Central Sleep Apnea: Mechanisms and Treatment Options

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CONFLICT OF INTEREST DISCLOSURES
SPEAKER:

☐ 1. I do not have any potential conflicts of interest to disclose, **OR**

☒ 2. I wish to disclose the following potential conflicts of interest

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	
Consultant	Zoll-Respicardia
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Financial support	
Other	

☐ 3. The material presented in this lecture has no relationship with any of these potential conflicts, **OR**

☐ 4. This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

Central Sleep Apnea

- Central Sleep Apnea: Pathophysiological Classification

Javaheri and Badr, SLEEPJ, 2022

Treatment of CSA

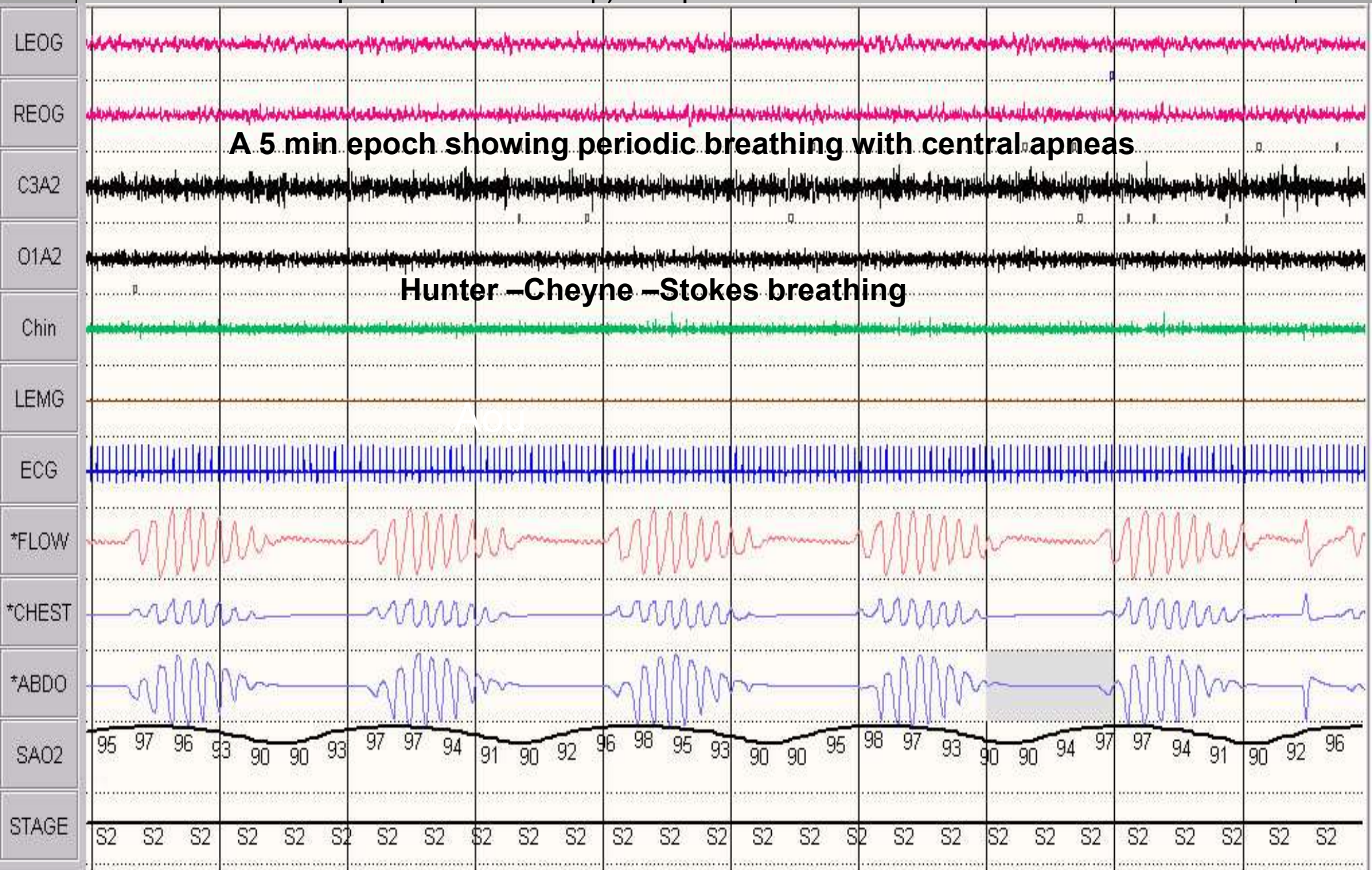
Devices (ASV, CPAP, PNS. Positional gadgets)

Pharmacological treatment

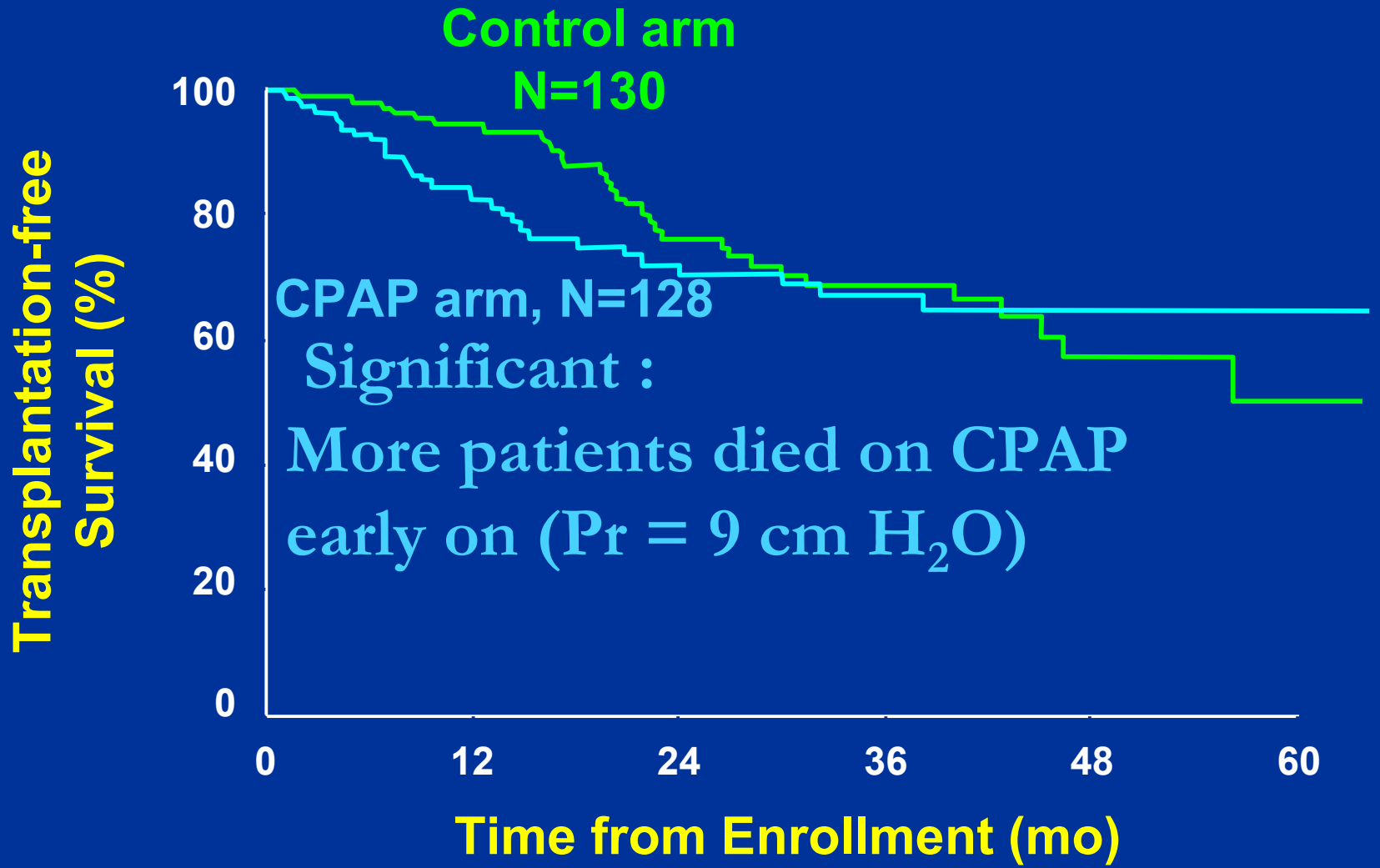
- Nocturnal O_2
- Acetazolamide
- Theophylline
- Buspirone

Combination therapy

Central sleep apnea in N2 sleep, in a patient with HFrEF



Increased CV mortality with CPAP



Bradley TD et al., *N Engl J Med* 2005

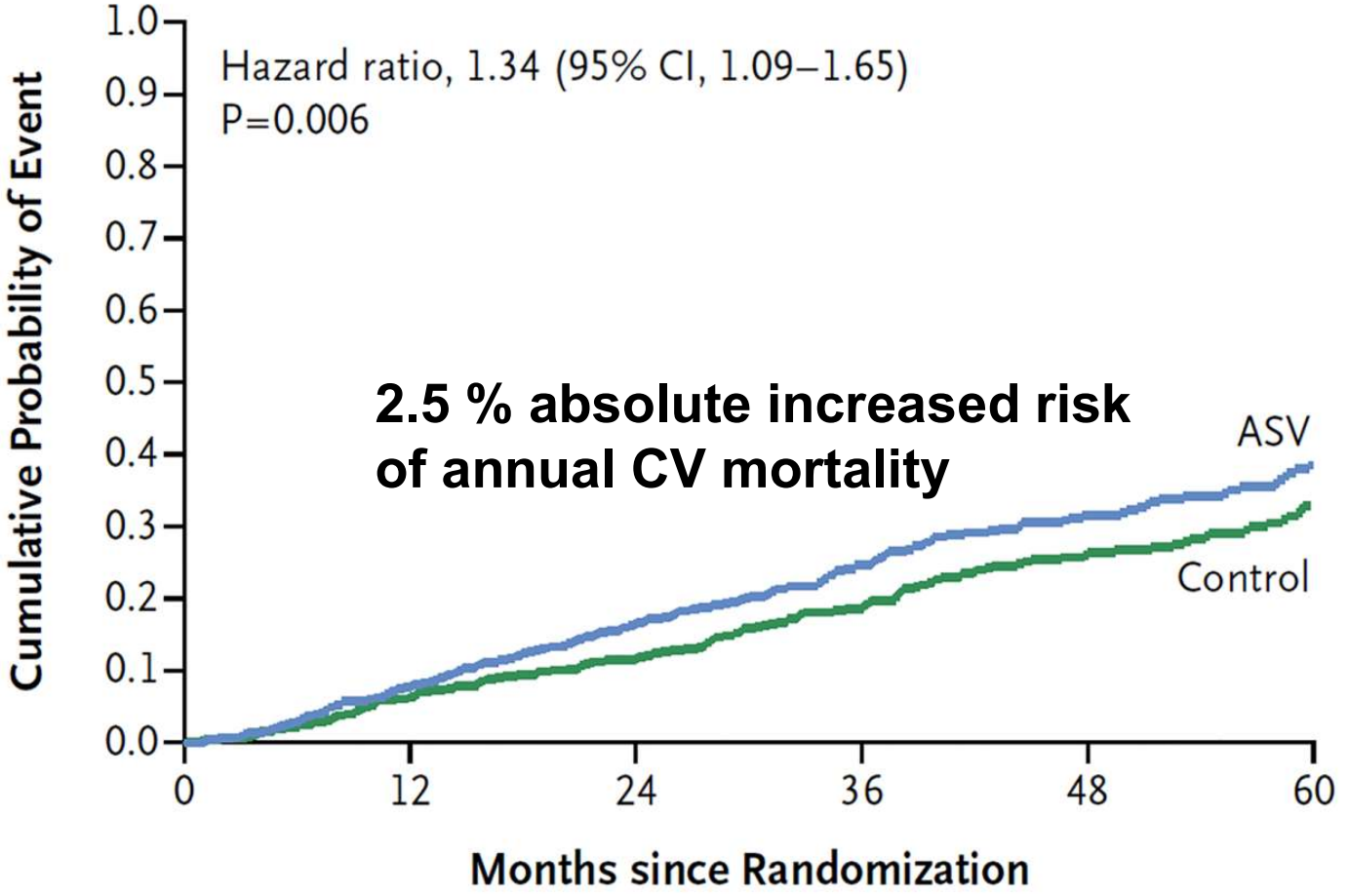
PAP RCTs in HFrEF:

Increased CV mortality with CPAP
CANPAP Trial NEJM, 2005

Increased intrathoracic Pr

Javaheri , CPAP should not be used to treat CSA in HF. JCSM, 2006

Death from Cardiovascular Causes



No. at Risk						
Control	659	563	493	334	213	117
ASV	666	555	466	304	189	97

2PAP RCTs in HFrEF:

Increased CV mortality with ASV

Increased CV mortality with CPAP

CANPAP Trial NEJM, 2005

1. Increased intrathoracic Pr
2. CSA is protective !

SERVE-HF: Javaheri et al SERVE-HF More Questions Than Answers Chest 2016

CANPAP : Javaheri , CPAP should not be used to treat CSA in HF. JCSM, 2006

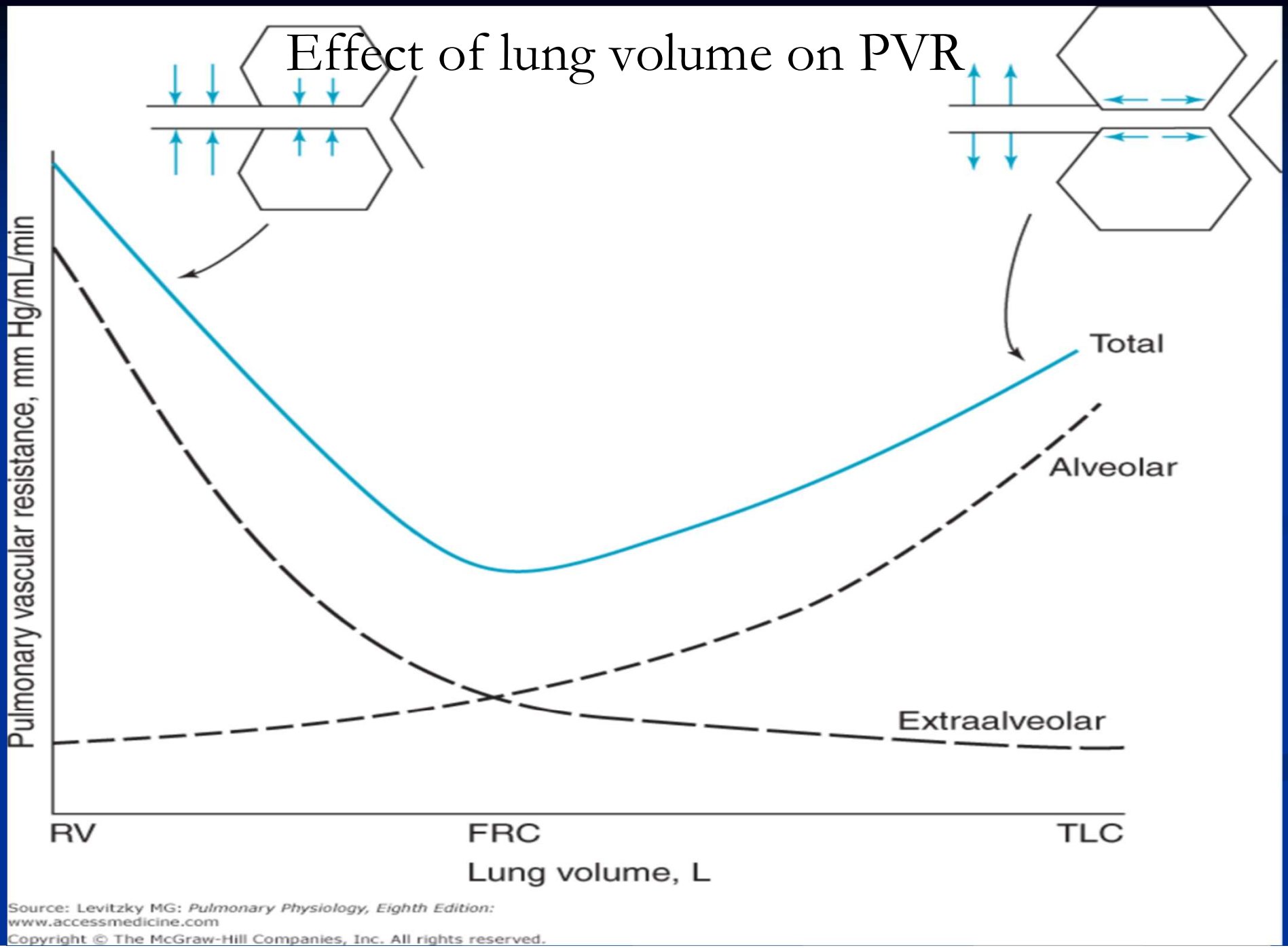
CV Consequences of increased intrathoracic pressure

1. Decreased RV preload

2. Increased RV afterload

3. Decreased LV afterload

Effect of lung volume on PVR



Source: Levitzky MG: *Pulmonary Physiology, Eighth Edition:*
www.accessmedicine.com

Issues with SERVE-HF
"ASV effectively treated sleep apnea"

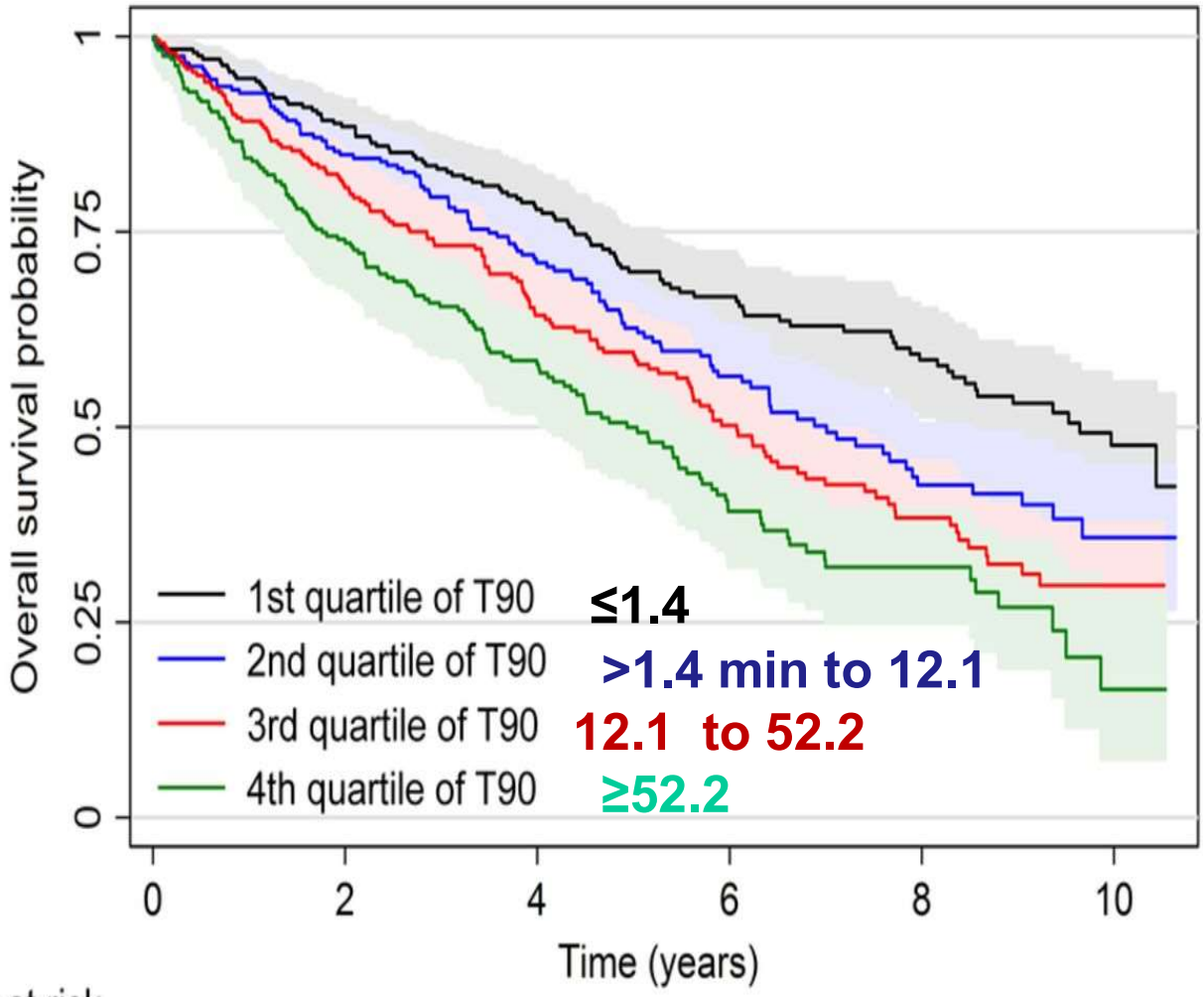
	Baseline	3m	12 m	24m	36m	48m
AHI, mean	31	7	7	6	7	7
AHI, range	10-115	0-72	0-51	0-46	0-61	0-38

SaO2< 90%, minutes

mean	51	19	20	18	19	25
range	0-459	0-344	0-268	0-285	0-291	0-278

Javaheri S, Brown LK, Randerath W, Khayat R.
SERVE-HF: More questions than answers. Chest 2016

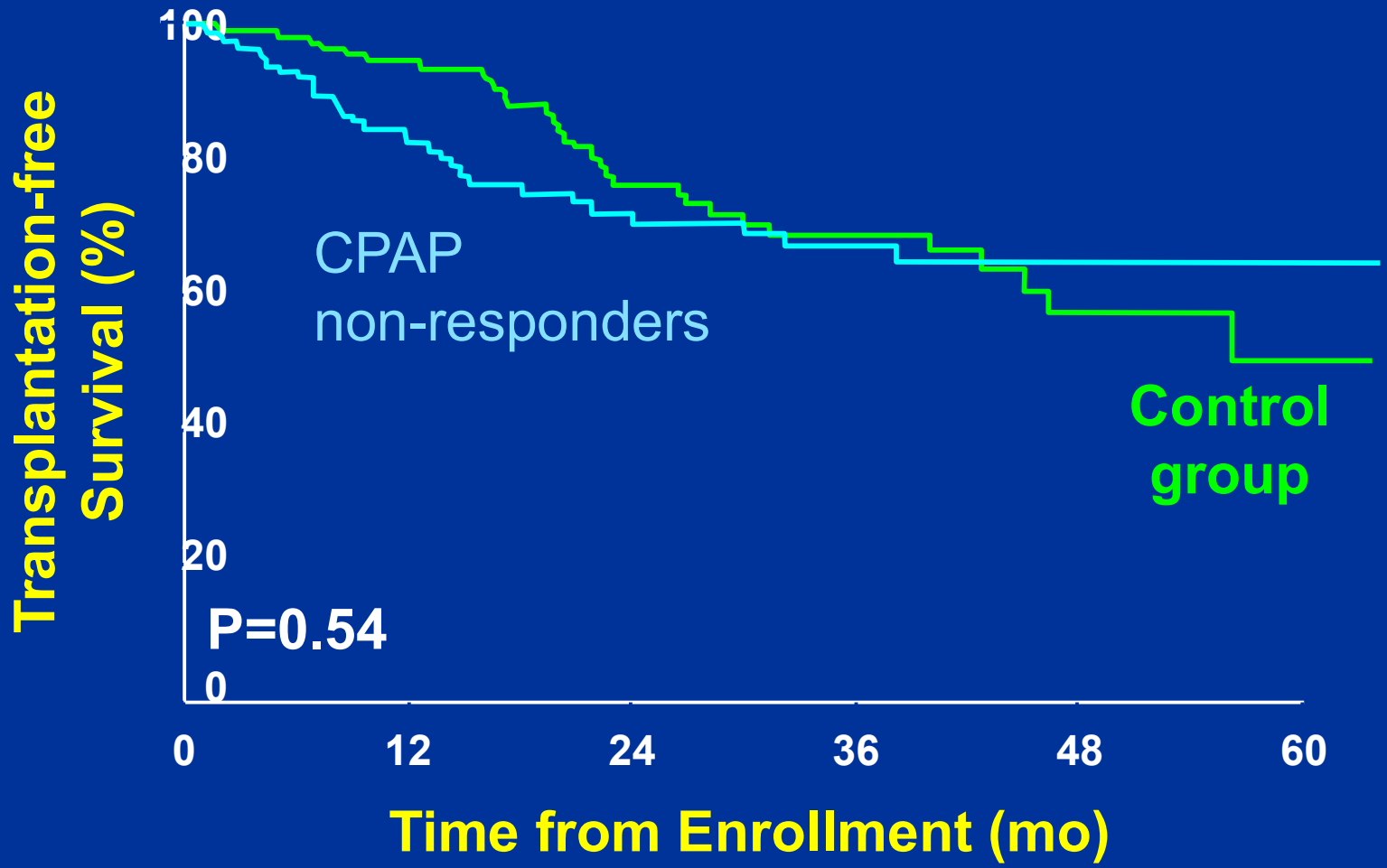
KM Survival based on time SaO_2< 90%



Number at risk

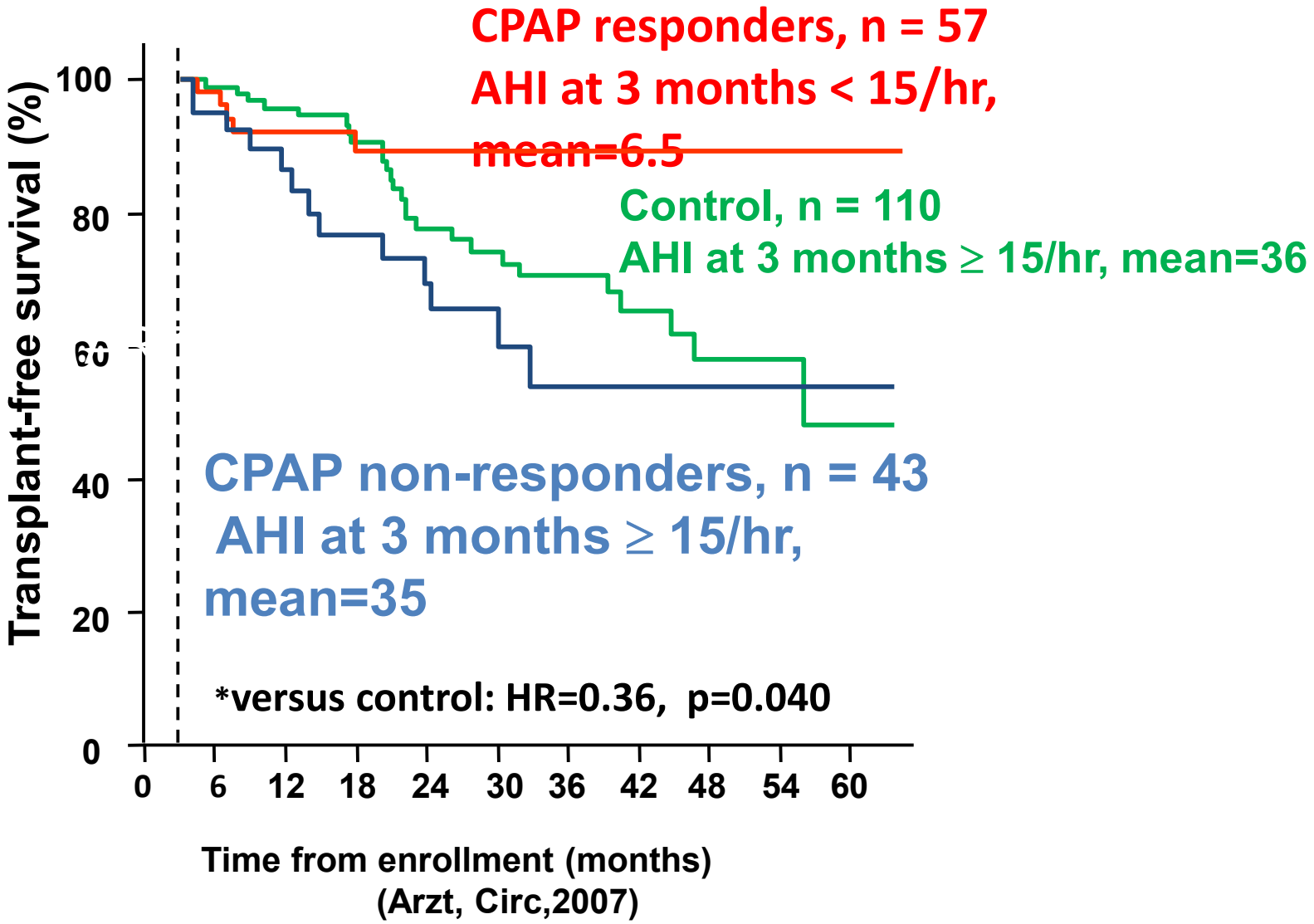
1st quartile	244	214	173	115	79	30
2nd quartile	237	191	141	82	42	11
3rd quartile	241	188	127	78	43	12
4th quartile	241	167	107	55	23	3

