TURIN,
October
25th-27th
2018
Starhotels
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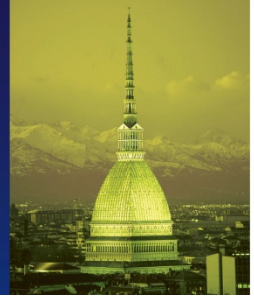
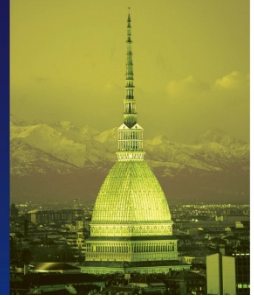


UNIVERSITÁ DEGLI STUDI DI TORINO

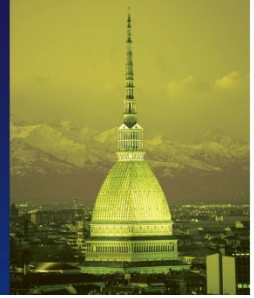
AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

The problem of PH in the setting of Heart Transplantation and LVAD

Maria Frigerio
2nd Section of Cardiology, Heart Failure & Cardiac Transplant Unit
DeGasperis CardioCenter, Niguarda Hospital, Milan, Italy



- PH in the setting of advanced HF with LV dysfunction
- PH as a risk factor for HTX
- PH reversibility for HTX candidacy: evaluation & maintenance
  - short-term strategies
  - long-term strategies
- LVAD for advanced HF with LV dysfunction & PH
- Post-HTX management of PH and RV dysfunction
- Perspectives



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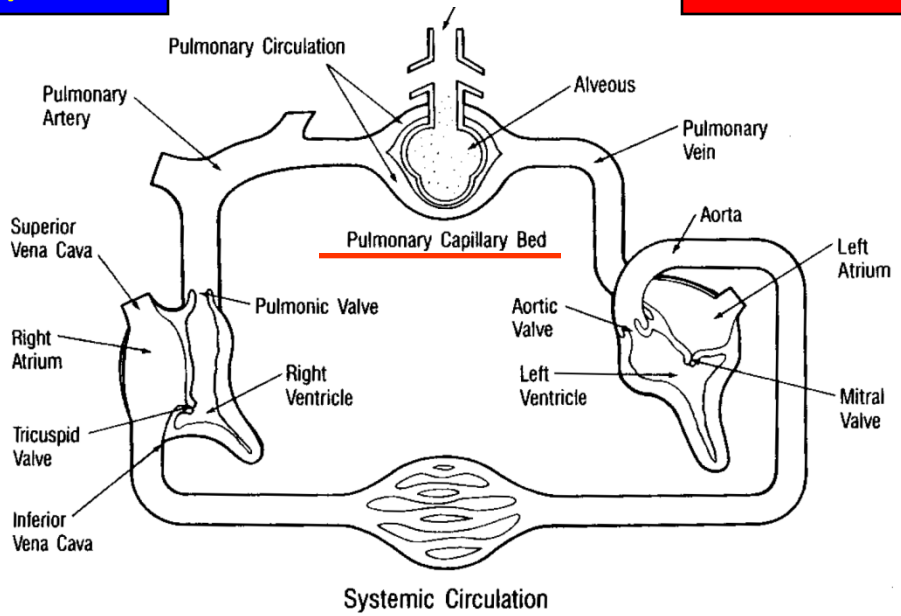
PRECAPILLARY PULMONARY HYPERTENSION (PAH)

POSTCAPILLARY PULMONARY HYPERTENSION (PH-LHD)



- ➢**PAPm ≥ 25 mmHg**
- ➢**WP ≤ 15 mmHg**
- ➢**PVR> 3WU**

- ✓**PAPm ≥ 25 mmHg**
- ✓**WP > 15 mmHg**

1. Pulmonary Arterial Hype
2. **Pulmonary Hypertensio Disease**
3. Pulmonary Hypertension Disease/Hypoxia
4. Chronic Thromboembolic Hypertension
5. Other/Unknown origin

Pulmonary Hypertension due to Left Heart Disease

2.1 LV systolic dysfunction

2.2 LV diastolic dysfunction

2.3 Valvular heart disease

2.4 LV outflow obstruction and congenital cardiomyopathy

2.5 Congenital/Acquired pulmonary vein stenosis

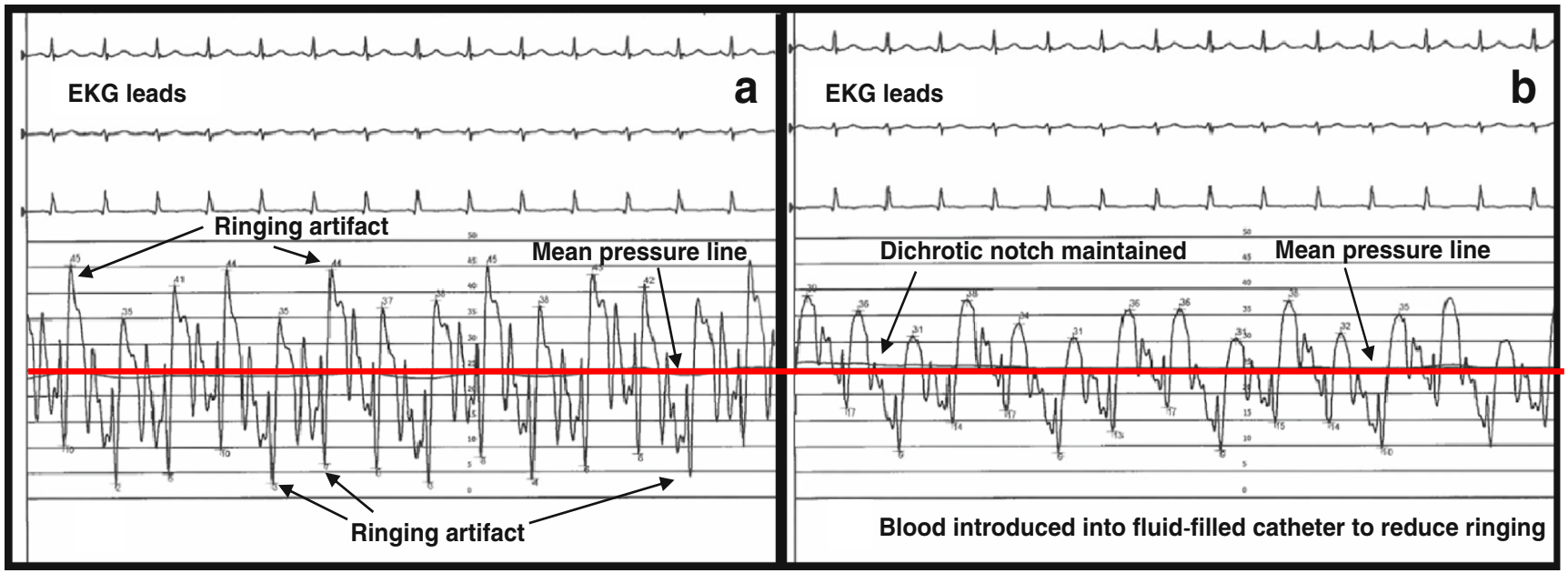
Hemodynamic variables to define the precapillary component of group 2 PH

Characteristic	TPG	DPG	PVR	PAC
Physiological background	-/+	+++	++ (+)	++
Independence from flow and filling pressures	-	+ (+)	-/+	-
Dependent on quality of PAWP recording	+	++	+	-
Marker of disease	+	+ (+)	++	-/+
Marker of prognosis	-/+	+	++	++
Historical variable	+++	-/+	+++	-
Level of confort for clinical use	++	+	+++	-

- ***PVR remains a robust variable to describe CpcPH***
- ***DPG and PAC may have value but may be limited by methodological uncertainties***

