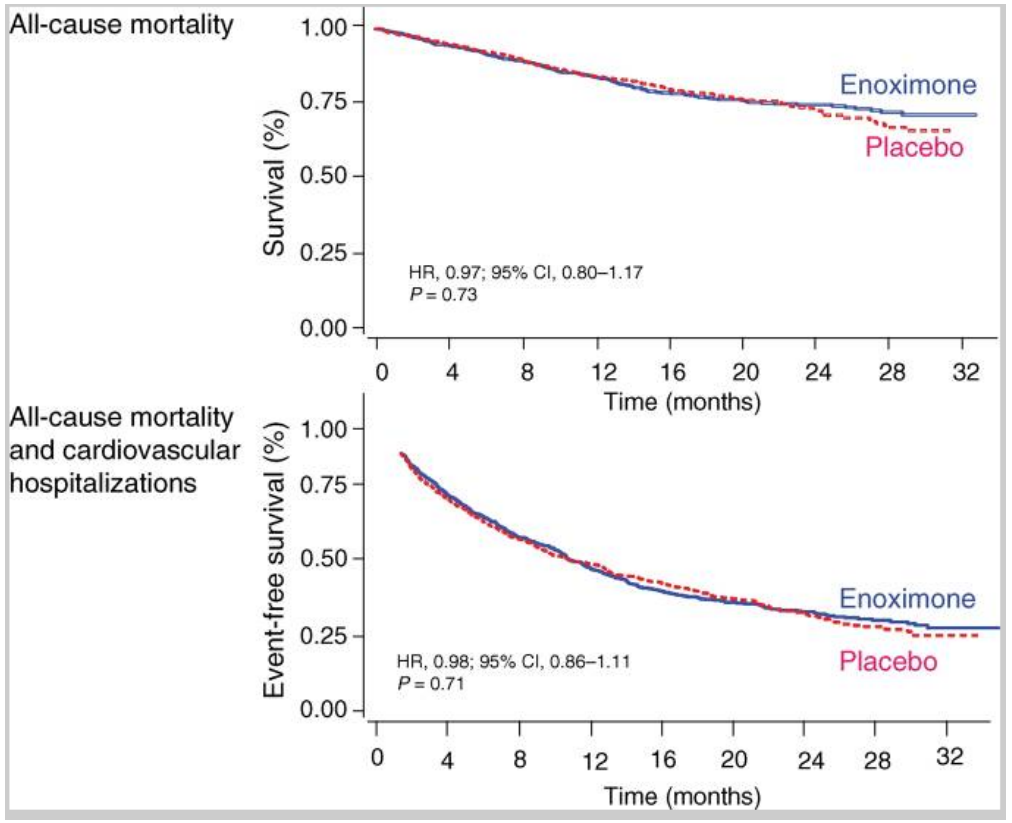
Vasodilator	Bolus	Infusion rate
Dobutamine	No	2–20 µg/kg/min (beta$^+$)
Dopamine	No	3–5 µg/kg/min; inotropic (beta$^+$)
		>5 µg/kg/min: (beta$^+$), vasopressor (alpha$^+$)
Milrinone	25–75 µg/kg over 10–20 min	0.375–0.75 µg/kg/min
Enoximone	0.5–1.0 mg/kg over 5–10 min	5–20 µg/kg/min
Levosimendan	12 µg/kg over 10 min (optional)	0.1 µg/kg/min, which can be decreased to 0.05 or increased to 0.2 µg/kg/min
Norepinephrine	No	0.2–1.0 µg/kg/min
Epinephrine	Bolus: 1 mg can be given i.v. during resuscitation, repeated every 3–5 min	0.05–0.5 µg/kg/min

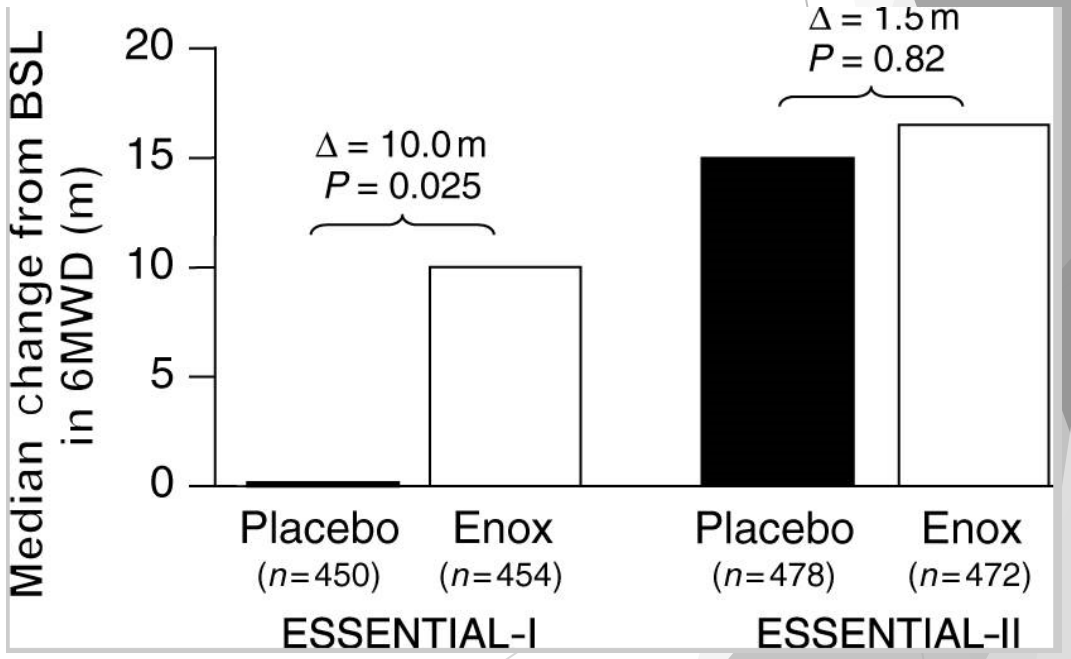
European Heart Journal (2016) **37**, 2129-2200 - doi:10.1093/eurheartj/ehw 128

