SAS et maladies cardiovasculaires
Ispahan 2015

Plan de la session

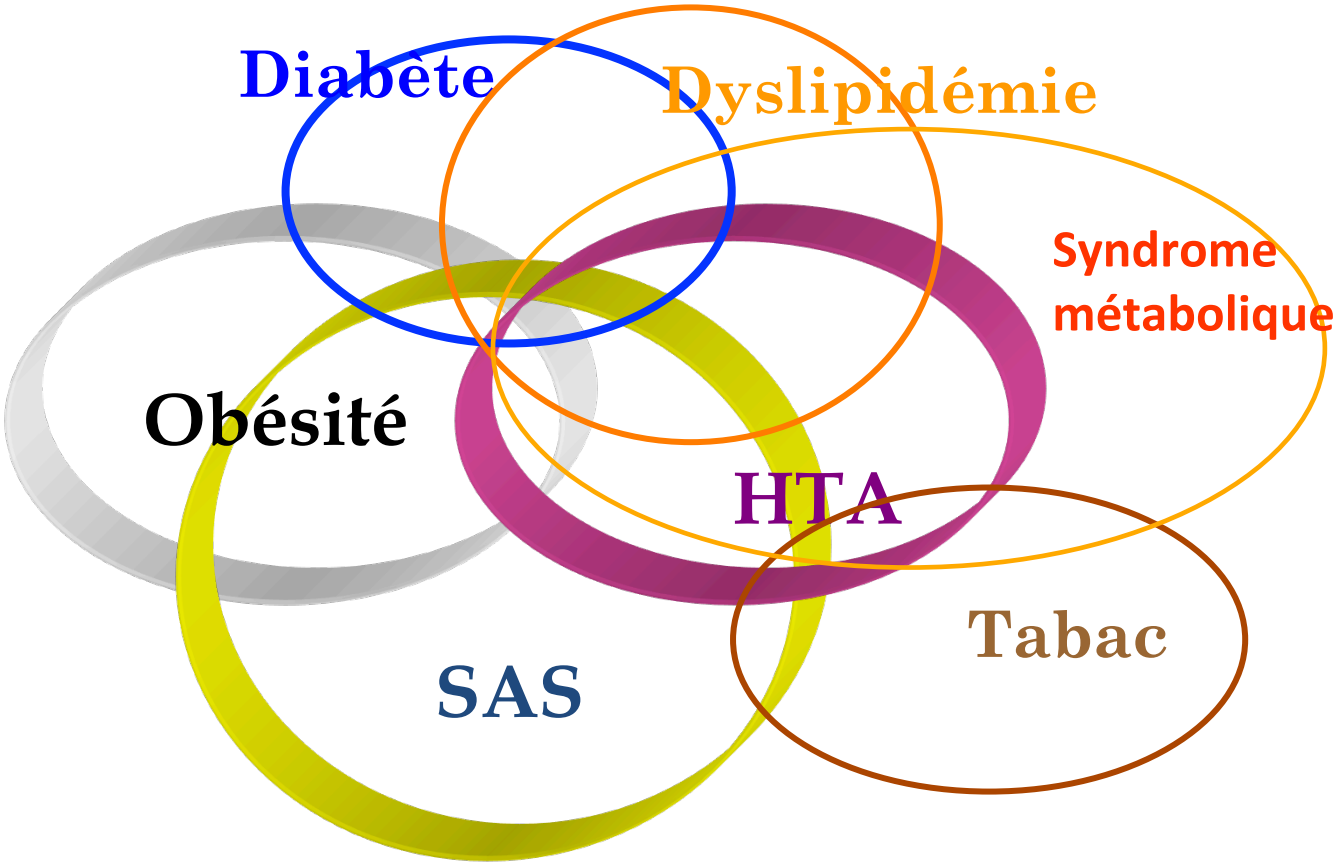
SAS et risque cardio-vasculaire	P. ESCOURROU, Clamart
SAS et troubles du rythme	J-M. DAVY, Montpellier
SAS et insuffisance cardiaque	M. GALINIER, Toulouse
Comment dépister et prendre en charge le SAS chez un malade cardiaque ?	Ph. BORDIER , Bordeaux

Facteurs de risque cardiovasculaire

- Facteurs de risque non modifiables:
  - Age (H>55, F>65)
  - Sexe (M>F)
  - Antécédents familiaux
  - Taille
- Facteurs de risque « théoriquement » modifiables
  - Tabagisme
  - Poids (>30kg/m²)
  - Sédentarité
- Situation où une intervention spécifique a été montrée bénéfique
  - Hypertension artérielle
  - Dyslipidémie
  - Diabète

–SAHOS??

