Levosimendan for weaning from ExtraCorporeal Life Support (ECLS)

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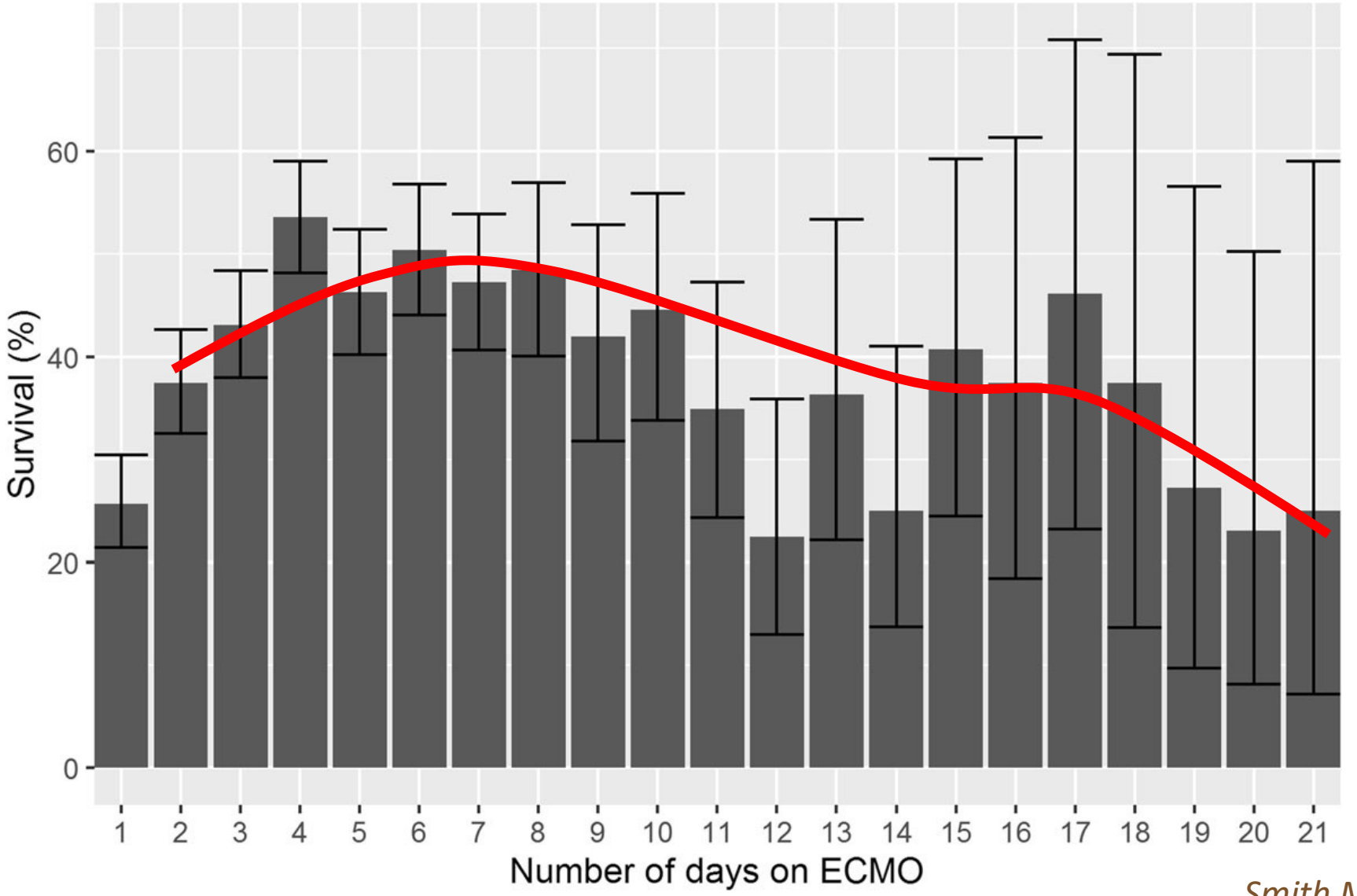
Conflicts of interest

