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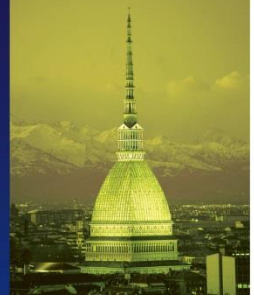
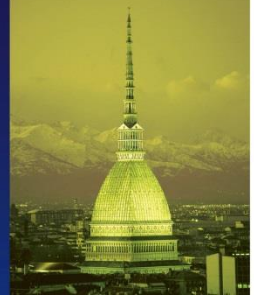


UNIVERSITÁ DEGLI STUDI DI TORINO

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

Medical Therapy after LVAD

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



- **Heart failure therapy in LVAD pts**
  - A complex framework
  - Current practices
  - Identify the goals of therapy
- **A pragmatic approach to LVAD-related issues**
  - Hypertension
  - Arrhythmias
  - RV dysfunction
  - Pulmonary hypertension

HF therapy in LVAD pts, a complex framework

	Pre-implant	Post-implant
Heart failure symptoms mainly due to…	LV dysfunction	RV dysfunction
Main mechanism of therapy	Neurohormonal antagonism	Mechanical unloading
Decisional threshold for LVEF	~35% (for prognosis, PP-ICD implantation)	~50% (for LVAD removal)

1. Is therapy modeled for HF with reduced LVEF (HF-rEF) useful also for HF with predominant RV dysfunction?
2. Is neurohormonal antagonism still useful when the LV is mechanically unloaded, and is mechanical unloading useful for myocardial recovery?
3. Is full /nearly full myocardial recovery the appropriate goal of LVAD therapy?

1. Left *vs.* Right Ventricular Dysfunction

	Left Ventricle	Right Ventricle
Diuretics	Yes	Yes
ACE-Inhibitors, ARB	Yes	?
Sacubitril/Valsartan	Yes	?
Beta-adrenoreceptor blockers	Yes	? /No
Mineralocorticoid-receptor antagonists	Yes	?/Yes

Gaps in evidences:

- Consensus statements on Acute RVD/RVF and on RVD/RVF with HF-pEF, but not on RVD/RVF with HF-rEF
- RV dysfunction and failure as markers of advanced HF-rEF due to LV disease, not as target of therapy
- Even if available, guidelines for RVD/RVF with HF-rEF could be or not be applicable to LVAD patients

2. Neurohormonal Antagonism & Mechanical Unloading

- **Neuhormonal antagonism**
  - Limited short-term hemodynamic benefit
  - Long-term biological changes in myocardial structure and function, vascular and microvascular reactivity, endothelial function, renal perfusion, and blood rheology
  - Reverse remodeling, contractile recovery (with reduced natriuretic peptides) as surrogate endpoints/ markers of survival benefit
- **Mechanical Unloading**
  - Early (immediate) hemodynamic benefit
  - “Passive” reduction of LVV and LVD is common
  - Limited and controversial data on the effects of mechanical unloading on myocyte structure and function (etiology and stage of disease; degree and modality of unloading; evaluation of myocardial recovery; concomitant pharmacological treatment…)

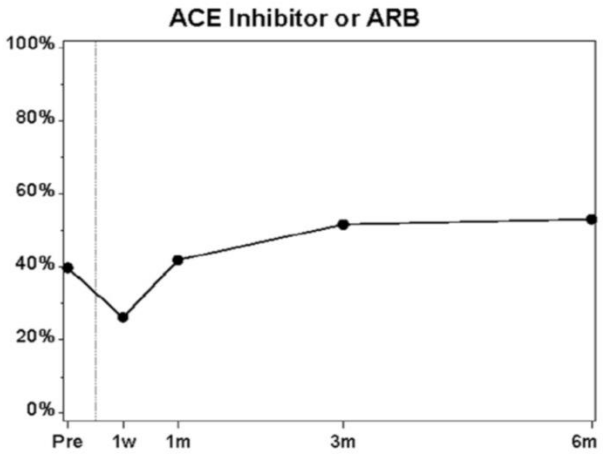
3. Myocardial Recovery, how much is enough?

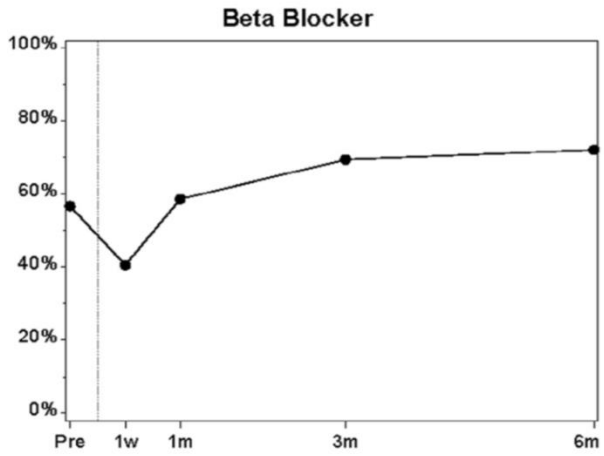
Therapy	LVEF Threshold	Implications
Drugs	≥ 35%	ICD, Primary prevention
CRT	≥ 35%	Low risk for SD
Drugs +/- CRT	≥ 45%	Low risk for cardiac events, good prognosis
Temporary MCS (de novo HF)	*+ 15-20% from baseline*	*Weaning*
Long term MCS (LVAD)	≥ 50%	LVAD Removal

