Hemodynamic effects of sacubitril-valsartan in heart failure with reduced-ejection fraction: are all doses created equal?

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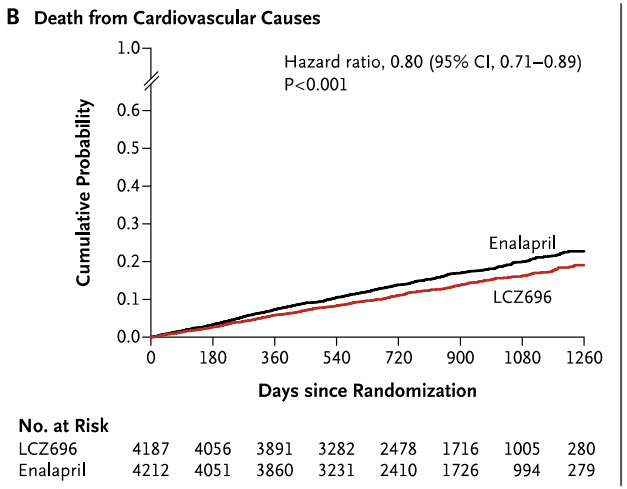
ISHLT Meeting 2020

Background

- Sacubitril/valsartan 97/103 mg b.i.d. reduces the risk of death and hospitalizations for HF.



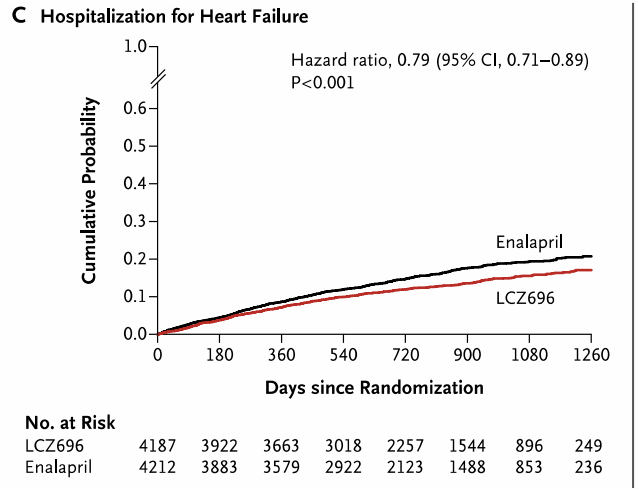


Table 3. Adverse Events during Randomized Treatment.*

Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001

PARADIGM-HF, McMurray JJ et al, N Engl J Med 2014;371:993-1004.

Open problems:

- ✓ The role of LCZ-696 in advanced HF is poorly explored
- ✓ Hemodynamic effects are uncertain
- ✓ Unknown role of drug doses lower than the full dose

Aim of the study: investigate the effect and tolerability of the drug in patients with advanced HF evaluated for HT/MCS, testing the hypothesis that its clinical effect could be related to changes in hemodynamics.

