LA SÍNDROME D'APNEES OBSTRUCTIVES DEL SON:

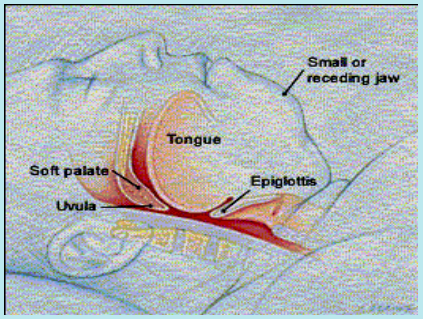
Conseqüències cardio-vasculars

Olga Parra
Servei de Pneumologia
Hospital Universitari del Sagrat Cor. Capio.
Universitat de Barcelona.

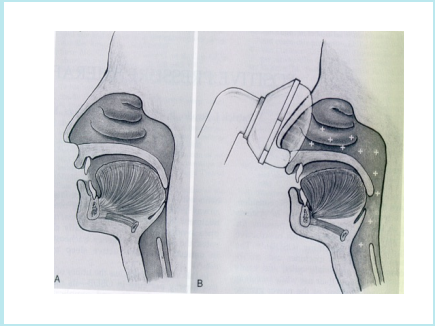
Maig 2012

LA SÍNDROME D' APNEES OBSTRUCTIVES DEL SON:

- MALALTIA LOCAL (VIA AÈREA SUPERIOR). CAUSA ANATÒMICA



- MALALTIA LOCAL. CAUSA ANATÒMICA-FUNCIONAL



- MALALTIA SISTÈMICA?

SAHS
Conseqüències cardio-vasculars/ tractament amb CPAP nasal

- HTA

- Insuficiència cardíaca
- Arítmies
- Cardiopatia isquèmica

- Ictus

- Síndrome metabòlica (HTA, dislipèmia, diabetis, obesitat)

- MORTALITAT CARDIO-VASCULAR

SAHS- CONSEQÜÈNCIES C-V/TRACTAMENT

Estudis randomitzats i controlats

EFICÀCIA TRACTAMENT

Estudis prospectius (longitudinals)

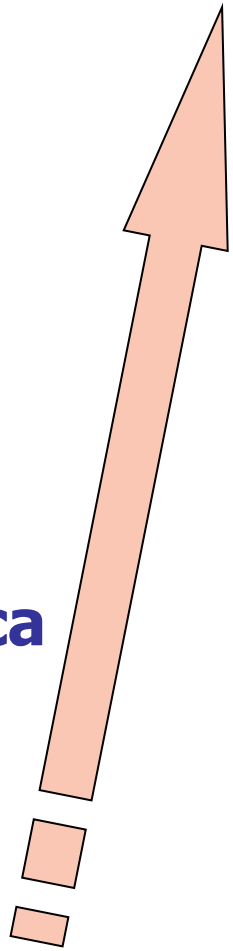
CAUSA-EFECTE

Estudis animals
Mediadors biològics
(inflamació, endoteli...)

FISIO-PATOLOGIA
Plausibilitat biològica

Estudis transversals

ASSOCIACIÓ



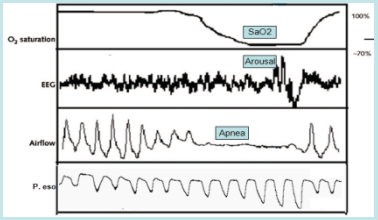
NIVELL EVIDÈNCIA

CPAP NASAL

?

APNEES

*DESSATURACIÓ
*PRESSIONS NEGATIVES
*DESPERTARS



SOMNOLÈNCIA
TS. NEURO COGNITIUS

AUGMENT ACTIVITAT SIMPÀTICA

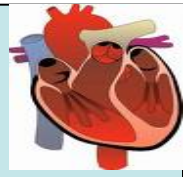
MEDIADORS INFLAMATORIS
PROCOAGULANTS
ESTRÈS OXIDATIU

DISFUNCIÓ ENDOTELIAL

FCS. PROARTERIO-ESCLERÒTICS

?

-HTA



-MORTALITAT CARDIO- VASCULAR

-C.ISQUÈMICA/
I. CARDÍACA/
ARÍTMIES

-ICTUS

-SDRE. METABÒLICA

FACTORS DE CONFUSIÓ: OBESITAT!!!

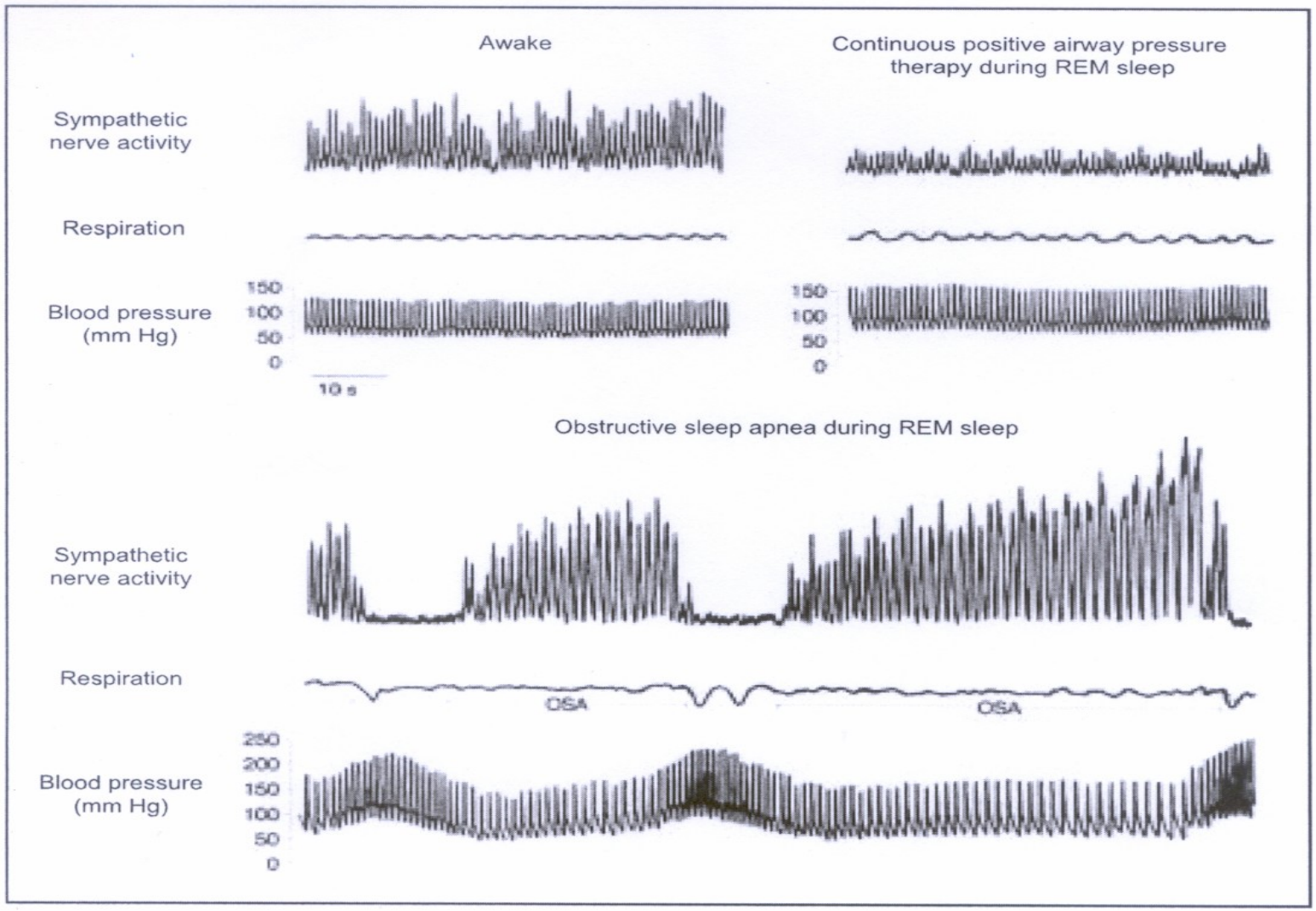
FACTORS GENÈTICS PROTECTORS

TEMPS

MECANISMES FISIO-PATOLÒGICS

ACTIVITAT SIMPÀTICA

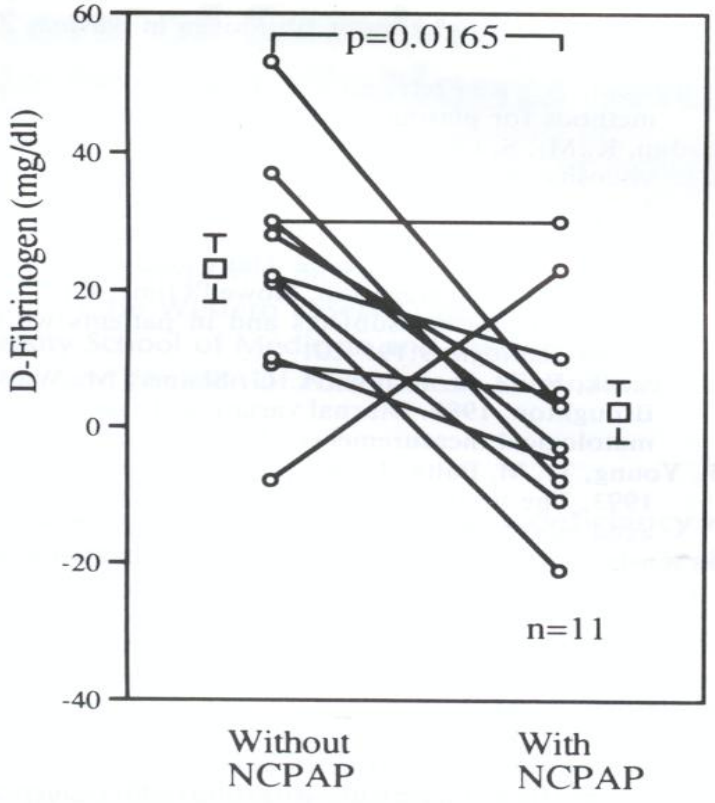
(Sommers et al. J. Clin Invest. 1995)