None

ECLS duration and outcomes



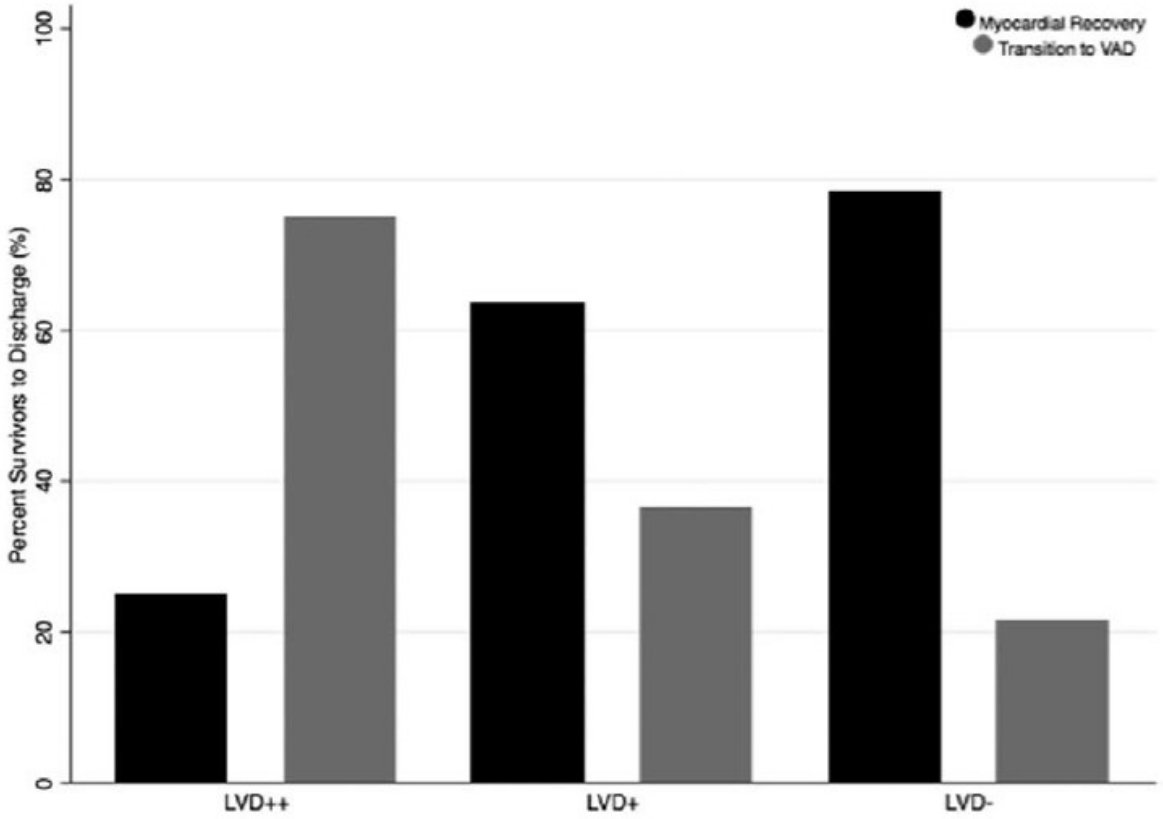
Smith M et al. Crit Care 2017; 21:45

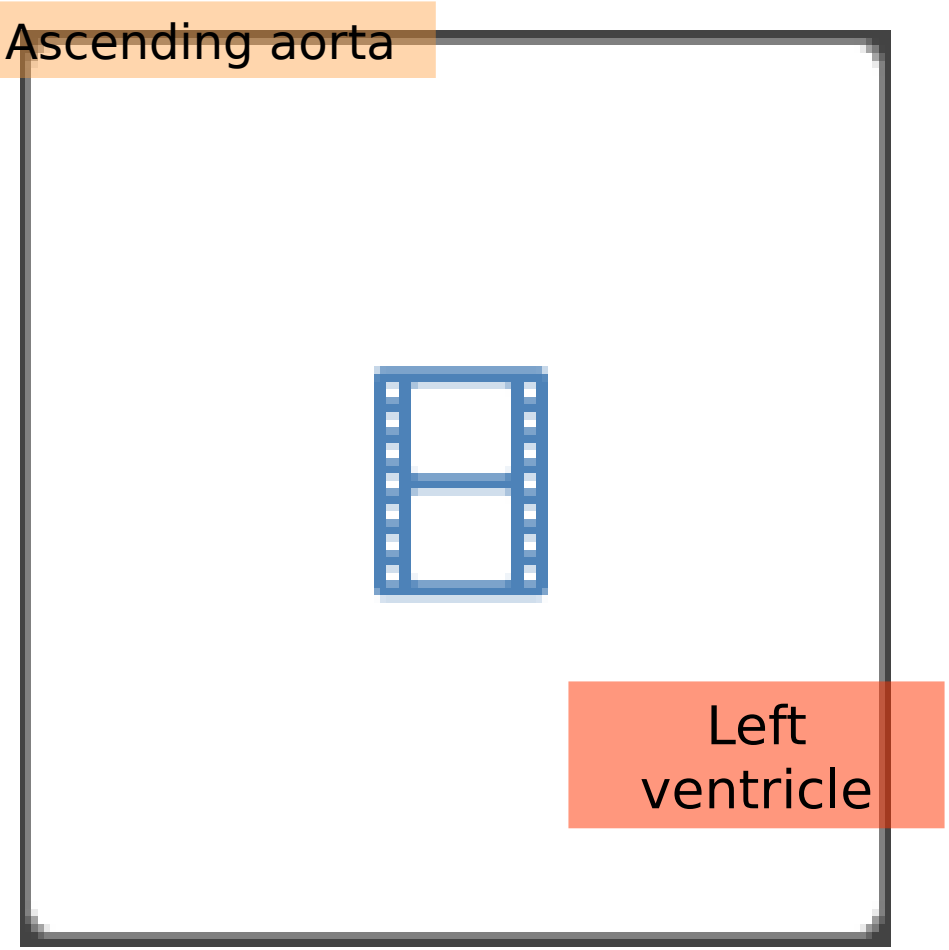
Table 10. Adverse Events During ECLS by Age and Indication

	Neonate (%)	Pediatric (%)	Adult (%)
Cardiac			
Mechanical: pump malfunction	1.5	1.8	0.8
Mechanical: oxygenator failure	6.1	7.2	6.6
Cannula site hemorrhage	10.7	15.6	18.5
Surgical site hemorrhage	29.3	28.9	20.2
Pulmonary hemorrhage	5.2	5.3	3.1
CNS hemorrhage	11.3	5.3	2.2
CNS infarction	3.4	5.0	3.8
Renal failure	12.3*	7.2*	12.3†
Hyperbilirubinemia	4.9	7.2	12.2
Infection	7.1	11.0	13.0