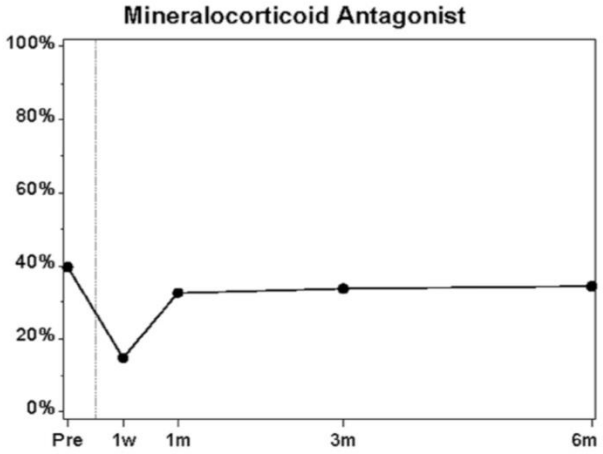
Paradoxes:

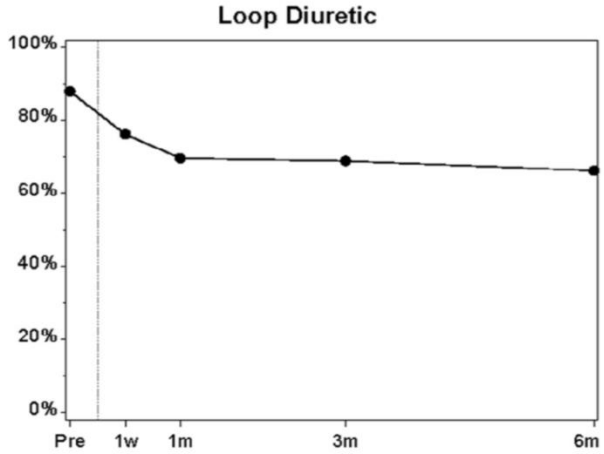
- We set the highest threshold in pts with most advanced disease, when the room for recovery is the lowest
- The expected implication of the highest effectiveness of LVAD therapy is ideally the removal of the therapy…

HF therapy in LVAD pts, current practices









INTERMACS Registry

LVAD implants 2008-13

N=9359

M	80%
Age 50-70	60%

Intention to treat

DT 36%

BTT	26%
BTC	36%

INTERMACS profile

1	15%
2	38%
3	28%
4	14%
5+	5%

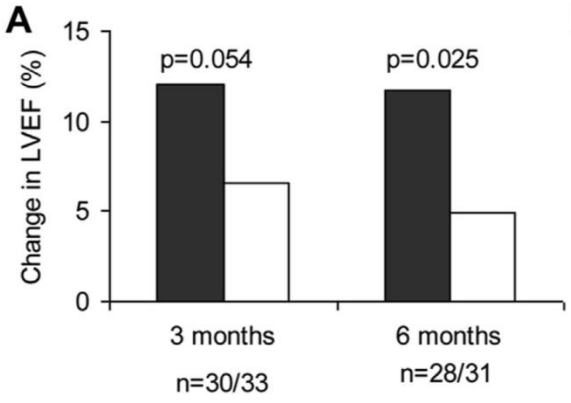
Khazanie P et al. J Cardiac Fail 2016; 22: 672-9

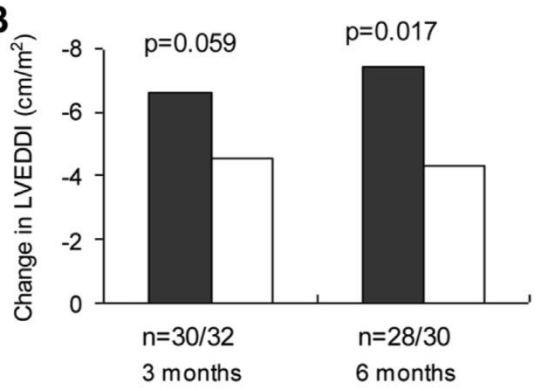
ISHLT recommendations - 2013

Therapy	May be used…	Class, evidence	Perceived risk
ACE-I/ARB	- For hypertension - In pts with CAD - In pts with diabetes - *Reverse remodeling*	I C I C I C -	- Hypotension - Renal insufficiency - Hyperkalemia
Beta-blockers	- For hypertension - For rate control - In pts with VT	I C I C IIa C	- Hypotension - RV dysfunction
MRA	- To reduce K+ suppl - *Antifibrotic effect*	I C I C	- Renal insufficiency - Hyperkalemia
Diuretic	- For volume overload - In pts with RVD	I C I C	- Hypovolemia
Digoxin	- In AFIB, rate control - In pts with RVD	I C I C	
PDE5-I	- *RVD, PH*	IIb, C	

