

# The Differential Diagnosis of Sleep Apnoea

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# Symptoms

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- (Witnessed) phases of apnoea of at least 10 seconds duration
- Restless sleep
- Excessive daytime sleepiness
- Morning headache
- Vertigo, particularly after getting up
- Waking up with a dry mouth / sore throat
- Nocturnal sweating
- Nocturia
- Sleepiness while driving
- Depression, forgetfulness, mood changes
- Decreased interest in sex, impotence, erectile dysfunction

# What Are We Talking About?

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- **Sleep-disordered breathing**

Umbrella term for different pathological entities that are associated with restless sleep



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Umbrella term for different pathological entities that are associated with restless sleep

- **Apnoea**

Cessation of oral or nasal air flow for  $>10$  seconds associated with a drop in oxygen saturation by more than 4 points

- **Hypopnoea**

Reduction of oral or nasal air flow by  $<50\%$  associated with a drop in oxygen saturation by more than 4 points



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Umbrella term for different pathological entities that are associated with restless sleep

- **Apnoea**

Cessation of oral or nasal air flow for >10 seconds associated with a drop in oxygen saturation by more than 4 points

- **Hypopnoea**

Reduction of oral or nasal air flow by <50% associated with a drop in oxygen saturation by more than 4 points

- **AHI**

Number of apnoeas or hypopnoeas per hour



# Screening for Sleep Apnoea Using Polygraphy

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# Polygraphy (PG) Report

## Charité Campus Virchow-Klinikum

Mittelallee 2  
13353 Berlin

### Patienteninformation

Nachname:	H	Geschlecht:	Männlich
Vorname:	R	Geburtsdatum:	N/A
Patienten-ID:	HR09.01.12	Größe:	entf.
Adresse:		Gewicht:	entf.
Stadt:		BMI:	entf.
Telefon:			

### Aufzeichnungsintervall

Datum:	09.01.2012
Start-Zeit:	21:29:51
Stopzeit:	07:00:00
Dauer:	570,2 Minuten

### Indizes

AHI:	41,5	Hoch
ODI:	44,8	Hoch
Apnoe Index:	24,4	
Hypopnoe-Index:	17,1	
RMI:	41,3%	
PBI:	11,3%	
Mittlere Pulsrate:	70,0 bpm	

### Ereigniszählung

Apnoen:	211
Obstructive Apnoen:	50
Zentrale/Gemischte Apnoen:	161
Hypnopnoen:	148
Entsättigung:	398
RMI-Perioden:	435
Paradoxe Perioden:	244
Atemzüge:	5512

### Analysierter Intervall

Start-Zeit:	21:30:12
Stopzeit:	06:50:01
Dauer:	559,8 Minuten
Gesch.Restzeit:	532,6 Minuten

### Datenintegrität

Anzahl der aufrechten Perioden oder Ausschaltungen des Geräts: **7** insgesamte Dauer: **19.0** Minuten.  
Anzahl der Bewegungsperioden: **13** insgesamte Dauer: **4.0** Minuten die von der Analyse ausgeschlossen wurden.  
Atemflusssignal war gültig für **98%** der Ruhezeit.  
Oximetriesignal war gültig für **100%** der Ruhezeit.

Alle Integritätswerte basieren auf dem analysierten Intervall.

### Terminologie

**AHI** - Apnoe/Hypopnoe Index, Anzahl von Apnoen und Hypopnoen pro Ruhestunde.  
**ODI** - Sauerstoffsättigungs-Index, Anzahl der Entsättigungen pro Ruhestunde.  
**RMI** - Respiratory Mechanics Instability, Dauer der RMI Episoden als Prozentsatz der Ruhezeit.  
**PBI** - Index paradoxer Atmung, Prozentsatz der Ruhezeit in der die Atmung aus der Phase fällt.



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Polysomnographie  
(PSG) in sleep  
lab





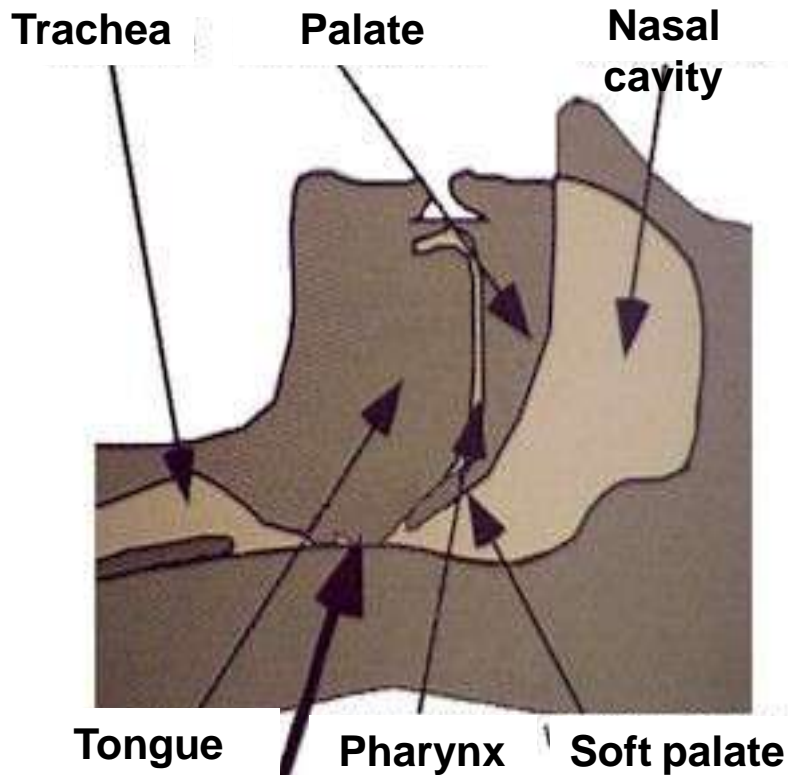
# Risk Factors

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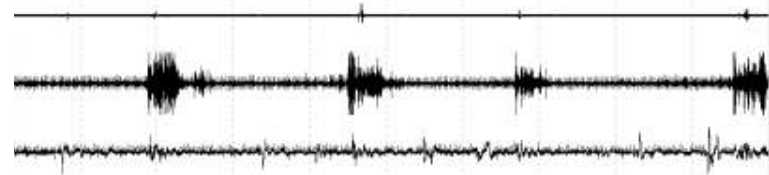
## **Obstructive Sleep Apnoea Syndrome**

- Obesity
- Impaired nasal breathing (polyps, septal deviation)
- Enlarged tonsils or enlarged soft tissue (e.g. acromegaly)
- Alcohol consumption, nicotin etc.

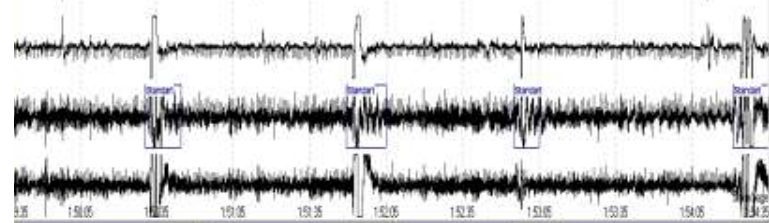
# Obstructive Sleep Apnoea



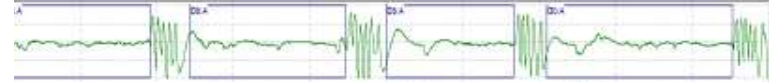
EMG



EEG



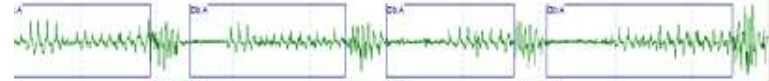
Airflow



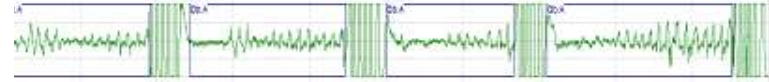
SaO<sub>2</sub>



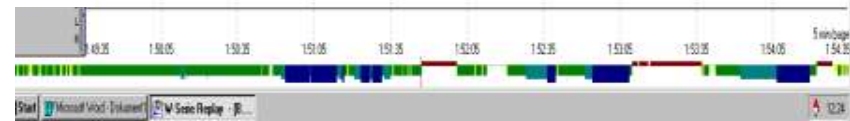
Thorax



Abdomen



Snoring



# Treatment of Obstructive Sleep Apnoea

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# Risk Factors

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## Obstructive Sleep Apnoea Syndrome

