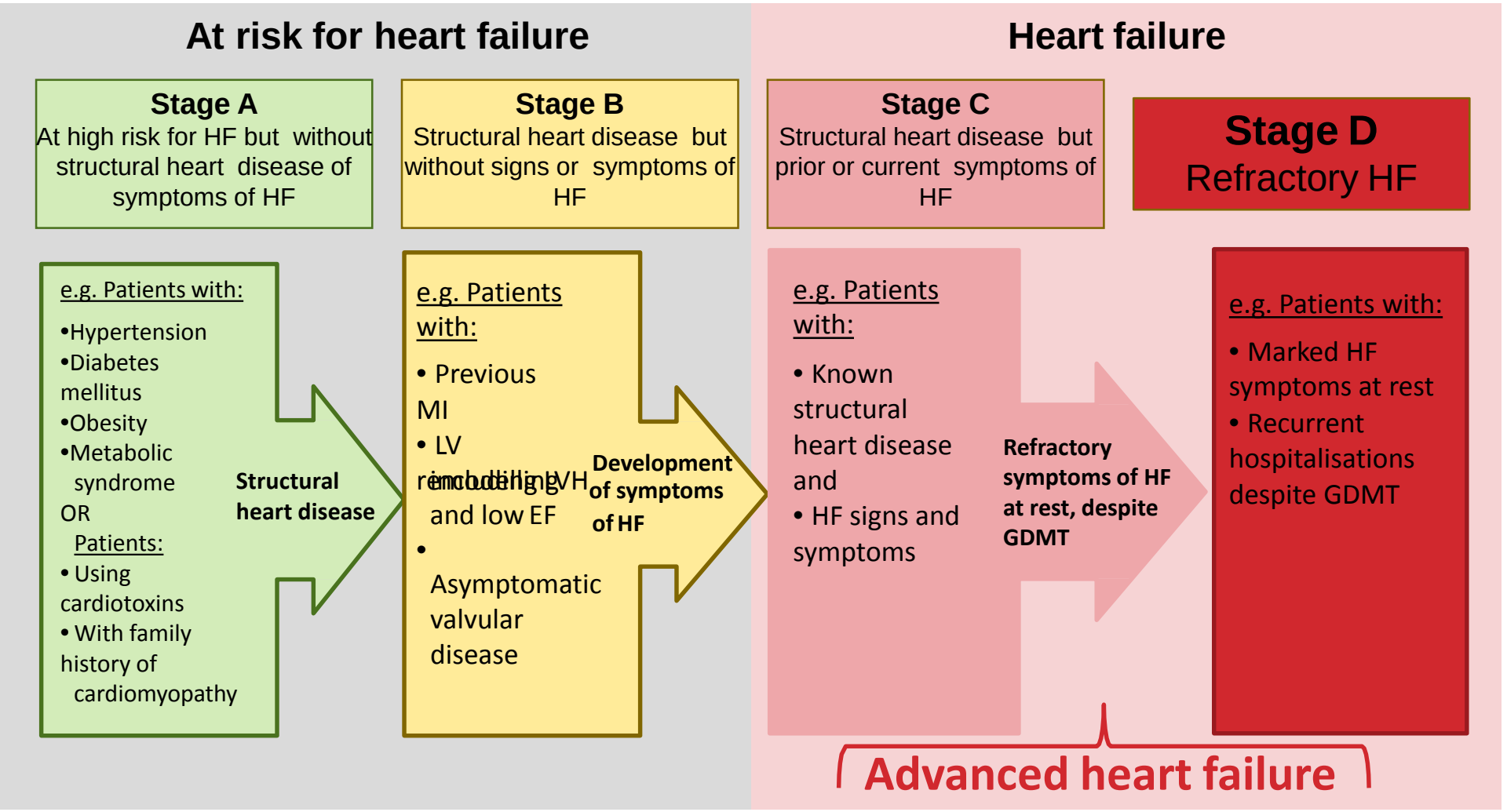
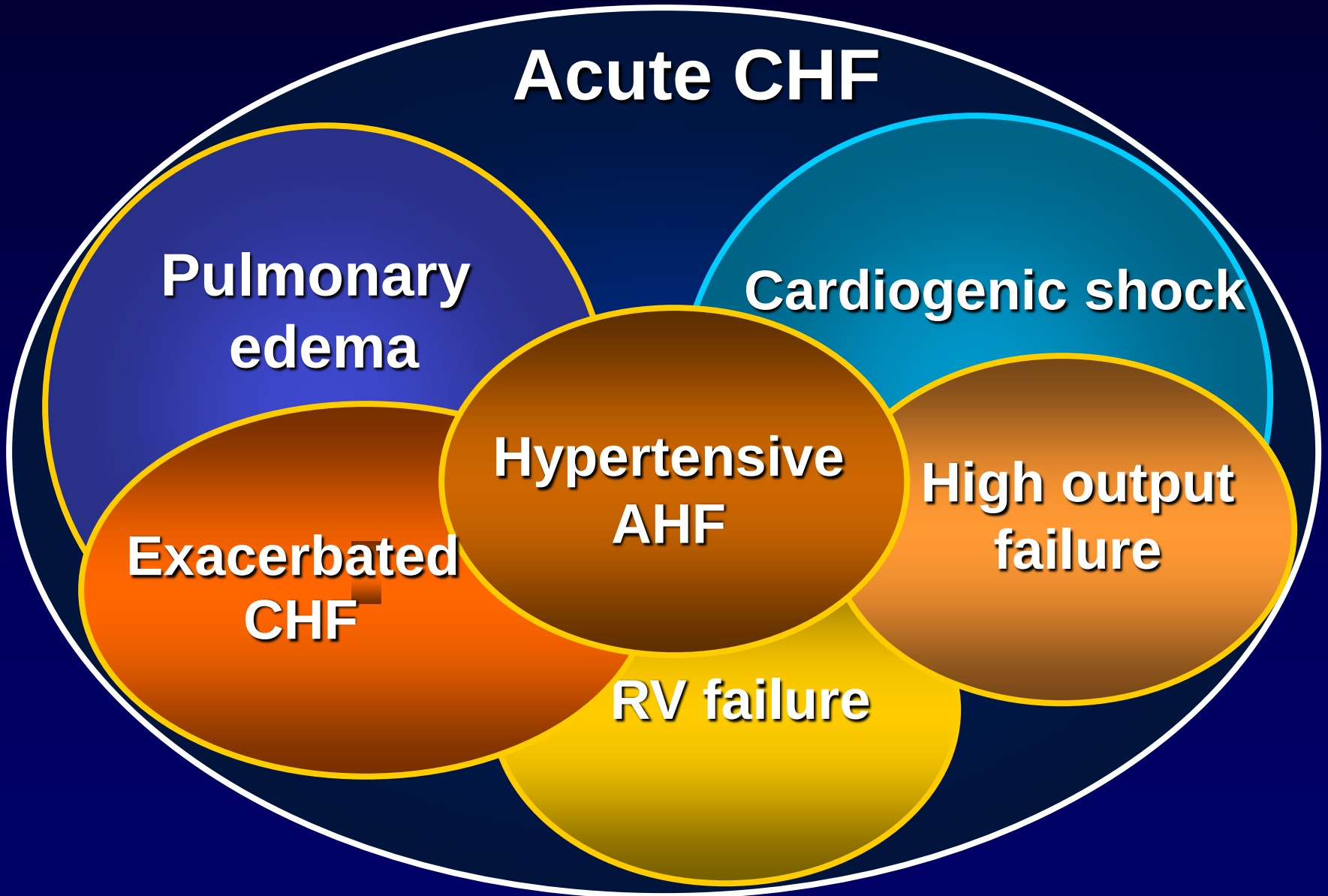
Stages and phenotypes of heart failure

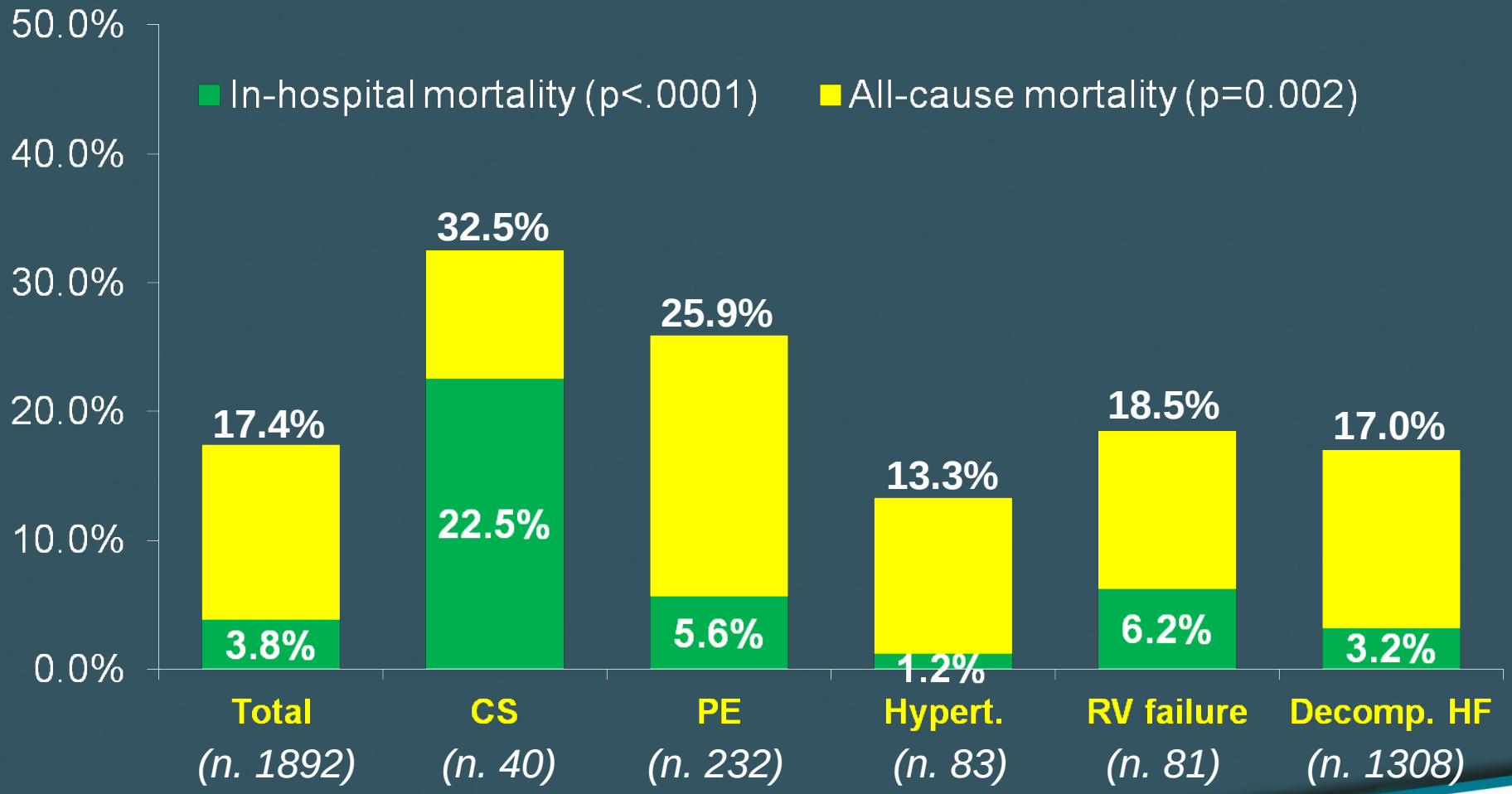


Yancy CW, et al. *J Am Coll Cardiol.* 2013;62:e147–239.

Acute CHF
Diagnosis of different clinical syndromes



Acute HF: All-cause mortality*: Overall and by clinical profile at entry



*median follow-up 356 days [325-366]

CS=Cardiogenic shock; PE=Pulmonary edema; RV=Right ventricular

www.escardio.org

EUROBservational Research Programme
Heart Failure PILOT

EUROPEAN SOCIETY OF CARDIOLOGY®

Demographics and other baseline characteristics of study population who performed 1-year FU

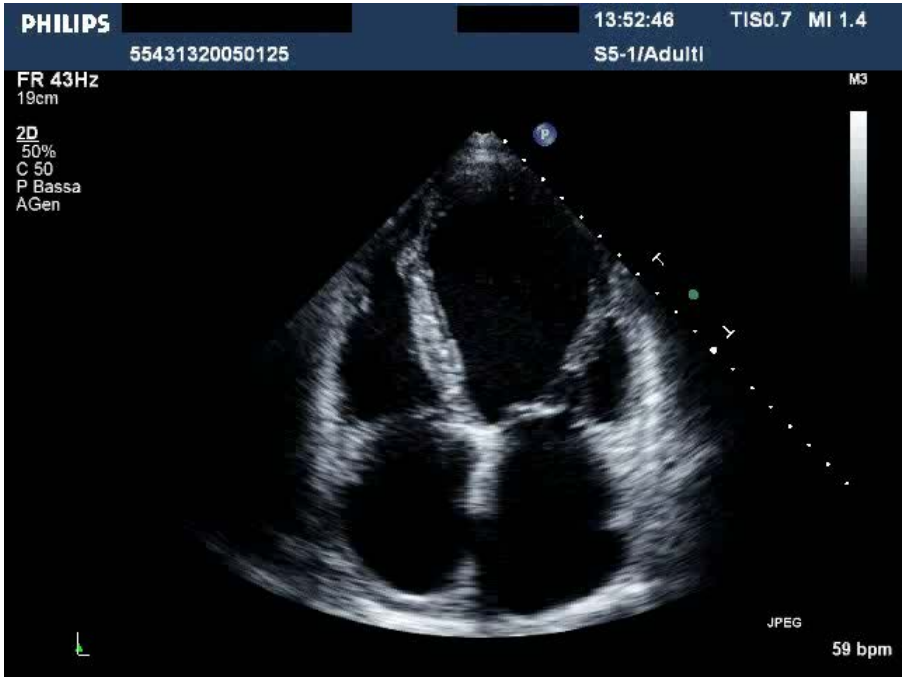
	Hospital n=4449	Outpatients n=7173	P-value
Age (years), mean ± SD Age (years), median [IQR] ≥75 years, %	69.35 ± 12.98 71 [61-79] 38.9	64.89 ± 13.30 66 [57-75] 26.0	<0.0001 <0.0001 <0.0001
Females, %	37.4	28.8	<0.0001
BMI (kg/m2), mean ± SD BMI (kg/m2), median [IQR]	28.67 ± 5.39 28 [25-31]	28.10 ± 5.04 28 [25-31]	<0.0001 <0.0001
SBP (mmHg), mean ± SD SBP (mmHg), median [IQR] SBP ≤110 mmHg, % HR (bpm), mean ± SD HR (bpm), median [IQR] HR ≥70 bpm, %	133.45 ± 28.17 130 [110-150] 25.2 90.82 ± 25.27 88 [73-102] 82.7	123.78 ± 20.73 120 [110-136] 31.0 72.70 ± 15.29 70 [62-80] 55.2	<0.0001 <0.0001 <0.0001 <0.0001 <0.0001 <0.0001
EF (%), mean ± SD (available for 9 198 pts) EF (%), median [IQR] (available for 9 198 pts) EF >45%, % EF >40%, % EF >50%, %	40.42 ± 14.89 39.00 [30-52] 33.4 41.6 25.7	37.21 ± 13.62 35.00 [28-45] 23.2 33.2 16.3	<0.0001 <0.0001 <0.0001 <0.0001 <0.0001