Pulmonary Vascular Disease: Hemodynamic Assessment and Treatment Selection—Focus on Group II Pulmonary Hypertension

Bhavadharini Ramu[1] · Brian A. Houston[1] · Ryan J. Tedford[1]



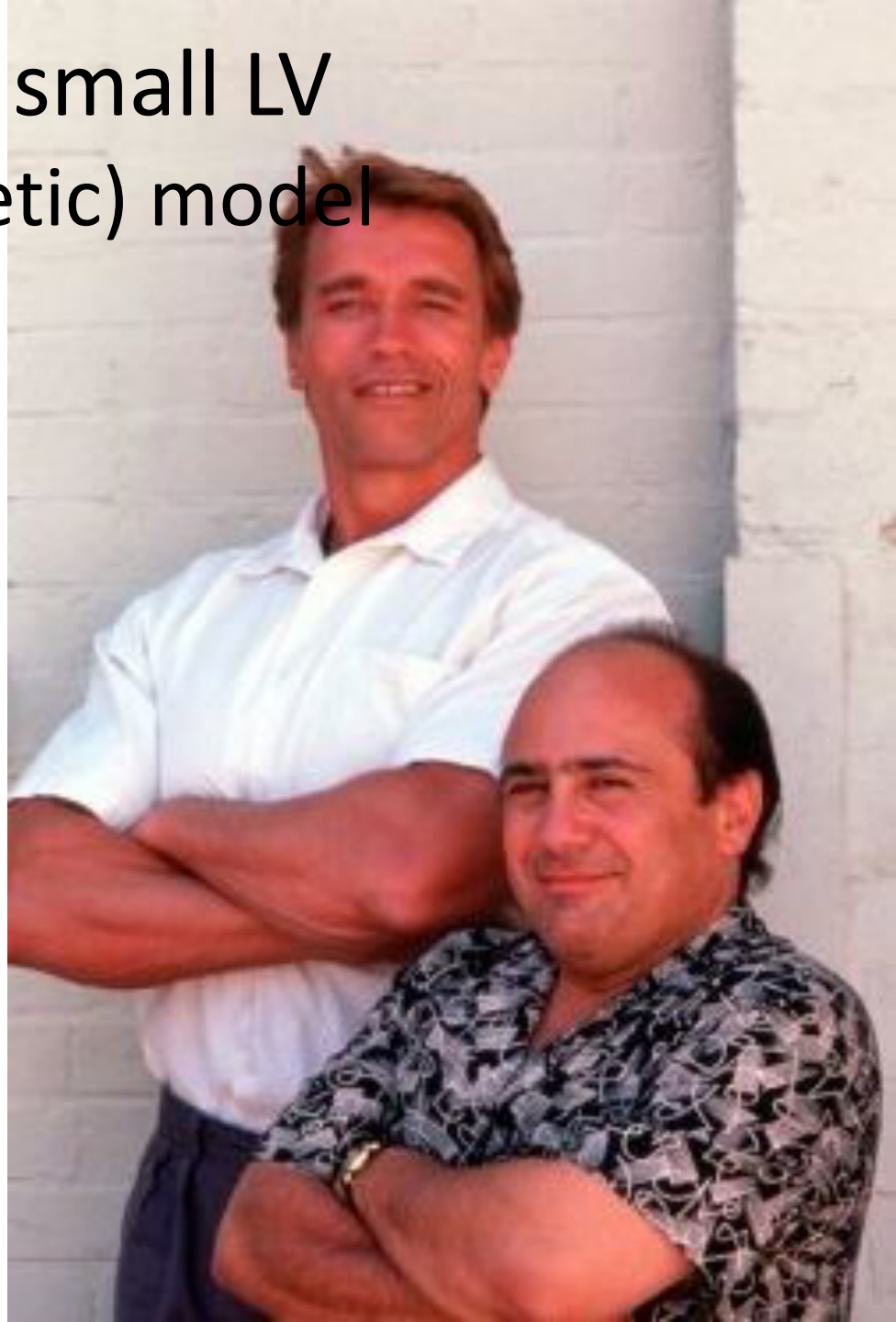
Accuracy and reproducibility of DPG and mPAP measurements

TF9 PROPOSAL FOR THE HEMODYNAMIC DEFINITION OF PH-LHD

- **Isolated post capillary PH (IpcPH)**
  - PAWP > 15 mmHg AND **PAPm > 20mmHg** AND PVR ≤ 3WU
- **Combined post and precapillary PH (CpcPH)**
  - PAWP > 15mmHg AND **PAPm > 20mmHg** AND PVR > 3WU

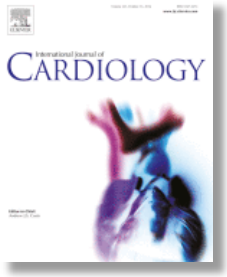
PH-LHD with large or small LV - the Large LV (hypokinetic) model

- the “classic” model (isolated postcapillary PH)
- Diastolic gradient <=0
- Worsening/severe PH is generally a late phenomenon, or is related with severe mitral regurgitation
- resistant/“fixed” PH is generally a late phenomenon
- RA pressure may be low or moderately high, except during worsening (congestive) HF episodes



PH-LHD with large or small LV
-the Small LV (restrictive) model

- The “insidious” model (combined post- & precapillary PH)
- Diastolic gradient >0
- Severe and resistant/“fixed” PH is a relatively early phenomenon, even when symptoms are mild to moderate
- RA pressure may be high or very high even when symptoms are mild to moderate
- Lately, RV dysfunction may mask established pulmonary vascular disease



Editorial

Do results of the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) study spell the end for non-selective endothelin antagonism in heart failure?

ENABLE 2002

Paul R. Kalra*, James C.C. Moon, Andrew J.S. Coats
Clinical Cardiology, National Heart and Lung Institute, Dovehouse Street, London SW3 6LY, UK

EUROPEAN RESPIRATORY *journal*

OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

Macitentan in pulmonary hypertension due to left ventricular dysfunction

Melody 1, 2018

Jean-Luc Vachiéry[1], Marion Delcroix[2], Hikmet Al-Hiti[3], Michela Efficace[4], Martin Hutyra[5], Gabriela Lack[6], Kelly Papadakis[7] and Lewis J. Rubin[8]

Sildenafil for improving outcomes in patients with corrected valvular heart disease and persistent pulmonary hypertension: a multicenter, double-blind, randomized clinical trial

SIOVAC 2018

Riociguat for Patients With Pulmonary Hypertension Caused by Systolic Left Ventricular Dysfunction

A Phase IIb Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Hemodynamic Study

LEPHT 2013

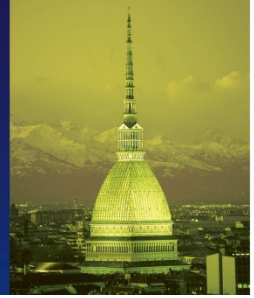
JAMA®
The Journal of the American Medical Association

SOCRATES 2015

Effect of Vericiguat, a Soluble Guanylate Cyclase Stimulator, on Natriuretic Peptide Levels in Patients With Worsening Chronic Heart Failure and Reduced Ejection Fraction

The SOCRATES-REDUCED Randomized Trial

Mihai Gheorghiade, MD; Stephen J. Greene, MD; Javed Butler, MD, MPH, MBA; Gerasimos Filippatos, MD; Carolyn S. P. Lam, MBBS; Aldo P. Maggioni, MD; Piotr Ponikowski, MD; Sanjiv J. Shah, MD; Scott D. Solomon, MD; Elisabeth Kraigher-Krainer, MD; Eliana T. Samano, MD; Katharina Müller, DiplStat; Lothar Roessig, MD; Burkert Pieske, MD; for the SOCRATES-REDUCED Investigators and Coordinators