Methods

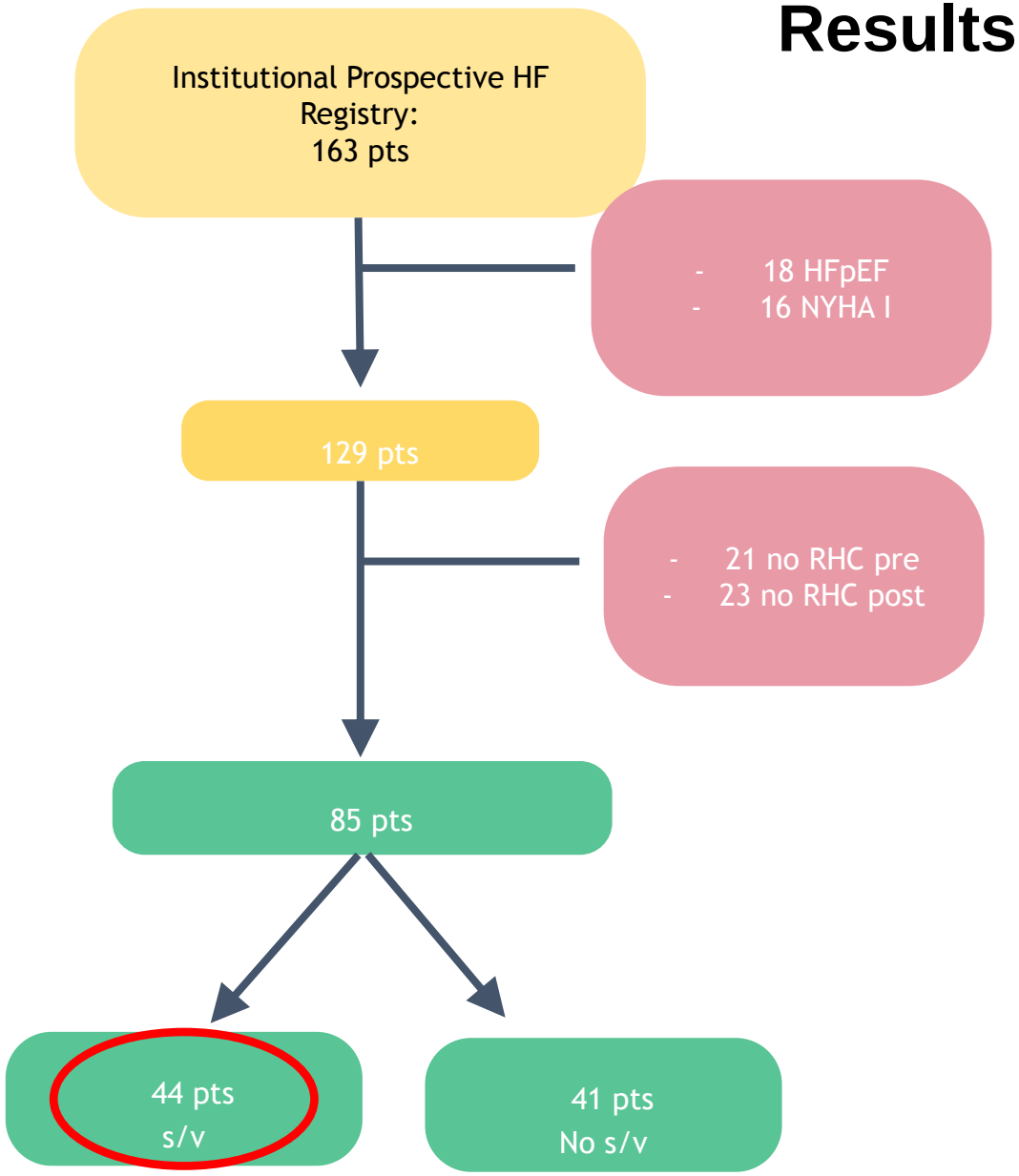
- Inclusion criteria
  - Patients included in our HF prospective Registry undergoing to two consecutive RHC (May 2017-April 2019)
  - S/V started in between (S/V group)

- Exclusion criteria:
  - NYHA I
  - already on S/V before the first RHC
  - HFpEF

- Data collected:
  - hemodynamic, clinical and echo variables
  - Dose of LCZ696 throught the follow up (expressed as % of the full dose)

- Endpoint:
  - Hemodynamic changes between the two RHC
  - Changes in symptoms, echo parameters and medical therapy
  - Comparison with a control group of patients with the same inclusion criteria not taking LCZ-696 (descriptive purposes)

Results: study population



	N=44	PARADIGM-HF
Sex (M, %)	88%	79%
Age (years)	54 ± 8	63.8 ± 11.5
CAD	45%	60%
SBP (mmHg)	108±17	122±15
LVEF (%)	27 ± 5	29.6±6.1
NYHA III-IV	46%	23.9%
Beta blockers	100%	93.1%
ACE-I/ARB	100% (62%/38%)	100%
Diuretics	100%	80.3%
Antialdosteronics	100%	54.2%
ICD	100%	14.9%
CRT	40%	7.0%

