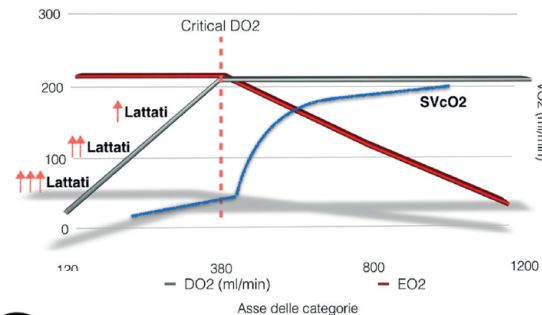
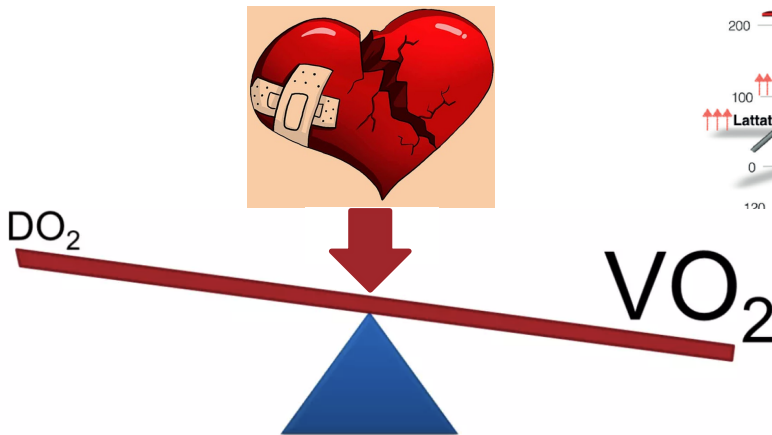
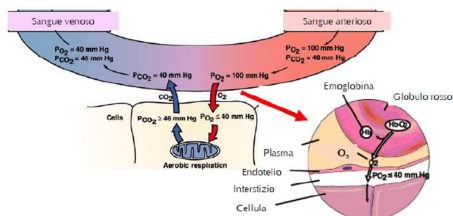


INSUFFICIENZA CARDIACA ACUTA

Shock cardiogeno: dai farmaci ai device

Roberta Della Bona, MD, PhD
UTIC-Cardiologia
Ospedale Policlinico S. Martino
Genova

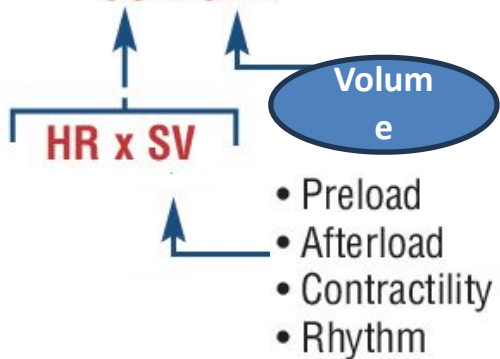
Cardiogenic shock: from 'hemo' to hemo-metabolic condition



Cardiogenic Shock is a complex clinical **syndrome** that begins with hemodynamic instability and can progress to **multi-organ failure** and profound **hemo-metabolic compromise**

Cardiogenic shock: the goal

$$\text{MAP} = \text{CO} \times \text{SVR}$$



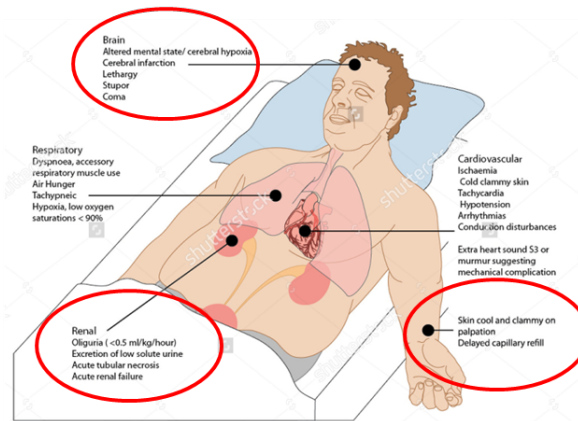
Ventricular arterial coupling

Inotropes/Vasopressors/Mechanical support



Tissue perfusion

Microcirculation alteration during cardiogenic shock



Inotropes and Vasoactive Agents: when?

SCAI Shock Classification

Stage A - At risk

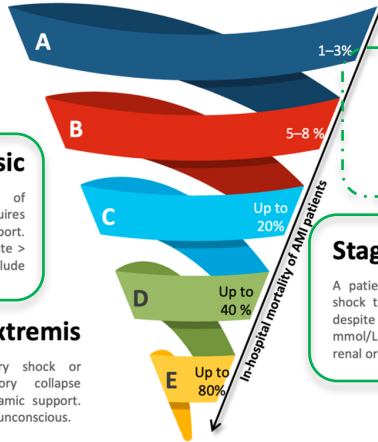
A hemodynamically stable patient who is not experiencing signs or symptoms of CS, but is at risk for its development

Stage C - Classic

A patient who has clinical of hypoperfusion that initially requires pharmacological or mechanical support. Hypotension is usually present. Lactate > 2 mmol/L. CI < 2.2 L/min/m². May include impairment of renal or liver function.

Stage E - Extremis

A patient with refractory shock or actual/impending circulatory collapse despite maximal hemodynamic support. Lactate > 8 mmol/L. Typical unconscious.



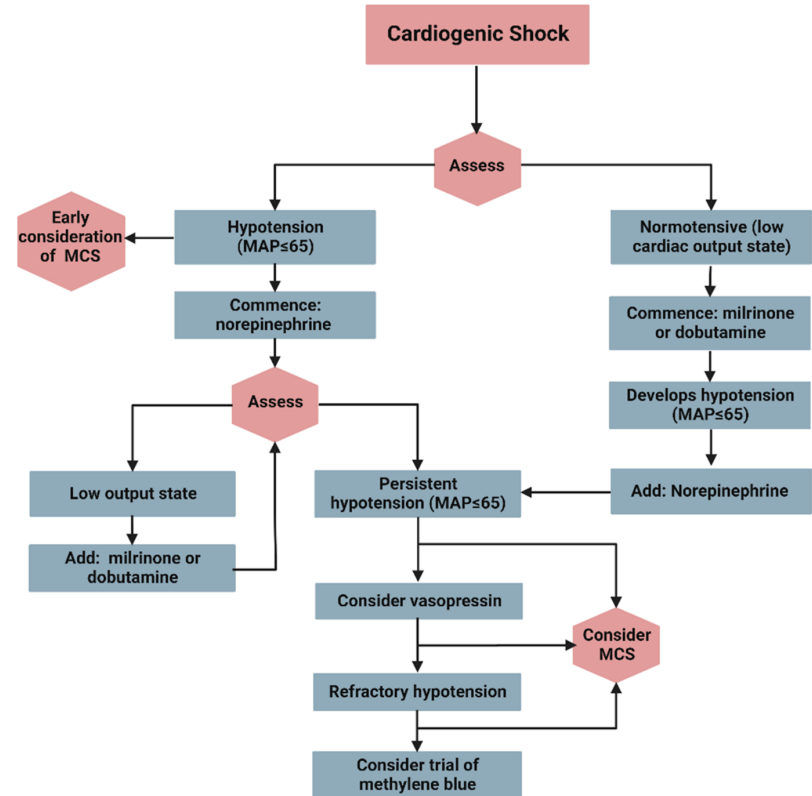
Stage B - Beginning

A patient who has clinical evidence of hemodynamically instability without hypoperfusion. SBP < 90 mmHg or MAP < 60 mmHg or drop > 30 mmHg from baseline, HR ≥ 100 bpm.

Stage D - Deteriorating

A patient who has clinical evidence of shock that worsens or fails to improve despite escalation therapy. Lactate > 2 mmol/L. May include deterioration of renal or liver function.

Proposed Vasoactive Treatment Strategy



Journal of the American Heart Association

CONTEMPORARY REVIEW

State of Shock: Contemporary Vasopressor and Inotrope Use in Cardiogenic Shock

Jason E. Bloom  BSc, MBBS; William Chan  MBBS, PhD; David M. Kaye  MBBS, PhD*; Dion Stub  MBBS, PhD*



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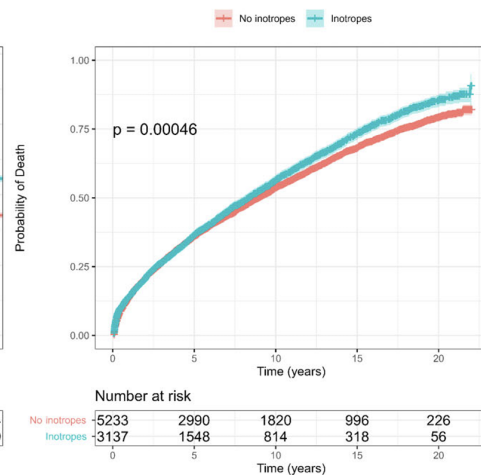
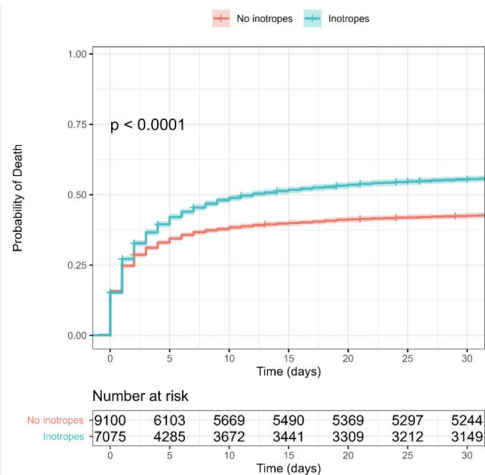
Vasoactive medication and RCTs: an impossible marriage

A review and introduction of the concept "enough"

We provide a brief overview of important physiology and the pharmacology of vasoactive drugs that are currently used in the ICU as well as newer agents, along with a concise review of recent publications comparing these agents. We attempt to answer the question what drug dose should be administered as well as what haemodynamic values to pursue, and how much fluids must be infused by introducing the concept of "enough".

In the intensive care unit (ICU) setting,
≈25% of admitted patients
receive
at least 1 vasoactive medication

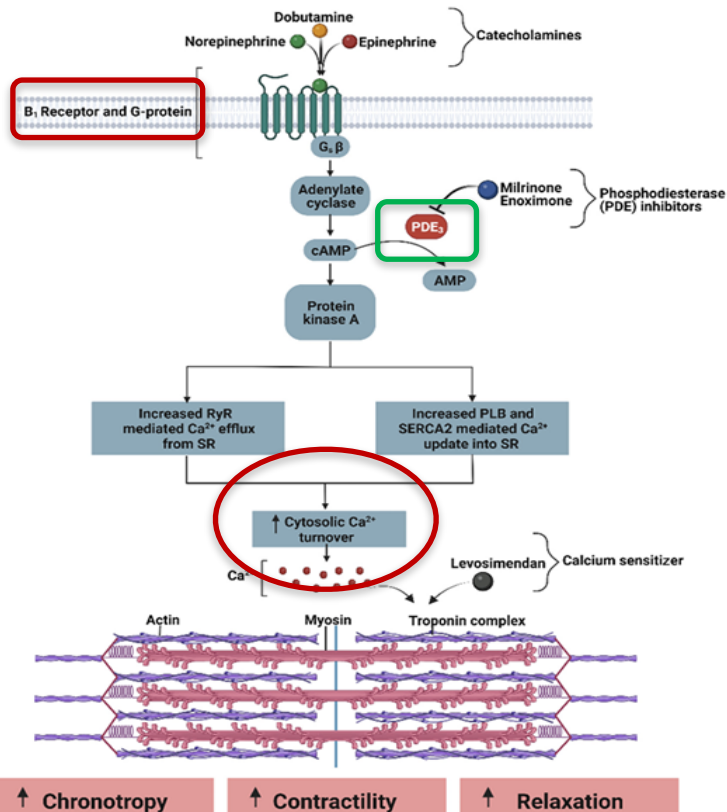
increasing to **>90%** in patients with **CS**



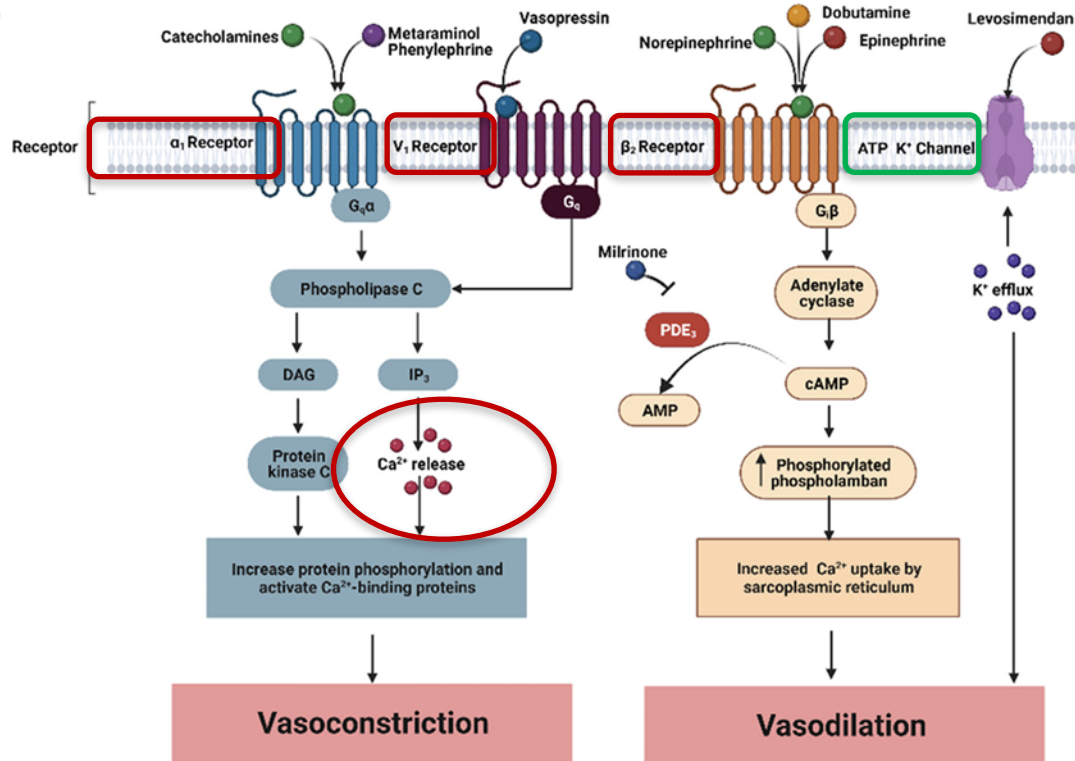
Indication to commence therapy	Hypotension (systolic blood pressure <90 mm Hg) and/or evidence of end-organ hypoperfusion				
Societal guideline	ESC HF	ACC/AHA HF	ESC STEMI	AHA CS	AHA AMI-CS
Recommendation and level of evidence	IIb - B/C	IIa - B	IIb - C	N/A	N/A
First-line agent	Hypotensive: Norepinephrine Low output: No recommendation	Hypotensive: Clinician preference Low output: Clinician preference	Hypotensive: Norepinephrine Low output: Dobutamine	Hypotensive: Norepinephrine or Dopamine Low output: Norepinephrine or Dopamine	Hypotension: Norepinephrine



Cardiac Tissue



Vascular Smooth Muscle



VASOCONSTRICTION

Which Inotropes and Vasoactive Agents?