Demographics and other baseline characteristics of study population who performed 1-year FU

	Hospital n=4449	Outpatients n=7173	P-value
NYHA III-IV, %	85.2	25.2	<0.0001
Pulmonary or peripheral congestion, %	84.8	74.4	<0.0001
Sound 3, %	31.8	5.6	<0.0001
Peripheral hypoperfusion/cold, %	14.9	3.4	<0.0001
Mitral regurgitation, %	44.2	25.8	<0.0001
Aortic stenosis, %	8.9	3.9	<0.0001
HF history with previous hospitalisation, % HF history without previous hospitalisation, % New onset HF	30.3 40.6 29.1	41.1 48.9 10.0	<0.0001
HF diagnosis >12 months, %	54.8	64.2	<0.0001
Ischemic heart disease, %	53.8	43.1	<0.0001
Atrial fibrillation, %	44.0	37.7	<0.0001
Diabetes mellitus, %	39.0	31.9	<0.0001
PAD, %	13.7	12.4	0.04

Demographics and other baseline characteristics of study population who performed 1-year FU

	Hospital n=4449	Outpatients n=7173	P-value
Hypertension, %	65.6	58.3	<0.0001
COPD, %	20.1	13.9	<0.0001
Sleep apnea, %	3.2	5.3	<0.0001
Prior stroke/TIA, %	12.5	9.5	<0.0001
Renal dysfunction, %	25.3	18.4	<0.0001
Hepatic dysfunction, %	7.7	3.4	<0.0001
Depression, %	7.4	7.7	0.65
PM, %	6.4	5.8	0.28


PHILIPS
13:52:46 TIS0.7 MI 1.4
55431320050125
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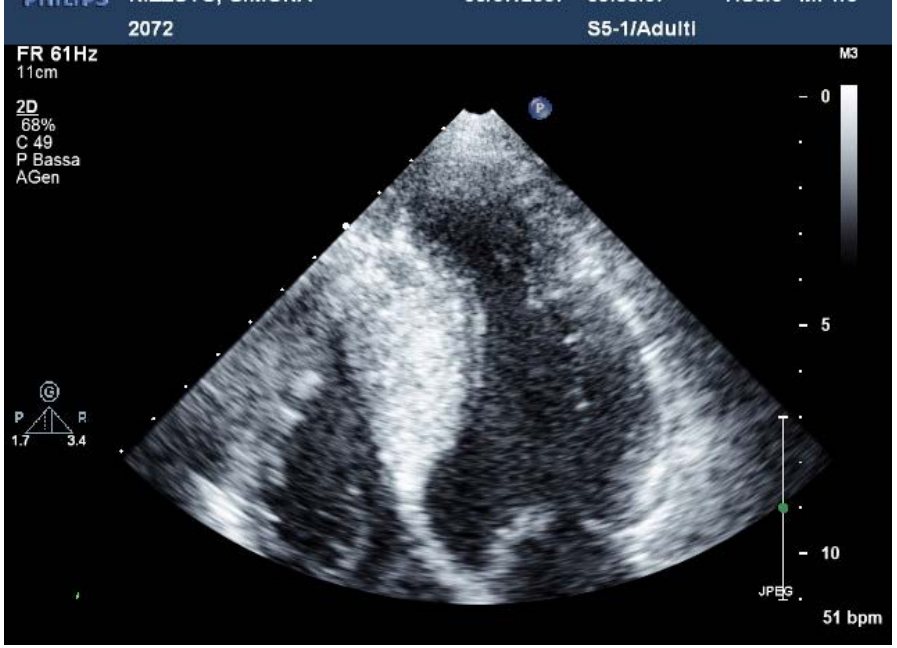
FR 43Hz
19cm
2D
50%
C 50
P Bassa
AGen
M3
JPEG
59 bpm


2072
S5-1/Adulti
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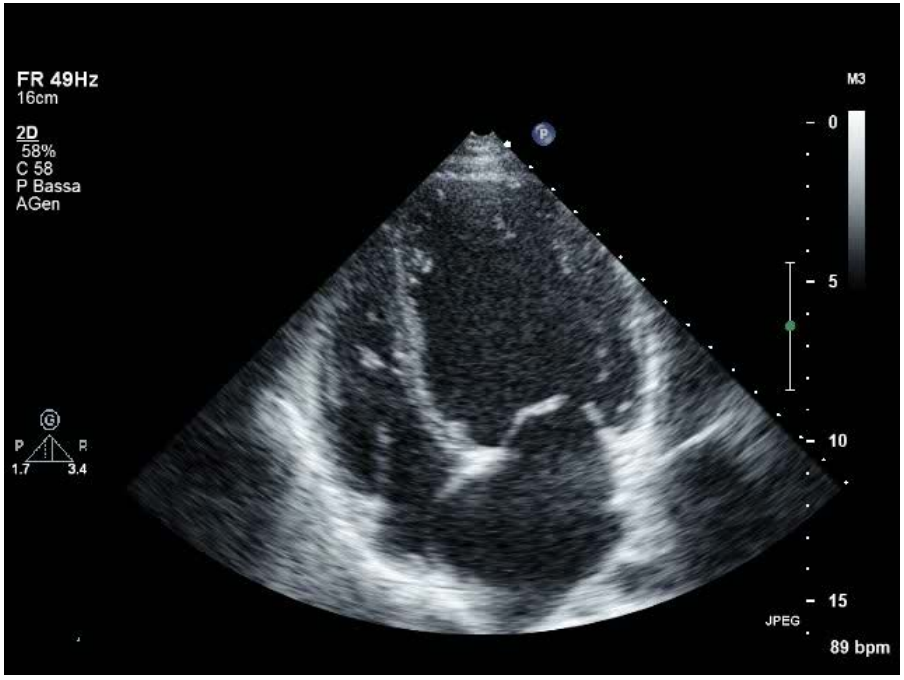
C 49
P Bassa
AGen
M3
0
5
10
1.7
3.4
JPEG
51 bpm


FR 49Hz
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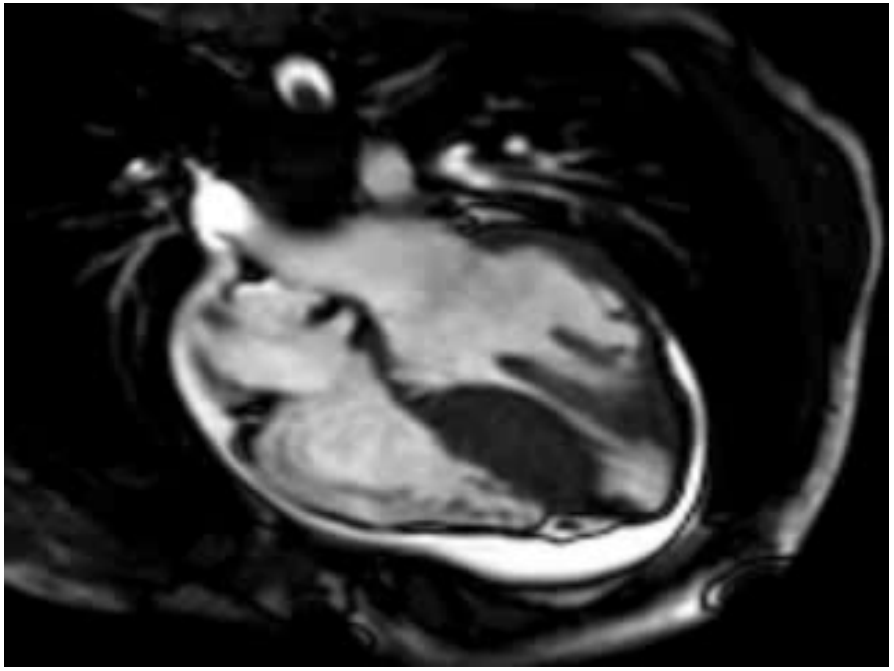
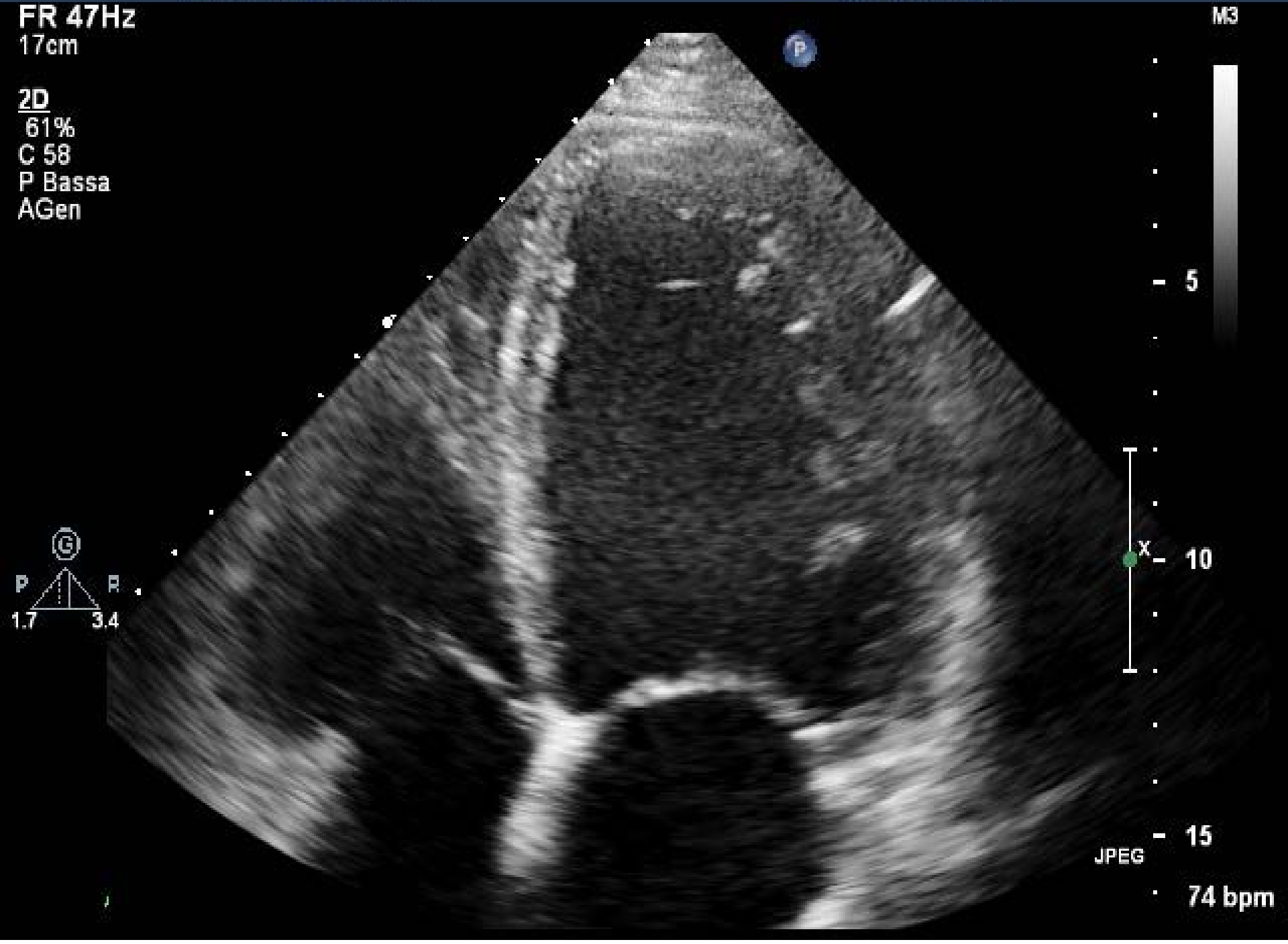
2D
58%
C 58
P Bassa
AGen
M3
0
5
10
15
1.7
3.4
JPEG
89 bpm



Scenario 1

23 aa; recente virosi; shock; PA 85/72 mmHg; FC 130 min; RS; Creatinina 1.3 mg/dl; lattati 5 mmmol/l; GOT/GPT 500/650 U/l; BNP 2500 pg/ml; TnI 4.2 ng/ml; rapida risposta a DBT


FR 47Hz
17cm
2D
61%
C 58
P Bassa
AGen
M3
5
10
15
74 bpm
JPEG
1.7
3.4

Scenario 2b

23 aa; recente virosi; shock; PA 85/70 mmHg; FC 130 min; RS; Creatinina 1.3 mg/dl; lattati 5 mmmol/l; GOT/GPT 500/650 U/l; BNP 2500 pg/ml; TnI 4.2 ng/ml; rapida risposta a DBT;

per FA parossistica-TVns, Amiodarone ev;

rapido peggioramento EGA con pO2 58 mmHg; CPAP; deterioramento IOT-ECMO;

BEM: miocardite;

in VI gg FEVsin 40%; stop ECMO in VII e inizio svezzamento inotropi;

inizia terapia convenzionale; RM: aree LE ++;

1 mese dopo; NYHA I, FEVsin 50%

Patient Selection and Treatment

ADEQUATE PERFUSION	CONGESTION --	CONGESTION +
+	A *dry-warm (N=123)*	B *wet-warm (N=222)*
–	L *dry-cold (N=16)*	C *wet-cold (N=91)*

Congestion at Rest

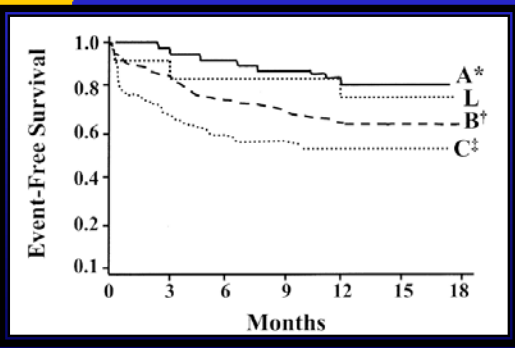
Low Perfusion at Rest	No	Yes
No	**Warm & Dry** PCWP normal CI normal (compensated) RARE	**Warm & Wet** PCWP elevated CI normal FAIRLY COMMON
Yes	**Cold & Dry** PCWP low/normal CI decreased RARE	**Cold & Wet** PCWP elevated CI decreased MOST PATIENTS Normal SVR High SVR

Natriuretic Peptides
Nesiritide

or

Vasodilators
Nitroprusside
Nitroglycerin

Inotropic Drugs
Dobutamine
Milrinone



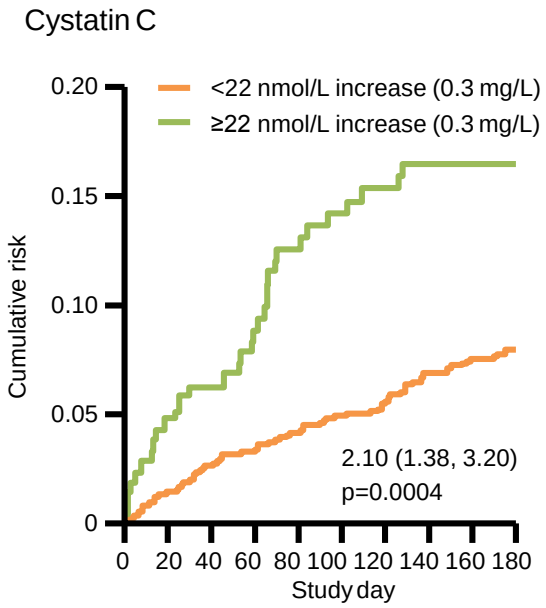
Fonarow GC. *Rev Cardiovasc Med.* 2001;2(suppl 2):S7–S12.