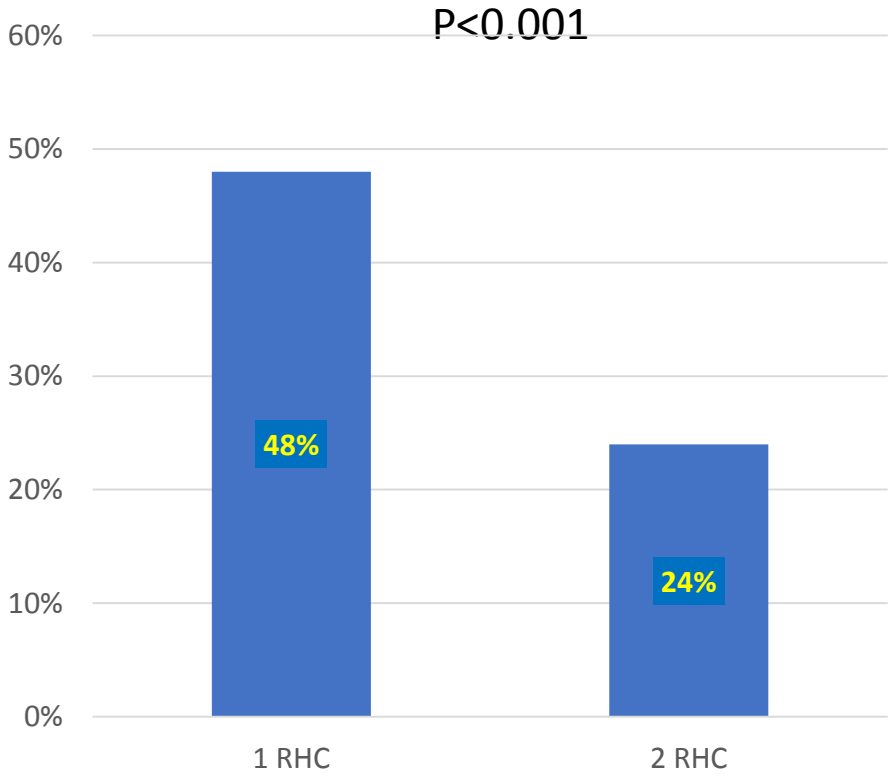
Results

hemodynamic effects

- First RHC perfomed 23 days (median value) after S/V initiation
- Second RHC: 179 ± 58 days after S/V initiation

	1 RHC	2 RHC	P
RAP (mmHg)	7.4 ± 3.5	5.4 ± 2.4	**0.0003**
mPAP (mmHg)	29.7 ± 10.6	25.9 ± 10.0	**< 0.0001**
PCWP (mmHg)	19.5 ± 7.6	17.4 ± 8.3	**0.002**
PVR (WU)	2.7 ± 1.7	2.2 ± 1.2	**0.01**
CO TD (L/min)	4.1 ± 1.2	4.2 ± 1.2	0.3
CI TD (L/min/m2)	2.1 ± 0.5	2.1 ± 0.6	0.4
Mean BP (mmHg)	83 ± 14	79 ± 14	**0.05**

Effects of ARNI on symptoms and echo data



NYHA III-IV

Echocardiographic parameters	1 RHC	2 RHC	P
EDD (mm)	68 ± 15	68 ± 16	0.8
EDV (ml)	262 ± 109	266 ± 105	0.4
EF (%)	26.3 ± 6.1	26.0 ± 6.6	0.9
Severe MR, n (%)	24%	14%	**0.04**

Echocardiographic data

Tolerability and changes in therapy after ARNI introduction

Pharmacological treatments	1 RHC	2 RHC	P value
ACE-I, % target dose	52 ± 27 %	--	—
ARB, % target dose (n)	33 ± 24 %	—	—
B-blocker, % target dose (n)	51 ± 28 %	52 ± 32 %	0.8
MRA, n	42	42	1
Furosemide (mg), (median)	181 ± 92	181 ± 106	0.9

- Diuretic dose was not changed after sacubitril/valsartan initiation
- No drug permanent discontinuation due to AEs

Role of different doses

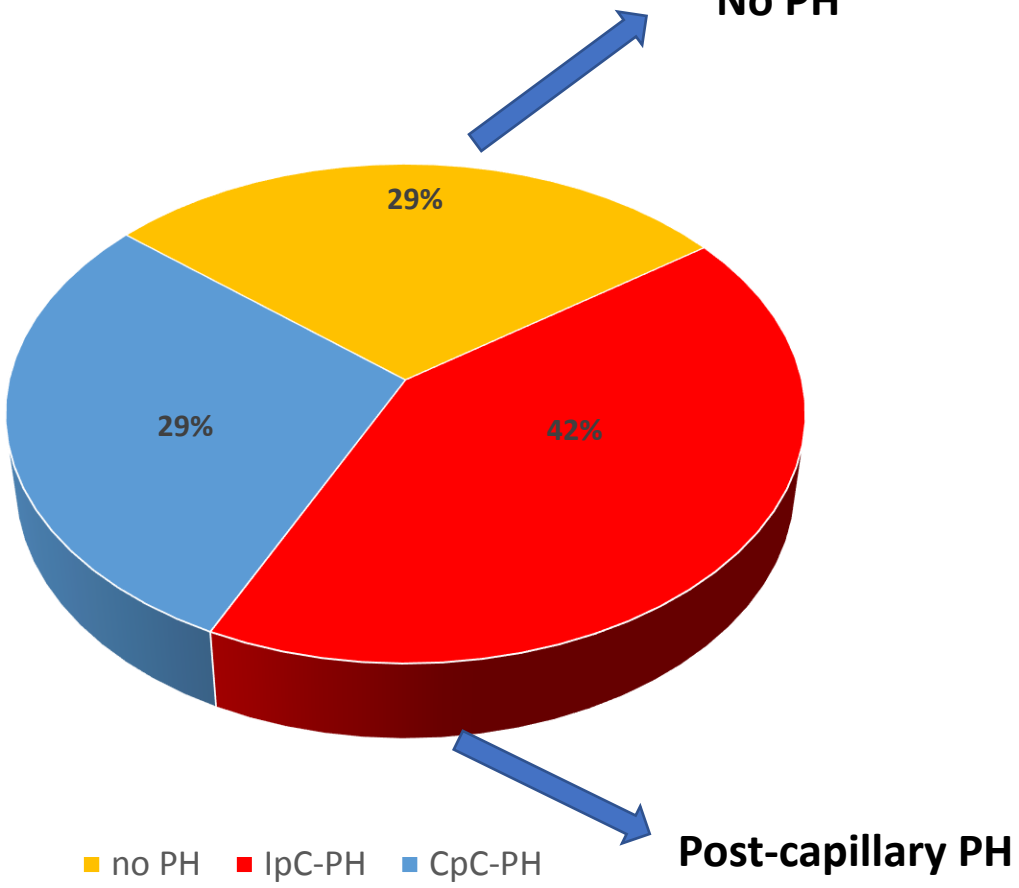
- Median dose: 37.5% of target dose (97/103 mg b.i.d.)