Heart-Transplantation-Free Survival

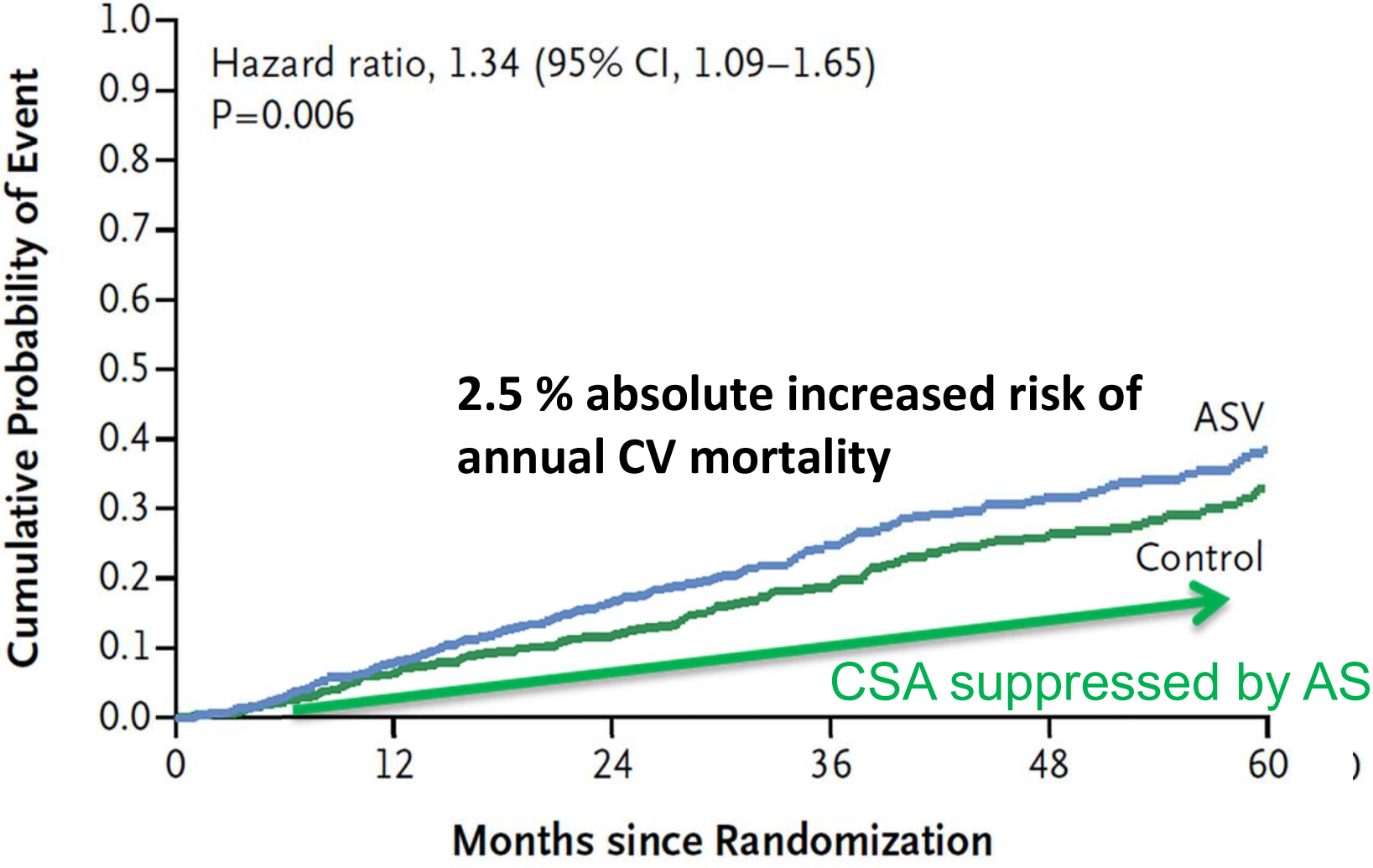


Bradley TD et al., *N Engl J Med* 2005

Transplant-free survival in the control group and according to effect of CPAP on CSA



Death from Cardiovascular Causes



No. at Risk

Control	659	563	493	334	213	117	7
ASV	666	555	466	304	189	97	7

Treatment of CSA

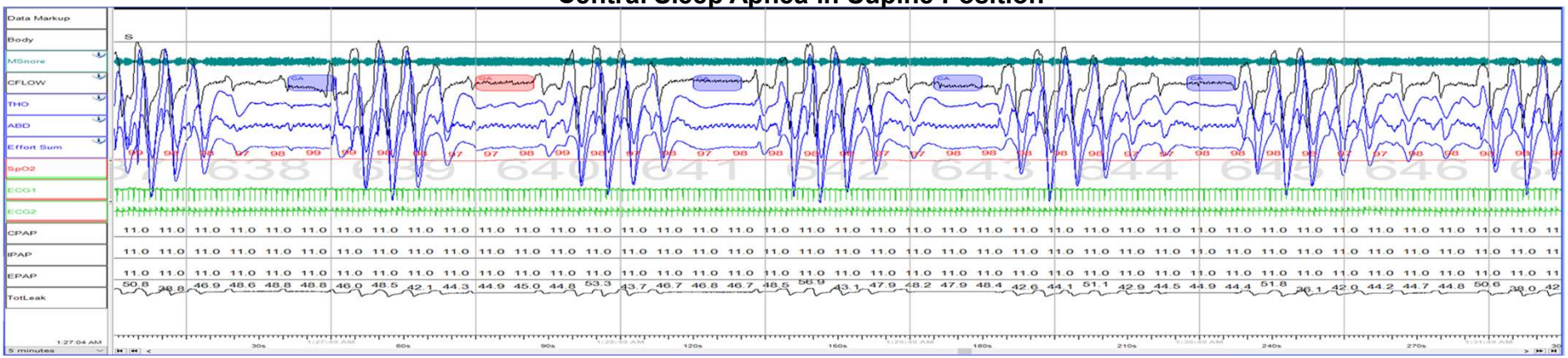
Devices (ASV, CPAP, PNS. Positional gadgets)

Pharmacological treatment

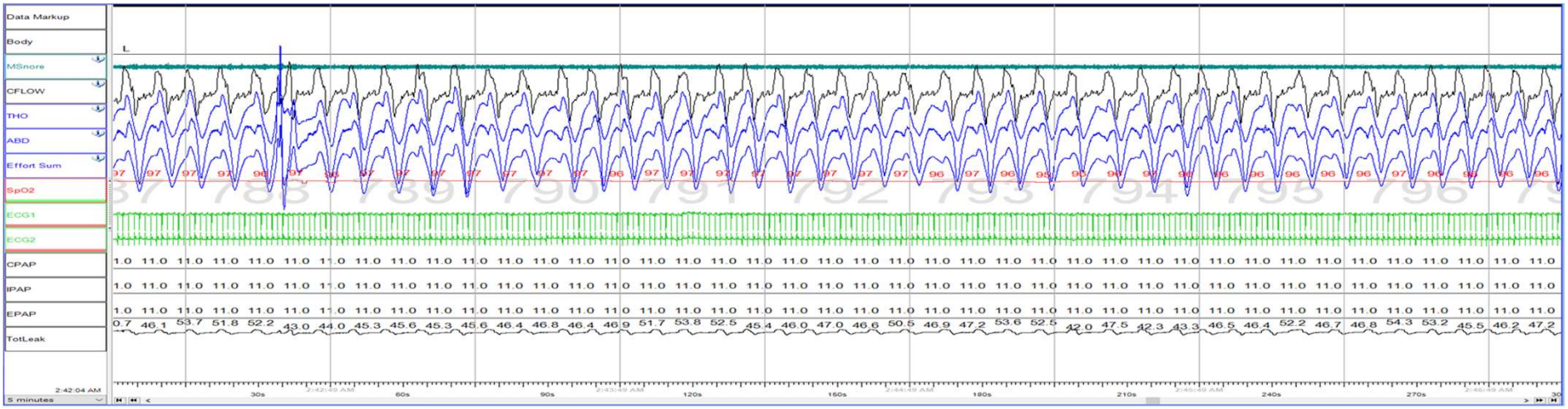
- Nocturnal O_2
- Acetazolamide
- Theophylline
- Buspirone