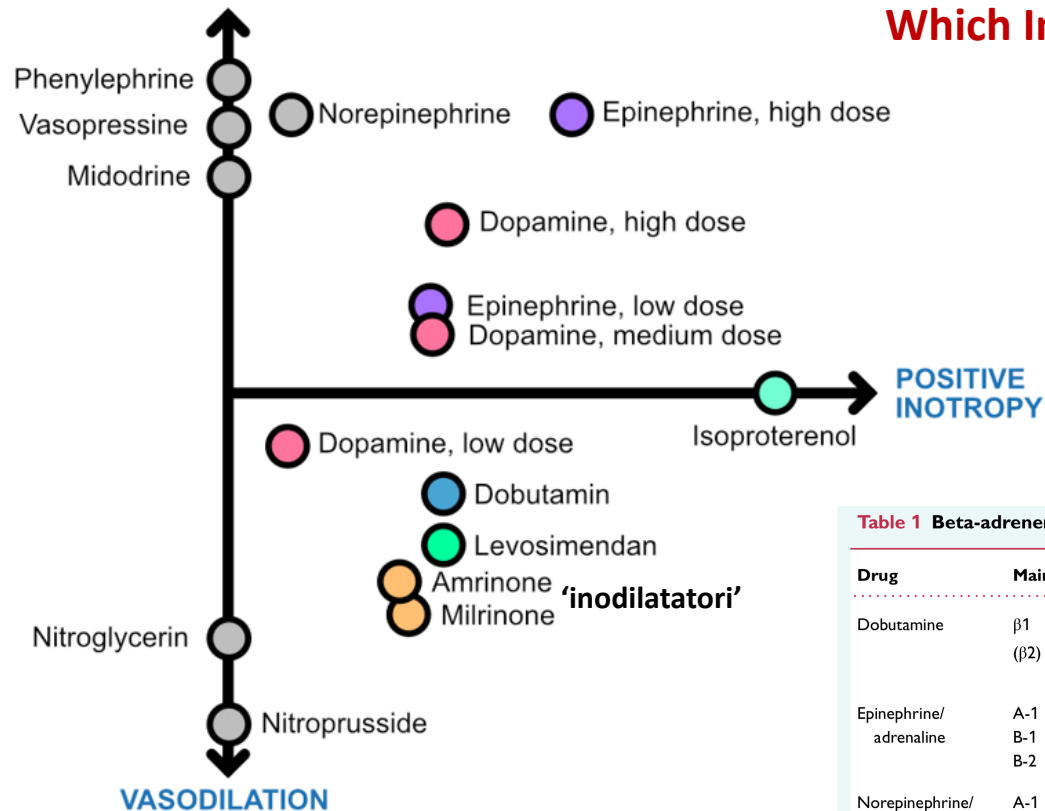
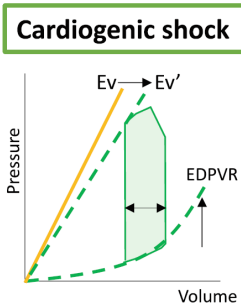
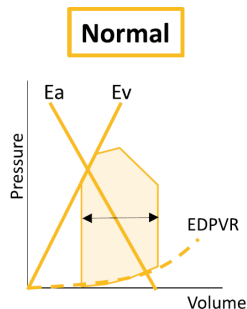


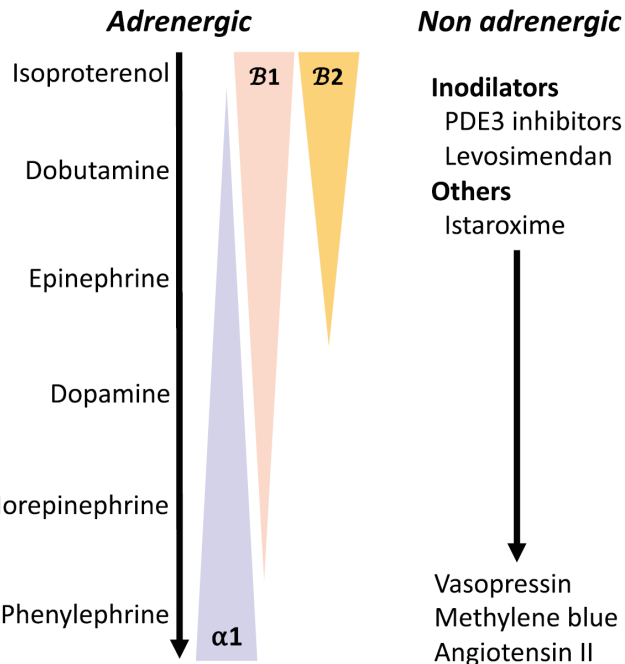
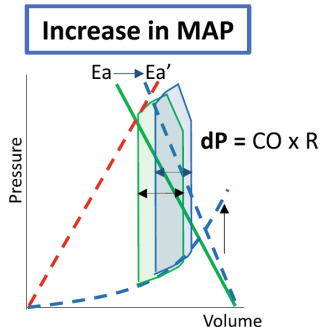
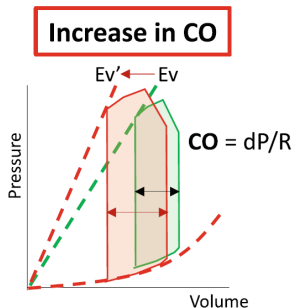
Table 1 Beta-adrenergic drugs: pharmacology and clinical effects

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 $\mu\text{g/kg/min}$	± 2 min
Epinephrine/ adrenaline	A-1 B-1 B-2	Inotropy Chronotropy Vasoconstriction	+	0.05–0.5 $\mu\text{g/kg/min}$	± 2.5 min
Norepinephrine/ noradrenaline	A-1 (B-1)	Vasoconstriction	–	0.2–1.0 $\mu\text{g/kg/min}$	± 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 $\mu\text{g/kg/min}$ High dose: >5 $\mu\text{g/kg/min}$	± 2 min

Pathophysiology



Inotropes



Vasopressors





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Sodium nitroprusside in acute heart failure: A multicenter historic cohort study

Laura Garatti^a, Simone Frea^b, Pier Paolo Bocchino^b, Filippo Angelini^b, Marco Cingolani^b, Alice Sacco^a, Giulia Maria Rondinara^a, Vincenzo Bagnardi^c, Isabella Maria Sala^c, Navin K. Kapur^d, Paolo C. Colombo^e, Gaetano Maria De Ferrari^b, Nuccia Morici^{f,*}

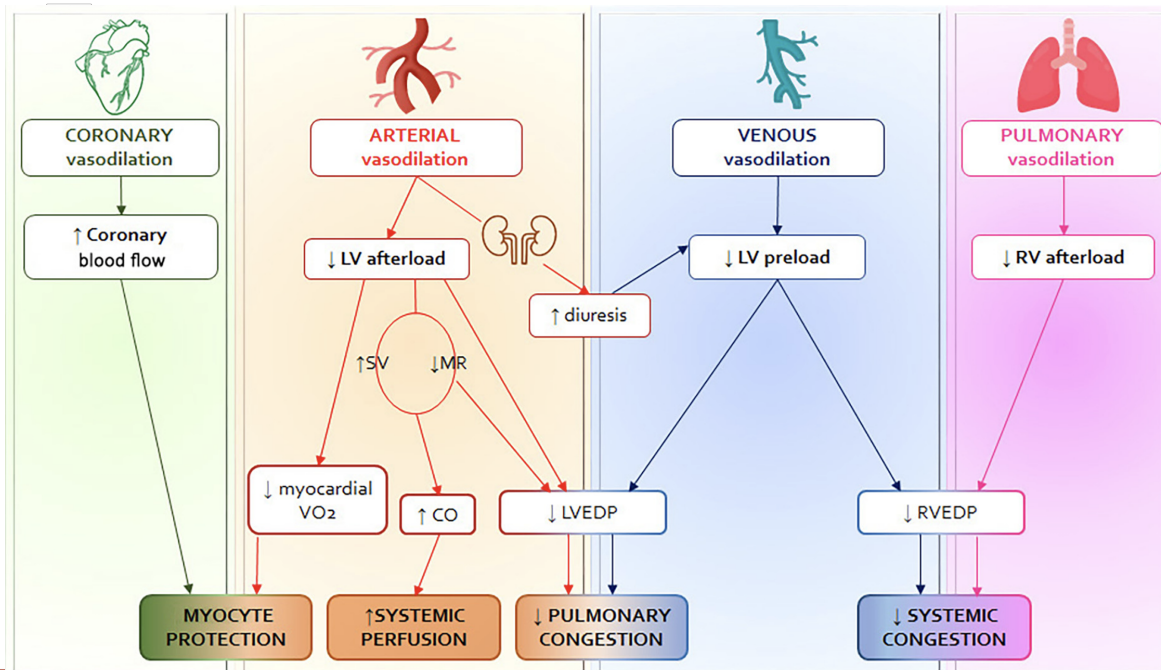
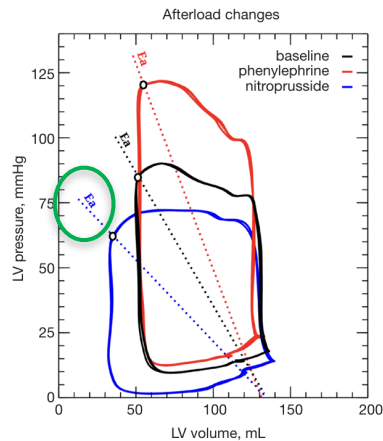




Table 2 Randomized controlled trials on the use of inotropes/vasopressors in cardiogenic shock

Trial, year	Drugs	No. of patients	Main inclusion criteria	Primary endpoint	Results	Safety
SOAP-II, 2010 ¹⁴	Dopamine vs. norepinephrine	1679 (dopamine $n=858$; norepinephrine $n=821$); among these patients, 280 had CS (135 in the dopamine group and 145 in the norepinephrine group)	Shock (defined as MAP <70 mmHg or SBP <100 mmHg with signs of hypoperfusion) with need for vasopressor agent	Death at 28 days	Increased rate of death among the 280 patients with CS treated with dopamine ($p=0.03$)	More arrhythmic events in the dopamine group (24.1%) vs. norepinephrine group (12.4%) ($p<0.001$)
CAT, 2008 ¹⁵	Epinephrine vs. norepinephrine	280 ($n=140$ in each treatment arm); among these, 128 had CS (64 in each treatment arm)	Need for infusion of epinephrine or norepinephrine for any cause	Time taken to achieve a MAP ≥ 70 mmHg for >24 h without vasopressors	No difference in the time to achieve MAP both in the whole population and in CS setting (RR 0.89, 95% CI 0.62–1.27, $p=0.49$)	Development of significant tachycardia and lactic acidosis with epinephrine, in addition to increased insulin requirements
OptimaCC, 2018 ¹⁶	Epinephrine vs. norepinephrine	57 (epinephrine $n=27$; norepinephrine $n=30$)	AMI-CS successfully revascularized, SBP <90 mmHg or MAP <65 mmHg, cardiac index <2.2 L/min/m ² , PCWP >15 mmHg, LVEF <40% and evidence of tissue hypoperfusion	Change in cardiac index (primary efficacy endpoint); occurrence of refractory CS (primary safety endpoint)	Cardiac index evolution was similar between groups ($p=0.43$). Higher incidence of refractory shock in the epinephrine group (37% vs. 7%, $p=0.008$)	HR increased significantly with epinephrine ($p<0.0001$); increase in cardiac double product ($p=0.0002$) and lactic acidosis ($p<0.0001$) with epinephrine
Levy et al., 2011 ¹⁷	Norepinephrine-dobutamine vs. epinephrine	30 ($n=15$ in each treatment arm)	Non-AMI-CS (defined as LVEF <30% and cardiac index <2.2 L/min/m ² , absence of hypovolaemia, lactate >2 mmol/L, MAP <60 mmHg or SBP <90 mmHg, urine output <0.5 mL/kg/h, signs of hypoperfusion, no signs of acute cardiac ischaemia)	Haemodynamic effects using the drugs to obtain a MAP of 65–70 mmHg	Both regimes increased cardiac index and oxygen-derived parameters in a similar manner	HR, lactate levels and PCO ₂ gap, a surrogate for splanchnic perfusion adequacy, increased in the epinephrine group ($p<0.05$, $p<0.01$ and $p<0.01$, respectively)
DOREMI, 2021 ¹⁸	Dobutamine vs. milrinone	192 ($n=96$ in each treatment arm)	CS SCAI B-D	Composite of in-hospital death from any cause, resuscitated cardiac arrest, cardiac transplant or MCS, non-fatal MI, TIA/stroke or RRT	Primary endpoint was 49% in the milrinone group vs. 54% in the dobutamine group (RR 0.90, 95% CI 0.69–1.19, $p=0.47$)	No significant differences in HR, MAP, serum lactate level, serum creatinine level, or hourly urine output between the treatment groups
Fuhrmann et al., 2008 ¹⁹	Enoximone vs. levosimendan	32 ($n=16$ in each group)	Refractory CS patients requiring additional therapy	Survival at 30 days	Survival rate at 30 days was higher in the levosimendan group (69% vs. 37%, $p=0.023$)	N/A
LIDO, 2002 ²⁰	Dobutamine vs. levosimendan	203 (levosimendan $n=103$; dobutamine $n=100$)	Low-output HF (including ADHF)	Proportion of patients with haemodynamic improvement at the end of the 24-h infusion period	Primary endpoint met in 28% of patients in the levosimendan group vs. 15% in the dobutamine group (hazard ratio 1.9, 95% CI 1.1–3.3, $p=0.022$)	Angina pectoris, chest pain, or myocardial ischaemia more frequent in the dobutamine group, in addition to a higher proportion of patients with rate and rhythm disorders; trend towards a higher frequency of headache or migraine in the levosimendan group
SURVIVE, 2007 ²¹	Dobutamine vs. levosimendan	1327 (levosimendan $n=664$; dobutamine $n=663$)	ADHF $\pm$ low cardiac output	All-cause mortality at 180 days	No significant difference in 180-day death (26% in the levosimendan group vs. 28% in the dobutamine group; hazard ratio 0.91, 95% CI 0.74–1.13, $p=0.40$)	Higher incidence of cardiac failure in the dobutamine group; higher incidence of AF, hypokalaemia and headache in the levosimendan group
Samimi-Fard et al., 2008 ²¹	Dobutamine vs. levosimendan	22 ($n=11$ in each group)	AMI-CS	Cardiac death at 12 months	No significant difference in 1-year cardiac death ($p=0.24$)	N/A
LEAF, 2013 ²²	Levosimendan vs. placebo	61 (levosimendan $n=30$; placebo $n=31$); among these, 9 had CS (levosimendan $n=4$; placebo $n=5$)	STEMI with signs of decreased wall motion in at least 3 of 16 segments of the LV with clinical HF	Wall motion score index at 5 days	Larger improvement from baseline to day 5 in the levosimendan group (from 1.94 ± 0.20 to 1.66 ± 0.31 vs. 1.99 ± 0.22 to 1.83 ± 0.26 , $p=0.031$)	Significantly more episodes of hypotension during study drug infusion in the levosimendan group (67% vs. 36%, $p=0.029$); in CS subgroup, NSVT was observed in 3 patients in the placebo group and in 1 in the levosimendan group