Management of Acute Heart Failure

JJ McMurray EHJ 2012

Prognostic value of 48 h end-organ damage 180-days mortality - RELAX-AHF

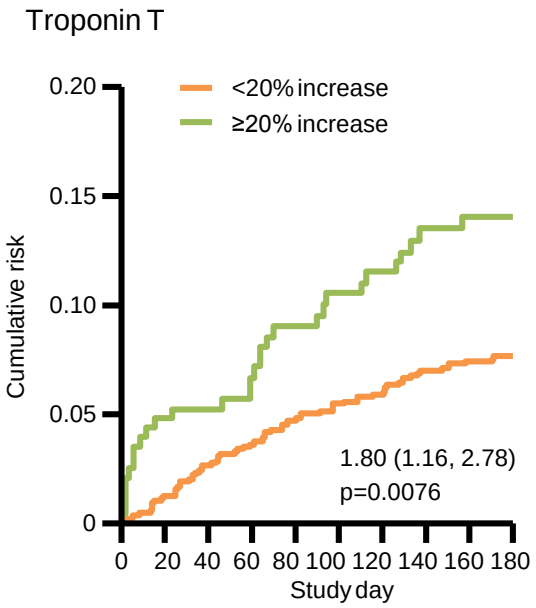
Renal



Number at risk:

<22nmol/L Increase	869	851	841	834	826	819	815	804	798	687
≥22nmol/L Increase	212	202	199	194	187	184	181	179	179	160

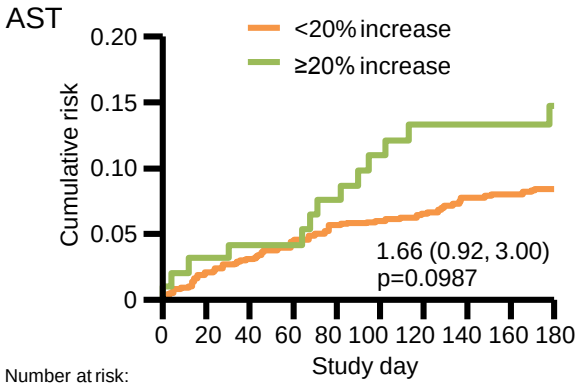
Cardiac



Number at risk:

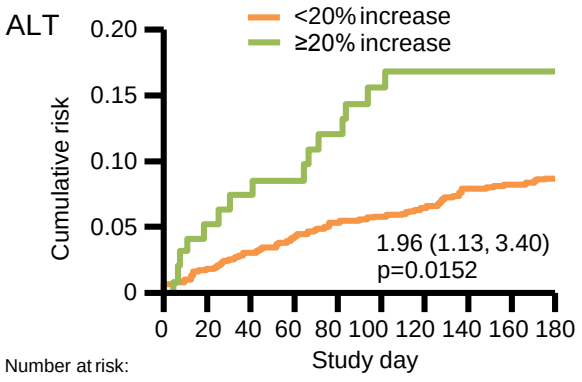
<20% Increase	825	810	799	790	782	775	771	762	759	654
≥ 20% Increase	231	219	218	216	210	207	204	200	199	174

Hepatic



Number at risk:

<20% Increase	906	882	872	861	852	845	841	830	827	718
≥ 20% Increase	99	96	95	95	92	89	87	87	86	71

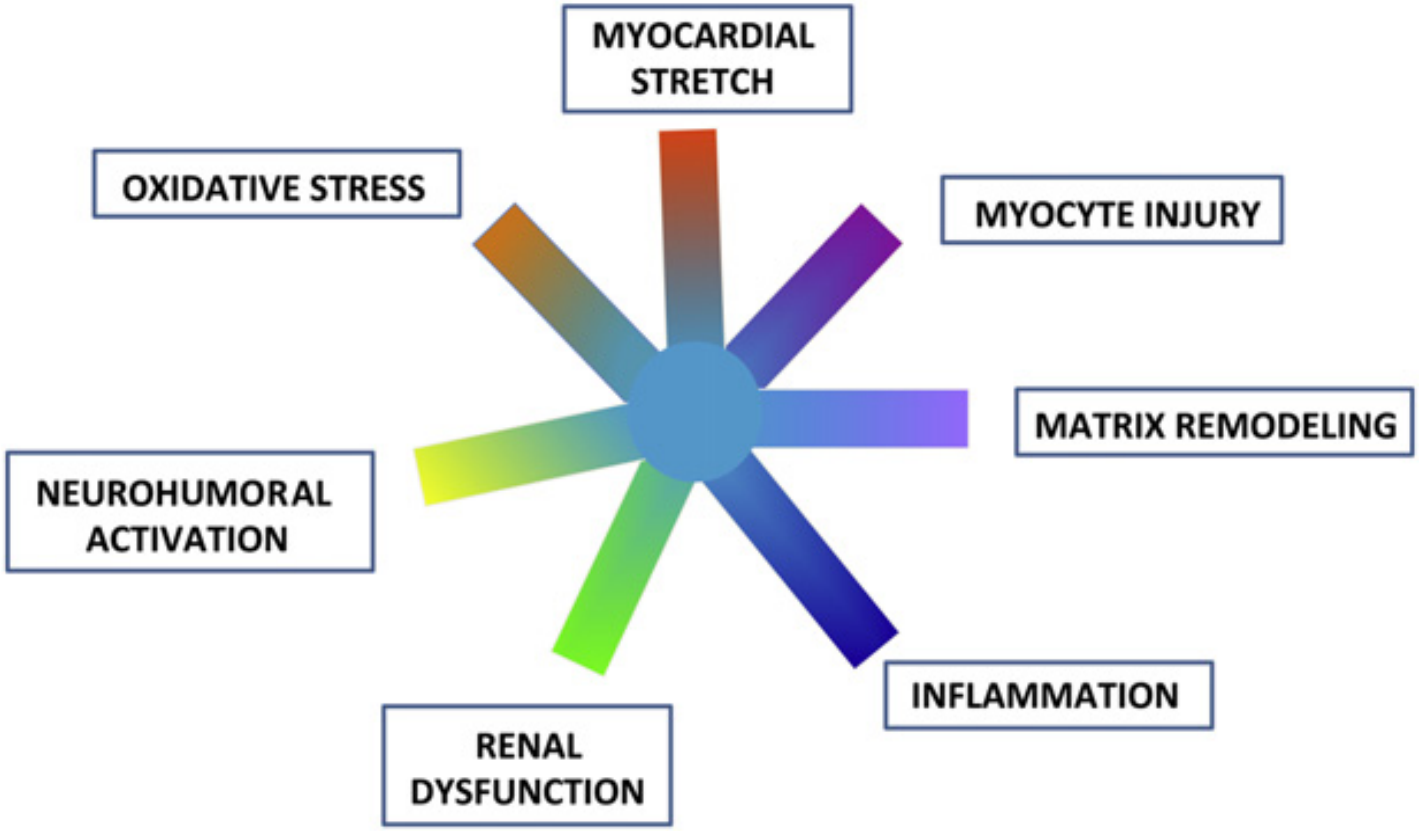


Number at risk:

<20% Increase	970	946	935	924	914	907	901	889	885	767
≥ 20% Increase	99	94	92	91	88	85	84	84	83	69

Metra M, et al. J Am Coll Cardiol 2013;61:196–206

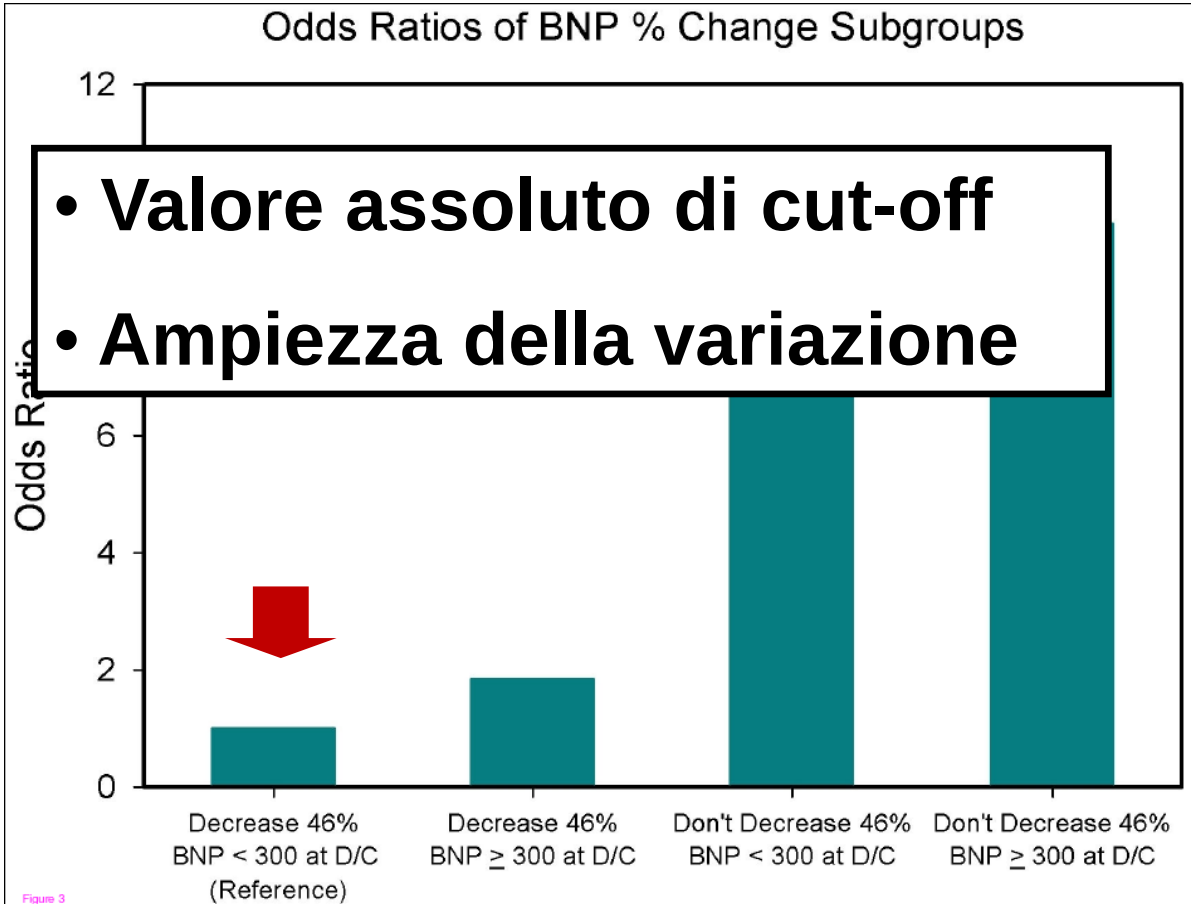
Multimarker Strategies



..but most cases are managed with "first line" data, i.e creatinine, Na, Hb, pH, lactate

BNP ingresso-dimissione (deltaBNP)

N° 287 – BNP mediano 822



- **Valore assoluto di cut-off**
- **Ampiezza della variazione**

I pazienti con valori di deltaBNP < 46% e BNP in dimissione > 300 pg/mL hanno il più alto rischio di eventi

Di Somma S. 2010 Critical Care 14 R116 Italian RED

RCT in ACUTE HF

Class	Drug	Trial	Year	Results
PDE-III inhibitors	Milrinone	OPTIME-CHF[1]	2002	n.s. mortality, ↑ side effects
Ca^{2+}-sensitizers	Levosimendan	SURVIVE,[2] REVIVE[3]	2007	n.s. outcomes (vs dobutamine), ↑ side effects (vs placebo)
Endothelin-antagonists	Tezosentan	VERITAS[4]	2007	n.s. dyspnea and outcomes
Vasopressin antagonists	Tolvaptan	EVEREST[5]	2007	Slight ↓dyspnea, n.s. outcomes
Adenosine A1 receptor antagonist	Rolofylline	PROTECT[6]	2010	Slight ↓dyspnea, n.s. outcomes; ↑ seizures
Natriuretic peptides	Nesiritde	ASCEND-HF[7]	2011	Slight ↓dyspnea, n.s. outcomes

n.s.=non significant;
PDE=phosphodiesterase

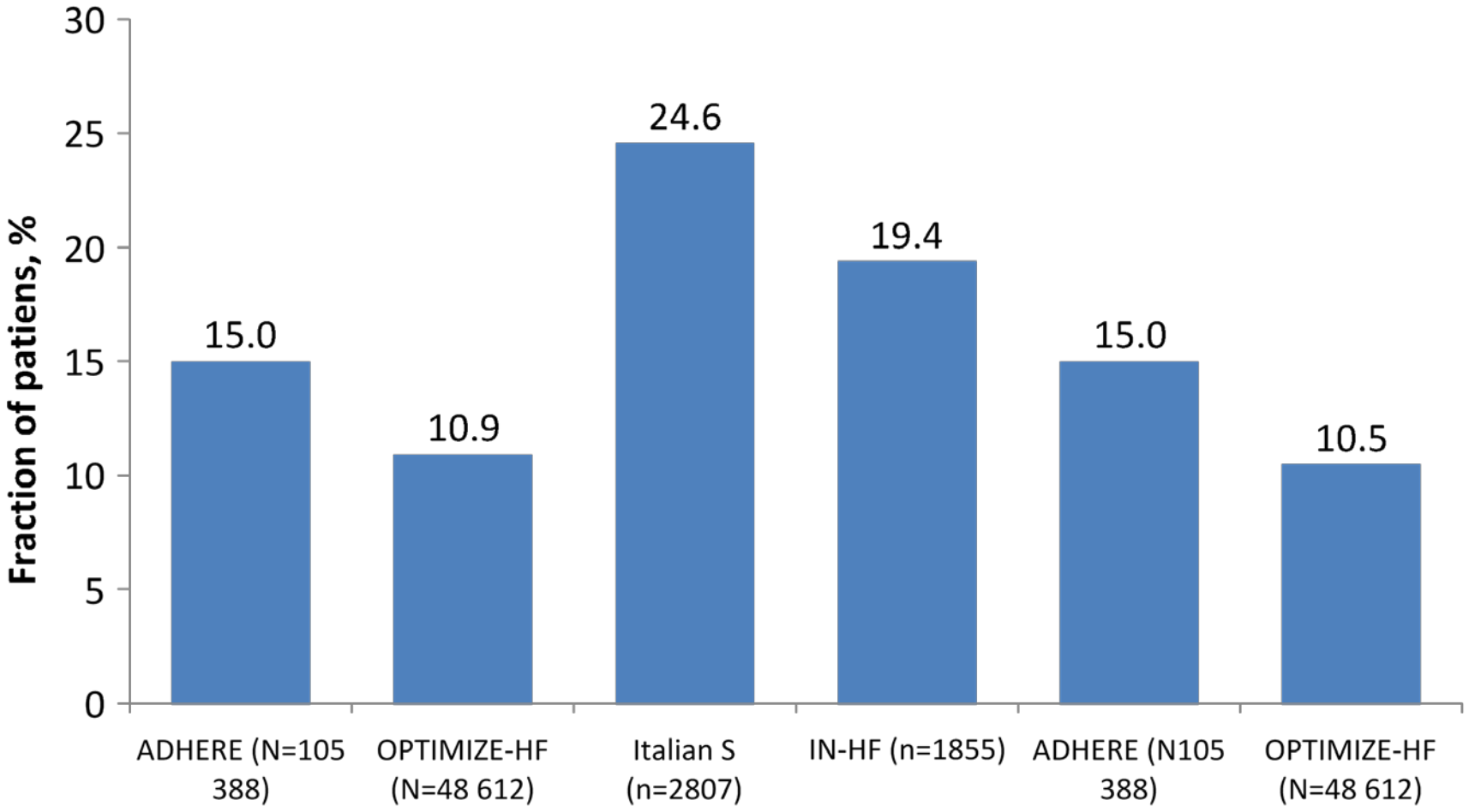
1. Cuffe et al. JAMA 2002;287:1541–7;
2. Mebazaa et al. JAMA 2007;297:1883–91;
3. Packer et al. J Am Coll Cardiol Heart Fail 2013;1:103–11;
4. McMurray et al. JAMA 2007;298:2009–19;
5. Konstam et al. JAMA 2007;297:1319–31;
6. Massie et al. N Engl J Med 2010;363:1419–28;
7. O'Connor et al. N Engl J Med 2011;365:32–43