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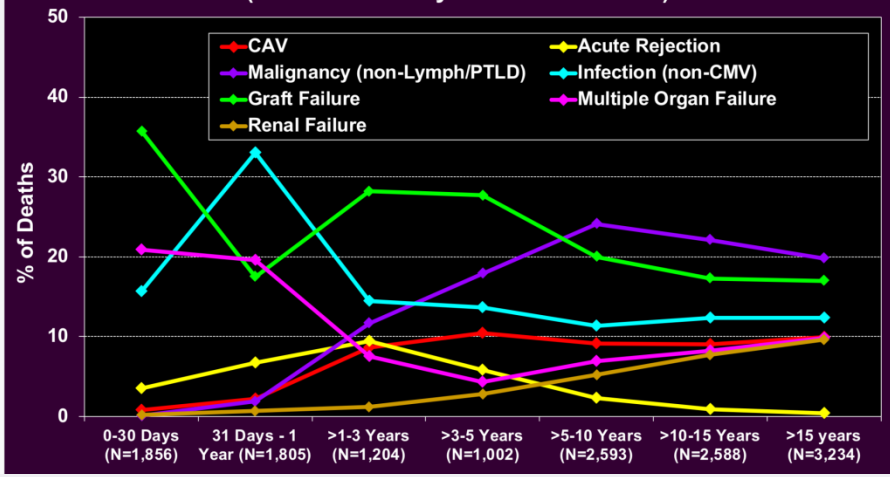
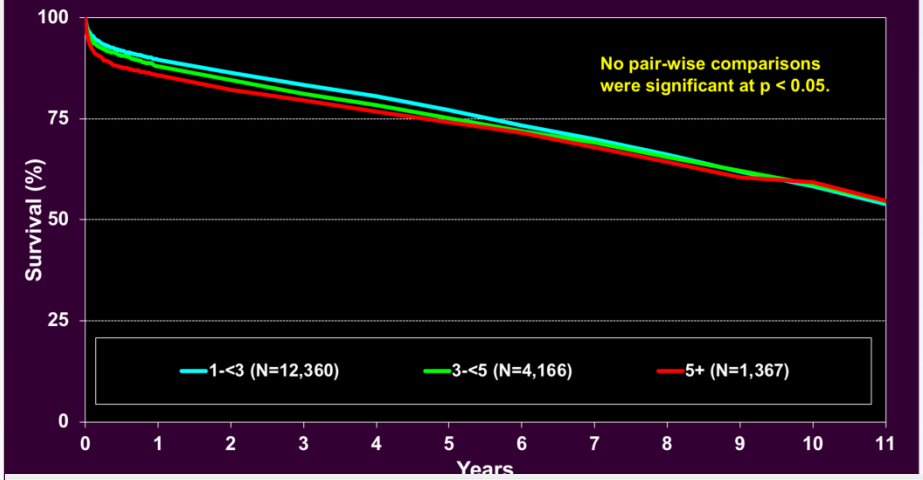
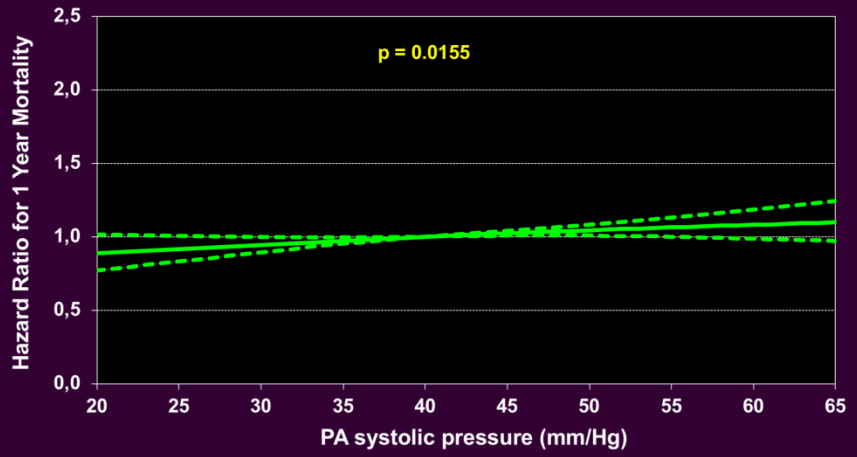
Adult Heart Transplants
Relative Incidence of Leading Causes of Death
(Deaths: January 2009 – June 2016)



Adult Heart Transplants
Kaplan-Meier Survival by PVR
(Transplants: January 2004 – June 2015)



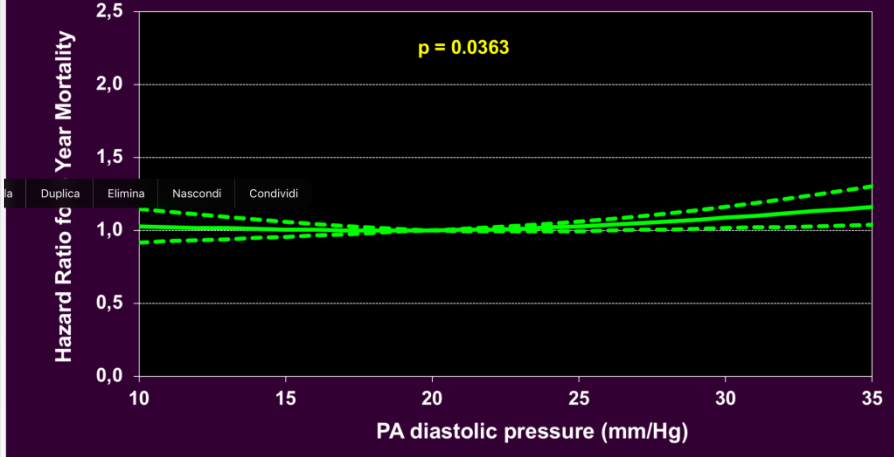
Adult Heart Transplants (2010-6/2015)
Risk Factors For 1 Year Mortality with 95% Confidence Limits
PA systolic pressure



(N = 21,614)

ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION 2017
JHLT. 2017 Oct; 36(10): 1037-1079

Adult Heart Transplants (2006-6/2011)
Risk Factors For 5 Year Mortality Conditional on Survival to 1 Year with 95% Confidence Limits
PA diastolic pressure