Inotropic agents and vasodilator strategies for the treatment of cardiogenic shock or low cardiac output syndrome (Review)



Cochrane
Library

Cochrane Database of Systematic Reviews

Authors' conclusions

(Survive Beta-blocker therapy)

Apart from low quality of evidence data suggesting a short-term mortality benefit of levosimendan compared with dobutamine, at present there are no robust and convincing data to support a distinct inotropic or vasodilator drug-based therapy as a superior solution to reduce mortality in haemodynamically unstable people with cardiogenic shock or LCOS.

Considering the limited evidence derived from the present data due to a generally high risk of bias and imprecision, it should be emphasised that there remains a great need for large, well-designed randomised trials on this topic to close the gap between daily practice in critical care medicine and the available evidence. It seems to be useful to apply the concept of 'early goal-directed therapy' in cardiogenic shock and LCOS with early haemodynamic stabilisation within predefined timelines. Future clinical trials should therefore investigate whether such a therapeutic concept would influence survival rates much more than looking for the 'best' drug for haemodynamic support.



Medical therapy of cardiogenic shock: Contemporary use of inotropes and vasopressors



CARDIOGENIC SHOCK

Inadequate cardiac output
PLUS
Clinical signs of hypoperfusion
AND/OR
Biochemical manifestations of
hypoperfusion



**Few evidence-
based data**

AMI-CS:
Lower SVR and trend towards higher CI
vs

ADHF-CS:
Higher SVR and lower CI

AMI-CS

First-line therapy:

- ☞ Norepinephrine (if hypotension prevails)
- ☞ Dobutamine OR Milrinone OR Levosimendan (if CS «normotensive»)

Second-line therapy:

- ☞ Norepinephrine + Dobutamine/Levosimendan

ADHF-CS

First-line therapy:

- ☞ Norepinephrine (if hypotension prevails)
- ☞ Dobutamine OR Milrinone OR Epinephrine + Sodium Nitroprusside OR Levosimendan (if CS «normotensive»)

Second-line therapy:

- ☞ Norepinephrine + Dobutamine/Levosimendan

RV-predominant CS

First-line therapy:

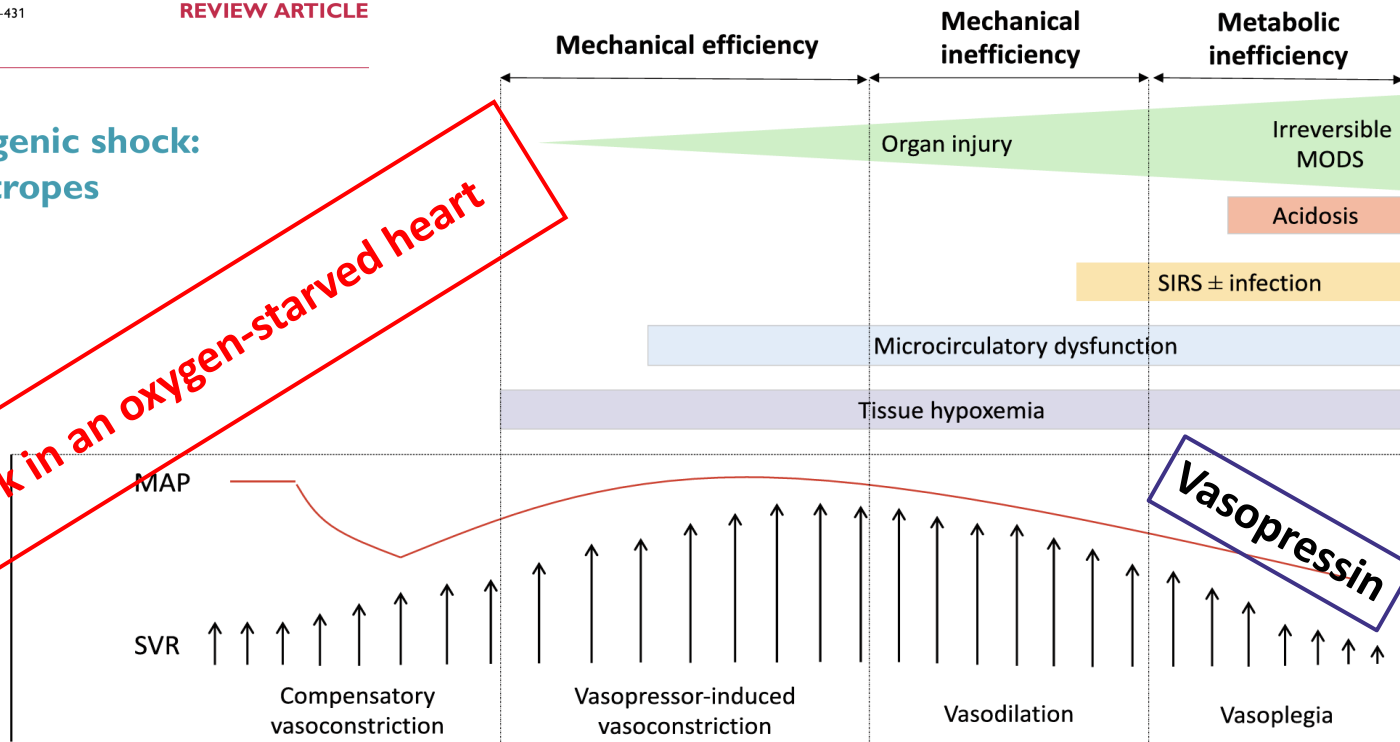
- ☞ Norepinephrine (if hypotension prevails)
- ☞ Milrinone OR Levosimendan (if CS «normotensive»)

Second-line therapy:

- ☞ Norepinephrine + Milrinone/Levosimendan/Dobutamine

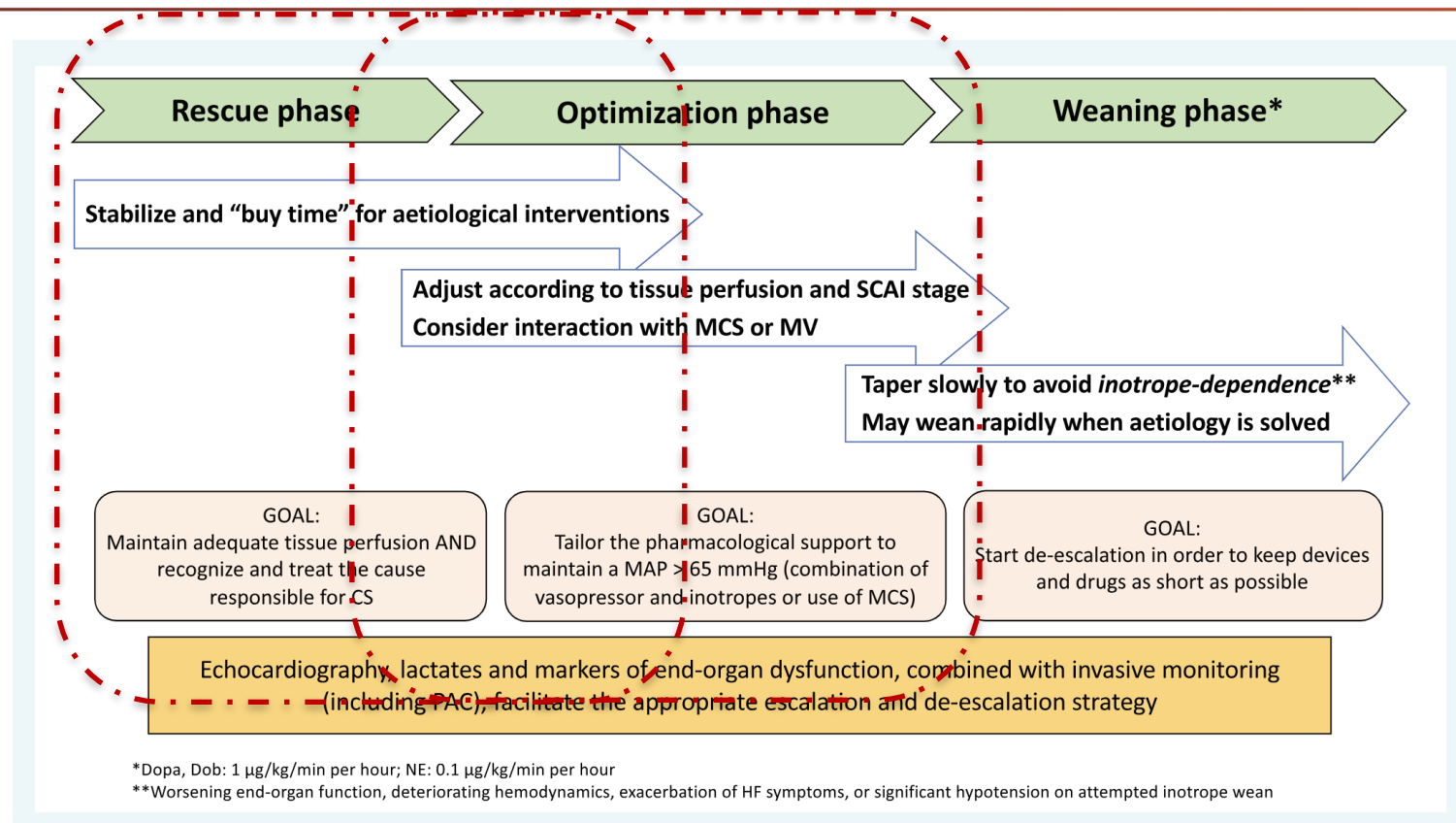
Medical therapy of cardiogenic shock: Contemporary use of inotropes and vasopressors

Increasing cardiac work in an oxygen-starved heart

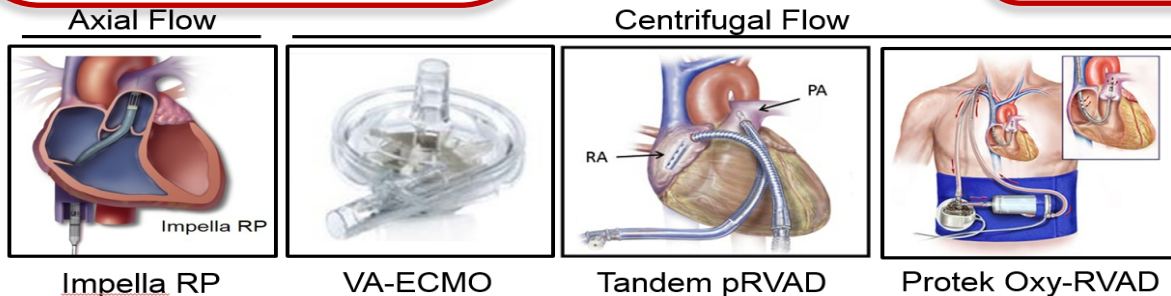
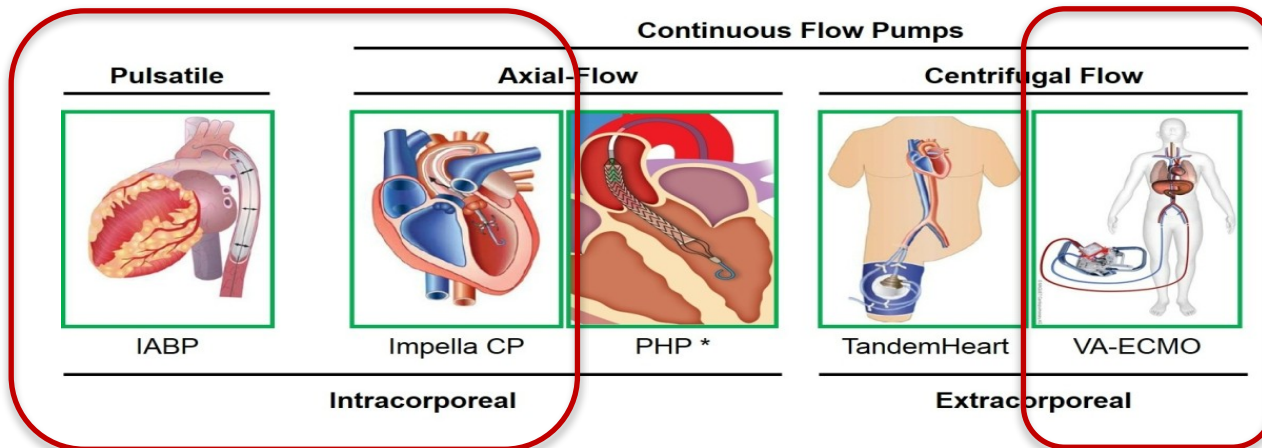