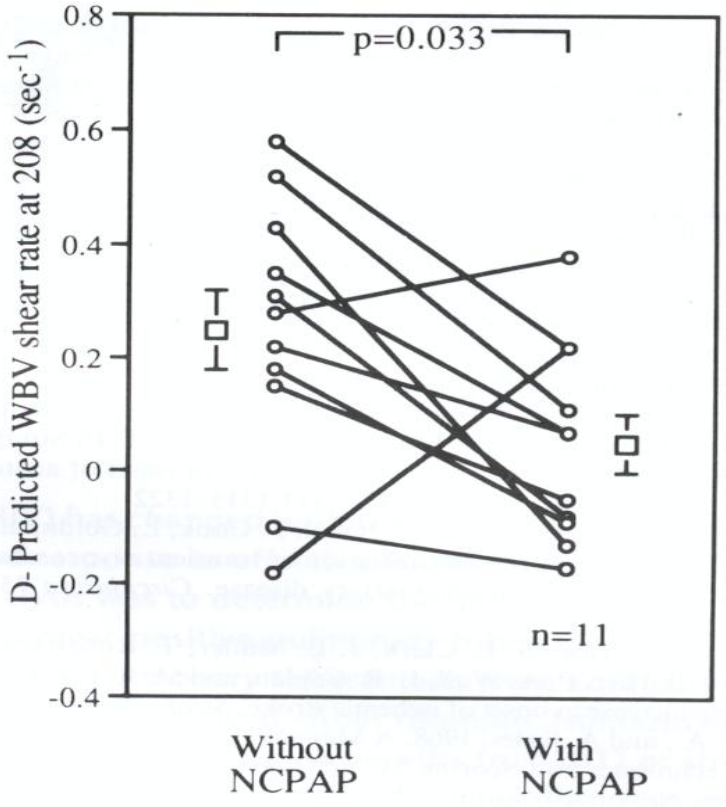


MECANISMES FISIOPA-TOLÒGICS

EFECTES DE LA CPAP NASAL SOBRE ELS NIVELLS DE FIBRINOGEN

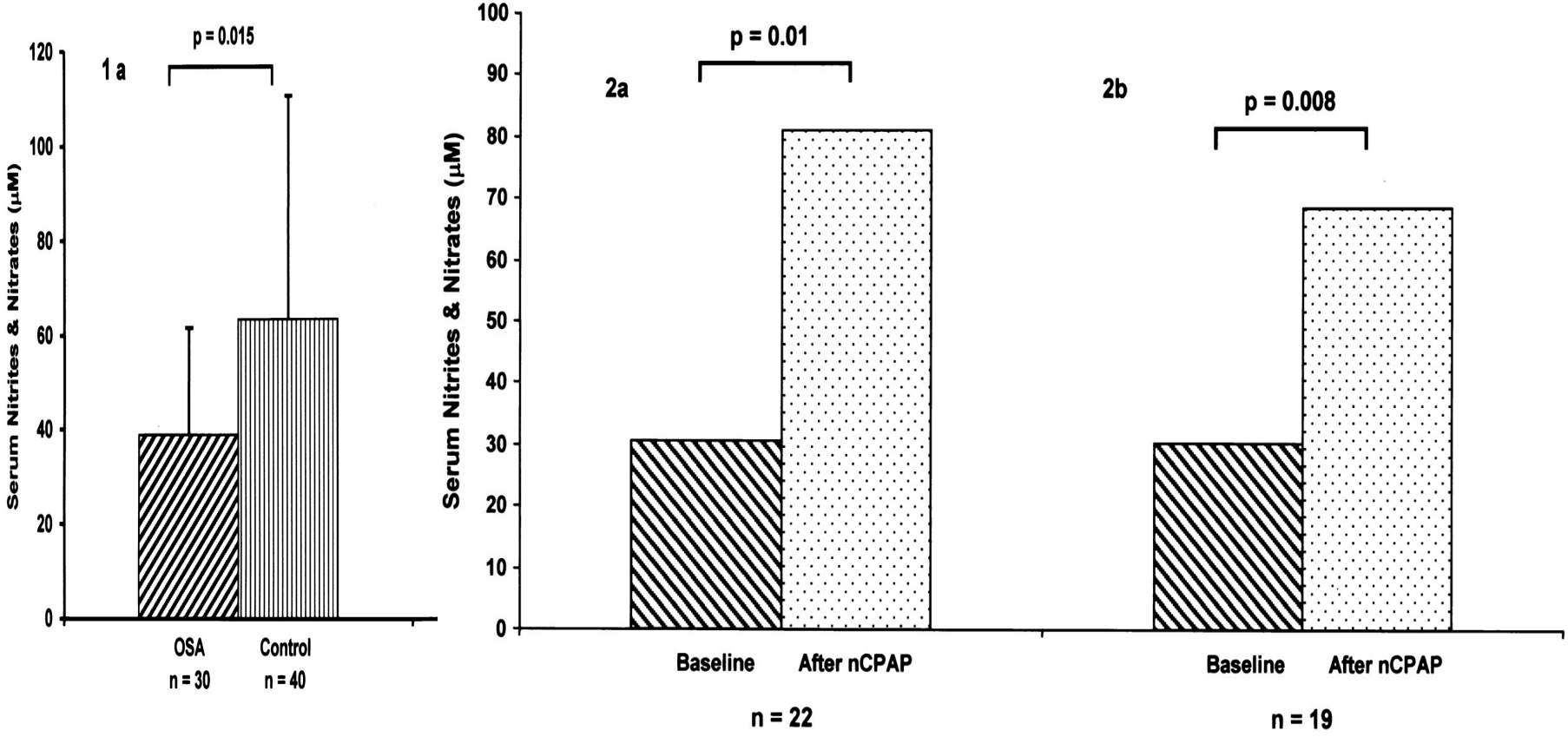
(Chin et al. Am J Respir Crit Care Med, 1996)





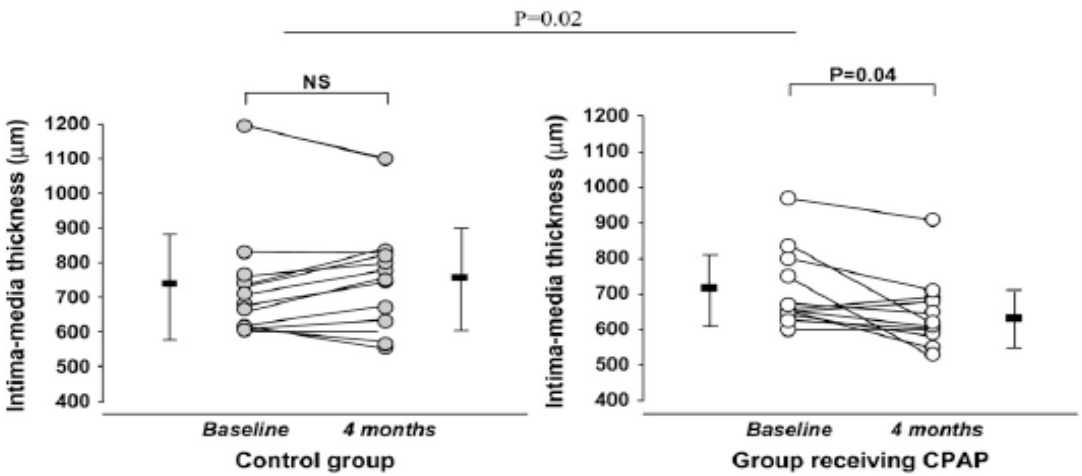
MECANISMES FISIO-PATOLÒGICS

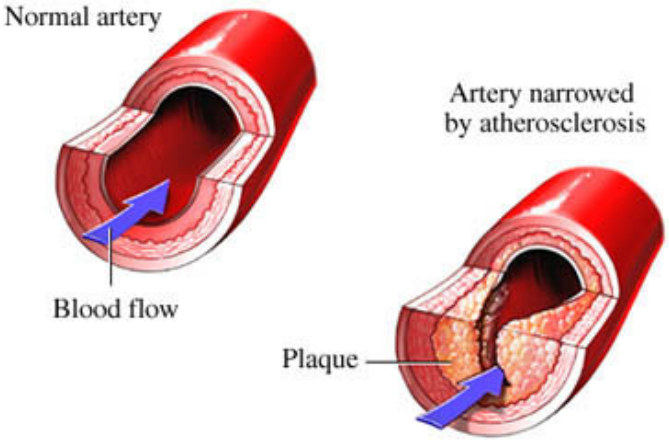
Circulating Nitric Oxid is Supressed in Obstructive Sleep Apnea and is reversed by NCPAP (Ip MS. AJRCCM. 2000; 162:2166-2171)