Combination therapy

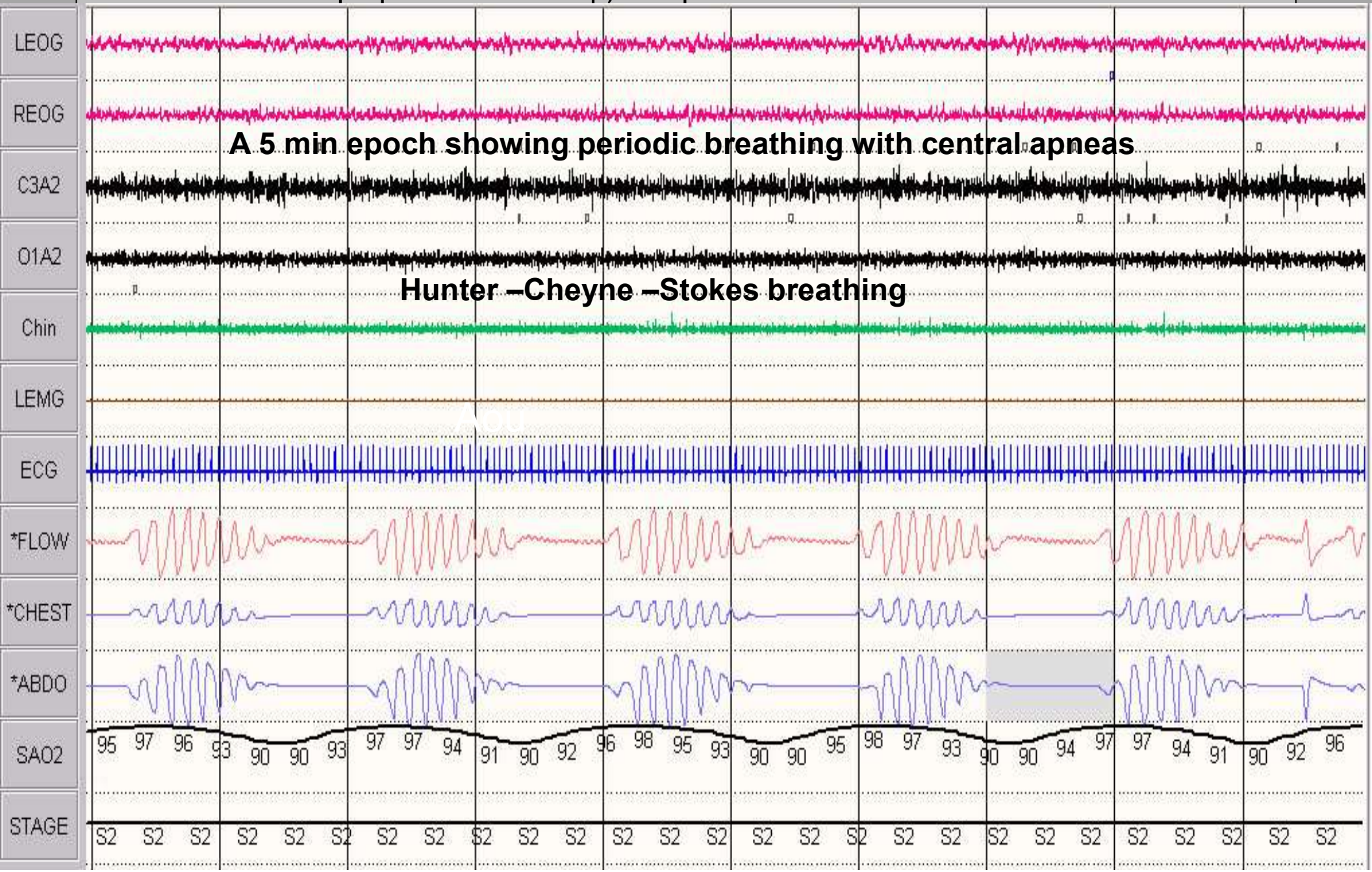
Central Sleep Apnea in Supine Position



Central Sleep Apnea in Non-Supine Position

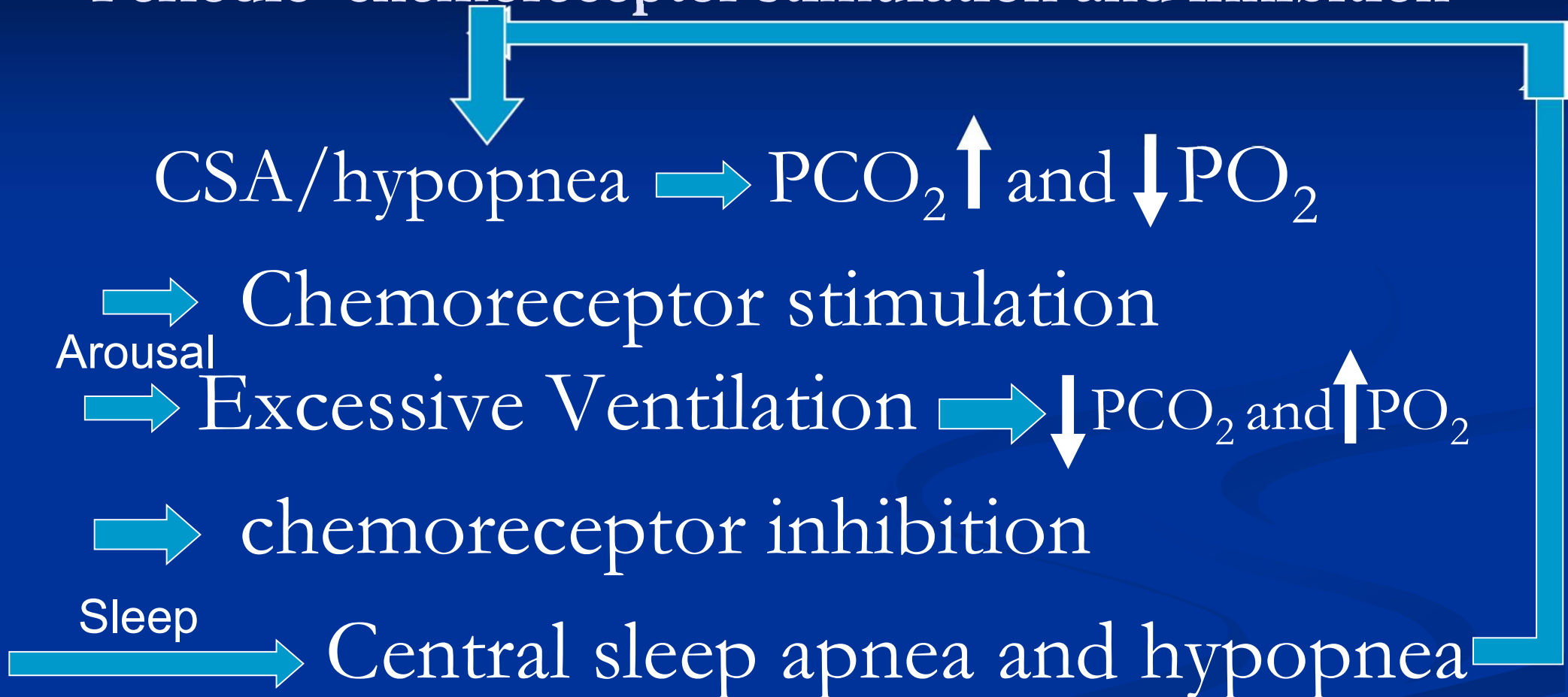


Central sleep apnea in N2 sleep, in a patient with HFrEF

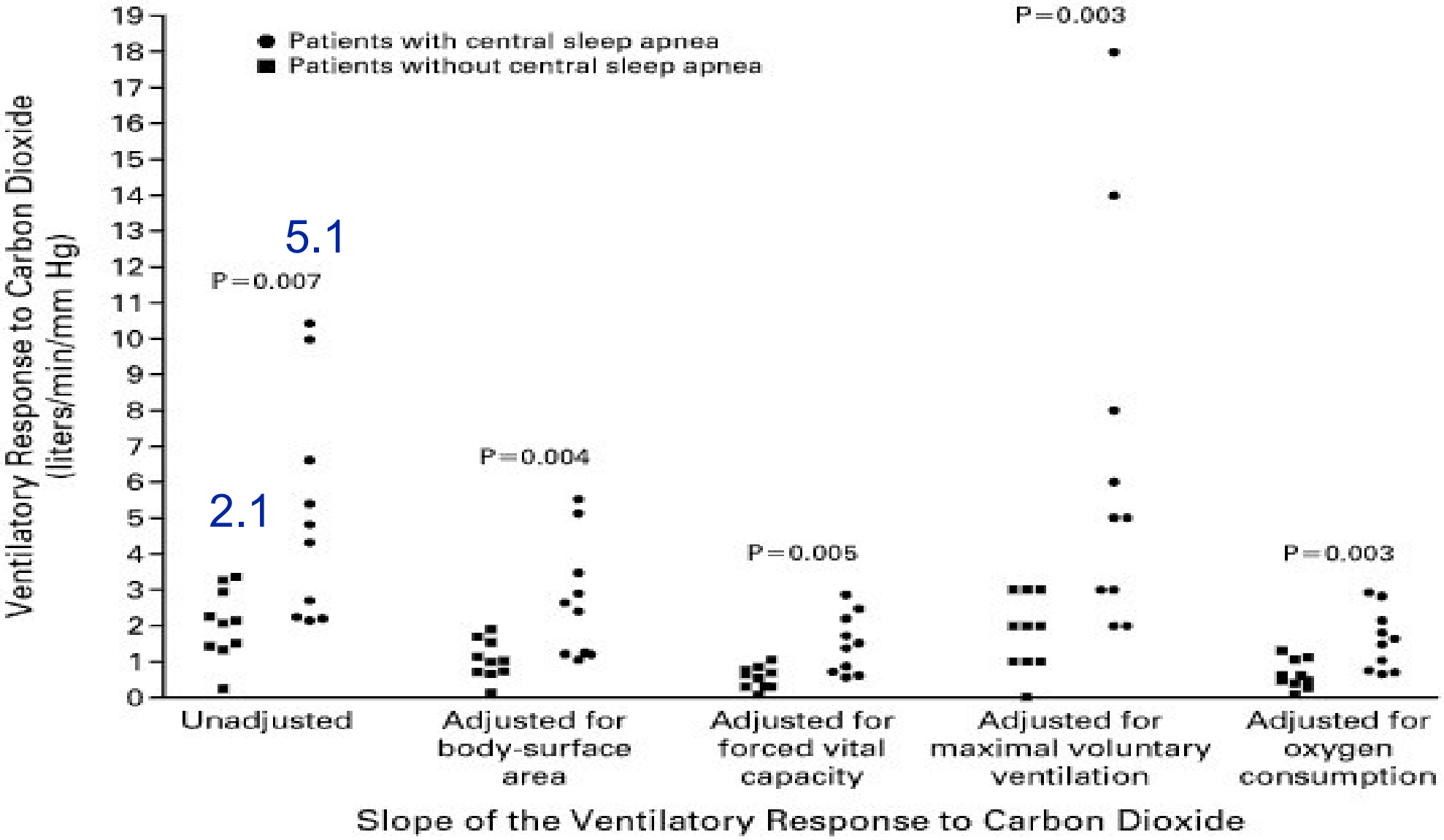


CSA Begets CSA

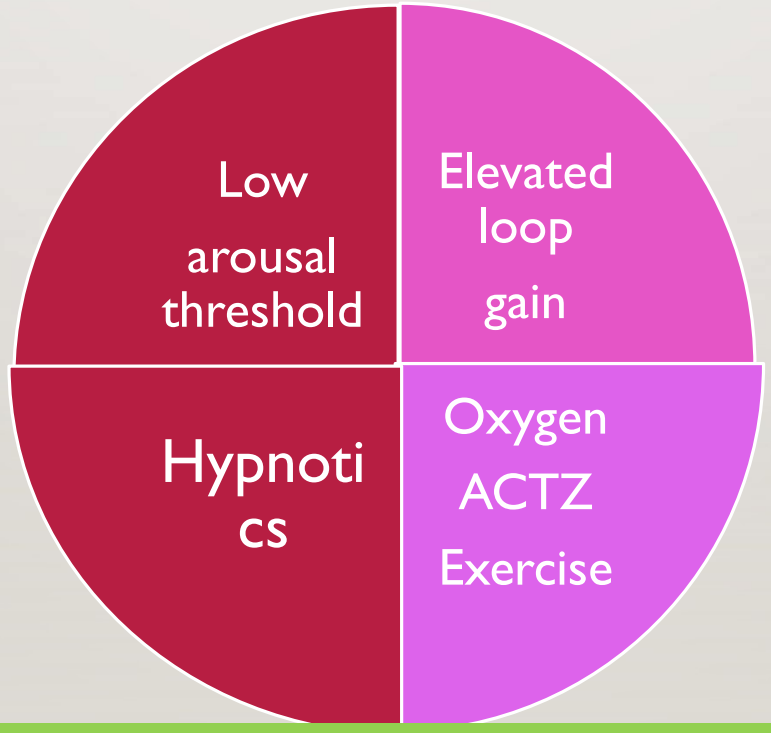
Periodic chemoreceptor stimulation and inhibition



High LG in HF(Javaheri, NEJM, 1999)



PHENOTYPE DIRECTED TREATMENT OF CSA IN HF



Interventions on multiple phenotypes: Phrenic Nerve Stimulation , ASV

Javaheri et al, CHEST,2020

Pharmacological therapy of CSA

1. Drugs downregulating

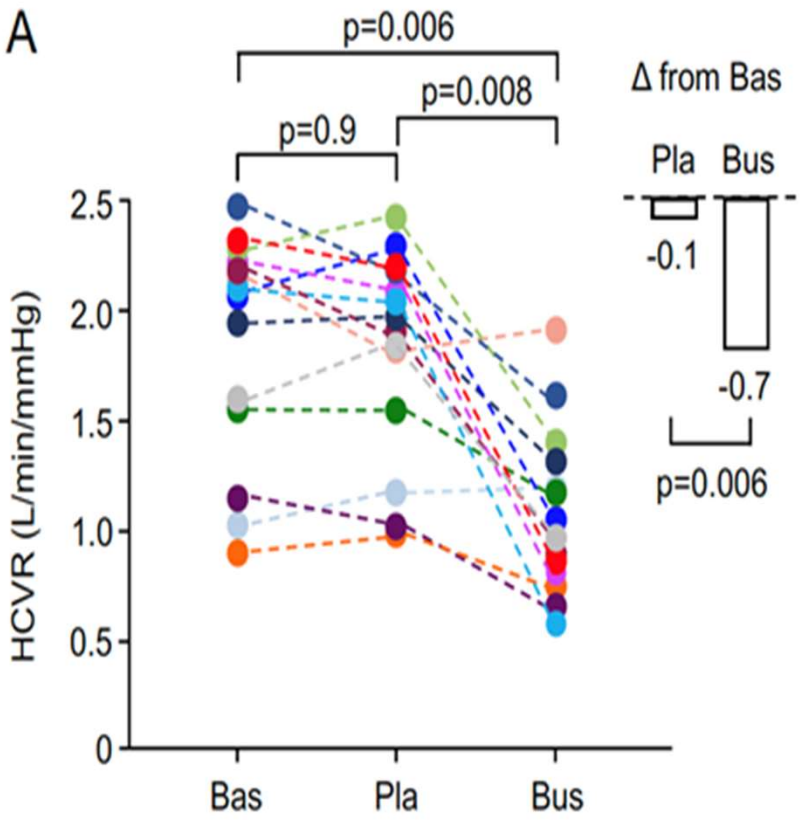
CCR (Buspirone)

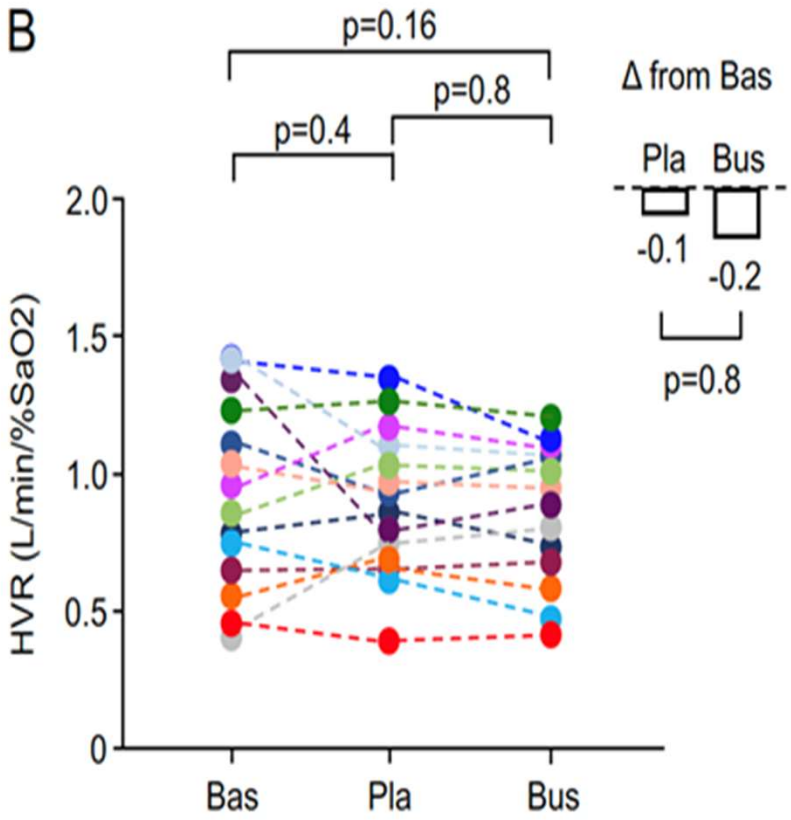
PCR (Oxygen)

2. Drugs decreasing the plant gain

Acetazolamide, theophylline, aspirin, progesterone

HCVR and HVR


A
p=0.006
p=0.008
p=0.9
Δ from Bas
Pla
Bus
-0.1
-0.7
p=0.006
HCVR (L/min/mmHg)
2.5
2.0
1.5
1.0
0.5
0
Bas
Pla
Bus


B
p=0.16
p=0.8
p=0.4
Δ from Bas
Pla
Bus
-0.1
-0.2
p=0.8
HVR (L/min/%SaO2)
2.0
1.5
1.0
0.5
0
Bas
Pla
Bus

Buspirone, a 5HT1A receptor agonist inhibits serotonergic chemoreceptor neurons

- In a crossover RCT, 16 patients (age 71 years, all males, LVEF=30%,BMI-27) were randomized to buspirone (15mg thrice daily) or placebo for 1 week, with week of wash-out