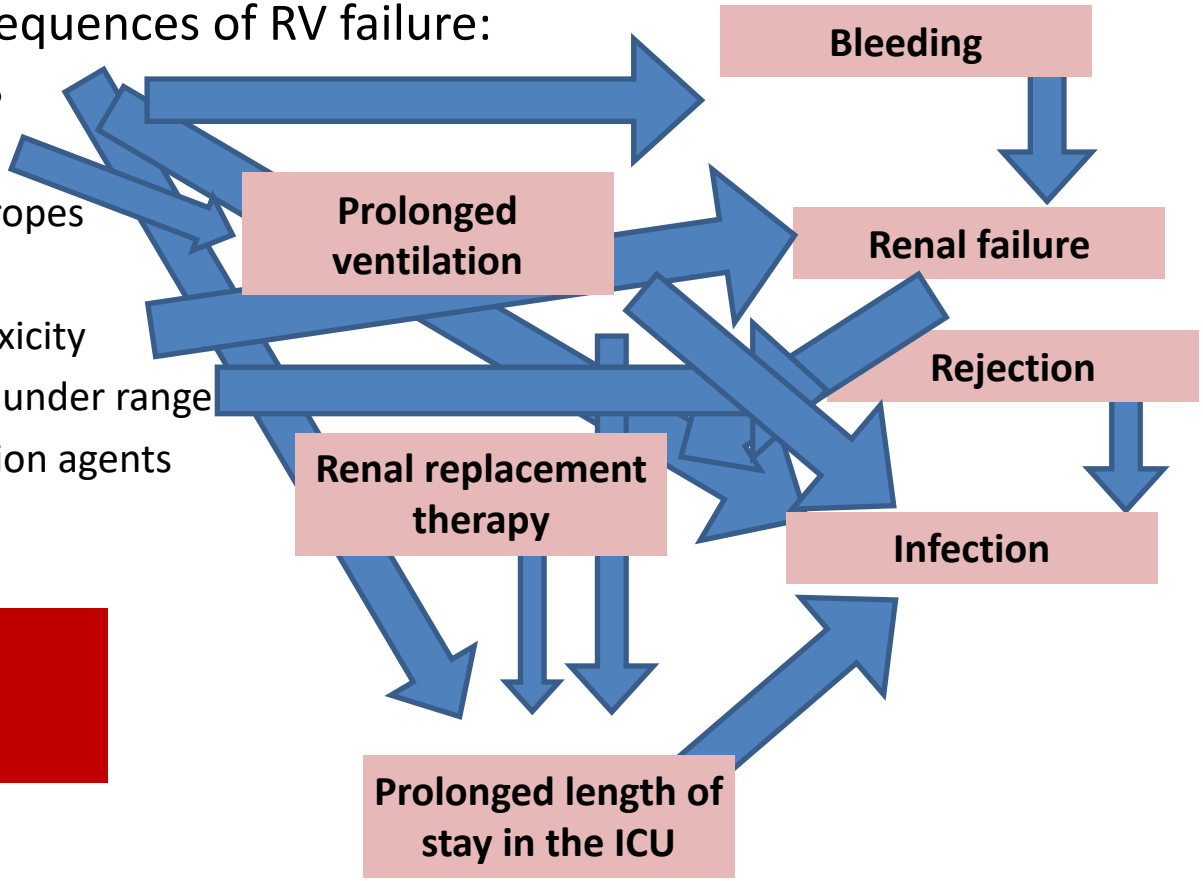


(N = 16,647)

ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION 2017
JHLT. 2017 Oct; 36(10): 1037-1079

PH as a risk factor for HTX

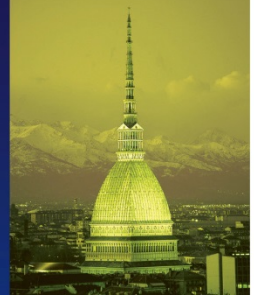
- Irreversible ("fixed") PH is associated with early Graft Failure due to RV failure
- Graft Failure is the leading cause of early death after HTX (≤30 days/In-hosp)
- Early deaths represent the most part of 1-year deaths
- Other unfavorable consequences of RV failure:
  - Need for temporary MCS
  - Need for prolonged NO
  - Need for prolonged inotropes
  - Congestion
  - Increased drug nephrotoxicity
  - Cyclosporine/Tacrolimus under range
  - Increased dose of induction agents



Multisystem organ failure

The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update

RECOMMENDATION	CLASS	LEVEL
A **vasodilator challenge** should be administered when the *pulmonary artery systolic pressure is >= 50 mm Hg* and either the *transpulmonary gradient is >= 15 mm Hg* or the *pulmonary vascular resistance (PVR) is > 3 WU* while maintaining a systolic arterial blood pressure > 85 mm Hg	I	C



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Today: is PH reversible?

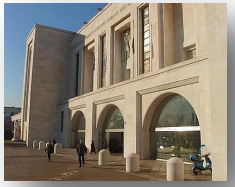
parameter	Target
PAPs	< 50 mmHg
PVR	< 3 Wood Units
TPG	< 15 mmHg
Systolic BP	≥ 85 mmHg

What	When and how
SNP	- Sys BP ≥ 90 mmHg, “acute” challenge - 2-3 days if partially responsive, with increased CO, limited by hypotension
Milrinone	- If partially responsive to SNP, with limited efficacy on CO
+ Dobutamine	- If partially responsive to SNP, limited by hypotension - May be less effective in pts on beta-blockers
Levosimendan	- If partially responsive to SNP, with limited efficacy on CO, and clinical reasons for hypothesizing repeated treatment
IABP	- Refractory HF, clinical - “Bridge” to LVAD

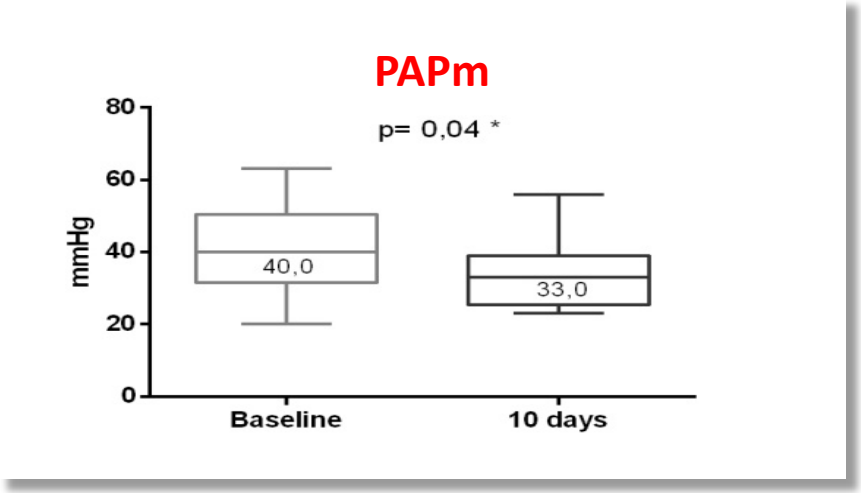
Tomorrow: how to keep HTX-compatible hemodynamics?

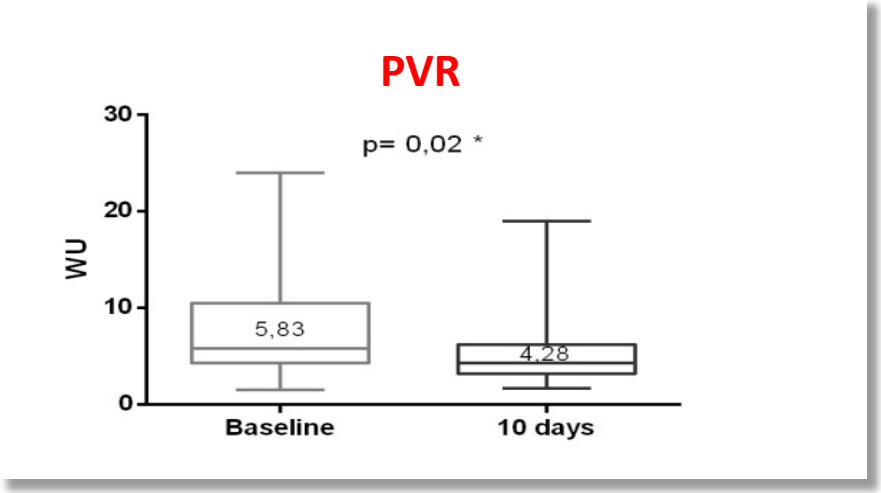
What	When and how
Long-term maintenance	- No/partial response to *acute* SNP
Repeated, planned Levosimendan	- 1st dose (partially) effective - 1st dose well tolerated - The patient can be discharged - Planned treatment @ 4 (3) weeks - Inpatient if low BP, arrhythmias - Outpatient/home based if stable (informed consent required)
Milrinone, continuous	- initially (partially) effective - initially well tolerated - Levosimendan not effective
Mitraclip?	- Severe MR - Good response to SNP - procedure success highly probable
LVAD	- Advanced/refractory HF - Low probability to get HTX - Suitable for LVAD