Milrinone for cardiac dysfunction in critically ill adult patients: a systematic review of randomised clinical trials with meta-analysis and trial sequential analysis



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





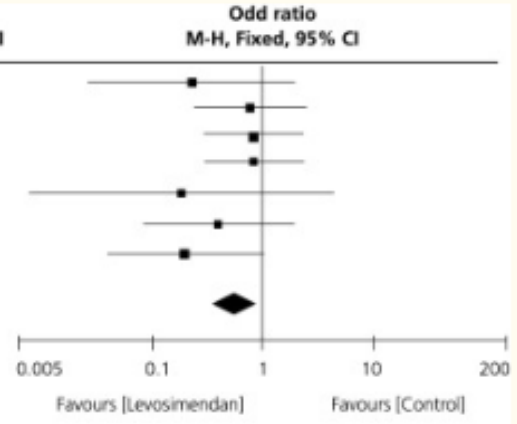
1854 patients were enrolled (904 patients in ESSENTIAL-I and 950 patients in ESSENTIAL-II).

Levosimendan in Acute and Advanced Heart Failure results for mortality and hospitalisations

a

Study or subgroup	Levosimendan Events	Levosimendan Total	Control Events	Control Total	Weight	Odd ratio M-H, Fixed, 95% CI
Altenberger J 2014	1	63	4	57	10.9%	0.21 [0.02, 1.97]
Berger R 2007	6	39	7	36	16.3%	0.75 [0.23, 2.50]
Bonies MJ 2012	14	42	8	21	18.8%	0.81 [0.27,2.42]
Comin-Colét 2015	14	48	7	21	18.2%	0.82 [0.27, 2.47]
Kleber FX 2009	0	18	1	10	4.9%	0.17 [0.01, 4.62]
Malfatto G MD 2012	4	22	4	11	11.5%	0.39 [0.08, 2.00]
Mavrogeni S 2007	2	25	8	25	19.4%	0.18 [0.03, 0.98]
Total (95% CI)		**257**		**181**	**100%**	**0.54 [0.32, 0.98]**
Total events	**41**		**39**			

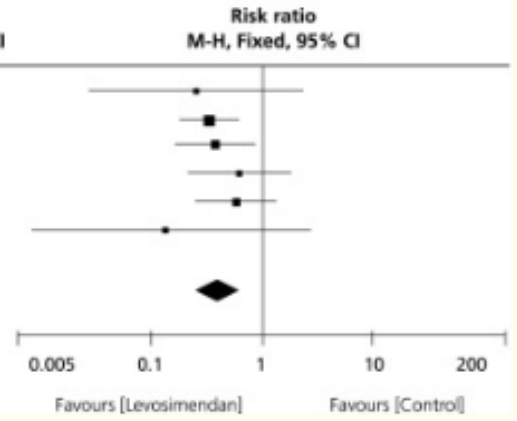
Heterogeneity: $Chi^2 = 4.28$, df = 6 (p=0.64); I^2 - 0%
Test for overall effect: Z = 2.32 (p=0.02)