- Compared to baseline, buspirone led to a
  - *41 % reduction in CO_2 chemosensitivity, P = 0.001*
  - *42 % reduction in AHI, P <0.01)*
  - *79% reduction in CAI, P <0.01)*
  - *77% reduction oxygen desaturation index P <0.01*
  - *No effect on HVR*

- No difference was observed after placebo administration (all P >0.05)

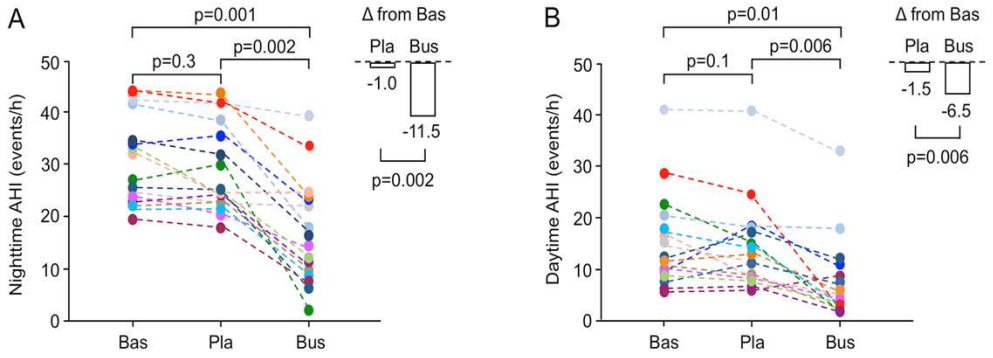
- No patient reported buspirone-related serious adverse events

Giannoni A, Borrelli C, Mirizzi G, Richerson GB, Emdin M, Passino C. Benefit of buspirone on chemoreflex and central apnoeas in heart failure: a randomized controlled crossover trial. Eur J Heart Fail 2020. Epub Ahead of Print

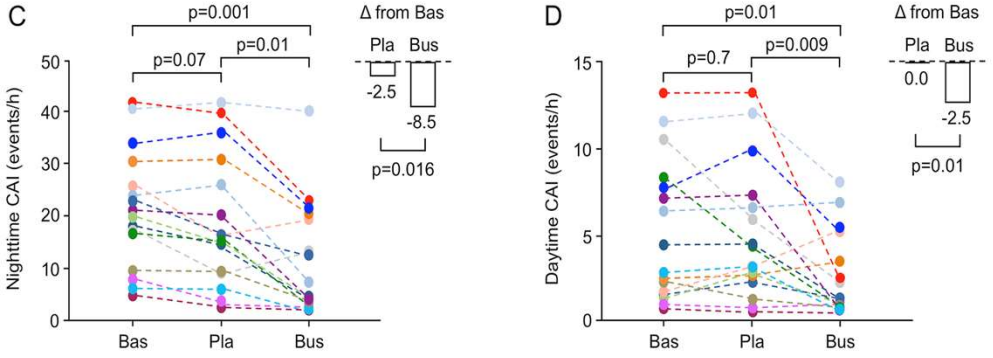
Nocturnal and Diurnal AHI and CAI

Nocturnal Diurnal

AHI/Hour of recording



CAI/hour of recording



Pharmacological therapy of CSA

1. Drugs downregulating

CCR (Buspirone)

PCR (Oxygen)

2. Drugs decreasing the plant gain

Acetazolamide, theophylline, aspirin, progesterone

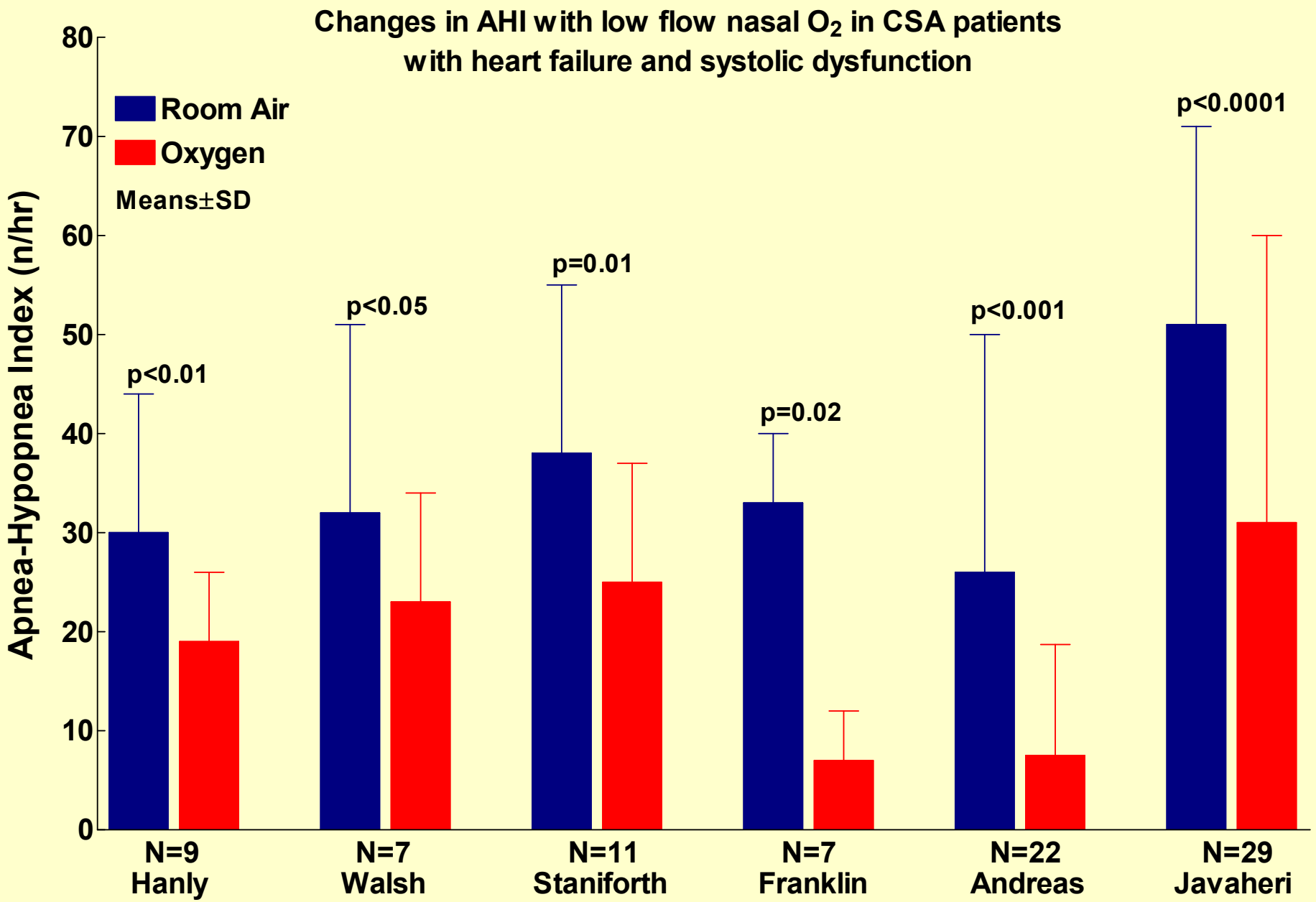
Mechanisms of O_2 Effects in CSA

↓ CB discharge Decrease hypoxic ventilatory drive

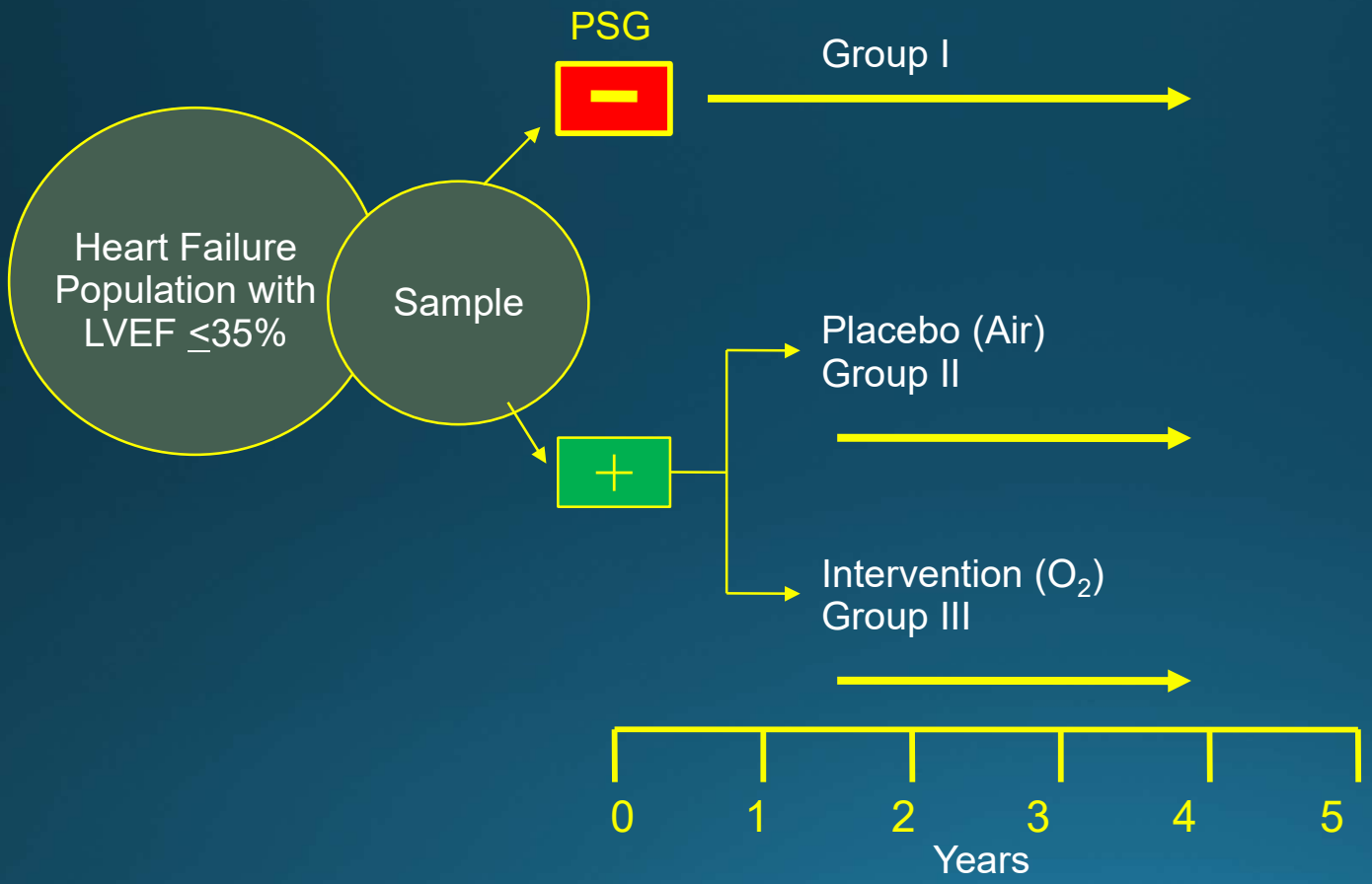
↓ Decrease in hypercapnic ventilatory drive

↑ O_2 stores which increases damping

(affecting PG)


Changes in AHI with low flow nasal O_2 in CSA patients with heart failure and systolic dysfunction
Room Air
Oxygen
Means±SD
Apnea-Hypopnea Index (n/hr)
0
10
20
30
40
50
60
70
80
p<0.01
p<0.05
p=0.01
p=0.02
p<0.001
p<0.0001
N=9
Hanly
N=7
Walsh
N=11
Staniforth
N=7
Franklin
N=22
Andreas
N=29
Javaheri

Structure of aborted VA Heart Failure O_2 Trial Javaheri and colleagues, 1988



Outcomes

Mortality

Hospitalization

Norepinephrine

LVEF

HRQOL

Sleep structure

Daytime sleepiness

6 min-walk

The Impact of **Lo**w **F**low Nocturnal Oxygen **T**herapy on Hospital Admissions and Mortality in Patients with **H**eart **F**ailure and Central Sleep Apnea

Shahrokh Javaheri MD

LOFT-HF Protocol Version J

September 28, 2020

Abraham and Redline

https://lofthf.study

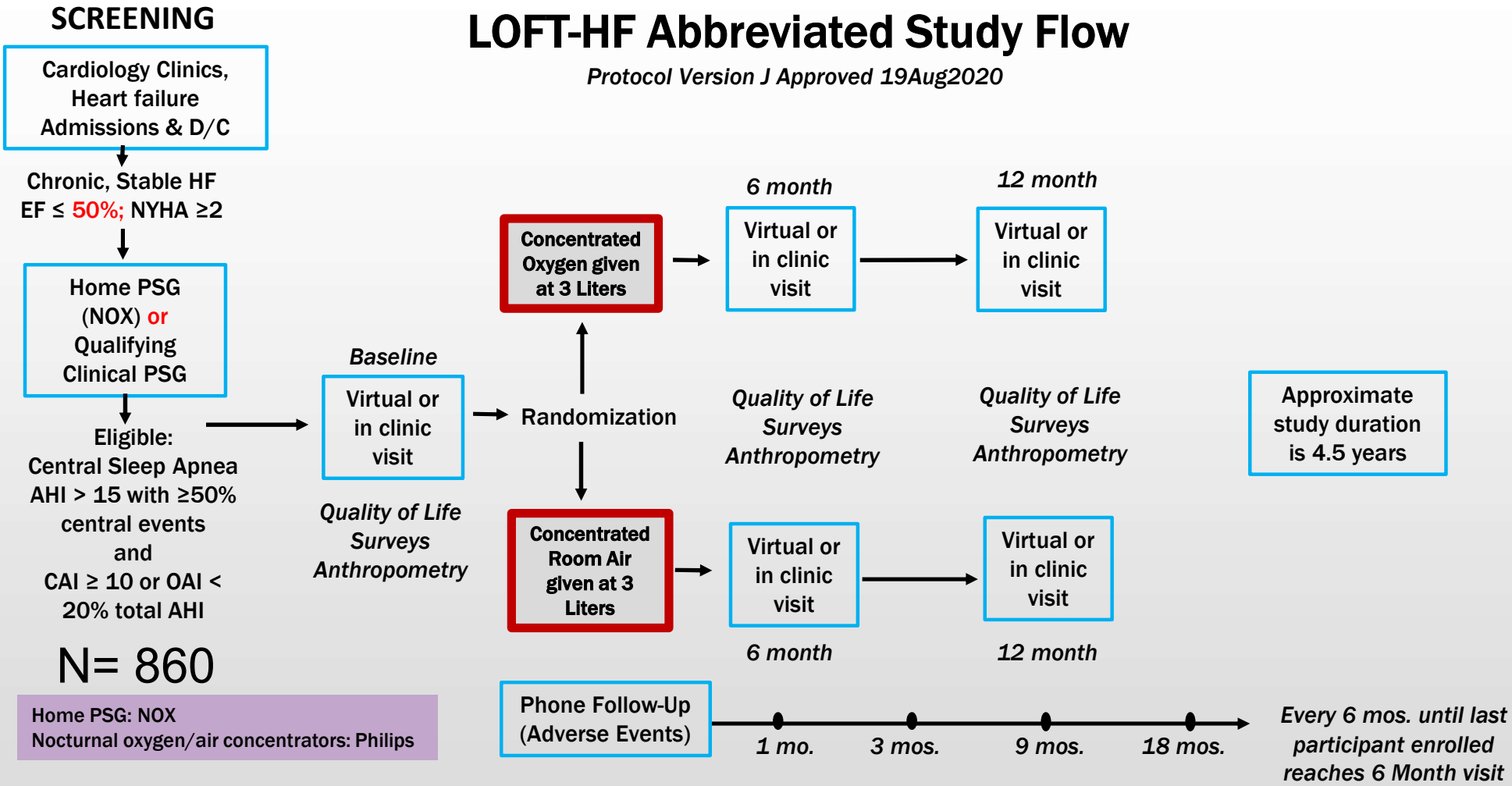
LOFT-HF

- NHLBI (2018-2024)
- Phase 3, multi-center, randomized, double-blind, sham-controlled outcomes trial
- Patients with HFrEF and predominant CSA
- Recruited from investigator's cardiology and sleep practices and from the institution's broad referral network
- Total sample of 858 subjects
- 429 patients in each arm