European Heart Journal (2012) 33, 1787–1847
doi:10.1093/eurheartj/ehs104

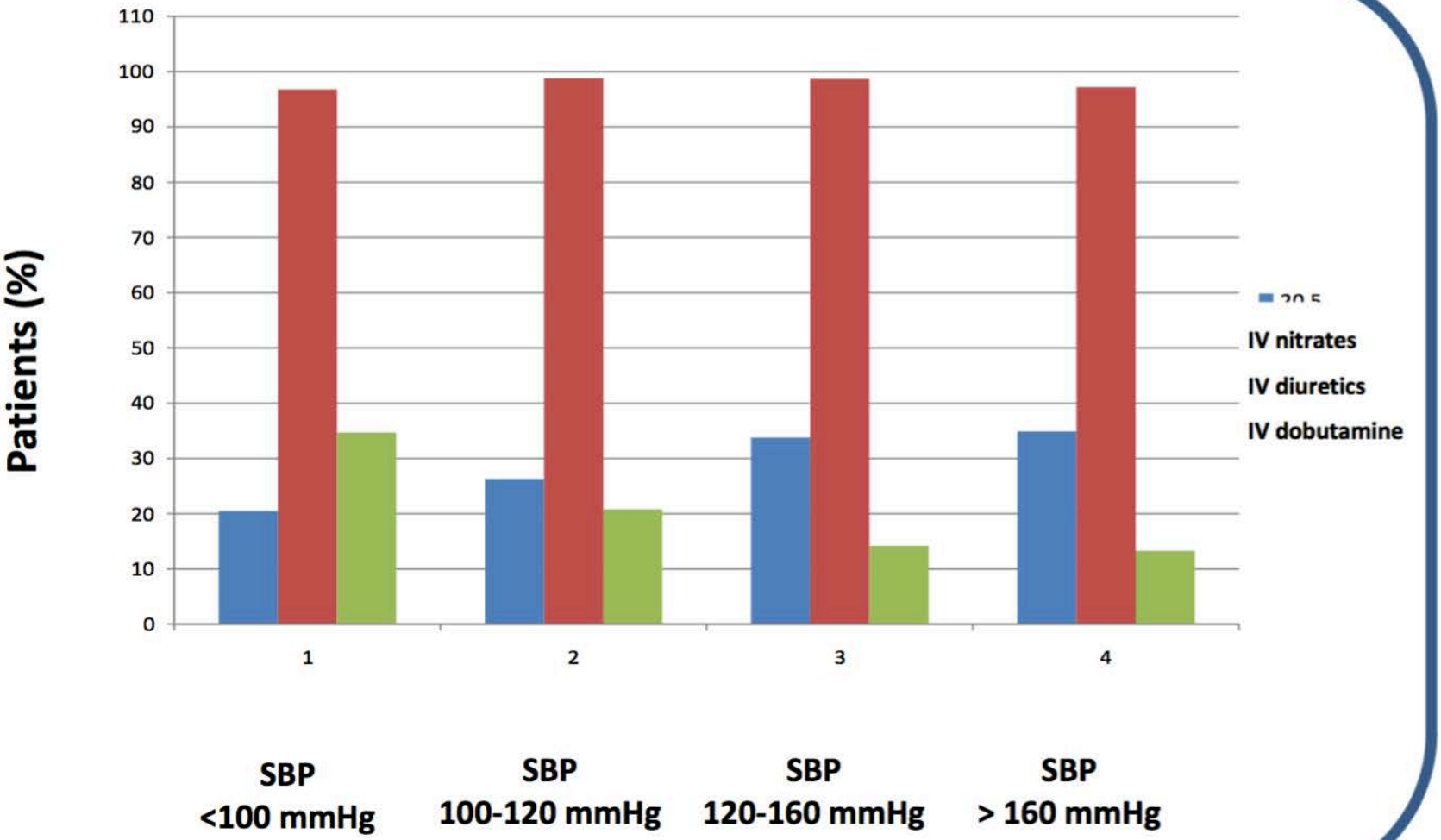
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

Inotropic agents are NOT recommended unless the patient is hypotensive (systolic blood pressure <85 mmHg), hypoperfused, or shocked because of safety concerns (atrial and ventricular arrhythmias, myocardial ischaemia, and death).	III	C	–
Patients with hypotension, hypoperfusion or shock			
Electrical cardioversion is recommended if an atrial or ventricular arrhythmia is thought to be contributing to the patient's haemodynamic compromise in order to restore sinus rhythm and improve the patient's clinical condition.	I	C	–
An i.v. infusion of an inotrope (e.g. dobutamine) should be considered in patients with hypotension (systolic blood pressure <85 mmHg) and/or hypoperfusion to increase cardiac output, increase blood pressure, and improve peripheral perfusion. The ECG should be monitored continuously because inotropic agents can cause arrhythmias and myocardial ischaemia.	IIa	C	–
Short-term mechanical circulatory support should be considered (as a 'bridge to recovery') in patients remaining severely hypoperfused despite inotropic therapy and with a potentially reversible cause (e.g. viral myocarditis) or a potentially surgically correctable cause (e.g. acute interventricular septal rupture).	IIa	C	–
An i.v. infusion of levosimendan (or a phosphodiesterase inhibitor) may be considered to reverse the effect of beta-blockade if beta-blockade is thought to be contributing to hypoperfusion. The ECG should be monitored continuously because inotropic agents can cause arrhythmias and myocardial ischaemia, and, as these agents are also vasodilators, blood pressure should be monitored carefully.	IIb	C	–
A vasopressor (e.g. dopamine or norepinephrine) may be considered in patients who have cardiogenic shock, despite treatment with an inotrope, to increase blood pressure and vital organ perfusion. The ECG should be monitored as these agents can cause arrhythmias and/or myocardial ischaemia. Intra-arterial blood pressure measurement should be considered.	IIb	C	–
Short-term mechanical circulatory support may be considered (as a 'bridge to decision') in patients deteriorating rapidly before a full diagnostic and clinical evaluation can be made.	IIb	C	–

Pts receiving i.v. inotropic agents: registry data



ALARM-HF: In-Hospital Treatment of Acute Pulmonary Edema Patients



Parissis JT, et al. Eur J Heart Fail 2010; 12:1193–1202

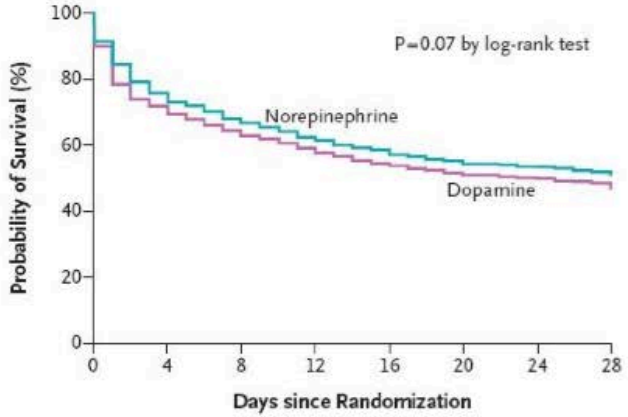
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 4, 2010 VOL. 362 NO. 9

Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chochrad, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators*

1679 pts in total, 280 Cardiogenic shock (16.7%)



No. at Risk								
Norepinephrine	821	617	553	504	467	432	412	394
Dopamine	858	611	546	494	452	426	407	386

Figure 2. Kaplan–Meier Curves for 28-Day Survival in the Intention-to-Treat Population.

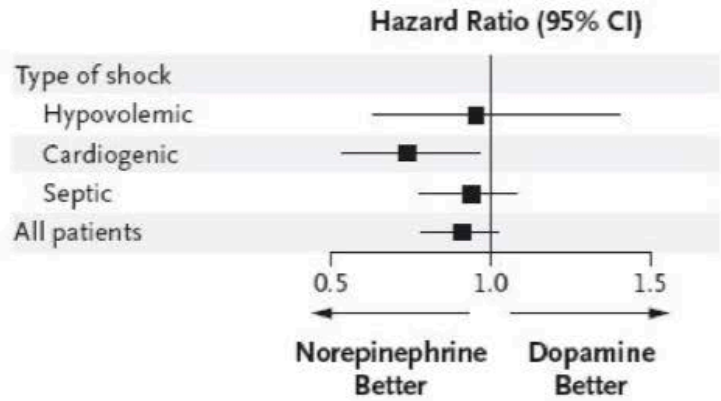
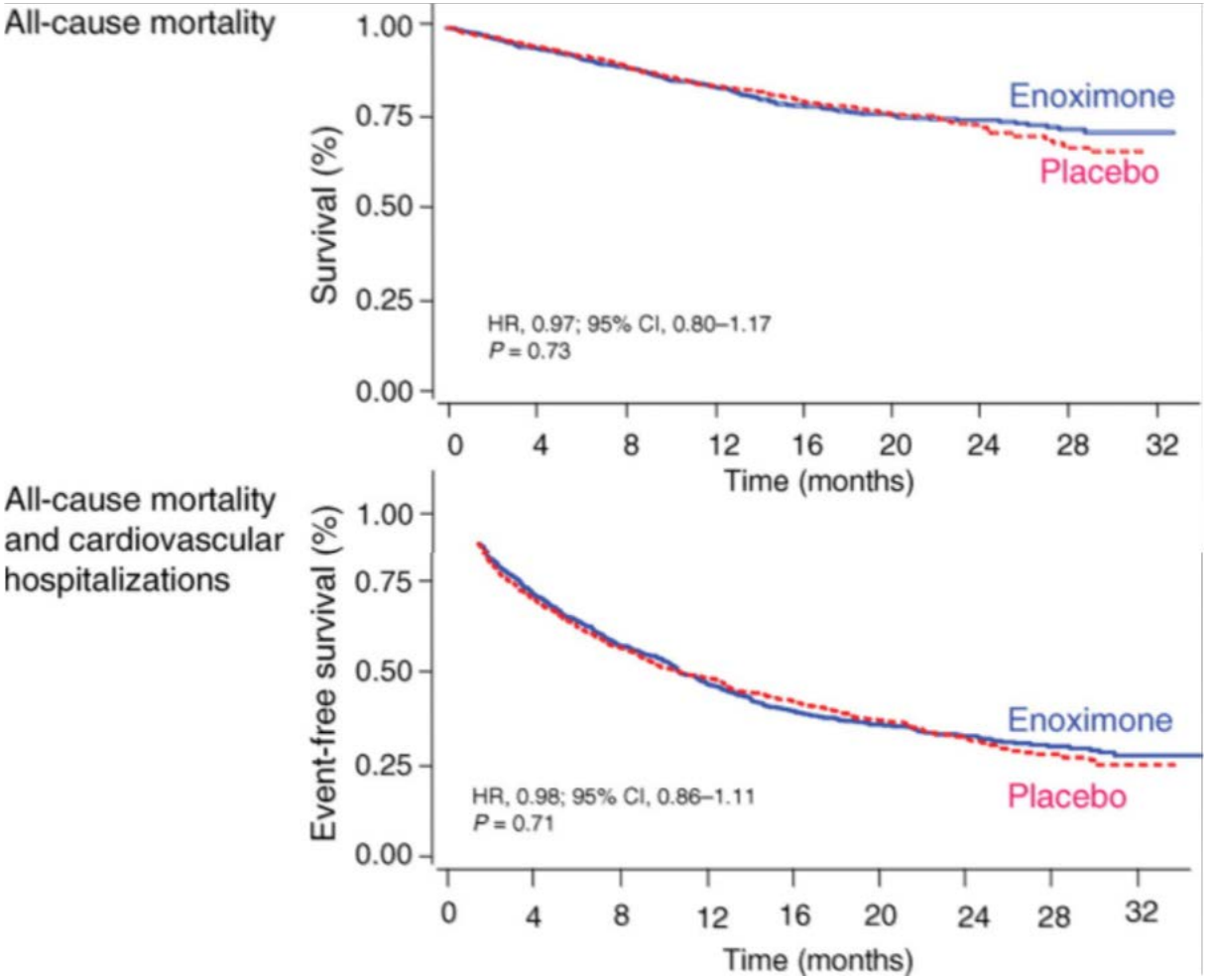


Figure 3. Forest Plot for Predefined Subgroup Analysis According to Type of Shock.

Kaplan–Meier estimates of the time to the safety endpoint of death (up) and to the primary endpoint of death or cardiovascular hospitalization (bottom).