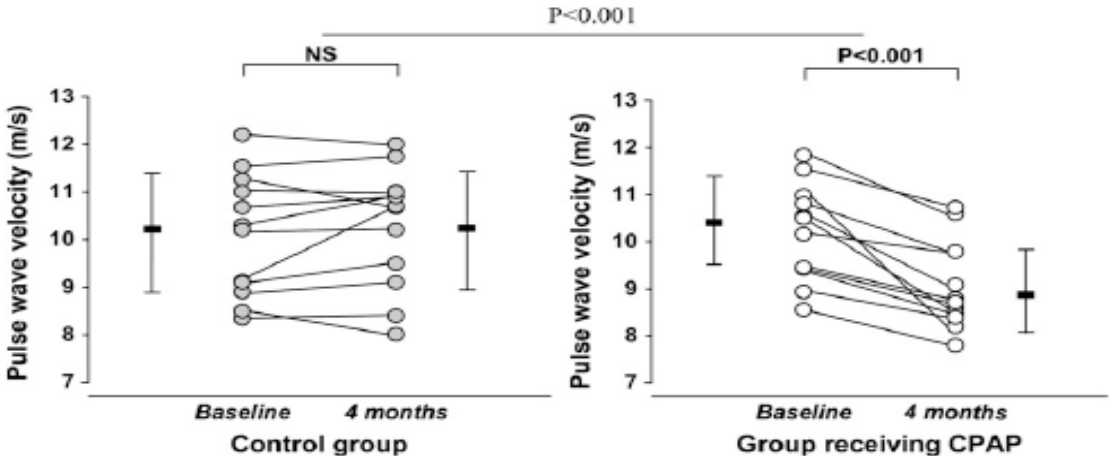


Effects of Continuous Positive Airway Pressure on Early Signs of Atherosclerosis in Obstructive Sleep Apnea

Luciano F. Drager[1], Luiz A. Bortolotto[1], Adelaide C. Figueiredo[2], Eduardo M. Krieger[1], and Geraldo Lorenzi-Filho[2]







"Aquest estudi randomitzat mostra que el tractament amb CPAPn, durant 4 mesos, millora significativament els signes d'arteriosclerosi en pacients amb SAHS greu. Això suggereix que la SAHS és un factor de risc independent per l'arteriosclerosi.

Am J Respir Crit Care Med 2007. 76.:706-712

INSUFICIÈNCIA CARDÍACA

Assatjos randomitzats i controlats

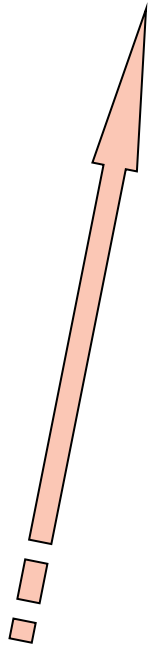
Estudis prospectius (longitudinals)

Estudis animals
Mediadors biològics
(inflamació, endoteli...)

Estudis: transversals
Cas Control

EFICÀCIA TRACTAMENT ???

CAUSA-EFECTE



FISIO-PATOLOGIA

ASSOCIACIÓ

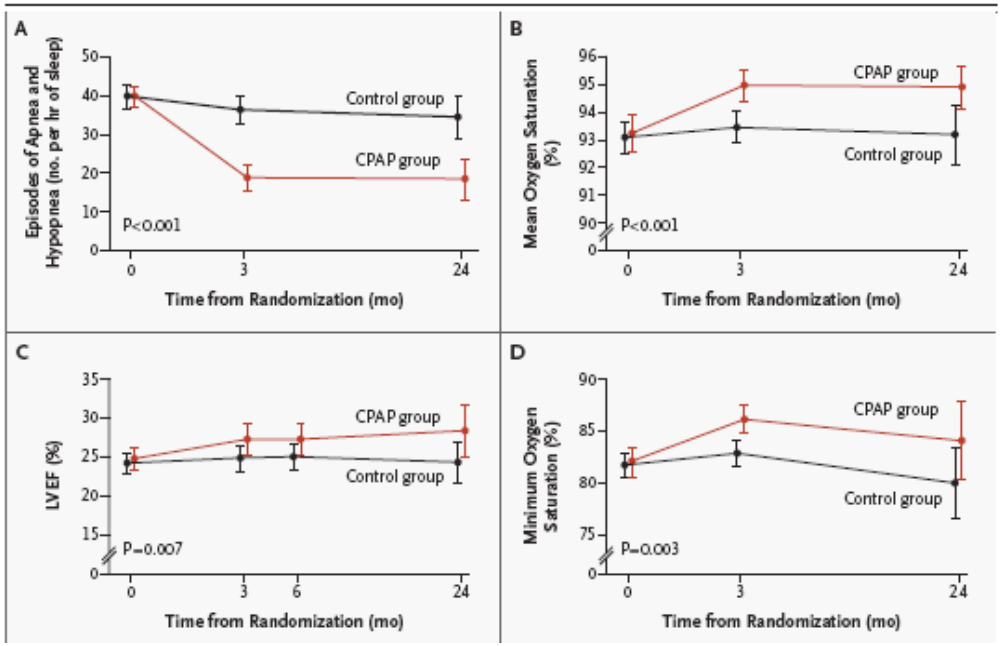
NIVELL EVIDÈNCIA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Continuous Positive Airway Pressure for Central Sleep Apnea and Heart Failure

T. Douglas Bradley, M.D., Alexander G. Logan, M.D., R. John Kimoff, M.D., Frédéric Sériès, M.D., Debra Morrison, M.D., Kathleen Ferguson, M.D., Israel Belenkie, M.D., Michael Pfeifer, M.D., John Fleetham, M.D., Patrick Hanly, M.D., Mark Smilovitch, M.D., George Tomlinson, Ph.D., and John S. Floras, M.D., D. Phil., for the CANPAP Investigators*



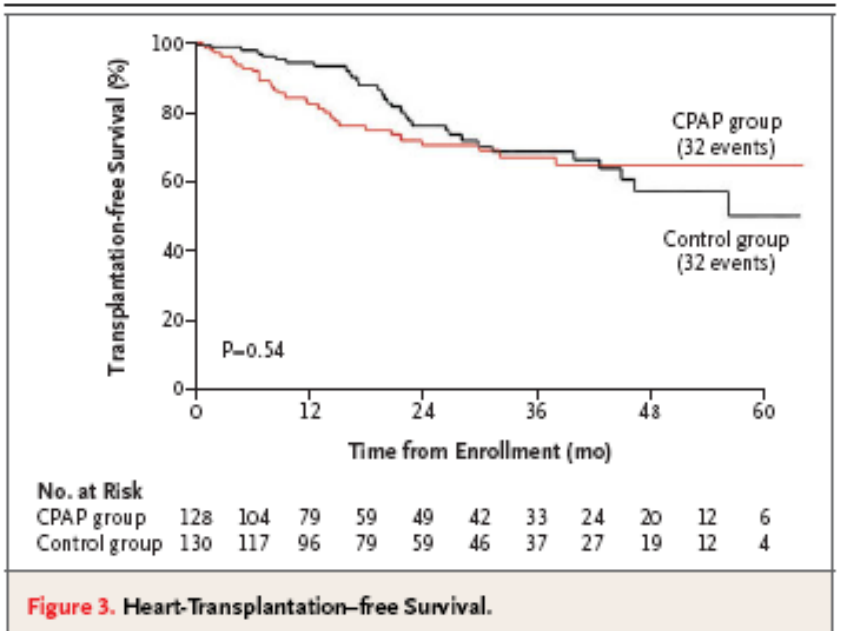


Figure 3. Heart-Transplantation–free Survival.