LV dilation associated with a worse prognosis

LVD++ (n=9)= Clinical
LVD+ (n=27)= Subclinical LVD
LVD- (n=85)= no signs of LVD





Truby LK et al. ASAIO Journal 2017;63:257-65

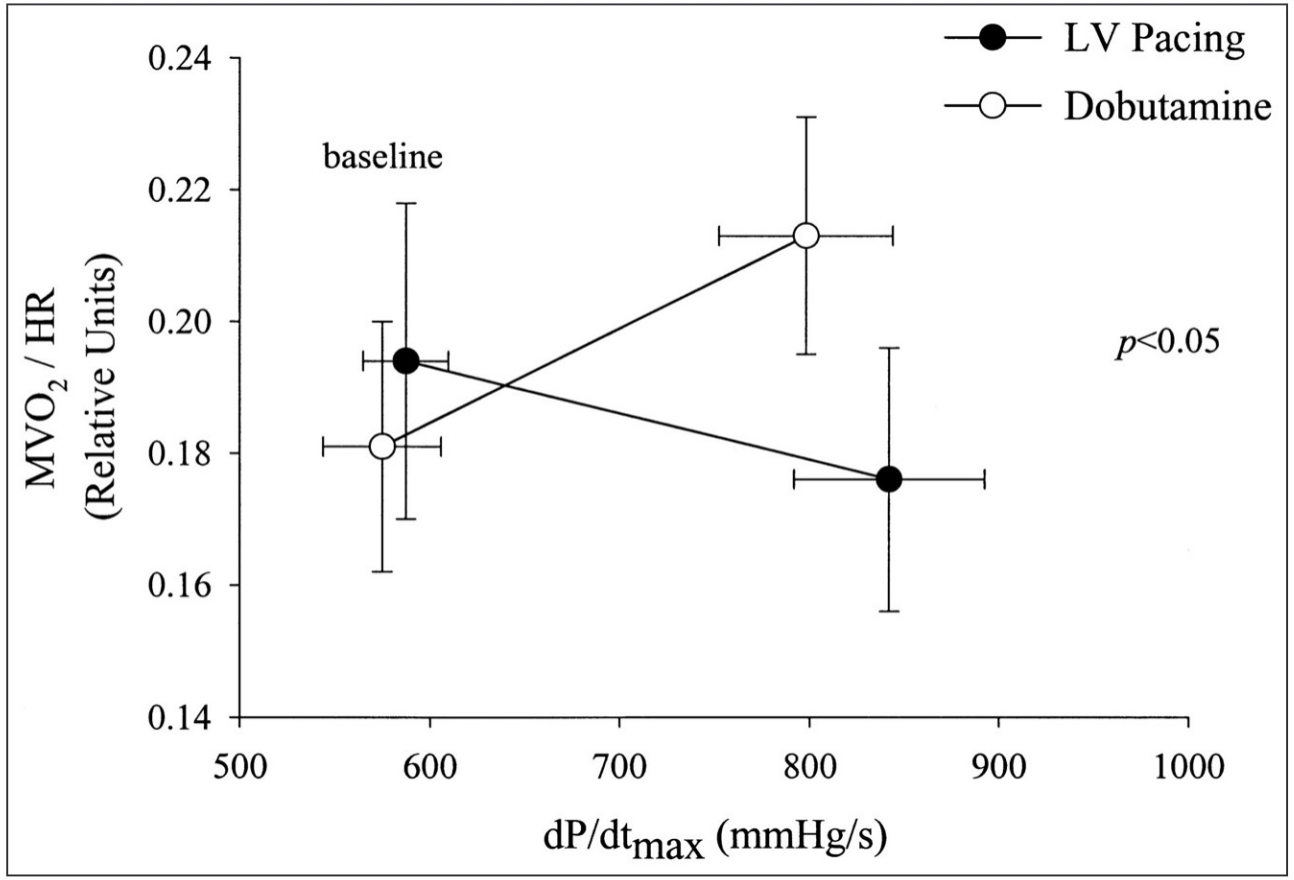
Puajara D et al. Semin Thoracic Surg 2015;27:17-23

The State of the Art in Extracorporeal Membrane Oxygenation

MANAGEMENT CONSIDERATIONS

Inotropic support and ventricular assist devices (eg, Impella, Abiomed; intra-aortic balloon pump; TandemHeart trans-septal cannula) should be maintained to facilitate the left-side chamber unloading if cardiac recovery is a possibility.

Dobutamine



- High incidence of arrhythmia
- Tolerance (receptor internalisation, decoupling….)
- Profound vasoldilation
- Increase MVO_2

Nelson GS et al. Circulation 2000; 102: 3053-9

Attractive pharmacological properties of Levosimendan

- Increase cardiac contractility without increasing intracellular calcium concentration
- No or less increase myocardial consumption
- Improve diastolic function (lusitropic effect)
- Anti-inflammatory and anti-oxydative effects
- Cardio-protective, anti-stunning and anti-ischemic effects through K+-ATP-dependent channel pathway

Lilleberg J et al. Eur J Heart 1998; 19:660-8

Nieminen MS et al. J Am Coll Cardiol 2000; 36:1903-12

Vita JA et al. Heart 2005; 91:1278-9

Disadvantages

- Peripheral vasodilation
- Onset of action (no bolus)
- Arrhythmia

Definition of weaning from ECLS

Weaning successful from ECLS is defined as device removal and no further requirement for mechanical support because of recurring CS over the following **1 to 30 days (alive patients)**

Aissaoui N et al. Intensive Care Med 2015;41:902-5

Comparison of Levosimendan and Milrinone for ECLS Weaning in Patients After Cardiac Surgery—A Retrospective Before-and-After Study

Patients under **ECLS for post-cardiotomy cardiac failure** (2007-2013)

Infusion milrinone or Levosimendan before starting ECLS weaning

Primary endpoint : successful weaning defined as 24 hour survival after removal ECLS

Successful weaning was comparable between groups (92% versus 79%, p=0.18)

Use of IABP was **less frequent in levosimendan group** (7.7% versus 40%, p=0.008)

ICU and hospital lengths of stay were longer in Levosimendan group

28-day mortality was comparable (35% versus 40%, p=0.28)

180-day mortality was comparable (50% versus 44%, p=0;80)

Jacky A et al. J Cardiothorac Vasc Anesth 2018;32:2112-

Impact of levosimendan on weaning from peripheral venoarterial extracorporeal membrane oxygenation in intensive care unit

Vally S et al. Ann Intensive Care 2019; 9:24

- Retrospective cohort study (2010-2017)
- 150 Patients under VA-ECMO in ICU
- All patients admitted in ICU and treated by VA-ECMO were evaluated (mixed origin)