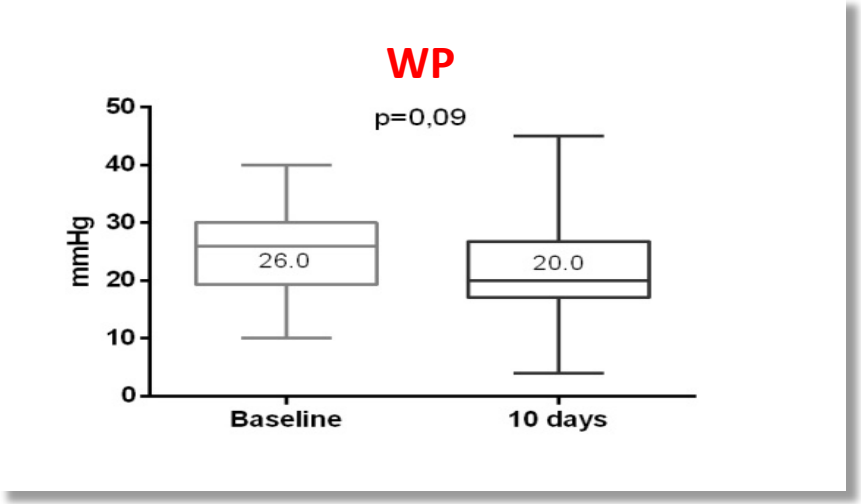
parameter	Target
PAPs	< 50 mmHg
PVR	< 3 Wood Units
TPG	< 15 mmHg
Systolic BP	≥ 85 mmHg

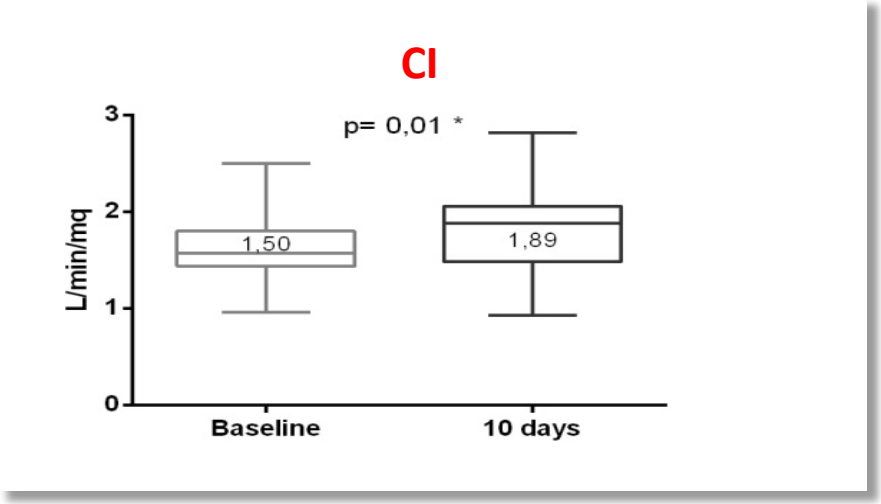


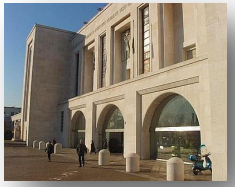
LEVOSIMENDAN BTT/BTC:
THE NIGUARDA EXPERIENCE (n=67)
Short-term effects