Feldman D et al. J Heart Lung Transplant 2013; 32: 157-87

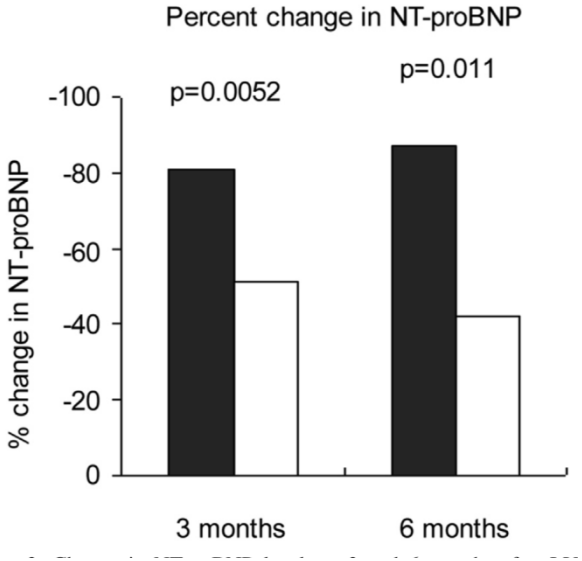
Neurohormonal antagonism in LVAD pts, observational study





Single-center study

LVAD implants, n	64
M	85%
Age	63 ± 12
Intention to treat	
DT	70%
BTT	30%
Baseline status	
On IABP	30%
On inotropes	75%



Incidence of morbidity and mortality end points at 6 months after LVAD

Clinical End Points	NHBDT (n=31)	No-NHBDT (n=33) No. with event (%)	P*
Cardiovascular death or hospitalization for HF†	0	6 (18.2)	0.013
Cardiovascular death	0	2‡ (6.1)	0.17
Hospitalization for HF	0	4§ (12.1)	0.046
All cause mortality	3¶ (9.7)	3‖ (9.1)	0.95

Grupper A et al. Am J Cardiol 2016; 1765-70

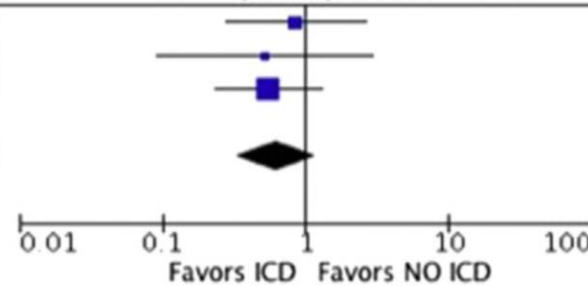
Arrhythmias in CF-LVAD: is ICD protective?

Mortality in all LVAD Patients

Study or Subgroup	ICD Events	ICD Total	no ICD Events	no ICD Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Enriquez et al.	9	62	6	36	27.8%	0.85 [0.28, 2.62]
Garan et al.	5	77	2	17	13.1%	0.52 [0.09, 2.94]
Lee at al.	18	64	15	36	59.1%	0.55 [0.23, 1.29]
Total (95% CI)		**203**		**89**	**100.0%**	**0.63 [0.33, 1.18]**
Total events	32		23			

Heterogeneity: $Chi^2 = 0.42$, df = 2 (P = 0.81); $I^2 = 0\%$
Test for overall effect: Z = 1.44 (P = 0.15)

Odds Ratio
M-H, Fixed, 95% CI

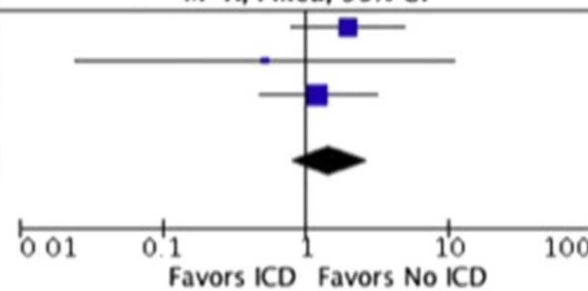


Survival in Bridge to Transplant LVAD Patients

Study or Subgroup	ICD Events	ICD Total	no ICD Events	no ICD Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Enriquez et al.	40	55	19	33	41.7%	1.96 [0.79, 4.88]
Garan et al.	34	37	9	9	8.9%	0.52 [0.02, 10.94]
Lee at al.	42	57	23	33	49.4%	1.22 [0.47, 3.14]
Total (95% CI)		**149**		**75**	**100.0%**	**1.47 [0.78, 2.76]**
Total events	116		51			

Heterogeneity: $Chi^2 = 0.99$, df = 2 (P = 0.61); $I^2 = 0\%$
Test for overall effect: Z = 1.19 (P = 0.23)