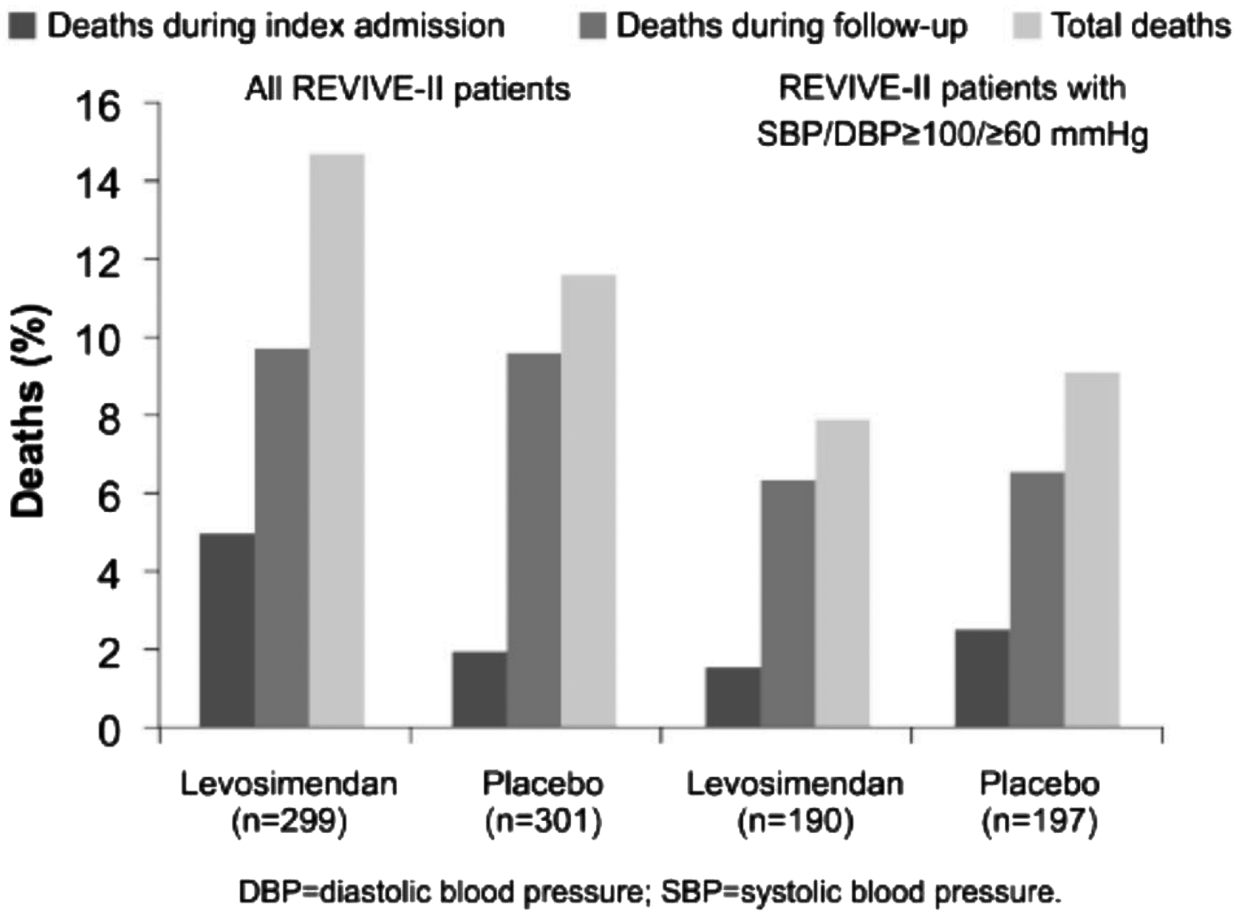
b

Study or subgroup	Levosimendan Events	Levosimendan Total	Control Events	Control Total	Weight	Risk ratio M-H, Fixed, 95% CI
Bonios 2012	1	19	3	15	6.4%	0.26 [0.03, 2.28]
Comin-Colét 2015	11	48	14	21	37.0%	0.34 [0.19, 0.63]
Garcia-González 2016	9	70	9	27	24.7%	0.39 [0.17, 0.87]
Kleber 2009	5	18	4	9	10.1%	0.63[0.22, 1.77]
Malfatto 2012	7	22	6	11	15.2%	0.58 [0.26, 1.32]
Mavrogeni 2007	0	30	3	30	6.6%	0.14 [0.01, 2.65]
Total (95% CI)		**207**		**113**	**100%**	**0.40 [0.27, 0.59]**
Total events	**33**		**39**			

Heterogeneity: $Chi^2 = 2.40$, df = 5 (p=0.64); I^2 - 0%
Test for overall effect: Z = 4.69 (p<0.00001)



Levosimendan revive study



DBP=diastolic blood pressure; SBP=systolic blood pressure.

Question 3

- Inotropic support is :
  - 1: a one size fits all
  - 2: as been proven to improve survival
  - 3: should be tailored to each clinical situation
  - 4: would prefer to ask Jonathan or Shelly

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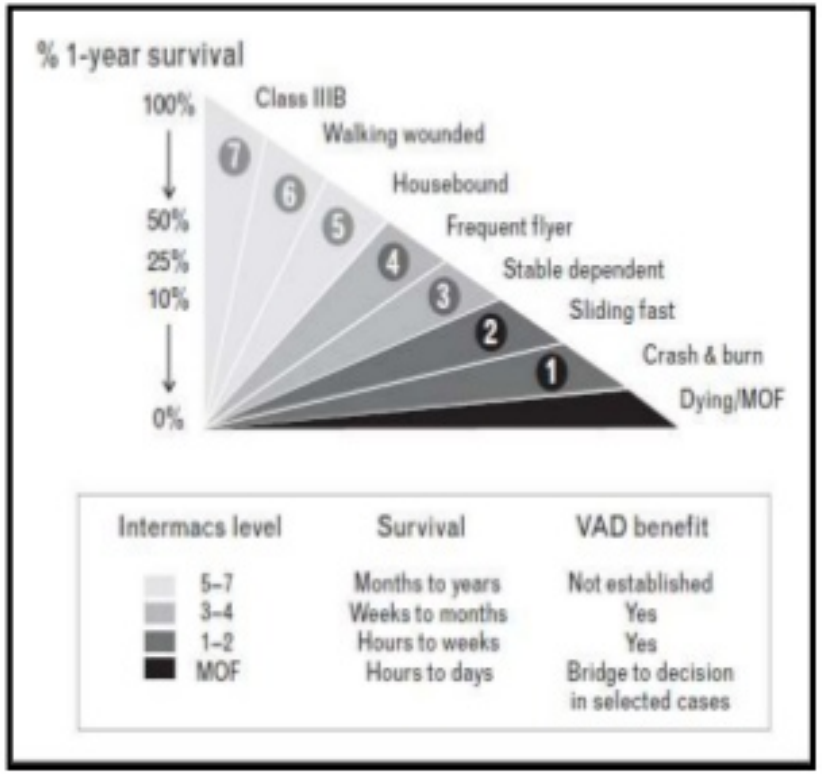
Sub types of clinical presentation