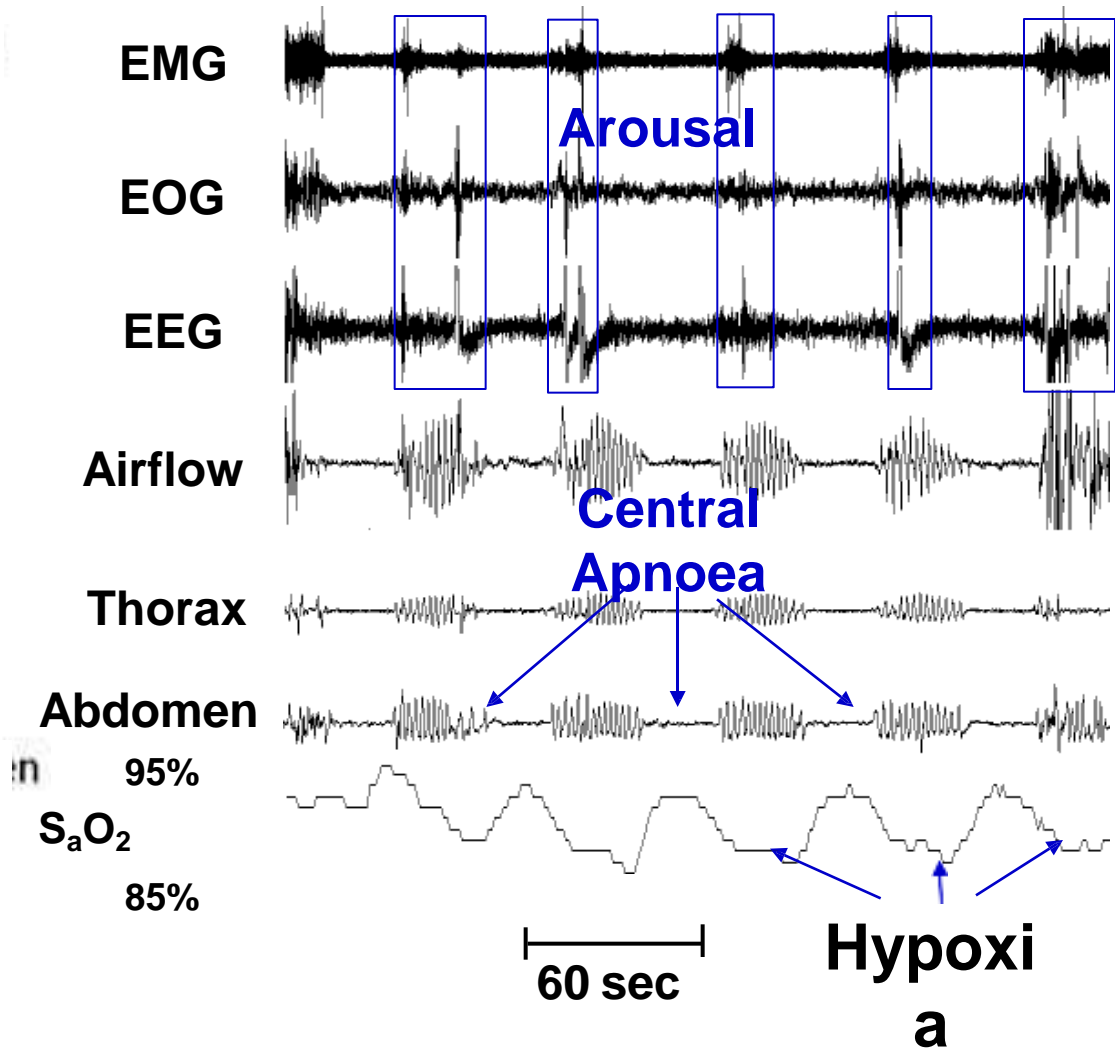
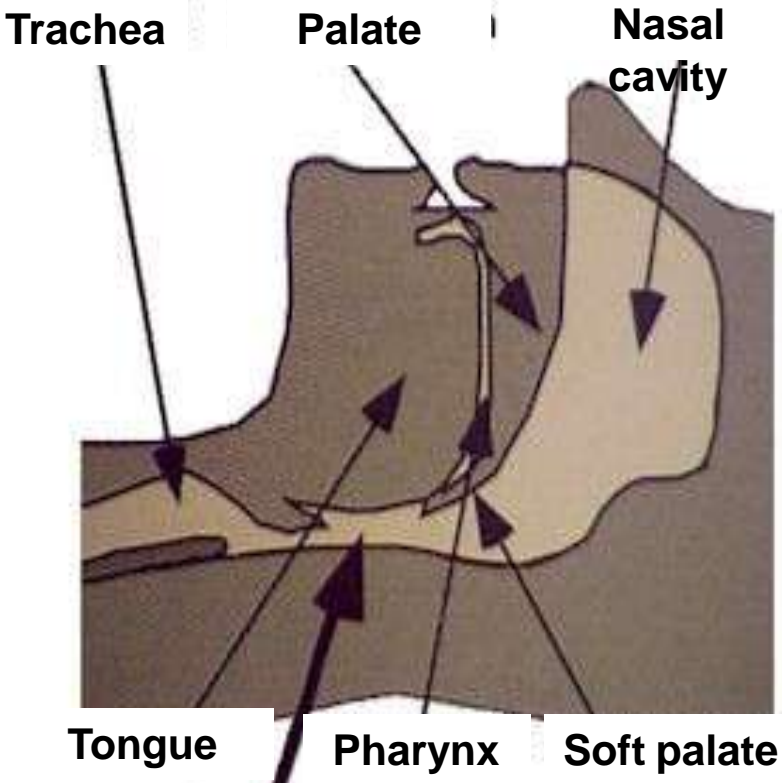
- Obesity
- Impaired nasal breathing (polyps, septal deviation)
- Enlarged tonsils or enlarged soft tissue (e.g. acromegaly)
- Alcohol consumption, nicotin etc.

## Central Sleep Apnoea Syndrome

- Cardiac disease (heart failure, hypertension, atrial fibrillation, ventricular arrhythmia, valve disease)
- Known carotid stenosis, history of stroke
- Male gender, advanced age, low body weight
- Diabetes mellitus



# Central Sleep Apnoea



# Heart failure and sleep disorders

Gianfranco Parati<sup>1-3</sup>, Carolina Lombardi<sup>1,2</sup>, Francesco Castagna<sup>1,2,4</sup>, Paola Mattaliano<sup>1,2</sup>, Pasquale Perrone Filardi<sup>5</sup> and Piergiuseppe Agostoni<sup>6,7</sup> on behalf of the Italian Society of Cardiology (SIC) Working Group on Heart Failure members

NATURE REVIEWS | CARDIOLOGY | VOLUME 13 | JULY 2016 |

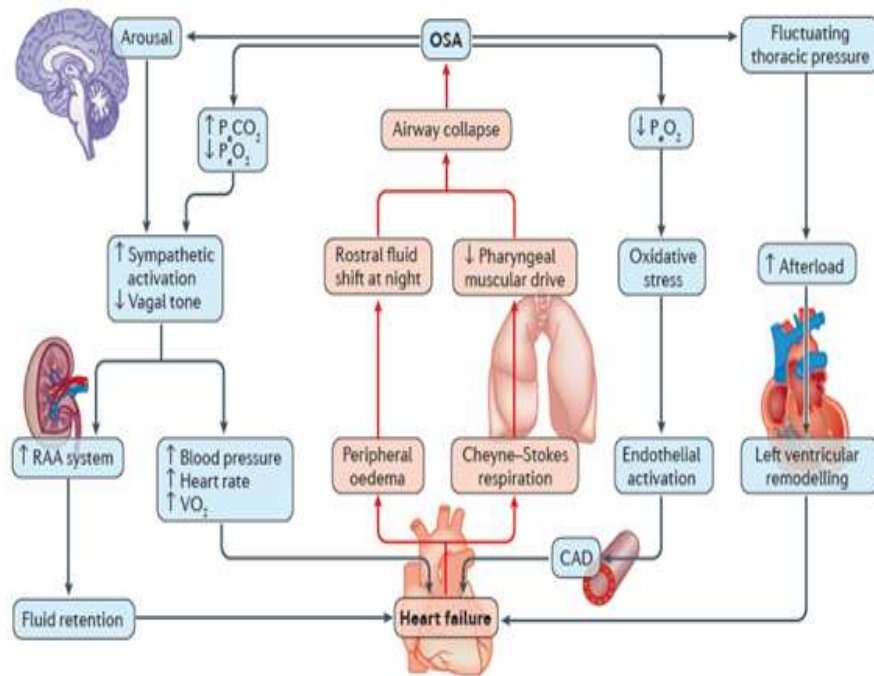


Figure 2 | Relationship between obstructive sleep apnoea (OSA) and heart failure. Schematic representation of the mutual interactions between OSA and heart failure. CAD, coronary artery disease;  $P_aCO_2$ , arterial partial pressure of  $CO_2$ ;  $P_aO_2$ , arterial partial pressure of  $O_2$ ; RAA, renin-angiotensin-aldosterone;  $VO_2$ , oxygen consumption rate.

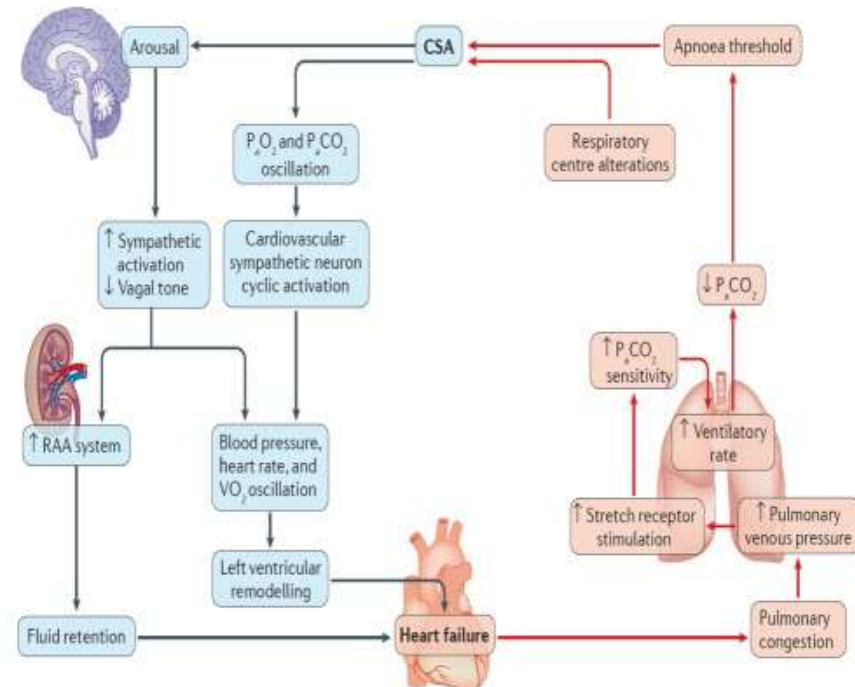


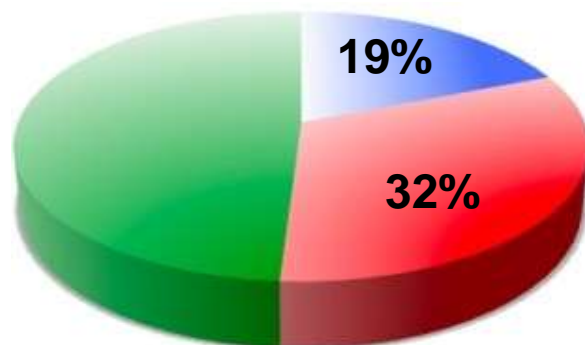
Figure 3 | Relationship between central sleep apnoea (CSA) and heart failure. Schematic representation of the mutual interaction between CSA and heart failure.  $P_aCO_2$ , arterial partial pressure of  $CO_2$ ;  $P_aO_2$ , arterial pressure partial of  $O_2$ ; RAA, renin-angiotensin-aldosterone;  $VO_2$ , oxygen consumption rate.