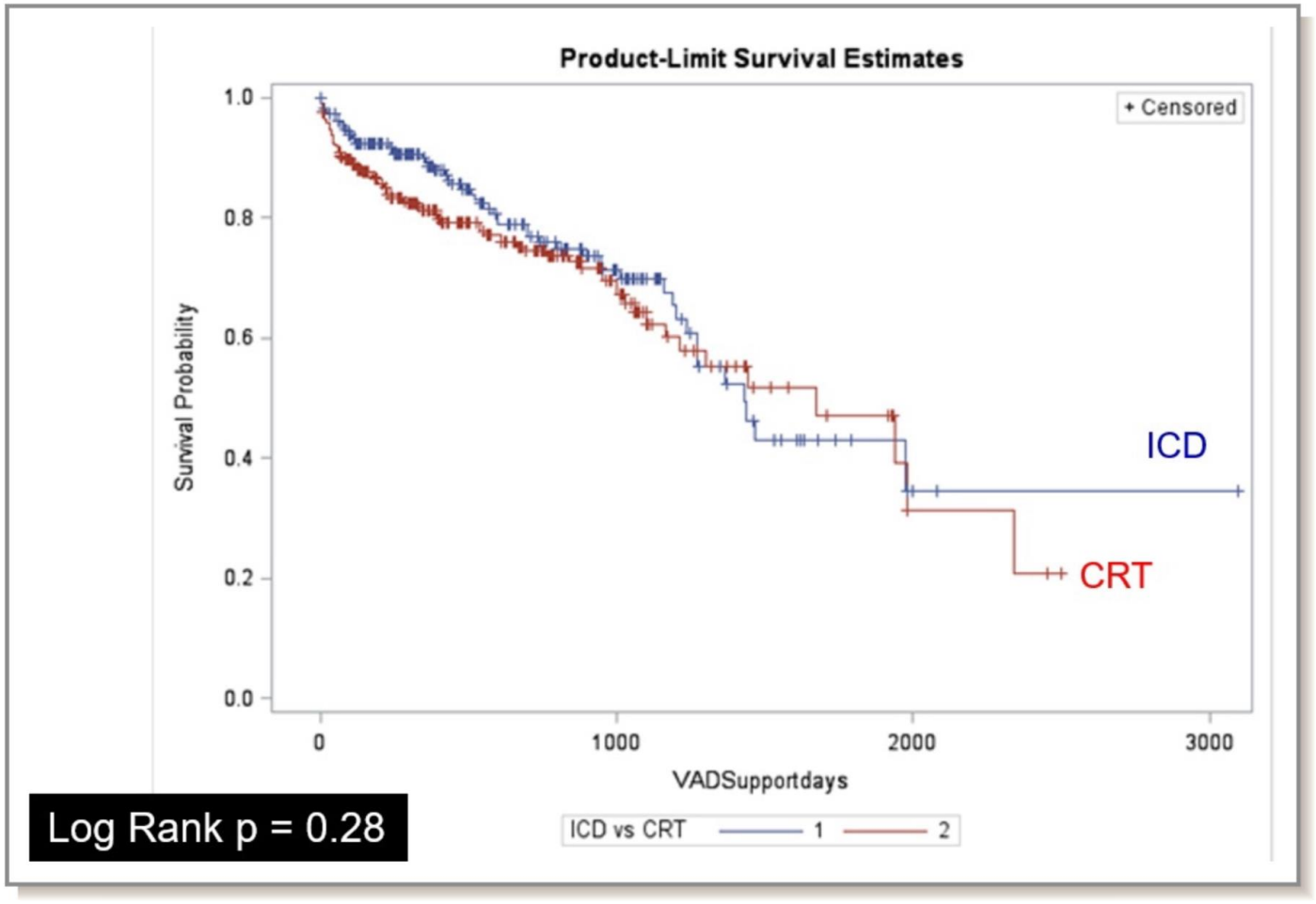
Odds Ratio
M-H, Fixed, 95% CI



Meta-analysis of observational studies, 292 pts

Agrawal S et al. Int J Cardiol 2016; 222: 379-84.

CRT in CF-LVAD



Observational multicenter study, 488 pts

Gopinathannair R et al. JAHA 2018; 7:e009091

Electric device therapy in LVAD pts

- **CRT**
  - No evidence for further benefit (or harm)
  - No rationale for withholding this therapy
  - The potential for improvement with CRT should be evaluated before LVAD implant
  - Potential complications when changing the generator
- **ICD**
  - Required in pts with implanted ICD and arrhythmias
  - Doubts concerning the need for *de novo* implantation for primary prevention
  - Potential complications when changing the generator
  - Warning: SVT/VF are tolerated without loss of consciousness only for a limited time in CF-LVAD pts