Disconnection macro-microcirculation

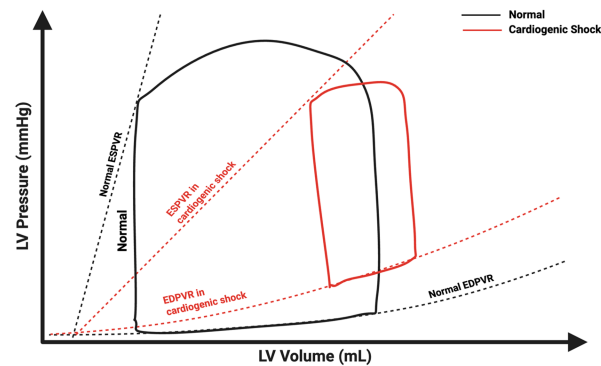
Desensitization of adrenoreceptors



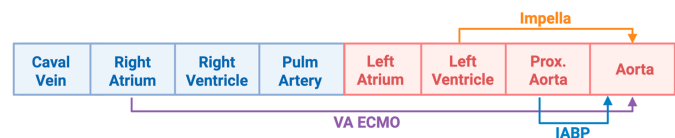
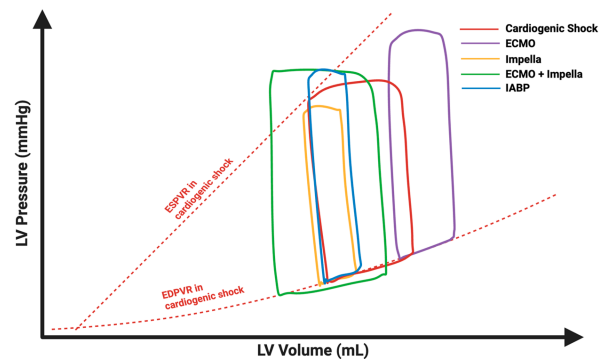
Mechanical circulatory supports



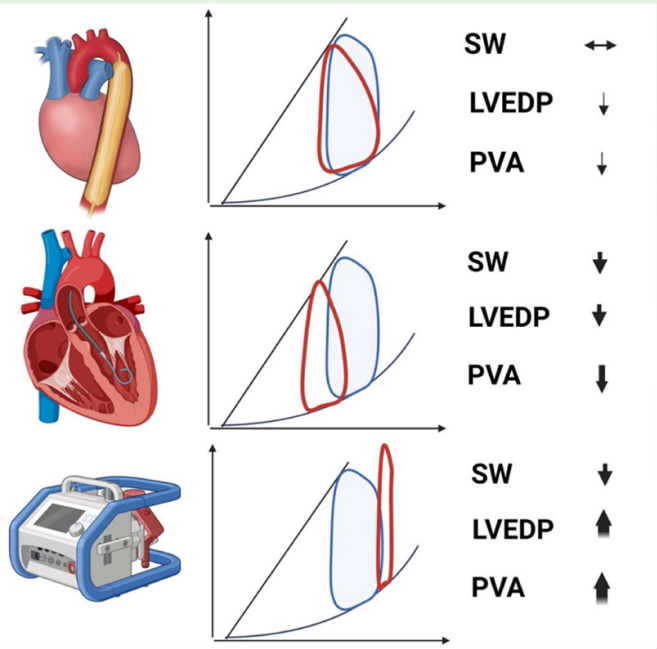
Hemodynamic consequence of cardiogenic shock



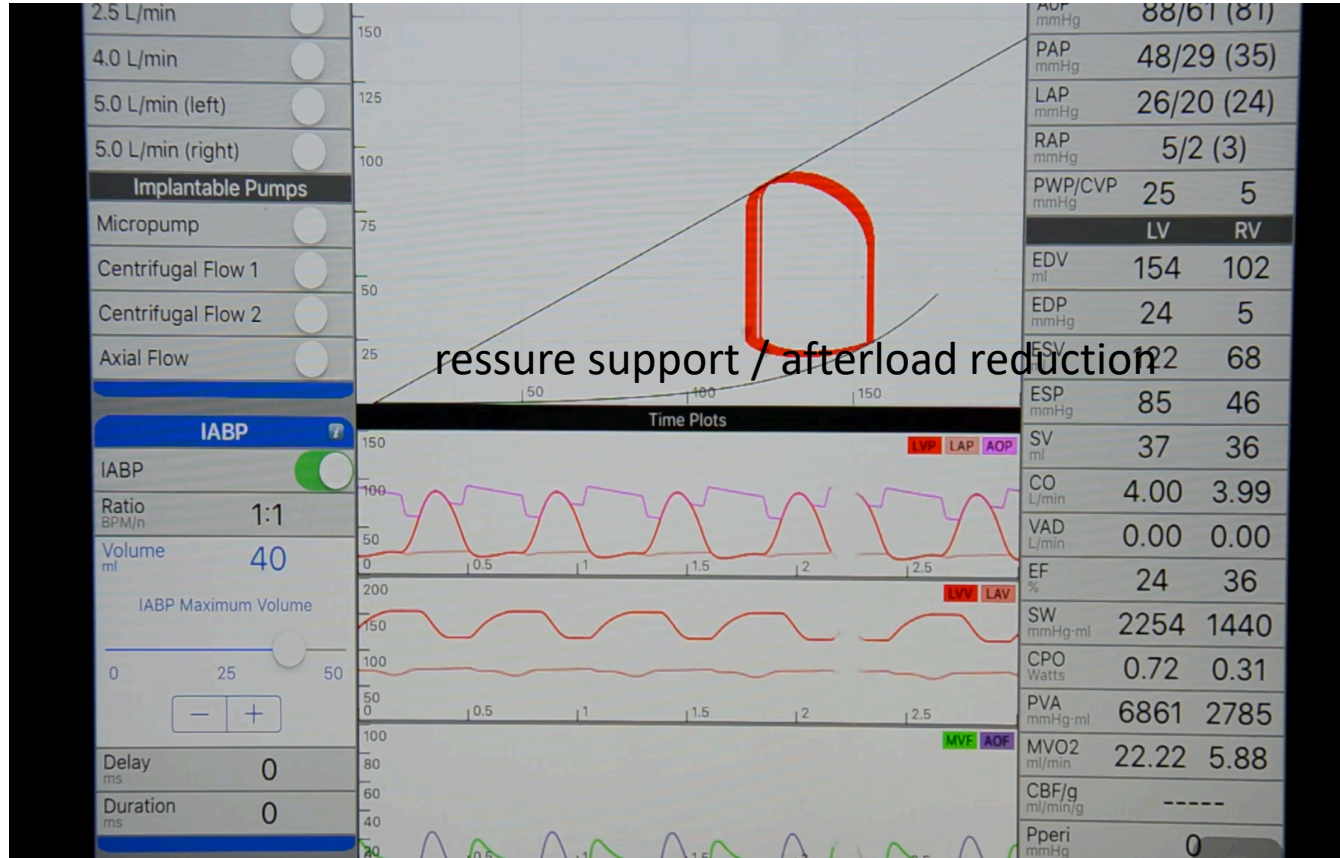
Impact of mechanical support devices on hemodynamics



EFFETTI EMODINAMICI



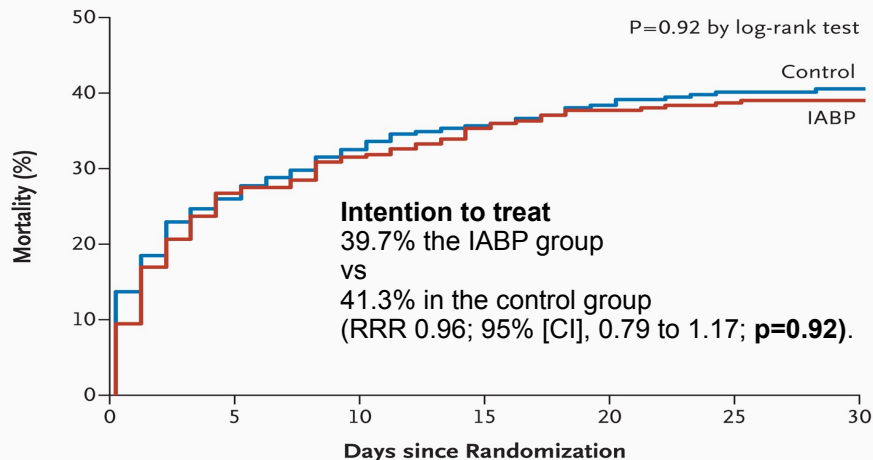
	IABP	Impella	VA-ECMO
Pump mechanism	Balloon inflation-deflation	Axial-flow continuous pump	Centrifugal-flow continuous pump
Cannula placement	Descending thoracic aorta	Left ventricle-to-Ascending Aorta (CP/5.5); Right Atrium-to-Pulmonary Artery (RP)	Right Atrium-to-Aorta
Peripheral resistance	Decreased	Mildly increased	Increased
Cardiac output	0.5–1 L/min	2.5–5.5 L/min	4–7 L/min
Arterial femoral access	7–8 Fr	13 Fr (2.5), 14 Fr (CP), 21 Fr (5.0 and 5.5), 9 Fr (ECP)	14–22 Fr
Venous access	None	None	17–28 Fr



LVEDP ↓
LAP ↓
PCWP ↓
Native LV SV ↑
Afterload ↓
MVO2 ↑↓



IABP does not reduce all-cause mortality at 30 days



Thiele et al. *N Engl J Med* 2012; 367:1287-1296

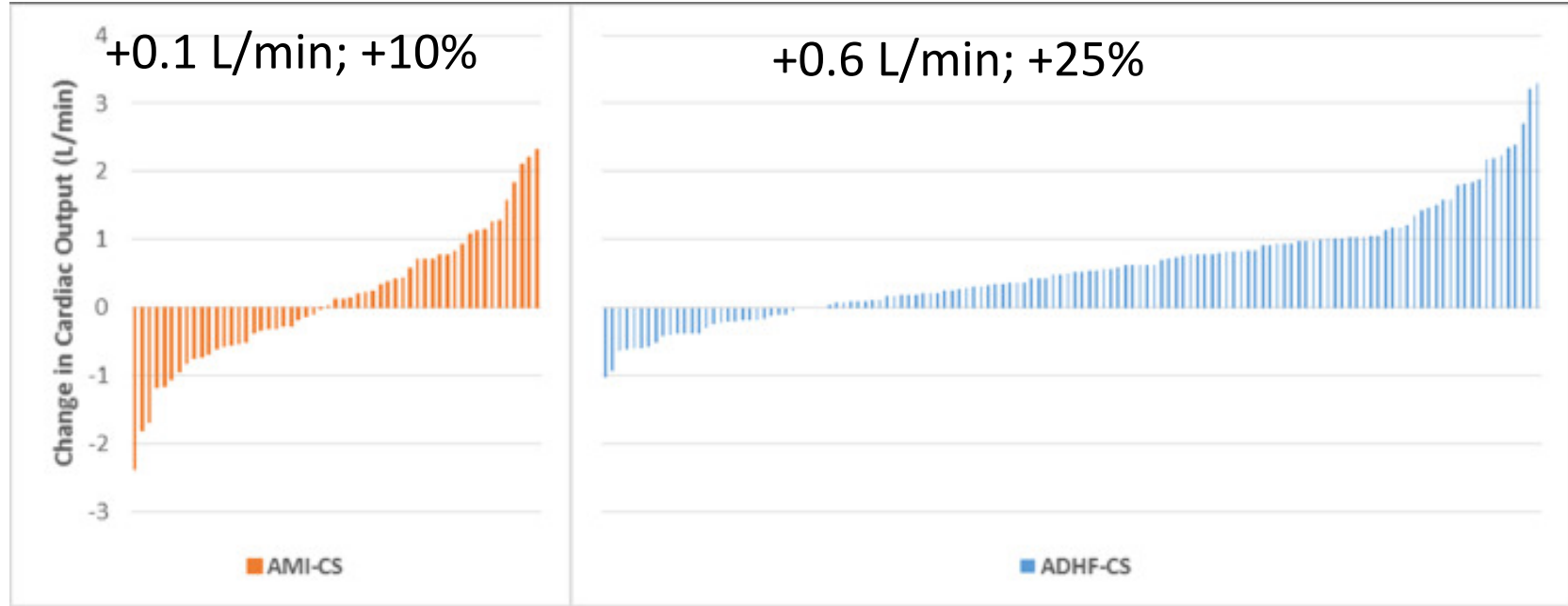
Limitations

- 10% asymmetrical cross-over through IABP arm;
- Lack of haemodynamic data and shock stage definition (probably class C which is not ideal for IABP);
- No information about contact to balloon/contact to unloading time;
- ~~Prevalent IABP use after PCI (86%) and not before~~

ESC Recommendation

	Class – LoE	
	2017	2023
IABP in STEMI-CS due to mechanical complications	IIaC	IIaC
«Routine» use of IABP in STEMI	III B	III B

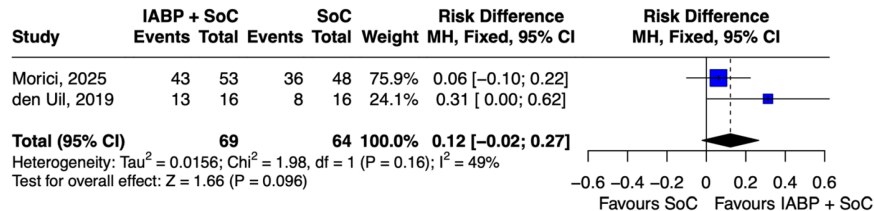
Haemodynamic changes observed after IABP insertion



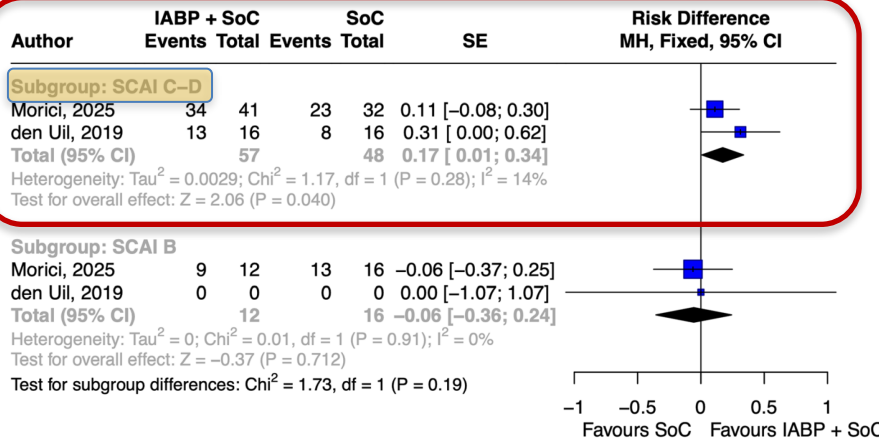
Intra-Aortic Balloon Pump in Heart Failure–Related Cardiogenic Shock: A Meta-Analysis of Randomized Clinical Trials