CANPAP:Multicèntric, 258 pacient (SAHS i pacients amb CA-CSR)
Efectes positius sobre FEVE, el resultat primari:
taxa combinada de mort i transplantament
no millora i té efectes potencialment deleteris.
S' ATURA L' ESTUDI

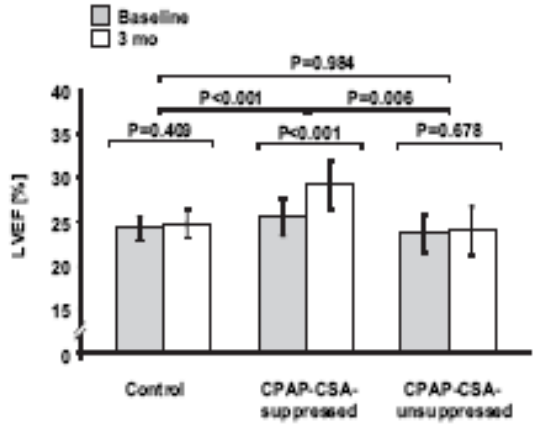
N Engl J Med 2005;353:2025-33.

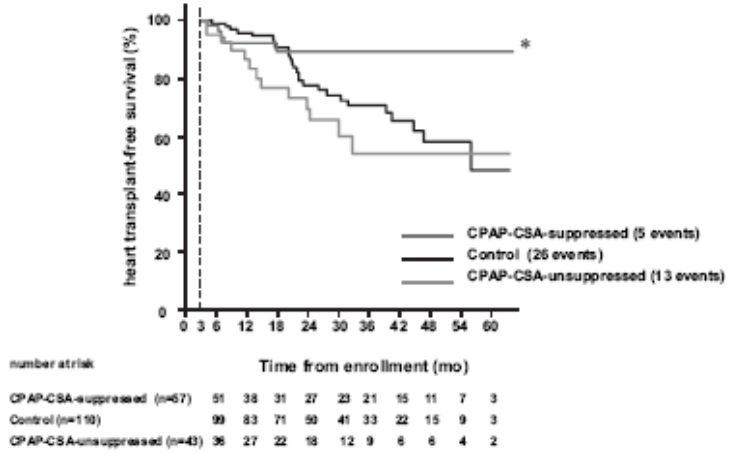
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Suppression of Central Sleep Apnea by Continuous Positive Airway Pressure and Transplant-Free Survival in Heart Failure

A Post Hoc Analysis of the Canadian Continuous Positive Airway Pressure for Patients With Central Sleep Apnea and Heart Failure Trial (CANPAP)

Michael Arzt, MD; John S. Floras, MD, DPhil; Alexander G. Logan, MD; R. John Kimoff, MD; Frederic Series, MD; Debra Morrison, MD; Kathleen Ferguson, MD; Israel Belenkie, MD; Michael Pfeifer, MD; John Fleetham, MD; Patrick Hanly, MD; Mark Smilovitch, MD; Clodagh Ryan, MD; George Tomlinson, PhD; T. Douglas Bradley, MD; for the CANPAP Investigators





Aquells que normalitzen CSA (<15) i per tant CPAP eficaç milloren la supervivència.

(*Circulation*. 2007;115:3173-3180.)

En resum: SAHS- INSUFICIÈNCIA CARDíACA

- CANPAP. Bradley D. et al. ***(N Engl J Med 2005; 353: 2025-33.)***

CANPAP posthoc analysis. Artz M. et al **(*Circulation*. 2007; 115: 3173-3180.)**

Recomana: "CPAP Should Be Used for Central Sleep Apnea in Congestive Heart Failure Patients"

(Journal of Clinical Sleep Medicine, Vol. 2, No. 4, 2006)

- Javiheri S.

Recomana no: "CPAP Should Not Be Used for Central Sleep Apnea in Congestive Heart Failure Patients"

(Journal of Clinical Sleep Medicine, Vol. 2, No. 4, 2006)

"En aquells no responedors, probablement per predomini CSA, valorar altres formes de ventilació."

Obstructive Sleep Apnea and the Recurrence of Atrial Fibrillation

Ravi Kanagala, MD; Narayana S. Murali, MD; Paul A. Friedman, MD; Naser M. Ammash, MD;
Bernard J. Gersh, MB ChB, DPhil; Karla V. Ballman, PhD;
Abu S.M. Shamsuzzaman, MD, PhD; Virend K. Somers, MD, PhD

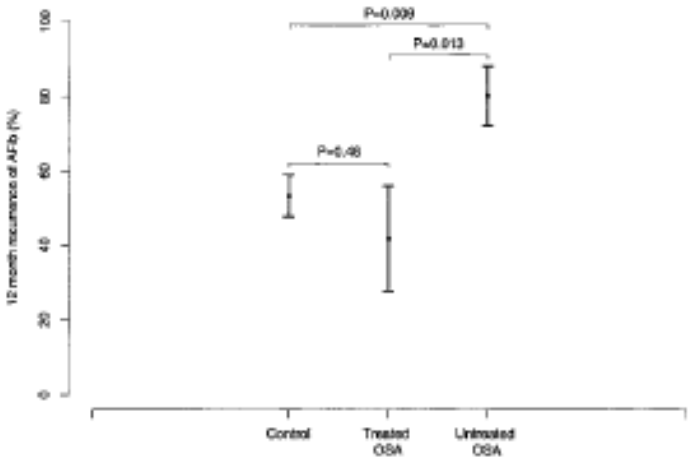


Figure 1. Recurrence of AF at 12 months comparing patients who did not have sleep studies (controls) with treated OSA patients and with untreated (including noncompliant) OSA patients (mean±SD).

(*Circulation*. 2003;107:2589-2594.)

ICTUS

Assajos randomitzats i controlats

Estudis prospectius (longitudinals)

Estudis animals
Mediadors biològics
(inflamació, endoteli...)

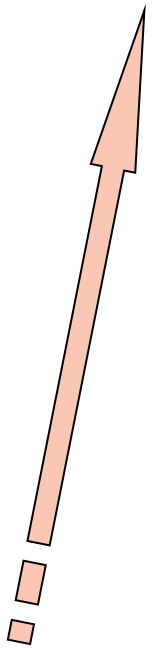
Estudis: transversals
Cas Control

EFICÀCIA TRACTAMENT ???

POCA INFORMACIÓ CAUSA-EFECTE

FISIO-PATOLOGIA

ASSOCIACIÓ



NIVELL EVIDÈNCIA

ESTUDIS DE FREQÜÈNCA EN L'ASSOCIACIÓ ICTUS-SAHS

TABLA I

Estudios que analizan la presencia de trastornos respiratorios del sueño en pacientes con ictus

Autores	Número	Edad media (años)	Método diagnóstico	Días desde el ictus	IAH medio (eventos/h)	IAH ≥ 10	IAH ≥ 30
Kapen et al[12]	47	62	PSG		28,2		
Mohsenin[13]	10	56	PSG		52		
Good et al[14]	19		PSG	18	35,6	95%	53%
Dyken et ak[15]	24	65	PSG	16	26	71%	37,5%
Bassetti y Aldrich[17]	48	60	PSG	9	32	58%	
Parra et al[19]	161	72	PSGR	2-3	21,2	71,4%	28%
Davieset al[20]	46	68	PSGR	90		41%	
Wessendorf et al[21]	147	61	PSG	46	34	43,5	
Harbison et al[22]	34	74	PSGR	9		94%	
Hui et al[25]	51	64,2	PSG	3	23	67%	
Iranzo et al[27]	50	66,8	PSG	1	27,7	62%	

IAH: índice de apneas-hipopneas; PSG: polisomnografía; PSGR: polisomnografía respiratoria.

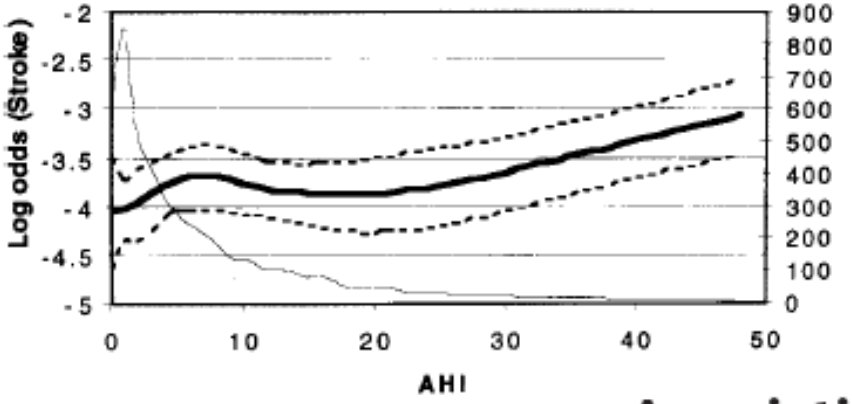
(O. Parra. Arch Bronconeumol, 2004)

TRANSVERSALS

Sleep-disordered Breathing and Cardiovascular Disease

Cross-sectional Results of the Sleep Heart Health Study

EYAL SHAHAR, CORALYN W. WHITNEY, SUSAN REDLINE, ELISA T. LEE, ANNE B. NEWMAN, F. JAVIER NIETO, GEORGE T. O'CONNOR, LORI L. BOLAND, JOSEPH E. SCHWARTZ, and JONATHAN M. SAMET for the Sleep Heart Health Study Research Group



Am. J. Respir. Crit. Care Med. 2001, 163:19.