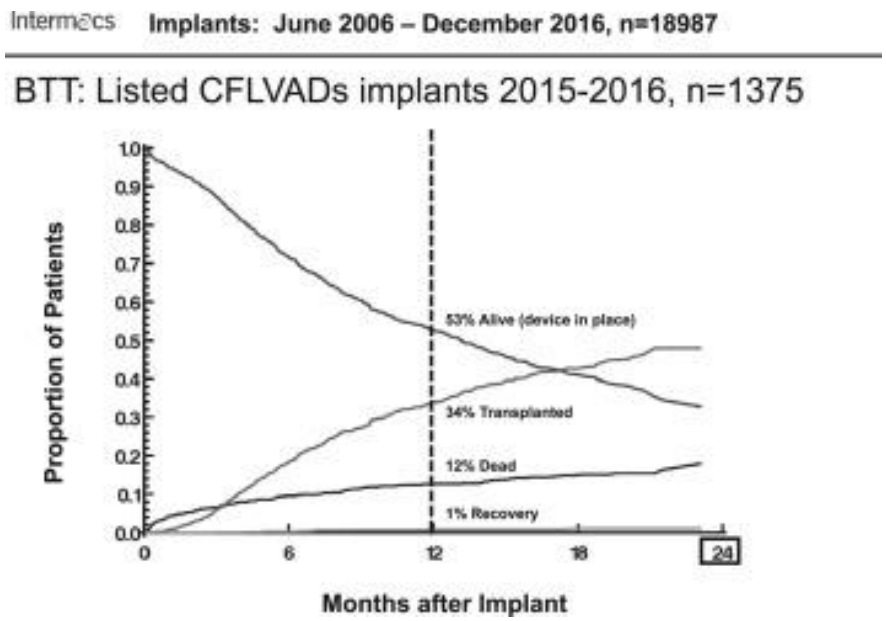
Goals & Targets of HF therapy

Condition	Reverse remodeling	SD Prevention	Reduce HF Symptoms	Other targets
Mild to moderate HF	XX	X	X	>> etiology >> mechanisms (MR, dyssynchrony..)
Severe HF	X	X	XX	>> precipitating factors
Acute *de novo* HF	XXX (recovery)	(X)	XX	>> etiology
Refractory, chronic HF	(X)	X	XX	>> advanced therapy
HTx candidates	(X)	X	XX	>> PH >> end-organ function
LVAD patients	(X?)	X	X	>> hypertension >> PH (BTT/BTC) >> complications >> arrhythmias

Is recovery a reasonable goal in LVAD pts?

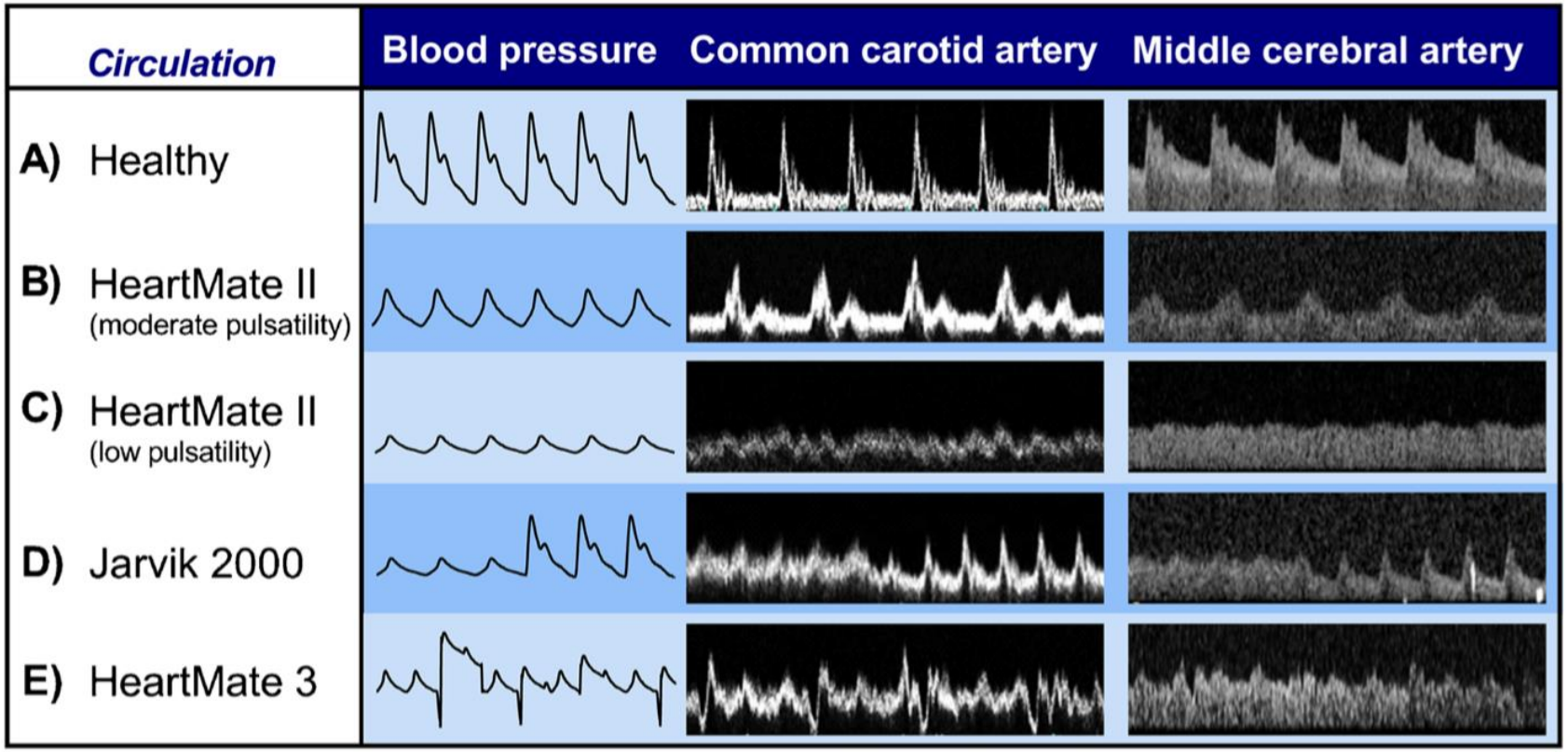
- **The patient**
  - Late stage disease
  - Extensive fibrosis
  - No/small contractile reserve
  - Reverse remodeling pursued and failed with standard therapy (chronic HF)
  - Estimated probability of recovery very low (*de novo* HF)

- **The device (CF-LVAD)**
  - Altered afterload (constant)
  - Increased vascular stiffness >> "afterload mismatch"
  - Complete unloading (preload) >> atrophy
  - Aortic insufficiency >> increased and abnormal loading (preload)



The rate of recovery that allows device removal is around 1% in a contemporary cohort