60-DAY SURVIVAL OR SUCCESSFUL BRIDGING TO HRT

Overall cohort



Subgroup testing for admission SCAI stage



AMI-CS

IABP may be considered in patients with cardiogenic shock as a BTR, BTD, BTB, including treatment of the cause of cardiogenic shock (i.e. mechanical complication of acute MI) or long-term MCS or transplantation.⁴⁵⁰

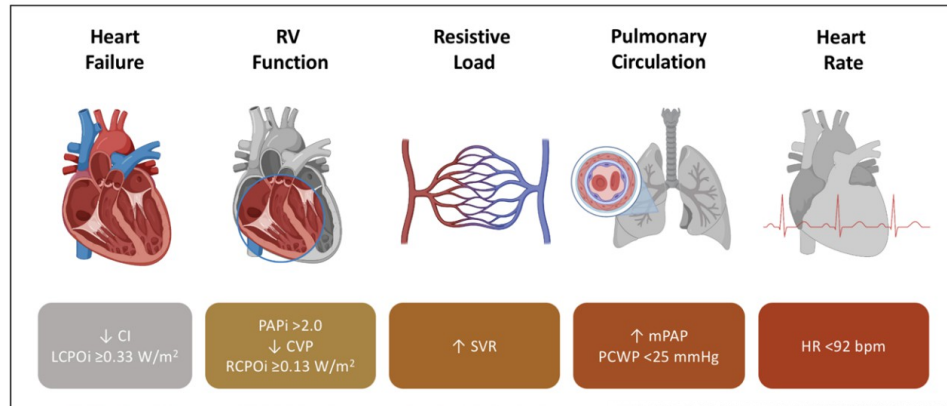
IABP is not routinely recommended in post-MI cardiogenic shock.^{500–502}

IIb	C
III	B

© ESC 2021

HF-CS

The IABP “best responder” phenotype in hypoperfused ADHF



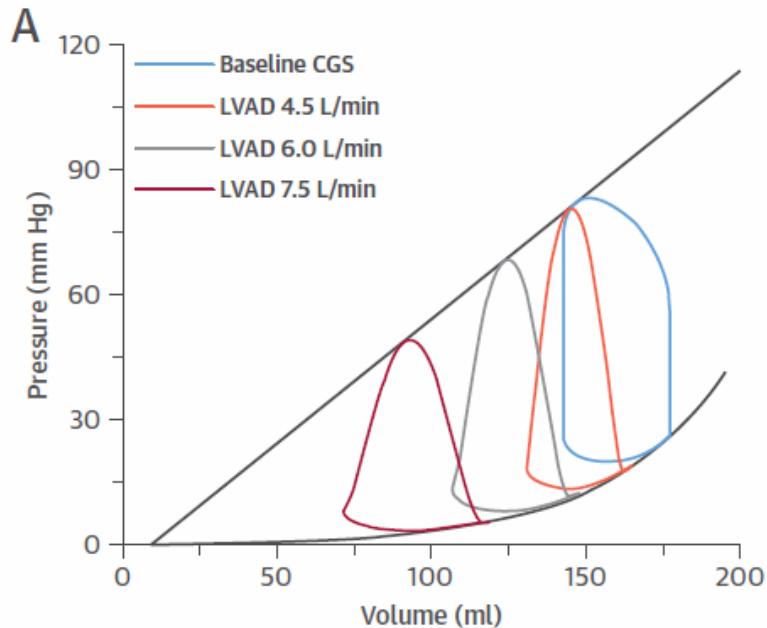
Microaxial flow pump (Impella)



Impella®
World's Smallest Heart Pump



Microaxial flow pump (Impella)



LVEDP ↓

LAP ↓

PCWP ↓

Native LV SV ↓

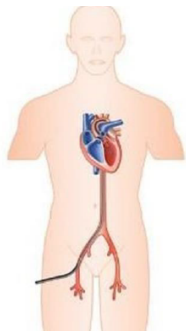
Afterload ↓

MVO2 ↓

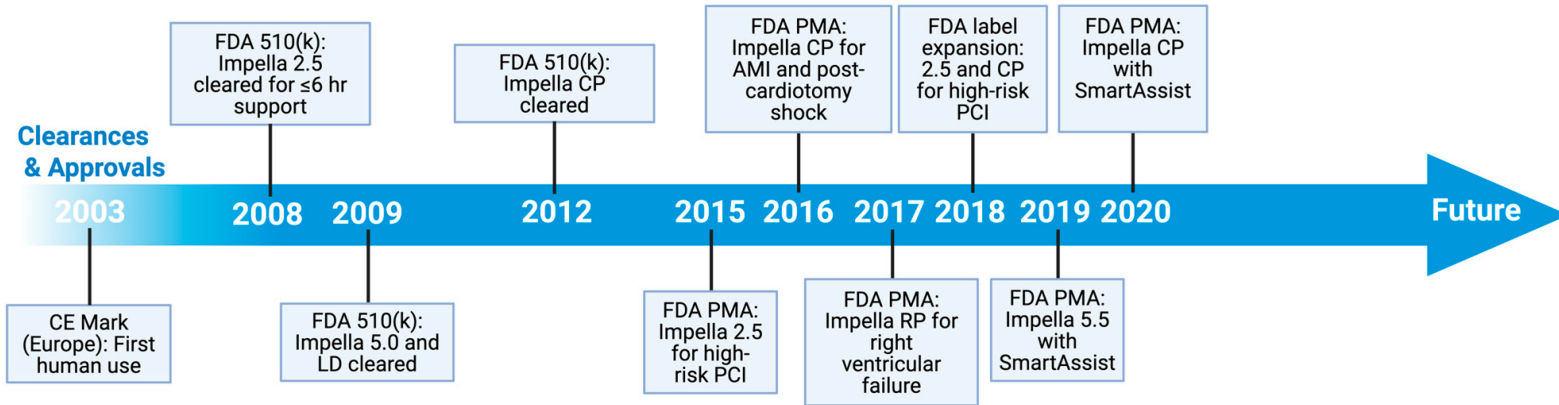


Impella CP

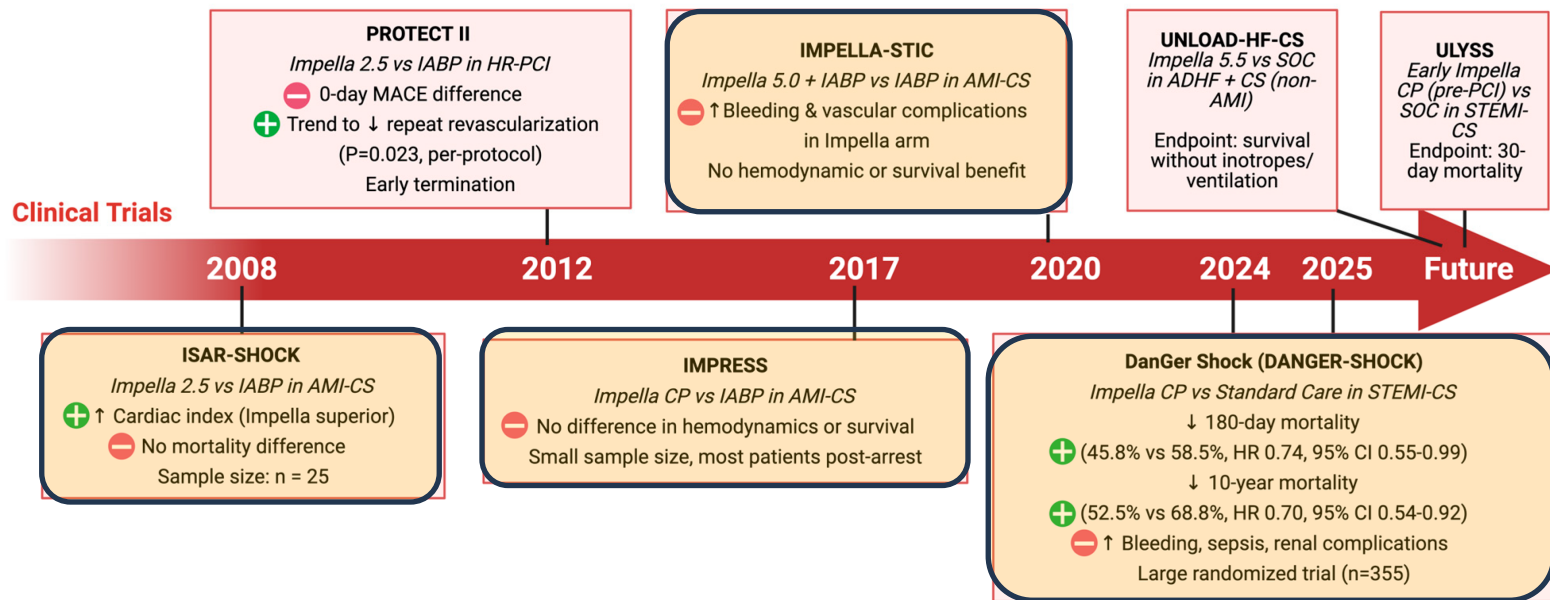


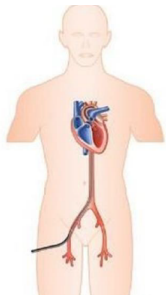


Clearances & Approvals



Clinical Trials

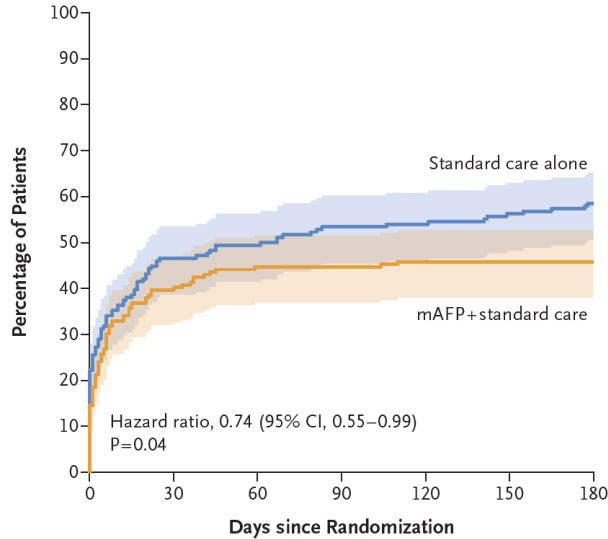




DANGER shock trial

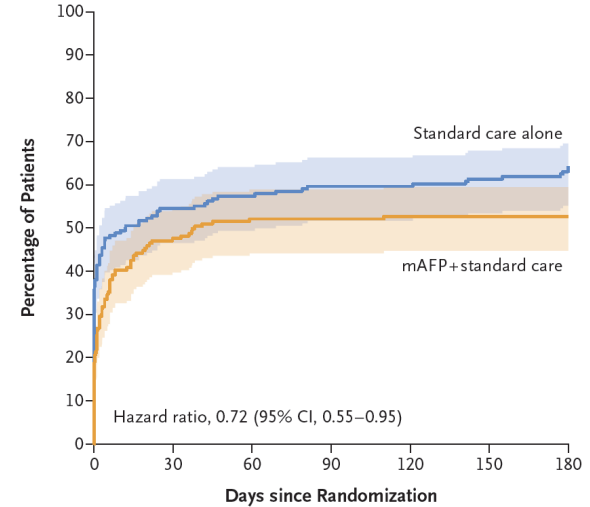
Shock cardiogeno in STEMI
Randomizzato, multicentrico, 360 pazienti
Mortalità a 180 gg, safety endpoint

A Death from Any Cause



No. at Risk							
Standard care	176	94	89	82	81	77	72
mAFP+standard care	179	108	99	99	97	97	97

B Secondary Composite Cardiac End-Point Event *



No. at Risk							
Standard care	176	80	75	71	71	68	64
mAFP+standard care	179	93	85	85	84	84	84

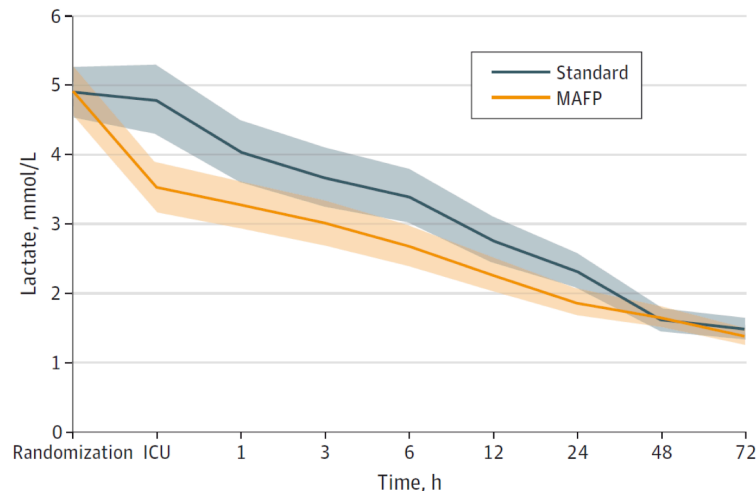
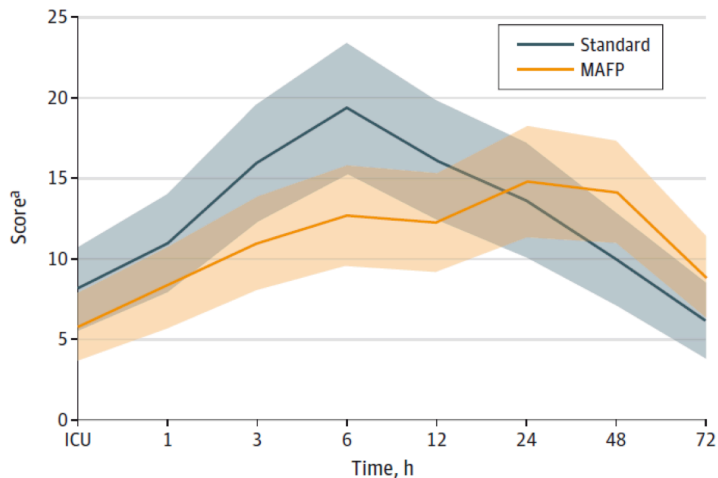
*escalation of treatment to additional MCS, heart transplantation, or death from any cause