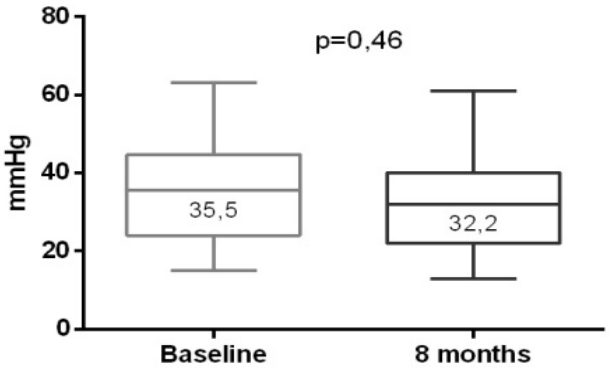




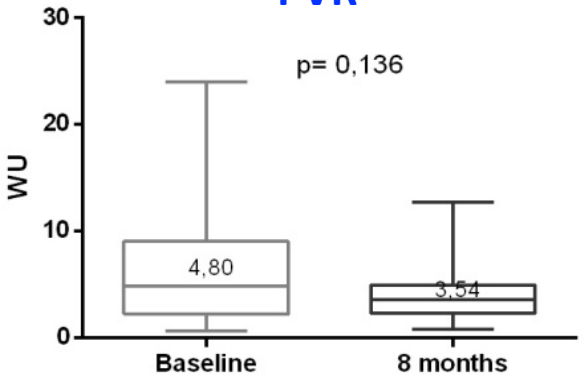


LEVOSIMENDAN BTT/BTC:
THE NIGUARDA EXPERIENCE – long term effects

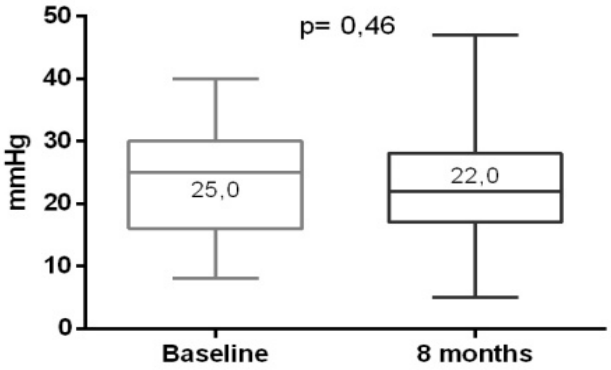
PAPm



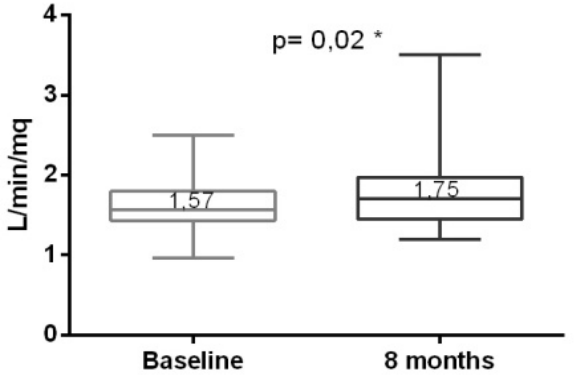
PVR

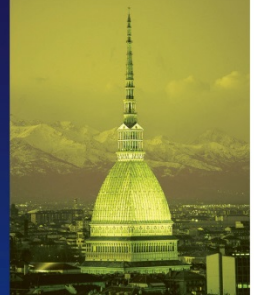


WP



CI





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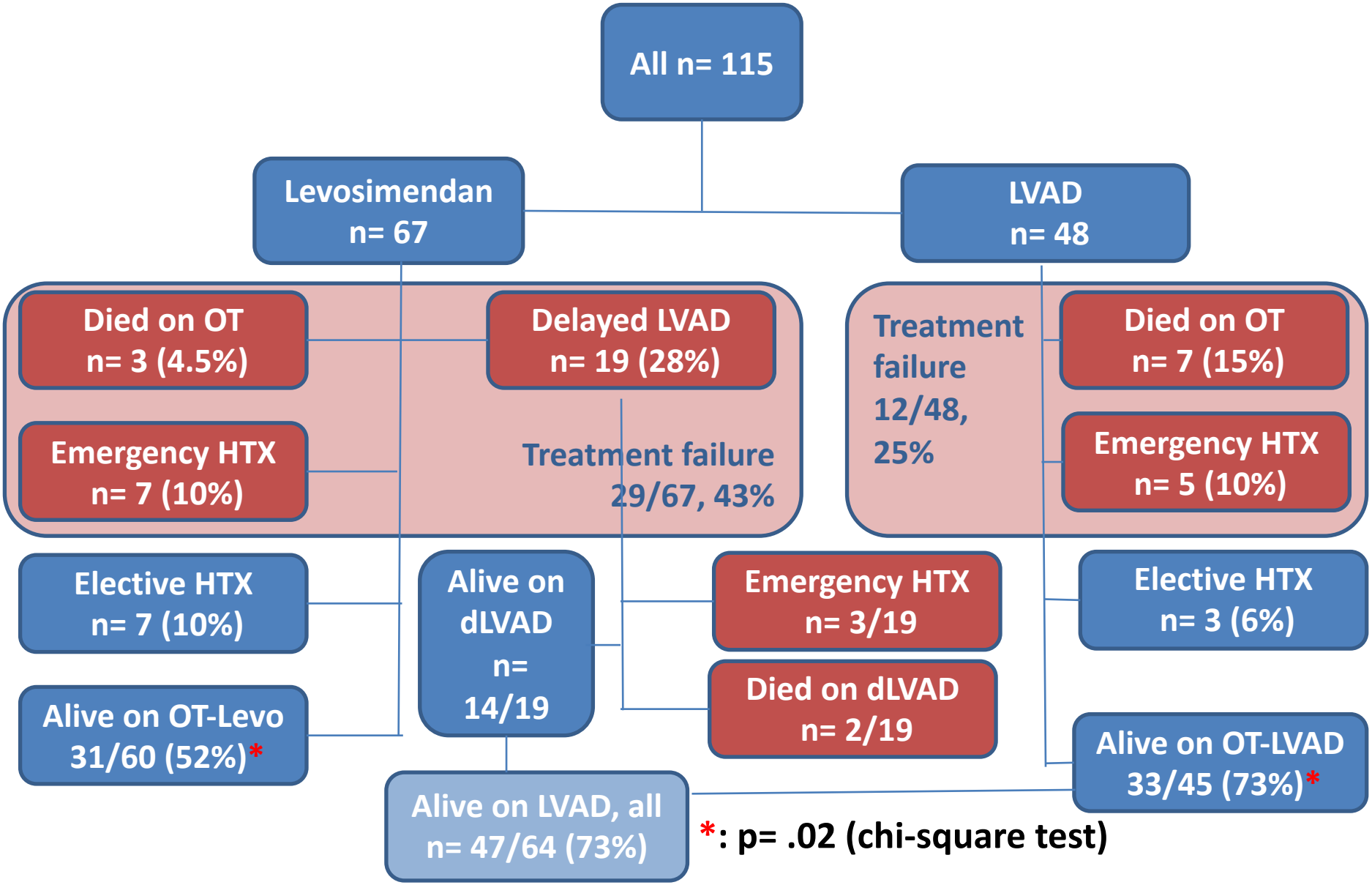
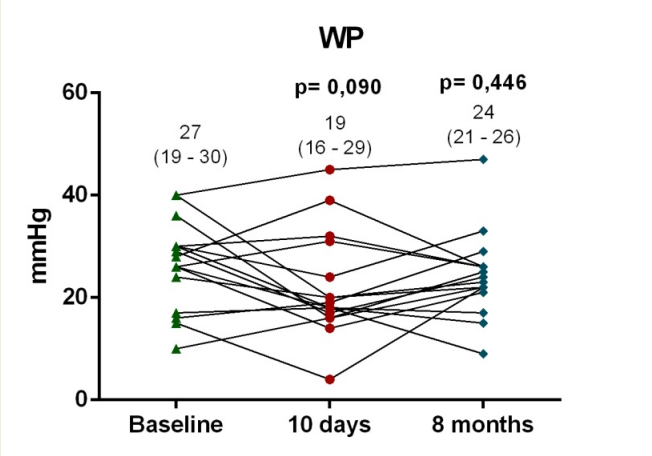
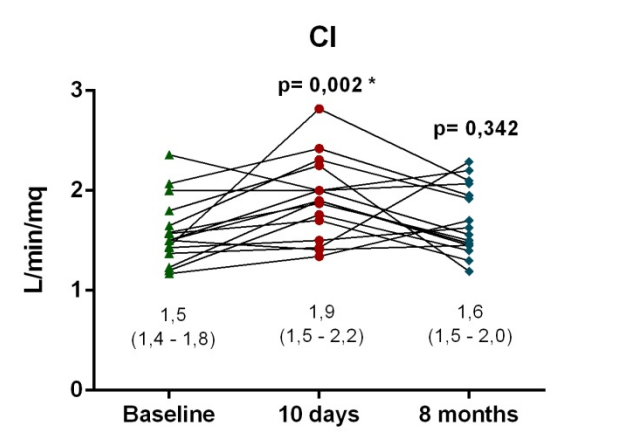
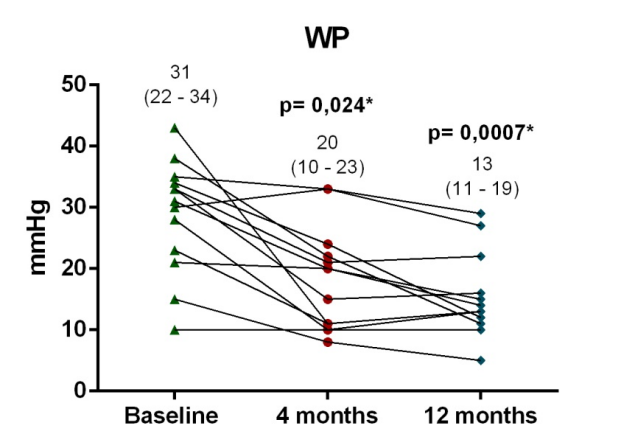
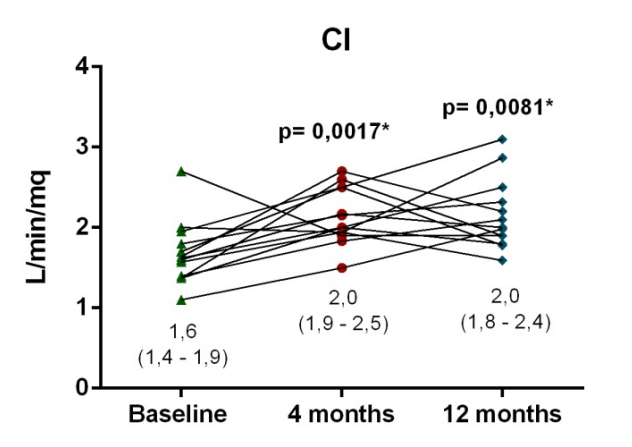
Repeated Levosimendan or LVAD BTT/BTC-1y