# Prevalence of Sleep Apnoea

## Prevalence SDB with AHI $\geq 15/h$

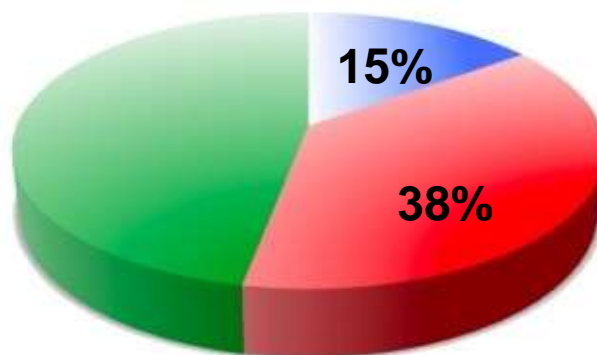
*n*=700

*NYHA  $\geq II$ , LVEF  $\leq 40\%$*



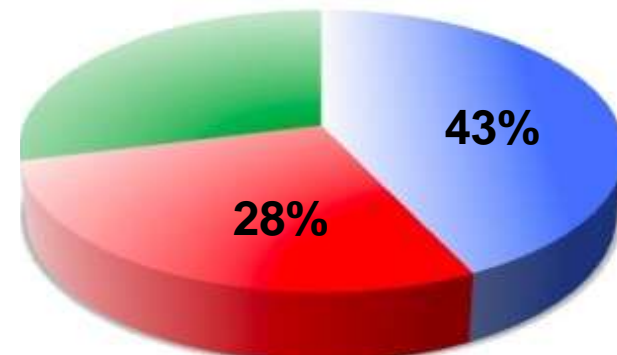
## Prevalence SDB with AHI $\geq 15/h$

*n*=55



## Prevalence SDB with AHI $\geq 10/h$

*N*=203



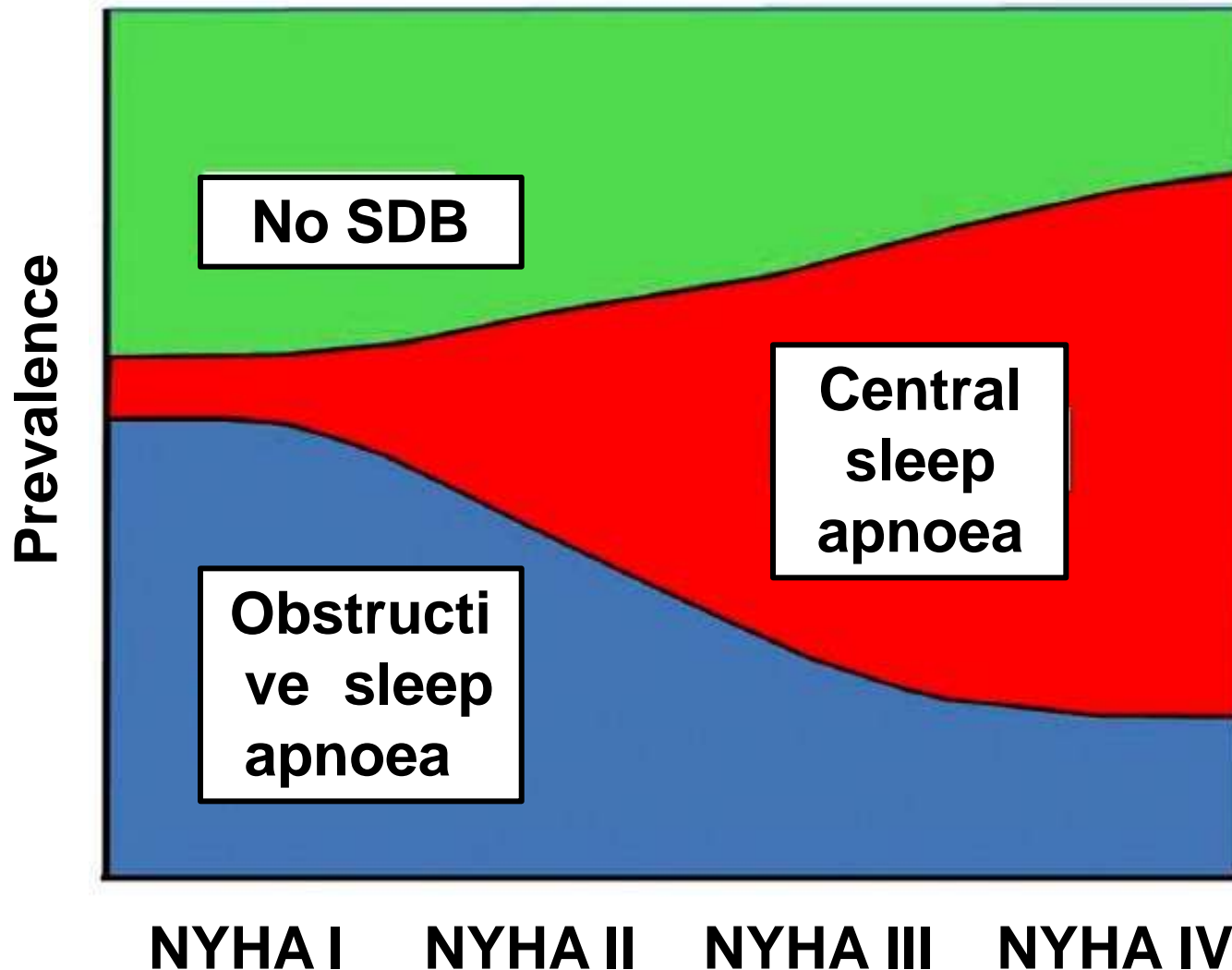
■ Keine SBAS ■ OSA ■ CSA

Oldenburg *et al.*  
**Eur J Heart Fail** 2007.

Vazir *et al.*  
**Eur J Heart Fail** 2007.

Schulz *et al.*  
**Eur Respir J** 2007.

# Prevalence of Sleep Apnoea in Heart Failure





# Epworth Sleepiness Scale

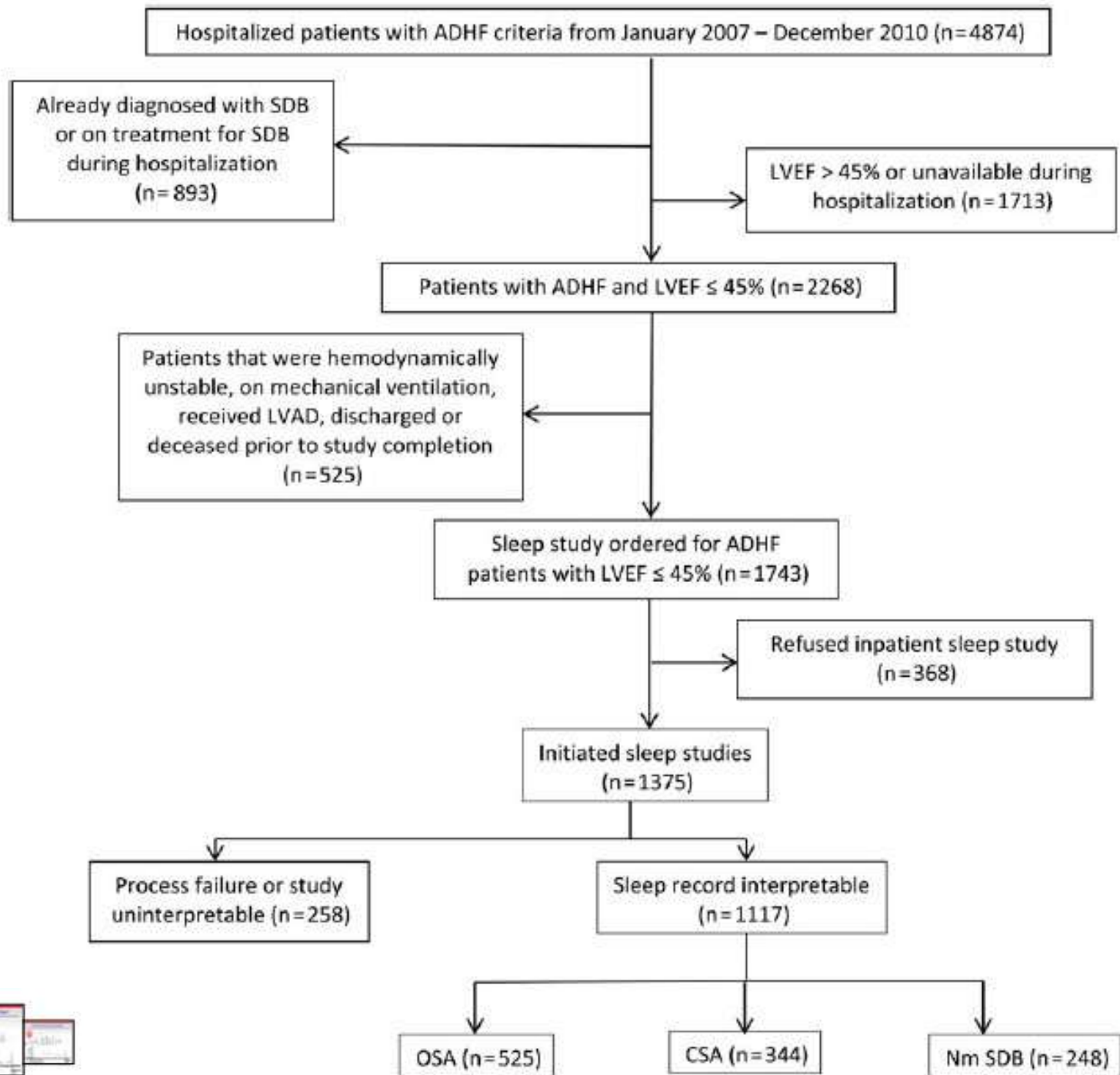
How likely are you to doze off or fall asleep in the following situations?  
Answer considering how you have felt over the past week or so.