89% posizionamento IMPELLA pre PCI

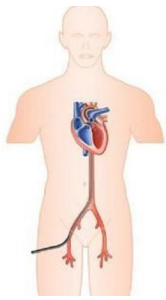
Solo 20% ACC

Post-Procedural Impact of MCS *Haemodynamics from the DanGer Shock Trial*

A Vasoactive inotropic score



Patients who received mAFP support required less inotropic support and had faster lactate clearance



DANGER shock trial

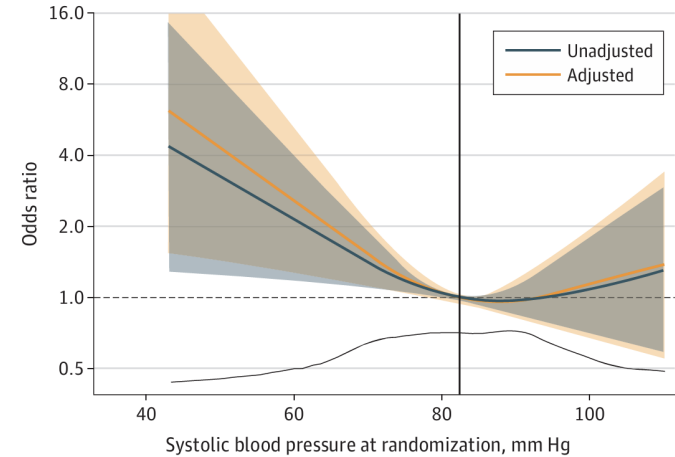


**Uomini
< 67 anni
PAM < 82**

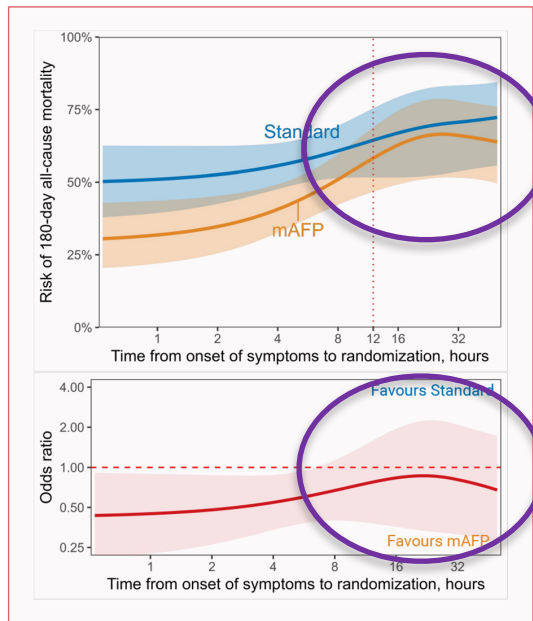
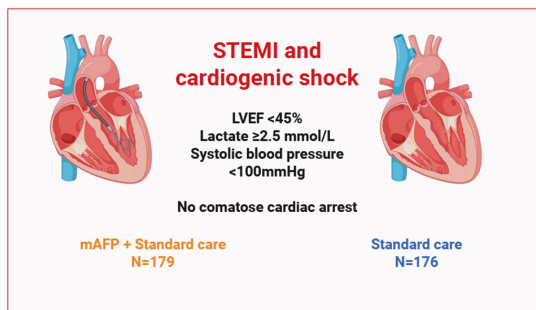
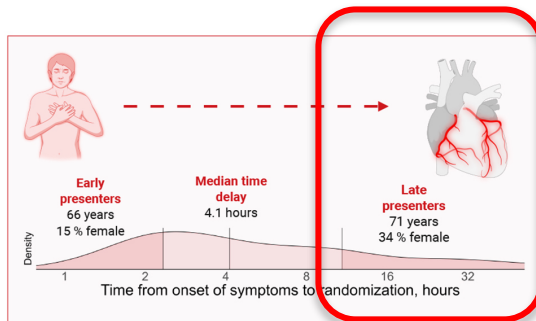
Subgroup	mAFP+ Standard Care no. of deaths/total no. (%)	Standard Care no. of deaths/total no. (%)	Hazard Ratio for Death from Any Cause at 180 Days (95% CI)
Overall	82/179 (45.8)	103/176 (58.5)	0.74 (0.55–0.99)
Sex			
Female	24/37 (65)	24/37 (65)	1.01 (0.58–1.79)
Male	58/142 (41)	79/139 (57)	0.66 (0.47–0.93)
Age			
≤67 yr	31/98 (32)	42/89 (47)	0.64 (0.40–1.02)
>67 yr	51/81 (63)	61/87 (70)	0.85 (0.59–1.24)
Arterial lactate level			
≤4.5 mmol/liter	31/88 (35)	45/92 (49)	0.68 (0.43–1.07)
>4.5 mmol/liter	50/90 (56)	58/84 (69)	0.74 (0.51–1.08)
Mean arterial pressure			
≤63 mm Hg	40/88 (45)	56/85 (66)	0.61 (0.41–0.92)
>63 mm Hg	40/87 (46)	45/86 (52)	0.88 (0.57–1.34)
LVEF			
≤25%	55/100 (55)	73/105 (70)	0.75 (0.53–1.06)
>25%	27/79 (34)	29/70 (41)	0.79 (0.47–1.34)
Location of STEMI			
Nonanterior	24/53 (45)	26/47 (55)	0.76 (0.44–1.32)
Anterior	58/126 (46)	77/129 (60)	0.73 (0.52–1.03)
No. of diseased vessels			
1	19/51 (37)	19/47 (40)	0.99 (0.52–1.87)
≥2	63/128 (49)	84/129 (65)	0.68 (0.49–0.94)
Year of randomization			
2013–2018	28/54 (52)	41/59 (69)	0.66 (0.41–1.07)
2019–2023	54/125 (43)	62/117 (53)	0.80 (0.56–1.15)
SCAI-CSWG stage			
C	35/100 (35)	45/97 (46)	0.73 (0.47–1.13)
D or E	47/79 (59)	58/79 (73)	0.74 (0.50–1.08)

0.5 1.0 1.5
mAFP+ Standard Care Better Standard Care Better

Figure 1. Odds Ratios for 180-Day Mortality by Systolic Blood Pressure at Randomization



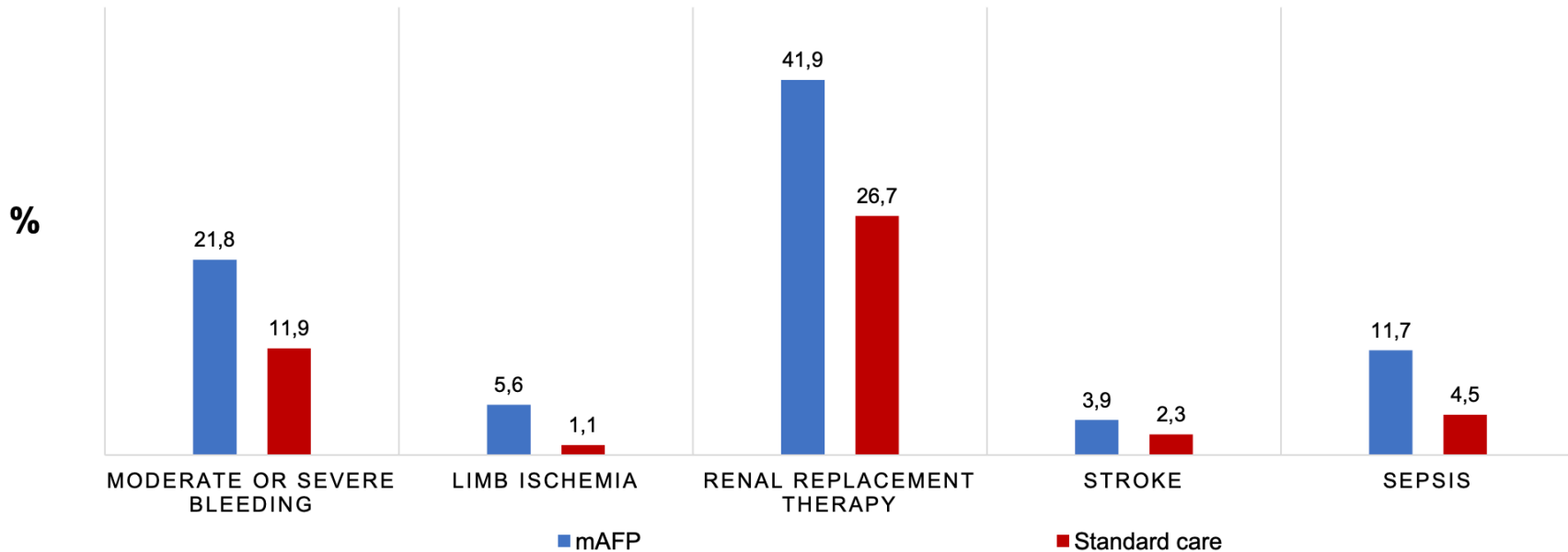
Delay from first symptoms in patients presenting with ST-segment elevation myocardial infarction and cardiogenic shock. Insights from the DanGer Shock trial



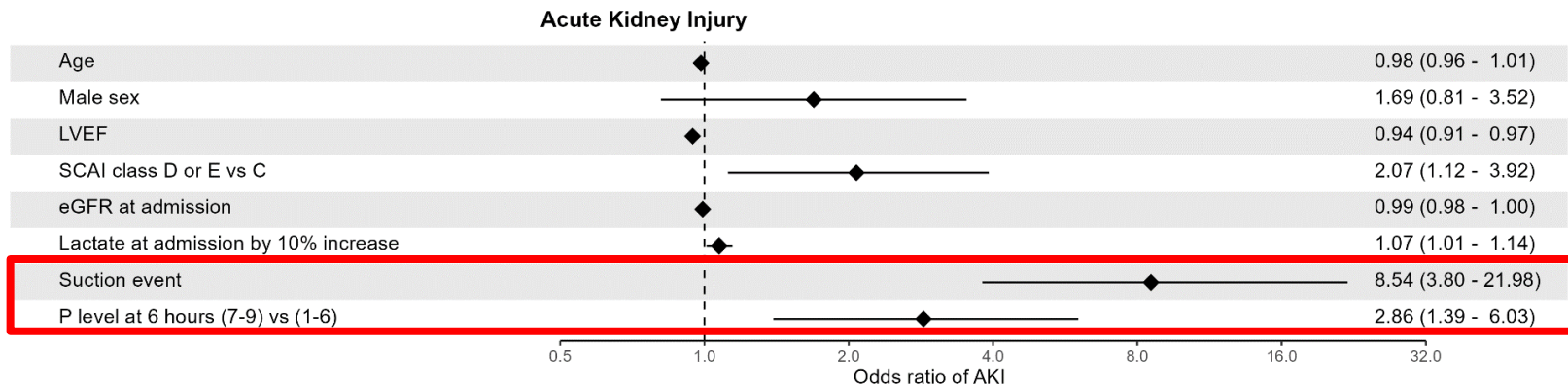
The delay from symptoms to shock diagnosis was associated with increased mortality. In patients with STEMI complicated with cardiogenic shock, the treatment benefit of mAFP seemed to be weakened with prolonged time from the onset of symptoms. This may be caused by latecomers being more frequent elderly women.



The DanGer shock trial



Post-Procedural Impact of MCS *A subanalysis from the DanGer Shock Trial*



In addition to clinical variable device related factors was associated with AKI

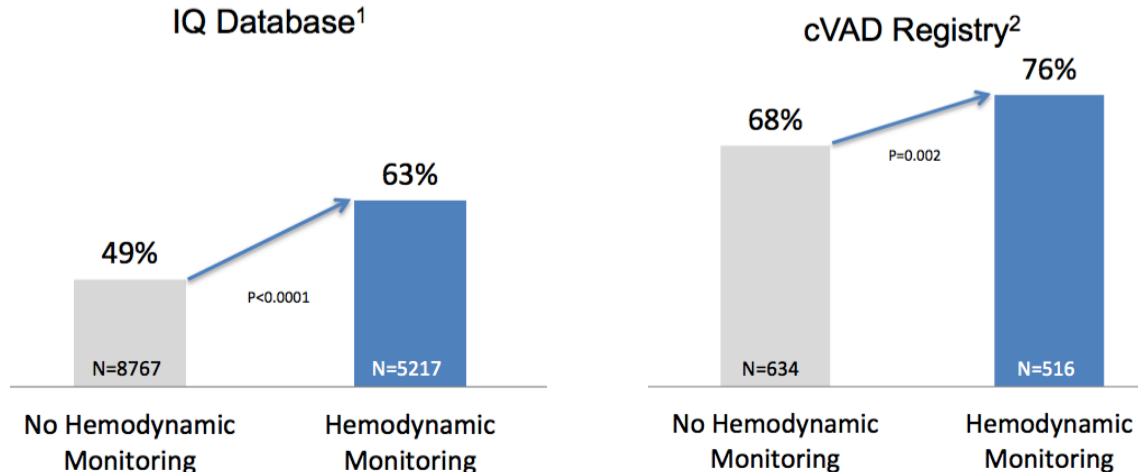


Consider Escalation!



If you want to use Impella, do not use it blindly!