SAS et risque CV: facteurs confondants



Etudes longitudinales de SAOS avec association significative à une comorbidité:

	Total	Outcome				
		Mortality	CV events[a]	Stroke[b]	Diabetes	Depression
Study, total number	26	10	9	4	2	1
Demographics						
Age	14/23	7/8	5/8	2/4	0/2	0/1
Sex	4/18	2/7	1/5	1/3	0/2	0/1
Race	1/8	1/2	0/4	0/2	–	–
History at baseline						
CV comorbidities	8/18	4/8	3/6	1/2	0/1	0/1
Pulmonary disease	4/9	4/6	0/3	–	–	–
Diabetes	6/20	3/8	2/8	1/3	–	0/1
Smoking status	4/22	1/7	2/9	1/3	0/2	0/1
Clinical exam						
BMI	3/24	3/10	0/8	0/4	0/1	0/1
Blood pressure	5/21	2/7	2/9	0/3	1/1	0/1
Disease characteristics						
AHI or equivalent	18/26	7/10	6/9	3/4	1/2	1/1
Ox desaturation	3/7	1/4	1/1	1/2	–	–
Arousal index	1/2	0/1	–	1/1	–	–
Sleep duration	1/1	1/1	–	–	–	–
OSA treatment	7/10	2/3	5/6	–	0/1	–
Time since baseline	1/1	–	1/1	–	–	–

Kendzerska Sleep Med Rev 2014

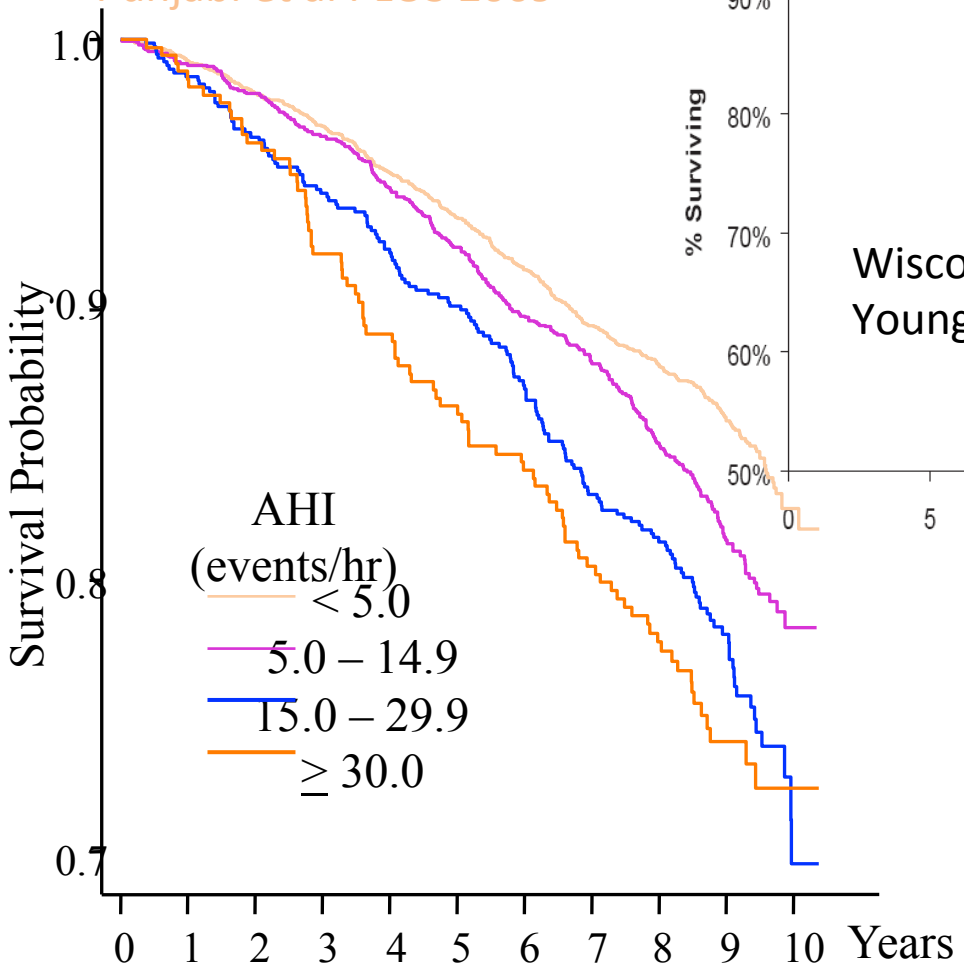
Etudes épidémiologiques
SAHOS et mortalité