- Primary endpoint: VA-ECMO weaning defined as survival at 24 hours without device
- Adjustment by Propensity score to assess use of LVSD on 30-day mortality

Results

- 51 patients were treated by levosimendan
- LVSD was given 3.2±2.8 days after VA ECMO canulation
- Weaning from ECLS was successful in 103 (69%) patients (82% versus 62%, p=0.01)

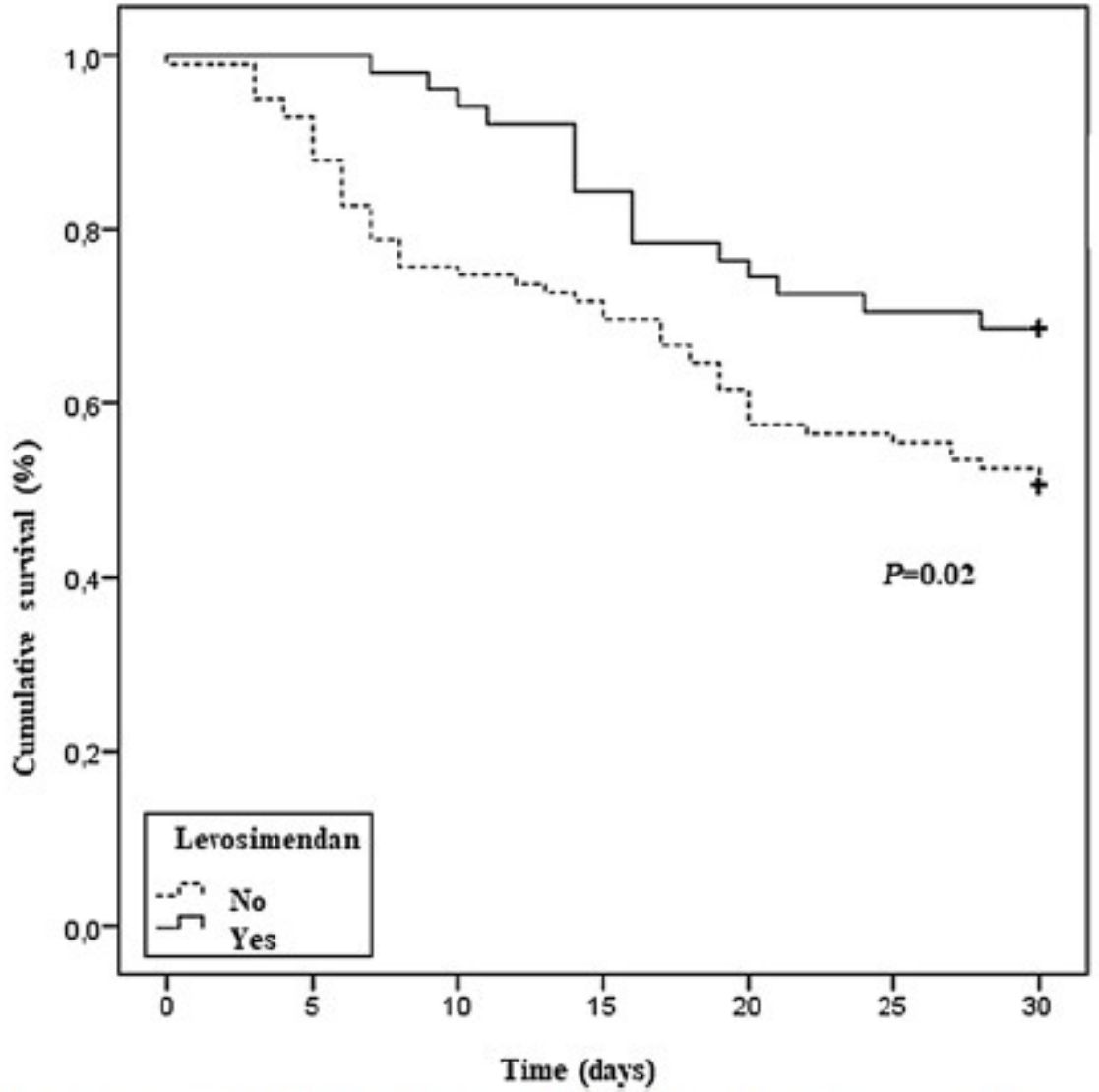


Fig. 2 Survival rate for patients with or without levosimendan by Kaplan–Meier analysis

After propensity score matching, the difference in 30-day mortality between both groups was not significant (HR 0.55 [0.27-1.10; p=0.09]

Can levosimendan reduce ECMO weaning failure in cardiogenic shock?: a cohort study with propensity score analysis

Enrique Guilherme[1], Matthias Jacquet-Lagrèze[1,2*], Matteo Pozzi[3], Felix Achana[4], Xavier Armoiry[5,6] and Jean-Luc Fellahi[1,2]

Guilherme E at al. Critical Care 2020;24:442

- Retrospective cohort study (2012-2018)
- 200 patients under VA-ECMO implanted for different causes
- Primary endpoint: VA-ECMO weaning failure defined as death during ECMO or within 24 h after VA-ECMO removal
- Adjustment by Propensity score (48 LVSD/78 control group)

Results

- 53 (26.5%) patients were treated by Levosimendan
- Duration of VA-ECMO was longer in LVSD group (10.6±4.8 vs 6.5±4.7 days, p<0.001)
- LVSD was given 6.62±2.8 days after VA ECMO implantation
- Failure weaning 28.3% vs 29.9% (OR 0.92, 95%CI [0.46-1.85]