- 0 = Would never doze
- 1 = Slight chance of dozing
- 2 = Moderate chance of dozing
- 3 = High chance of dozing

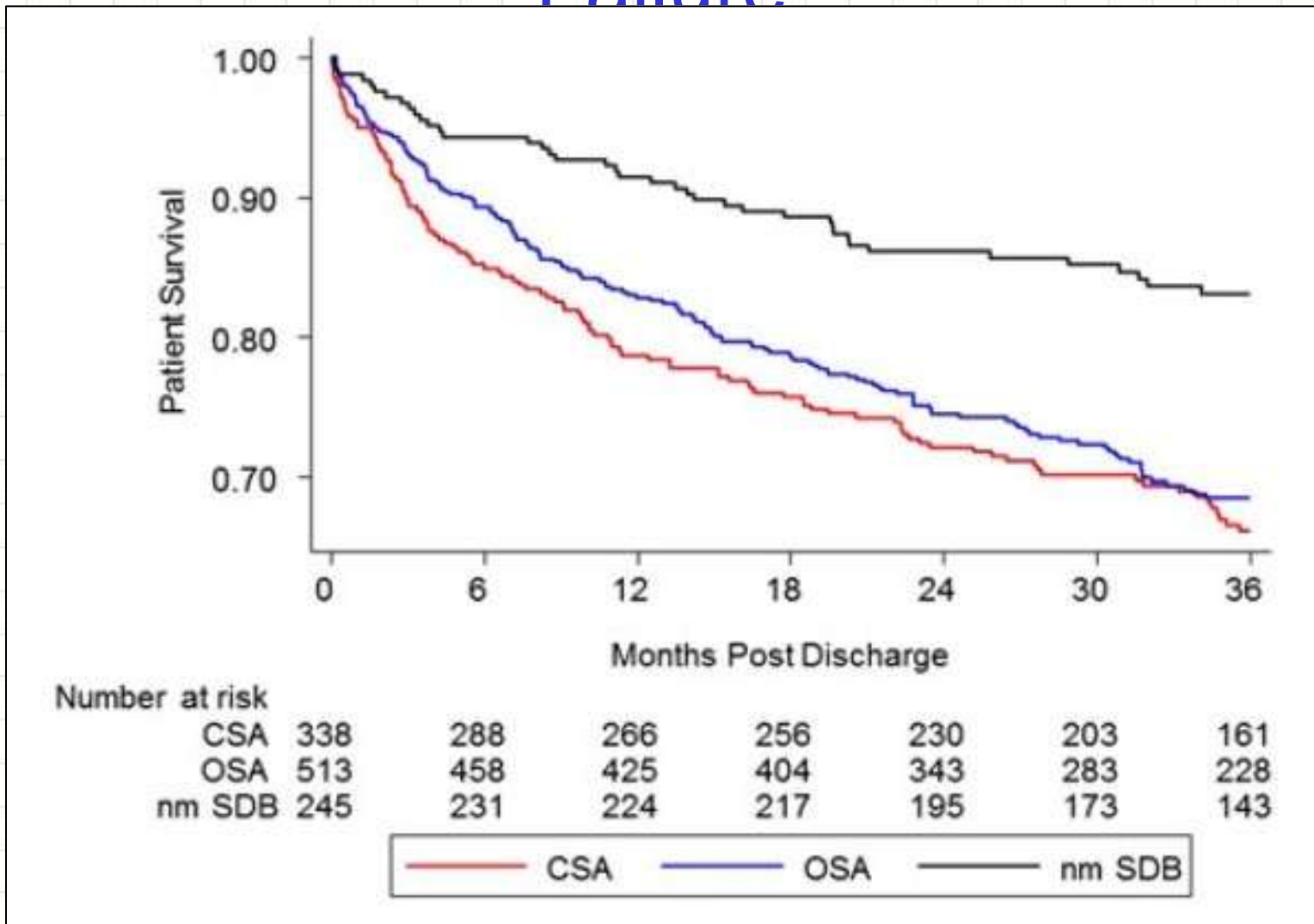
**Normal: <10**

1. Sitting and reading	<input type="text"/>
2. Watching TV	<input type="text"/>
3. Sitting inactive in a public place (e.g., theater or meeting)	<input type="text"/>
4. As a passenger in a car for an hour without a break	<input type="text"/>
5. Lying down to rest in the afternoon when able	<input type="text"/>
6. Sitting and talking to someone	<input type="text"/>
7. Sitting quietly after a lunch without alcohol	<input type="text"/>
8. In a car while stopped for a few minutes in traffic	<input type="text"/>

