Con il patrocinio di

Associazione Italiana Pneumologi Ospedalieri

Ospedale San Giuseppe
MultiMedica S.p.A.

PNEUMOLOGIA 2016

Milano, 16 – 18 giugno 2016 · Centro Congressi Palazzo delle Stelline

Convegno Pneumologia 2016
Milano 16-18 giugno 2016
Centro Congressi
Palazzo delle Stelline

Trattamento delle Apnee Notturne: Più Domande che Risposte

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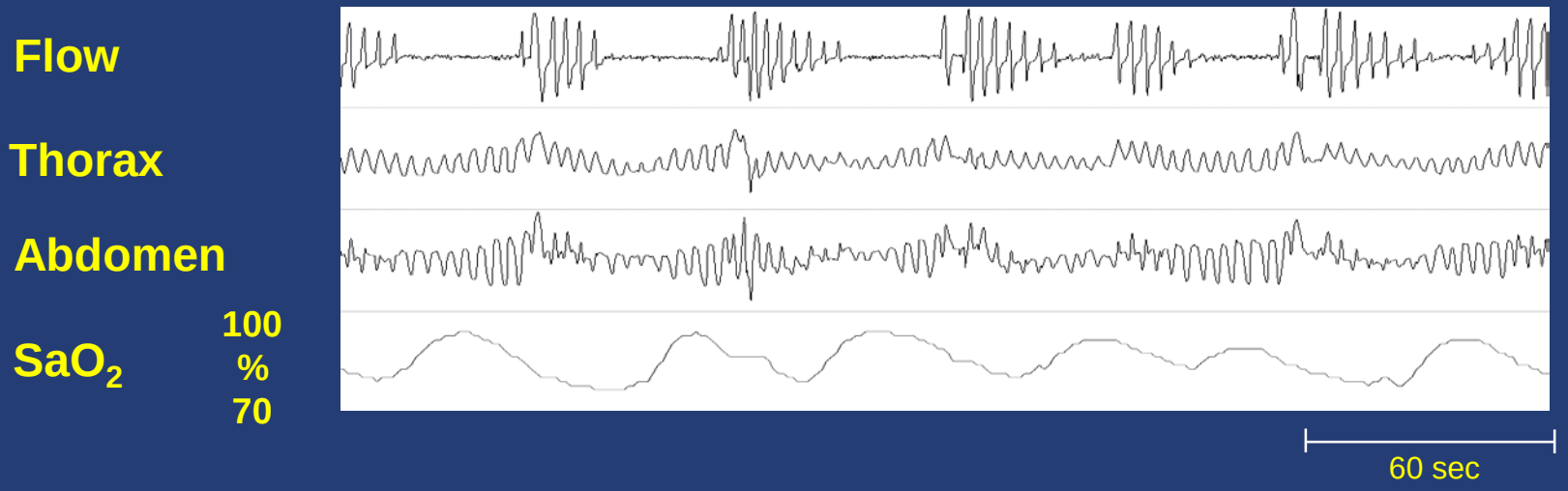
Clinical Definitions

- **Central apnea**
  - ≥10 second cessation of airflow, without effort
- **Obstructive apnea**
  - ≥10 second cessation of airflow, while effort continues
- **Hypopnea**
  - 30% reduction in airflow for 10 sec with a 4% fall in oxygen saturation
- **Apnea-Hypopnea Index (AHI)**
  - Number of apneas and hypopneas per hour of sleep
  - Mild (5-14/hour), Moderate (15-29/hour), and Severe (≥ 30/hour)
- **Arousals**
  - Number of arousals per hour of sleep
- **Oxygen Desaturation Index (ODI) 4%**
  - Number of times oxygen saturation drops by 4% or more per hour

2007 AASM Guidelines

Types of SDB: OSA

- Obstructive sleep apnoea (OSA):
  - ≥10 second cessation of airflow, while effort continues
  - Most common type of SDB
  - Caused by recurrent collapse of the upper airway
  - Causes intermittent hypoxia, negative intrathoracic pressure swings, sympathetic activation, systemic inflammation, oxidative stress

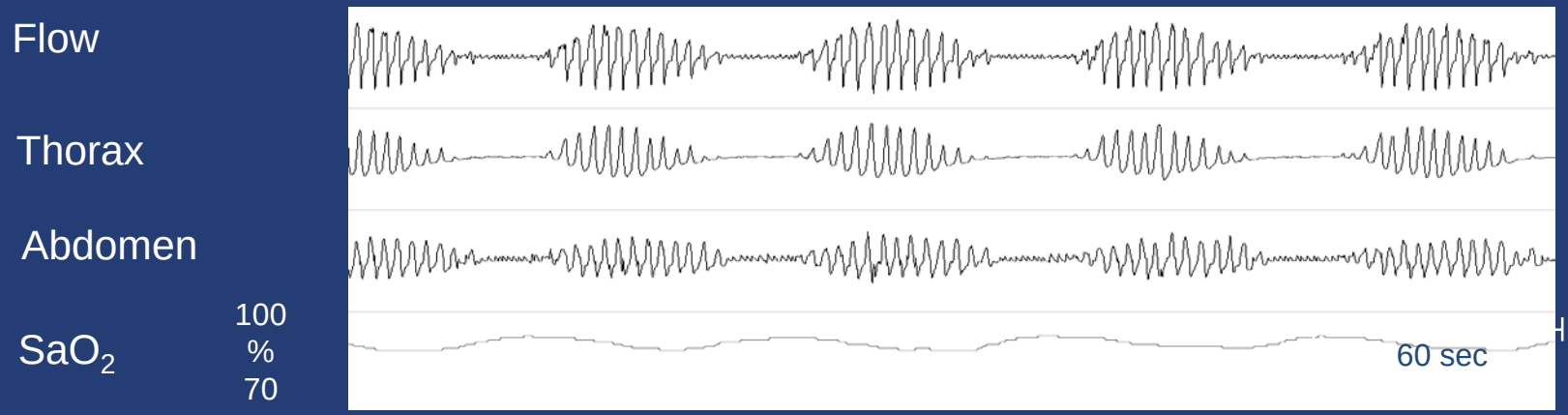


Cowie et al. Eur Cardiol Rev 2015.

Types of SDB: CSA

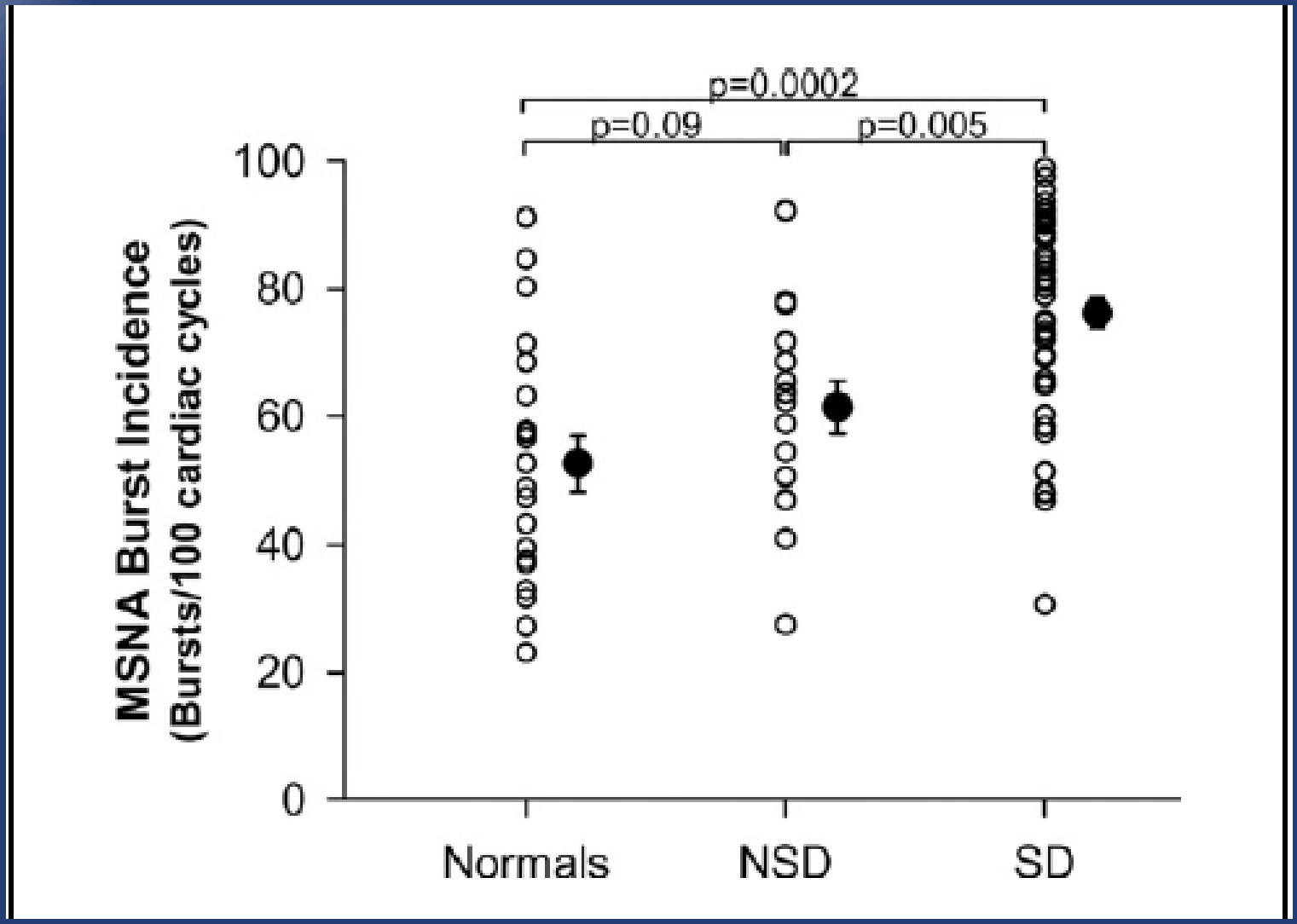
- Central sleep apnoea (CSA):
- ≥10 second cessation of airflow, without effort
  - Dysregulation of respiratory control (lack of drive to breathe during sleep)
  - Repetitive periods of reduced ventilation
  - May manifest at CSR (central apnoeas alternating with periods of crescendo-decrescendo respiratory tidal volume)

- **Causes increases sympathetic nervous system activity, greater cardiac electrical instability, low frequency oscillations in heart rate and blood pressure**



Cowie et al. Eur Cardiol Rev 2015.