Table 2 Balance of covariates before and after matching

	Unmatched*			Matched		
	Levosimendan ($n = 48$)	Control ($n = 128$)	p	Levosimendan ($n = 48$)	Control ($n = 78$)	p
Variable (mean)						
Age (years)	53.9	52.6	0.575	54.3	54.7	0.866
Male (%)	62	65	0.692	0.62	0.65	0.785
Potential for recovery	2.32	2.12	0.104	2.31	2.35	0.747
SAPS-II	53.5	51.7	0.424	52.7	52.1	0.824
SOFA	11.5	11.8	0.530	11.3	11.5	0.687
LVEF (%)	18	20.2	0.241	18	17	0.690
VA-ECMO duration (days)	10.6	6.5	**<0.001**	10.8	10.2	**0.478**
Serum lactate level (mmol/L)	6.4	7.5	0.178	6.3	6.1	0.816

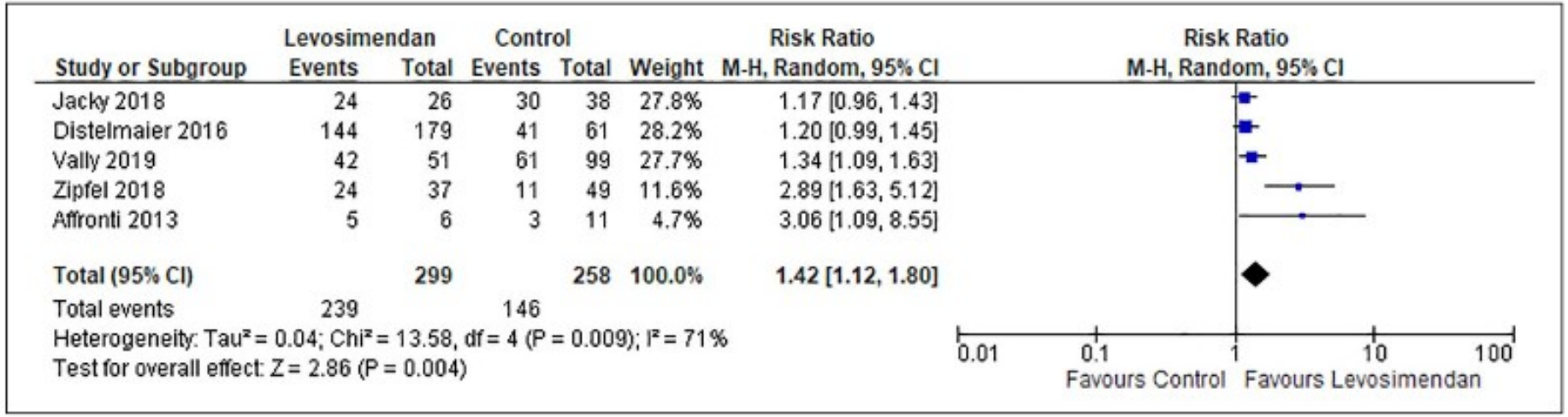
Myocardial recovery potential: *High 1* intermediate *2*, *Low 3* *SAPS-II* simplified acute physiology score, *SOFA* sequential organ failure assessment, *LVEF* left ventricular ejection fraction. Data are expressed as mean. The *p* value refers to a comparison between the levosimendan group and the control group. *Compared to the entire cohort ($n = 200$), the unmatched population had 176 patients since there were 24 patients with missing data on some of the variables used in the analysis

VA-ECMO weaning failure	**29.1% vs 35.4%**	**OR 0.69; 95%CI [0.25-1.88]**
28 days mortality	41.0% vs 41.6%	OR 1.08 95%CI [0.42-2.81]
6 month-mortality	50.0% vs 54.3%	OR 0.79; 95%CI [0.30-2.07]