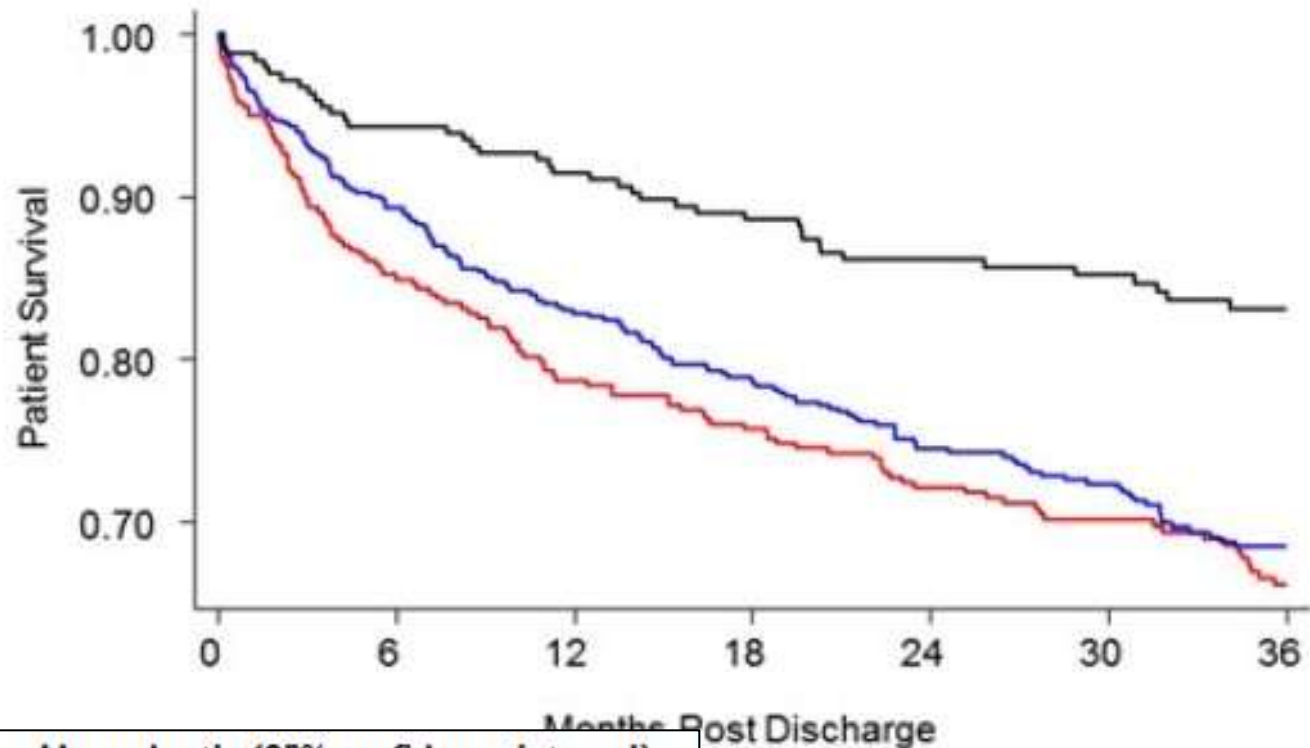




# Prognosis of Sleep Apnoea in Acute Heart Failure



# Prognosis of Sleep Apnoea in Acute Heart Failure

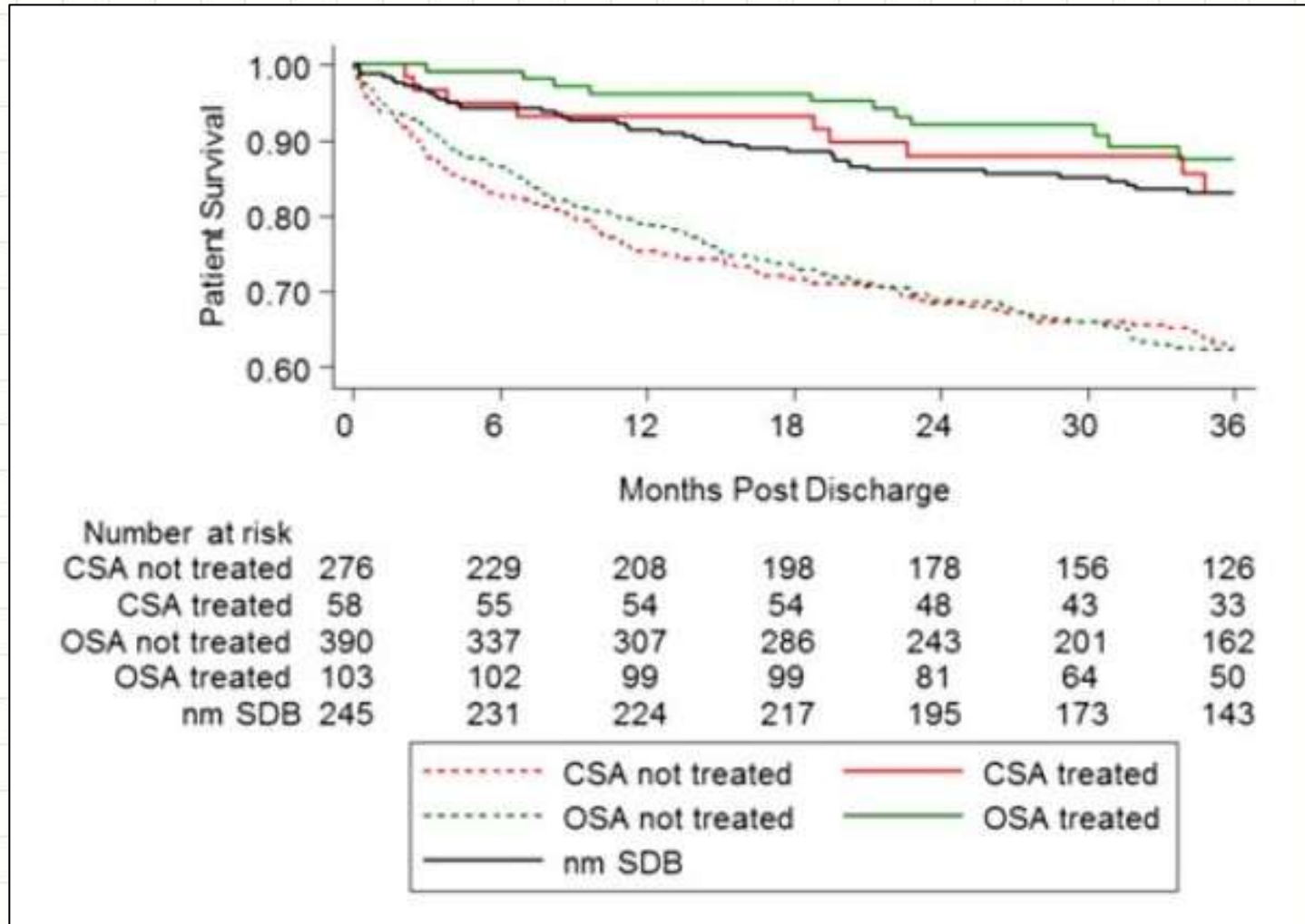


Model	Hazard ratio (95% confidence interval), P-value	
	CSA vs. nmSDB	OSA vs. nmSDB
Univariate	2.17 (1.5, 3.1) P < 0.001	2.00 (1.4, 2.9) P < 0.001
Multivariable <sup>a</sup>	1.61 (1.1, 2.4) P = 0.02	1.53 (1.1, 2.2) P = 0.02

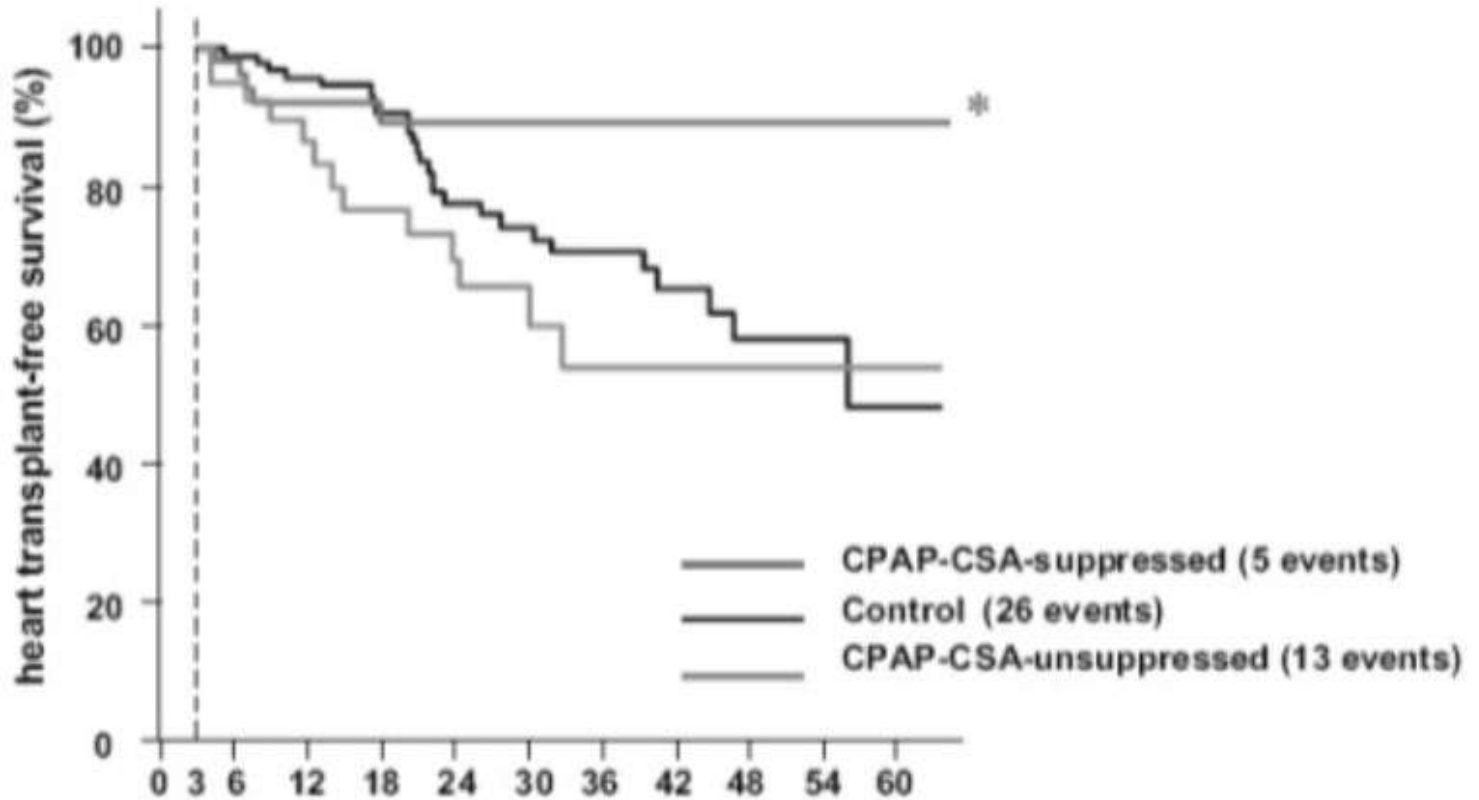
256	230	203	161
404	343	283	228
217	195	173	143

— OSA    — nm SDB

# Prognosis of Sleep Apnoea ± Treatment



# CANPAP Trial



number at risk

Time from enrollment (mo)

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

# Inclusion Criteria



## **Inclusion Criteria:**

Patients must be over 18.

Chronic heart failure at least 12 weeks since diagnosis

LVEF <40%

NYHA class III or IV at the time of inclusion or NYHA class II with at least one hospitalisation for HF in the last 12 months

No hospitalisation for heart failure for at least 4 weeks prior to inclusion

Optimised medical treatment according to applicable guidelines with no new class of disease modifying drug for more than 4 weeks prior to randomisation.

SDB (AHI  $\geq$  15/h) with > 50% central events and a central AHI  $\geq$  10/h



# Patients' Baseline



## Demographics

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.\***

Characteristic	Control (N=659)	Adaptive Servo-Ventilation (N=666)
Age — yr	69.3±10.4	69.6±9.5
Male sex — no. (%)	599 (90.9)	599 (89.9)
Body weight — kg	86.1±17.5	85.6±15.8
Body-mass index†	28.6±5.1	28.4±4.7
NYHA class — no./total no. (%)		
II	194/654 (29.7)	195/662 (29.5)
III	454/654 (69.4)	456/662 (68.9)
IV	6/654 (0.9)	11/662 (1.7)
Left ventricular ejection fraction — %‡		
Mean	32.5±8.0	32.2±7.9
Range	9.0–71.0	10.0–54.0
Diabetes mellitus — no./total no. (%)	252/653 (38.6)	254/660 (38.5)
Cause of heart failure — no./total no. (%)		
Ischemic	366/642 (57.0)	390/653 (59.7)
Nonischemic	276/642 (43.0)	263/653 (40.3)
Blood pressure — mm Hg		
Systolic	122.1±19.6	122.3±19.0
Diastolic	73.3±11.5	73.7±11.3
Electrocardiographic finding — no./total no. (%)		
Left bundle-branch block§	65/295 (22.0)	79/304 (26.0)
Sinus rhythm	395/646 (61.1)	372/650 (57.2)
Atrial fibrillation	147/646 (22.8)	178/650 (27.4)
Other	104/646 (16.1)	100/650 (15.4)
Implanted device — no. (%)		
No device	295 (44.8)	304 (45.6)
Non-CRT pacemaker	29 (4.4)	32 (4.8)
ICD	161 (24.4)	163 (24.5)
CRT-P	21 (3.2)	14 (2.1)
CRT-D	153 (23.2)	153 (23.0)
Hemoglobin — g/dl	13.9±1.5	13.8±1.6
Creatinine — mg/dl¶	1.4±0.6	1.4±0.6
Estimated GFR — ml/min/1.73 m <sup>2</sup>	59.3±20.8	57.8±21.1
6-Min walk distance — m	337.9±127.5	334.0±126.4