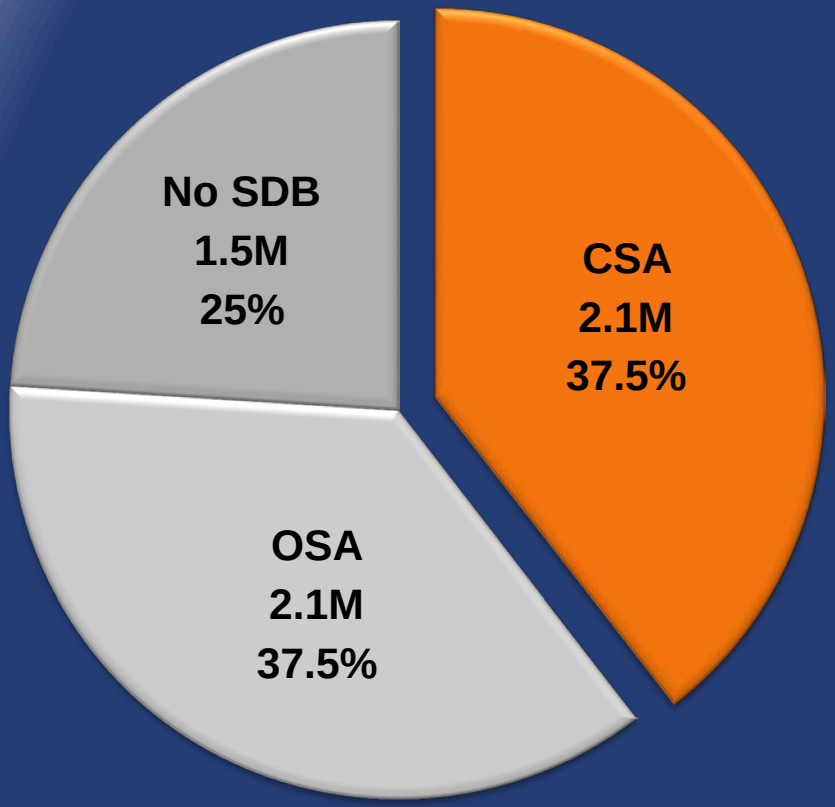
Muscle Sympathetic Burst Incidence at Rest in Subjects With and Without HF



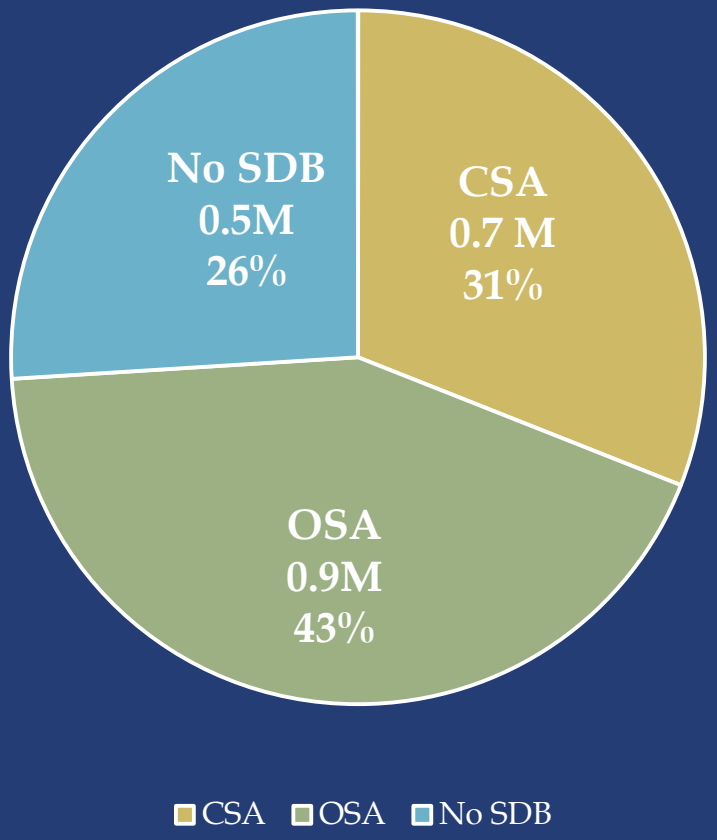
Floras JACC 2009

Central Sleep Apnea is Common in Heart Failure and Atrial Fibrillation Patients

United States
Heart Failure Population
5.7 Million



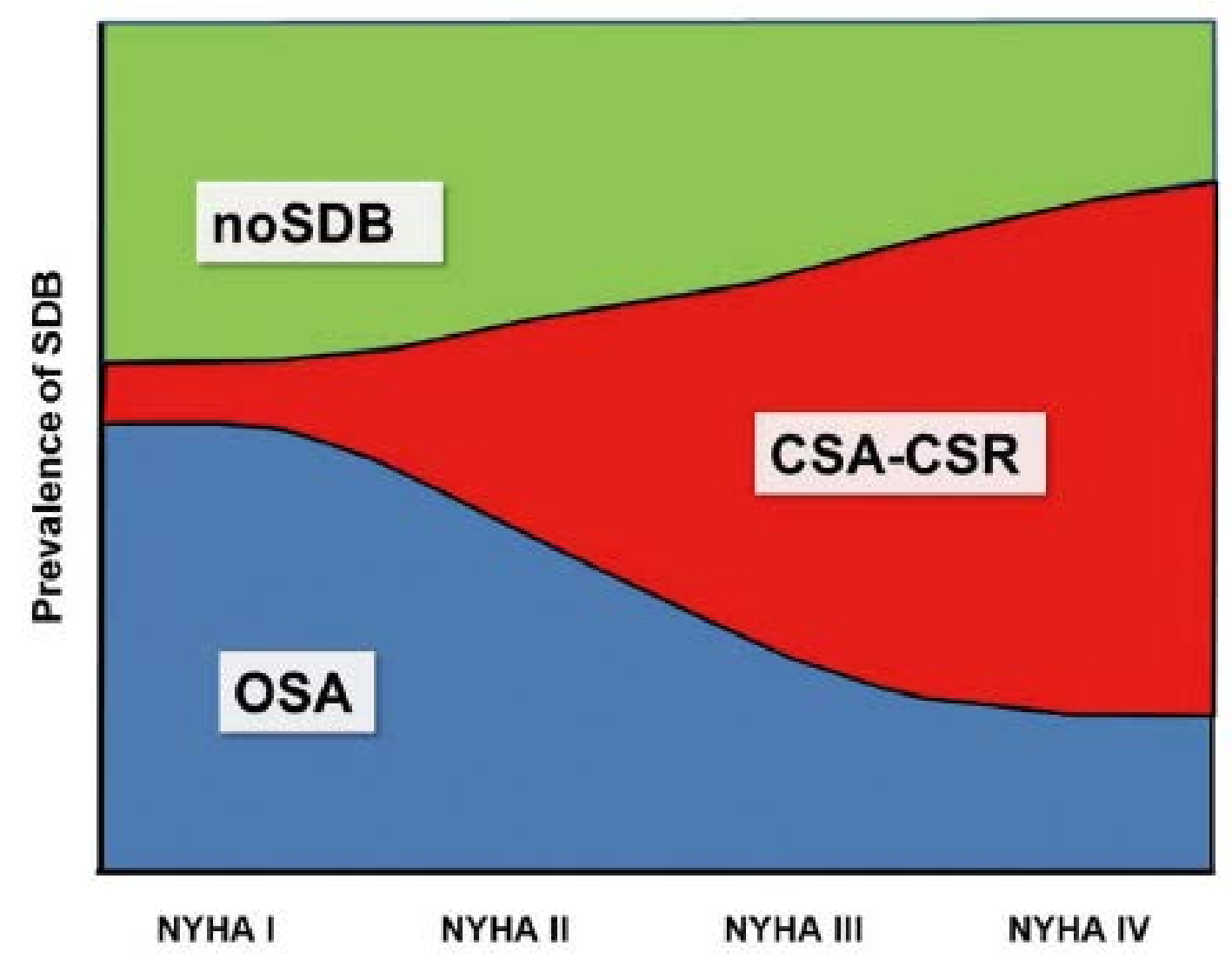
United States
Atrial Fibrillation Population
2.1 Million



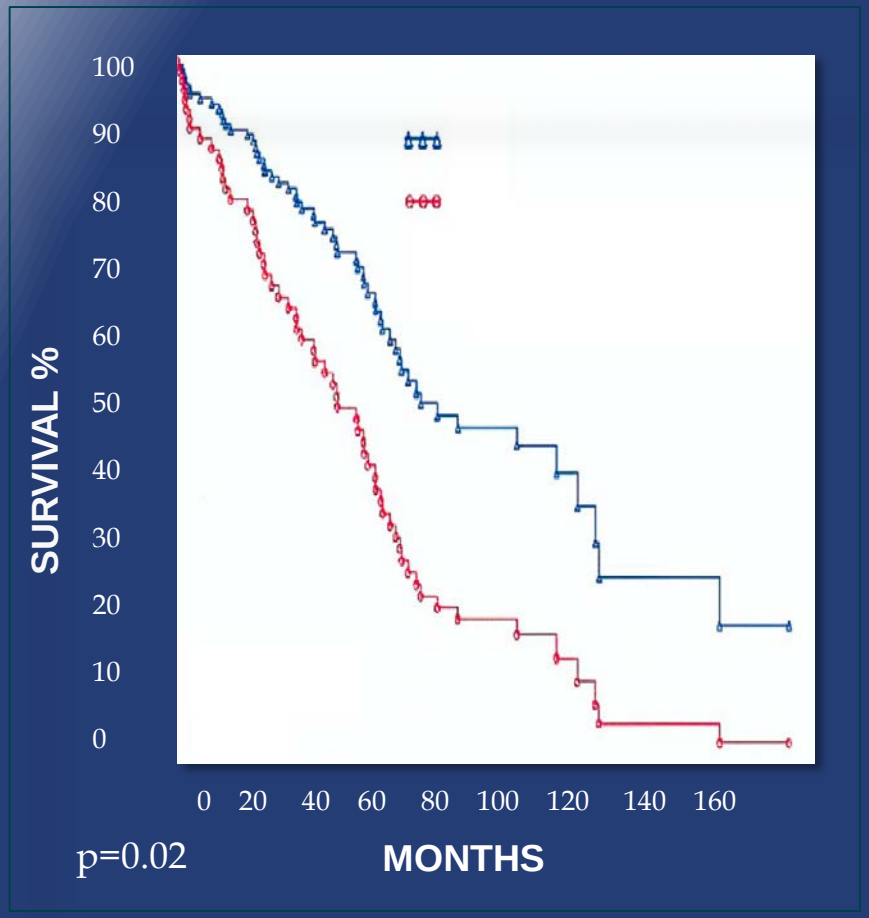
Roger et al. Circulation 2011;123:e18-209
Oldenburg et al. Eur J Heart Fail;20079:251-7

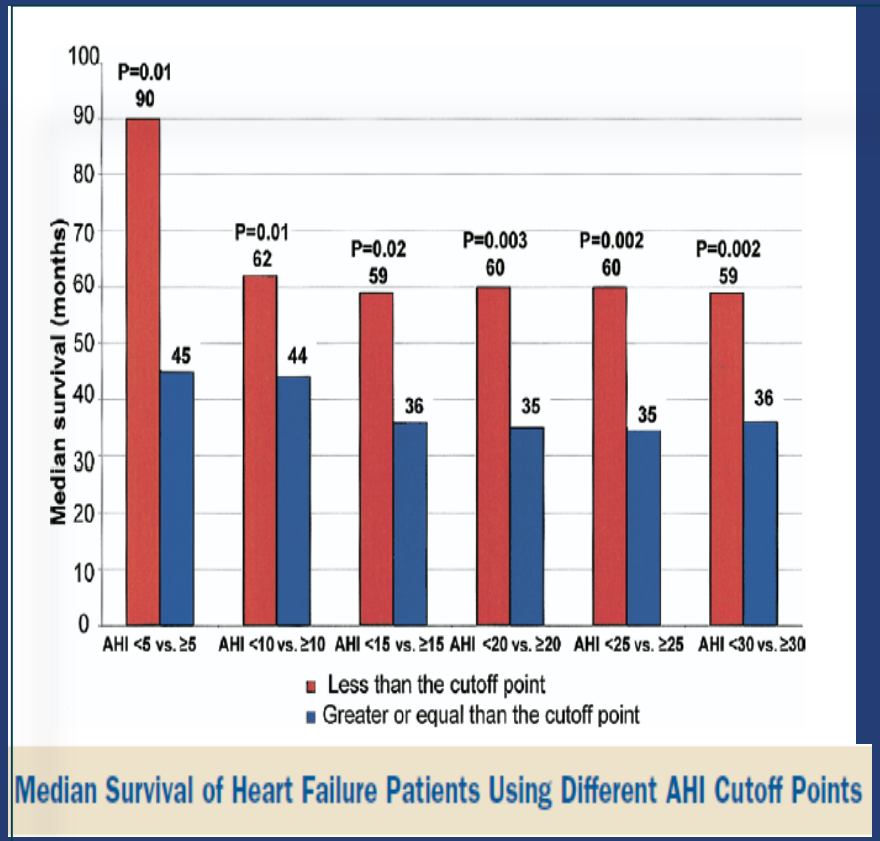
Bitter et al. Dtsch Arztebl Int 2009;106:164–70