https://lofthf.study

LOFT-HF Abbreviated Study Flow

Protocol Version J Approved 19Aug2020



Oxygen concentrators are delivered to patients from central DME-managed by DCC or study team
Home PSG and oximetry are housed in the cloud and interpreted by the SRC

PRIMARY ENDPOINTS

- Mortality
- Life-saving CV intervention
  - Ex. Cardiac transplantation, long-term ventricular assist device implantation, resuscitation of sudden cardiac arrest, or shock from an implantable cardioverterdefibrillator (ICD) associated with sudden loss of consciousness associated with ventricular tachycardia or ventricular fibrillation
- Unplanned hospitalization for worsening HF
  - Admitted to hospital inpatient bed, observation unit, or ED for worsening signs and/or symptoms of HF requiring treatment with intravenous (IV) diuretics and/or IV vasoactive medications for HF

https://lofthf.study

Pharmacological therapy of CSA

1. Drugs downregulating
   CCR (Buspirone)
   PCR (Oxygen)

2. Drugs decreasing the plant gain
Acetazolamide, theophylline, aspirin, progesterone

These drugs most effective, if they do not upregulate CCR

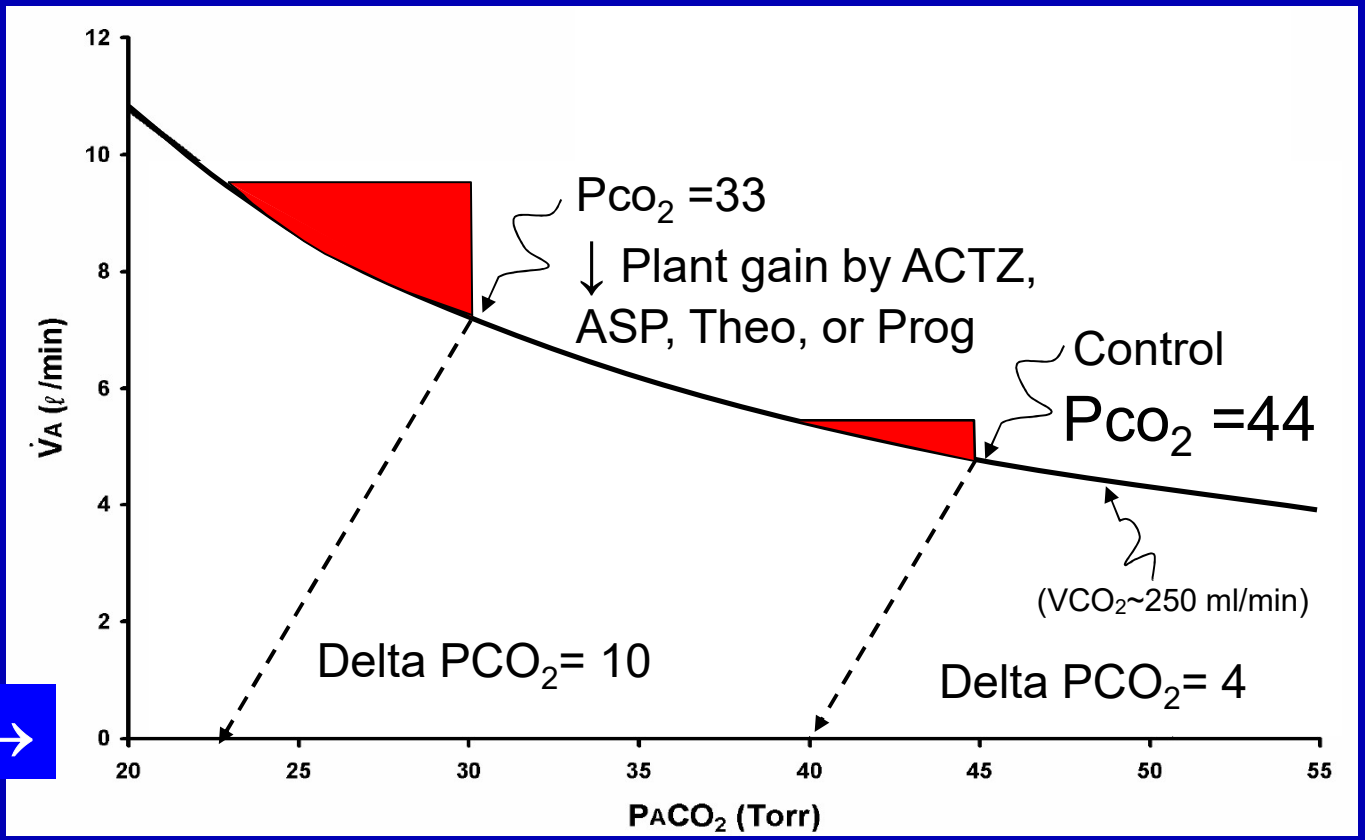
In HF, Loop Gain is Upregulated

† Loop Gain = † controller gain x † plant gain x † mixing gain

Controller gain	x	Plant gain	x	Mixing gain
VE/ $PaCO_2$	x	$PaCO_2$	x	Circulation time
> < eupnea		VE		Delay

These components of LG are state-independent

A ↓ steady state eupneic $PaCO_2$ will ↓ plant gain and protect against central apnea / instability!



APNEA→

RCT: Disordered breathing events of 12 SHF patients with CSA treated with single dose of acetazolamide before bedtime

Variable	Baseline	Placebo	Actz	*p*
AHI, n/h	55	57	34*†	0.002
CAI, n/h	44	49	23*†	0.004
OAI, n/h	1	1	2	0.6
DBArI, n/h	25	20	13	0.06

p < 0.05 versus baseline † = *p* < 0.05 versus placebo

Javaheri, Am J Respir Crit Care Med, 2006

Arterial Blood Gas and [H^+] in 12 SHF Patients with Central Sleep Apnea Treated with Acetazolamide

Variable	Baseline	Placebo	Actz	*p*
PaO_2, mm Hg	84	84	92	0.1
$PaCO_2$, mm Hg	37	38	34*†	0.001
[H^+], nmol/l	37	37	44*†	0.001
[HCO_3^-], mmol/l	25	26	19*†	0.001

* $p < 0.05$ versus baseline † = $p < 0.05$ versus placebo

Mechanism of Action of ACTZ

Condition (N)	ΔPCO_2 (ET-AT) mm Hg
Normal (6)	-5.1
ACTZ (6)	-6.7*
Met. Alk (5)	-3.7*
Hypoxia (6)	-4.1*

* Significant when compared to normal.

Nakayama et al, Am J Respir Crit Care Med, 2002

Patients' Perception of Their Sleep Quality and Daytime Symptoms Comparing Acetazolamide with Placebo

Variable	Placebo	Actz	*p*
Sleep quality	7/8 (88)	1/8 (13)	0.003
Daytime naps	4/5 (80)	1/5 (20)	0.06
Unrested at rise	8/10 (80)	2/10 (20)	0.007
Daytime fatigue	7/9 (78)	2/9 (22)	0.02
Fall asleep unintentionally	5/5 (100)	0/5 (0)	0.002

RCT : Theophylline Improves CSA

Variable	Baseline	Placebo	Theo
N	15	15	15
Gender, M/F	15/0	15/0	15/0
Age, y	66	66	66
Ht, cm	175	175	175
Wt, kg	89	88	88
Theo, *u*g/ml	ND	ND	11

Values are means; ND=not detectable

Javaheri et al., NEJM, 1996, 335, 562-7

Theophlline improves CSA in HF Patients

Variable	Baseline	Placebo	Theo
AHI, n/h	47	37	18*
CAI, n/h	26	26	6*
OAI, n/h	2	2	2
MAI, n/h	2	2	1
DBArI, n/h	24	17	8*

Values are means; * $p < 0.05$

Javaheri et al., NEJM, 1996, 335, 562-7

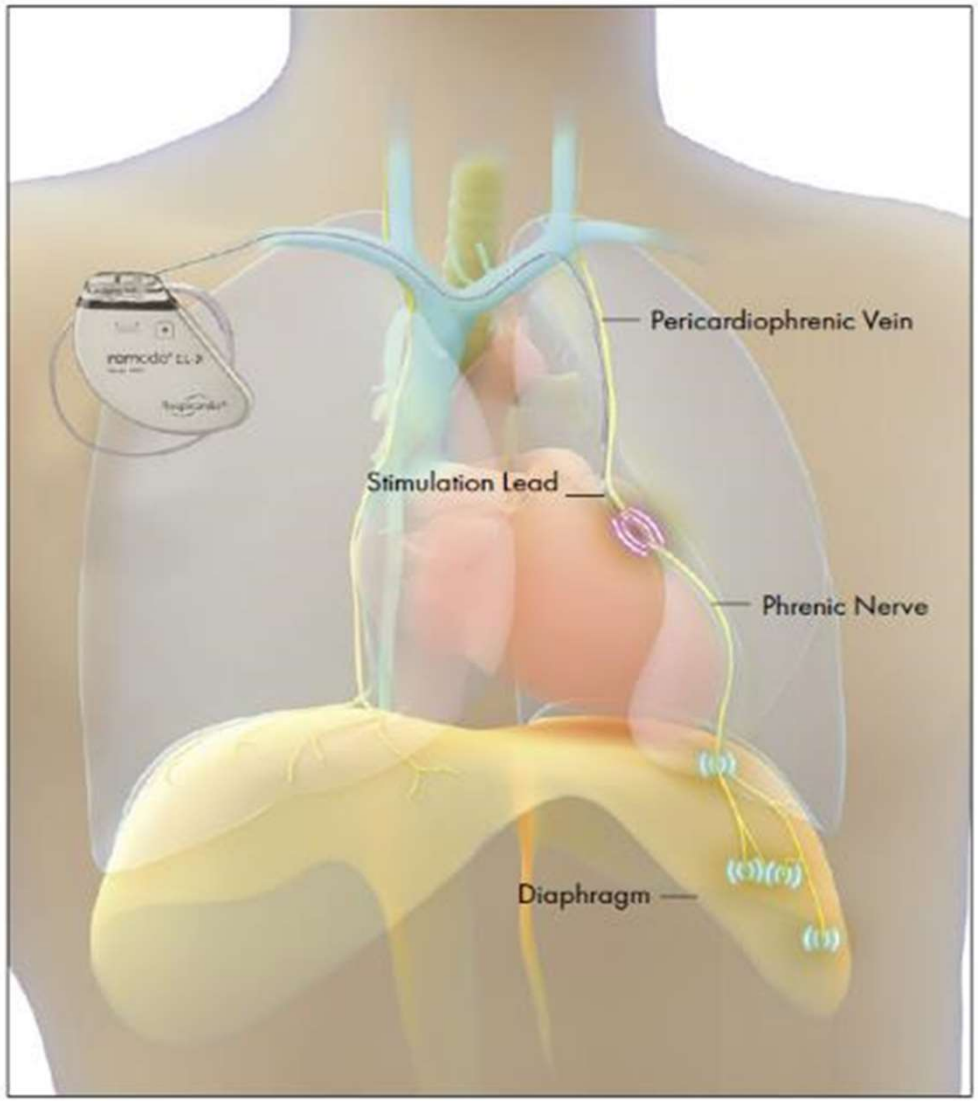
Research Priorities for Patients with Heart Failure and Central Sleep Apnea