Association of Sleep-disordered Breathing and the Occurrence of Stroke

Michael Arzt, Terry Young, Laurel Finn, James B. Skatrud, and T. Douglas Bradley

TABLE 2. ADJUSTED ODDS RATIOS FOR THE PREVALENCE OF STROKE FOR SUBJECTS GROUPED BY THE APNEA-HYPOPNEA INDEX

	Model 1A		Model 2A		Model 3A	
AHI (*events/h*)	OR (95% CI), adjusted for age, sex, BMI, alcohol, and smoking	p Value	OR (95% CI), adjusted for age, sex, BMI, alcohol, smoking, and hypertension	p Value	OR (95% CI), adjusted for age, sex, BMI, alcohol, smoking, diabetes, and hypertension	p Value
< 5*	1.0		1.0		1.0	
⩾ 5 to < 20	0.50 (0.11–2.33)	0.38	0.48 (0.10–2.27)	0.36	0.49 (0.10–2.81)	0.36
⩾ 20	4.33 (1.32–14.24)	0.02	3.87 (1.19–12.63)	0.02	3.83 (1.17–12.56)	0.03

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CI = confidence interval; OR = odds ratio.
* This category served as the reference group.

Am J Respir Crit Care Med 2005; 172: 1447.

The NEW ENGLAND JOURNAL of MEDICINE

LONGITUDINAL

ORIGINAL ARTICLE

Obstructive Sleep Apnea as a Risk Factor for Stroke and Death

H. Klar Yaggi, M.D., M.P.H., John Concato, M.D., M.P.H., Walter N. Kernan, M.D., Judith H. Lichtman, Ph.D., M.P.H., Lawrence M. Brass, M.D., and Vahid Mohsenin, M.D.

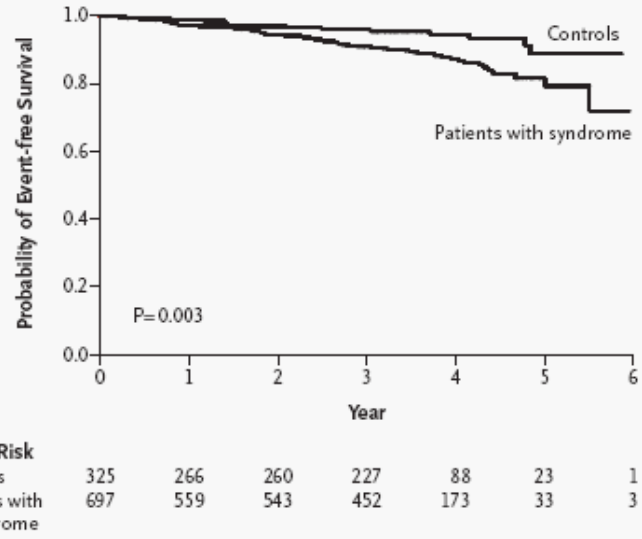


Figure 1. Kaplan–Meier Estimates of the Probability of Event-free Survival among Patients with the Obstructive Sleep Apnea Syndrome and Controls.

Table 3. Trend Analysis for the Relationship between Increased Severity of the Obstructive Sleep Apnea Syndrome and the Composite Outcome of Stroke or Death from Any Cause (N=1022).*

Severity of Syndrome	Stroke or Death		Mean Follow-up Period	Hazard Ratio (95% CI)
	No. of Events	No. of Patients		
			yr	
AHI ≤3 (reference score)	13	271	3.08	1.00
AHI 4–12	21	258	3.06	1.75 (0.88–3.49)
AHI 13–36	20	243	3.09	1.74 (0.87–3.51)
AHI >36	34	250	2.78	3.30 (1.74–6.26)

* P=0.005 by the chi-square test for linear trend. AHI denotes apnea–hypopnea index, and CI confidence interval.

Eur Respir J 2004; 24: 267–272
DOI: 10.1183/09031936.04.00061503

PRONÒSTIC

Sleep-related breathing disorders: impact on mortality of cerebrovascular disease

O. Parra*, A. Arboix#, J.M. Montserrat¶, L. Quintó+, S. Bechich*, L. García-Eroles*

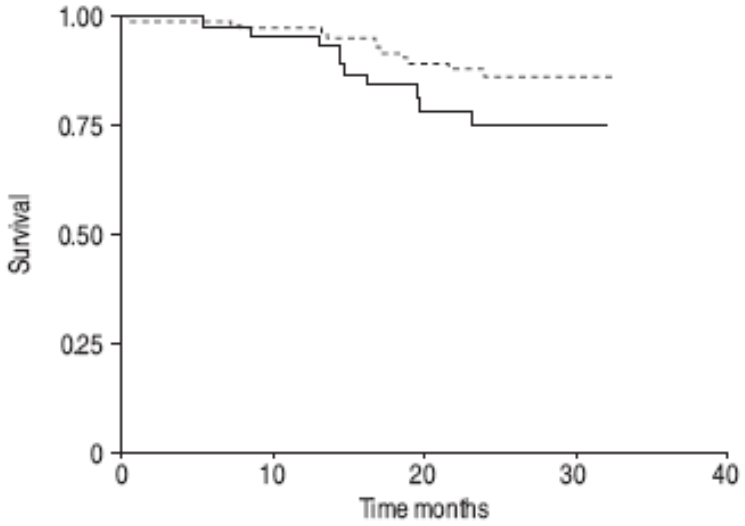


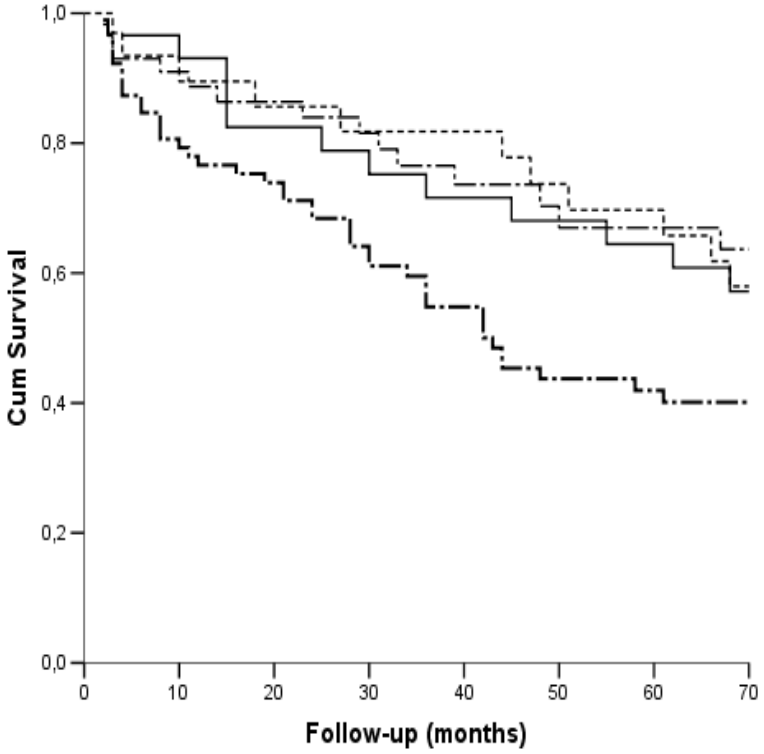
Fig. 1.–Kaplan-Meier survival estimates in patients with an apnoea/hypopnoea index (AHI) of <30 (----) and in those with an AHI of ⩾30 (——). Greater mortality is evident in patients with an AHI above the cut-off point of 30.

Table 4.–Cox's proportional-hazards model (multivariate analysis)

	Hazard ratio (95% CI)	p-value
Age	1.14 (1.06–1.21)	0.000
AHI	1.05 (1.01–1.08)	0.004
MCA involvement	2.86 (1.04–7.84)	0.04
Coronary disease	3.25 (1.05–10.03)	0.04

CI: confidence interval; AHI: apnoea/hypopnoea index; MCA: middle cerebral artery.