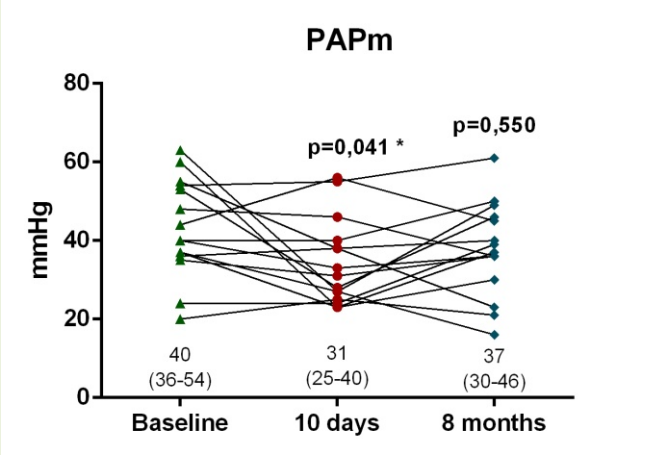
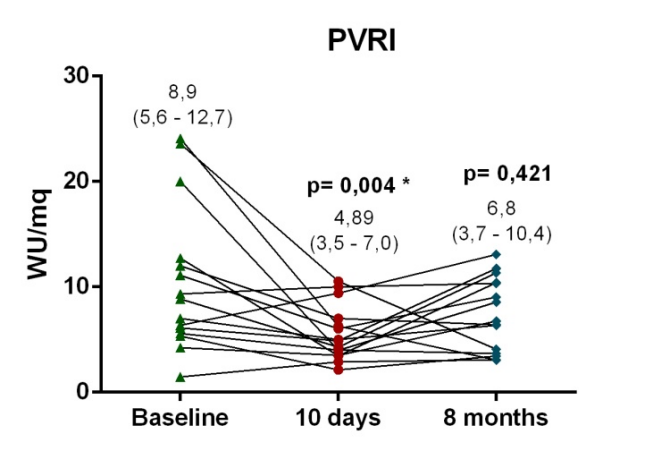
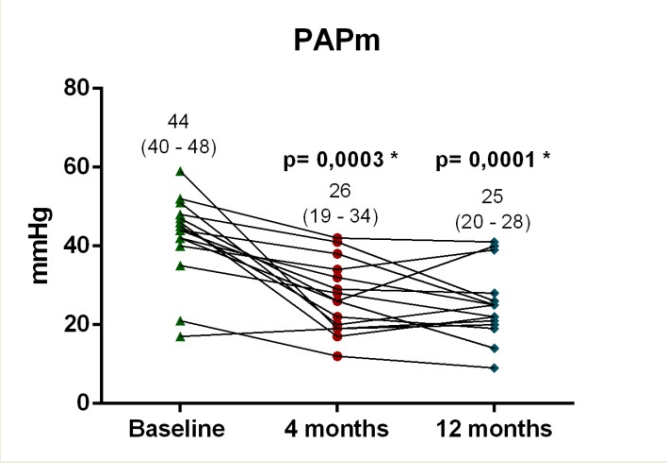
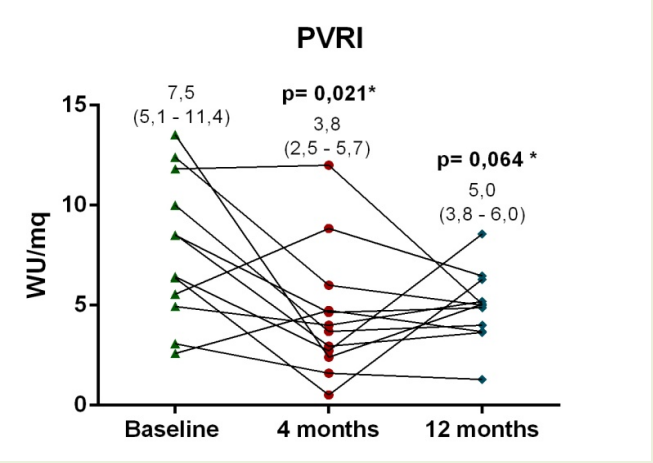
Repeated Levosimendan and LVAD

Right heart catheterization - 1

	Wedge Pressure	Cardiac Index
LEVOSIMENDAN		
LVAD		

Repeated Levosimendan and LVAD

- Right heart catheterization 2

	Mean Pulmonary Arterial Pressure	Indexed Pulmonary Vascular Resistances
LEVOSIMENDAN		
LVAD		

LVAD: *THE NIGUARDA EXPERIENCE*

Pre-LVAD PH, ALL

Parameter	Pre-LVAD (N = 48)	6 M Post-LVAD N= 48	1-2 aa Post-LVAD N= 26	> 2aa Post-LVAD N= 11
PAPm (mmHg)	**41.1** ± 11.4	**22.2** ± 7.1	**24.1** ± 8	**23.1** ± 7.4
PCWP (mmHg)	**29.4** ± 9.8	**13.6** ± 6.7	**15.5** ± 6.7	**14.2** ± 5
CI (l/min/m2)	**1.6** ± 0.4	**2.1** ± 0.4	**2** ± 0.4	**2.1** ± 0.2
TPG (mmHg)	**11.6** ± 5.9	**9.1** ± 4.4	**8.2** ± 5	**8.9** ± 3.1
PVR (WU)	**4.1** ± 2.2	**2.1** ± 1	**2.1** ± 0.9	**1.8** ± 0.5

LVAD: *THE NIGUARDA EXPERIENCE*

	Pre-LVAD PH, ALL, n=48		*Pre-LVAD "fixed" PH, n=14*		*Post-LVAD PH, n=15*	
Parameter	Pre-LVAD	6 M Post	Pre-LVAD	6 M Post	Pre-LVAD	6 M Post
RAP (mmHg)	9 ± 3.8	n.a.	10.1 ± 4.7	8 ± 5.2	8.6 ± 4.6	11.5 ± 5.2
PAPm (mmHg)	41.1 ± 11.4	22.2 ± 7.1	42.8 ± 8.3	25 ± 7.4	37.8 ± 12	30 ± 7.3
PCWP (mmHg)	29.4 ± 9.8	13.6 ± 6.7	30.7 ± 7.3	16.7 ± 6.8	25.7 ± 9.5	21.2 ± 6.7
CI (l/min/m2)	1.6 ± 0.4	2.1 ± 0.4	1.4 ± 0.3	2 ± 0.4	1.5 ± 0.3	2 ± 0.4
TPG (mmHg)	11.6 ± 5.9	9.1 ± 4.4	12 ± 6.1	8.3 ± 3.9	12.8 ± 6	11.5 ± 4.6
PVR (WU)	4.1 ± 2.2	2.1 ± 1	4.2 ± 2.2	2.1 ± 1	4.3 ± 2.2	2.4 ± 1

Baseline hemodynamics, pre-LVAD

Parameter	LVAD, All (N= 59)	PH, All (N=48)	Non rev Pre-LVAD (N 14)	Non rev Post-LVAD (N=15)
PVC (mmHg)	7.6 ± 4.7	9 ± 3.8	10.1 ± 4.7	8.6 ± 4.6
PAPs (mmHg)	57.2 ± 18.2	64.1 ± 18.2	69.2 ± 12.6	60 ± 17.4
PAPd (mmHg)	23.5 ± 9.2	27 ± 9.1	27.9 ± 7	25.1 ± 9.2
PAPm (mmHg)	36.4 ± 11.9	41.1 ± 11.4	42.8 ± 8.3	37.8 ± 12
PCWP (mmHg)	25.7 ± 9.8	29.4 ± 9.8	30.7 ± 7.3	25.7 ± 9.5
CO (l/min)	3.2 ± 0.8	3 ± 0.7	2.7 ± 0.7	3.1 ± 0.8
CI (l/min/m2)	1.68 ± 0.4	1.6 ± 0.4	1.4 ± 0.3	1.5 ± 0.3
TPG (mmHg)	10.5 ± 6	11.6 ± 5.9	12 ± 6.1	12.8 ± 6
PVR (WU)	3.7 ± 2.2	4.1 ± 2.2	4.2 ± 2.2	4.3 ± 2.2

Predictors of persistent PH post-LVAD

Variable	p-value
HF duration >8 years	0.4
PVR >3 UW	0.09
DPG > 0	0.06
PAC > 1.5	0.9
HM II	0.6
HVAD	0.4
Early RVF	0.02

- No Echo or RHC parameter significantly different between pts with / without postop RVF
- Related to early RVF
  - Ischemic etiology (61%) vs non-ischemic (40%), p 0.04
  - Disease duration, 11 vs. 8 y, p 0.09
  - Bilirubin, 1.6 vs 1.2 mg/dl, p 0.08
  - Creatinine, 1.5 vs 1.1 mg/dl, p 0.02

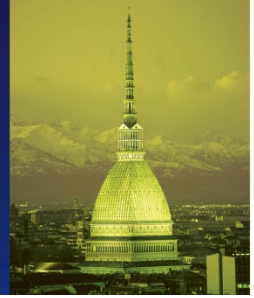
PAH drugs for PH after LVAD? *(personal viewpoint)*

