

SOMNIO
FORUM



7 & 8 décembre 2018, Berlin

Obstructive sleep apnea and hypertension: why treatment does not consistently improve blood pressure?

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Sleep Disorder Center

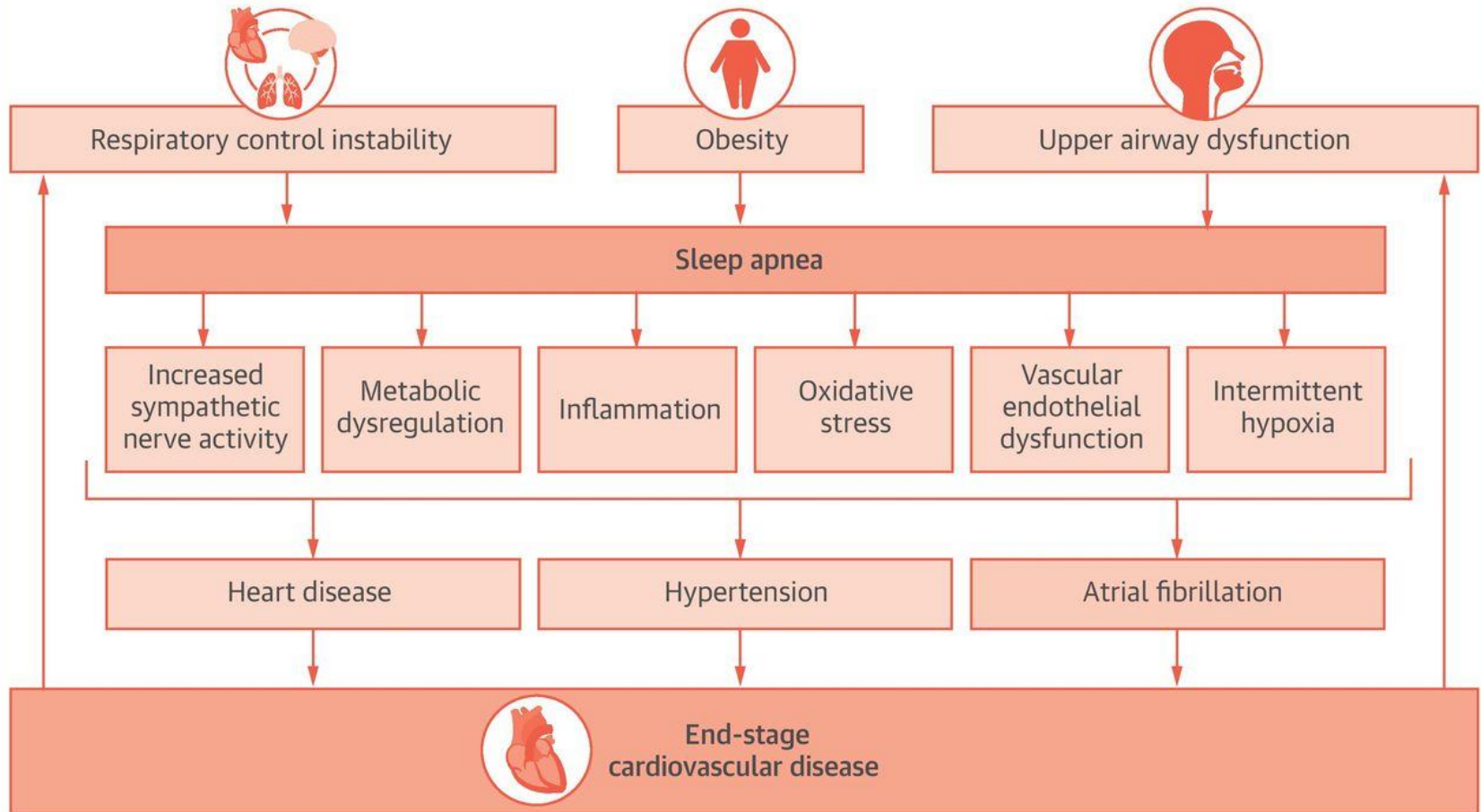
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Milan - Italy

APNÉE OBSTRUCTIVE DU SOMMEIL ET L'HYPERTENSION ARTÉRIELLE

CENTRAL ILLUSTRATION: Potential Etiological Risk Factors for Sleep Apnea and the Downstream Consequences



Javaheri, S. et al. J Am Coll Cardiol. 2017;69(7):841-58.

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Sir Austin Bradford Hill (1897-1991)

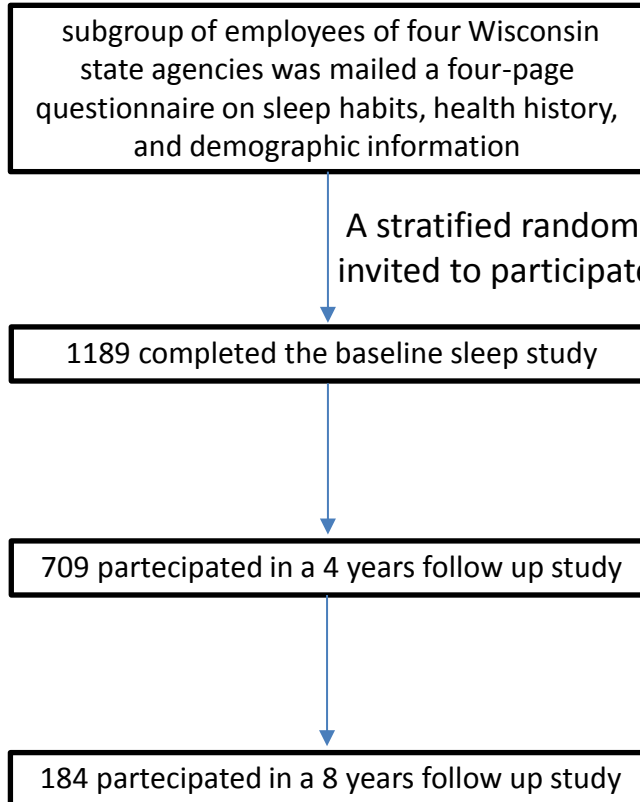
- strength of association
- consistency
- specificity
- temporality
- biological gradient
- coherence
- experiment
- analogy

**Do Yellow Nails
Cause Lung Cancer?**



APNÉE OBSTRUCTIVE DU SOMMEIL ET L'HYPERTENSION ARTÉRIELLE

Temporality: exposure must precede the onset of disease

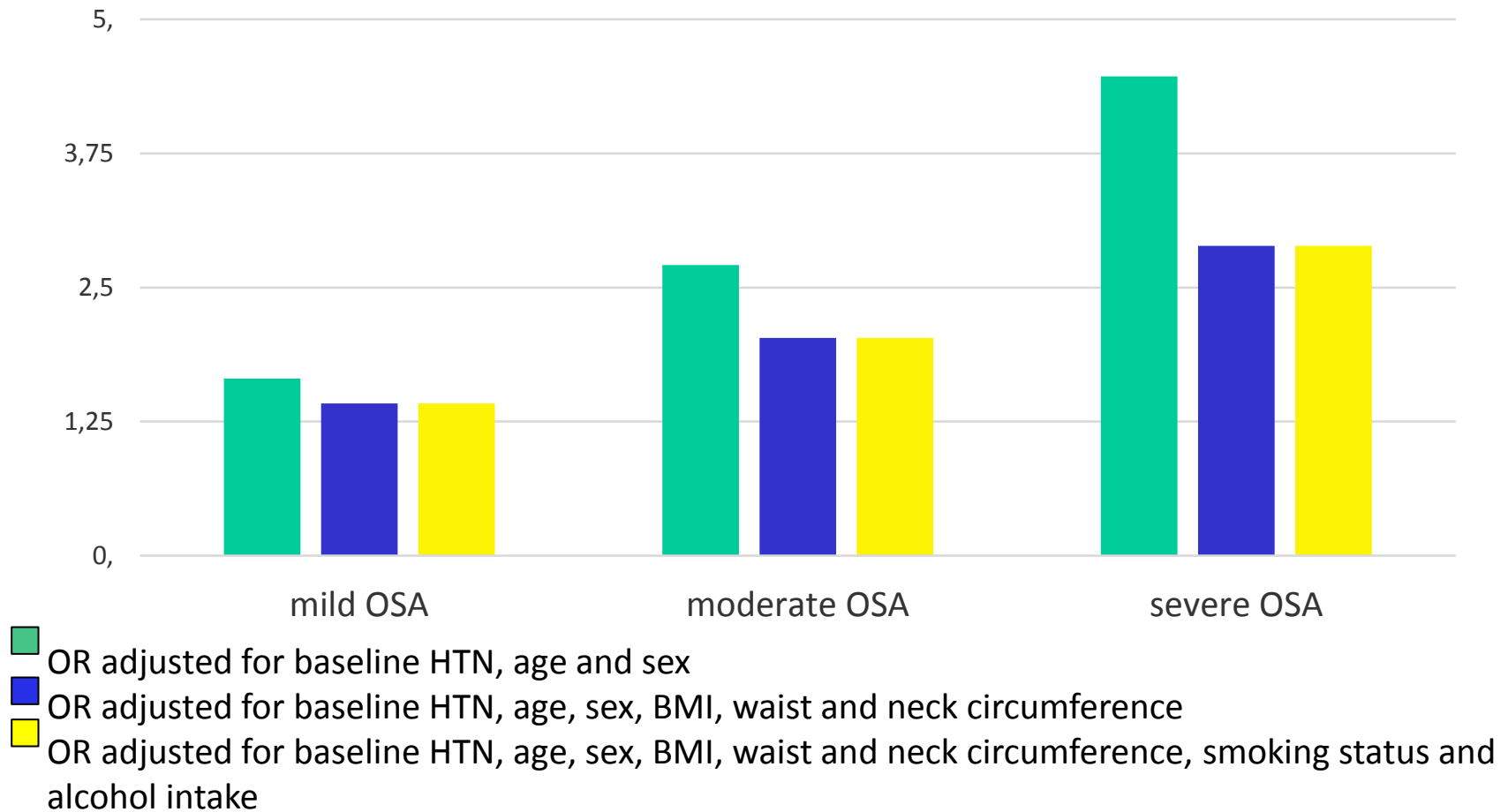


A stratified random sample of respondents was invited to participate in the study