Table 5. Initial Vasoactive Management Considerations in Types of CS

Cause or Presentation of CS	Vasoactive Management Considerations	Hemodynamic Rationale
Classic wet and cold	Norepinephrine or dopamine[144]Inotropic agent[210,211]*	This subtype has low CI and high SVR. Consider hemodynamic stabilization with norepinephrine (preferred in ↑HR or arrhythmias) or dopamine (↓HR preferred but associated with higher risk of arrhythmias)Consider addition of inotropic agent when stabilized and after revascularization (MI only)
Euvolemic cold and dry	Norepinephrine or dopamine[144]Inotropic agent[210,211]Small fluid boluses	Consider hemodynamic stabilization with norepinephrine (preferred in ↑HR or arrhythmias) or dopamine (↓HR preferred but associated with higher risk of arrhythmias)Consider addition of inotropic agent when stabilized and after revascularization (MI only)LVEDP may be low, and patients may tolerate fluid boluses
Vasodilatory warm and wet or mixed cardiogenic and vasodilatory	NorepinephrineConsider hemodynamics-guided therapy	This subtype has low SVR
RV shock	Fluid boluses[144,145]Norepinephrine, dopamine, or vasopressin[144,212,213]Inotropic agents[144]*Inhaled pulmonary vasodilators[214]	Hemodynamic goals include maintaining preload, lowering RV afterload (PVR), treating absolute or relative bradycardias, and maintaining atrioventricular synchronyDopamine (↓HR preferred but associated with arrhythmia risk)Vasopressin may raise SVR and have neutral effect on PVRConsider adding or transitioning to inotrope after initial hemodynamic stabilization and revascularization
Normotensive shock	Inotropic agent or vasopressor	Initial inotropic therapy may be appropriate given that this subtype has SBP >90 mm Hg and relatively high SVR
Aortic stenosis	Phenylephrine or vasopressinIn patients with reduced LVEF, echocardiography- or PAC-guided dobutamine titration	Shock caused by aortic stenosis is an afterload-dependent stateInotropy may not improve hemodynamics if LVEF is preservedDefinitive therapies will be defined by underlying cause and may include surgical aortic valve replacement or balloon valvuloplasty and/or transcatheter aortic valve replacement
Aortic regurgitation	Dopamine Temporary pacing	Maintaining an elevated HR may shorten diastolic filling time and reduce LVEDPDefinitive therapies will be defined by underlying cause and may include surgical aortic valve replacement
Mitral stenosis	Phenylephrine or vasopressin Esmolol or amiodarone	Shock resulting from mitral stenosis is a preload-dependent stateAvoiding chronotropic agents, slowing the HR (and thereby increasing diastolic filling time), and maintaining atrioventricular synchrony may improve preloadDefinitive therapies will be defined by underlying cause and may include surgical mitral valve replacement or balloon valvuloplasty
Mitral regurgitation	Norepinephrine or dopamineInotropic agents*Temporary MCS, including IABP[144]	After hemodynamic stabilization with vasopressor, consider addition of inotropic agentAfterload reduction may help reduce LVEDPIABP may reduce regurgitation fraction by reducing afterload and increasing CIDefinitive therapies will be defined by underlying cause and may include surgical mitral valve replacement/repair and percutaneous edge-to-edge repair
Postinfarction ventricular septal defect	See classic wet and cold considerations Temporary MCS, including IABP[144]	IABP may reduce shunt fraction by reducing afterload and increasing CICardiac surgical referral for repair or percutaneous interventional umbrella closure
Dynamic LVOT obstruction	Fluid boluses[215,216]Phenylephrine or vasopressin[215,216]Avoid inotropic agents[215,216]Avoid vasodilating agents[215,216]Esmolol or amiodarone[215]RV pacing	Dynamic gradients may be reduced by increasing preload and afterload, reducing inotropy and ectopy, maintaining atrioventricular synchrony, and inducing ventricular dyssynchrony
Bradycardia	Chronotropic agents or Temporary pacing	Treatment should also focus on identifying and treating underlying cause of bradycardiaChronotropic agents may include atropine, isoproterenol, dopamine, dobutamine, and epinephrine
Pericardial tamponade	Fluid bolus Norepinephrine	Pericardiocentesis or surgical pericardial window required for definitive therapy

INTERMACS SCORE

Interagency Registry for Mechanically Assisted Circulatory Support



Long-Term LVAD

Ideal candidates are INTERMACS classes 3-4

Short-Term LVAD

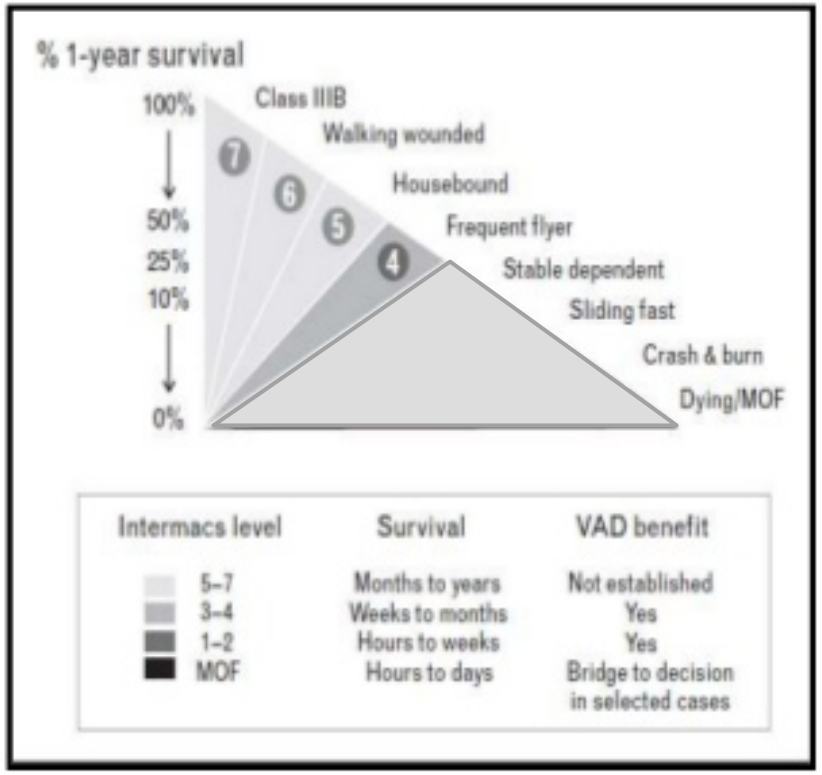
Candidates are INTERMACS classes 1-2

Not a LVAD Candidate

INTERMACS 1 or those with multisystem organ failure

INTERMACS SCORE

Interagency Registry for Mechanically Assisted Circulatory Support



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Not a LVAD Candidate
INTERMACS 1 or those with multisystem organ failure

INTERMACS profiles and outcomes of ambulatory advanced heart failure patients: A report from the REVIVAL Registry