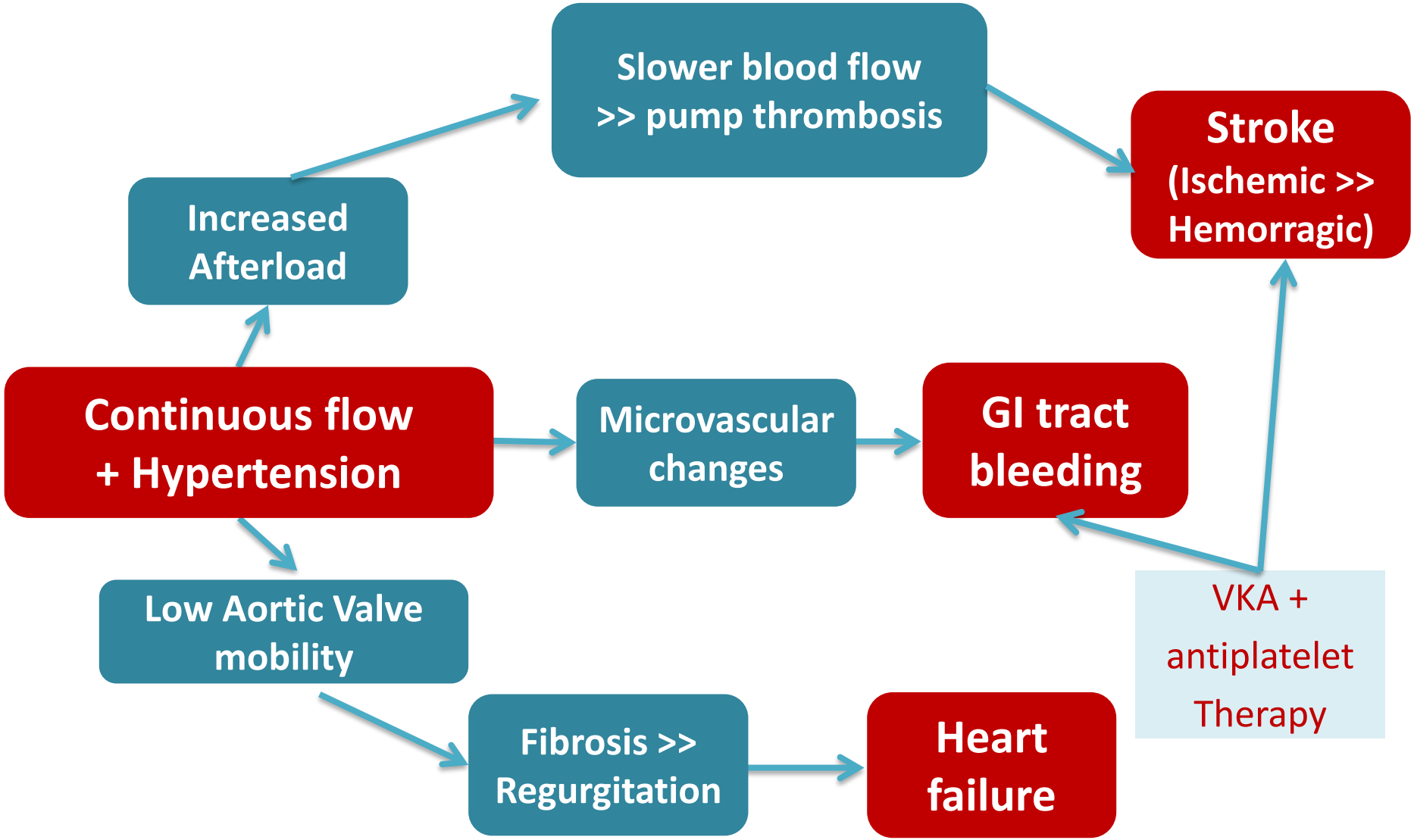
CF-LVAD: central and peripheral flow



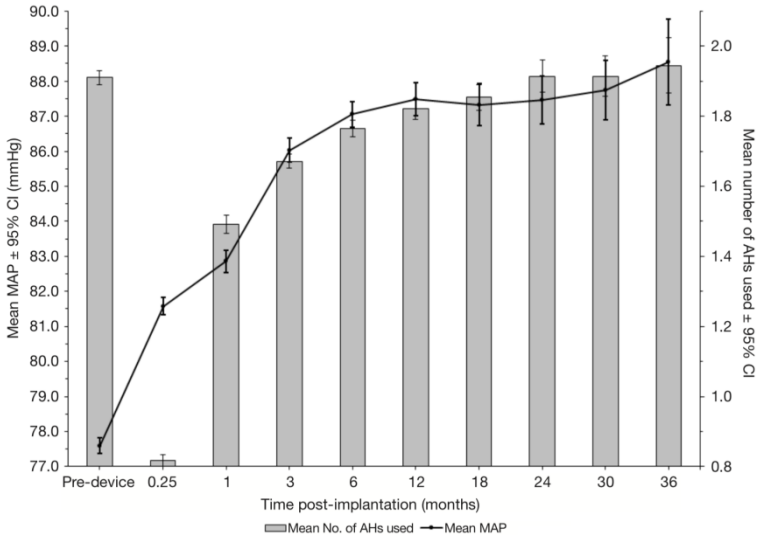
HeartMate II, Jarvik 2000: axial flow pump [MAP target $\leq$ 90 (85) mmHg];
HeartMate 3: centrifugal pump (MAP target $\leq$ 80 mmHg)