ODDS RATIO (MODERATE OSA-HYPERTENSION), ADJUSTED FOR BASE-LINE HYPERTENSION STATUS, NONMODIFIABLE RISK FACTORS, HABITUS, AND WEEKLY ALCOHOL AND CIGARETTE USE = 2.89 (1.46–5.64) (p for trend 0,002)

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biological gradient: if a dose response is seen, it is more likely that the association is causal



P < 0,05 for the linear trend of the logistic regression coefficients (log of the ORs)

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Consistency: same finding replicated by other studies and in multiple different populations

Wisconsin Sleep Study (n=709), follow up 8 years

- 30-60 yo american males and females
- Wisconsin state employes

Sleep Heart Health Study (n=6841), follow up 3 years

- drawn from nine existing parent cohorts; most relevant ethnicities represented
- aged 40 years and older

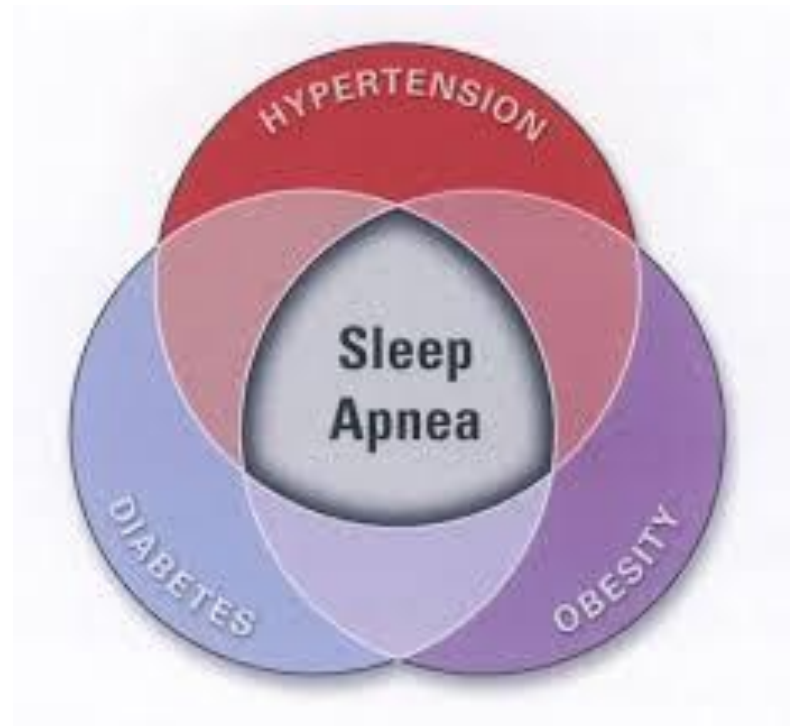
Wisconsin Sleep Study			Sleep Heart Health Study		
Punto de corte IAH	Prevalencia HTA (%)	OR* (IC del 95%)	Punto de corte IAH	Prevalencia HTA (%)	OR* (IC del 95%)
0	17	1	< 1,5	43	1
0,1-4,9	28	1,39 (1,04-1,84)	1,5-4,9	53	1,07 (0,91-1,26)
5-14,9	48	1,92 (1,09-3,39)	5-14,9	59	1,20 (1,01-1,42)
≥ 15	60	2,66 (1,13-6,25)	15-29,9	62	1,25 (1,00-1,56)
			≥ 30	67	1,37 (1,03-1,83)

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Strength of association: the larger an association between exposure and disease, the more likely it is to be causal

ISSUES:

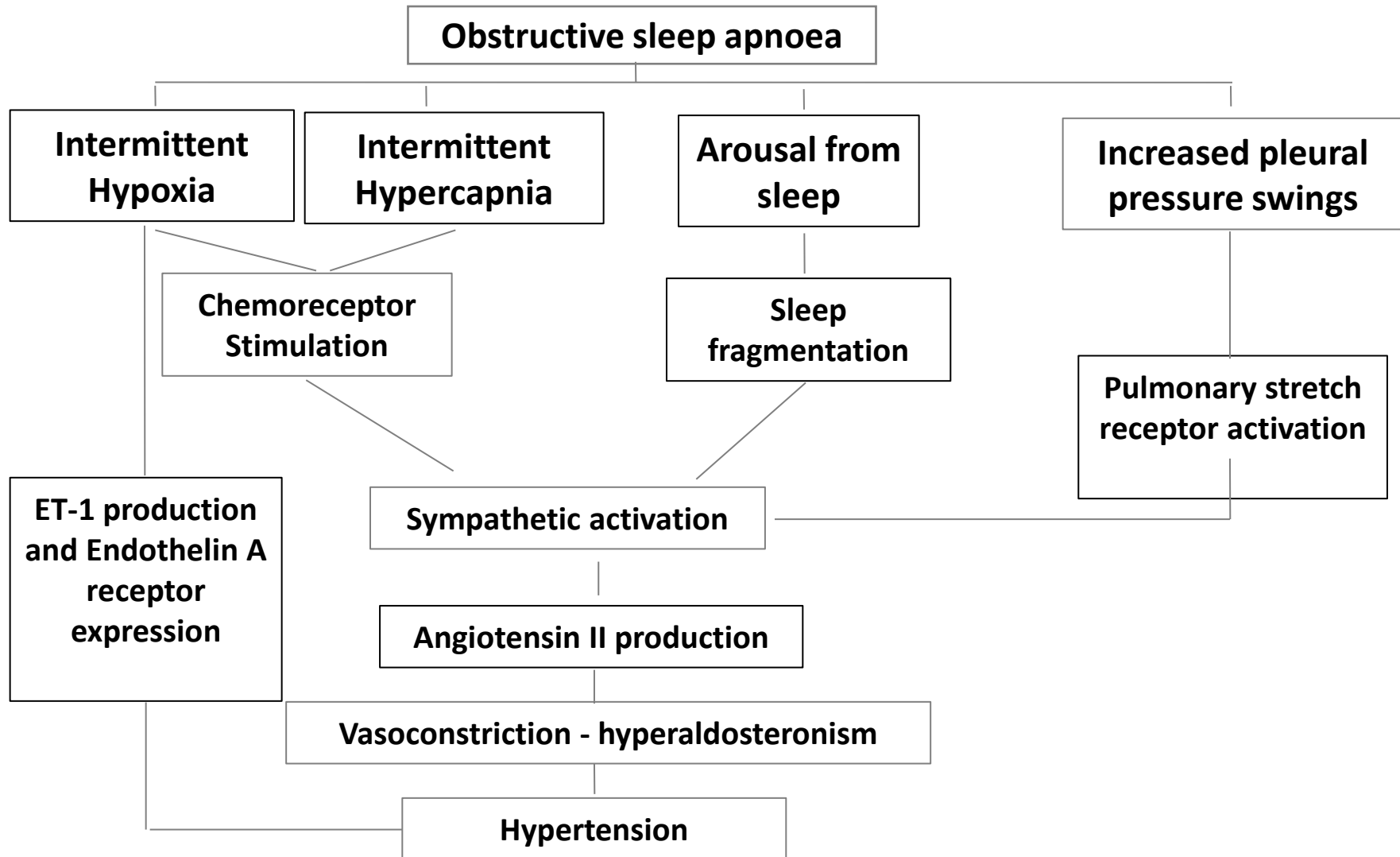
- OSA screening and diagnosis
- HT assessment (office/ambulatory)
- OSA cut offs
- Co morbidities
- Lack of matching (BMI)



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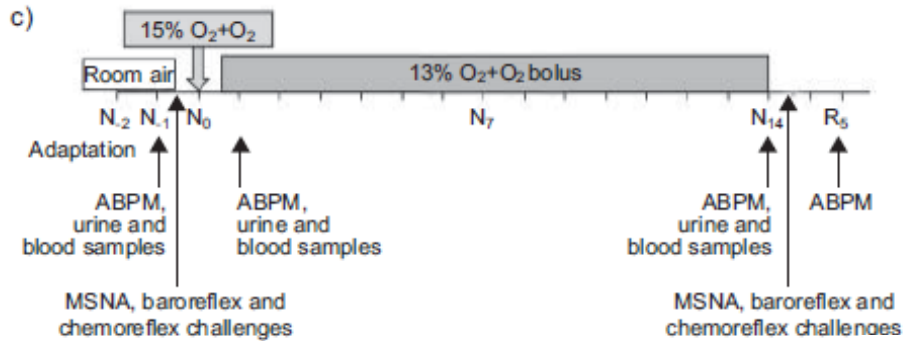
biological plausibility and coherence:

biological models must exist to explain the association

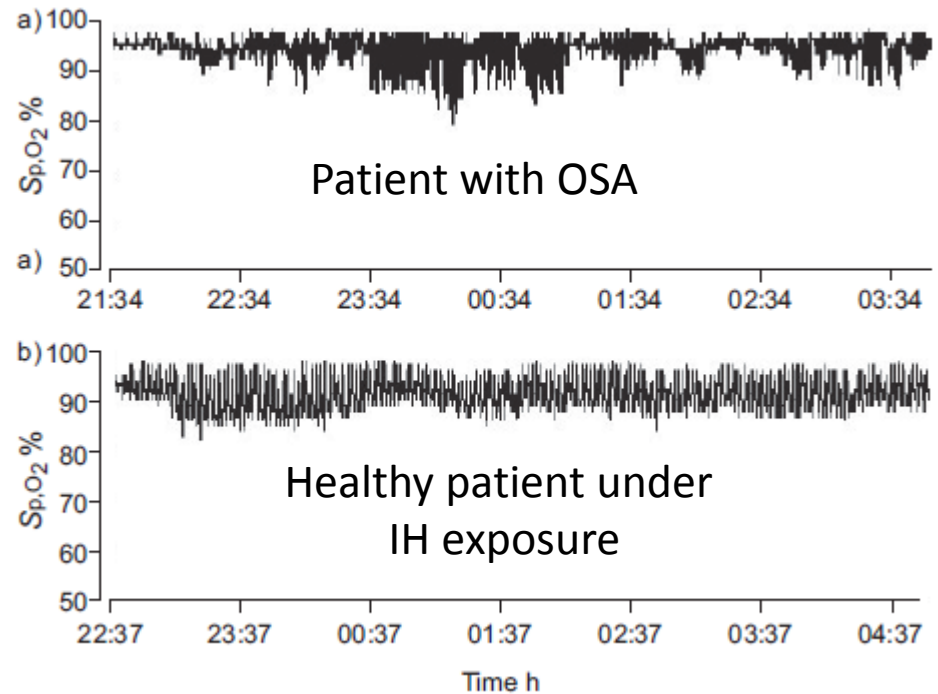
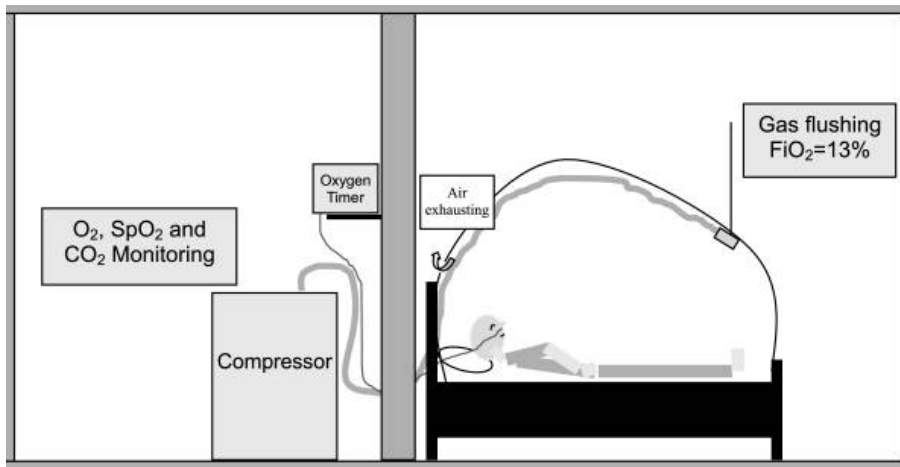


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Specificity: the exposure causes only one disease

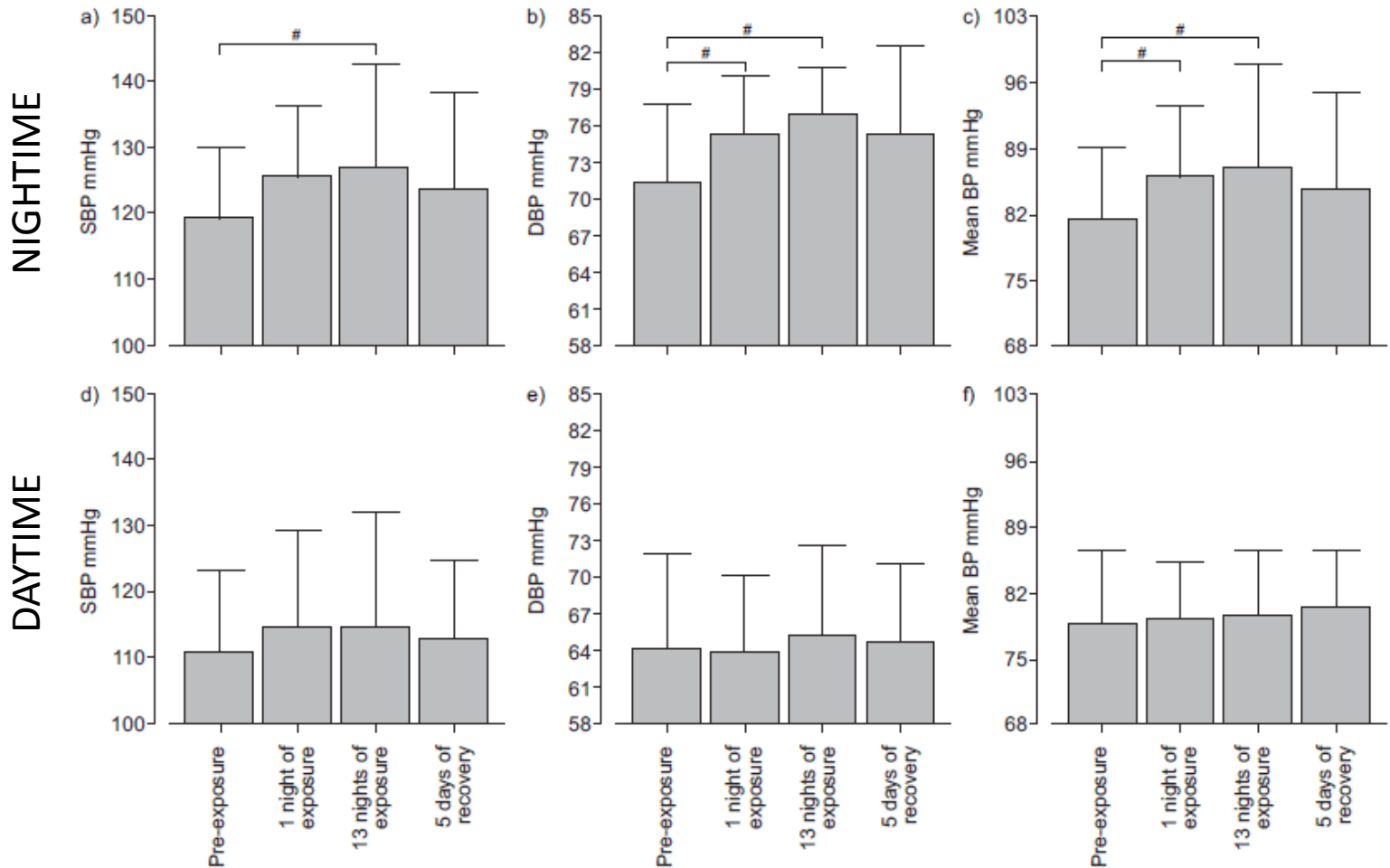


12 healthy, nonsmoking, normotensive subjects (two of whom were female), with a mean age of 23 (6) years (body mass index (BMI) 21.7 (1.9) kg/m²), free of vasoactive medications were enrolled