SDB in Heart Failure



CENTRAL SLEEP APNEA SIGNIFICANTLY INCREASES MORTALITY IN HF PATIENTS



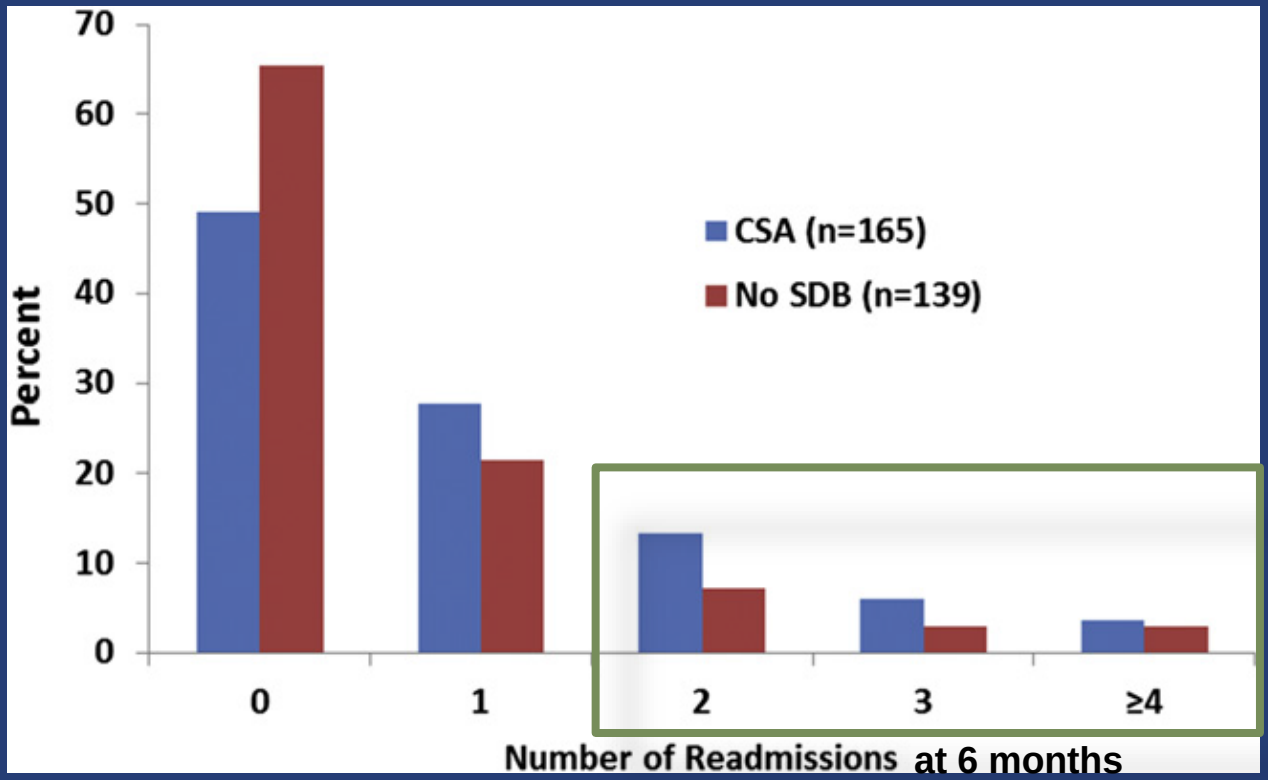


Median Survival of Heart Failure Patients Using Different AHI Cutoff Points

Javaheri, et. al.: JACC 49(20):2028-34, 2007

Central Sleep Apnea Increases the Risk for HF Readmissions

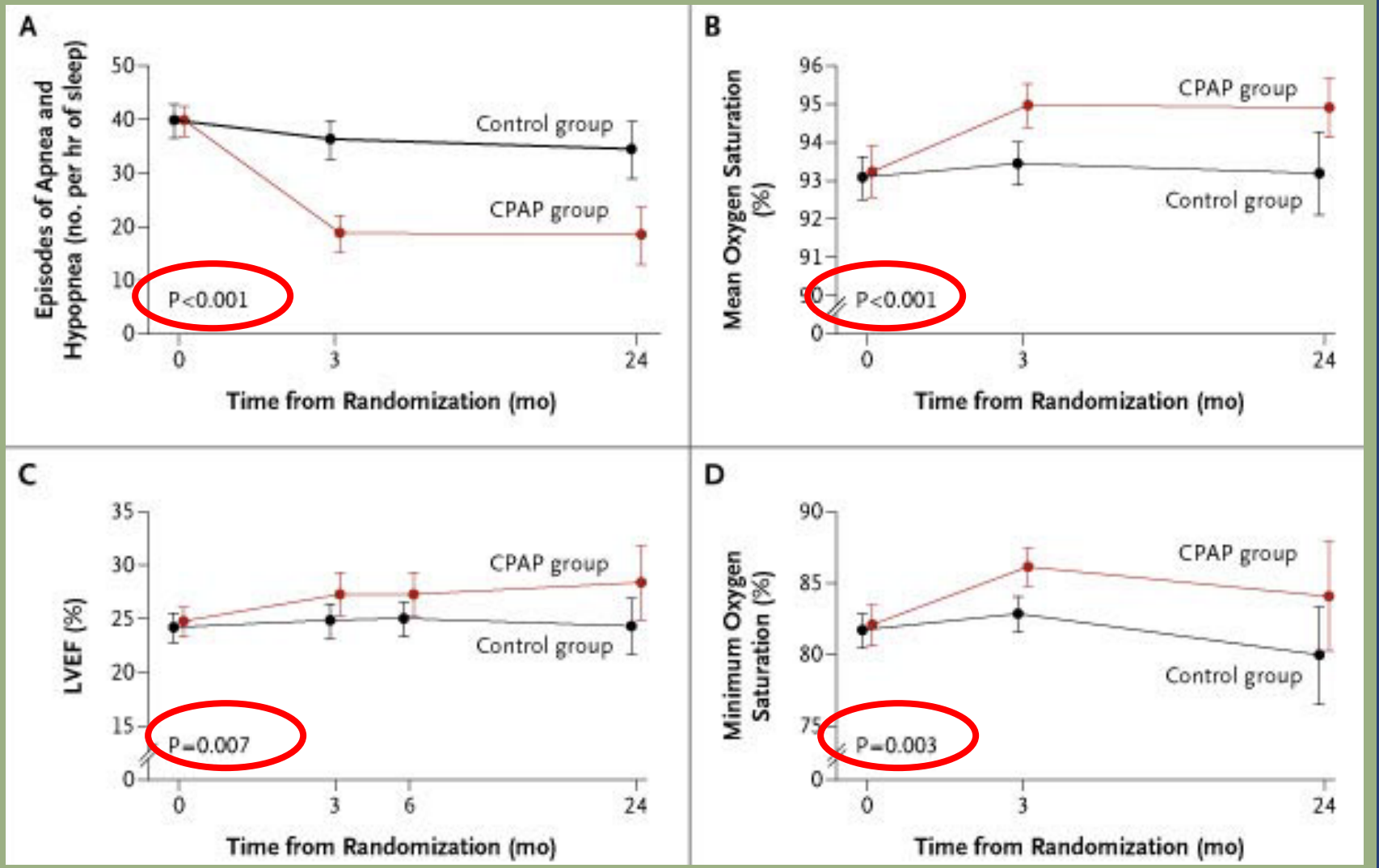
*50% of heart failure patients with central sleep apnea were **readmitted** at 6 months*



*Over 25% of heart failure patients with central sleep apnea had **2 or more readmissions** within 6 months*

Khayat et al. J Card Fail 2012;18:534-540

Effect of CPAP on the Frequency of Episodes of Apnea and Hypopnea, Mean and Minimal Nocturnal Oxygen Saturation, and Left Ventricular Ejection Fraction



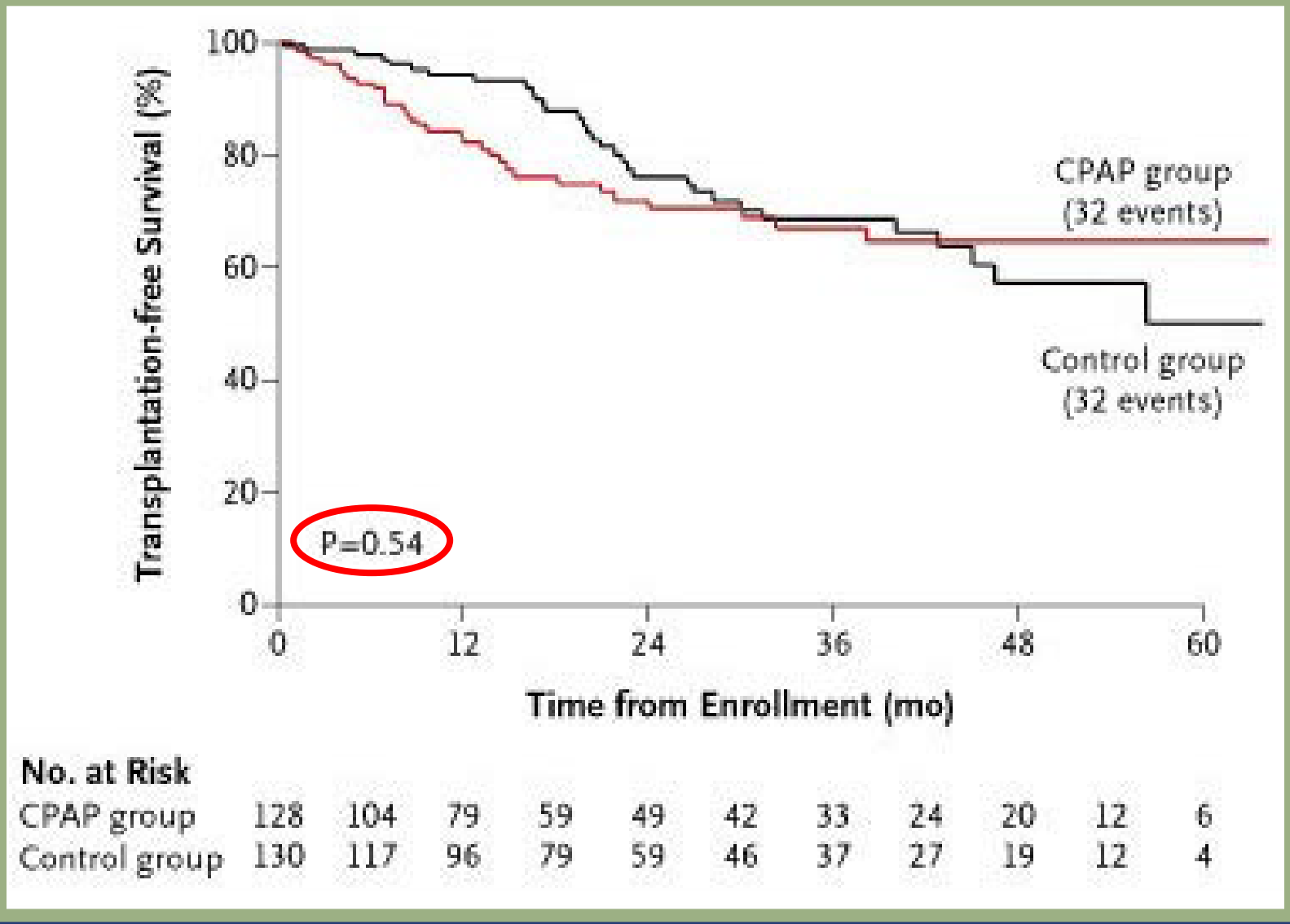
Bradley T et al. N Engl J Med 2005;353:2025-2033

The NEW ENGLAND JOURNAL of MEDICINE

Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP)