# Patients' Baseline



## Demographics

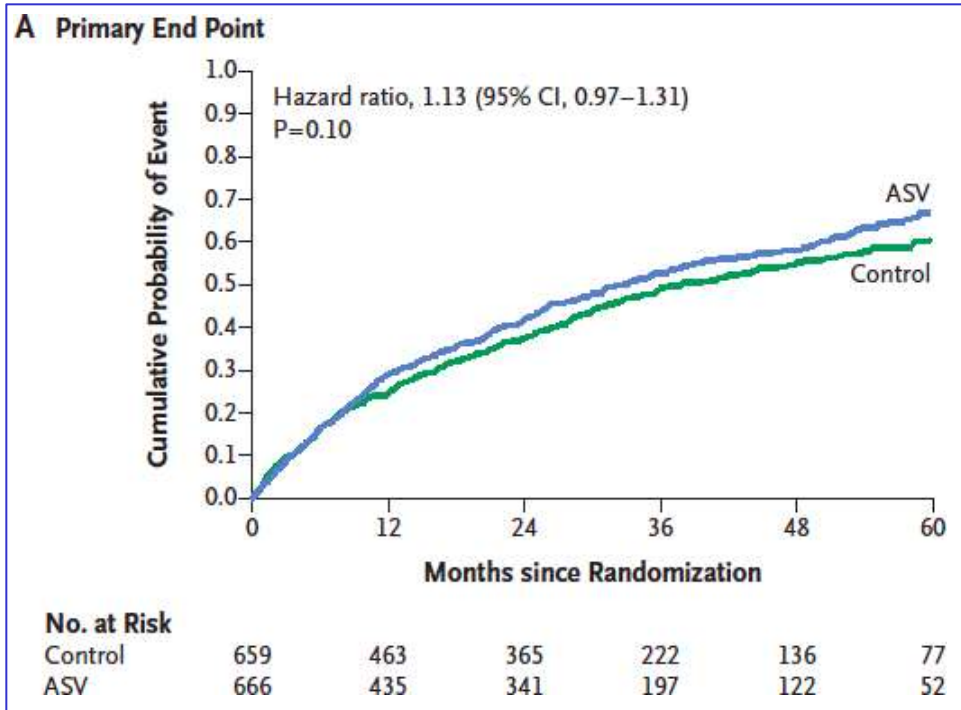
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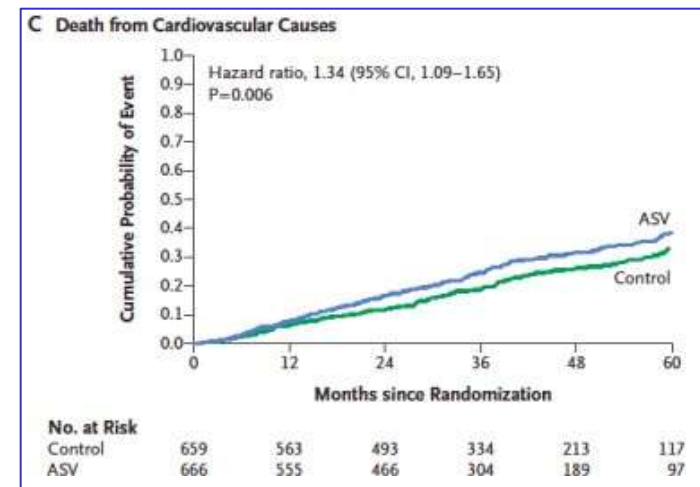
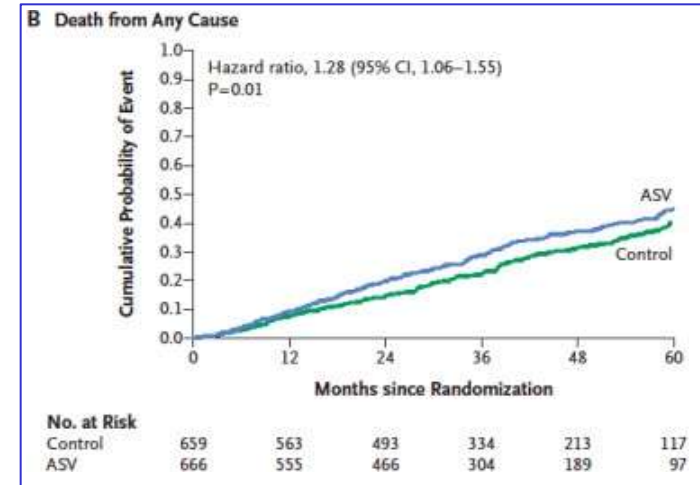
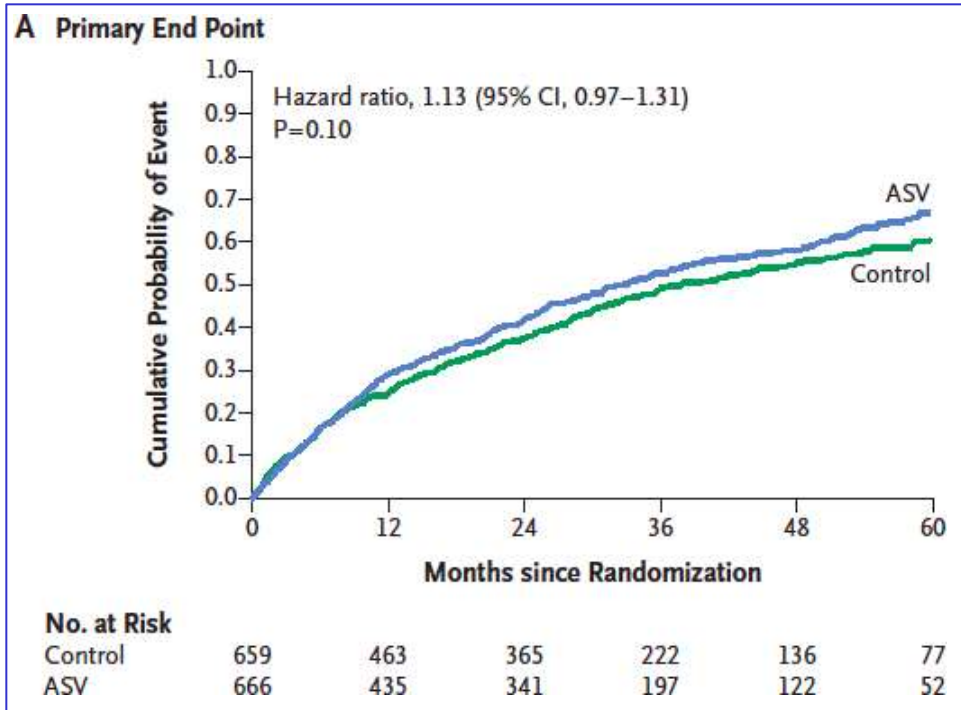
**Table 2. Respiratory Characteristics at Baseline.\***

Characteristic	Control (N=659)	Adaptive Servo-Ventilation (N=666)
Epworth Sleepiness Scale score‡	7.1±4.6	7.0±4.3
AHI — no. of events/hr	31.7±13.2	31.2±12.7
Central apnea index/total AHI — %	46.5±30.0	44.6±28.9
Central AHI/total AHI — %	81.8±15.7	80.8±15.5
Oxygen desaturation index — no. of events/hr‡	32.8±19.0	32.1±17.7
Oxygen saturation — %		
Mean	92.8±2.5	92.8±2.3
Minimum	80.3±7.5	80.7±7.0
Time with oxygen saturation <90% — min	55.7±73.9	50.5±68.2

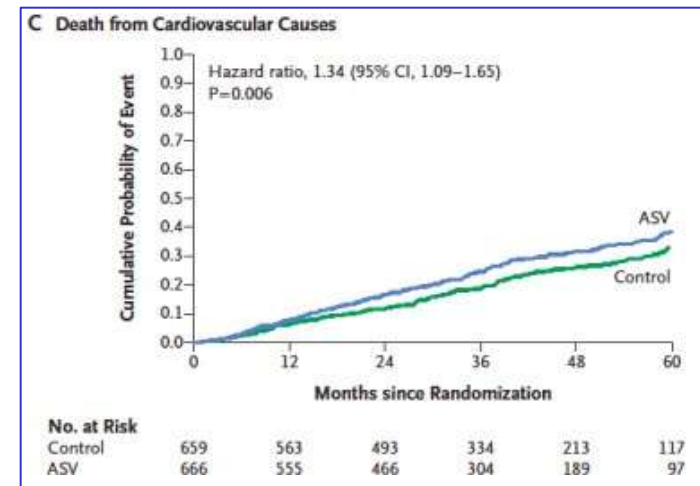
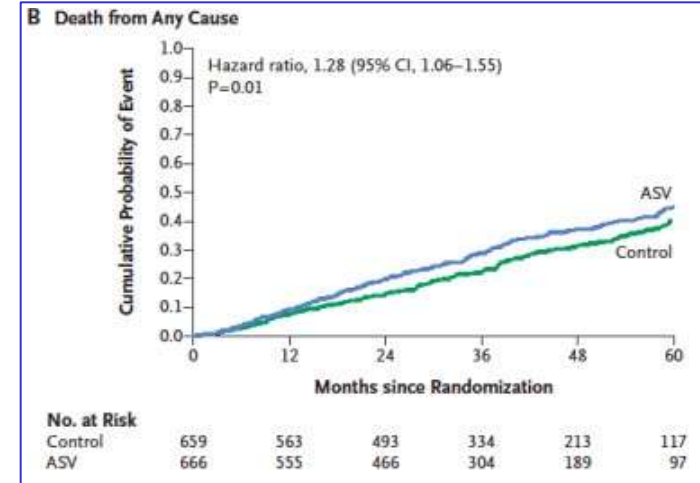
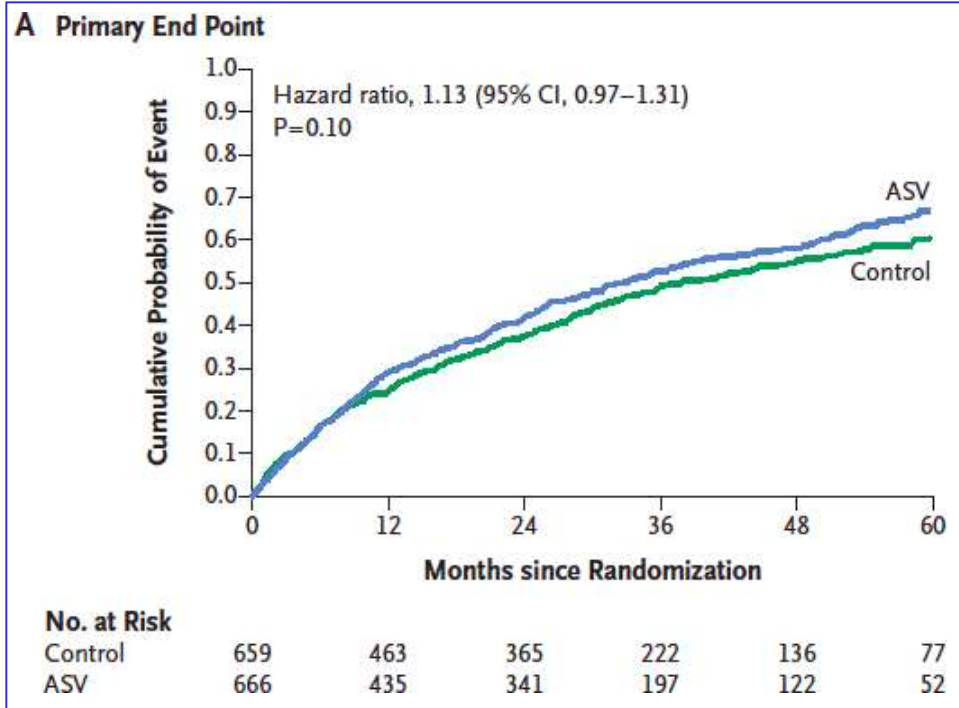
# Results & Conclusions