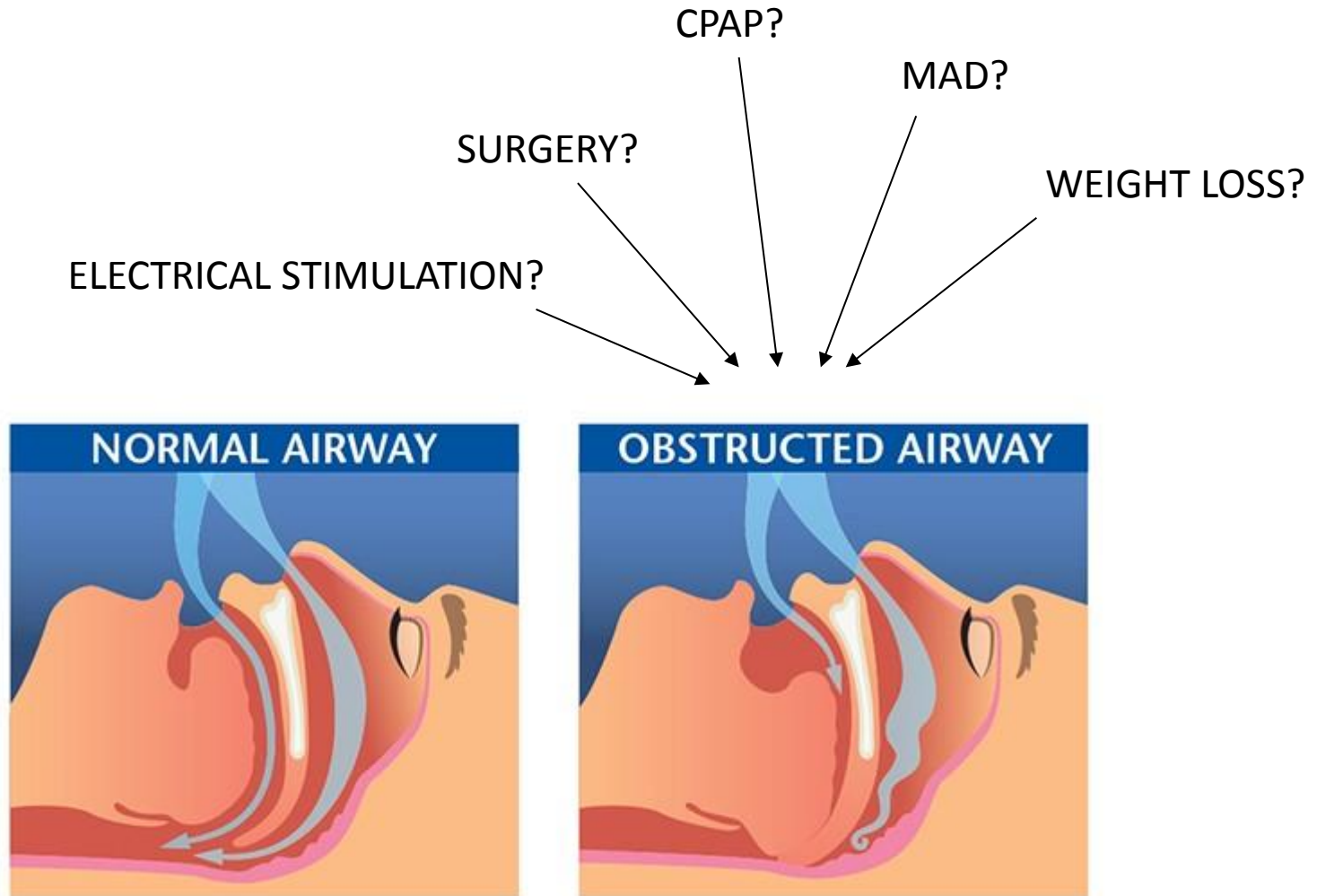
APNÉE OBSTRUCTIVE DU SOMMEIL ET L'HYPERTENSION ARTÉRIELLE

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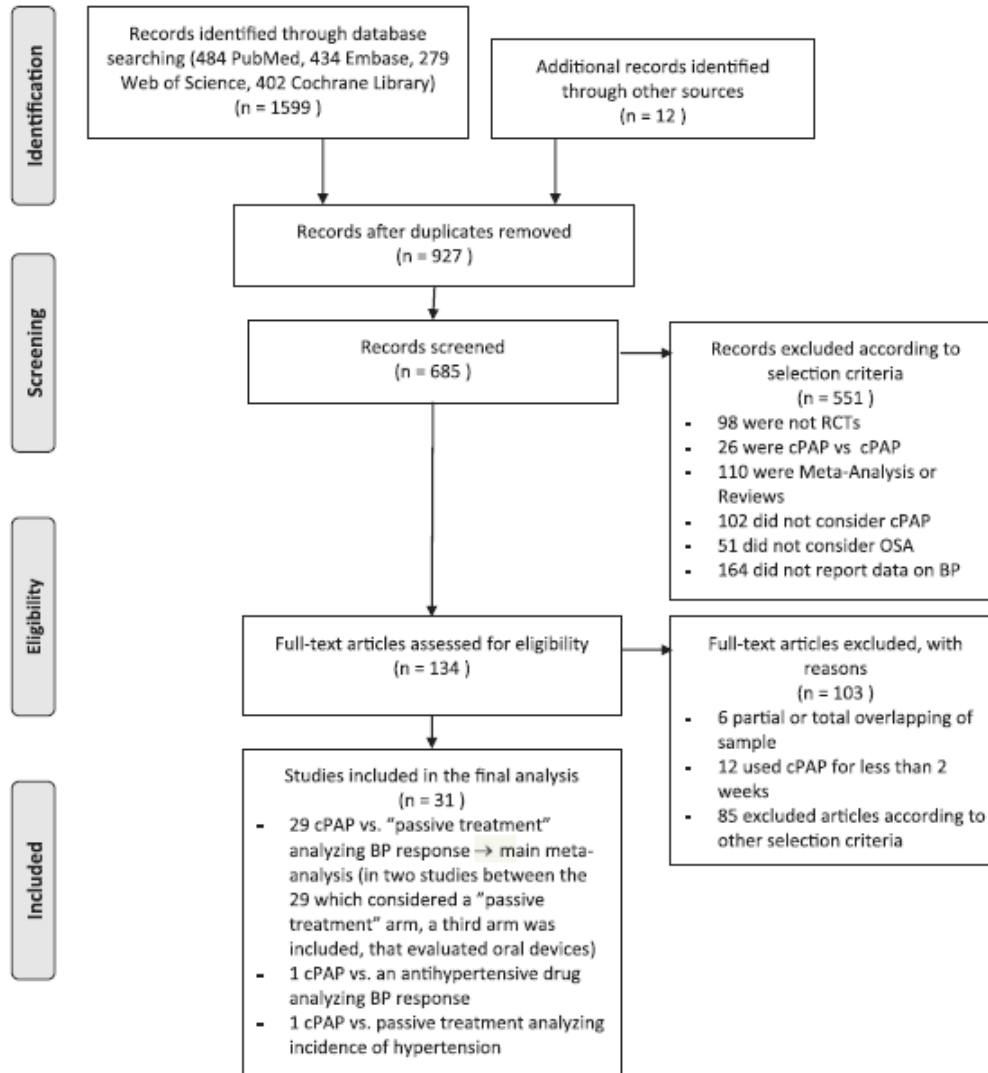
APNÉE OBSTRUCTIVE DU SOMMEIL ET L'HYPERTENSION ARTÉRIELLE

reversibility: treating OSA must correspond to reducing blood pressure



APNÉE OBSTRUCTIVE DU SOMMEIL ET L'HYPERTENSION ARTÉRIELLE

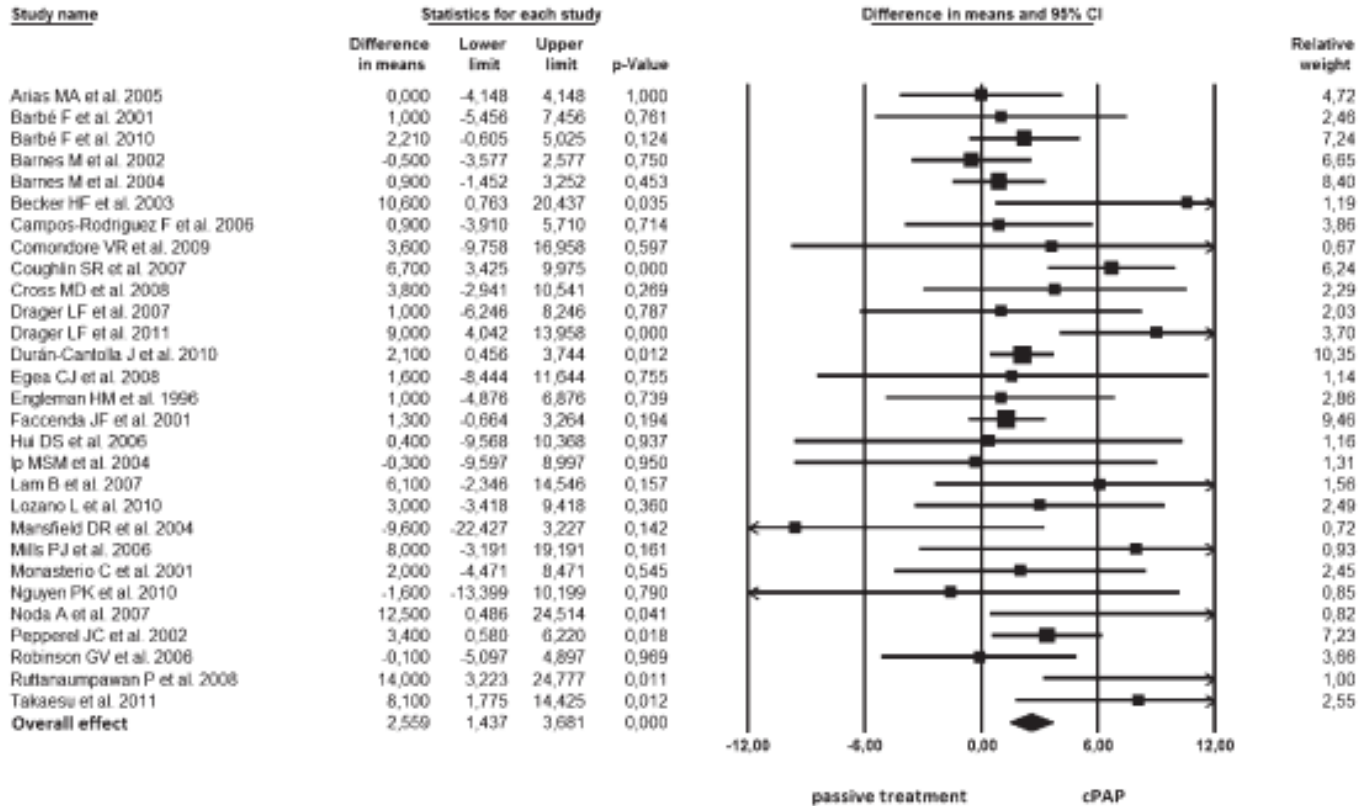
reversibility: treating OSA with CPAP must correspond to reducing blood pressure



**CPAP vs passive treatment
(29 RCTs, 1,820 subjects)**

APNÉE OBSTRUCTIVE DU SOMMEIL ET L'HYPERTENSION ARTÉRIELLE

reversibility: treating OSA with CPAP must correspond to reducing blood pressure



OVERALL

SBP 2.6 (0.6) mmHg
DBP 2.0 (0.4) mmHg

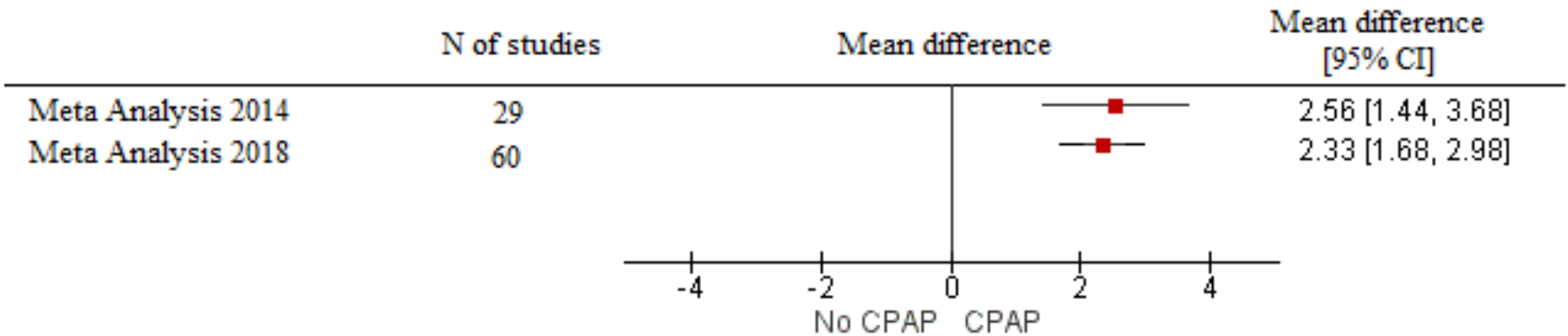
DAYTIME (ABPM)

SBP 2.2 (0.7) mmHg
DBP 1.9 (0.6) mmHg

NIGHTTIME (ABPM)

SBP 3.8 (0.8) mmHg
DBP 1.8 (0.6) mmHg

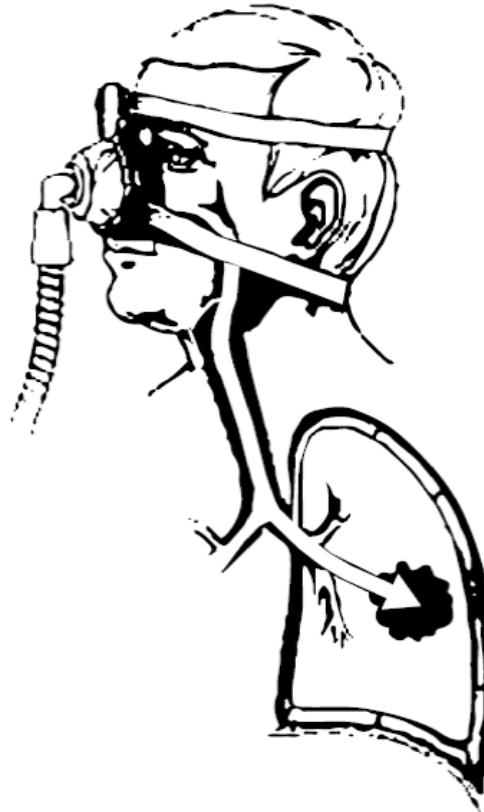
APNÉE OBSTRUCTIVE DU SOMMEIL ET L'HYPERTENSION ARTÉRIELLE



APNÉE OBSTRUCTIVE DU SOMMEIL ET L'HYPERTENSION ARTÉRIELLE

PROS

- CPAP abolishes apnoeas and hypopnoeas ensuring a normal respiratory control and blood pressure profile
- CPAP reduces sleep fragmentation, improving sleep quality and restoring nocturnal BP dipping
- CPAP improves nocturnal oxygenation therefore reducing renin-angiotensin-aldosterone system and improving BP profile