	INTERMACS profile				
Characteristics	Total cohort (*N* = 400)	Profile 4 (*n* = 33)	Profile 5 (*n* = 83)	Profile 6 (*n* = 155)	Profile 7 (*n* = 129)
Age, years	62 (54–68)	62 (54–67)	60 (54–68)	62 (54–69)	62 (57–68)
Female	99 (25%)	7 (21%)	19 (23%)	42 (27%)	31 (24%)
Race					
White	277 (69)	23 (70)	63 (76)	96 (62)	95 (74)
African American/Black	100 (25)	10 (30)	13 (16)	48 (31)	29 (23)
Hispanic or Latino	30 (8)	2 (6)	11 (13)	11 (7)	6 (5)
NYHA class [c]					
I	6 (2%)	0 (0%)	0 (0%)	4 (3%)	2 (2%)
II	113 (28%)	1 (3%)	8 (10%)	42 (27%)	62 (48%)
III	240 (60%)	24 (73%)	61 (74%)	92 (59%)	63 (49%)
IIIb	31 (8%)	6 (18%)	9 (11%)	14 (9%)	2 (2%)
IV	10 (3%)	2 (6%)	5 (6%)	3 (2%)	0 (0%)

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Volume 39, Issue 1, Pages 16-26 (January 2020)

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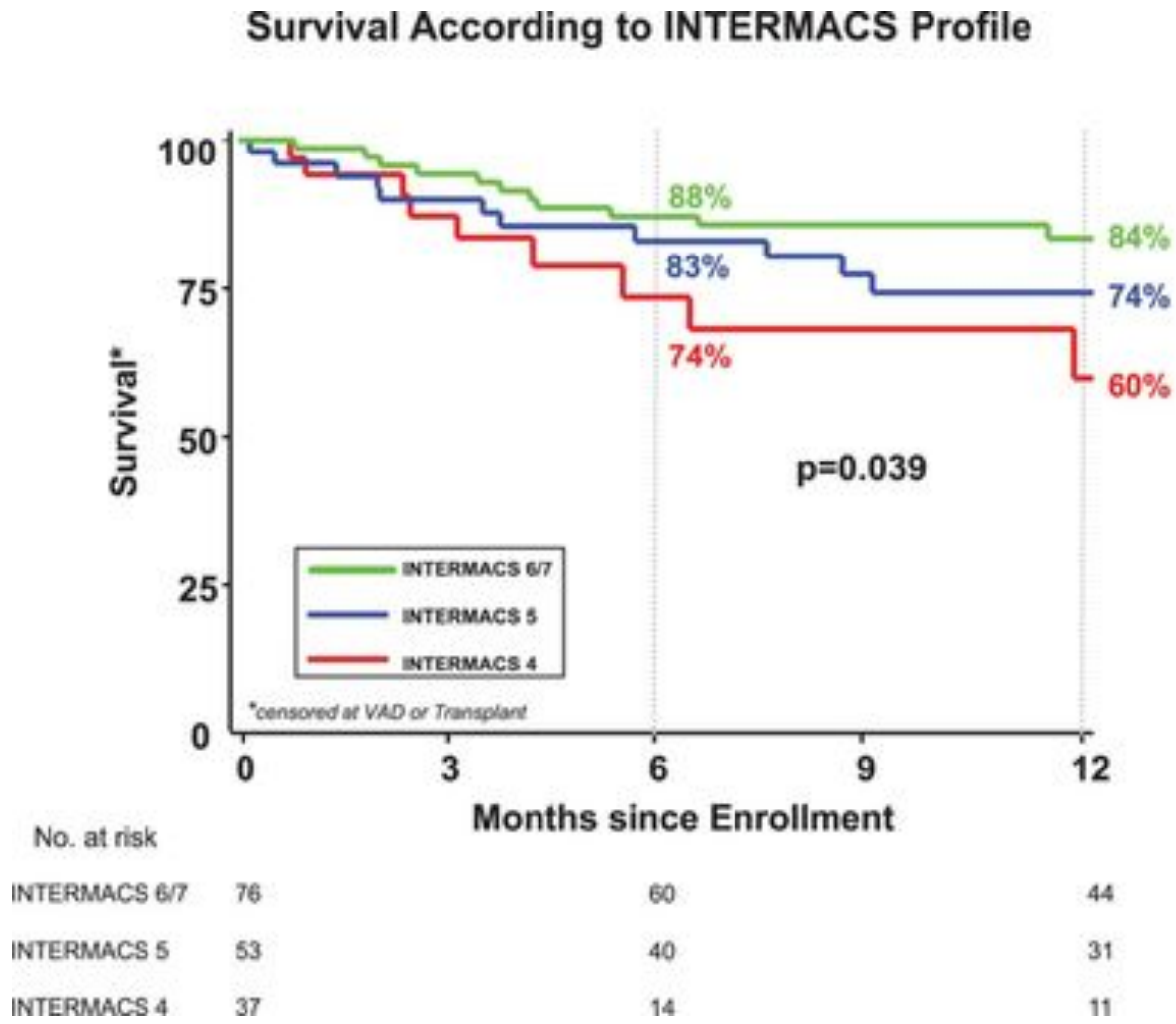