- Randomized, controlled clinical trial involving 258 HF patients with CSA (mean LVEF= 24.5)
- Hypothesis: Does continuous positive airway pressure (CPAP) improve both survival without heart transplantation and cardiovascular function
- Randomized 128 CPAP/130 Control
- Endpoints
  - Transplant-free survival
  - EF
  - Exercise capacity
  - Quality of life
  - Neurohormonal changes

Heart-Transplantation-Free Survival



No. at Risk

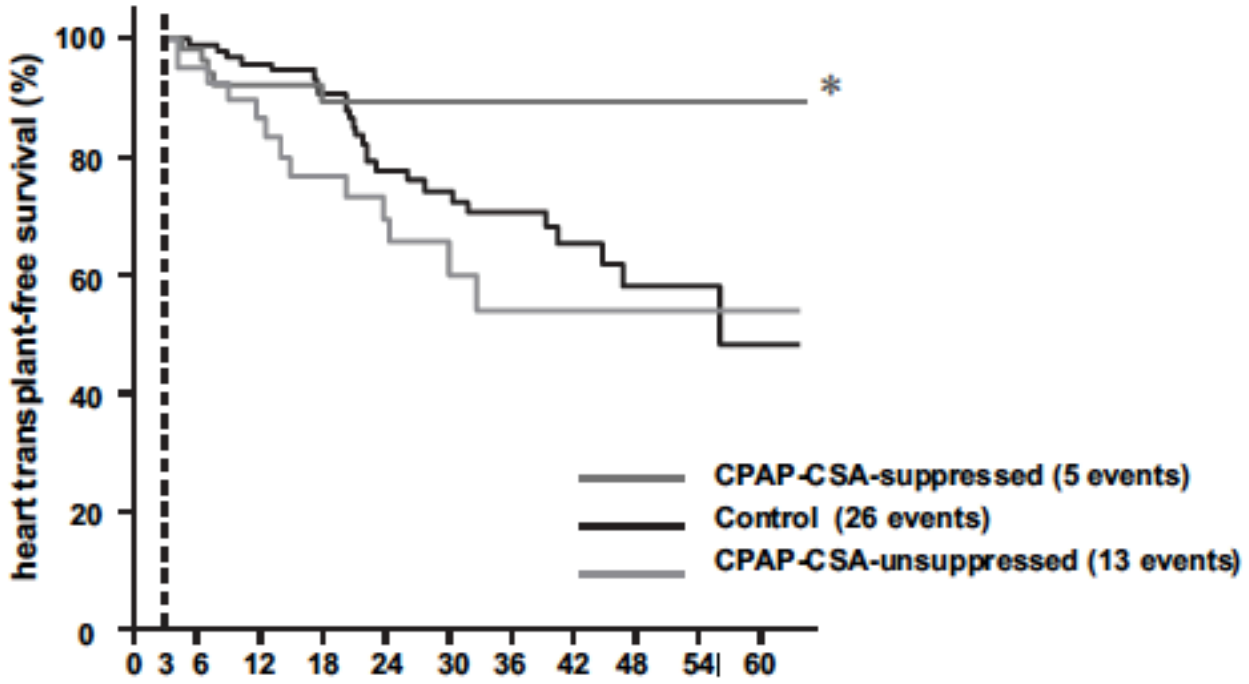
CPAP group	128	104	79	59	49	42	33	24	20	12	6
Control group	130	117	96	79	59	46	37	27	19	12	4

Bradley T et al. N Engl J Med 2005;353:2025-2033

The NEW ENGLAND JOURNAL of MEDICINE

CANPAP trial : early suppression of CSA by CPAP to an AHI below 15/hr may improve LVEF and transplant-free survival

Artz M et al Circulation. 2007;115:3173-3180



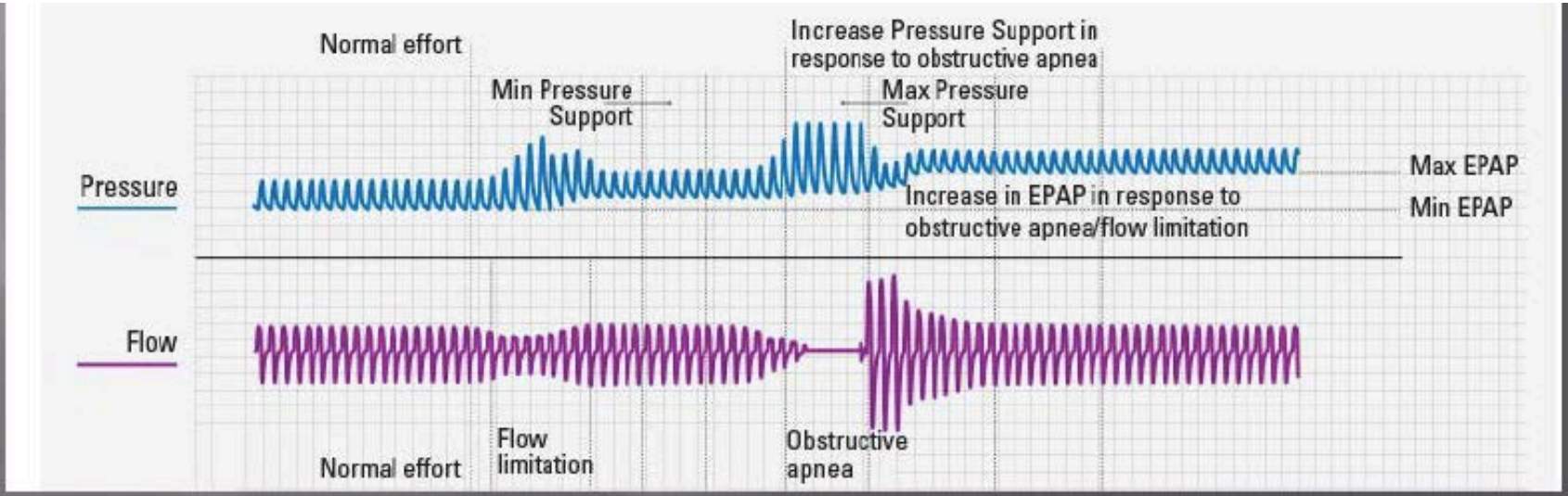
number at risk

CPAP-CSA-suppressed (n=57)	51	38	31	27	23	21	15	11	7	3
Control (n=110)	99	83	71	50	41	33	22	15	9	3
CPAP-CSA-unsuppressed (n=43)	36	27	22	18	12	9	6	6	4	2

Adaptive Servoventilation

Stabilises breathing and maintains upper airway open.

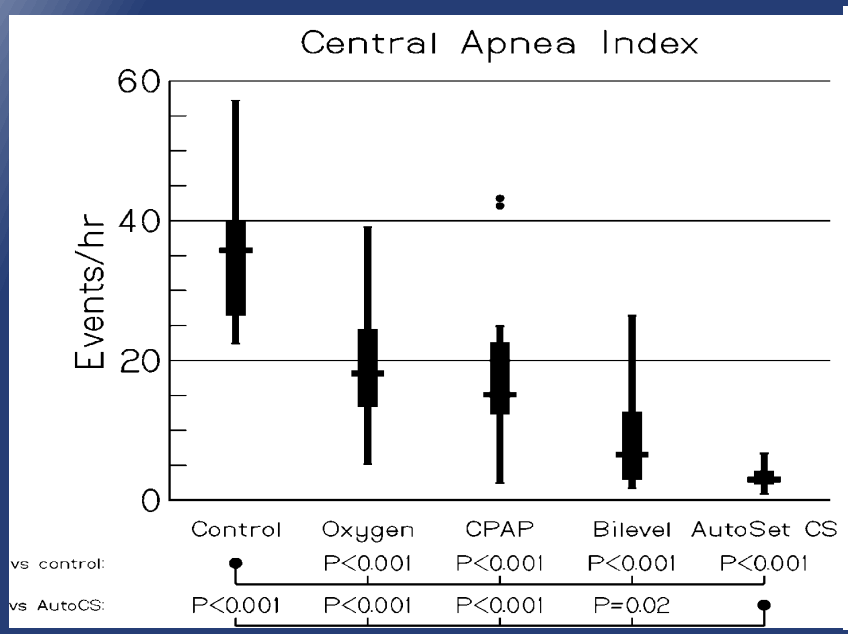
Continually adjusting inspiratory and expiratory pressure with variable, on-demand, back up rate.

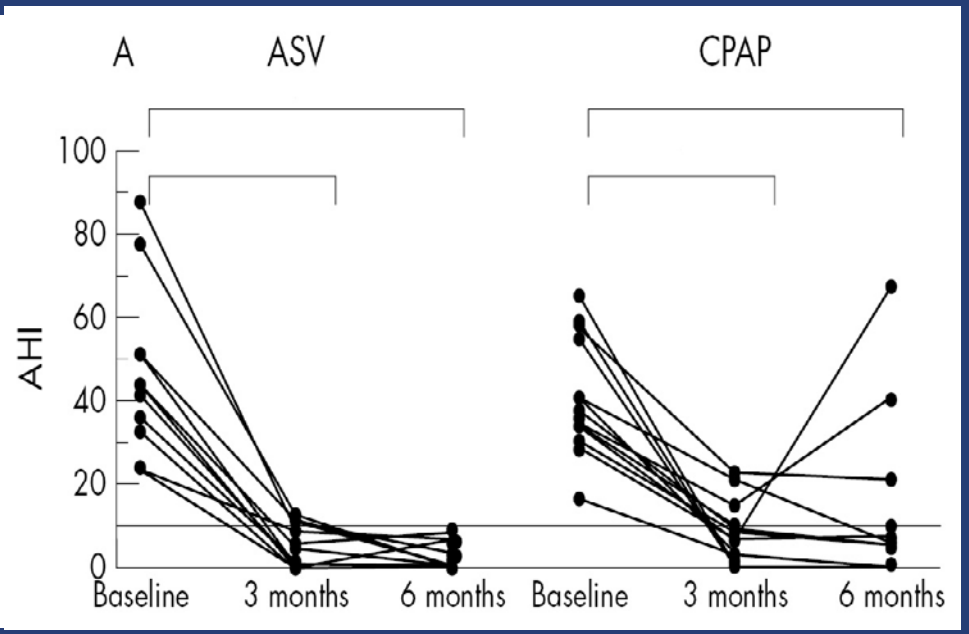


Allam, J.S., et al. Chest, 2007. 132(6): 1839-46.

SERVE-HF: Background (3)

- **ASV is more effective than CPAP for treating CSA/CSR**





- **HF patients comply better with ASV vs CPAP therapy**
- **Patients prefer ASV over both CPAP and bilevel PAP**

Teschler et al. AJRCCM 2001; Philippe et al. Heart 2006; Kasai et al. Circ Heart Fail 2010.

ASV STUDIES: SERVE-HF

- ✓CSA patients only with heart failure (completed 12/14)
  - ✓Heart failure, EF < 45%, AHI > 15, ≥ 50% central events
- ✓1100 patients (approximately 800 patients enrolled)
- ✓All cause mortality or heart failure hospitalization
- ✓Secondary endpoints
  - ✓Time to first shock
  - ✓NYHA
  - ✓MLWHF
  - ✓Renal Function
  - ✓6 Min Hall Walk Test
- ✓Denmark, France, Germany, Norway, Sweden, UK

SERVE-HF: Baseline

	Control (n=659)		ASV (n=666)
Age, years	69.3±10.4		69.6±9.5
Male	90.0%		89.9%
NYHA class III or IV, n (%)	70.3%		70.5%
LVEF, %	32.5±8.0		32.2±7.9
Ischaemic HF aetiology, n (%)	57.0%		59.7%
Implanted device, n (%)	55.2%		54.5%
eGFR, mL/min/1.73m^2	59.3±20.8		57.8±21.1
Six-minute walk distance, m	337.9±127.5		334.0±126.4
ACEI/ARB, n (%)	91.5%		92.0%
β-blockers, n (%)	92.7%		91.9%
Antiarrhythmics, n (%)	13.5%	p=0.005	19.2%

Cowie et al. NEJM 2015, 1 Sep [Epub ahead of print].