AGAINST

- CPAP can cause hyperinflation of the chest, respiratory system overload with consequent sympathetic upregulation
- Mask leaks can cause patient discomfort and nocturnal awakenings with consequent sympathetic hyperactivation
- Low CPAP compliance leave sleep disordered breathing and the related blood pressure swings untreated

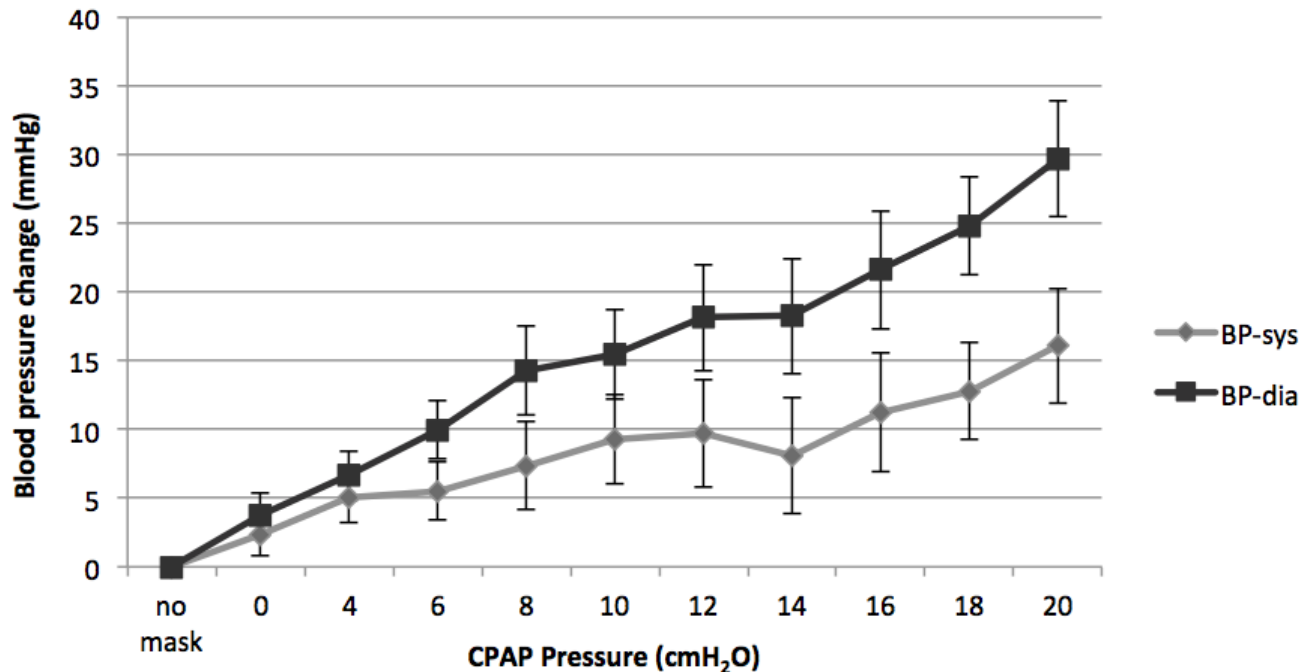
APNÉE OBSTRUCTIVE DU SOMMEIL ET L'HYPERTENSION ARTÉRIELLE

16 patients (13males, 47(10)years, BMI 38.5(5.8)kg/m²) were studied.

Baseline BP was 131.0(10.2)/85.1(9.1)mmHg.

BP increased with incremental CPAP (systolic BP $r=0.960, p<0.001$, diastolic BP $r=0.961, p<0.001$; systolic.

sEMG correlated with both systolic ($r=0.464, p=0.032$) and diastolic BP ($r=0.747, p=0.009$).



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BMI at baseline?

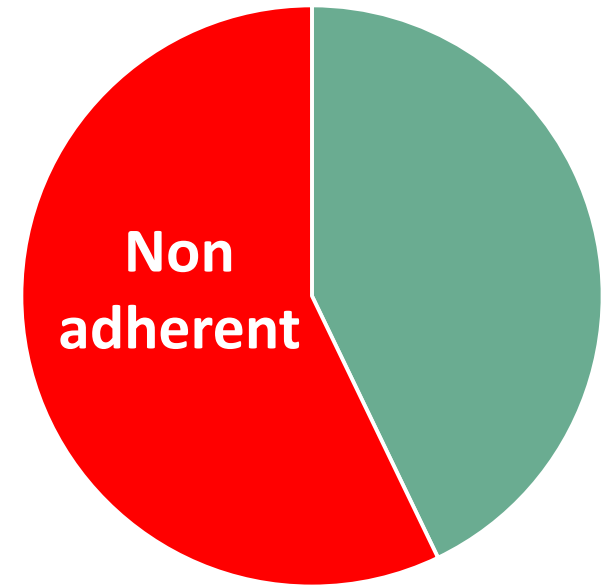
Daytime sleepiness?

BP at baseline?

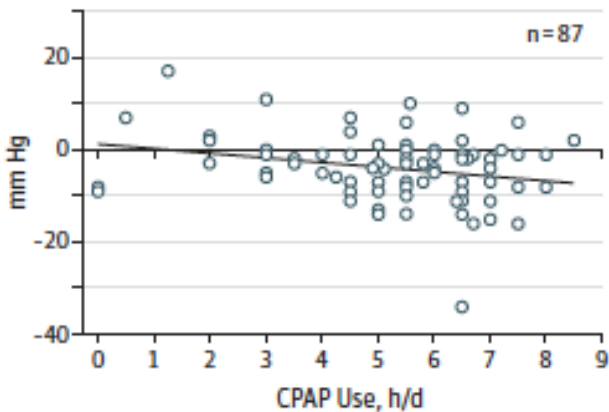
OSA severity?

Pulse rate at baseline as a surrogate for SNS activation?

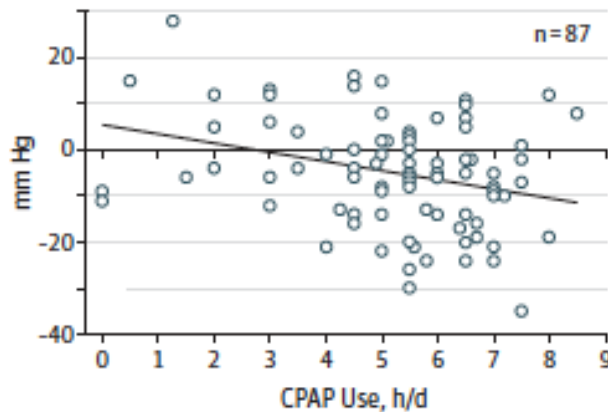
compliance/adherence?