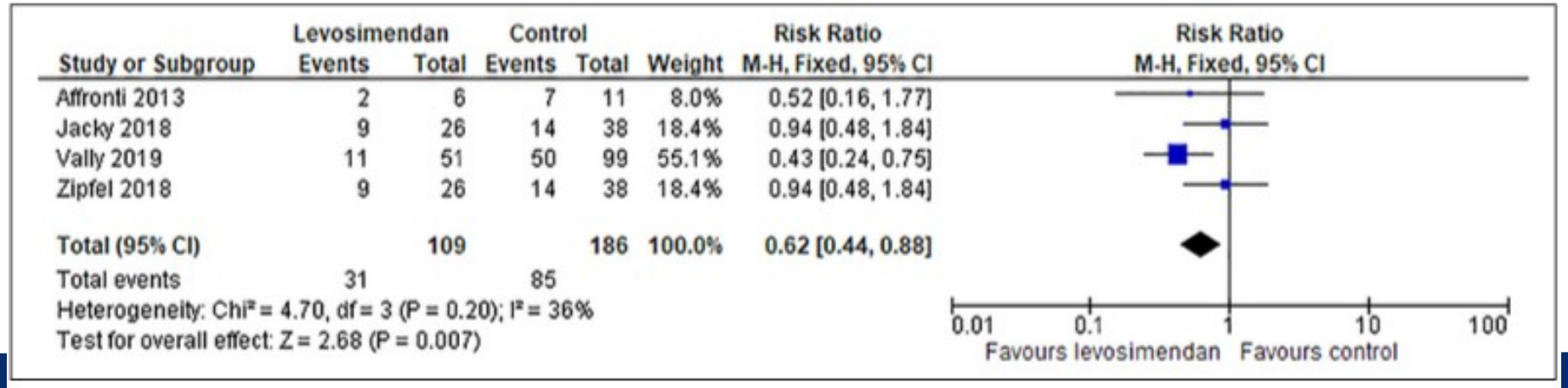
	First author	Year	Patients	Design	Clinical context	Study period	Num	Levosimendan infusion time	Dose (µg/kg/min)	Primary endpoint	Main results	Other
1	Pandey	2013	Children	Case report	Post cardiotomy LCOS	NA	1	24 hours before ECLS weaning	Bolus 12.5 µg/kg and 0.2			
2	Feltracco	2015	Adults	Case report	Lung transplant (RV dysfonction)	NA	1	2 days before ECMO weaning	0.15			
3	Braun	2006	Adults	Single center retrospective before-after study	Post cardiotomy LCOS	2000-2004	38 (9/29)	Weainng from CPB and ICU	Bolus 20 µg/kg and 0.1 to 0.2	Use of inotropes	Higher dose of epinephrine in ICU	Reduced duration of RRT and ICU, hospital and 180-day mortality
4	Affronti	2013	Adults	Single center retrospective before-after study	Medical and surgical (Refractory CS)	Jan to Dec 2011	17 (6/11)	24 hours before planned ECLS weaning	0.05-0.2	Successful weaning	83.3% vs 27.3% (p=0.0498)	IH mortality NS
5	Sangalli	2016	Adults	Single center prospective non comparative study		2000-2004	10		0.1	Endothelial function and haemodynamic effects	Improved endothelial function. Increased CI	ECMO weaning 90%
6	Distelmaier	2016	Adults	Single center retrospective before-after study (**Propensity score**)	Post cardiotomy LCOS	2003-2014	240 (179/61)	24 hours following ECMO insertion	12 mg/50 ml for 24 hours	30-day mortality and weaning from ECMO (death during ECMO or within 24 h after removal)	ECMO weaning failure (adjusted OR 0.41, P=0.008) Reduced mortality (Adjusted OR 0.52, P=0.016)	
7	Jacky	2018	Adults	Single center retrospective before-after study (milrinone vs LVSD)	Post-cardiotomy LCOS	2007-2013	64 (26/38)	24 hours before ECLS weaning		Successful weaning from ECMO (alive at 24 hours after removal without assistance)	92% vs 79% (p=0.18)	ICU and hospital length of stay longer. No significant difference for mortality
8	Vally	2019	Adults	Single center retrospective before-after study (**Propensity score**)	ICU patients with refractory CS	2010-2017	150 (51/99) After PS 103 (38/65)	3.2±2.8 days after ECMO cannulation (ECMO duration 11.6±11 days)	0.2 (no bolus)	Successful weaning from ECMO	Un-adj 82.4% vs 61.6% (P=0.01)	Un-adjusted 30-day survival rate (78.4% versus 49.5%, P=0.02). After adjustment by PS p=0.09)
9	Guillerme	2020	Adults	Single center retrospective before-after study (**Propensity score**)	Medical and surgical (Refractory CS)	2012-2018	200 (53/147) After PS 126 (48/78)	6.6±5.4 days after ECMO cannulation (ECMO duration 10.6±4.8 days)	0.1 to 0.2 during 24 hours	Weaning failure from ECMO (death under ECMO or within 24 h after removal)	28.3% vs 29.9% (NS) After PS 29.1% vs 35.4% (NS)	No significant difference for 28-day and 180-day mortality
10	Pan	2020	Children	Single center retrospective before-after study (Propensity score)	Post cardiotomy LCOS	2012-2018	145 (54/91)		12.5 µg/kg and 0.2 over 24-hours	Weaning failure from ECMO (death within 24 hours or need for ECMO)	Adj RR 0.20 [0.07-0.57]	Adjusted RR for in-hospital mortality (0.45 [0.26-0.76])

Effects of levosimendan on weaning and survival in adult cardiogenic shock patients with veno-arterial extracorporeal membrane oxygenation: systematic review and meta-analysis

Successful weaning from VA ECMO in patients treated with levosimendan

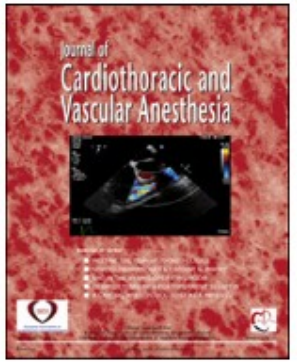


All cause mortality



Burgos LM et al. Perfusion 2020

The Effectiveness of Levosimendan on Veno-Arterial Extracorporeal Membrane Oxygenation Management and Outcome: A Systematic Review and Meta-Analysis



Study or Subgroup	Levosimendan Events	Total	Comparator Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Affronti 2013	5	6	3	11	5.3%	13.33 [1.07, 166.37]	2013
Distelmaier 2016	144	179	41	61	24.8%	2.01 [1.05, 3.84]	2016
Sangalli 2016	9	10	0	10	3.3%	133.00 [4.81, 3674.23]	2016
Zipfel 2018	24	37	16	49	20.0%	3.81 [1.55, 9.38]	2018
Haffner 2018	21	27	29	36	14.9%	0.84 [0.25, 2.88]	2018
Jacky 2018	24	26	30	38	10.4%	3.20 [0.62, 16.49]	2018
Vally 2019	42	51	61	99	21.4%	2.91 [1.27, 6.64]	2019
Total (95% CI)		**336**		**304**	**100.0%**	**2.89 [1.53, 5.46]**	
Total events	269		180				

Heterogeneity: Tau² = 0.31; Chi² = 11.77, df = 6 (P = 0.07); I² = 49%
Test for overall effect: Z = 3.28 (P = 0.001)

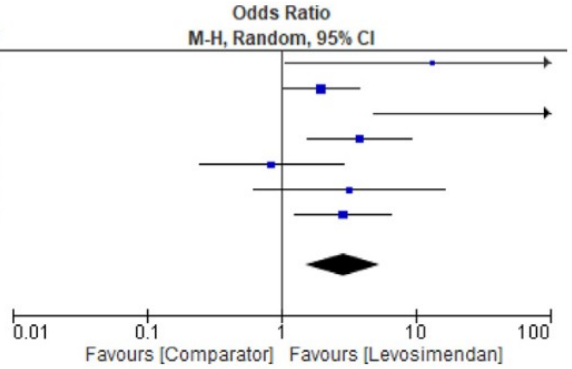


Fig 2. Forest plot—veno-arterial extracorporeal membrane oxygenation weaning success.