Baseline Respiratory Characteristics

	Control (n=659)	ASV (n=666)
AHI, /h	31.7±13.2	31.2±12.7
cAI/total AHI, %	46.5±30.0	44.6±28.9
cAHI/total AHI, %	81.8±15.7	80.8±15.5
Desaturation index (3%), /h	32.8±19.0	32.1±17.7
Average SaO_2, %	92.8±2.5	92.8±2.3
Minimum SaO_2, %	80.3±7.5	80.7±7.0
Time with SaO_2 <90%, min	55.7±73.9	50.5±68.2
Epworth Sleepiness Scale score	7.1±4.6	7.0±4.3

Cowie et al. NEJM 2015;373:1095-105.

Adherence and CSA Control

- ASV effectively controlled sleep-disordered breathing:
  - Mean AHI 31.2/h at baseline, decreased to 6.2–6.8/h during 48 months' treatment ($p<0.001$ vs baseline)
  - Mean central AHI 25.2/h at baseline, decreased to 3.2–4.0/h during 48 months' treatment ($p<0.001$ vs baseline)
  - Mean ODI 32.1/h at baseline, decreased to 8.6–9.9/h during 48 months' treatment ($p<0.001$ vs baseline)
- ASV usage for ≥3 h/night in 60% of patients
  - Usage rates constant over time (mean 3.9 and 3.7 h/night at 3 and 48 months, respectively)

Cowie et al. NEJM 2015, 1 Sep [Epub ahead of print].

ASV Device Performance

Device pressures:

- **Median IPAP 9.7 cmH2O first night, and constant at 9.6–10.1 cmH2O during 48 months' treatment**
- **Median EPAP 5.5 cmH2O first night, and constant at 5.5–6.1 cmH2O during 48 months' treatment**

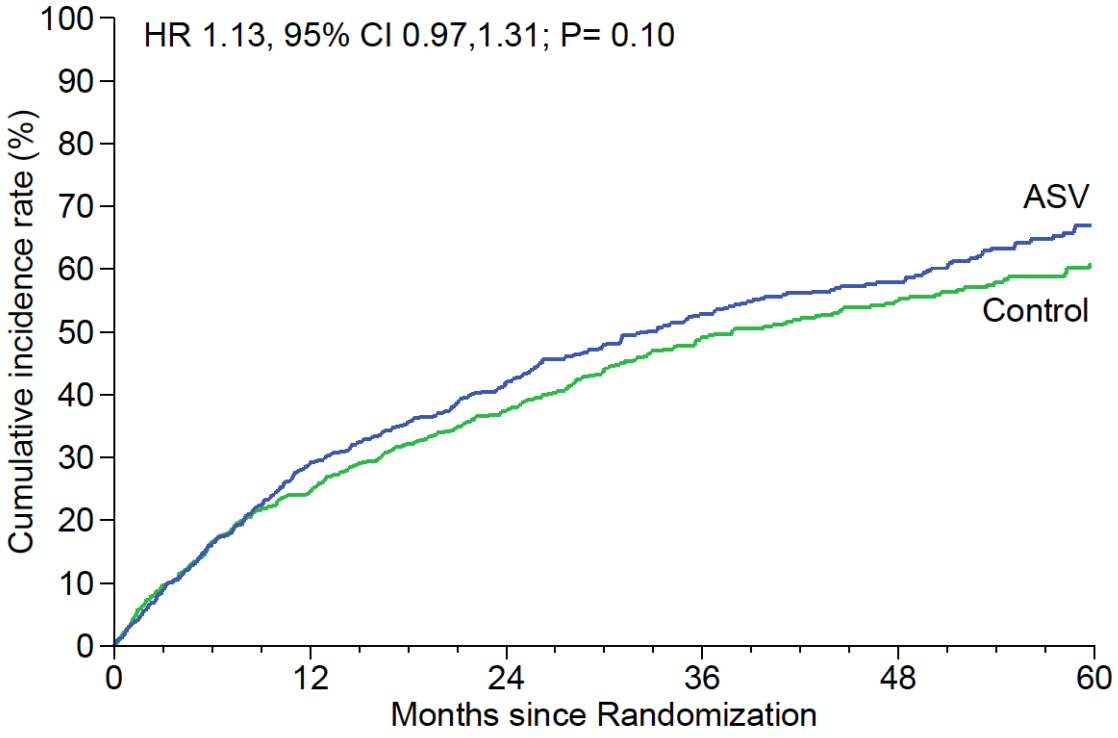
Mask leak:

- **95th percentile 21.7 L/min first night, and reduced over time to 16.1–18.8 L/min during 48 months' treatment**

Cowie et al. NEJM 2015;373:1095-105.

Primary Endpoint Neutral

Time to first event of all-cause death, life-saving cardiovascular intervention, or unplanned hospitalization for worsening chronic HF



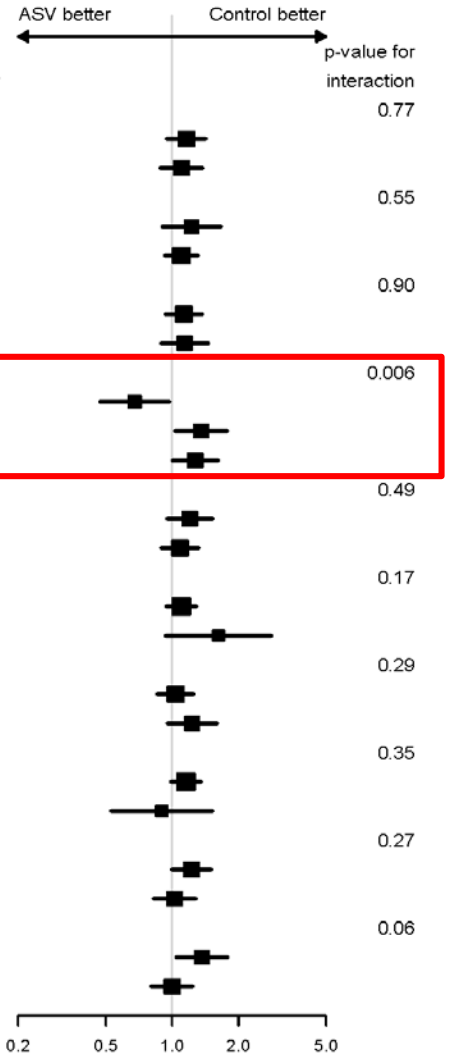
No. at Risk

Control	659	463	365	222	136	77
ASV	666	435	341	197	122	52

Cowie et al. NEJM 2015, 1 Sep [Epub ahead of print].

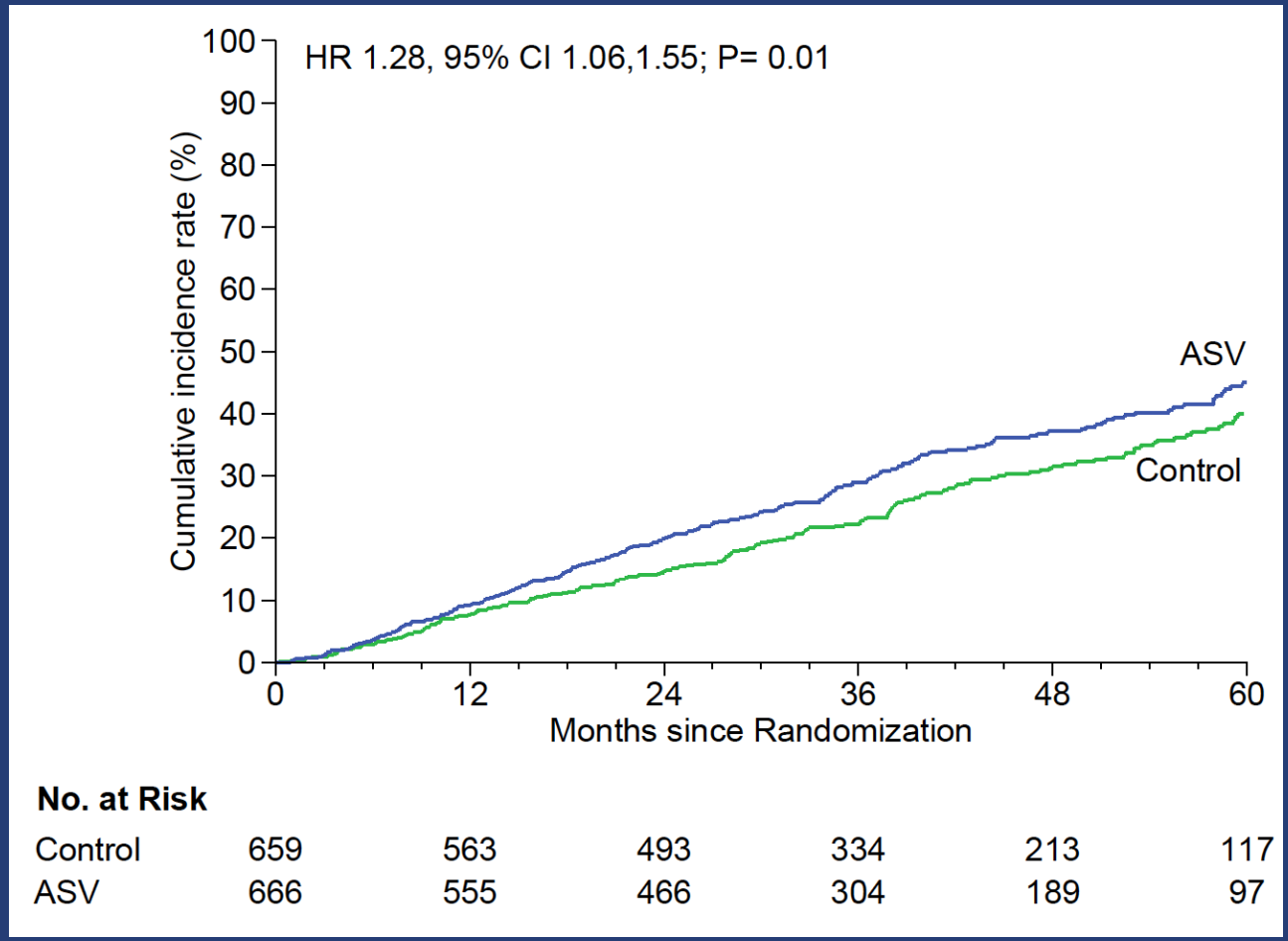
Subgroup Analysis: 1° Endpoint

Subgroup	Patients total n	ASV incidence	Control per p-year	p-value for interaction
SDB (AHI events/hour)				0.77
< 30	697	0.252	0.214	
≥ 30	627	0.236	0.210	
NYHA				0.55
= II	389	0.180	0.144	
≥ III	927	0.277	0.248	
Etiology of HF				0.90
ischemic	756	0.274	0.242	
other	539	0.209	0.175	
CSR				0.006
< 20%	237	0.174	0.270	
20-50%	439	0.239	0.172	
> 50%	490	0.304	0.224	
Age (yr)				0.49
< 70	590	0.215	0.173	
≥ 70	735	0.272	0.247	
Gender				0.17
male	1198	0.250	0.223	
female	127	0.205	0.121	
estimated GFR (ml/min/1.73 m2)				0.29
< 60	686	0.327	0.313	
≥ 60	580	0.165	0.131	
Beta blockers				0.35
yes	1223	0.243	0.207	
no	102	0.269	0.298	
BMI (median split)				0.27
< 28	648	0.287	0.230	
≥ 28	660	0.203	0.194	
LVEF (%)				0.06
< 30	326	0.459	0.313	
≥ 30	743	0.178	0.177	