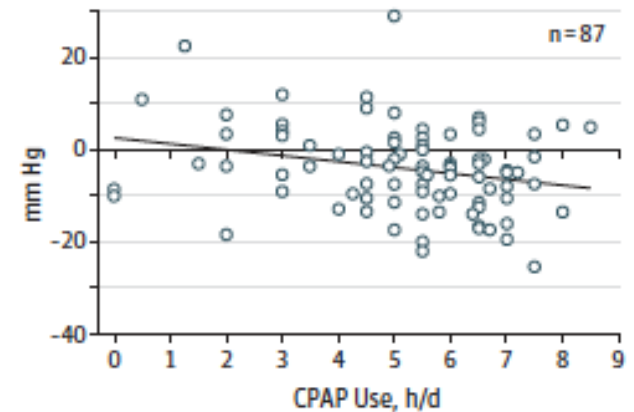
Change in diastolic blood pressure



Change in systolic blood pressure



Change in 24-h mean blood pressure



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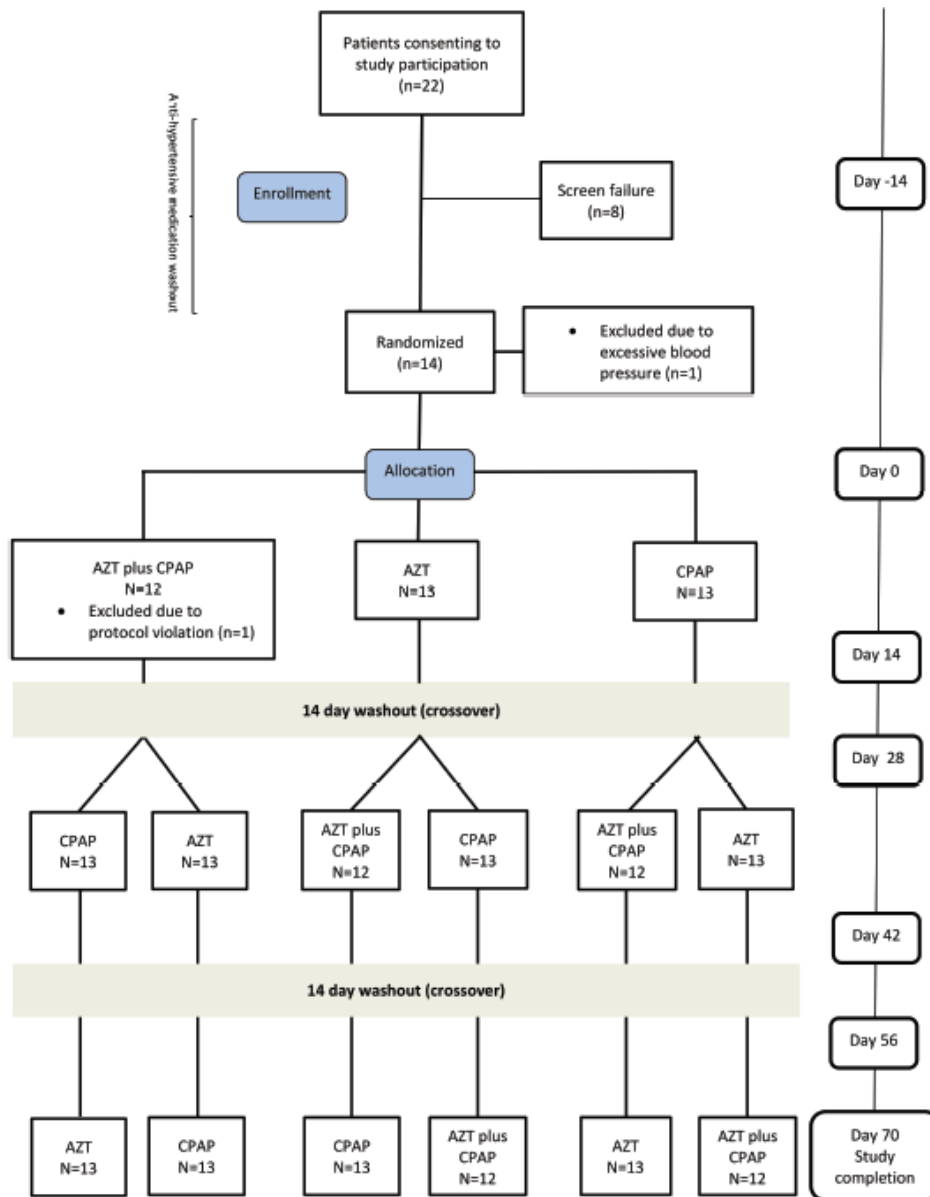
Open-label, randomized, multicenter clinical trial of parallel groups with blinded end point design
 194 patients were randomly assigned to receive CPAP (n = 98) or no CPAP (control; n = 96)
 The mean AHI was 40.4 (SD, 18.9) and an average of 3.8 antihypertensive drugs were taken per patient.
 The percentage of patients using CPAP for 4 or more hours per day was 72.4%.

	Mean (SD)				Intergroup Crude ^a Differences (95% CI)	P Value	Intergroup Adjusted ^b Differences (95% CI)	P Value
	CPAP Group (n = 98)		Control Group (n = 96)					
	Baseline	Follow-up	Baseline	Follow-up				
BP variables, mm Hg ^c								
24-h mean BP	103.9 (9.6)	99.8 (14.6)	102.9 (9.6)	102.1 (18.2)	3.1 (0.6 to 5.6)	.02	3.9 (1.3 to 6.6)	.004
24-h SBP	144.9 (11.7)	140.2 (13.1)	143.5 (13.2)	142.3 (17.1)	3.1 (-0.6 to 6.7)	.10	4.2 (0.4 to 8.0)	.03
Diurnal	147.2 (12.1)	144.0 (13.7)	145.1 (13.3)	142.5 (16.2)	-0.3 (-4.0 to 3.5)	.89	1.1 (-2.9 to 5.2)	.59
Nocturnal	141.2 (15.8)	134.6 (16.4)	140.4 (16.8)	137.8 (19.4)	3.7 (-0.8 to 8.2)	.11	5.8 (1.1 to 10.5)	.02
24-h DBP	83.4 (11.1)	79.5 (11.5)	82.6 (10.0)	82.1 (12.7)	3.2 (1.0 to 5.4)	.005	3.8 (1.4 to 6.1)	.002
Diurnal	85.7 (11.6)	82.7 (12.5)	84.6 (10.4)	83.2 (13.2)	1.5 (-0.8 to 3.9)	.20	2.3 (-0.1 to 4.8)	.07
Nocturnal	78.5 (12.4)	75.4 (11.7)	78.6 (11.1)	77.5 (13.5)	2.1 (-0.6 to 4.7)	.13	3.3 (0.5 to 6.1)	.02

...ET SI LES MÉDICAMENTS FONCTIONNENT MIEUX QUE LE CPAP?



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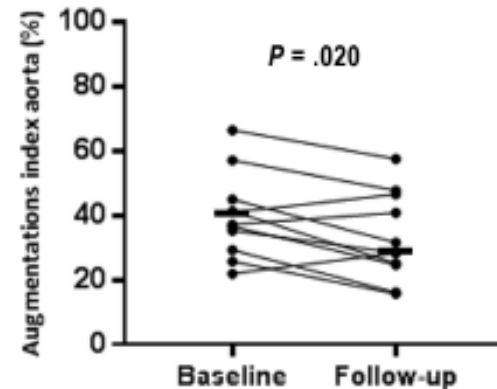
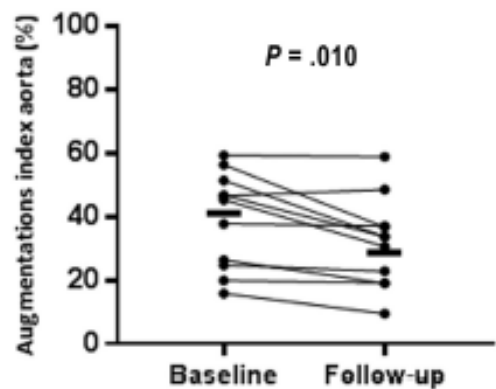
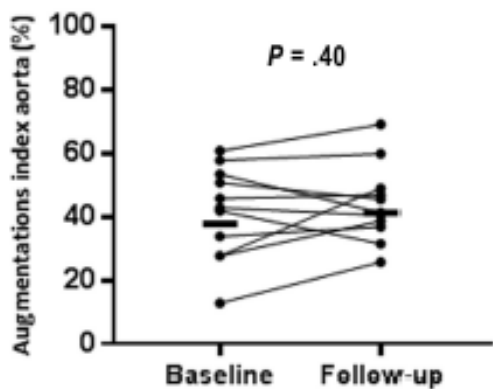
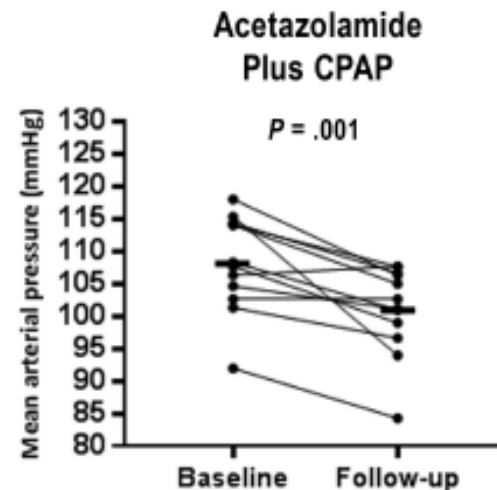
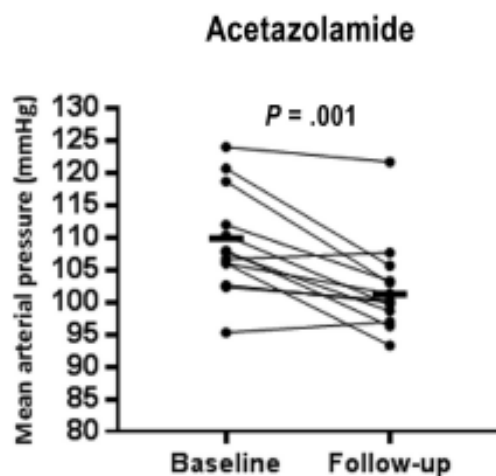
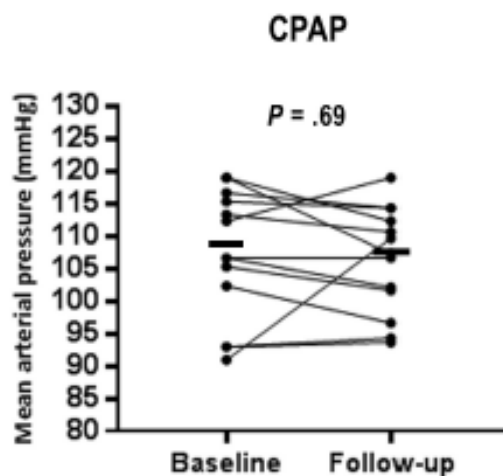
13 male patients with hypertension and moderate to severe OSA
age 64 ± 7 years,
Body mass index 29 ± 4 kg/m²,
apnea-hypopnea index 37 ± 23 events/h

Received acetazolamide (AZT) a carbonic anhydrase inhibitor, CPAP, or AZT plus CPAP for 2-week periods.