An Official American Thoracic Society Research Statement

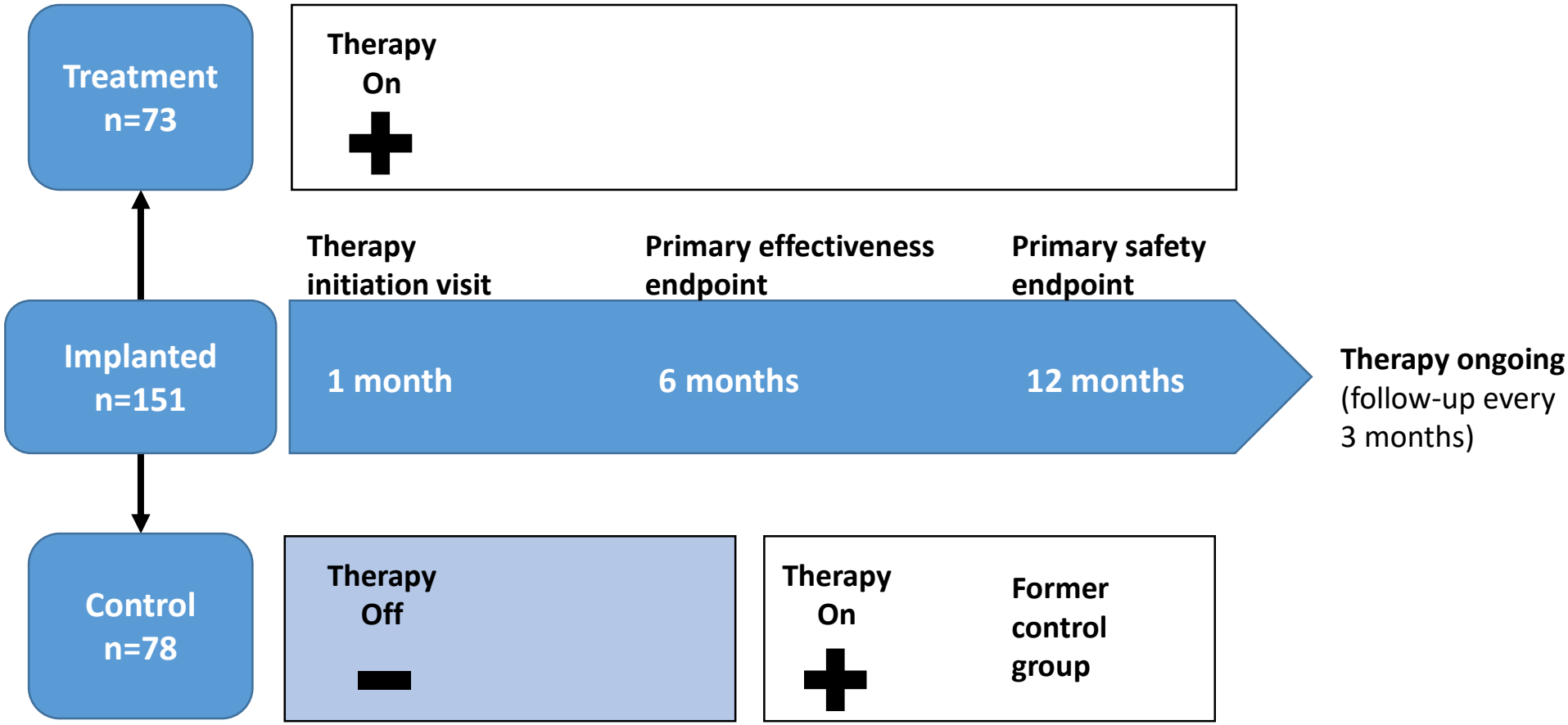
Orr JE, Ayappa I, Eckert DJ, Feldman JL, Jackson C L, Javaheri S, Khayat RN, Martin JL, Mehra R, Naughton ML, Randerath WJ, Sands SA, Somers VK, Badr MS; on behalf of the American Thoracic Society Assembly on Sleep and Respiratory Neurobiology

Am J Respir Crit Care Med

2021; 203, Iss 6, pp e11–e24


Pericardiophrenic Vein
Stimulation Lead
Phrenic Nerve
Diaphragm

Prospective, Multicenter, Randomized Control Pivotal Trial of the PNS



Costanzo MR, Augostini R, Goldberg LR, et al. Design of the remedē® System Pivotal Trial: A Prospective, Randomized Study in the Use of Respiratory Rhythm Management to Treat Central Sleep Apnea. J Card Fail. 2015;21:892-902.

The Pivotal Trial (Lancet, 2016)
BASELINE DEMOGRAPHICS

VARIABLE	TREATMENT (N=73)	CONTROL (N=78)
Age (years)	65 ± 12	65 ± 13
Male gender	86%	92%
Body mass index (kg/m^2)	30.8 ± 5.3	31.3 ± 6.6
Ejection fraction (%)	40.6 ± 12.8 *(n=71)*	39.4 ± 12.2 *(n=75)*
Heart failure[1] (% [NYHA I / II / III / IV])	66% (13 / 44 / 44 / 0%)	62% (25 / 42 / 33 / 0%)
Atrial fibrillation	44%	40%
Concomitant cardiac device	42%	42%
Apnea hypopnea index (events/hr)	48.8 ± 19.3	43.7 ± 16.8
Central apnea index (events/hr)	30.0 ± 18.0	26.6 ± 16.1
Oxygen desaturation index 4% (events/hr)	43.2 ± 21.7	37.5 ± 17.5
Rapid eye movement (%)	10.4 ± 7.2	11.8 ± 7.1
Arousal index (events/hr)	45.5 ± 17.9	43.6 ± 19.1
Epworth sleepiness scale (points)	10.2 ± 5.2	9.5 ± 5.8

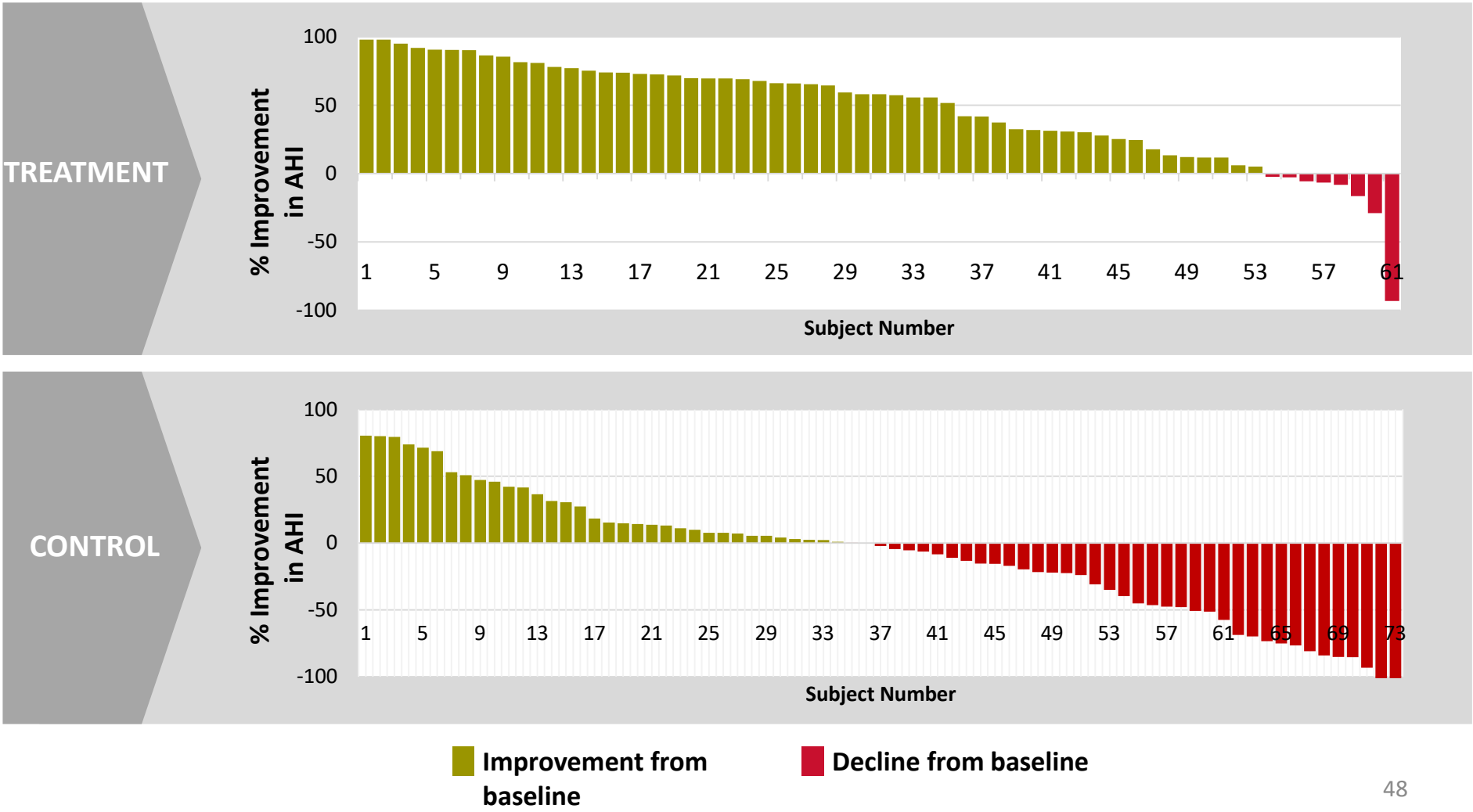
[1] *Required the investigator to assign a NYHA Class at the Baseline physical exam*

Mean ± SD for continuous variables/Percent for categorical variables. All nominal p-values ≥ 0.075 except Mixed Apnea Index (p-value 0.029)

Costanzo MR, Ponikowski P, Javaheri et al, Lancet 2016

The Pivotal Trial

87% OF TREATMENT PATIENTS DEMONSTRATED AN AHI IMPROVEMENT



Costanzo MR, Ponikowski P, Javaheri et al, Lancet 2016

The Pivotal Trial (Lancet 2016)

	BASELINE		6 MONTHS		CHANGE FROM BASELINE		BETWEEN GROUP DIFFERENCE	
	Treatment N=58	Control N=73	Treatment N=58	Control N=73	Treatment N=58	Control N=73		P-value
AHI (events/hour)	50	44	26	45	-24	1.1	**-25**	**<0.0001**
CAI (events/hour)	32	26	6.0	23.3	-26	-2.9	**-23**	**<0.0001**
ODI4 (events/hour)	44	37	25	41	-19	3.6	**-23**	**<0.0001**
ArI (events/hour)	46	44	25	39	-20	-5.0	**-15**	**<0.0001**
Percent of sleep in REM	11	12	13	11	1.8	-0.6	**2.4**	**0.0244**

Costanzo MR, Ponikowski P, Javaheri et al, Lancet 2016

The between group difference is the difference in the change from baseline.

The Pivotal Trial
Improvements in Sleep Architecture

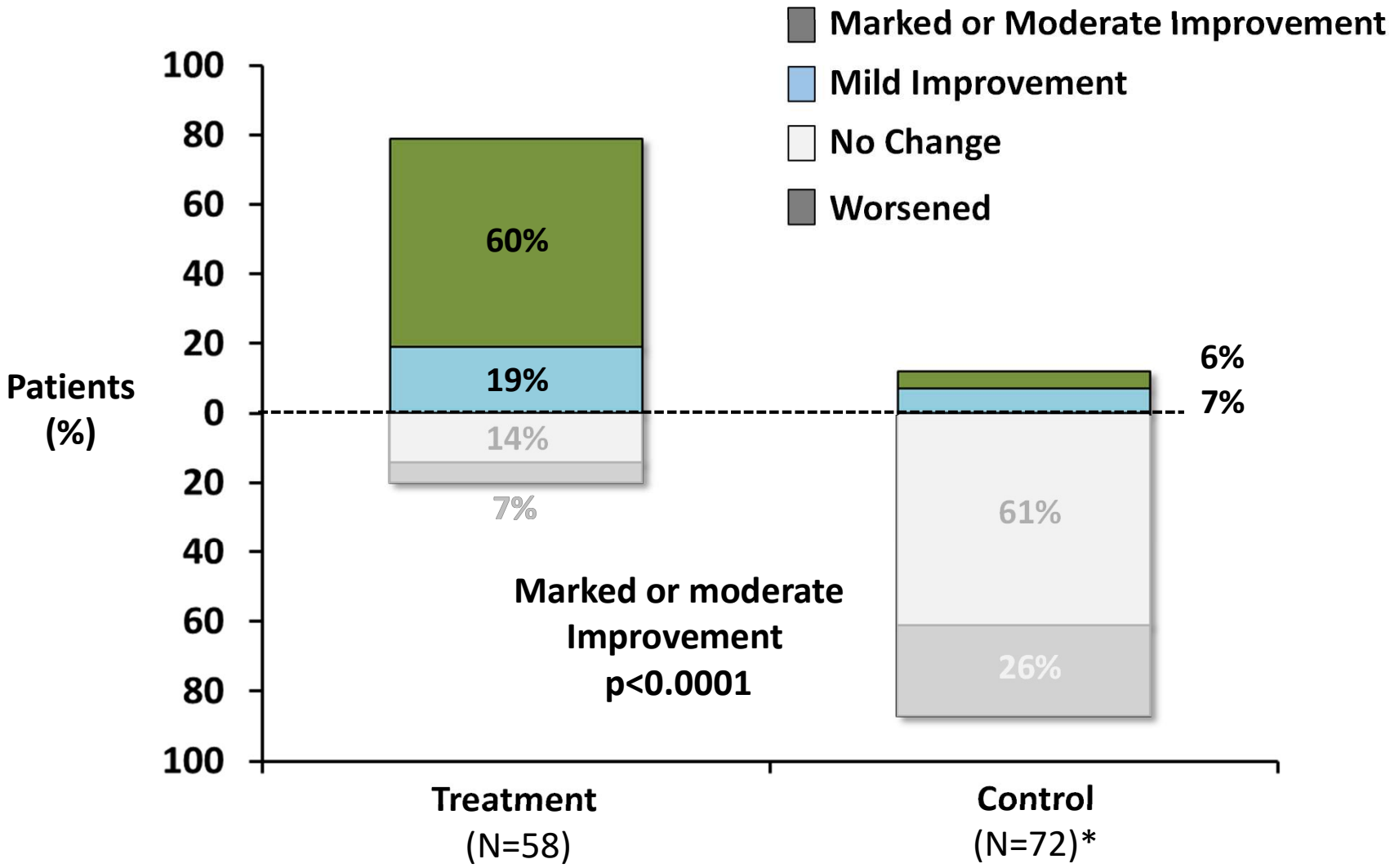
	BASELINE		6 MONTHS		CHANGE FROM BASELINE		BETWEEN GROUP DIFFERENCE	
	Treatment N=58	Control N=73	Treatment N=58	Control N=73	Treatment N=58	Control N=73		P-value
N1 (% of sleep time)	33	30	28	36	-5	6	**-11**	**0.0030**
N2 (% of sleep time)	50	50	54	47	4	3	**6**	**0.0460**
N3 (% of sleep time)	6	9	5	6	-1	-3	**2**	**0.0463**
REM (% of sleep time)	11	12	13	11	2	-1	**2**	**0.0244**
ArI (events/hour)	46	44	25	39	-20	-5.0	**-15**	**<0.0001**

The between group difference is the difference in the change from baseline.