Continuous Positive Airway Pressure Treatment Reduces Mortality in Patients with Ischemic Stroke and Obstructive Sleep Apnea A 5-Year Follow-up Study



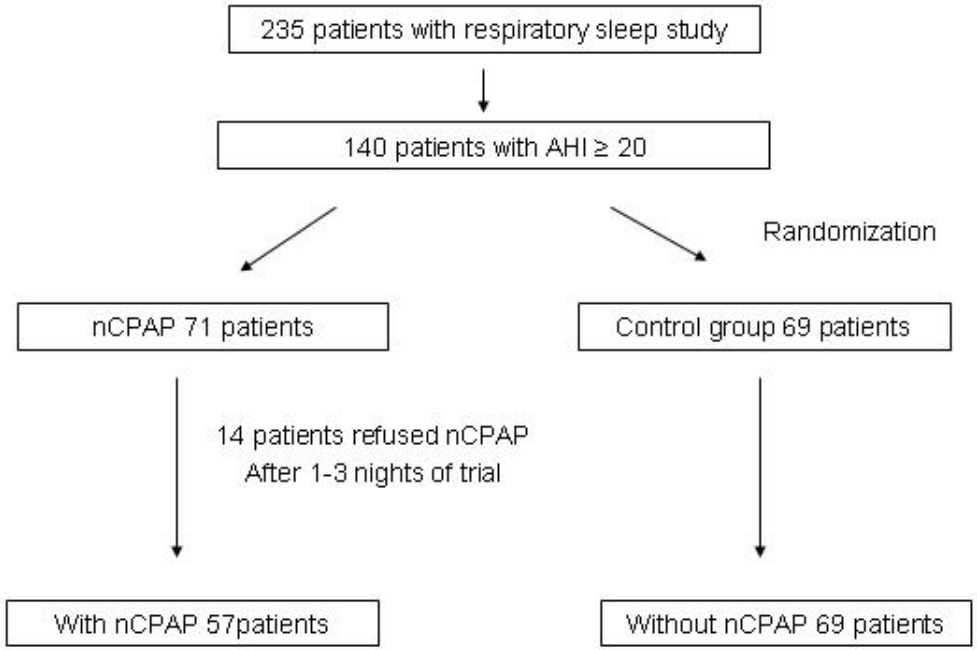
IAH 0-9 (n=31; 11 deaths)
IAH 10-19 (n=39; 15 deaths)
IAH≥20 with CPAP (n=28; 12 deaths)

IAH≥20 without CPAP (n=63;43 deaths)

Martínez-García et al. *Am. J. Respir. Crit. Care Med.* 2009; 180: 36-41

Early treatment of obstructive apnea and stroke outcome after 2 years: a randomized controlled trial

Olga Parra, Ángeles Sánchez-Armengol, Marc Bonnin, Adrià Arboix, Francisco Campos-Rodríguez, José Pérez-Ronchel, Joaquín Durán-Cantolla, Germán de la Torre, José R. González Marcos, Mónica de la Peña, M. Carmen Jiménez, Fernando Masa, Ignacio Casado, M. Luz Alonso, José L. Macarrón

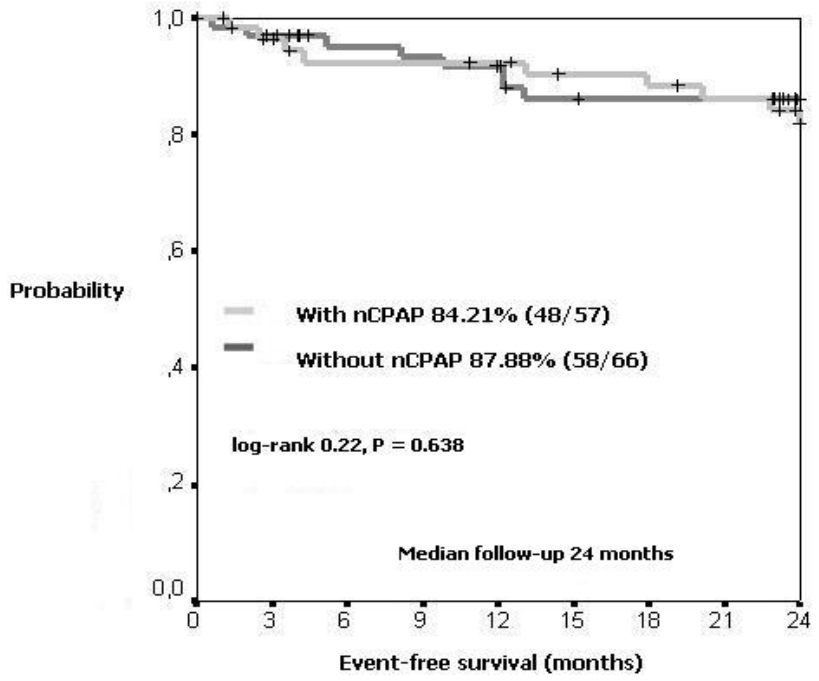


Eur Respir J. 2011; 37(5):1128-36.

Early treatment of obstructive apnea and stroke outcome after 2 years: a randomized controlled trial

O.Parra et al.

Supervivència lliure d'events en el grup amb CPAPn i en el controls.



	TOTAL (n=235)	SAHS CPAP (n=57)	SAHS NO CPAP (n=69)	NO SAS (n=109)
Exitus	10 (4,3%)	2 (3,5%)	4 (5,8%)	4 (3,7%)

Eur Respir J. 2011; 37(5):1128-36.

En resum: SAHS-ICTUS

- Hi ha dades que suggereixen associació
- Indicis de causalitat
- La influència del tractament amb CPAP nasal, un cop establert l'Ictus, no està gens clara.

SÍNDROME METABÒLICA

Assajos Random. i controlats

Estudis prospectius (longitudinals)

Estudis animals
Mediadors biològics
(inflamació, endoteli...)

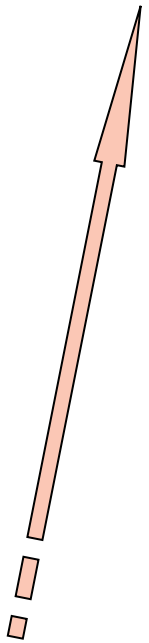
Estudis: transversals
Cas Control

EFICÀCIA TRACTAMENT ???

POCA INFORMACIÓ
CAUSA-EFECTE

FISIO-PATOLOGIA

ASSOCIACIÓ



NIVELL EVIDÈNCIA

EFECTES DE LA CPAP EN EL METABOLISME DE LA GLUCOSA

TABLE 3. STUDIES EXAMINING THE EFFECT CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT ON GLUCOSE METABOLISM

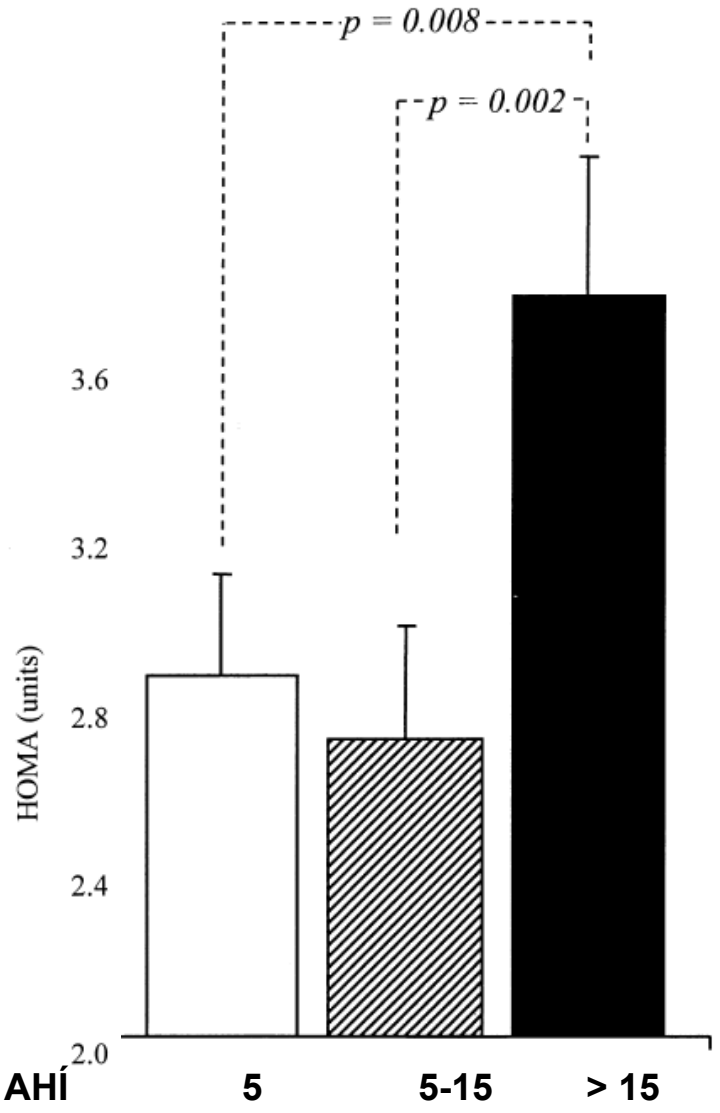
Reference	Treatment Period	Study Population	Measures of Glucose	Main Results
Positive studies				
Brooks and colleagues (51)	4 mo	10 Severely obese patients with diabetes with OSA	Hyperinsulinemic euglycemic clamp	Improvement in insulin sensitivity
Harsh and colleagues (54)	3 mo	40 Patients without diabetes with OSA	Hyperinsulinemic euglycemic clamp	Improvement in insulin sensitivity (at 2 d and 3 mo)
Harsh and colleagues (52)	3 mo	9 Patients with diabetes with OSA	Hyperinsulinemic euglycemic clamp	Improvement in insulin sensitivity (at 3 mo)
Babu and colleagues (55)	3 mo	25 Patients with diabetes with OSA	72-h interstitial glucoseHemoglobin A1c	Improvement in 1-h postprandial glucose and decrease in hemoglobin A1c
Hassaballa and colleagues (142)	3–4 mo	38 Patients with diabetes with OSA	Hemoglobin A1c	Slight decrease in hemoglobin A1c
Lindberg and colleagues (53)	3 wk	28 Men with OSA28 Matched control men without OSA	Fasting insulin and HOMA	Reductions in fasting insulin levels and insulin resistance
Negative studies				
Saini and colleagues (59)	1 Night	8 Patients with OSA	Profiles of glucose and insulin at night	No change in nocturnal glucose and insulin profiles
Cooper and colleagues (60)	1 Night	6 Obese men without diabetes with OSA	Profiles of glucose and insulin at night	No change in nocturnal glucose and insulin profiles
Stoohs and colleagues (47)	2 mo	5 Patients with OSA	Fasting glucose and insulin	Increase in fasting and nocturnal glucose levels
			Profiles of glucose and insulin at night	No change in fasting or nocturnal insulin levels
Saarlainen and colleagues (143)	3 mo	7 Patients with OSA	Hyperinsulinemic euglycemic clamp	No improvement in insulin sensitivity
Ip and colleagues (61)	6 mo	9 Patients with OSA	Fasting glucose and insulin	No change in fasting glucose and insulin levels
Sumurra and colleagues (144)	2 mo	16 Patients with OSA	Hyperinsulinemic euglycemic clamp OGTT	No change in insulin sensitivity and glucose tolerance
Czupryniak and colleagues (62)	1 night	9 Patients without diabetes with OSA	Nocturnal interstitial glucose Fasting insulin and HOMA	Increase in nocturnal glucose No difference in fasting insulin levels and insulin resistance
Coughlin and colleagues (12)	6 wk	34 Obese patients with OSA	HOMA	No change in insulin sensitivity with therapeutic CPAP compared with placebo CPAP
West and colleagues (63)	3 mo	42 Patients with OSA	Hemoglobin A1c, HOMA, and euglycemic clamp	No change in hemoglobin A1c or insulin sensitivity with therapeutic CPAP compared with placebo CPAP