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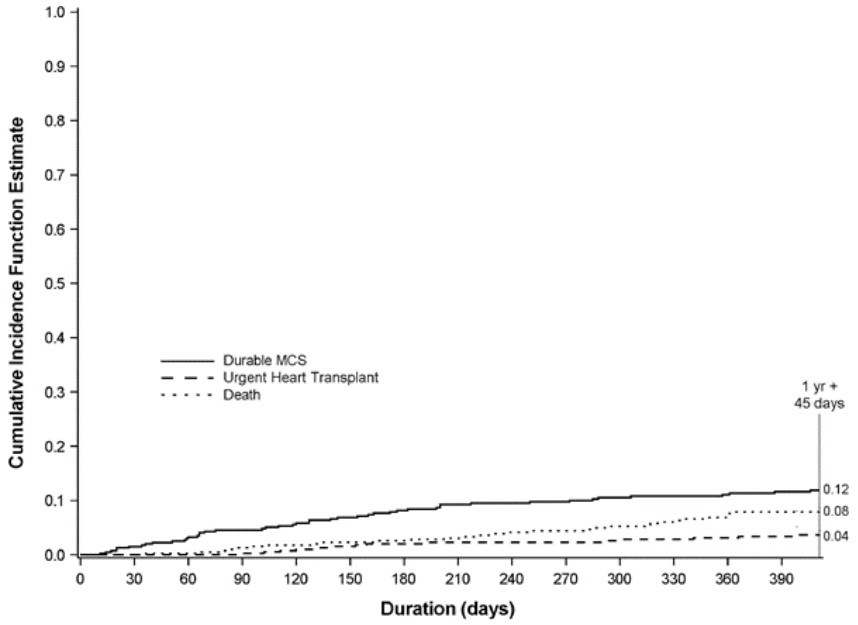
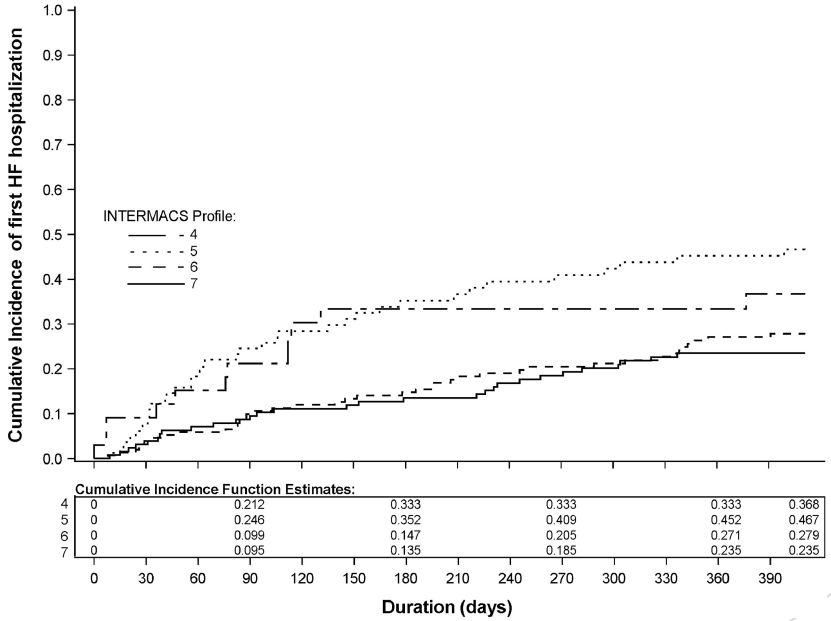




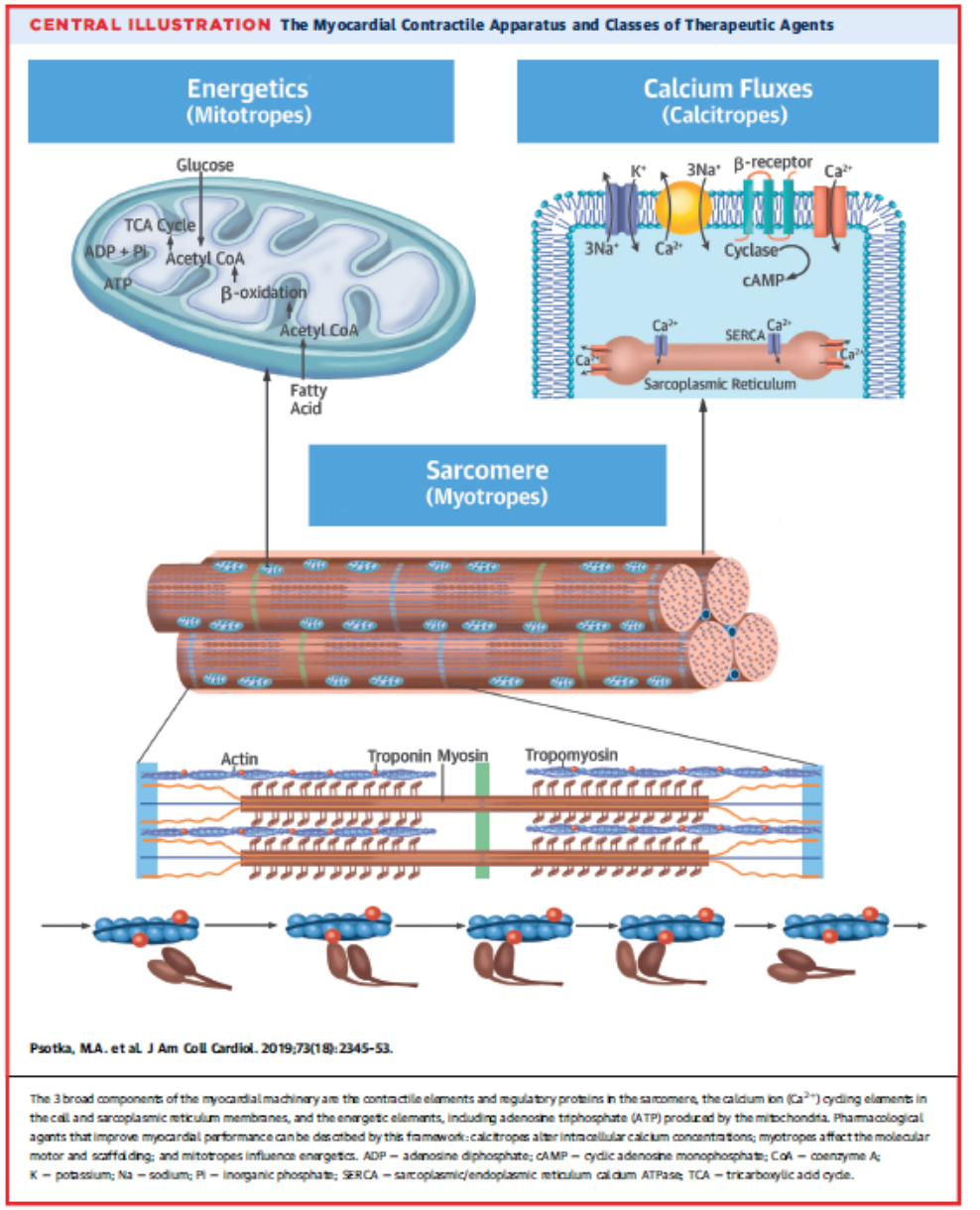
New classification:

Calcitropes
Myotropes
Mitotrophes

Inotropy produced by conventional agents, including catecholamines, phosphodiesterase-3 inhibitors, and cardiac glycosides (e.g., digitalis), all increase myocardial force production by altering the concentration of intracellular Ca+

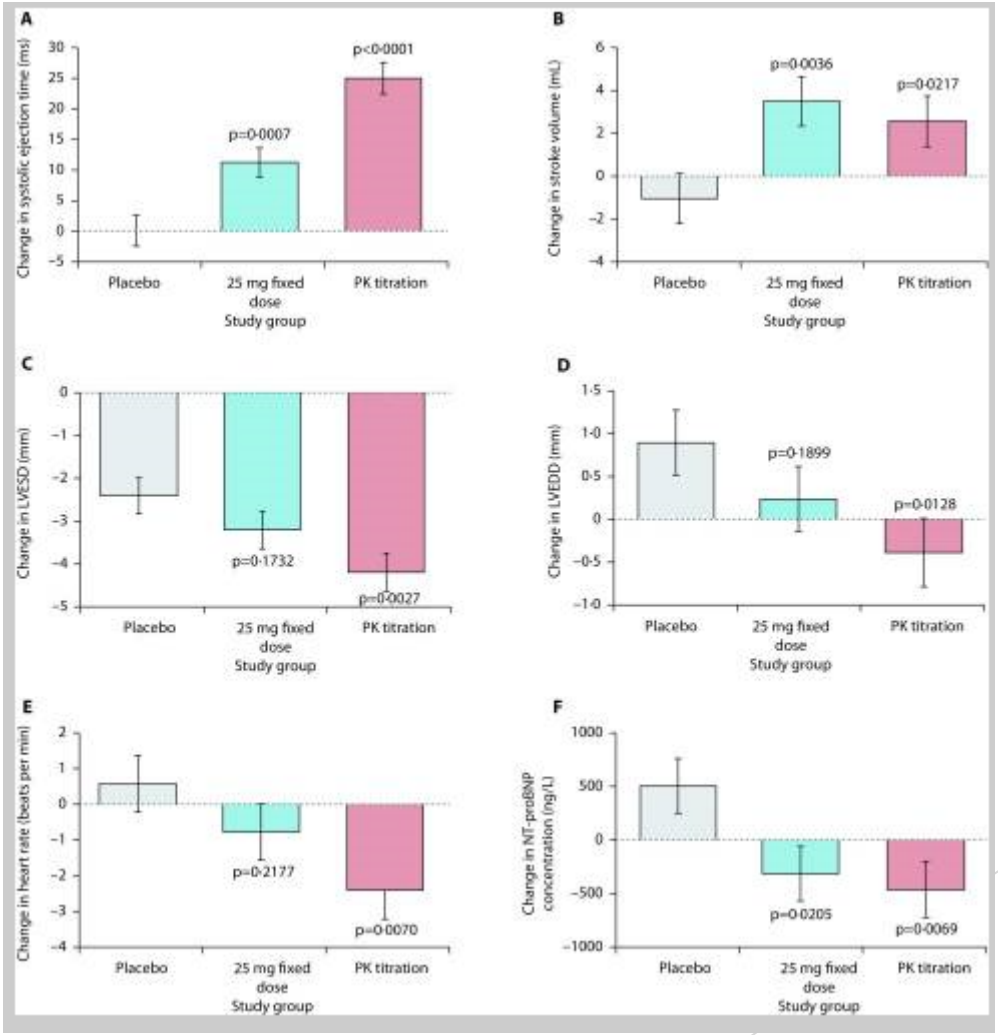
Because myosin is the central actor of the sarcomere, therapeutics that target the myosin, actin, the associated regulatory proteins, or other structural elements of the sarcomere through calcium independent mechanisms

Myocardial energetics are centered around mitochondrialenergy production, and drugs acting at the mitochondria are therefore proposed to be called mitotropes.