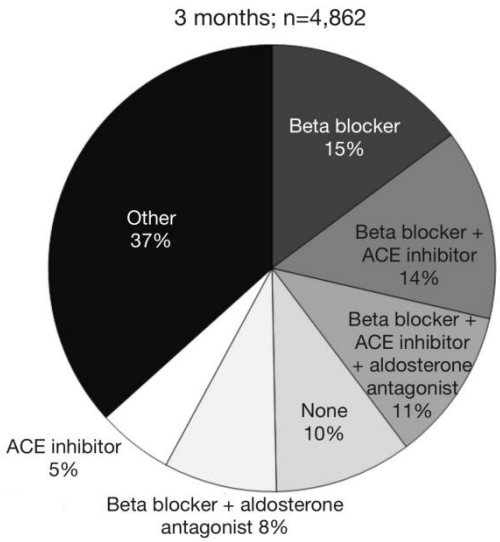
Castagna F et al. Curr Hypertens Rep 2017; 19: 85

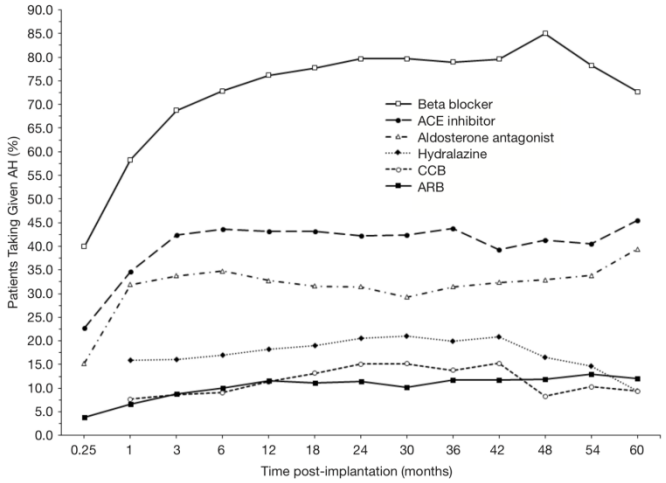
Hypertension with CF-LVAD



Hypertension therapy in LVAD pts







INTERMACS Registry

LVAD implants 2006-14

N=10329

M	79%
Age 50-70	60%

Intention to treat

DT	37%
BTT	22%
BTC	32%

INTERMACS profile

1	15%
2	37%
3	28%
4+	21%

Elmously A et al. J Thorac Dis 2018; 10: 2866-75

Arrhythmias in CF-LVAD

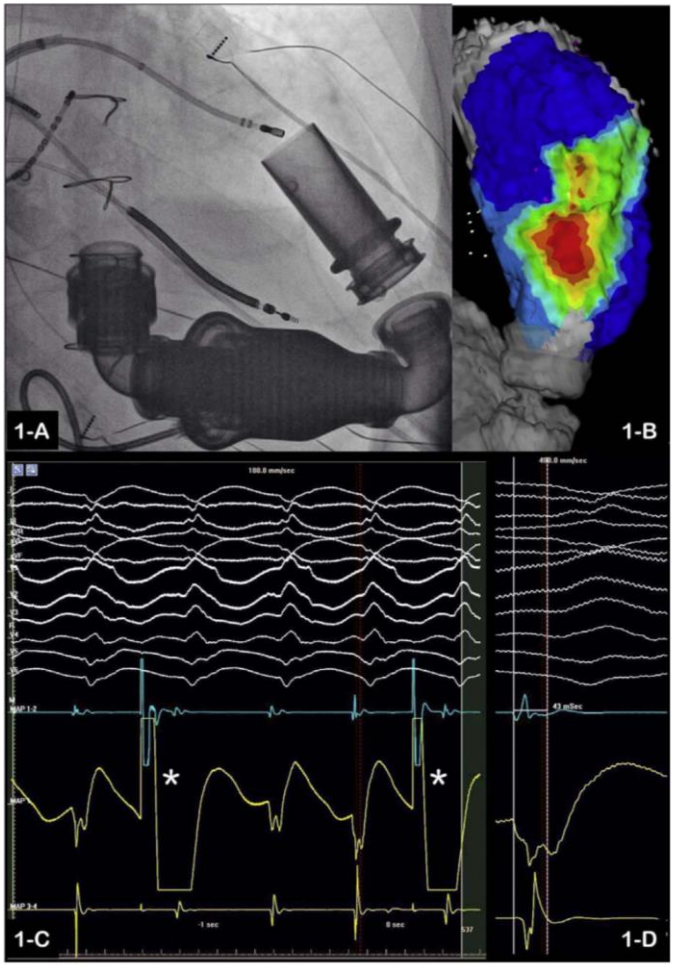
- Tachyarrhythmia events effects
  - Heart failure
  - Low output
  - Loss of consciousness (>> trauma)
  - Cardiac arrest
- Proarrhythmicg effects of LVAD?
  - Underlying disease
  - Apical myocardial injury & scarring
  - Suction phenomena
  - (Inotropic drugs)

Aggressive medical therapy
Interventional therapy (ablation)