Study or Subgroup	Levosimendan Events	Total	Comparator Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Affronti 2013	2	6	7	11	4.0%	0.29 [0.04, 2.32]	2013
Distelmaier 2016	111	179	45	61	28.9%	0.58 [0.30, 1.11]	2016
Jacky 2018	9	26	14	35	13.8%	0.79 [0.28, 2.28]	2018
Zipfel 2018	18	37	38	49	16.9%	0.27 [0.11, 0.70]	2018
Haffner 2018	9	27	13	36	13.9%	0.88 [0.31, 2.53]	2018
Vally 2019	11	51	50	99	22.4%	0.27 [0.12, 0.58]	2019
Total (95% CI)		**326**		**291**	**100.0%**	**0.46 [0.30, 0.71]**	
Total events	160		167				

Heterogeneity: Tau² = 0.06; Chi² = 6.23, df = 5 (P = 0.28); I² = 20%
Test for overall effect: Z = 3.52 (P = 0.0004)

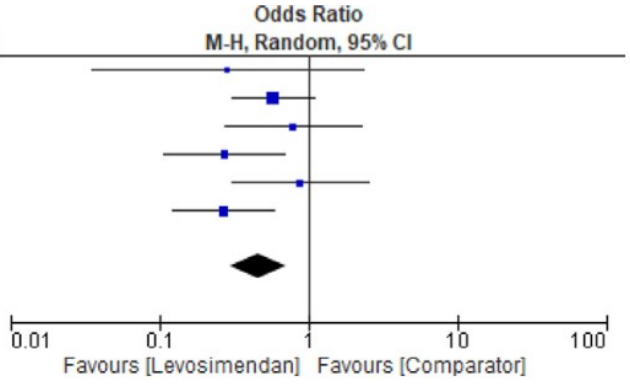


Fig 3. Forest plot—mortality.

Kadourra R, et al. JCTVA, 2021

REVIEW Open Access

Levosimendan in the light of the results of the recent randomized controlled trials: an expert opinion paper

Bernard Cholley[1,2,3*], Bruno Levy[4], Jean-Luc Fellahi[5,6], Dan Longrois[7,8], Julien Amour[9,10], Alexandre Ouattara[11,12,13] and Alexandre Mebazaa[8,14]

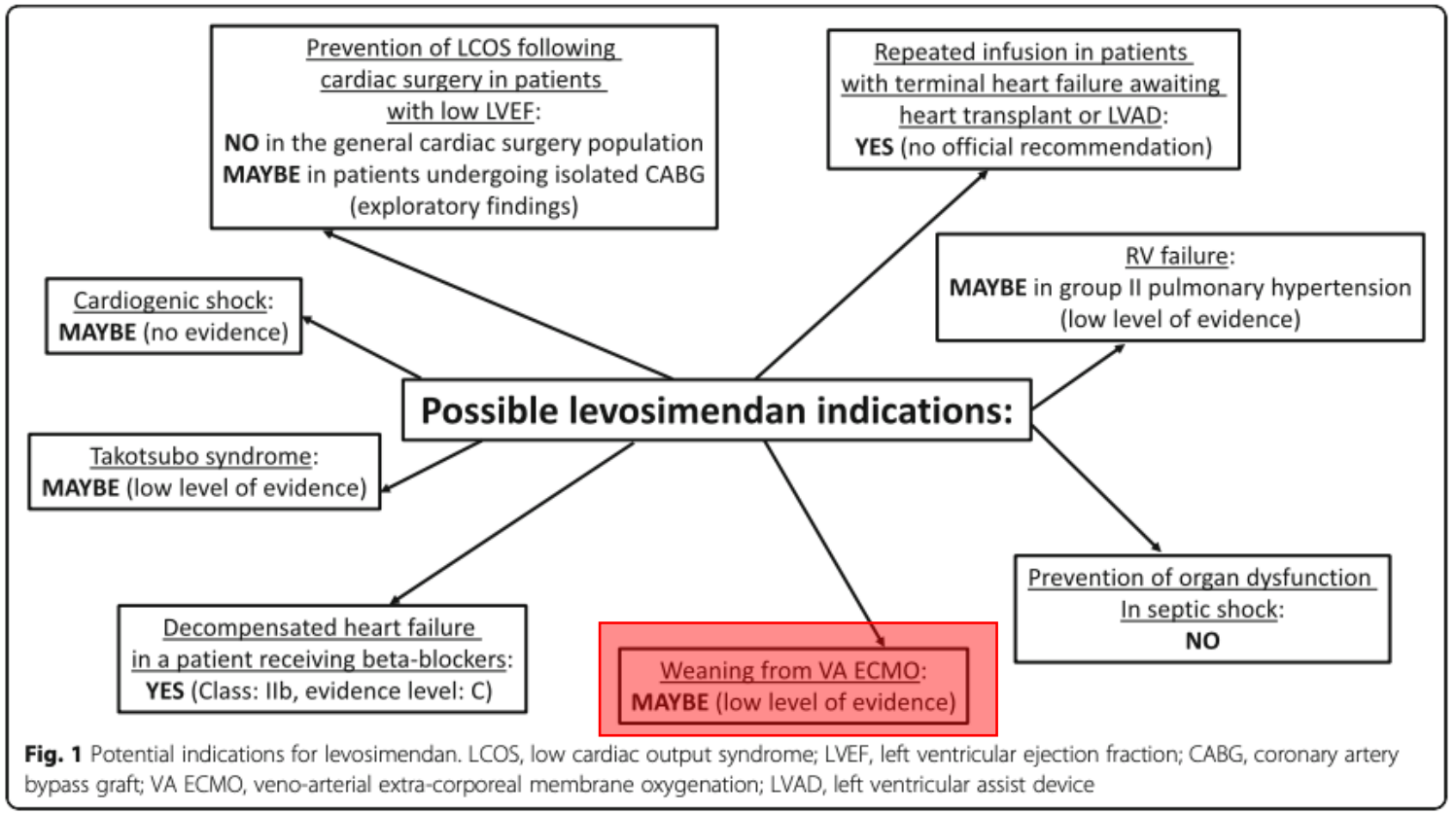


Fig. 1 Potential indications for levosimendan. LCOS, low cardiac output syndrome; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass graft; VA ECMO, veno-arterial extra-corporeal membrane oxygenation; LVAD, left ventricular assist device

Cholley et al. Critical Care (2019) 23:385

And Tomorrow ? Cocorico?