Cowie et al. NEJM 2015, 1 Sep [Epub ahead of print]

All-Cause Death

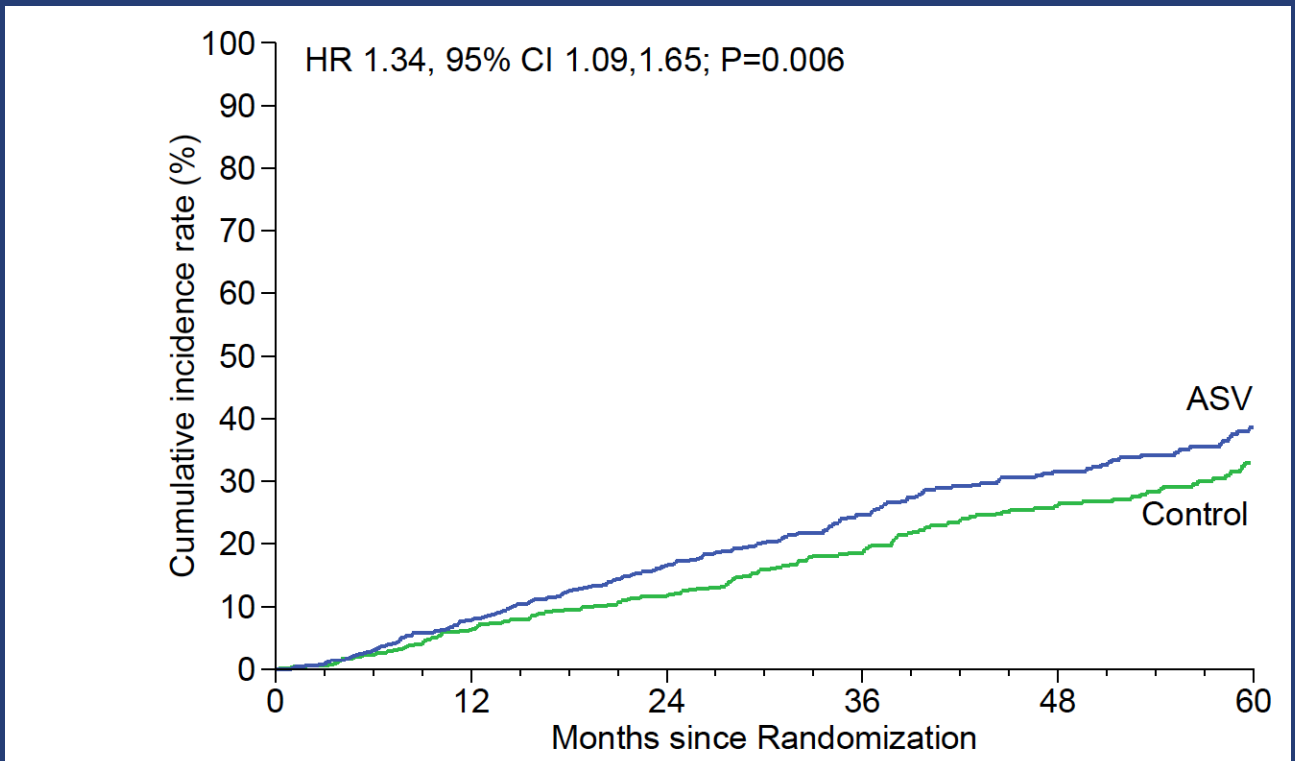


No. at Risk

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

Cowie et al. NEJM 2015, 1 Sep [Epub ahead of print].

Cardiovascular Death

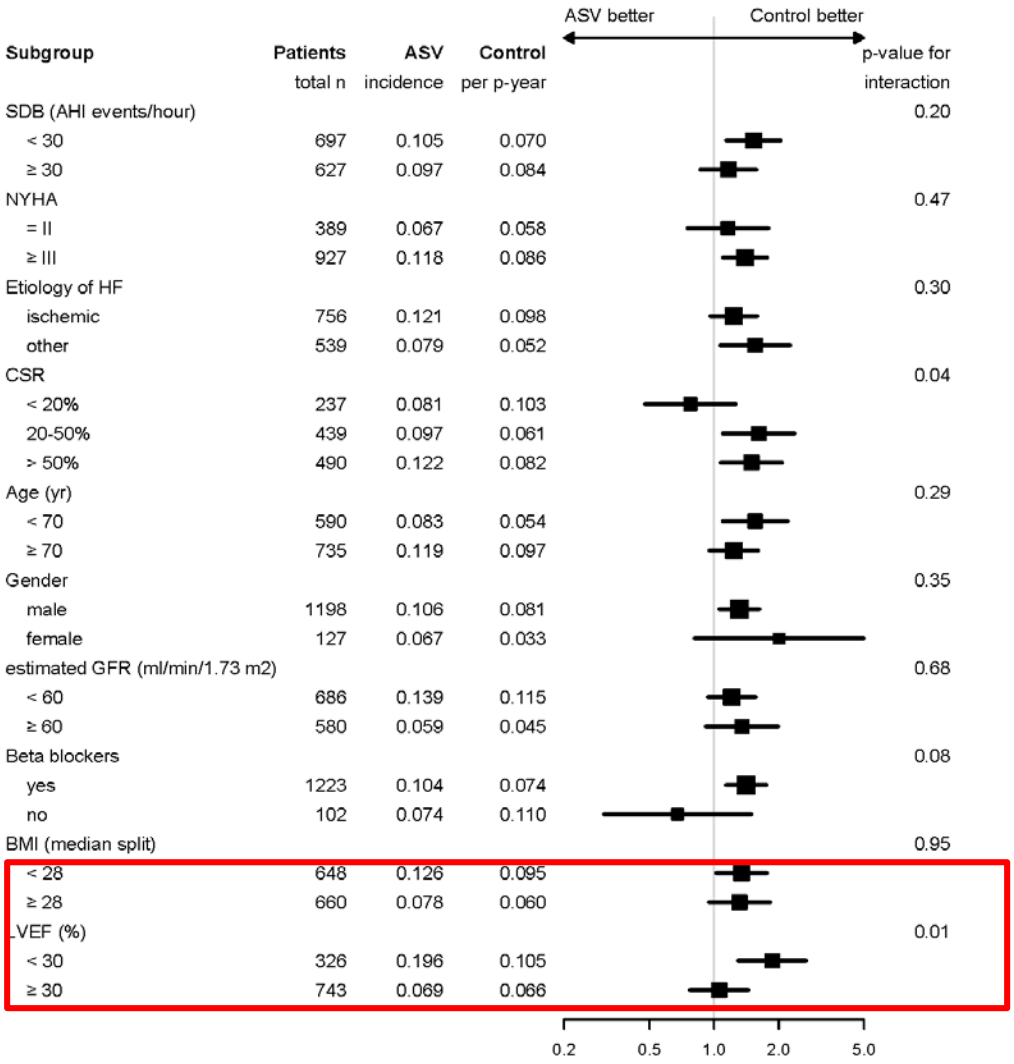


No. at Risk

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

Cowie et al. NEJM 2015, 1 Sep [Epub ahead of print].

Subgroup Analysis: CV Death



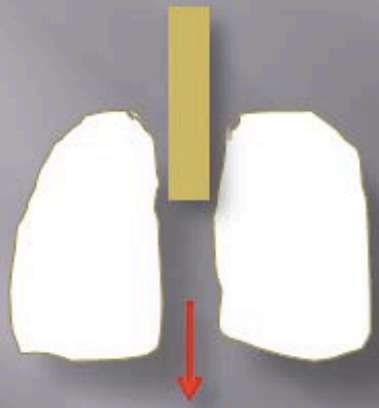
Cowie et al. NEJM 2015, 1 Sep [Epub ahead of print].

CURRENT ASV STUDIES: CAT-HF

- ✓CSA and OSA patients with heart failure
  - ✓Testing in the hospital and starting on ASV therapy prior to leaving the hospital
  - ✓Survival free from CV hospitalization and 6 MHWT composite
  - ✓AHI > 15
  - ✓215 patient randomized to therapy vs. control
- ✓Germany and US

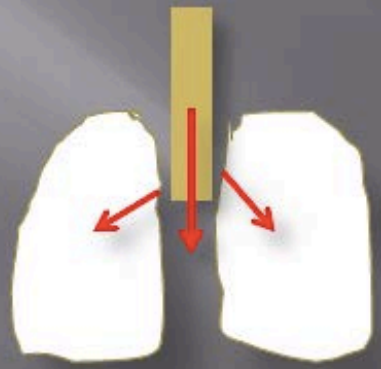
COMPARISON OF NORMAL INSPIRATION WITH CSA THERAPIES

Normal Breathing



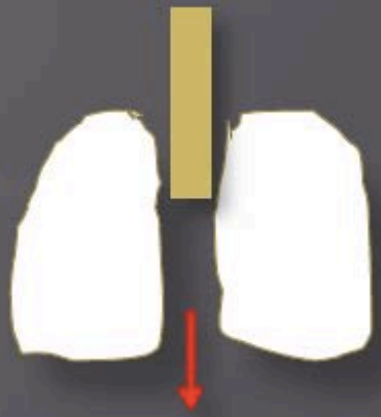
Diaphragm ***pulls*** air into the lungs

Mask Therapies (ASV, CPAP)



Ventilation ***pushes*** air into the lungs via positive intrathoracic pressure

Remedē® System



The remedē® System ***pulls*** air into the lungs using the same mechanism of action as normal breathing

HOW IS THE REMEDĒ® SYSTEM IMPLANTED?

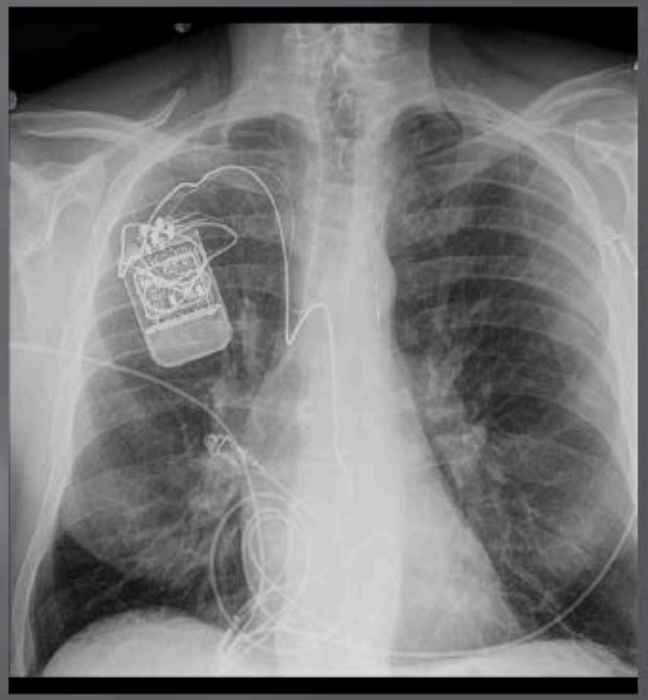
The **rem**edē® System implant takes place in the ***EP laboratory*** by cardiologists experienced with CRT

Light sedation is used to keep patients comfortable

The device is placed ***under the skin*** in either the right or left chest

A ***stimulation lead*** is placed either in the left pericardiophrenic or right brachiocephalic vein

A second lead to ***sense respiration*** is placed in the azygos vein

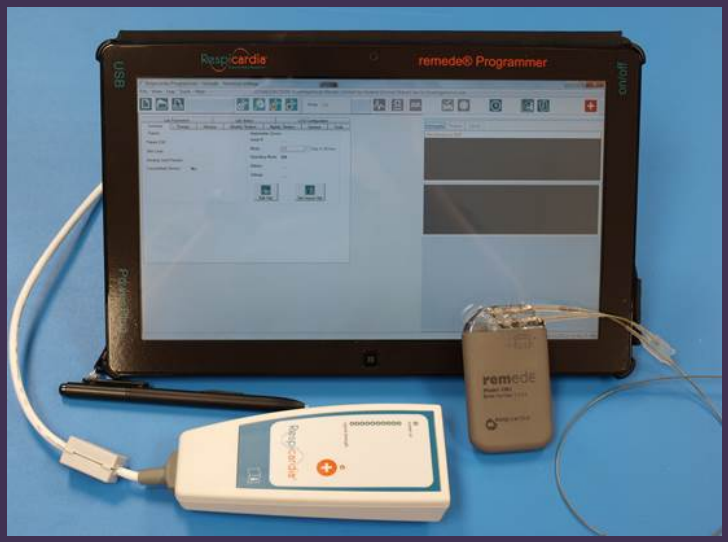


CAUTION Investigational device. Limited by Federal (or United States) law to investigational use.
AVAILABLE FOR SALE IN THE EU/EEA.