Refractory VTs after LVAD – a case report

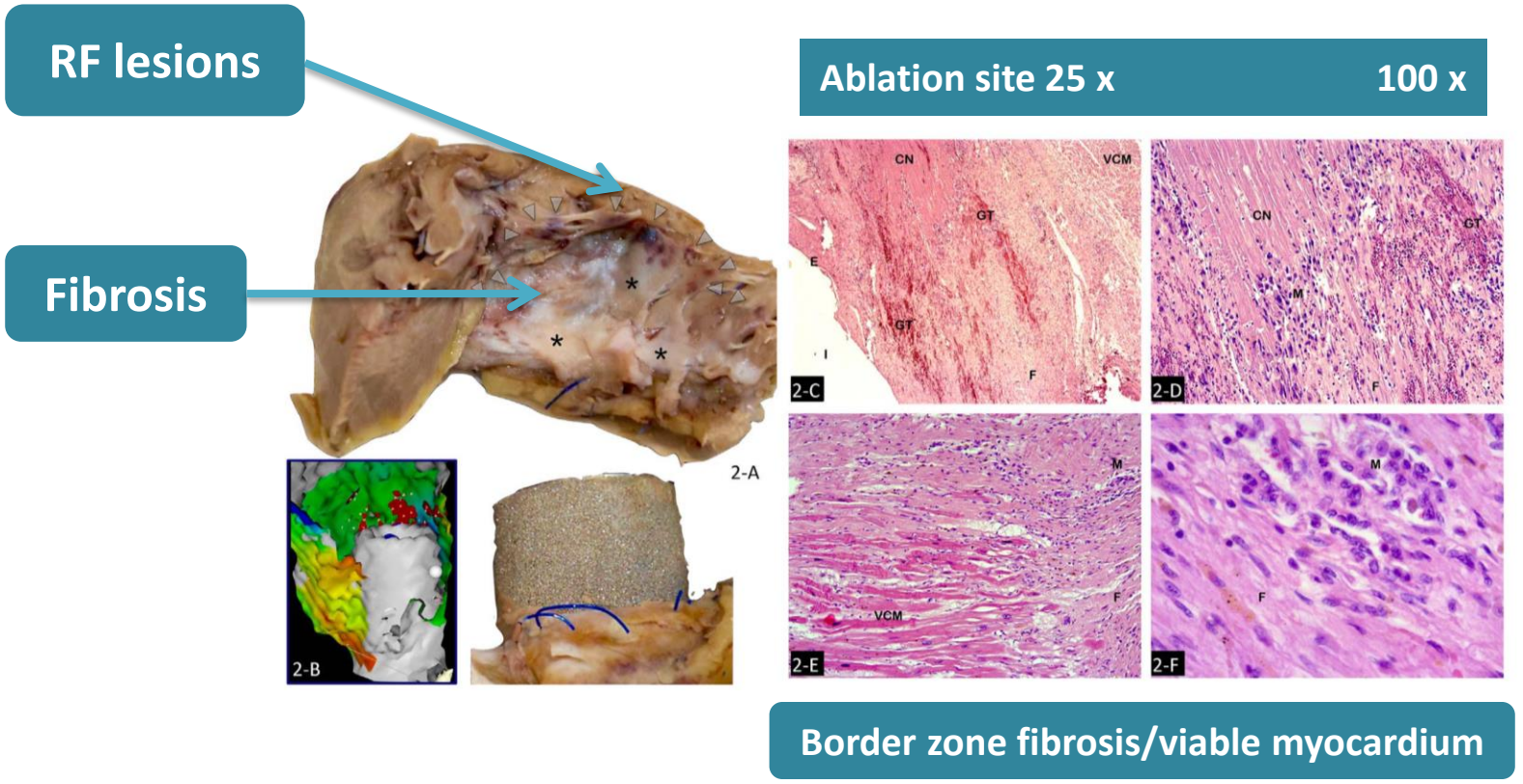
- M, 58 y, IDCM
- End-stage HF
- ICD- primary prevention
- No arrhythmias pre-LVAD
- VTD >400 ml, LVEF 16%
- NTproBNP >6000
- PCWP 26 mmHg
- IC 1.4 l/min/m2
- RVP 4, “fixed” PH
- **Intermacs 4 + PH >> HeartMate II implant**
- Excellent postop course (prompt hemodynamic and functional improvement)
- Recurrent monomorphic VTs since p.o. day 11th
- EPS reproduced clinical VT
- Short term succesful RF ablation
- Recurrence with head trauma and subdural hematoma

➢ Succesful HTX (alive, NYHA I, > 2 years)



Pedretti S et al. J Arrhythmia 2017; http://dx.doi.org/10.1016/j.joa.2017.04.007

Case report – cont'd



Pedretti S et al. J Arrhythmia 2017; http://dx.doi.org/10.1016/j.joa.2017.04.007

Summary *(my personal viewpoint)*

- No clear evidence of benefit (or harm) from standard HF therapy after LVAD implant
- The goals of therapy and the biological, myocardial, and hemodynamic substrate may be different before and after LVAD implant
- Reverse remodeling to the point that allows device removal is very rare as far as LVAD is a therapy for end-stage HF
- Specific post-LVAD issues such as hypertension, arrhythmias and right ventricular dysfunction must be pragmatically addresses
- Large RCTs with survival or hospitalization as primary endpoints do not appear the best tool for improving our knowledge in this field, since main causes of death are stroke, infection, and device thrombosis/malfunction.