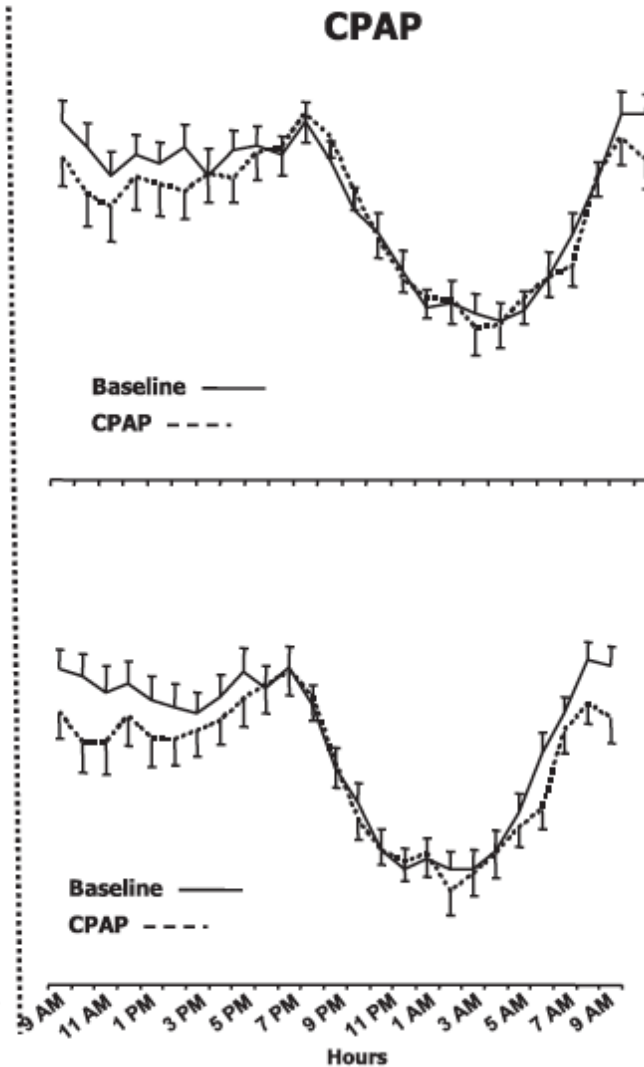
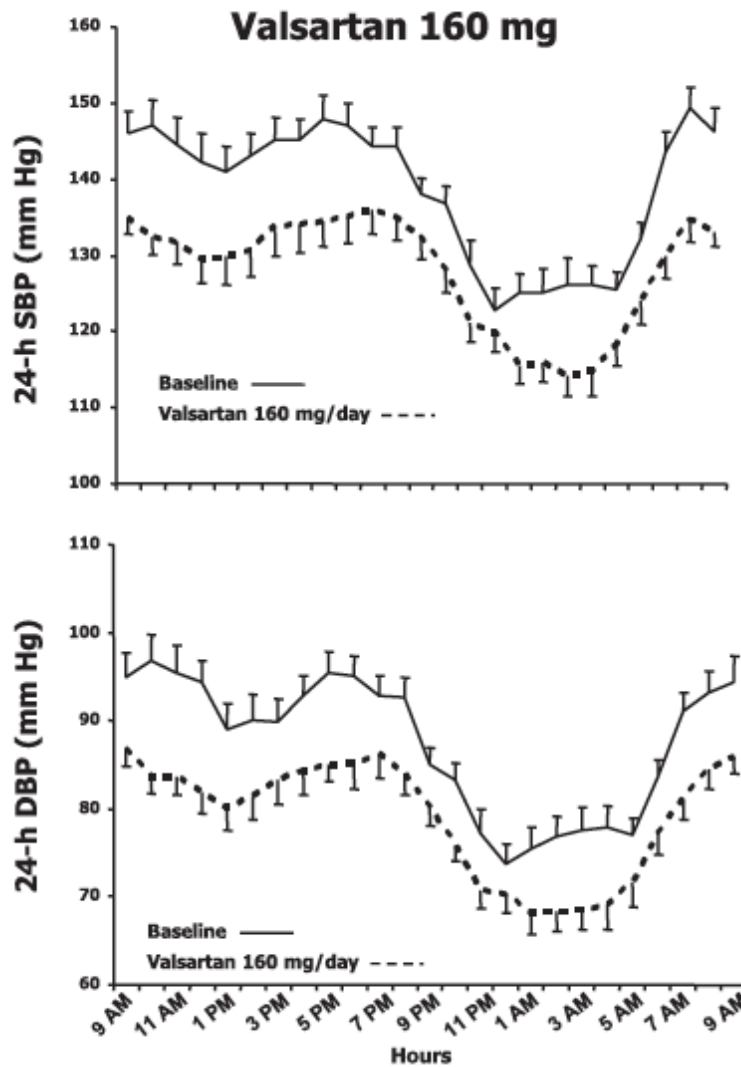
Antihypertensive medication was washed out.

Office and 24-hour blood pressure, arterial stiffness, polygraphic sleep study data, and blood chemistry were compared.

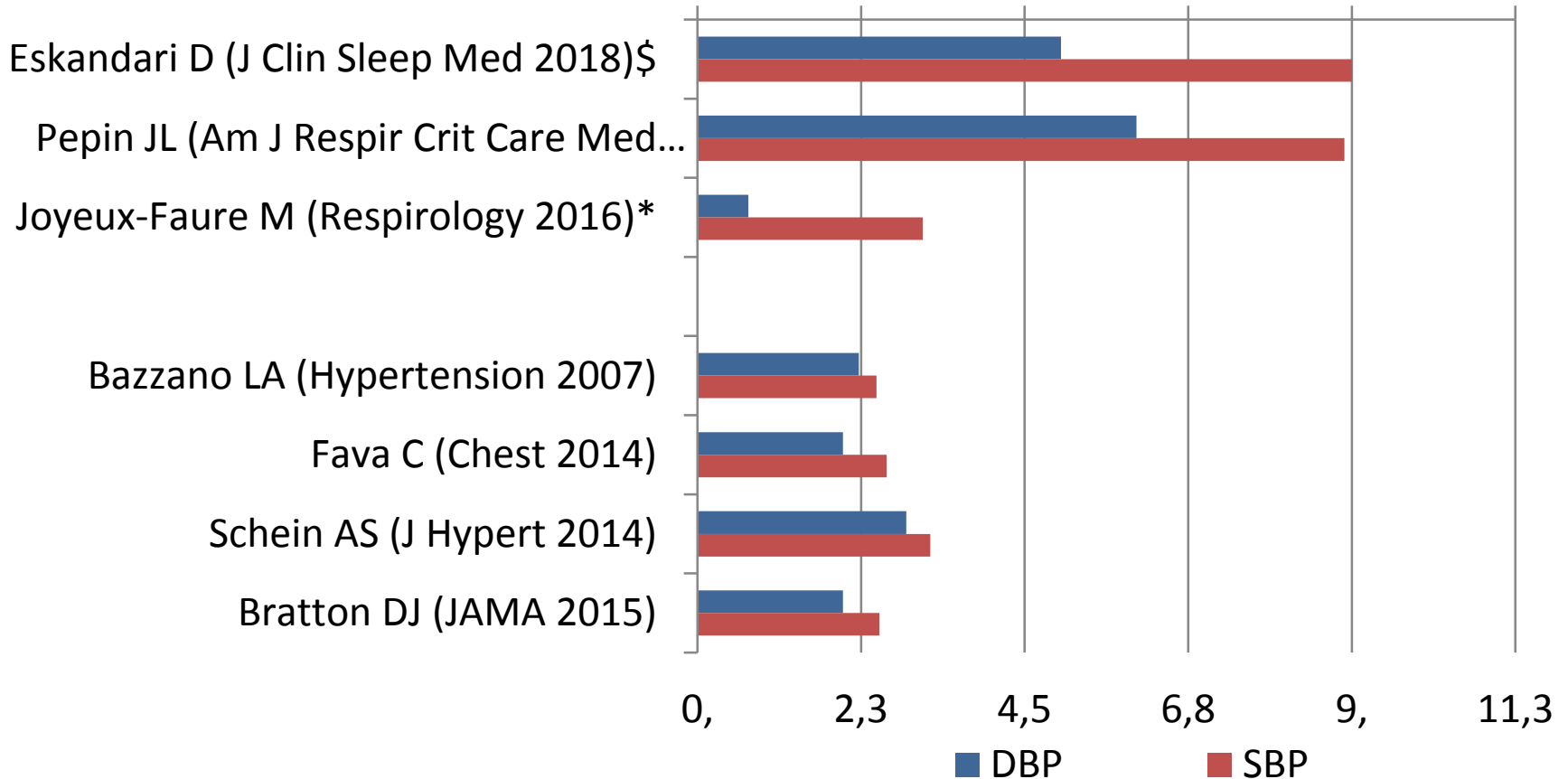
...ET SI LES MÉDICAMENTS FONCTIONNENT MIEUX QUE LE CPAP?



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* Difference in office BP change (bosentan-CPAP), p value NS for both SBP and DBP.

SBP=systolic blood pressure, DBP=diastolic blood pressure

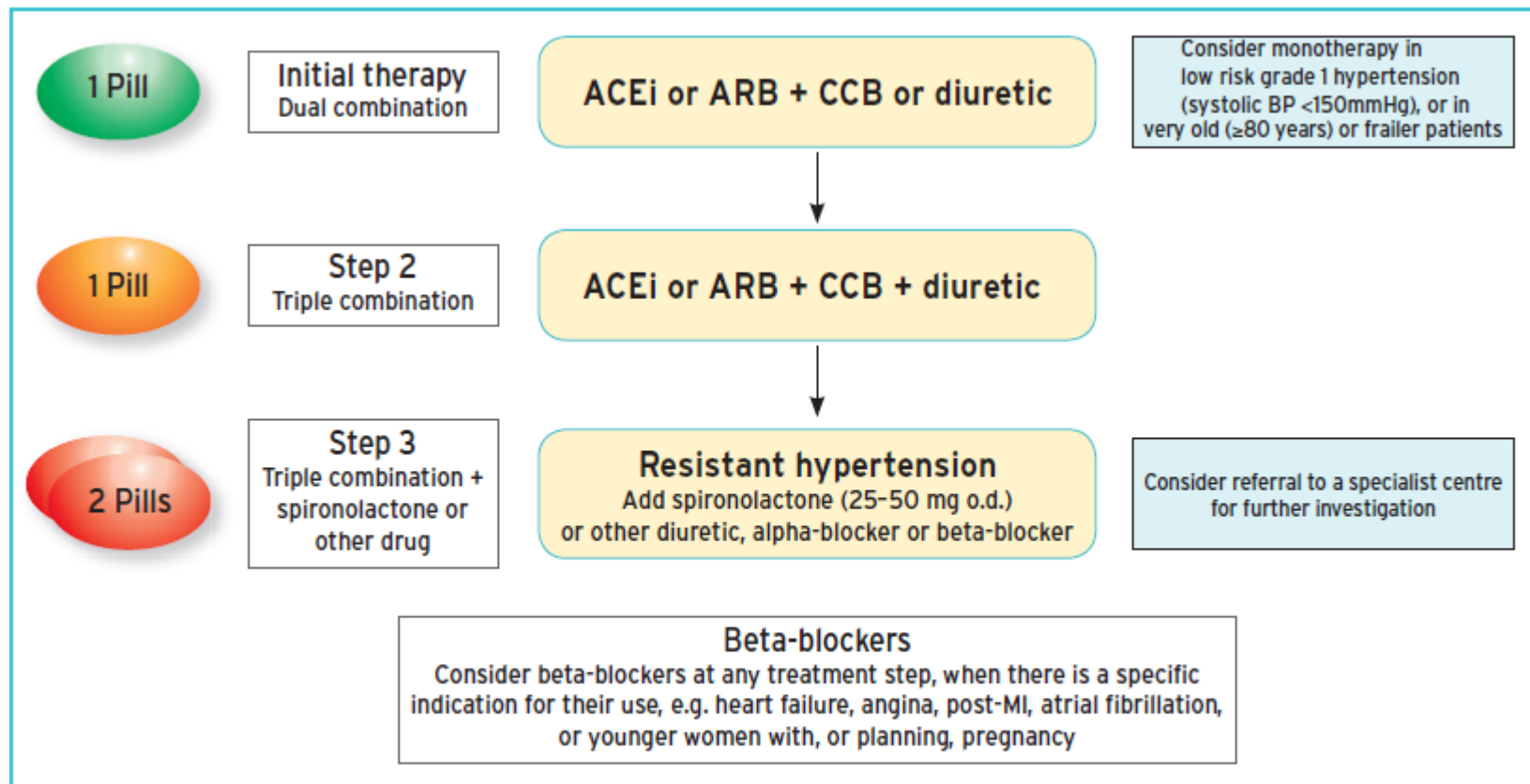
Difference in 24h BP change (valsartan-CPAP), p values <0.001 for SBP and 0.002 for DBP.