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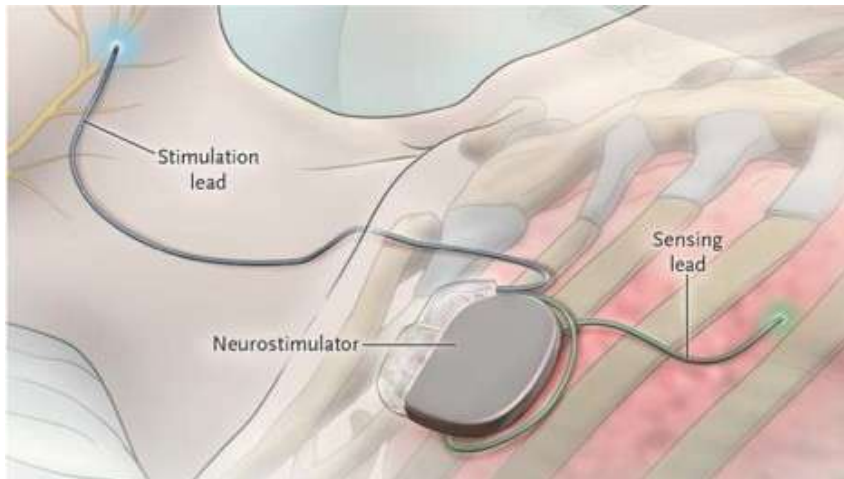
# Results & Conclusions



Recommendations	Class <sup>a</sup>	Level <sup>b</sup>	Ref <sup>c</sup>
<b>Sleep apnoea</b>			
Adaptive servo-ventilation is not recommended in patients with HFrEF and a predominant central sleep apnoea because of an increased all-cause and cardiovascular mortality.	III	B	473

Cowie *et al.* *New Engl J Med* 2015.

# Treatment of OSA



- **Currently available device is surgically implanted** with two leads that causes tongue protrusion by stimulation of the **hypoglossal nerve** via a cuff electrode that open the palate to decrease obstructive sleep apnea
- **Screened patients who did not tolerate or accept CPAP**
- **Required endoscopy while sleeping** to determine if patient had complete airway collapse

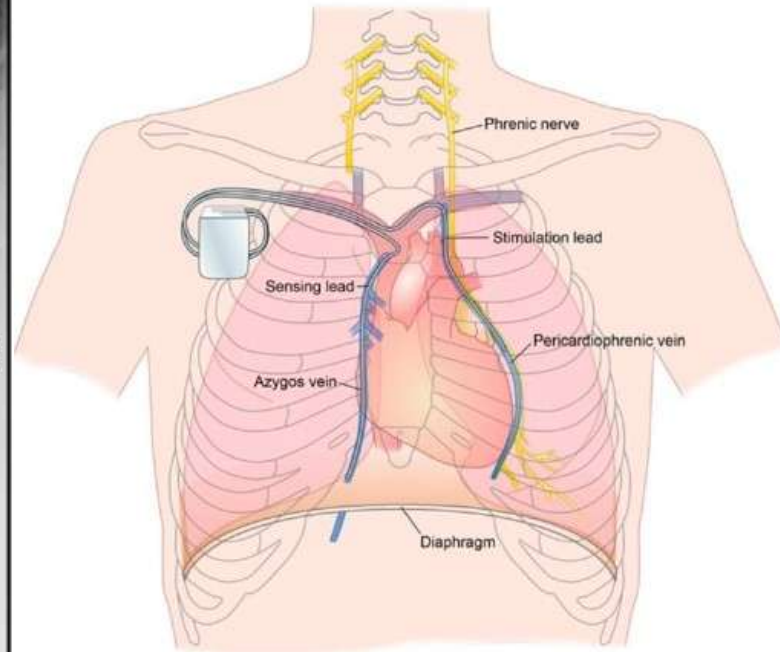
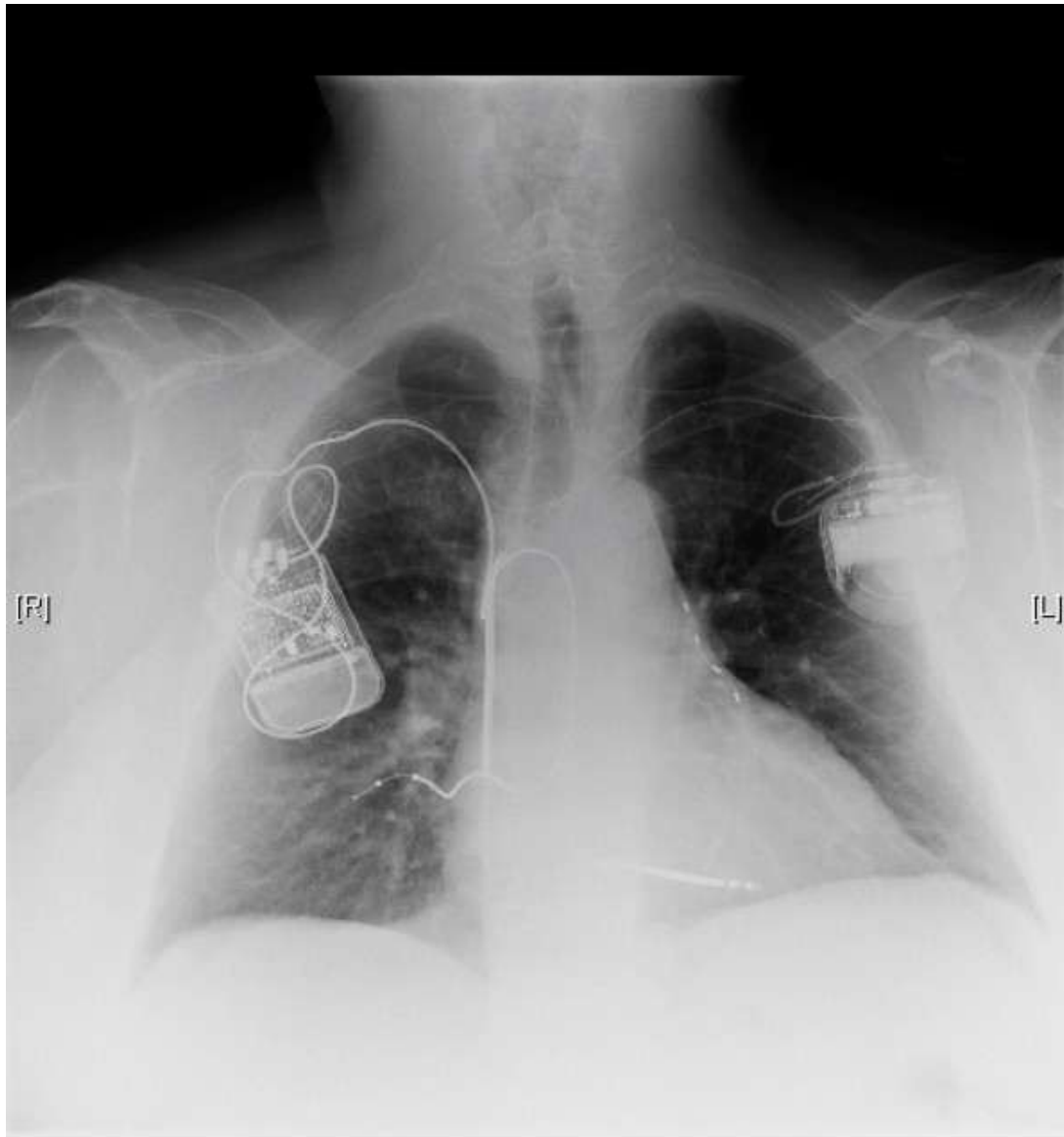
# STAR Trial

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## Primary outcomes:

- **Significant change in AHI at 12 months compared to baseline (32 to 15 events/hour) ( $p < 0.001$ )**
- **Significant change in ODI at 12 months compared to baseline (29 to 14 events/hour) ( $p < 0.001$ )**
- **66% responders by AHI (50% reduction in AHI and AHI  $< 20$  events/hour)**
- **75% responders by ODI (25% reduction; events/hour)**

# Phrenic Nerve Stimulation Device *In Situ*



# Phrenic Nerve Stimulation: The PIVOTAL Trial

## PATIENT POPULATION

Randomized (n=151)

### Intention-to-Treat Population

Treatment  
(n=73)

Control  
(n=78)

6 Month  
ITT Primary Effectiveness  
(n=68)

6 Month  
ITT Primary Effectiveness  
(n=73)

### Per-protocol Population

6 Month  
Secondary hierarchically  
tested endpoints  
(n=58)

6 Month  
Secondary hierarchically  
tested endpoints  
(n=73)

- Subjects without results (n=5)
- Unrelated death (n=2)
  - Patient exit (n=1)
  - Missed visit (n=1)
  - Medical issues (n=1)

- Per Protocol defined exclusion criteria (n=6)
- Unsuccessful implant (n=2)
  - Failed/missing inclusion criteria (n=3)
  - Therapy programmed off (n=1)

- Without 6 Month PSG results (n=4)
- Device explant (n=3)
  - Missed visit (n=1)

- Subjects without results (n=5)
- Unrelated death (n=2)
  - Patient exit (n=2)
  - Lost to follow-up (n=1)





# Phrenic Nerve Stimulation: The PIVOTAL Trial

## INTENTION TO TREAT

PRIMARY EFFECTIVENESS ENDPOINT	BETWEEN GROUP DIFFERENCE	TREATMENT	CONTROL	P-VALUE <sup>1</sup>
Comparison of the proportion of subjects with $\geq 50\%$ reduction in AHI	<b>41%</b> (25%, 54%)	51% (35/68) (39%, 64%)	11% (8/73) (5%, 20%)	<b>&lt;0.0001</b>

<sup>1</sup> P-value from 1-sided Fisher's Exact Test



# Phrenic Nerve Stimulation: The PIVOTAL Trial

## SECONDARY ENDPOINTS HIERARCHICALLY TESTED IN THE PER-PROTOCOL POPULATION

	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
CAI (events/hour)	31.7 ± 18.6	26.2 ± 16.2	6.0 ± 9.2	23.3 ± 17.4	-25.7 ± 18.0	-2.9 ± 17.7	-22.8 ± 17.8	<0.0001
AHI (events/hour)	49.7 ± 18.9	43.9 ± 17.3	25.9 ± 20.5	45.0 ± 20.3	-23.9 ± 18.6	1.1 ± 17.6	-25.0 ± 18.1	<0.0001
Ari (events/hour)	45.6 ± 18.9	44.0 ± 19.5	25.4 ± 14.3	38.9 ± 19.5	-20.2 ± 18.9	-5.0 ± 18.1	-15.2 ± 18.5	<0.0001
Percent of sleep in REM	10.8 ± 6.6	11.8 ± 7.2	12.6 ± 8.7	11.2 ± 7.4	1.8 ± 8.2	-0.6 ± 7.8	2.4 ± 7.9	0.0244
Moderate or marked improvement in PGA	NA	NA	60% (47%, 73%)	6% (2%, 14%)	NA	NA	55% (40%, 68%)	<0.0001
ODI4 (events/hour)	43.8 ± 21.5	37.3 ± 18.0	24.7 ± 21.0	40.9 ± 21.3	-19.1 ± 18.4	3.6 ± 17.3	-22.7 ± 17.8	<0.0001
ESS	10.7 ± 5.3	9.3 ± 5.7	7.1 ± 4.1	9.4 ± 6.1	-3.6 ± 5.6	0.1 ± 4.5	-3.7 ± 5.0	<0.0001

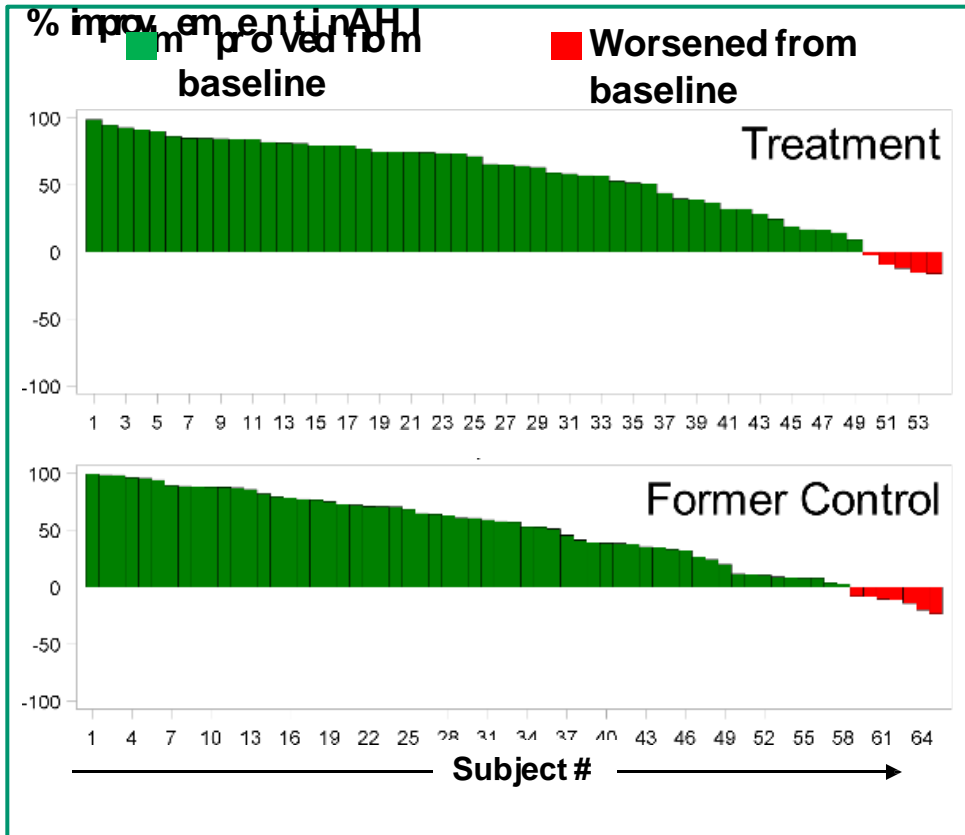
Mean ± SD for continuous and % (95% CI) for categorical

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

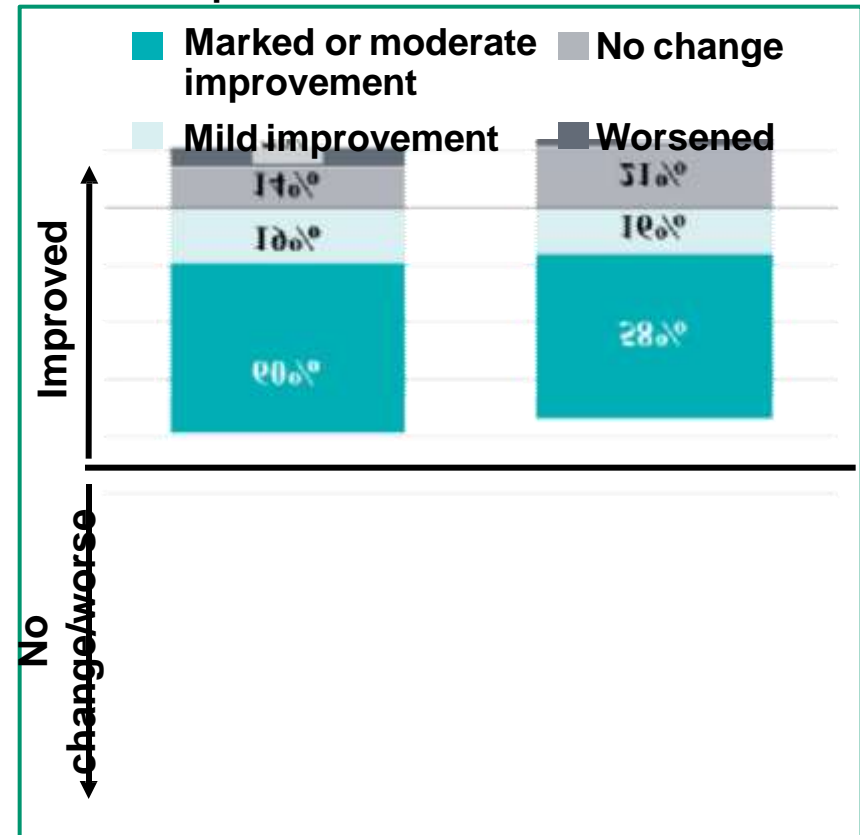


# Treatment Effect in the Former Control Group

Change in AHI for treatment group versus former control<sup>1</sup>



Patient Global Assessment (Quality of Life)  
 % of total patients



# Conclusions

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- SDB is highly prevalent in patients with HF: >50% are affected;
- Risk profiles differ between obstructive & central sleep apnoea;
- Patients with more severe HF are more likely to suffer from mixed or central sleep apnoea;

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- Rather than screening, surveillance is necessary;
- AHI >5 indicates the presence of sleep apnoea;

# Conclusions

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- Risk profiles differ between obstructive & central sleep apnoea;
- Patients with more severe HF are more likely to suffer from mixed or central sleep apnoea;
- Sleepiness scales may not be reliable in HF patients;
- Rather than screening, surveillance is necessary;
- AHI >5 indicates the presence of sleep apnoea;
- The first step is to achieve guideline-recommended therapy;
- CPAP, BiPAP and ASV may be beneficial in OSA.
- CPAP improves 6-MWT & LVEF but not prognosis in CSA.