Difference between the two RHC	LOW (n=19)	HIGH (n=25)	P
Δ RAP	-2.2±3.9	-2.1± 3.2	0.90
Δ mPAP	-5.4± 7.4	-4.6± 7.0	0.71
Δ PCWP	-4.4± 6.5	-2.2± 5.8	0.24
Δ PVR	-0.3± 0.8	-0.9± 1.9	0.24
Δ mSAP	-5.2± 8.9	-5.3± 19.4	1
Δ CI TD	-0.1± 0.5	0.0± 0.5	0.4

Subgroups analysis:
NYHA III-IV vs II

Changes in RHC parameters	NYHA II (n=23)	NYHA III-IV (n=21)	P
Δ RAP	-1.9± 3.1	-2.4± 3.9	0.59
Δ mPAP	-5.1± 7.6	-4.8± 6.7	0.92
Δ PCWP	-3.8± 6.8	-2.5± 5.4	0.50
Δ PVR	-0.3± 1.2	-1.0± 1.8	0.14
Δ mSAP	-3.9± 19.4	-6.8± 10.3	0.54
Δ CI TD	-0.1± 0.5	0± 0.5	0.60

Subgroups analysis:
Post-capillary PH vs no PH



	1 RHC	2 RHC	P
RAP (mmHg)	6.1 ± 2.9	5.6 ± 2.6	0.6
mPAP (mmHg)	19.1 ± 4.4	18.5 ± 4.7	0.6
PCWP (mmHg)	12.7 ± 4.4	11.3 ± 4.3	0.2
PVR (WU)	1.5 ± 0.6	1.7 ± 0.6	0.4
dSAP (mmHg)	68 ± 8	66 ± 8	0.4
mSAP (mmHg)	85 ± 9	82 ± 7	0.4
CO TD (L/min)			1
CI TD (L/min/m2)			0.8

	1 RHC	2 RHC	P
RAP (mmHg)	8.3 ± 3.8	5.4 ± 2.4	0.0003
mPAP (mmHg)	36.1 ± 7.8	29.4 ± 9.8	< 0.0001
PCWP (mmHg)	24.0 ± 5.6	20.1 ± 8.3	0.006
PVR (WU)	3.3 ± 1.6	2.4 ± 1.4	0.006
mSAP (mmHg)	84 ± 9	80 ± 10	0.1
CO TD (L/min)	4.0 ± 1.1	4.2 ± 1.1	0.3
CI TD (L/min/m2)	2.0 ± 0.5	2.2 ± 0.6	0.4

ARNI vs control group

	S/V (n=44)	Control (n=41)	P
RAP	7.4±3.5	7.1±3.8	0.5
mPAP	29.7±10.6	25.9±9.5	**0.02**
PCWP	19.5±7.6	17.3±8.2	**0.04**
PVR	2.7±1.7	2.2±1.3	**0.04**
CI (TD)	2.1±0.5	2.2±0.5	0.10
SBP	83±14	79±8	**0.006**
LVAD	2%	23%	**0.04**

No differences about demographics, echo and clinical parameters between the two groups

No changes in hemodyanmics between the two RHC in the control group

Conclusions

- Limitations: small sample size, retrospective, ARNI started in pts with worse hemodynamic profile.

- Sacubitril-valsartan improves hemodynamics and symptoms in pts with advanced HFrEF by reducing pulmonary and left ventricular filling pressures and PVR already 6 months after its initiation.

- The benefit is evident within the group with post-capillary PH and seems to be independent by dose and NYHA class.

- Good tolerability even in a context of patients with lower BP

- Our results suggest that LCZ696 can lead to a significant clinical and hemodynamic improvement even at low doses, thus supporting the concept that the target dose should be patient-specific according to its tolerability.