Definition of abbreviations: CPAP = continuous positive airway pressure; HOMA = homeostatic model assessment; OGTT = oral glucose tolerance test; OSA = obstructive sleep apnea.

Proc Am Thorac Soc. 2008; 5: 207-217

Sleep-Disordered Breathing, Glucose Intolerance, and Insulin Resistance

S. METABÒLICA Transversal



The Sleep Heart Health Study.
N: 2656

La SAHS s'associa a disfunció metabòlica després d'ajustar-se per diversos factors de confussió.

Punjabi et al. Am J Epidemiol 2004; 160: 521

Association of Sleep Apnea and Type II Diabetes
A Population-based Study

Kevin J. Reichmuth, Diane Austin, James B. Skatrud, and Terry Young

Department of Medicine, University of Wisconsin Medical School; and Department of Population Health Sciences, University of Wisconsin, Madison, Wisconsin

Am J Respir Crit Care Med Vol 172. pp 1590–1595, 2005

TRANVERSAL/ LONGITUDINAL

Wisconsin Sleep Cohort, a population-based longitudinal study of sleep disorders

TRANSVERSAL (n: 1387)

IAH > 15: 15 % diabetis

IAH < 5: 2,8 % diabetis

TABLE 4. ODDS RATIOS FOR 4-YR INCIDENCE OF PHYSICIAN-DIAGNOSED DIABETES FOR TWO LEVELS OF SLEEP-DISORDERED BREATHING

	Odds Ratio	95% Confidence Interval	p Value
Adjusted for sex and age			
AHI 5–15 vs. AHI < 5	2.81	1.51–5.23	0.001
AHI ⩾ 15 vs. AHI < 5	4.06	1.86–8.85	0.0004
Adjusted for sex, age, and body habitus*			
AHI 5–15 vs. AHI < 5	1.56	0.80–3.02	0.19
AHI ⩾ 15 vs. AHI < 5	1.62	0.67–3.65	0.24

Definition of abbreviation: AHI = apnea–hypopnea index.
* Body habitus measures: waist girth.

Conclusions: La diabetis és més prevalent en els pacients amb SAHS i aquesta relació és independent d'altres factors de risc. Tanmateix, no està clar que la SAHS sigui un factor causal de diabetis.

En resum: SAHS- S. METABÒLICA

- **Estudis transversals demostren que la SAHS està associada a la resistència a la insulina, però una relació causa-efecte no s'ha confirmat per estudis longitudinals ni per la influència del tractament.**

- **Els efectes de diversos factors de confusió, especialment l'obesitat, no permeten en el moment actual establir una relació clara entre la SAHS i la Síndrome Metabòlica.**

- **Falten estudis randomitzats i controlats amb més mostra i a més llarg termini amb control de compliment del tractament.**

IAH>30.
AUGMENTA MORTALITAT
DISMINUIEX LA SUPERVIVÈNCIA

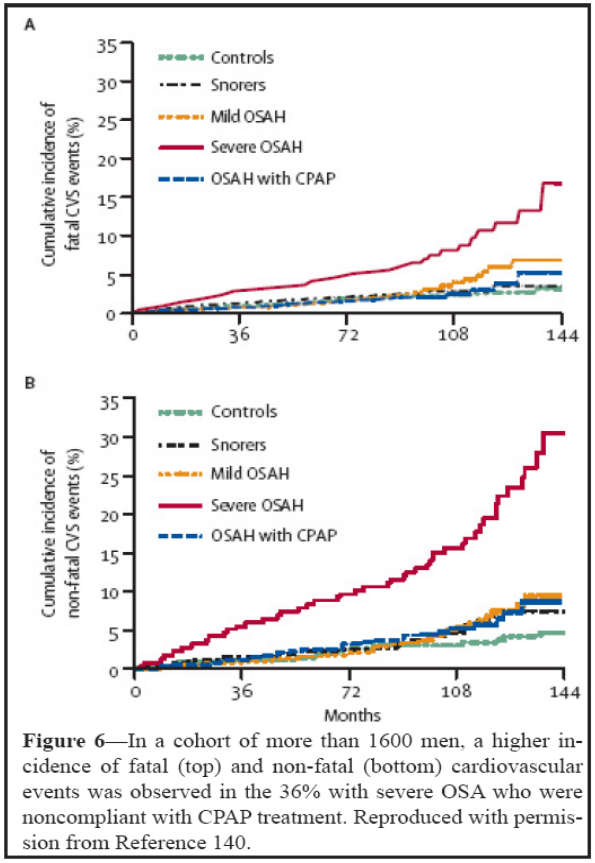
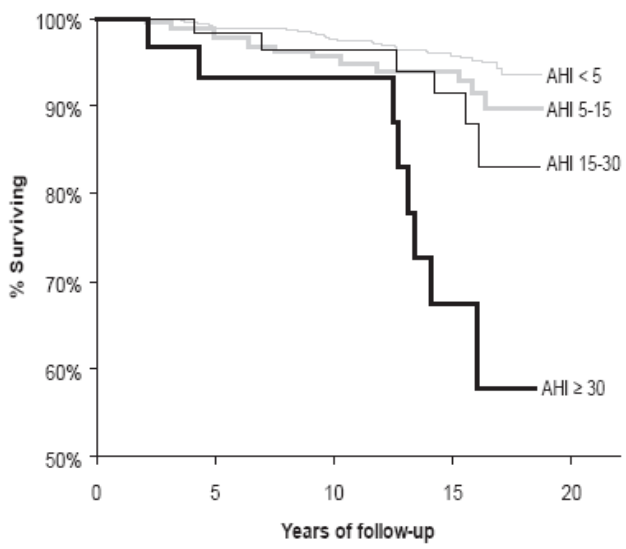
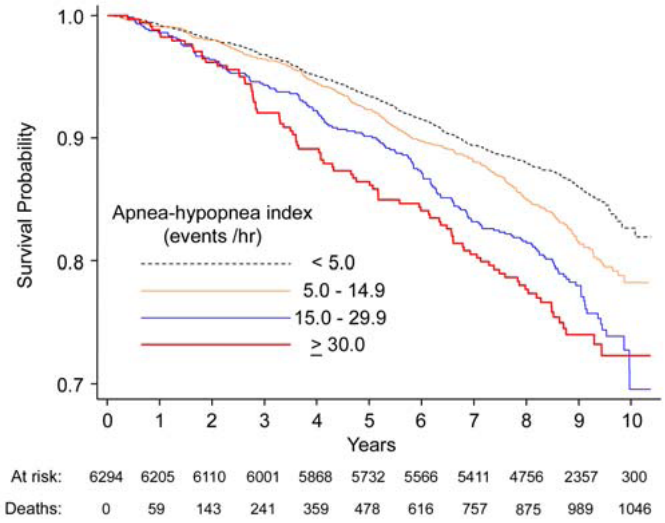


Figure 6—In a cohort of more than 1600 men, a higher incidence of fatal (top) and non-fatal (bottom) cardiovascular events was observed in the 36% with severe OSA who were noncompliant with CPAP treatment. Reproduced with permission from Reference 140.