\$ Difference in office change (acetazolamide-CPAP), p values n/a

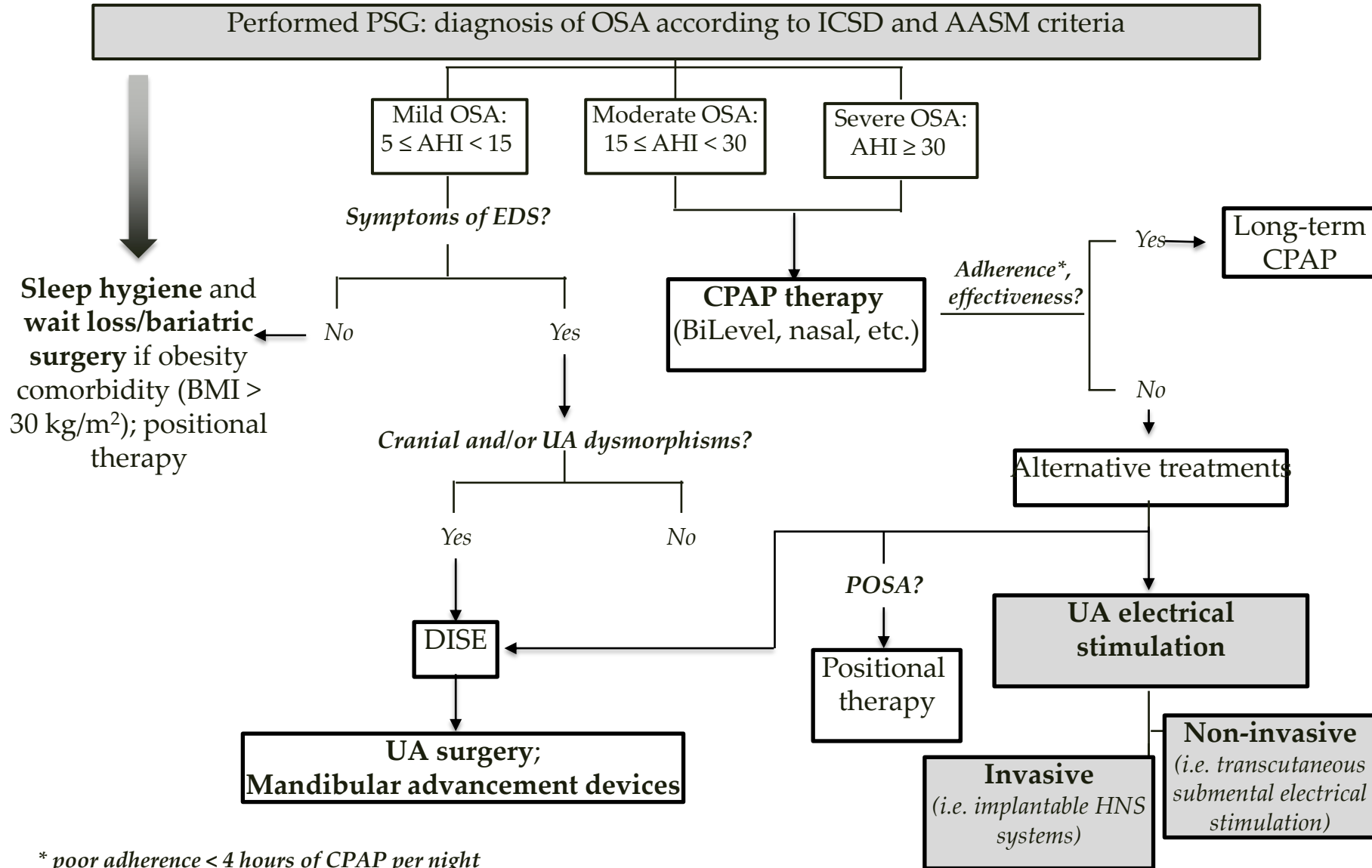
DANS CETTE CONFUSION, QUE FERONS-NOUS?



HYPERTENSION: A RISK FACTOR FOR CARDIOVASCULAR DISEASES



SLEEP APNEA: A SLEEP RELATED BREATHING DISORDER

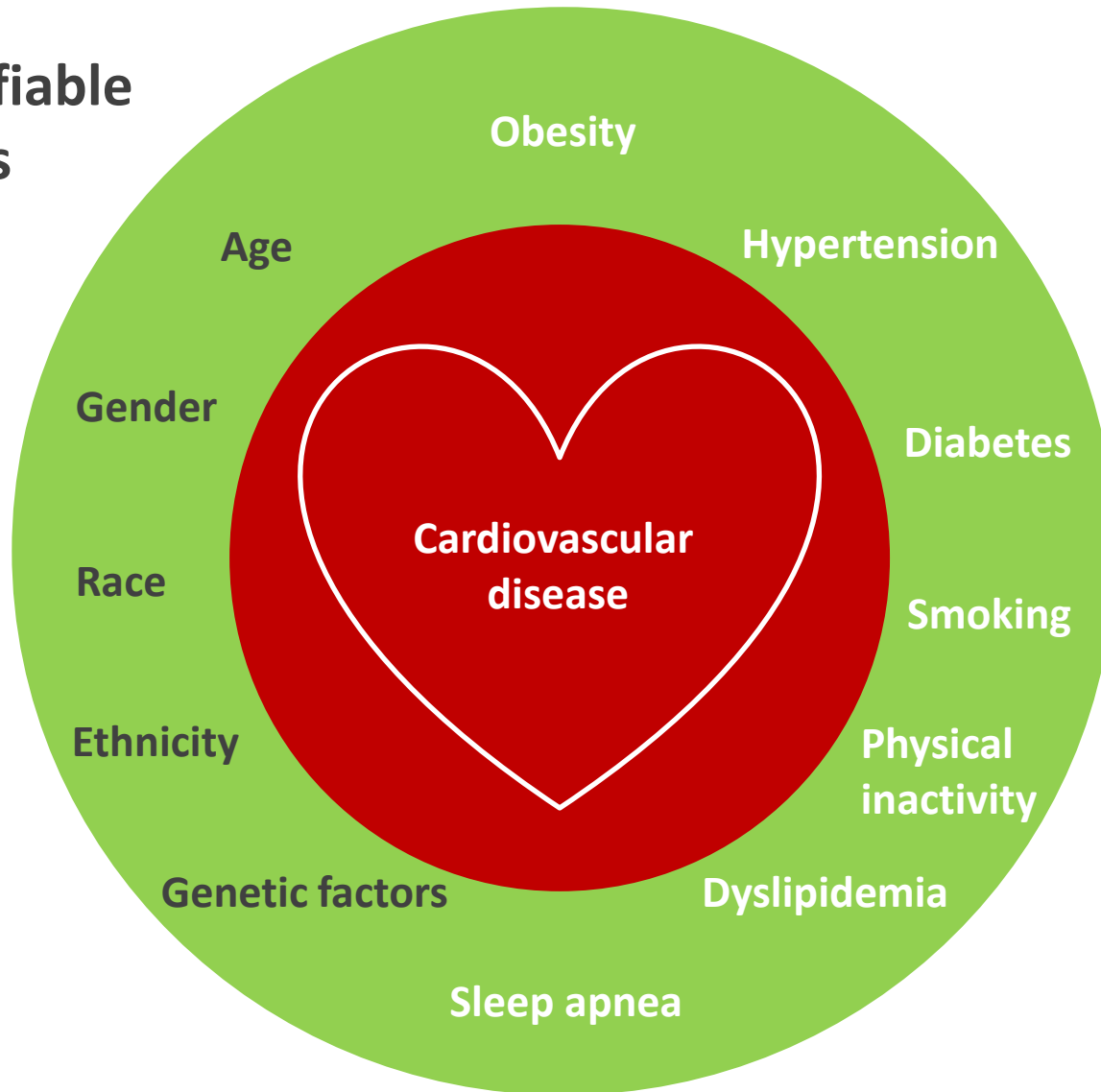


* poor adherence < 4 hours of CPAP per night

PRIMARY AIM IS TO REDUCE CARDIOVASCULAR RISK

**Non-modifiable
risk factors**

**Modifiable
risk factors**



TAKE HOME MESSAGE

- Association between OSA and hypertension is well documented and a causal relationship can be postulated according to the Bradford Hill criteria
- However, treating OSA does not always mean reducing blood pressure as RCTs showed contrasting results
- Furthermore, the results of the SAVE trial showed that treating OSA does not prevent cardiovascular disease in high risk patients
- Precision medicine and better phenotypisation could help better defining patients who benefit more from treatment

AUXOSLEEP
Clinical Sleep Update™



Milan 18th May 2019

San Luca Hospital, Istituto Auxologico Italiano, Milan

**SAVE
THE DATE!**

MERCI DE VOTRE ATTENTION

**Je saisis cette occasion pour vous inviter à Clinical
Update Sleep: une conférence internationale qui
aura lieu à Milan en mai 2019**