Costanzo MR, Ponikowski P, Javaheri et al, Lancet 2016

The Pivotal Trial (Lancet, 2016)

Secondary Endpoints (Patient Global Assessment)

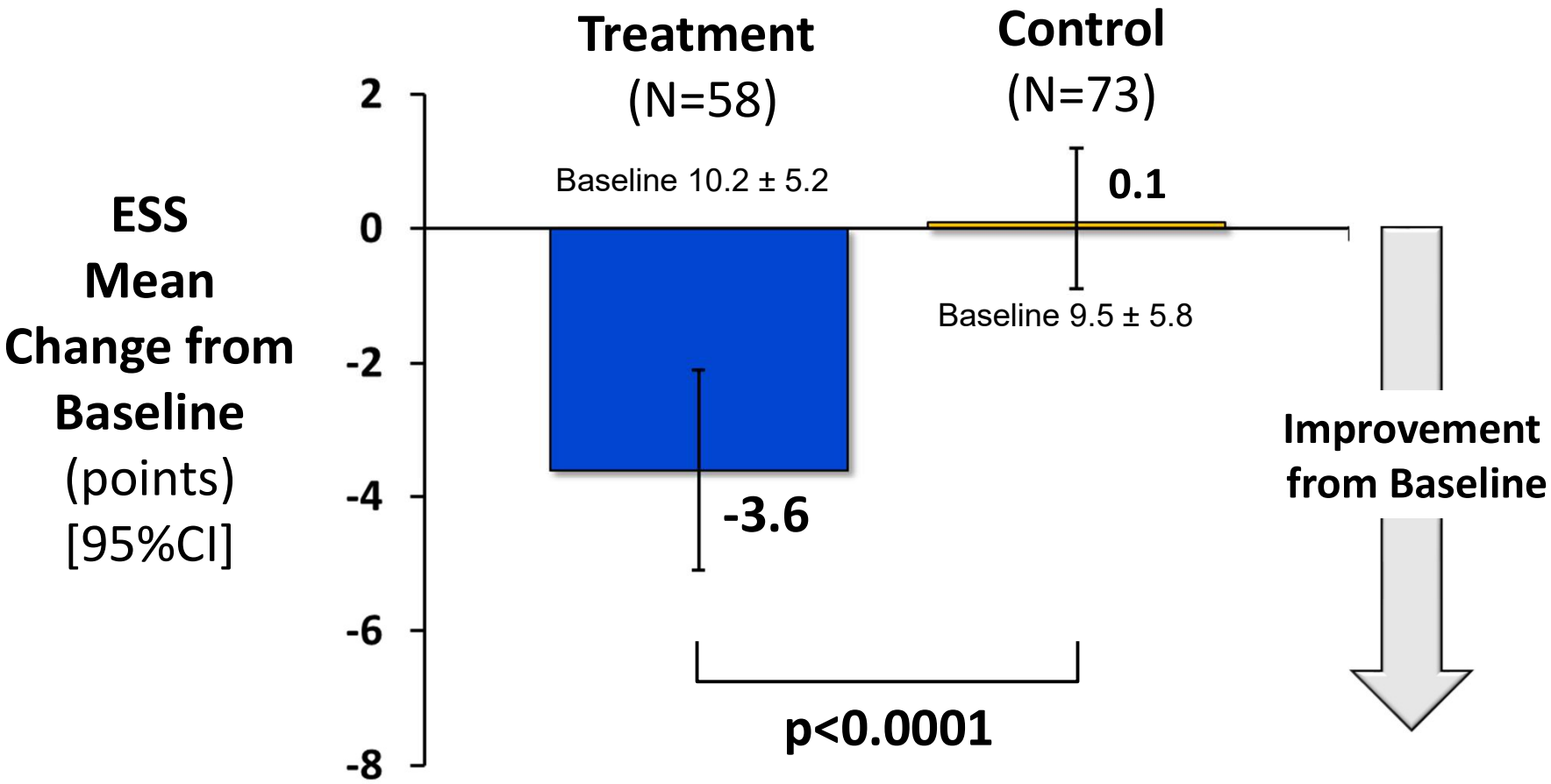


Per Protocol Population

**One patient did not complete the PGA assessment at 6 months*

Costanzo et al. The Lancet 2016;388:974-82.

The Pivotal Trial (Lancet,2016)
Secondary Endpoints: ***ESS***

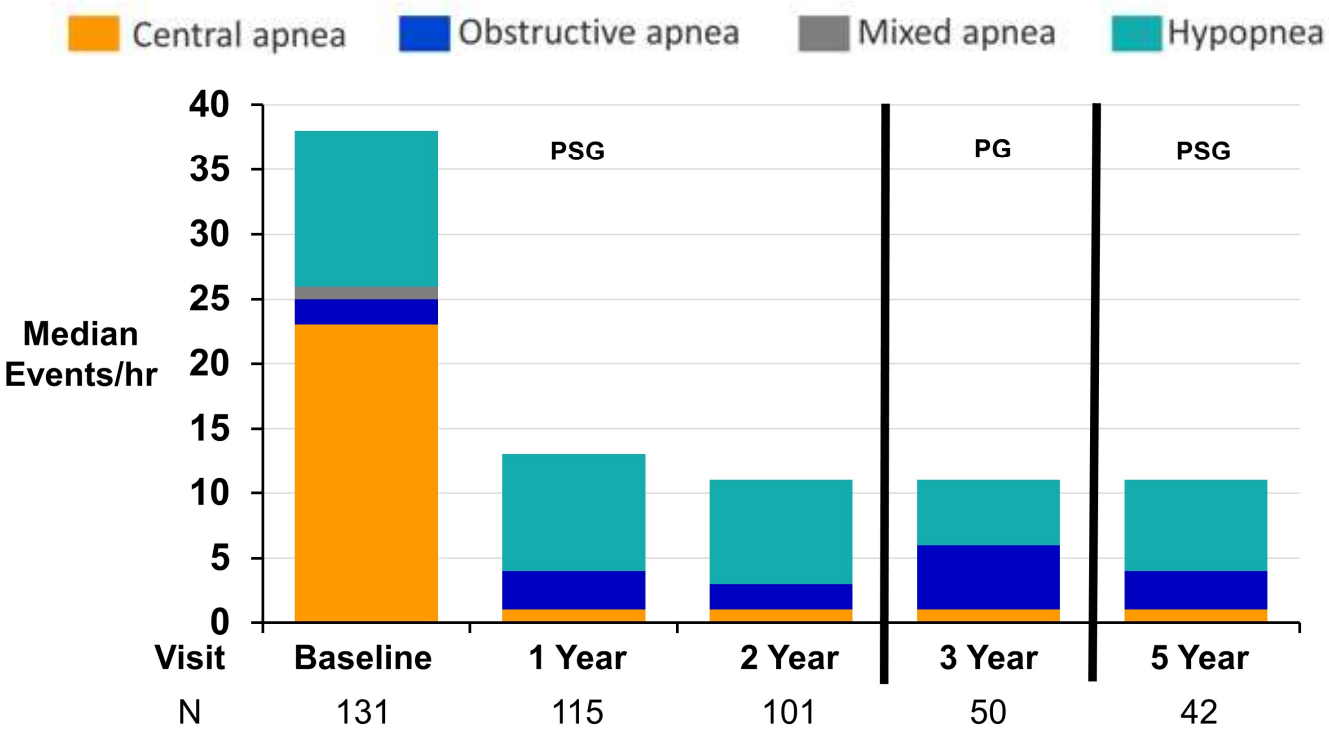


Per Protocol Population

Costanzo et al. The Lancet 2016;388:974-82.

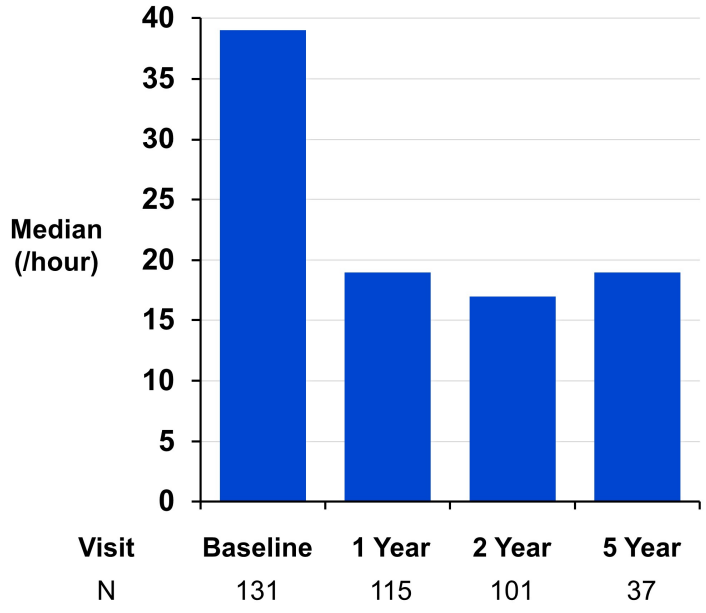
Sustained Improvement in Sleep Metrics
based on centrally scored sleep studies

Apnea Hypopnea Index



AHI median paired change from baseline [IQR]: **-22 [-42, -7]**
P<.001

Arousal Index

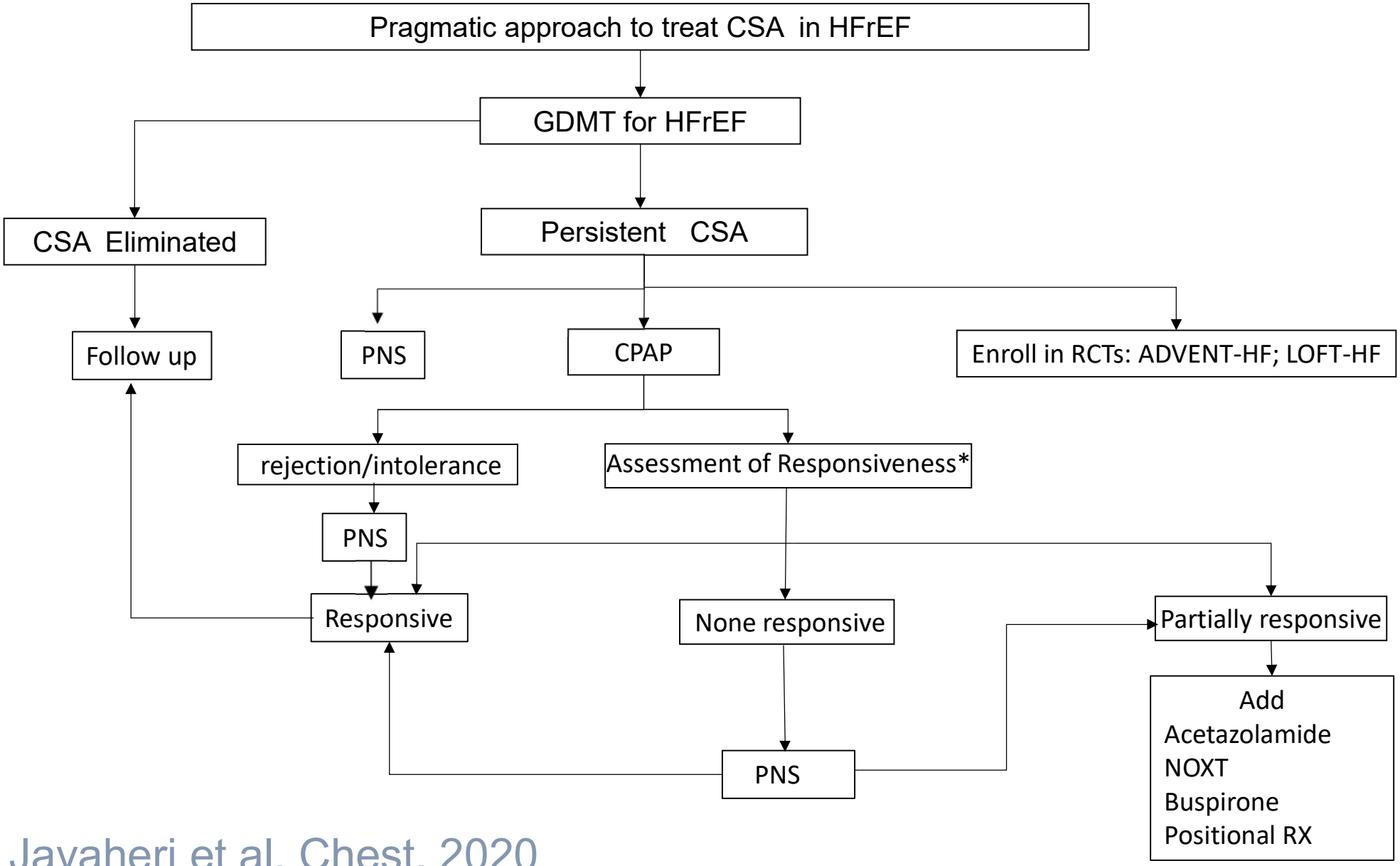


Median paired change from baseline [IQR]: **-14 [-22, -2]**
P<.001

Costanzo, Javaheri et al. Nature and Science of Sleep 2021:13 515–526

Effects of various RX options on AHI in in HF Patients with CSA

Therapy	Baseline	Placebo	RX	J
Theo	47	37	18*	NEJM
O_2	45	-	28*	BJ
O_2	38	38	25*	EHJ
O_2	38	-	18 *	Sleep
ACTZ	55	57	34*	BJ
CPAP	45	-	27*	BJ
CPAP	40	-	20 *	NEJM
CPAP	51	-	37 *	Circ
PNS	50	RCT	22 *	Lancet



Javaheri et al, Chest, 2020