Marín et al. Lancet 2005; 365:1046-1053



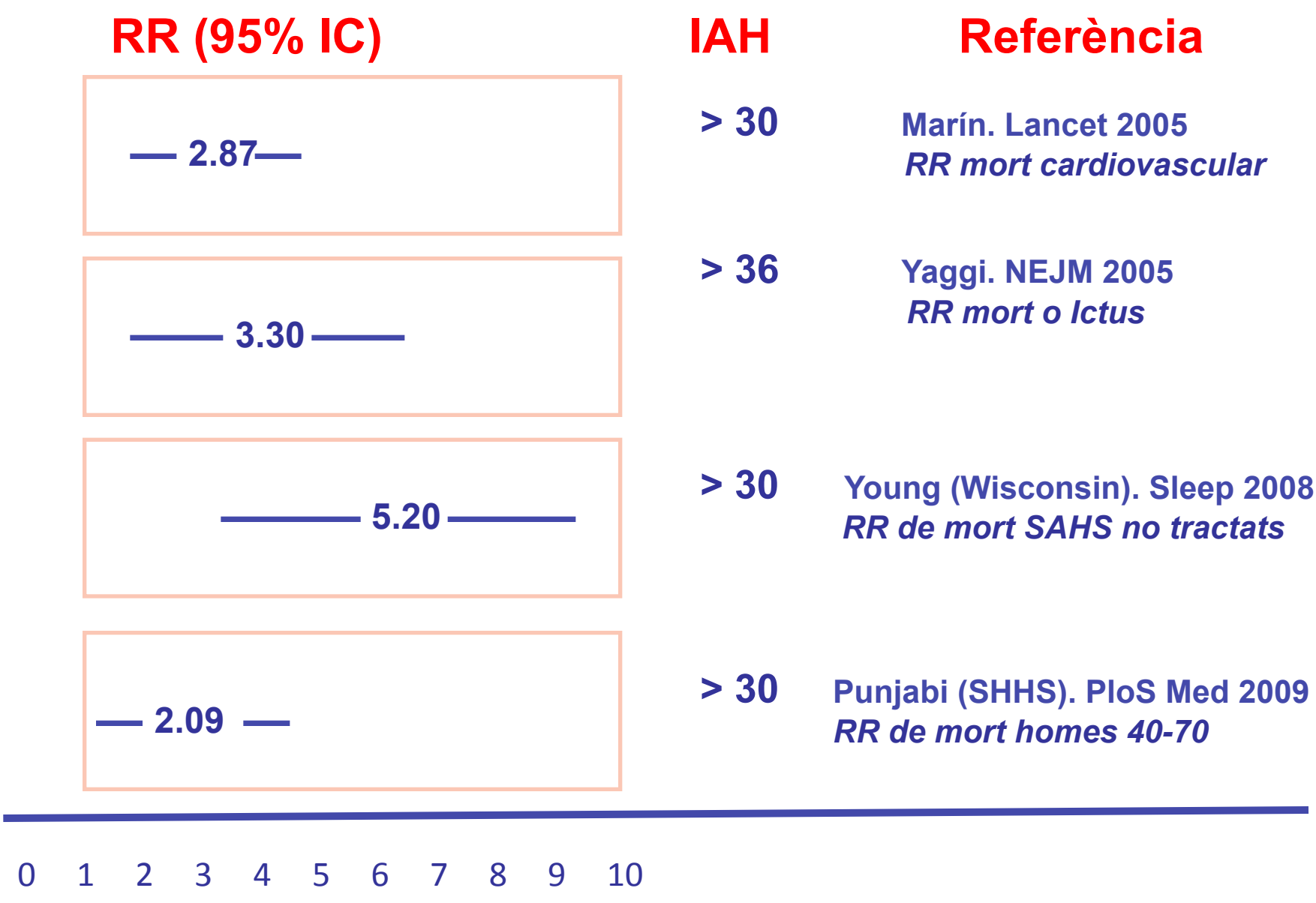
***Young T. Wisconsin. SLEEP* 2008;31 1071-1078.**



***Punjabi N. SHHS*. Plos Medicine 2009 | Volume 6 | Issue 8 | e1000132.**

"RISC RELATIU DE MORT CARDIO-VASCULAR EN LA SAHS. Models ajustats".

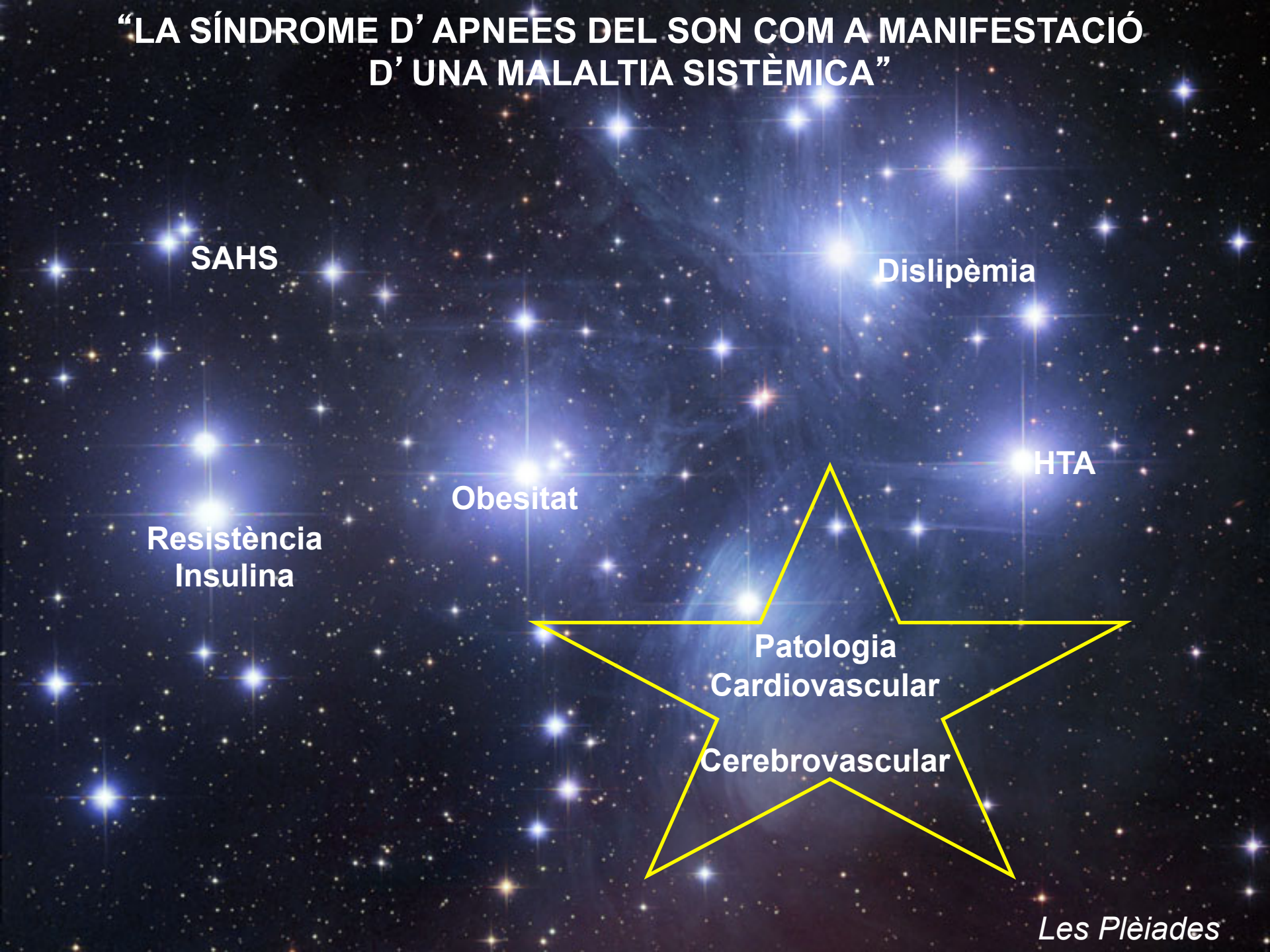
↑ Mortalitat



En resum: SAHS- MORTALITAT

- Indicis de causalitat.
- Ho mirem com vulguem els diferents articles coincideixen a demostrar que l'IAH >30 s'associa a un major risc de mortalitat cardiovascular.
- Pot haver-hi influència del tractament amb CPAP nasal en la mortalitat cardio-vascular, especialment ens SAHS Greu.

“LA SÍNDROME D’ APNEES DEL SON COM A MANIFESTACIÓ D’ UNA MALALTIA SISTÈMICA”



Les Plèiades