A New Option for Treating Central Sleep Apnea: The remedē® System Therapy

The **rem**edē® System is:

- A ***neurostimulation*** technology (Respiratory Rhythm Management™) which provides unilateral stimulation of the phrenic nerve
- Designed to restore ***normal sleep and breathing*** to patients with central sleep apnea by stabilizing CO_2
- A fully implantable ***transvenous system*** which activates automatically when the patient sleeps



CAUTION Investigational device. Limited by Federal (or United States) law to investigational use.

How does the remedē® System Activate Therapy?

- Is it the Scheduled Sleep Time?
- Is the Activity level below Activity Threshold?
- Is the patient in sleeping posture (below Pitch Threshold)?
- Is the Stimulation Lead Impedance within acceptable limits?
- Is therapy delivery time less than maximum?

All Yes → **Therapy Automatically Starts**

CAUTION Investigational device. Limited by Federal (or United States) law to investigational use.
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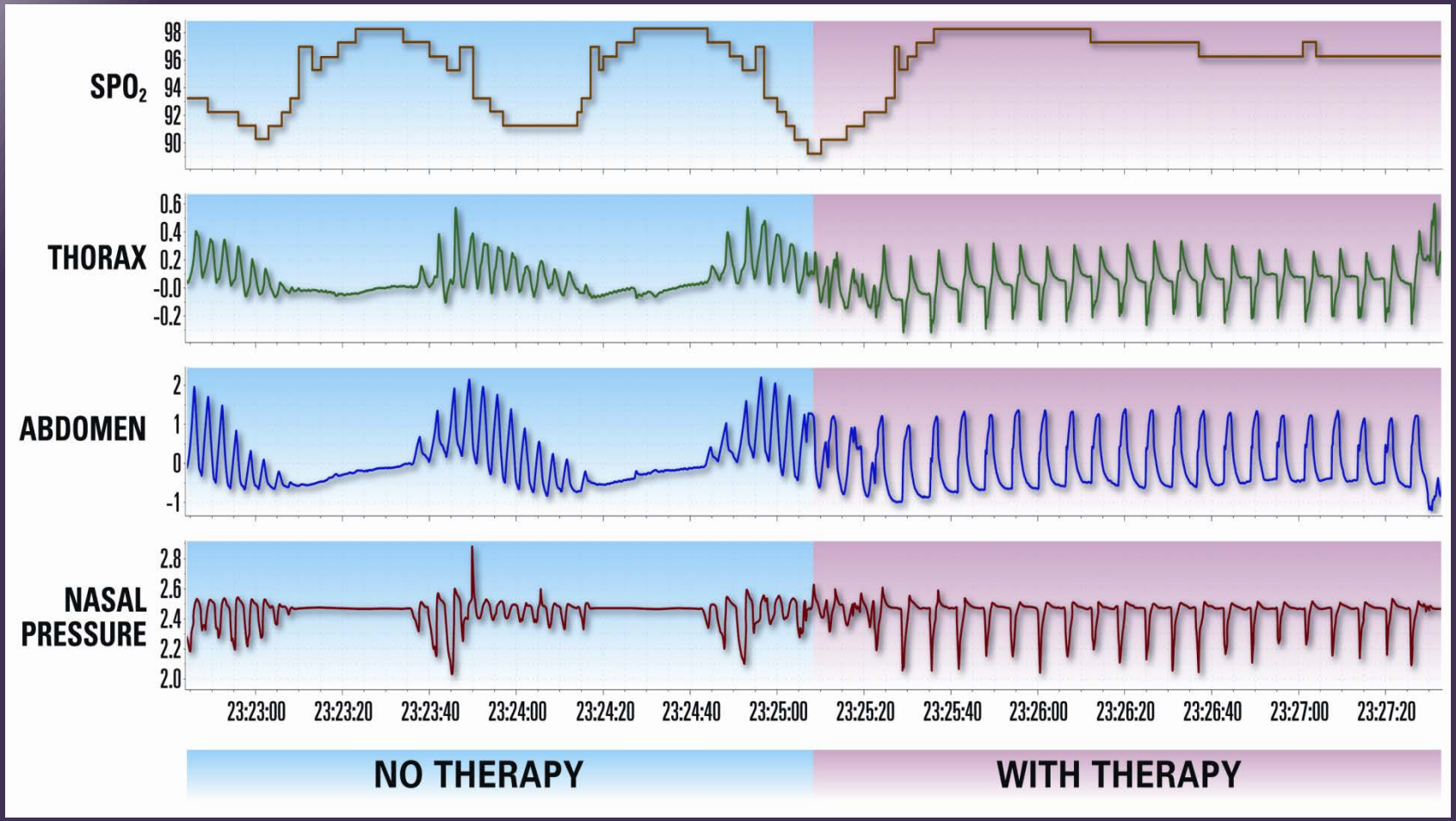
Acute Feasibility Study
remedē® System Therapy Activated



Eur Heart J (2012) 33(7): 889-894

Acute Feasibility Study – Patient Characteristics

Patients on optimal medical therapy

Demographics (N=16)	Mean ± SD or % of patients
Age	57 ± 12 years
Male	100%
Heart rate (bpm)	73 ± 17
Atrial fibrillation	19%
BMI	27.5 ± 3.3
NYHA Class I/II/III	19% / 50% / 31%
LVEF	30% ± 12%
Ischemic	44%
ICD/Pacemaker	25%

Medications	% of patients
Beta-blockers	94%
ACE-I/ARB	88%
Diuretic	100%
Aldosterone Antagonist	56%
Statin	67%
Digoxin	18%
Anti-coagulant	44%
Anti-Diabetic	25%

CAUTION Investigational device. Limited by Federal (or United States) law to investigational use.

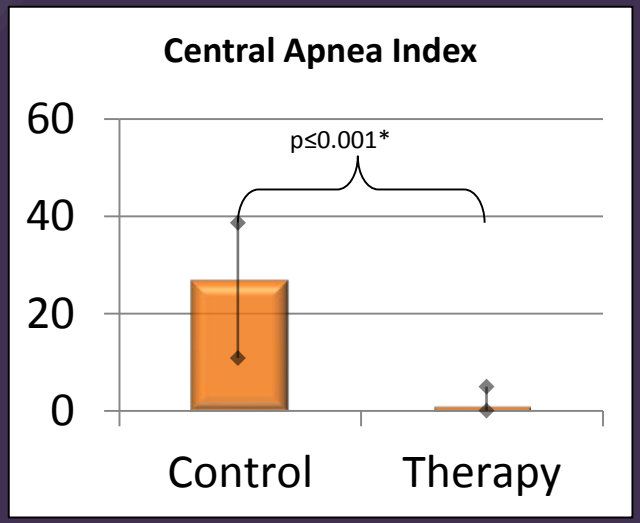
Eur Heart J (2012) 33(7): 889-894

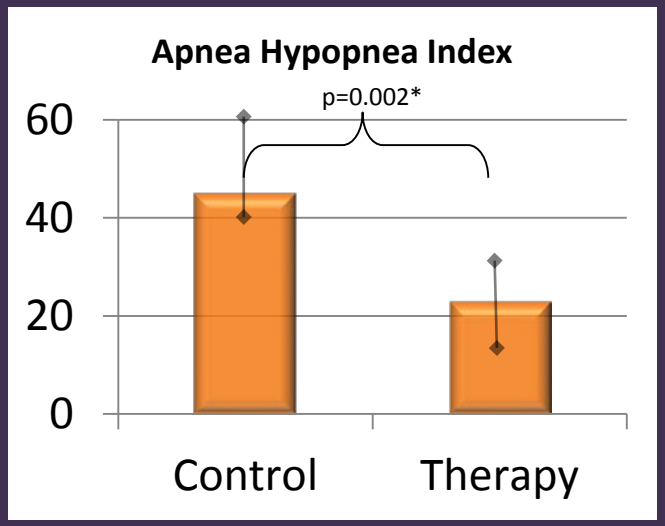
Acute Feasibility Study - Clinical Results

All values are medians with corresponding inter-quartile ranges and expressed as events/hour.

↓ 90%

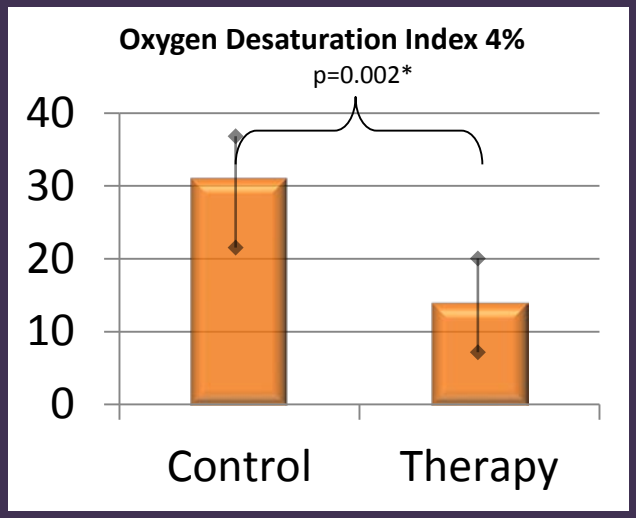
15/16 patients had ≥ 70% reduction in CAI