Metra M et al. Eur Heart J 2009;30:3015-3026

Levosimendan vs Dobutamine for Patients With Acute Decompensated Heart Failure

The SURVIVE Randomized Trial

Alexandre Mebazaa,

JAMA. 2007;297:1883-1891

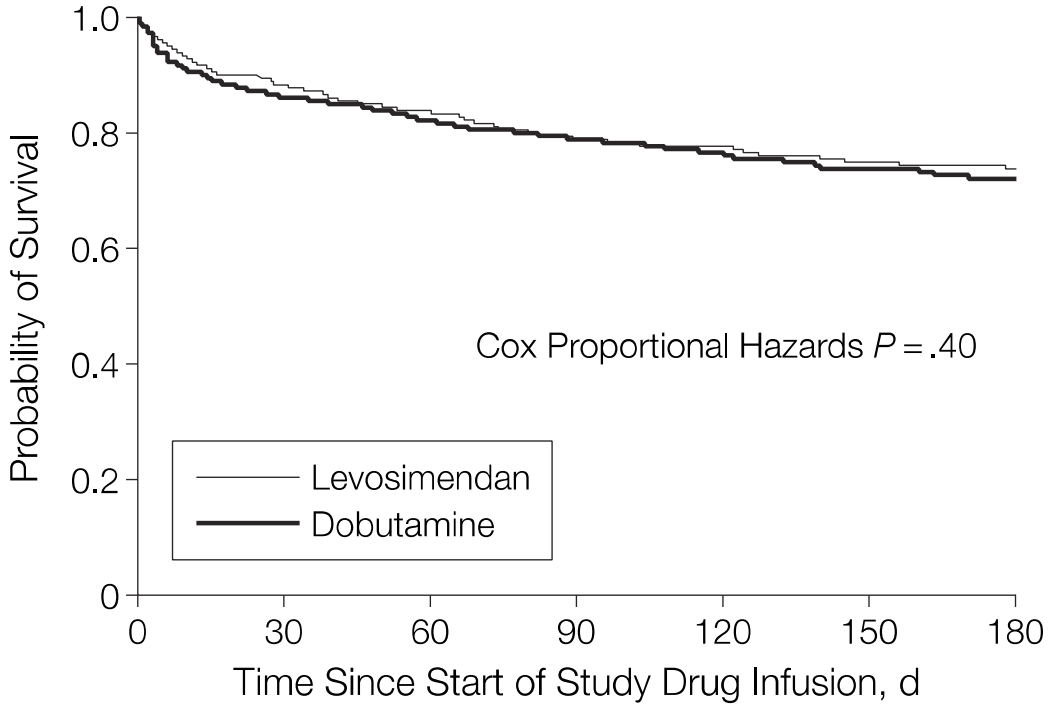
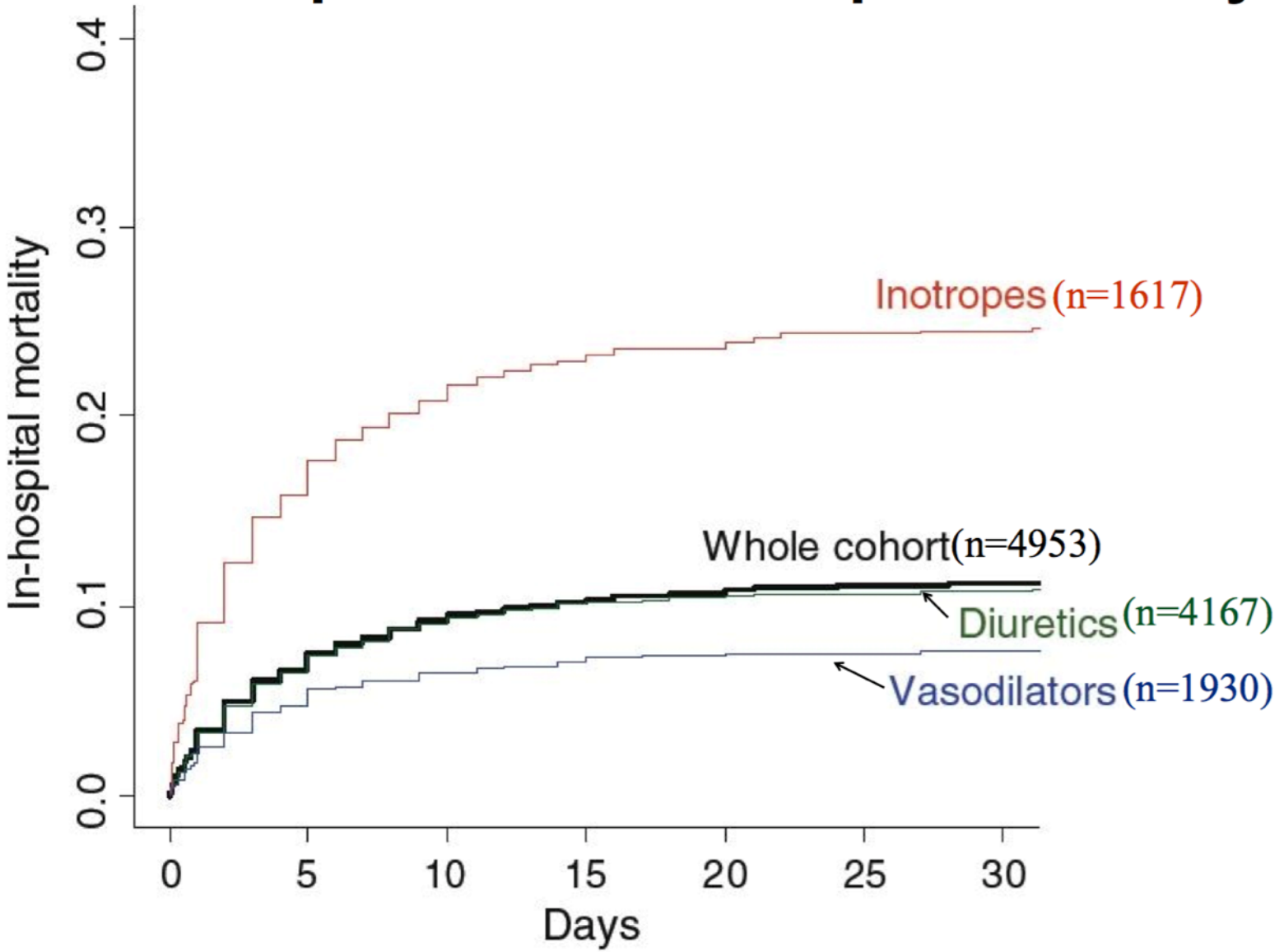


Table 2. Primary, Secondary, and Post Hoc All-Cause Mortality End Points*

	No. (%) of Patients†			
	Levosimendan (n = 664)	Dobutamine (n = 663)	HR (95% CI)	*P* Value
Primary end point				
All-cause mortality at 180 d	173 (26)	185 (28)	0.91 (0.74-1.13)	.40‡
Secondary end point				
All-cause mortality at 31 d	79 (12)	91 (14)	0.85 (0.63-1.15)	.29‡
Mean change in BNP at 24 h from baseline, pg/mL	(n = 628) −631	(n = 611) −397		<.001§
Mean No. of days alive and out of the hospital during 180 d	120.2	116.6		.30‖
Dyspnea assessed at 24 h; ≥mild improvement¶	544 (82)	550 (83)		.96‖
Global assessment at 24 h; ≥mild improvement¶	531 (80)	537 (81)		>.99
Cardiovascular mortality during 180 d	157 (24)	171 (26)	0.90 (0.72-1.12)	.33‡
Post hoc all-cause mortality				
5 d	29 (4)	40 (6)	0.72 (0.44-1.16)	.17‡
14 d	59 (9)	69 (10)	0.84 (0.59-1.19)	.33‡
90 d	139 (21)	138 (21)	0.99 (0.78-1.25)	.91‡

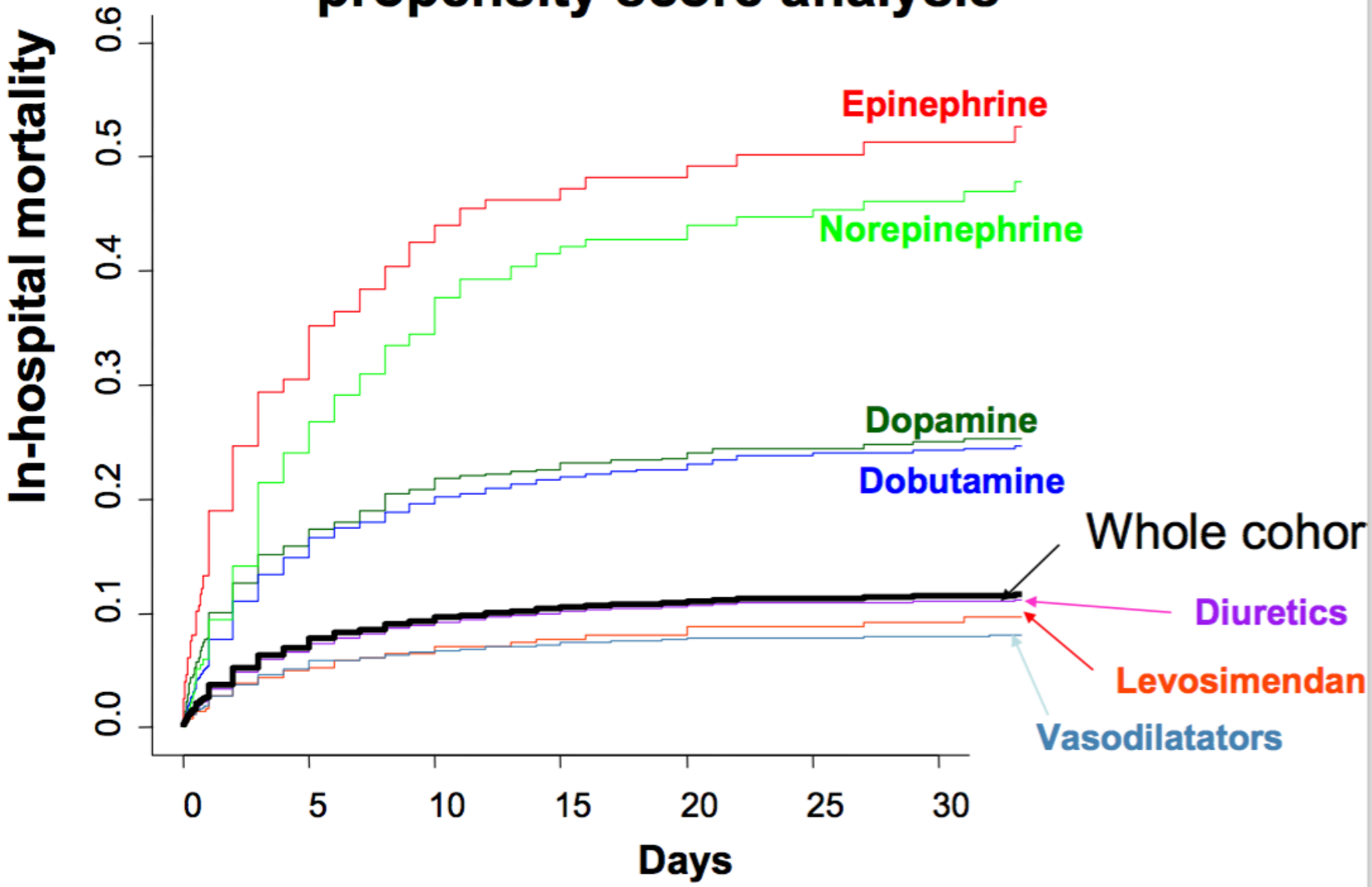
IMPROVING LONG-TERM SURVIVAL BY SHORT-TERM INOTROPIC THERAPY IN PTS WITH ADVANCED HF….TOO HARD ENDPOINT??

Effect of IV drugs given during the first 48 hours in AHF patients on in-hospital mortality



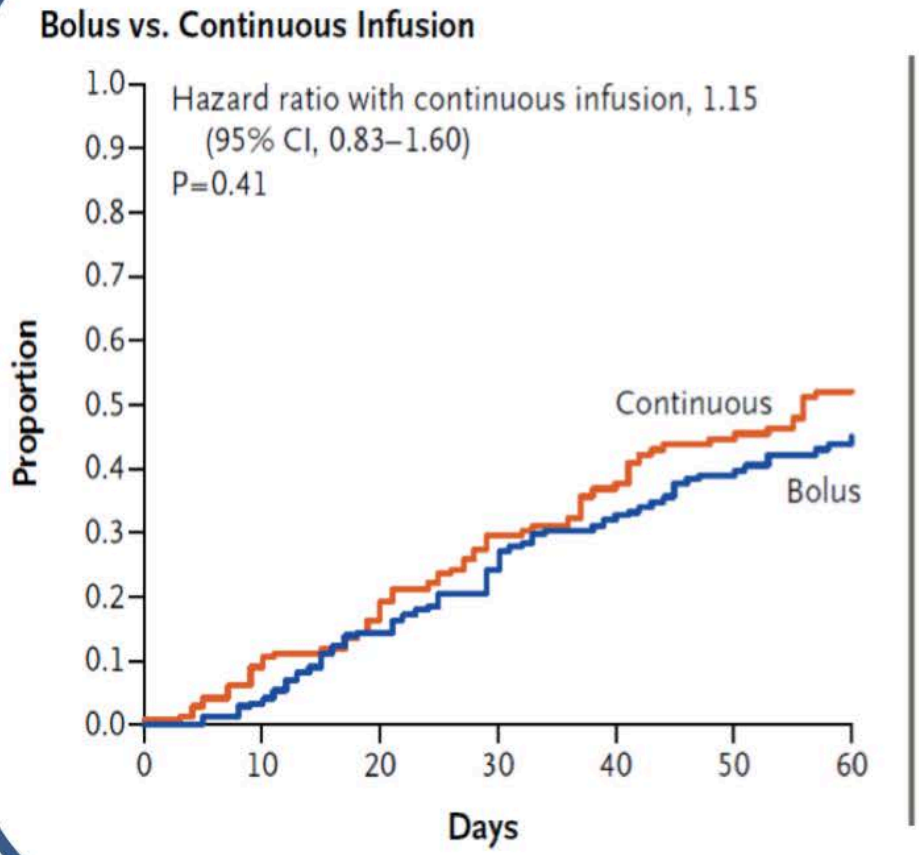
Mebazaa et al Intensive Care Medicine 2011