LEVOSIMENDAN to facilitate weaning from ECMO in refractory cardiogenic shock patients – “LEVOECMO”

Levosimendan in venoarterial ECMO weaning. Rational and design of a randomized double blind multicentre trial WEANILEVO

LEVOSIMENDAN to facilitate weaning from ECMO in refractory cardiogenic shock patients – “LEVOECMO”

Coordinating Investigator

Pr A. COMBES (Intensive Care Unit, Hospital Pitié Salpêtrière, Paris, France)

Double Blind Randomized multicentre trial (N=206 patients)
Adults patients with refractory cardiogenic shock placed on VA-ECMO
A continuous infusion of Levosimendan administered over 24 h (up to 0.2 µg/kg/min)

Main objective: Efficacy of early Levosimendan infusion (<48 h after ECMO implantation) on the **time to successful weaning within the 30 days following randomization.**

Primary endpoint: Successful ECMO defined **as being alive, without ECMO**, other mechanical circulatory support device or heart transplantation **7 days after ECMO removal**.

Exclusion criteria

Resuscitation >30 minutes before ECMO

Irreversible neurological pathology

End-stage cardiomyopathy with no hope of LV function recovery

Mechanical complication of myocardial infarction

ECMO for cardiotoxic drug intoxication…

Levosimendan in venoarterial ECMO weaning. Rational and design of a randomized double blind multicentre trial

Coordinating Investigator : Pr Guinot , CHU Dijon

Double Blind Randomized multicentre trial (N=206 patients)
Adults patients with refractory cardiogenic shock placed on VA-ECMO
A continuous infusion of Levosimendan administered over 24 h (up to 0.2 µg/kg/min)

Main objective: Efficacy of Levosimendan infusion in reducing VA-ECMO weaning failure, **when weaning is decided**

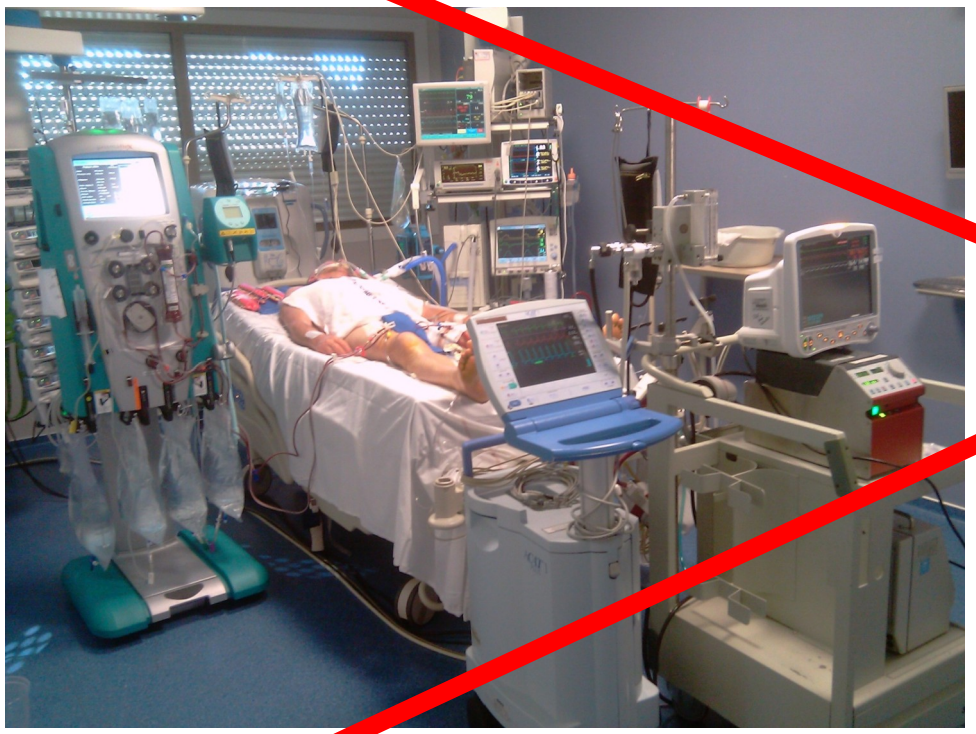
Primary endpoint: **VA-ECMO weaning failure**, defined as the absence of VA-ECMO weaning, recourse to another VA-ECMO or Impella or IABP or death within **7 days of VA-ECMO** weaning.

Table 2 Inclusion criteria of the WEANILEVO trial

- Patient aged ≥18 years
- Acute circulatory heart failure treated with VA-ECMO
- VA-ECMO weaning criteria defined as:
  VA ECMO flow at 1.0–1.5 L/min and/or VA-ECMO pump speed at 1500 rpm and
  Left ventricular ejection fraction >20% and subaortic velocity time integral >10 cm
  VIS ≤ 10
  Arterial lactate ≤2 mmol/L
  Right ventricular fractional area change >30%
  Right ventricular end-diastolic diameter <35 mm
  Combined fraction of inspired oxygen for VA ECMO and ventilator <80%
- VA ECMO weaning expected within 48 h
- No documented or suspected bacterial infection within 48 h before inclusion (no antibiotic introduced during the previous 48 h)

In bedside practice ?

No recommendations, only expert opinion



ECMO VA Bridge to… ?

- …Decision
- …Recovery (acute myocardial infarction, post-cardiotomy…)
- …Bridge (LVAD or BiVAD or total artificial heart)
- …Transplantation

MAYBE YES

YES (but are you sure ?)

NO

NO or after