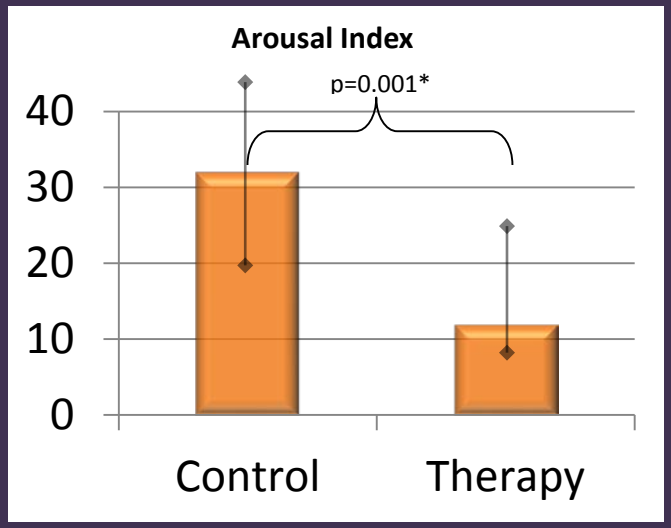




↓ 48%

↓ 50%





↓ 49%

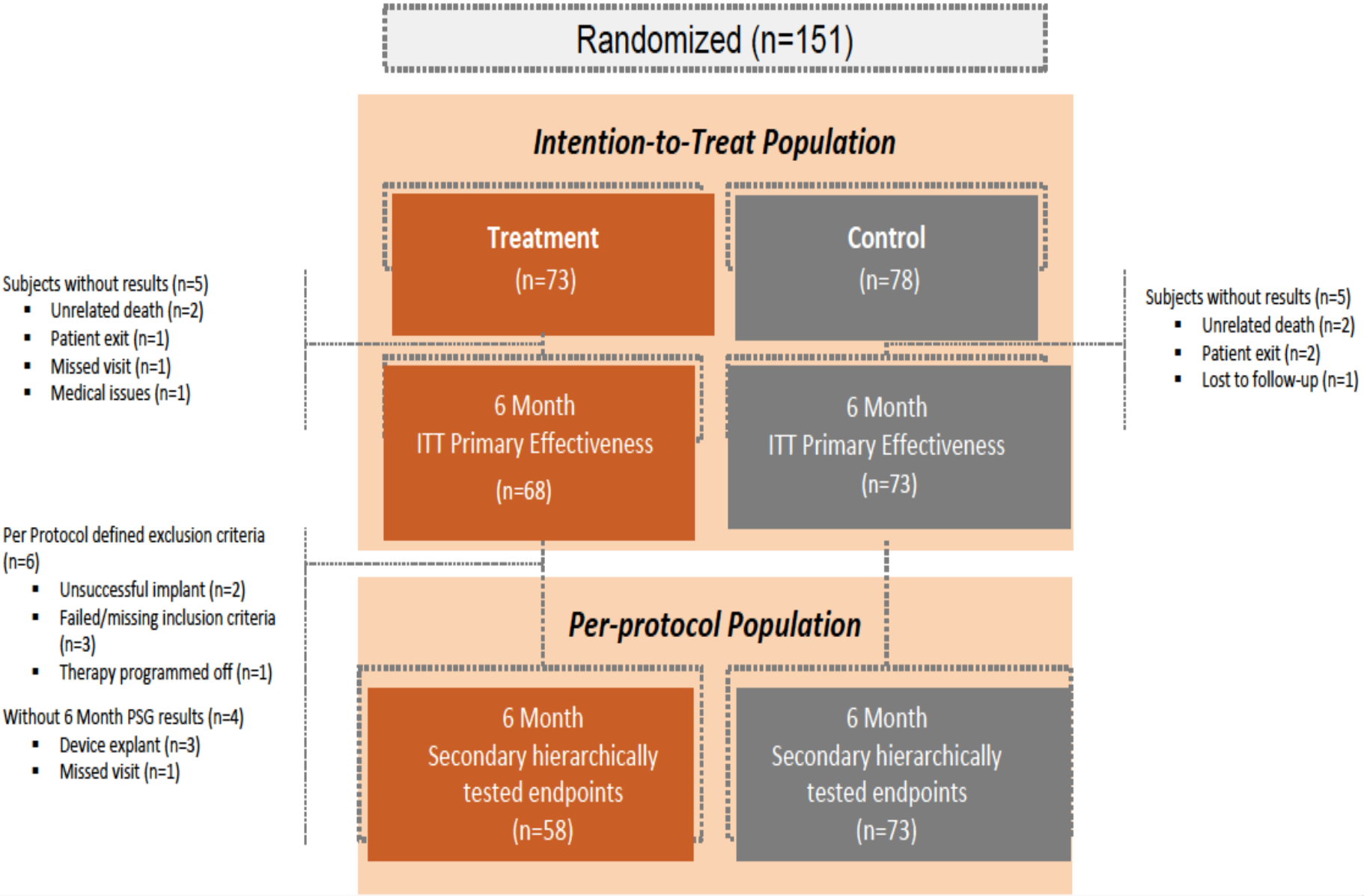
**Wilcoxon matched pair signed ranks test*

Eur Heart J (2012) 33(7): 889-894

CAUTION Investigational device. Limited by Federal (or United States) law to investigational use.

The remedē® System Pivotal Trial

PATIENT POPULATION



The **rem**edē® System Pivotal Trial

ENDPOINTS

ENDPOINT	DESCRIPTION	POPULATION
Primary Effectiveness (6 months)	**Comparison of the proportion of subjects with ≥50% reduction in AHI between treatment and control**	**Intention to Treat (ITT)**
Primary Safety (12 months)	Freedom from serious adverse events associated with implant, the remedē system, or delivered therapy	Intention to Treat
Secondary Hierarchical (6 months)	1. Central Apnea Index (CAI) 2. Apnea Hypopnea Index (AHI) 3. Arousal Index (ArI) 4. Rapid Eye Movement (REM) 5. Patient Global Assessment (PGA) 6. Oxygen Desaturation Index 4% (ODI4) 7. Epworth Sleepiness Scale (ESS)	Per-protocol

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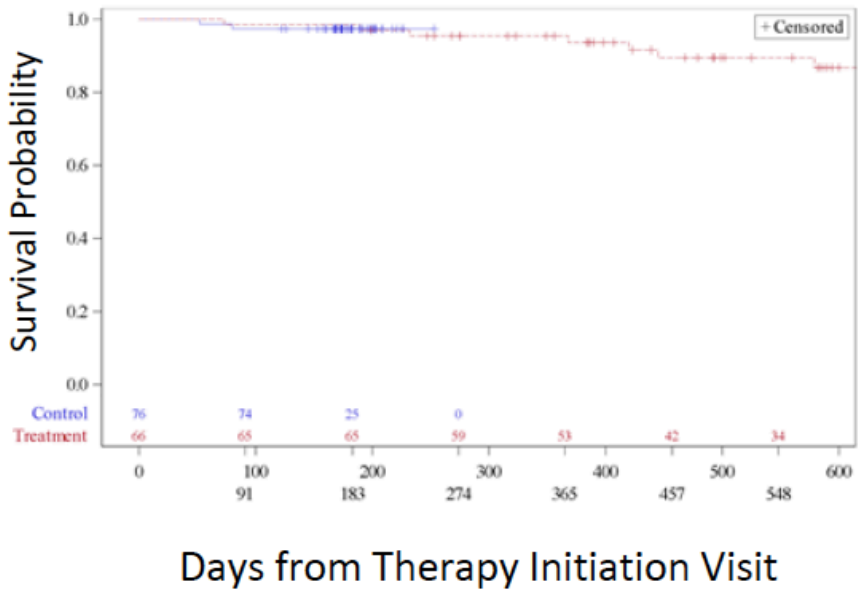
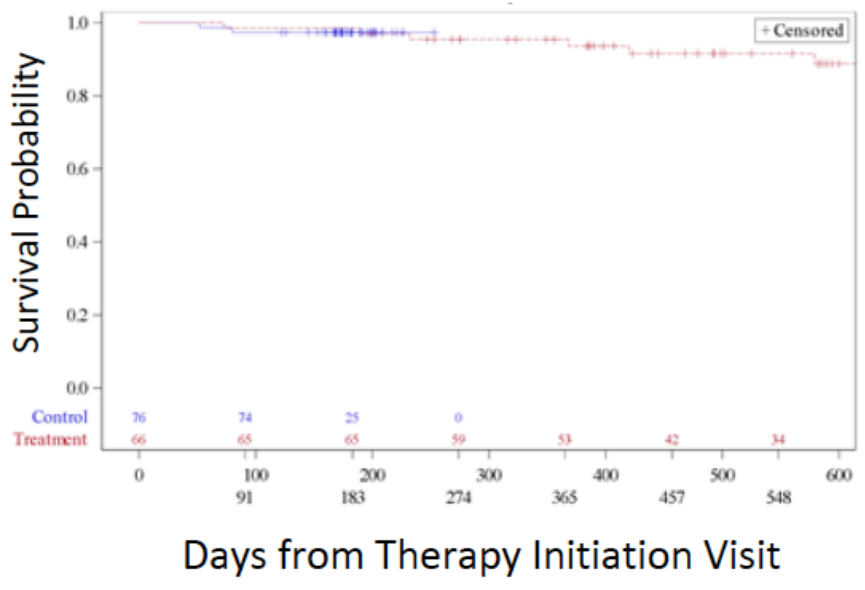
SAFETY

Kaplan-Meier Curve of Time to Death (ITT)



Kaplan-Meier Curve of Time to Cardiovascular Death (ITT)

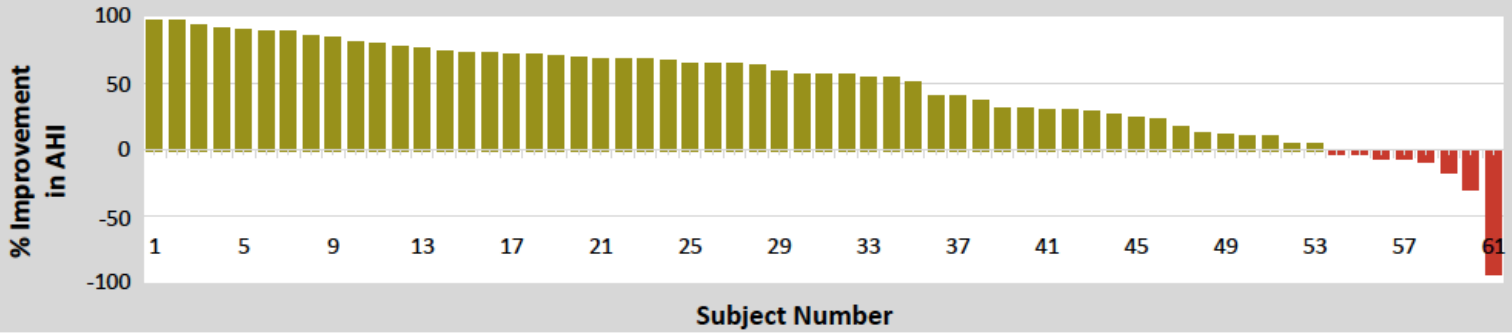


GROUP
Control
Treatment

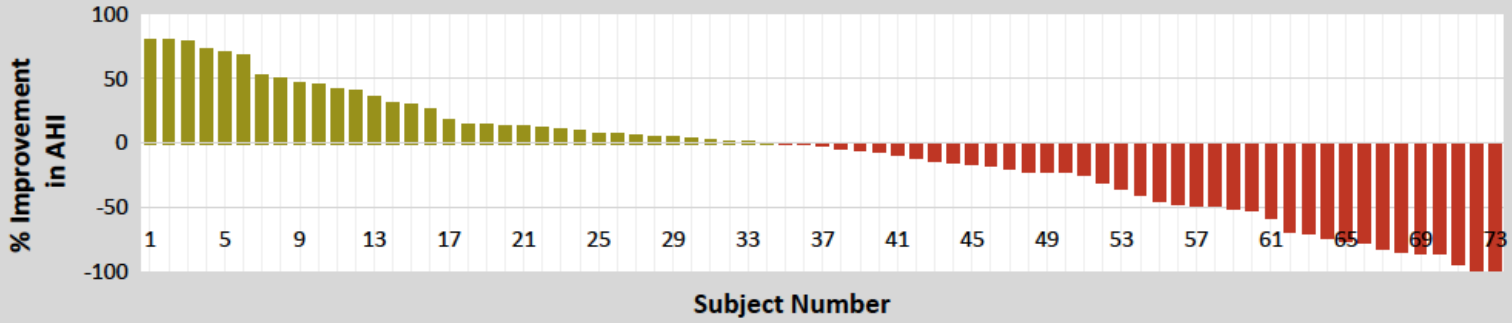
The remedē® System Pivotal Trial

87% OF TREATMENT PATIENTS DEMONSTRATED AN AHI IMPROVEMENT

TREATMENT



CONTROL



Improvement from baseline Decline from baseline

MR Costanzo, LBCT HFA 2016

Conclusions

- Both OSA and CSA are highly prevalent in patients with HF and significantly increase their morbidity and mortality.
- Screening for SDB should be included in evaluation of all patients with HF.
- In HF patients with OSA mask-based therapies have consistently improved both clinical signs/symptoms and outcomes.
- In HF patients with CSA CPAP improves symptoms/signs but not transplant-free survival.
- Trials of ASV in HF patients with CSA neutral.
- Phrenic nerve stimulation appears safe for the treatment of CSA and is currently being evaluated in a multicenter, randomized clinical trial.