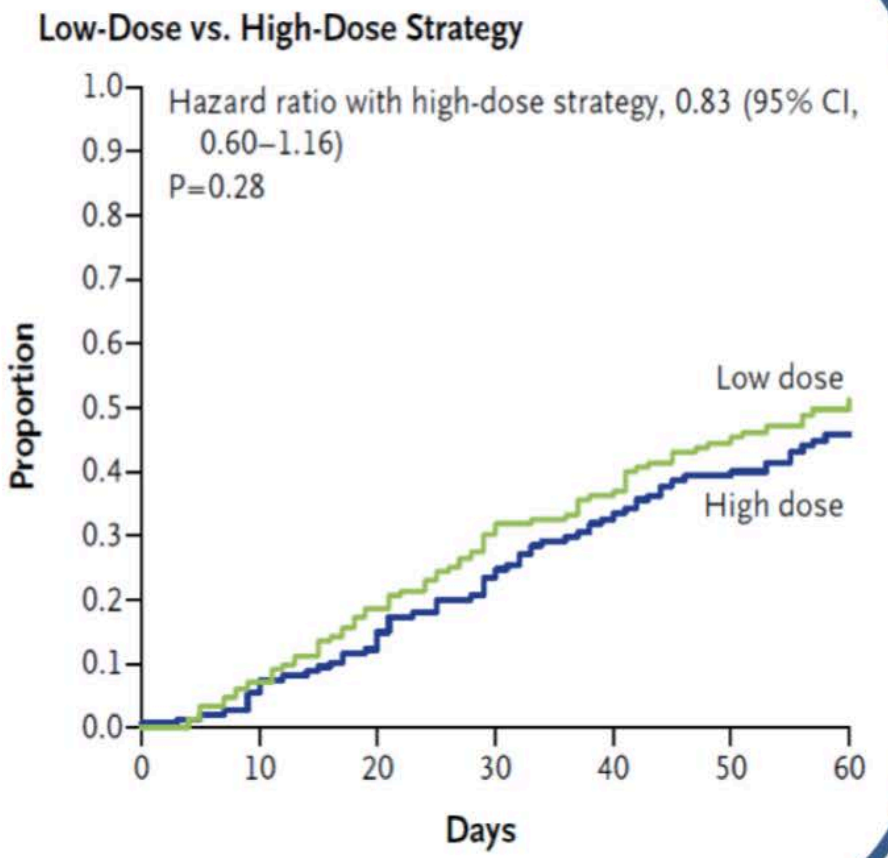
Effect of IV drugs in-hospital mortality: propensity score analysis



•*Mebazaa et al Intensive Care Medicine 2011*

The DOSE Trial





Felker GM, et al. N Engl J Med 2011;364:797-805

Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome

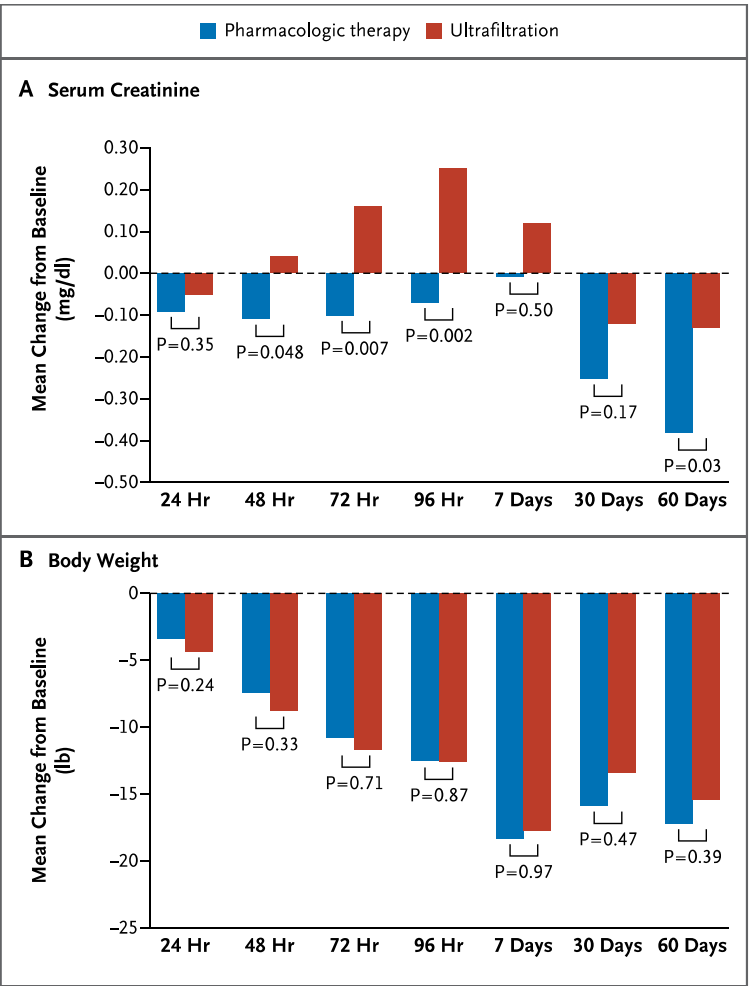


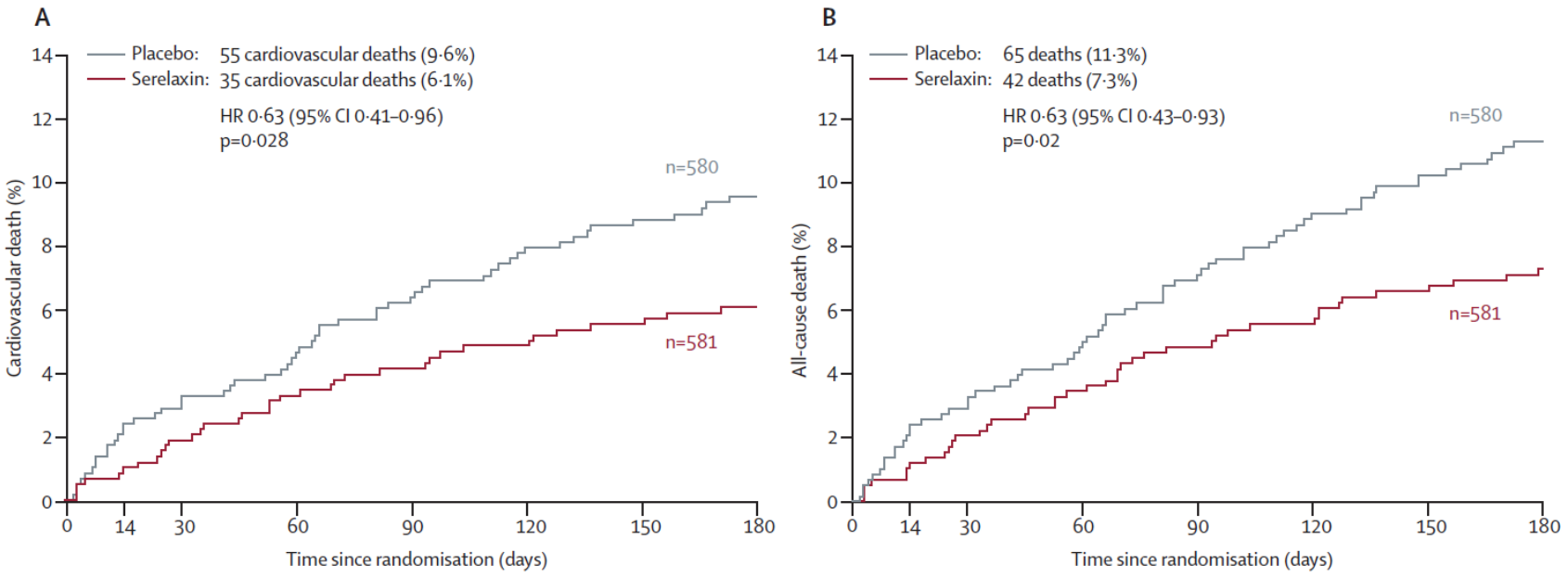
Table 2. Secondary End Points.*

End Point	Pharmacologic Therapy (N=94)	Ultrafiltration (N=94)	P Value
Significant body weight loss and renal improvement — no. (%)†			
At 96 hr	20 (21)	16 (17)	0.62
At 7 days	20 (21)	15 (16)	0.52
Worsening condition or crossover during the first 7 days — no./total no. (%)‡	17/94 (18)	21/93 (23)	0.45
Clinical decongestion at 96 hr — no./total no. (%)§	7/80 (9)	8/82 (10)	0.83
Change in sodium from baseline to 96 hr — mmol/liter	0.0±3.6	−2.3±3.5	<0.001
Change in hemoglobin from baseline to 96 hr — g/dl	0.38±0.76	−0.01±0.92	0.002
Change in NT-proBNP from baseline to 96 hr — pg/ml	−979±2902	−814±9239	0.30
Change in cystatin C from baseline to 96 hr — mg/liter	0.14±0.52	0.22±0.52	0.37
Change in blood urea nitrogen from baseline to 96 hr — mg/dl	5.68±18.29	12.54±24.81	0.02
Change in glomerular filtration rate from baseline to 96 hr — ml/min/1.73 m^2	1.67±10.94	0.93±14.60	0.66
Change in score on global well-being scale from baseline to 96 hr¶	22.8±25.8	13.7±27.9	0.33
Change in score on dyspnea assessment scale from baseline to 96 hr¶	20.5±27.8	16.5±29.2	0.57
Total net fluid loss from randomization to 96 hr — ml	7082±4183	7443±4329	0.59
Change in furosemide-equivalent dose from preadmission to discharge — mg/day	2.2±166.5	−20.6±116.0	0.18
Death — no. (%)	13 (14)	16 (17)	0.55
Hospitalization — no./total no. (%)			
For heart failure	24/93 (26)	23/90 (26)	0.97
For any cause	37/93 (40)	46/90 (51)	0.12
Unscheduled emergency department or clinic visit — no./total no. (%)	13/93 (14)	19/90 (21)	0.21

Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial

John R Teerlink, Gad Cotter, Beth A Davison, G Michael Felker, Gerasimos Filippatos, Barry H Greenberg, Piotr Ponikowski, Elaine Unemori, Adriaan A Voors, Kirkwood F Adams Jr, Maria I Dorobantu, Liliana R Grinfeld, Guillaume Jondeau, Alon Marmor, Josep Masip, Peter S Pang, Karl Werdan, Sam L Teichman, Angelo Trapani, Christopher A Bush, Rajnish Saini, Christoph Schumacher, Thomas M Severin, Marco Metra, for the RELAXin in Acute Heart Failure (RELAX-AHF) Investigators

Lancet 2013; 381: 29–39



Number at risk

Placebo	580	567	559	547	535	523	514	444
Serelaxin	581	573	563	555	546	542	536	463

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Serelaxin	581	573	563	555	546	542	536	463

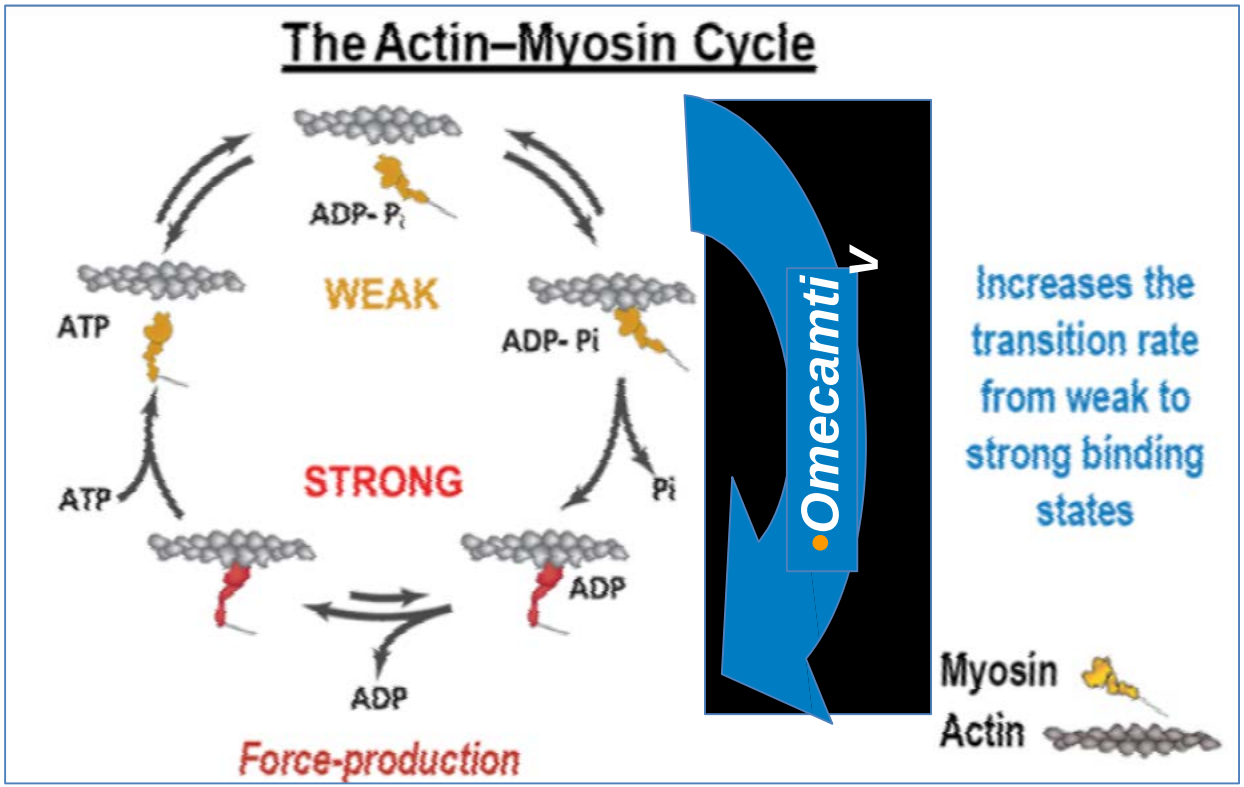
European Journal of Heart Failure (2015) 17, 750–752
doi:10.1002/ejhf.313

INVITED EDITORIAL

Cardiac myosin activators: up and coming

Mitchell A. Psotka[1] and John R. Teerlink[1,2]*

[1]School of Medicine, University of California San Francisco, San Francisco, CA, USA; and [2]Section of Cardiology, San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA



Inotropic agents under investigation

Drug	Mechanism
Na+/K+-ATPase inhibitors Istaroxime	Sarcolemma Na+-K+ pump inhibition: cytosolic calcium increase SERCA2a stimulation
Myosin activators omecamtiv mecarbil	Myosin stimulation: ↑ ejection phase duration, no change in ejection rate or calcium
RyR stabilizers JTV-519, S107	RyR2/calstabin 2 interaction, ↓SR calcium leakage
SERCA2a activators SERCA2a adeno-associated viral vector,...	↑ uptake of cytosolic calcium into the SR during diastole: better relaxation and increased calcium release during systole
Metabolic modulators Perhexiline, trimetazidine, ranolazine, GL-P1	Carnitine palmitoyl transferase 1 inhibition: myocardial substrate shift from FFAs to glucose; other mechanisms
Urocortin 2	Myocardial and vascular CRF2 receptors

Ongoing randomized clinical trials in acute HF

Drug	Trial name	No of patients	Endpoint
TReVena120027	BLAST-AHF	500	Composite
Ularitide (24 h infusion)	TRUE-AHF	2,116	Hierarchical clinical composite
Serelaxin (48 h infusion)	RELAX-AHF-2	6,375	Mortality to Day 180