- Limited observational experiences, mostly with PDE-5 inhibitors
- Some (smaller) experiences with endothelin-receptors antgonists
- Inconsistent data on hemodynamic, clinical, and survival endpoints
- In clinical trials on PAH, the pure hemodynamic effects of these drugs are modest

The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update

RECOMMENDATION	CLASS	LEVEL
Use of MCS should be considered for patients with pharmacologically irreversible pulmonary hypertension, with subsequent re-evaluation to establish candidacy	IIb	C

RECOMMENDATION	CLASS	LEVEL
If medical therapy fails to achieve acceptable hemodynamics and if the LV cannot be effectively unloaded with mechanical adjuncts, including an intra-aortic balloon pump (IABP) and/or LVAD, it is reasonable to conclude that the pulmonary hypertension is irreversible.	IIb	C

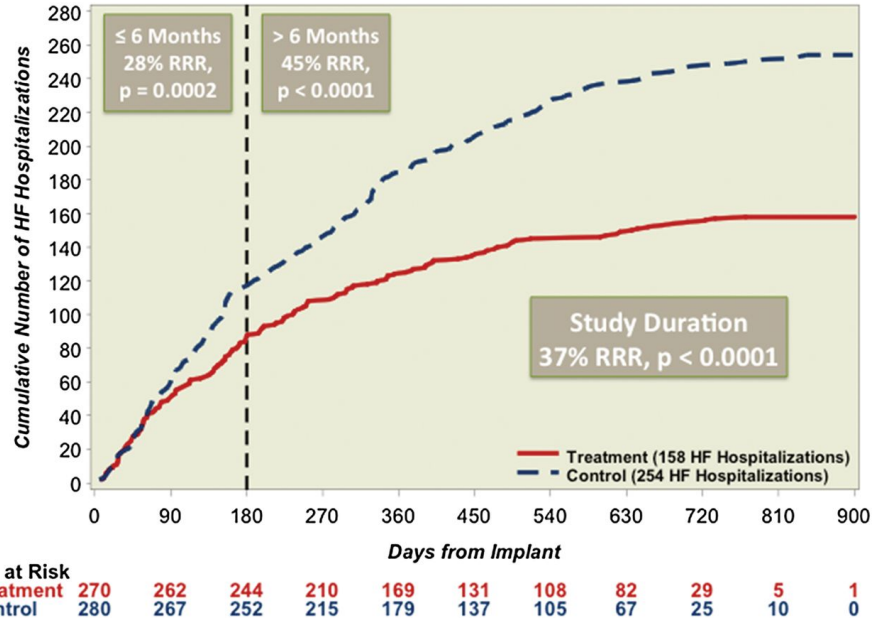


- PH in the setting of advanced HF with LV dysfunction
- PH as a risk factor for HTX
- PH reversibility for HTX candidacy: evaluation & maintenance
  - short-term strategies
  - long-term strategies
- LVAD for advanced HF with LV dysfunction & PH
- Post-HTX management of PH and RV dysfunction

➢ Perspectives

Perspective: Monitoring

- Current condition, unmet needs
  - RHC invasive and episodical
  - Noninvasive estimate (ECHO) inaccurate
  - Occasional measurements for critical decisions (to list or not to list)
- Perspective:
  - chronic hemodynamic monitoring: CardioMEMs (from occasional measurements to “PH burden”?)



CHAMPION RCT, 550 pts, Lancet 2011; 357:658

Perspective: Medical Therapy

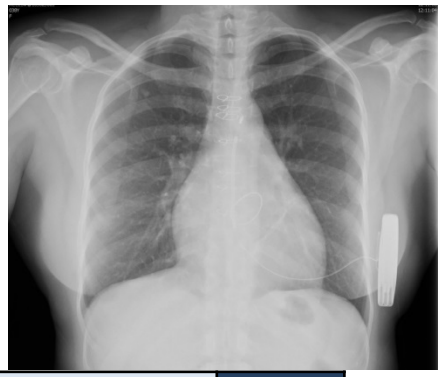
- Current condition, unmet needs
  - i.v. Inotropic Therapy: symptomatic and hemodynamic improvement, survival benefit not shown, possible risks, temporary effectiveness
  - LVAD: high rate of complications, difficult to justify only for PH control
- Perspective:
  - Explore the potential of ARNI (Sacubitril/Valsartan) in advanced HF
  - Background: first drug with combined hemodynamic and neurohormonal effect, robust evidence of benefit in stable, less severe HF patients
  - Limitations: reverse remodeling has not been systematically studied; changes of natriuretic peptides are difficult to interprete
  - Risks: hypotension, renal insufficiency, inadequate titration

GC, born 1956, IHD, h 175 cm, w 94 Kg - listed for HTX 2013

Date / Parameter	May 2013	May 2016, Baseline	Id., + SNP	Oct 2017	Jan 2018*
Standard MT	Y	Y	Y	Stop ACE-I	Id
Levosimendan			Start		Stop
Sacubitril/ Valsartan				Start	154+156 mg
RAP, mmHg	2	6	2	2	1
PAP, S/D (M) mmHg	30/13 (19)	71/25 (41)	29/10 (17)	38/17 (24)	29/11 (18)
PCWP, mmHg	14	33	10	15	11
CI, l/min/m2	1.5	1.55	1.65	1.6	2.0
PVR, WU	1.5	2.6	2.1	2.8	1.7
SysBP, mmHg	105	115	105	120	110

*: CLINICALLY STABLE TO PRESENT

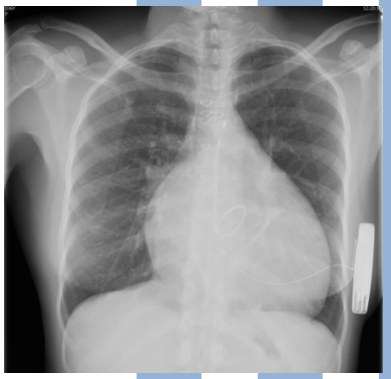
OE, F, born 1980, Peripartum DCM



Start Sacubitril/Valsartan*

2010		2015	2016	FEB 2017		SEPT 2017	OCT 2017	* 50 >> >> 200 mg	OCT 2018

Diagnosis of peripartum DCM, severe MR >> Anuloplasty >> start MT (ACE-I + BB)



HTx Workout >> HTX listed
LVEDV 340, EDD 85, EF 17%
PAPm 32 >>22, PCWP 18>>14,
CI 1.5 >> 2 NTproBNP >4000
VO2 max 13.6 (39%) VE/VCO2 49

Repeated Levosimendan at local Hosp

Worsening >> NYHA III >> prophylactic ICD >> recurrent hospitalization for ADHF

Follow-up: NYHA I/II,
LVEDV 200, EDD 60, EF 38%,
PAPm 13, PCWP 9, CI 2.5,
NTproBNP <100
>> stop Levosimendan
>> delisted for improvement

Summary

1. **PH-LVD is common** in advanced HF under consideration for HTX or LVAD
2. **Drugs for PAH are not recommended** in PH-LVD
3. Severe, resistant **PH is a major risk factor for HTX**, and a contraindication when deemed irreversible ("fixed")
4. **New insights** on intra-patient variability and time course of PH could be provided by **long term remote PAP monitoring** (CardioMEMS)
5. In **HTX candidates with reversible PH**, suitability for HTX should be verified (**periodic RHC**) and actively pursued (**maintenance therapy**)
6. **Repeated Levosimendan** may be effective, at least for some months
7. **LVAD** is effective unless in case of RVF, or inadequate LV unloading, and may be used **as a bridge or permanent therapy**
8. The role of **drugs for PAH after LVAD** remains **uncertain**
9. The **possible role of Sacubitril/Valsartan** in PH-LVD deserves to be explored
10. Patients with PH-LVD and **small LV (restrictive model)** have earlier and more severe PH, and **limited maintenance options**, thus some **priority** for donor allocation may be justified.

ACKNOWLEDGEMENTS