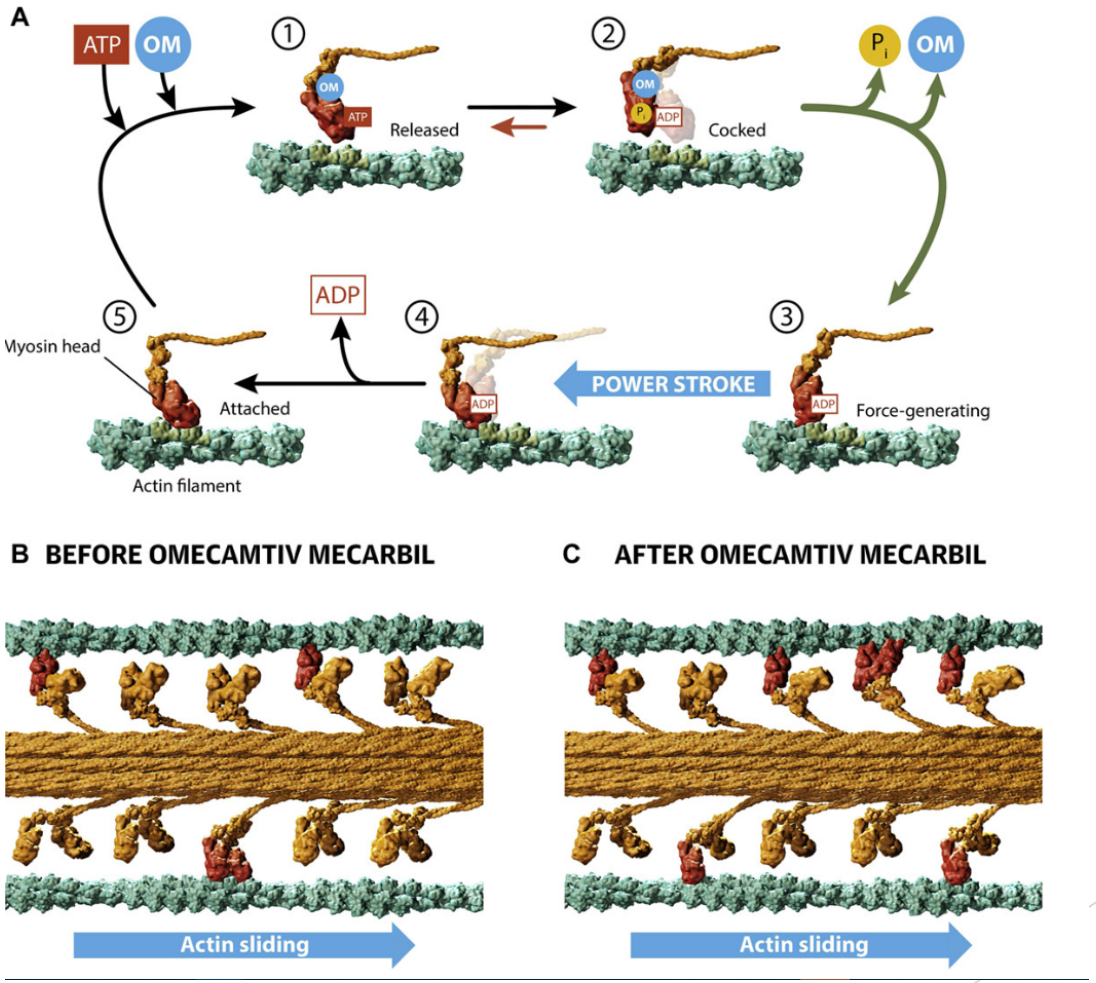
COSMIC-HF trial

The Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF trial) was a randomised, parallel-group, double-blind, placebo-controlled phase II study conducted over 87 sites in 13 countries



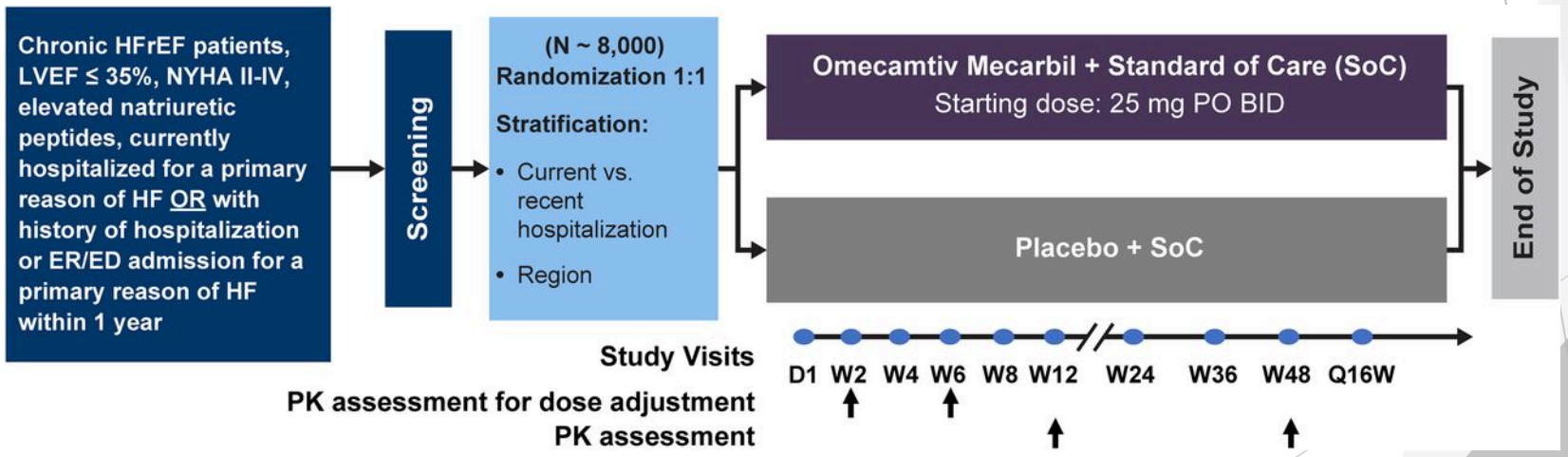
GALACTIC HF

- The primary efficacy outcome is the time to cardiovascular death or first HF event. The study has 90% power to assess a final hazard ratio of approximately 0.80 in cardiovascular death, the first secondary outcome



GALACTIC-HF Trial

- 8256 participants
- Estimated Primary Completion Date : January 27, 2021
- pharmacokinetic-guided dose titration strategy using doses of 25, 37.5, or 50 mg twice daily.



Conclusions

- When the going gets tough
  - In a Pandemic
  - In ADHF
  - You have to react
- Given appropriately
  - Inotropes can improve hemodynamics
  - With minimal harm
- New mitoptopes and myotropes are coming
  - To improve symptoms
  - And hopefully reduce hospitalisations and mortality

Thank you

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