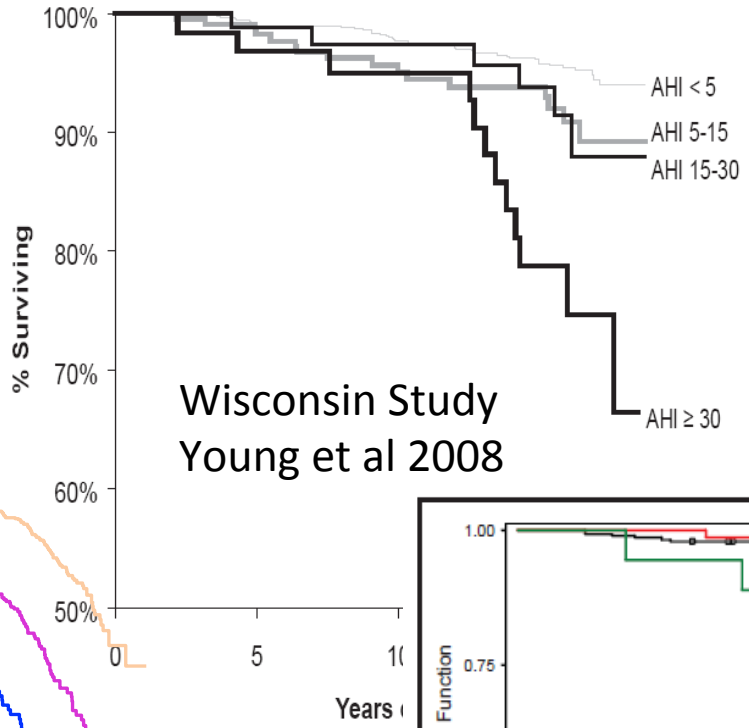
Cohortes cliniques	ref	prédicteurs	Non contrôlés
	Lavie 2005	AHI, âge <50, BMI	CV comorbidités
	Marti, 2002	AHI, âge>60	
	Nakamura 2009	AHI, âge, sexe	tabac, CV comorbidités
	Kenderska 2014	Desat, TTS, éveils, somnolence	

Population générale	ref	cohortes	prédicteurs
1522 sujets	Young Sleep 2008	Wisconsin SC	AHI
6342	Punjabi PLOS 2009	Sleep Heart Health	AHI (H)
380	Marshall Sleep 2008	Busselton	AHI, âge, PA, DT2, tabac

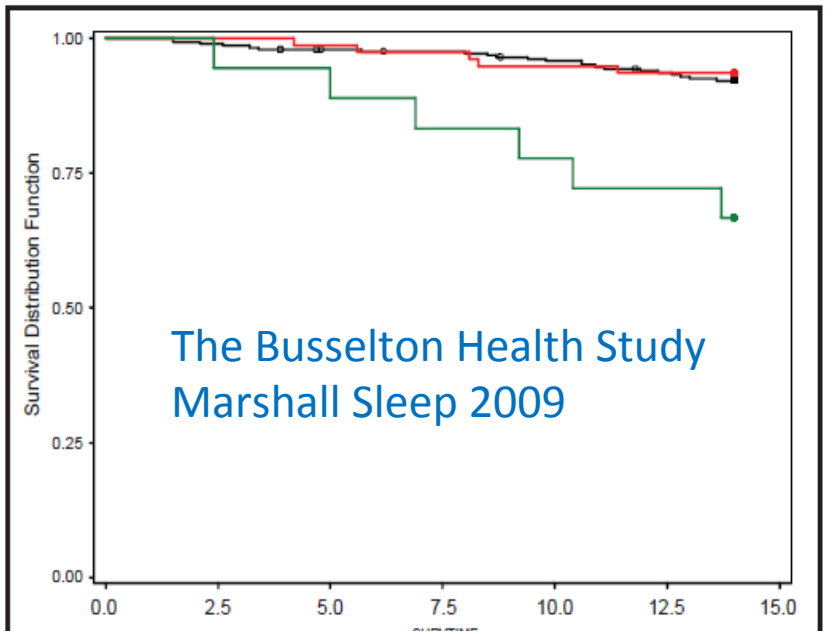
SAHOS: mortalité globale (études de population)