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Vol 61,No. 6, 2013
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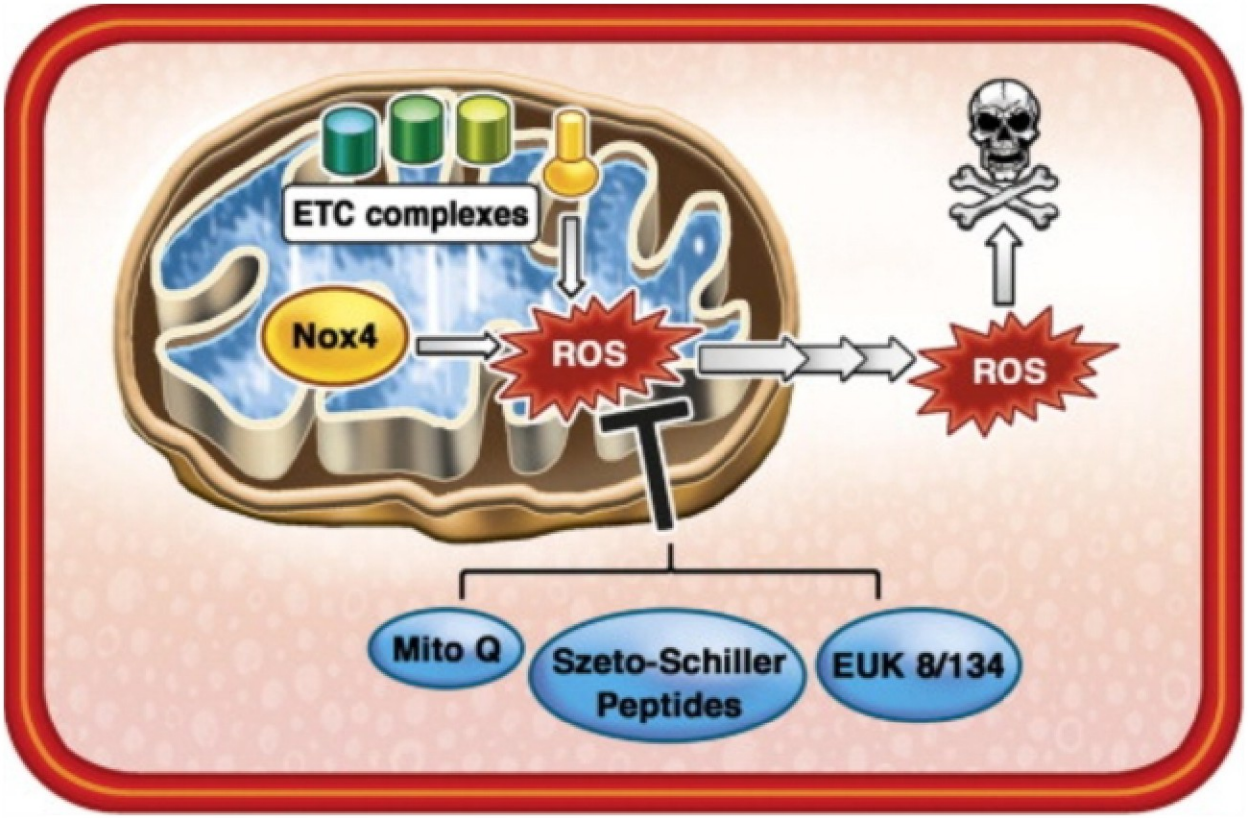
STATE-OF-THE-ART PAPER

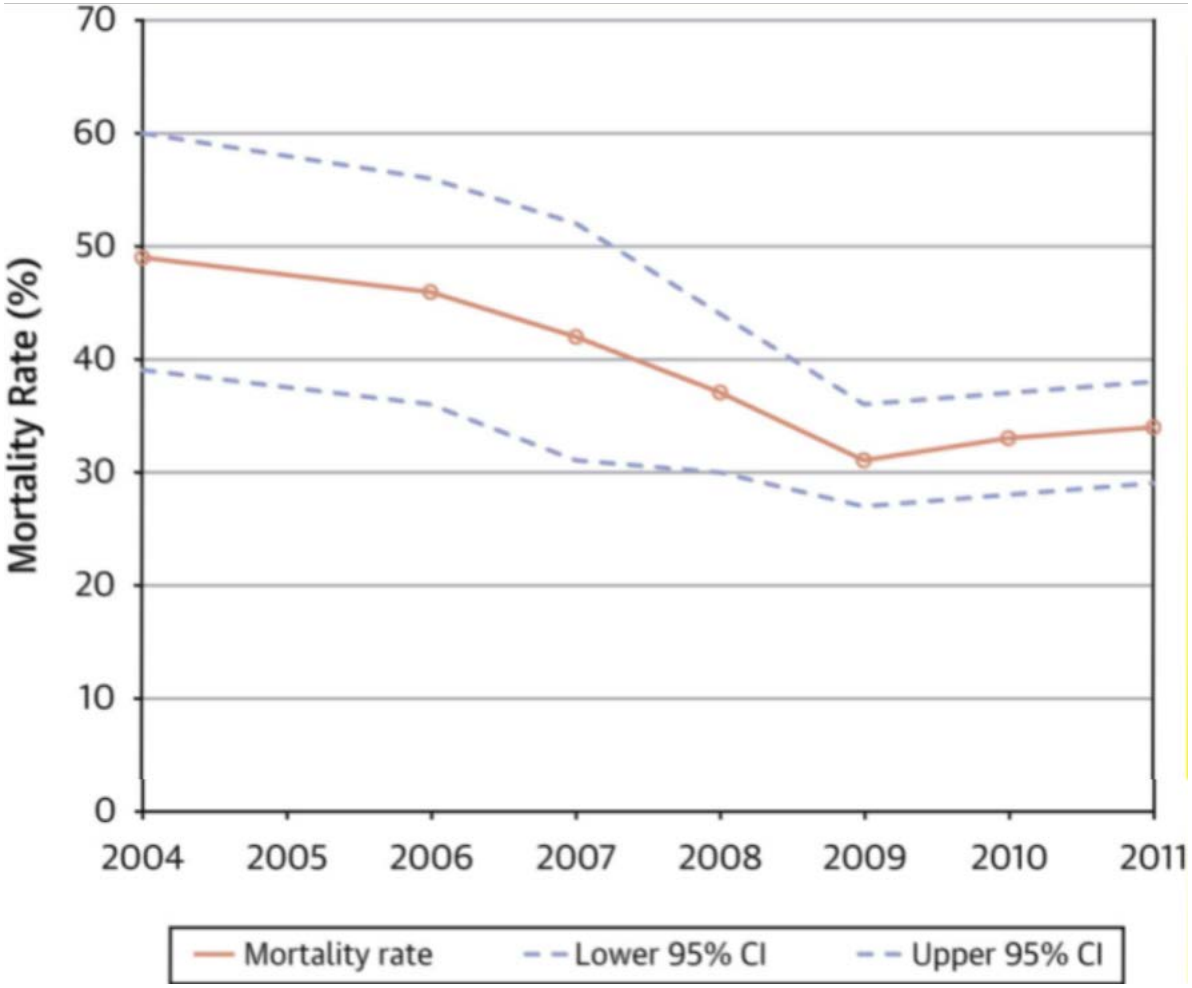
Mitochondria as a Therapeutic Target in Hearl Failure

i\llarina Bayeva, PHD/' l\lliliai Gheorghiade, l\ID,t Hossein Ardehali, f\ID, PHD•

Chicago, Illinois



Mortality Rate Associated With Short-Term Mechanical Circulatory Support (2004 to 2011)



Stretch et al. J Am Coll Cardiol. 2014;64(14):1407-1415

Percutaneous Circulatory Support in Cardiogenic Shock
Interventional Bridge to Recovery

Biswajit Kar, MD; Sukhdeep S. Basra, MD, MPH; Nishant R. Shah, MD; Pranav Loyalka, MD

Table 2. Comparison of Currently Available Percutaneous Ventricular Assist Devices

	IABP	TandemHeart	Impella Recover System	ECMO
Pump mechanism	Pneumatic	Centrifugal	Axial	Centrifugal
Insertion	Retrograde 7–9F balloon catheter into the descending aorta via the femoral artery	21F inflow cannula into the left atrium via the femoral vein and transseptal puncture and 15/17F outflow cannula into the femoral artery	12F catheter (13F sheath) retrograde across the aortic valve via the femoral artery	18–31F inflow cannula into the right atrium via the femoral vein and 15–22F outflow cannula into the descending aorta via the femoral artery
Difficulty of insertion	+	++++	+++	++
Degree of circulatory support (with ideal SVR)	+ (Increased CO by 0.5 L/min)	+++ (Increased CO by 3.5–4.5 L/min)	++ (Increased CO by 2.5 L/min)	++++ (Increased CO to ≥4.5 L/min)
Implantation time, min	10	25–65	11–25	10–15
Limb ischemia risk	+	+++	++	+++
Hemolysis	0	++	++++	+++
Bleeding risk	+	+++	++	++++
510k Approval duration, h		6	6	
Evidence of efficacy	Increased CO and coronary and peripheral perfusion; deceased afterload	Increased CO, MAP, Mvo_2, and urine output; decreased lactic acid, creatinine, and PCWP	Increased CO and MAP; decreased lactic acid and PCWP	Increased CO, MAP, and oxygenation

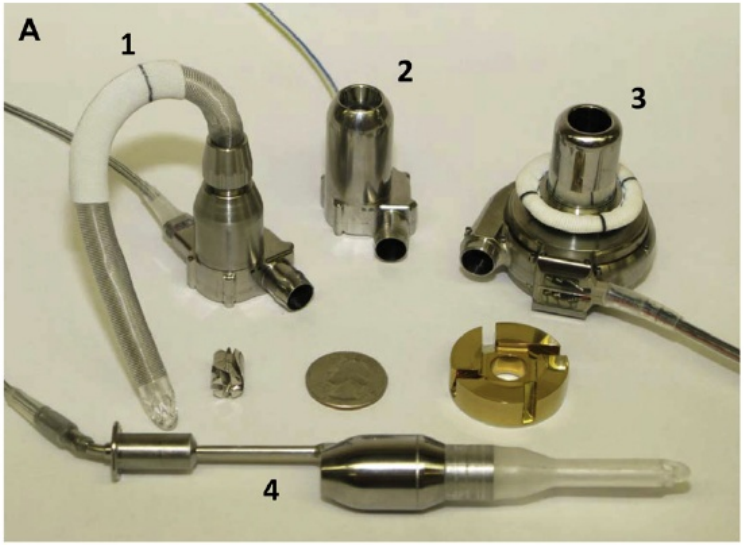
SVR indicates systemic vascular resistance; CO, cardiac output; MAP, mean arterial pressure; Mvo_2, mixed venous oxygen saturation; and PCWP, pulmonary capillary wedge pressure.

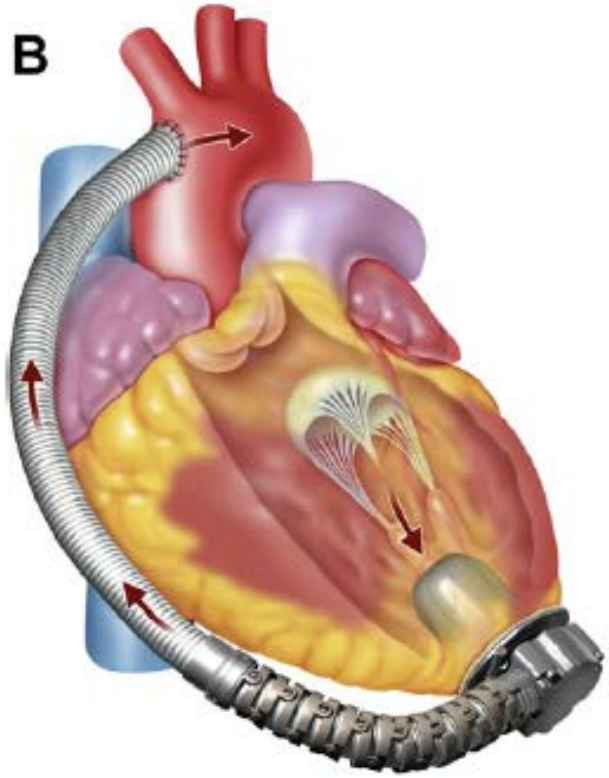
TandemHeart PVAD

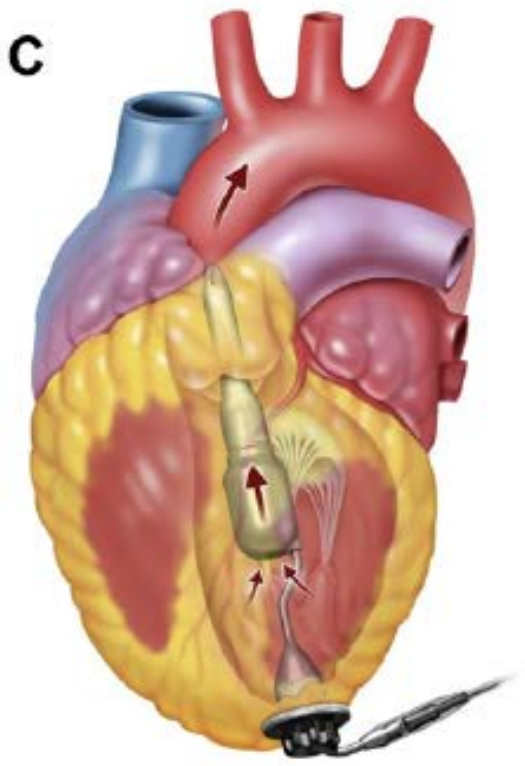
Impella Recover 2.5 PVAD

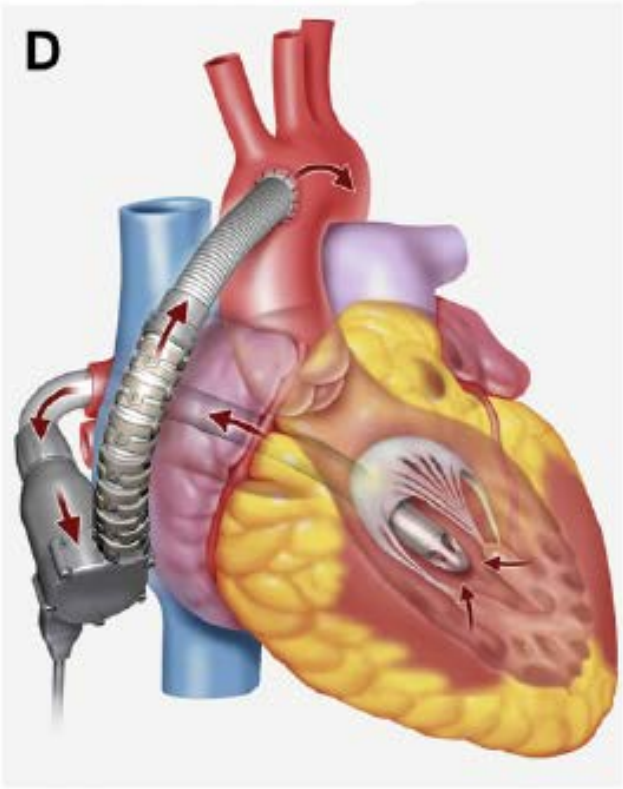
The Future of Adult Cardiac Assist Devices: Novel Systems and Mechanical Circulatory Support Strategies

Carlo R. Bartoli, PhD[a], Robert D. Dowling, MD[b,*]