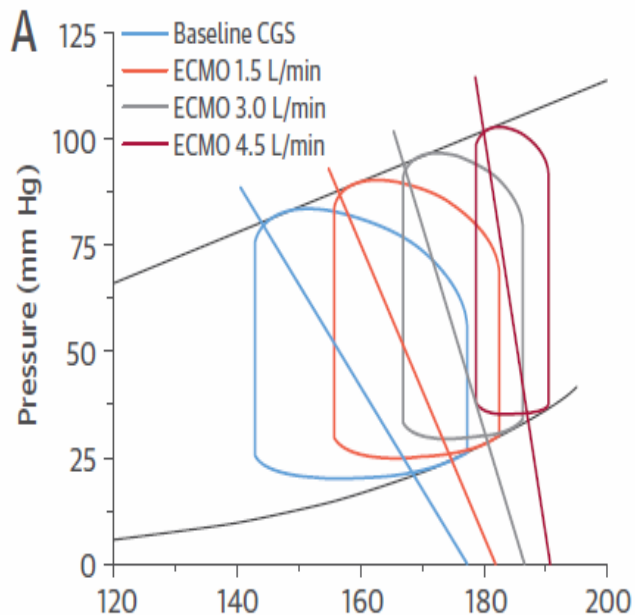
HEMODYNAMIC MONITORING IN IMPELLA RECIPIENTS



1. Abiomed Impella Quality (IQ) Database, US AMI/CGS Apr 2009– Jan 2017. Survival to Explant. Danvers, MA: Abiomed.
2. cVAD survival to explant 2009-2016

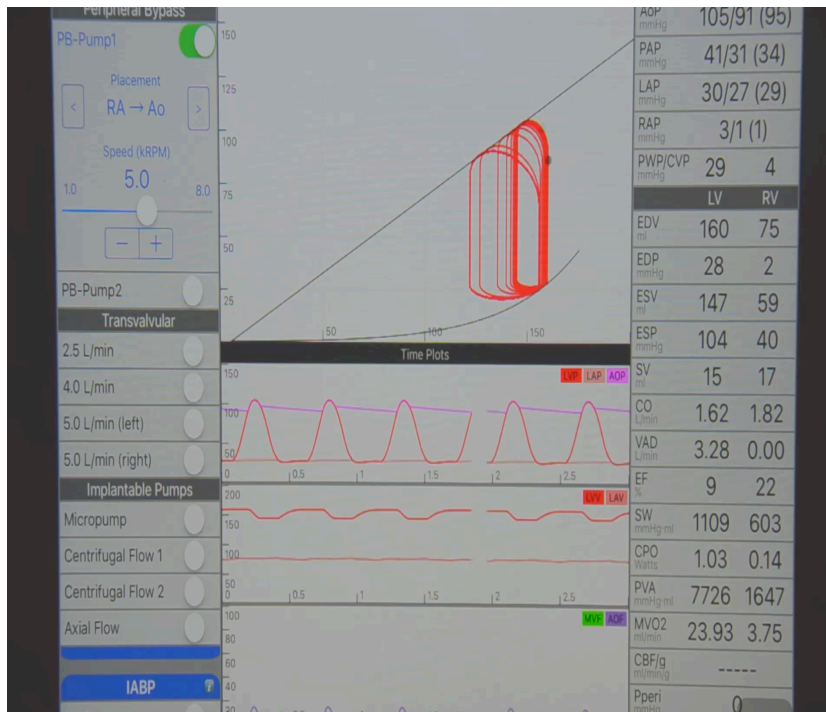


ECMO: PV Loops tell the whole story



LVEDP ↑ LAP ↑ PCWP ↑

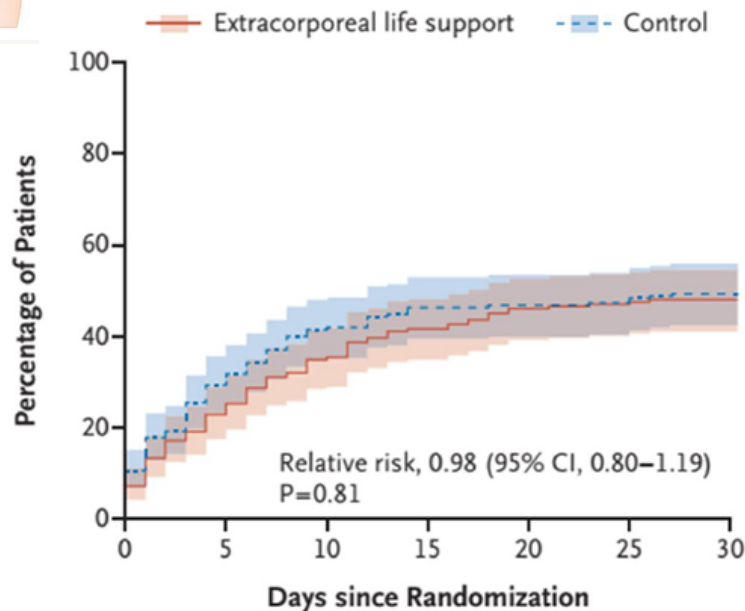
Native LVSV ↓ Afterload ↑ MVO2 ↑



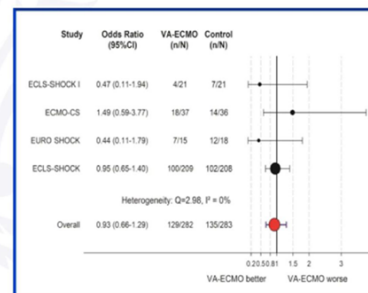


ECLS shock trial

Shock cardiogeno post SCA
Randomizzato, multicentrico, 420 pazienti
Mortalità a 30 giorni



Venoarterial extracorporeal membrane oxygenation in patients with infarct-related cardiogenic shock: an individual patient data meta-analysis of randomised trials

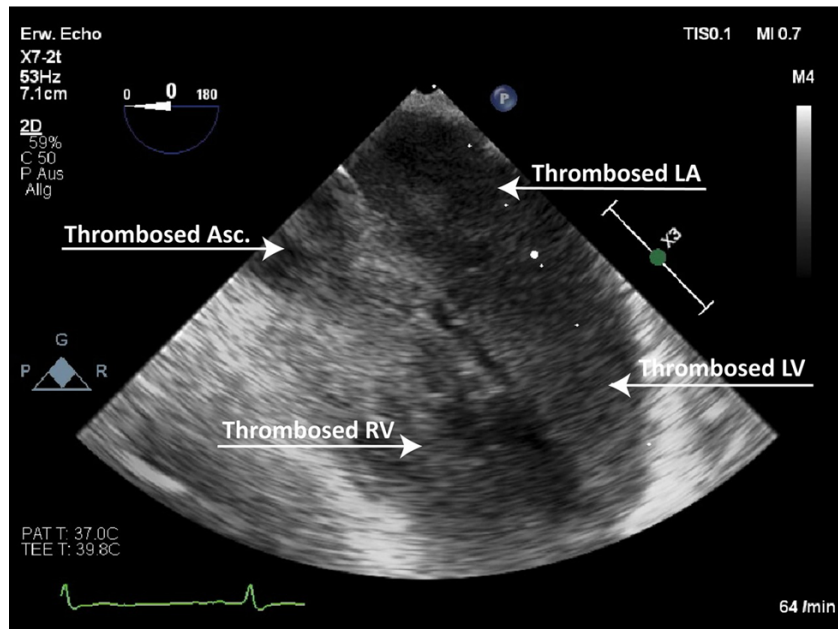


VA-ECMO did not reduce 30-day death rate compared with medical therapy alone in patients with infarct-related cardiogenic shock, and an increase in major bleeding and vascular complications was observed.

Zeymer U et al- Venoarterial extracorporeal membrane oxygenation in patients with infarct-related cardiogenic shock: an individual patient data meta-analysis of randomised trials. *Lancet*. 2023

There is no such a thing as a free lunch

CONSEQUENCES OF LV OVERLOAD

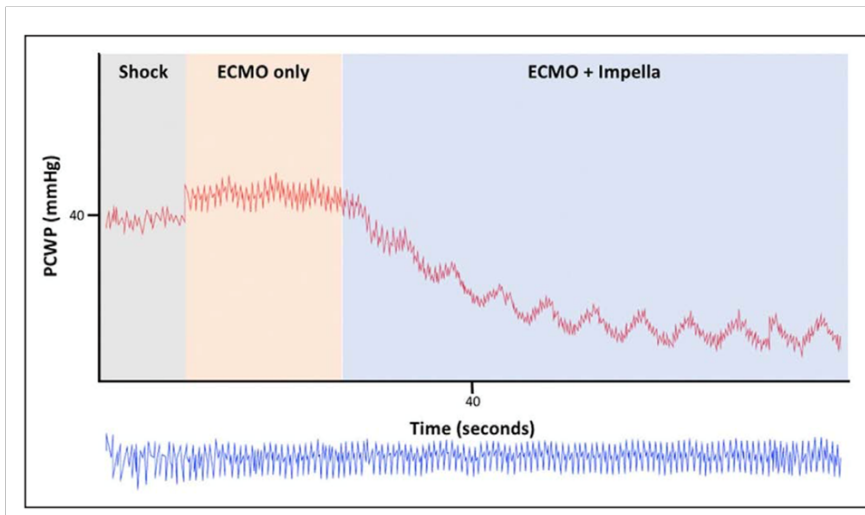


Belohlavek J, Hunziker P, Donker DW. Left ventricular unloading and the role of Ecpella.
Eur Heart J Suppl. 2021;23(Suppl A):A27-A34.



LV UNLOADING: ECPELLA

- Crucial for outcome
- Multidevice support in VA ECMO patients (ECPELLA)
- Stepwise approach

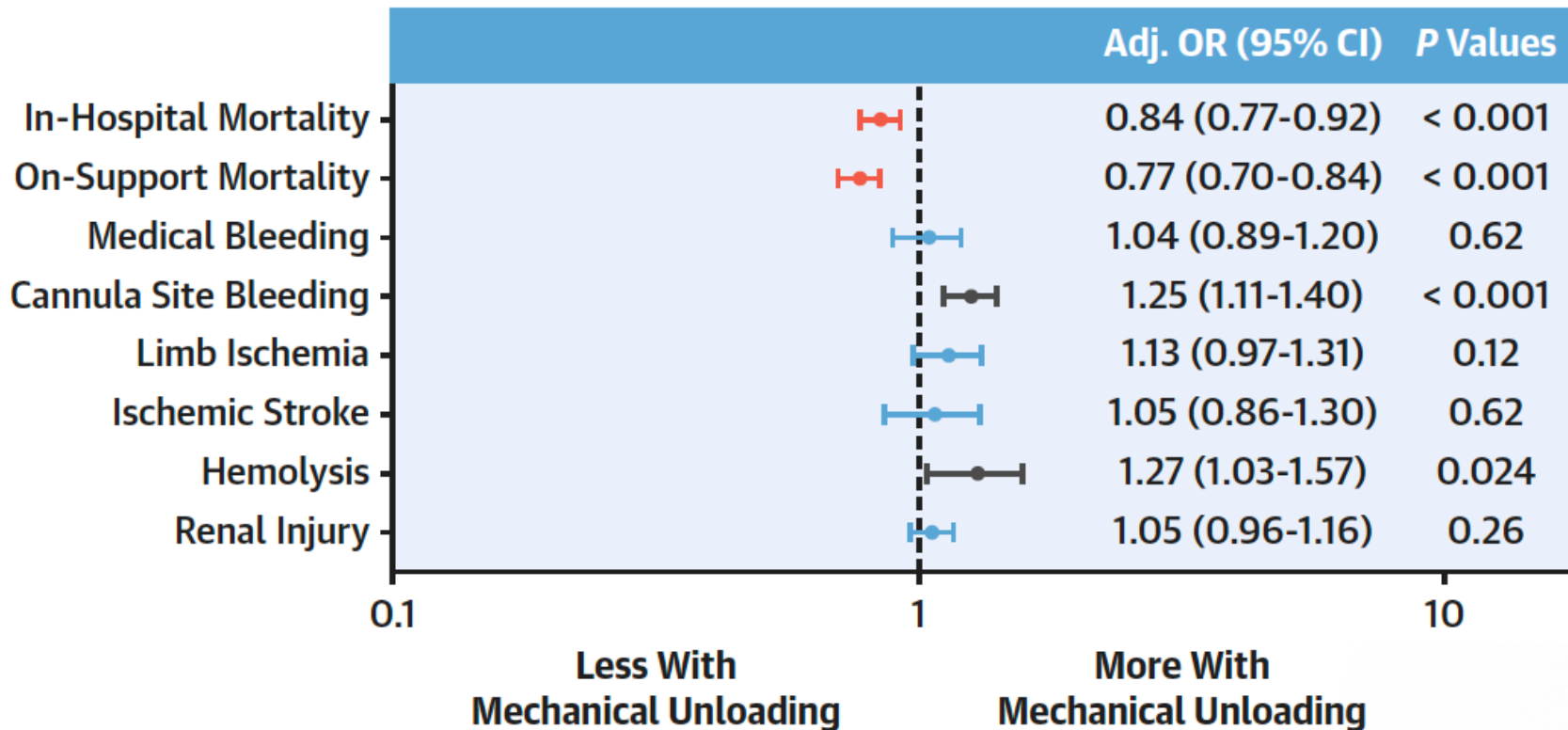


Schrage B, et al. Unloading of the left ventricle during venoarterial extracorporeal membrane oxygenation therapy in cardiogenic shock. JACC Heart Fail. 2018;6:1035–1043.



There is no such a thing as a free lunch

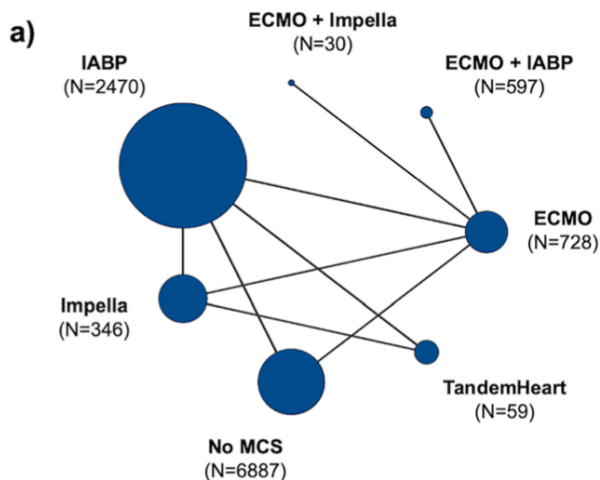
B



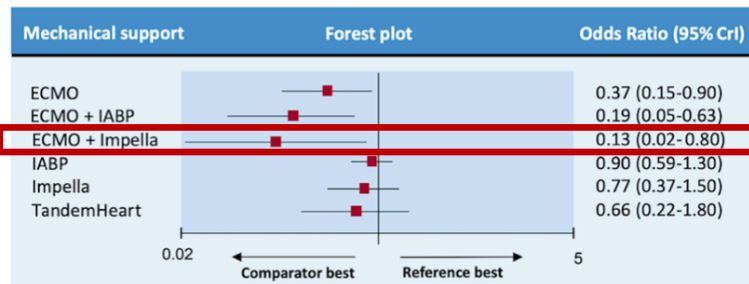
Grandin EW, et al. J Am Coll Cardiol. 2022;79(13):1239-1250.