Stratificazione dei pazienti

gli stadi INTERMACS

Table 3. INTERMACS Patient Profiles and Timing of Mechanical Circulatory Support*

Patient Profile†	Patient Characteristics	Time Frame Until Intervention
1	Critical cardiogenic shock despite escalating support	Within a few hours
2	Progressive decline with inotrope dependence	Within a few days
3	Clinically stable with mild to moderate inotrope dependence	Elective implantation over the next few weeks
4	Recurrent, not refractory, advanced heart failure that can be stabilized with intervention	Elective implantation over weeks to months
5	Exertion intolerant but is comfortable at rest and able to perform activities of daily living with slight difficulty	Variable; depends on nutrition, organ function, and activity
6	Exertion limited; is able to perform mild activity, but fatigue results within a few minutes of any meaningful physical exertion	Variable, depends on nutrition, organ function, and activity
7	Advanced NYHA functional class III	At this time, mechanical circulatory support is not indicated

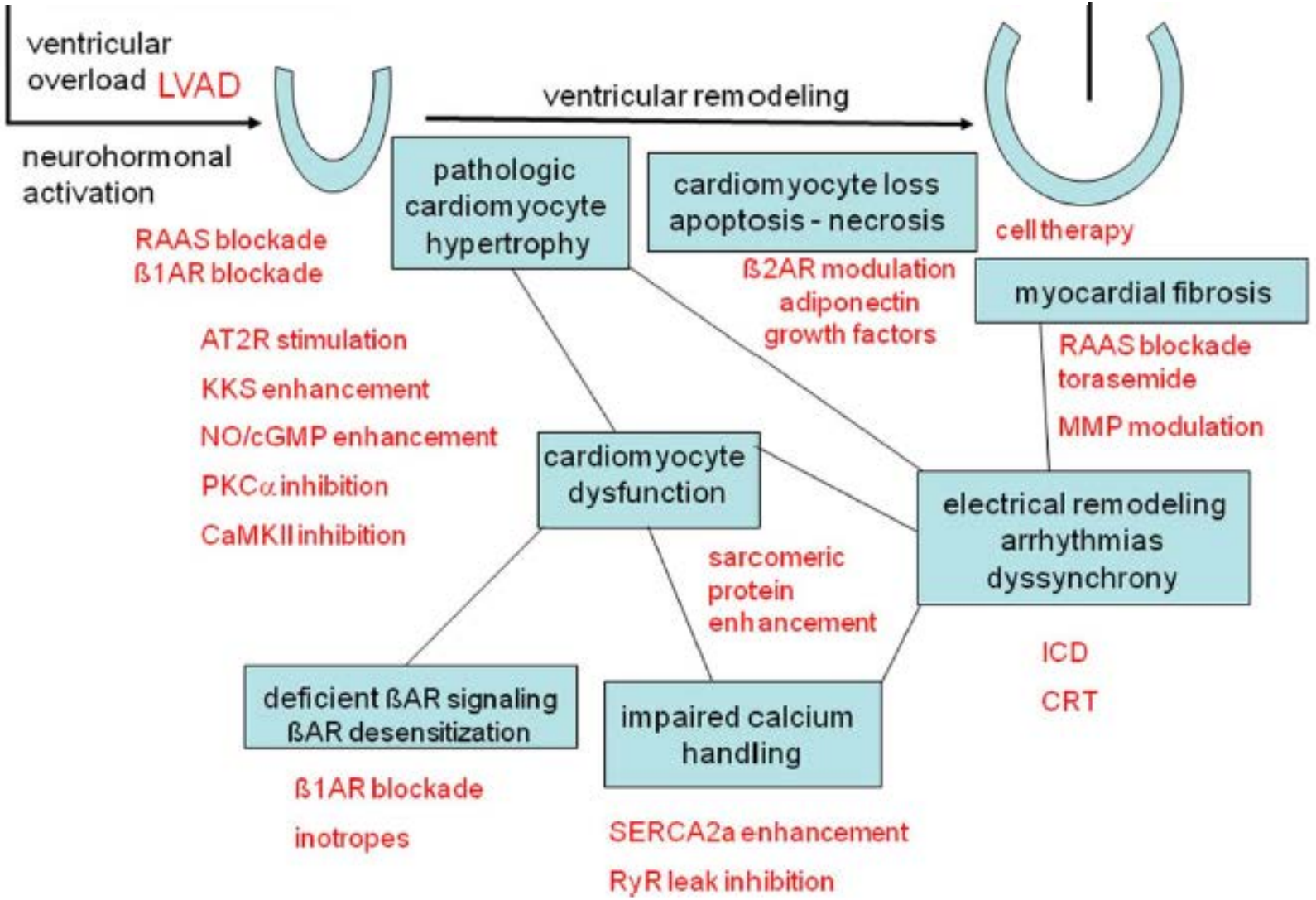
NYHA indicates New York Heart Association.

*Adapted from Stevenson et al.[15]

†Arrhythmia modifier (A), recurrent ventricular tachyarrhythmias (may be added to any INTERMACS level except 7).

Molecular targets of current and prospective heart failure therapies

Elie R Chemaly, Roger J Hajjar, Larissa Lipskaia



Chemaly ER, *et al. Heart* 2013;**99**:992–1003. doi:10.1136/heartjnl-2012-302970

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http://dx.doi.org/10.1016/j.jchf.2013.09.008

Design of a Phase 2b Trial of Intracoronary Administration of AAV1/SERCA2a in Patients With Advanced Heart Failure

The CUPID 2 Trial (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b)

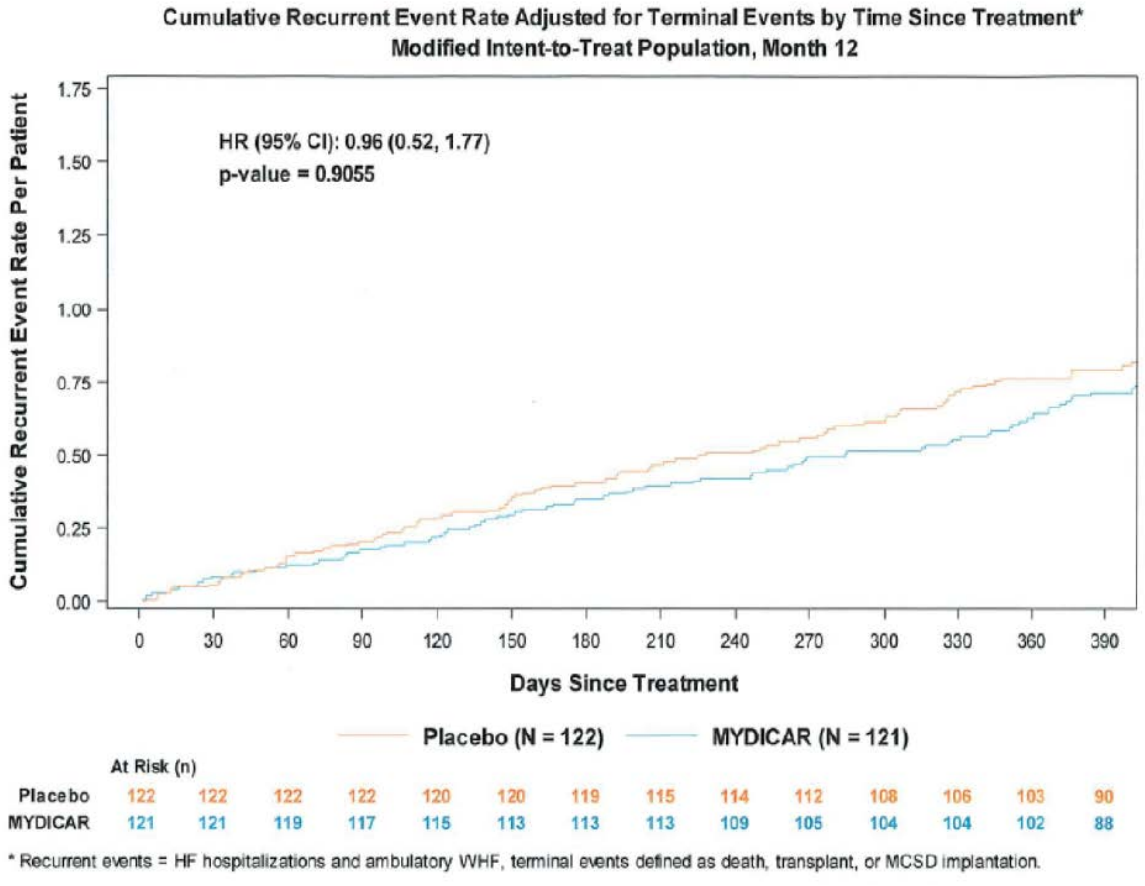
Barry Greenberg, MD,* Alex Yaroshinsky, PHD,† Krisztina M. Zsebo, PHD,‡ Javed Butler, MD, MPH,§ G. Michael Felker, MD,|| Adriaan A. Voors, MD,¶ Jeffrey J. Rudy, BS,‡ Kim Wagner, MA,‡ Roger J. Hajjar, MD#

San Diego and San Andreas, California; Atlanta, Georgia; Durham, North Carolina; Groningen, the Netherlands; and New York, New York

Potential Reasons for the Neutral Results of CUPID 2

- Deficiency in the Target, SERCA2a
- Virus concentration too low
- Myocardial uptake insufficient
- Delivery method inadequate

PRIMARY ENDPOINT



Europace (2010) 12, 1480–1489
doi:10.1093/europace/euq275

CONSENSUS STATEMENT

EHRA Expert Consensus Statement on the management of cardiovascular implantable electronic devices in patients nearing end of life or requesting withdrawal of therapy

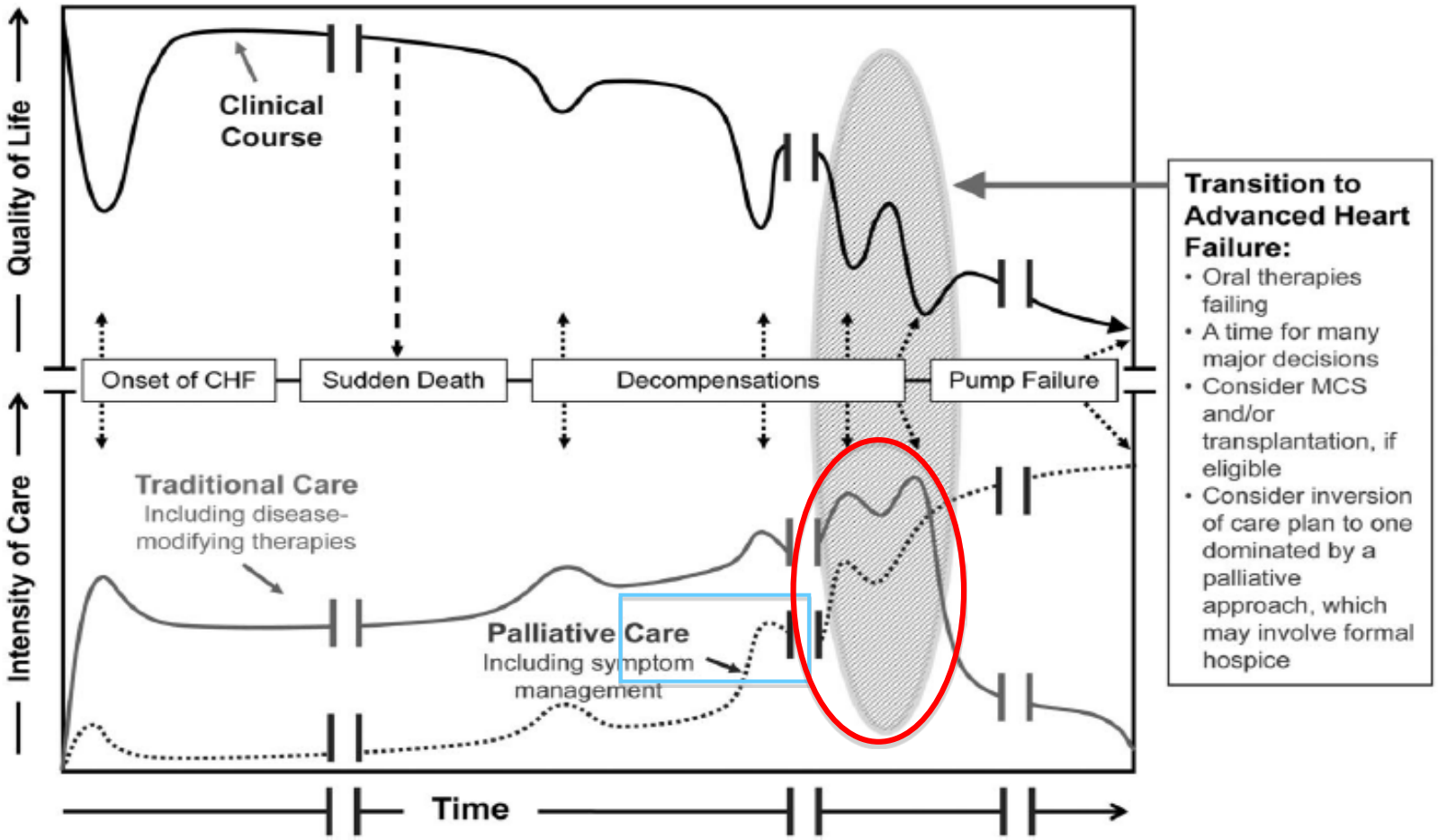
Luigi Padeletti[1*], David O. Arnar[2], Lorenzo Boncinelli[3], Johannes Brachman[4], John A. Camm[5], Jean Claude Daubert[6], Sarah Kassam[6], Luc Deliens[7], Michael Glikson[8], David Hayes[9], Carsten Israel[10], Rachel Lampert[11], Trudie Lobban[12], Pekka Raatikainen[13], Gil Siegal[14], and Panos Vardas[15]

Reviewers: Paulus Kirchhof[16], Rüdiger Becker[17], Francisco Cosio[18], Peter Loh[19], Stuart Cobbe[20], Andrew Grace[21], and John Morgan[22]

Implantable cardioverter- defibrillator-implanted patients may develop terminal illness due to worsening of their underlying heart disease or other chronic non-cardiac disease. Terminally ill patients develop ….hypoxia, sepsis, pain, heart failure, and electrolyte disturbances predisposing them to arrhythmias and ….frequency of shock therapy. Shocks can be painful and stressful, without prolonging a life of acceptable quality. Therefore, it is appropriate to consider ICD deactivation when the patient's clinical status worsens and death is near.

Decision Making in Advanced Heart Failure : A Scientific Statement From the American Heart Association

Larry A. Allen, Lynne W. Stevenson, Kathleen L. Grady, Nathan E. Goldstein, Daniel D. Matlock, Robert M. Arnold, Nancy R. Cook, G. Michael Felker, Gary S. Francis, Paul J. Hauptman, Edward P. Havranek, Harlan M. Krumholz, Donna Mancini, Barbara Riegel and John A. Spertus



(*Circulation*. 2012;125:1928-1952.)