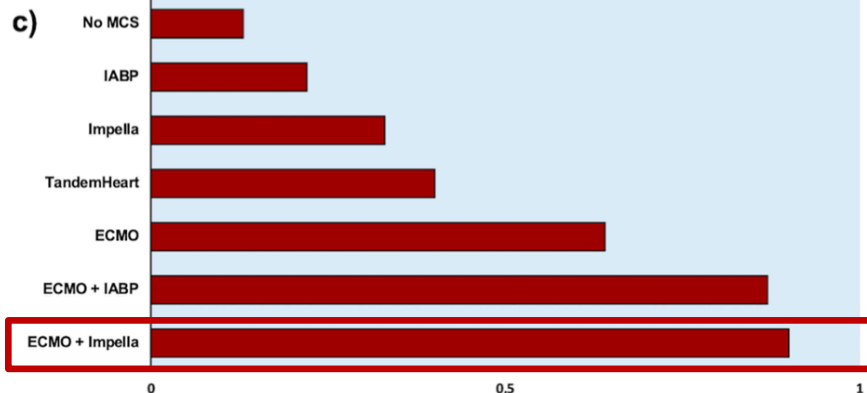
Results for 30-day mortality



b)



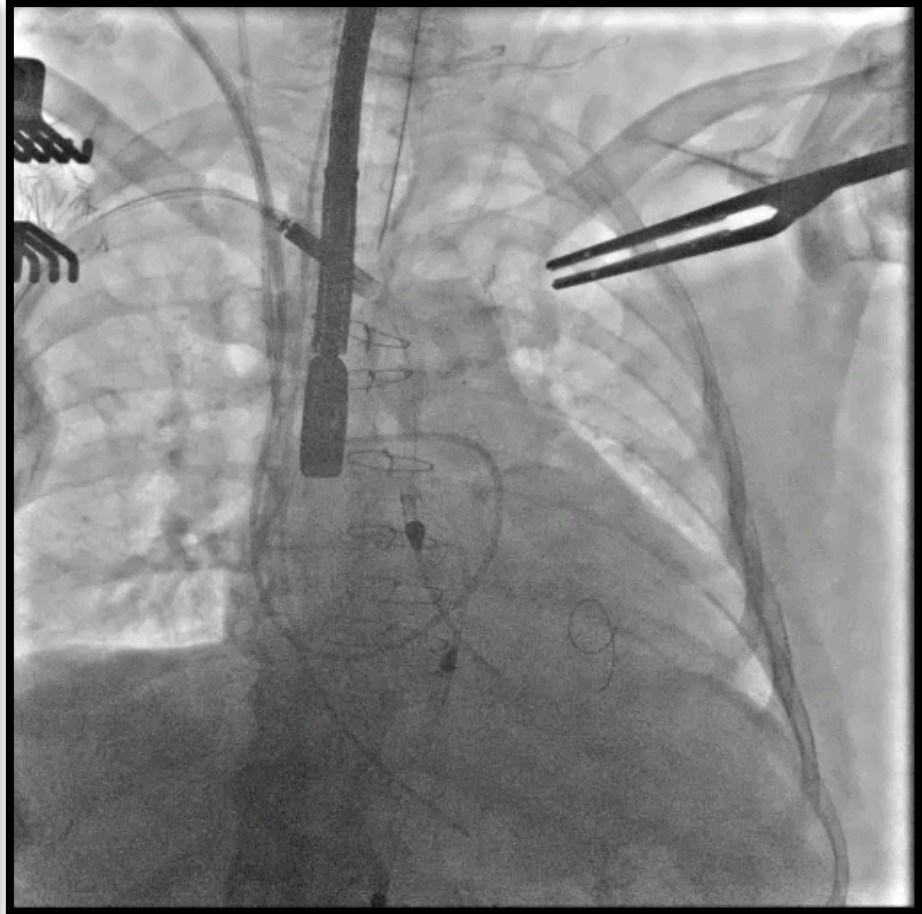
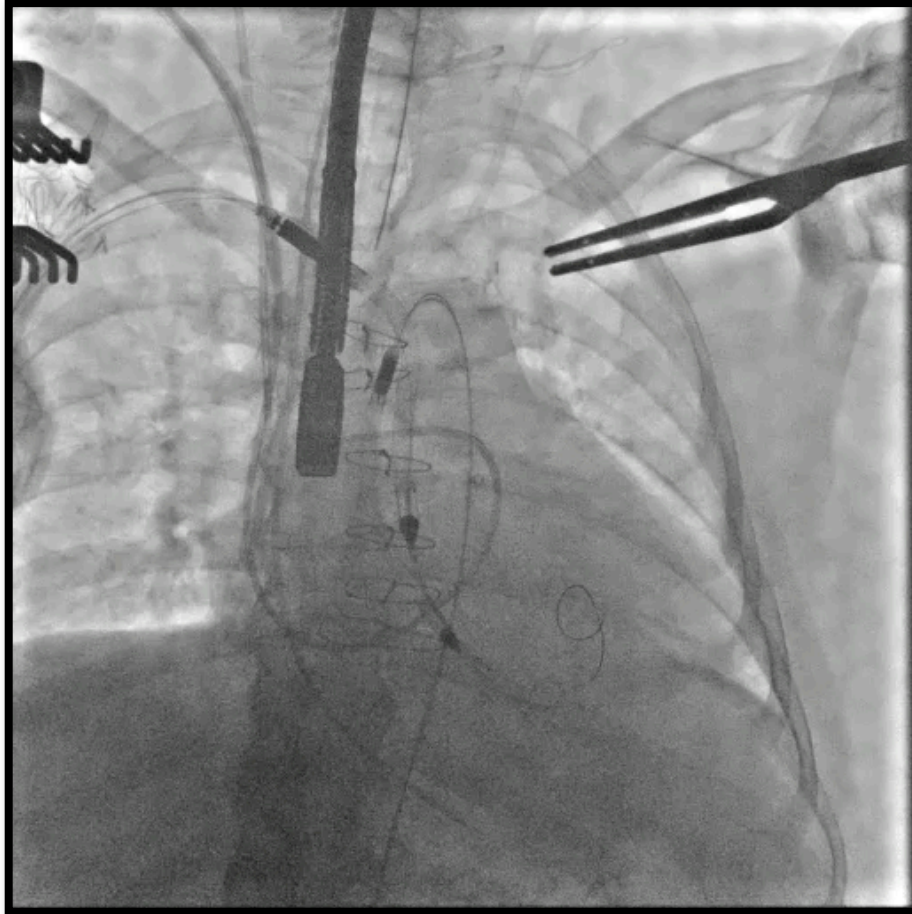
Treatment ranking



Mechanical circulatory support in patients with cardiogenic shock not secondary to cardiectomy: a network meta-analysis



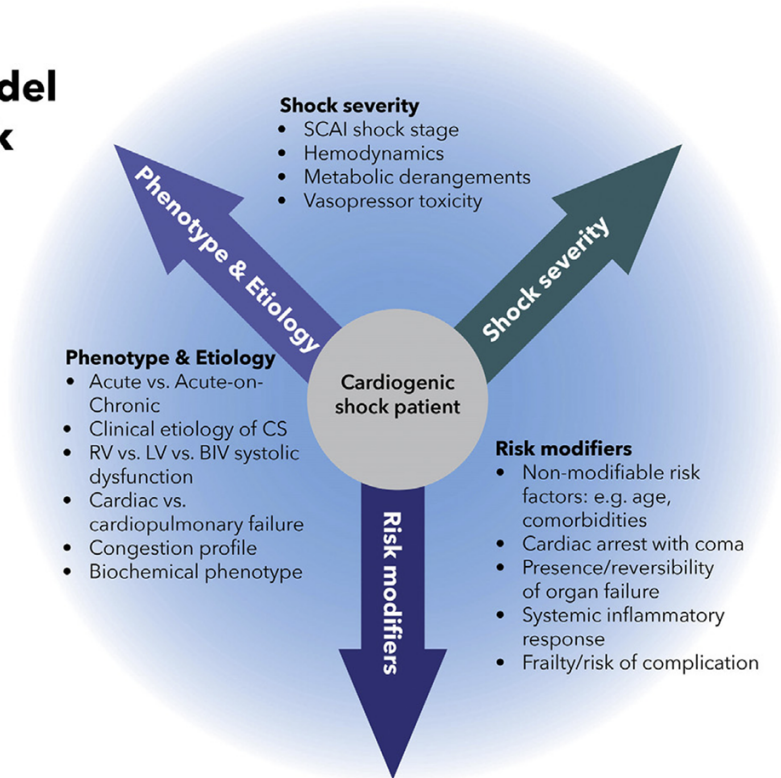
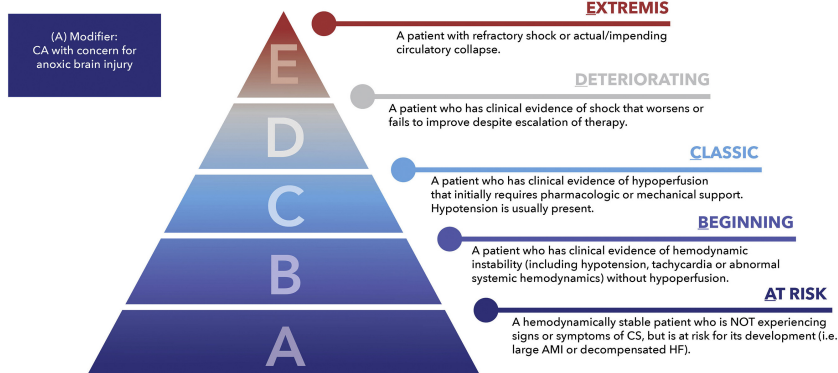
The HSM Shock Team approach: IMPELLA CP→5.0



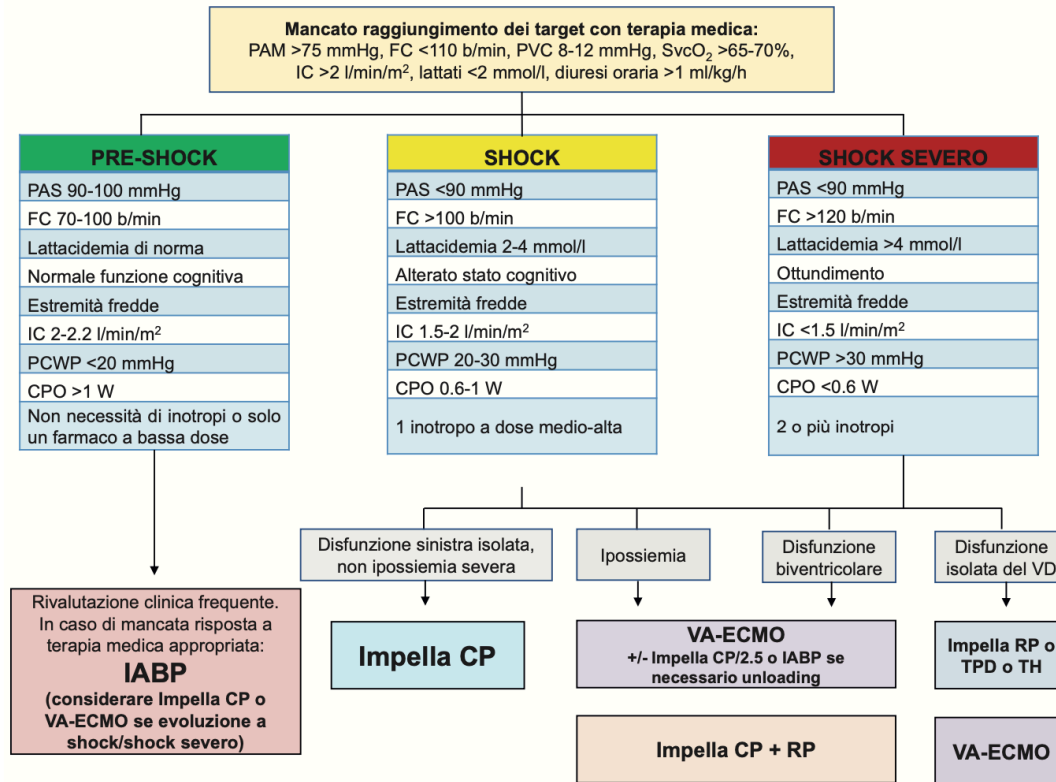
The HSM Shock Team approach



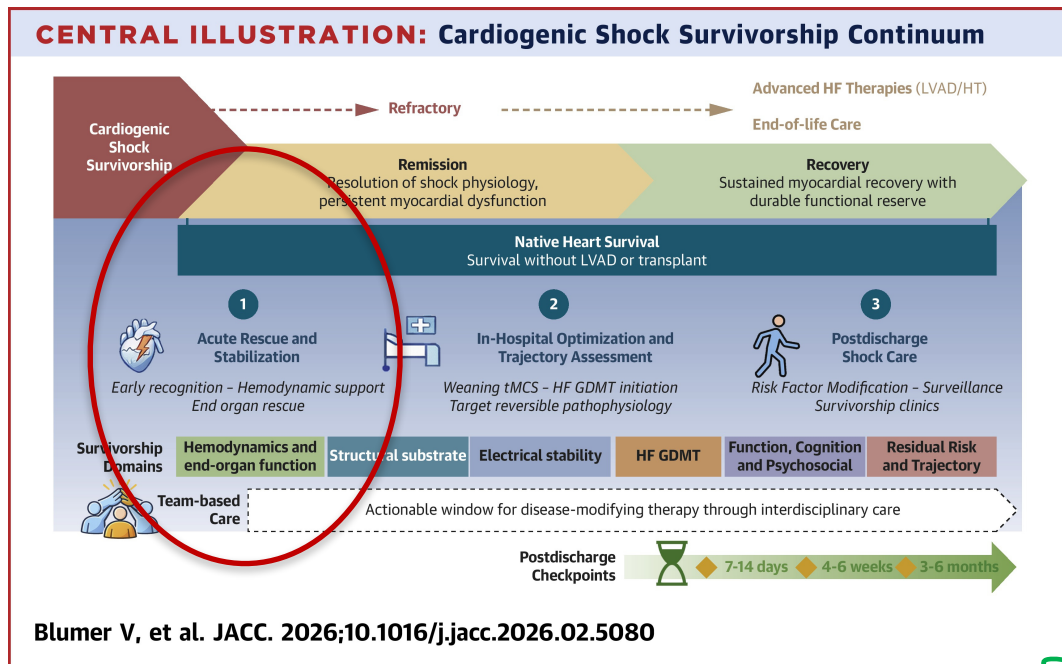
Proposed 3-axis model of cardiogenic shock evaluation and prognostication



The HSM protocol



Inotropes and vasopressors as a bridge to interventions and strategies that improve outcomes



roberta.dellabona@gmail.com

Grazie per l'attenzione!