Sleep Heart Health Study
Punjabi et al PLOS 2009





Wisconsin Study
Young et al 2008



The Busselton Health Study
Marshall Sleep 2009

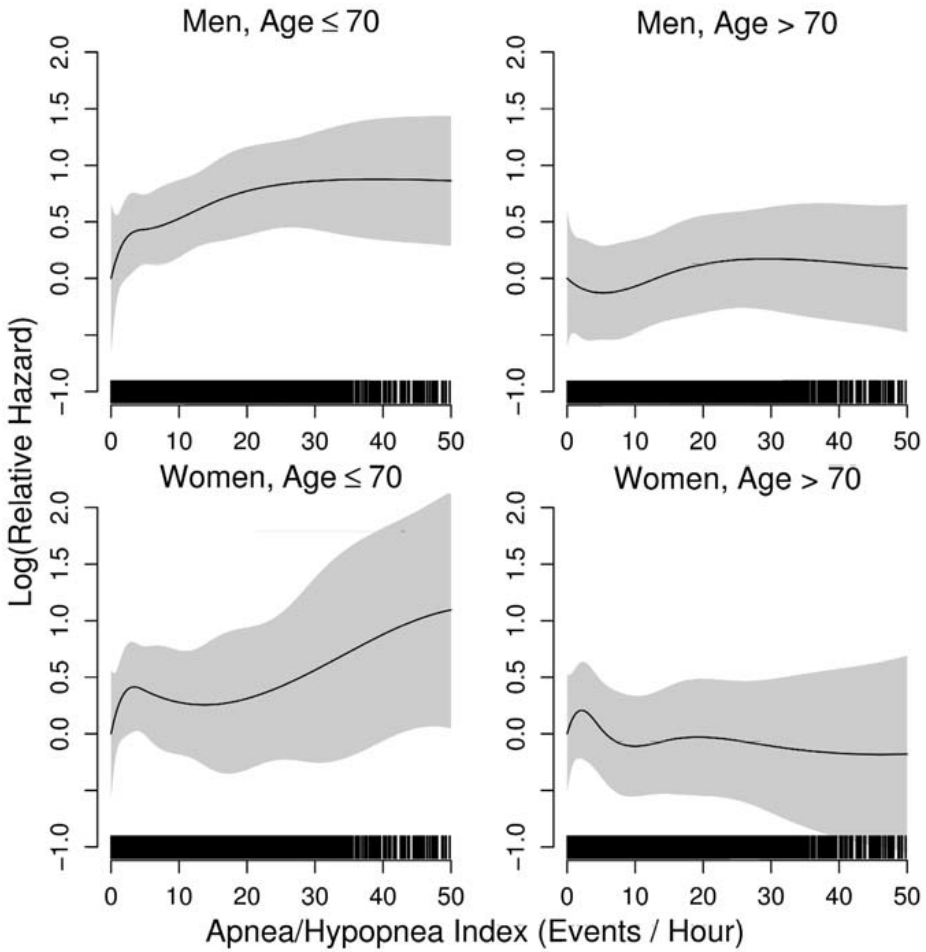
Sleep-Disordered Breathing and Mortality: A Prospective Cohort Study

Naresh M. Punjabi PLOS 2009

Augmentation de la mortalité chez **les hommes** < 70ans

Mais pas pour les femmes

	Men	Women
AHI	Hazard Ratios	Hazard Ratios
< 5.0	1.00	1.00
5.0 – 14.9	1.01 (0.83–1.24)	0.83 (0.66–1.04)
15.0 – 29.9	1.27 1.00–1.65	1.01 (0.73–1.38)
≥ 30	1.54 (1.15–2.08)	1.40 (0.89–2.22)



Etudes épidémiologiques
SAHOS et morbi-mortalité CV

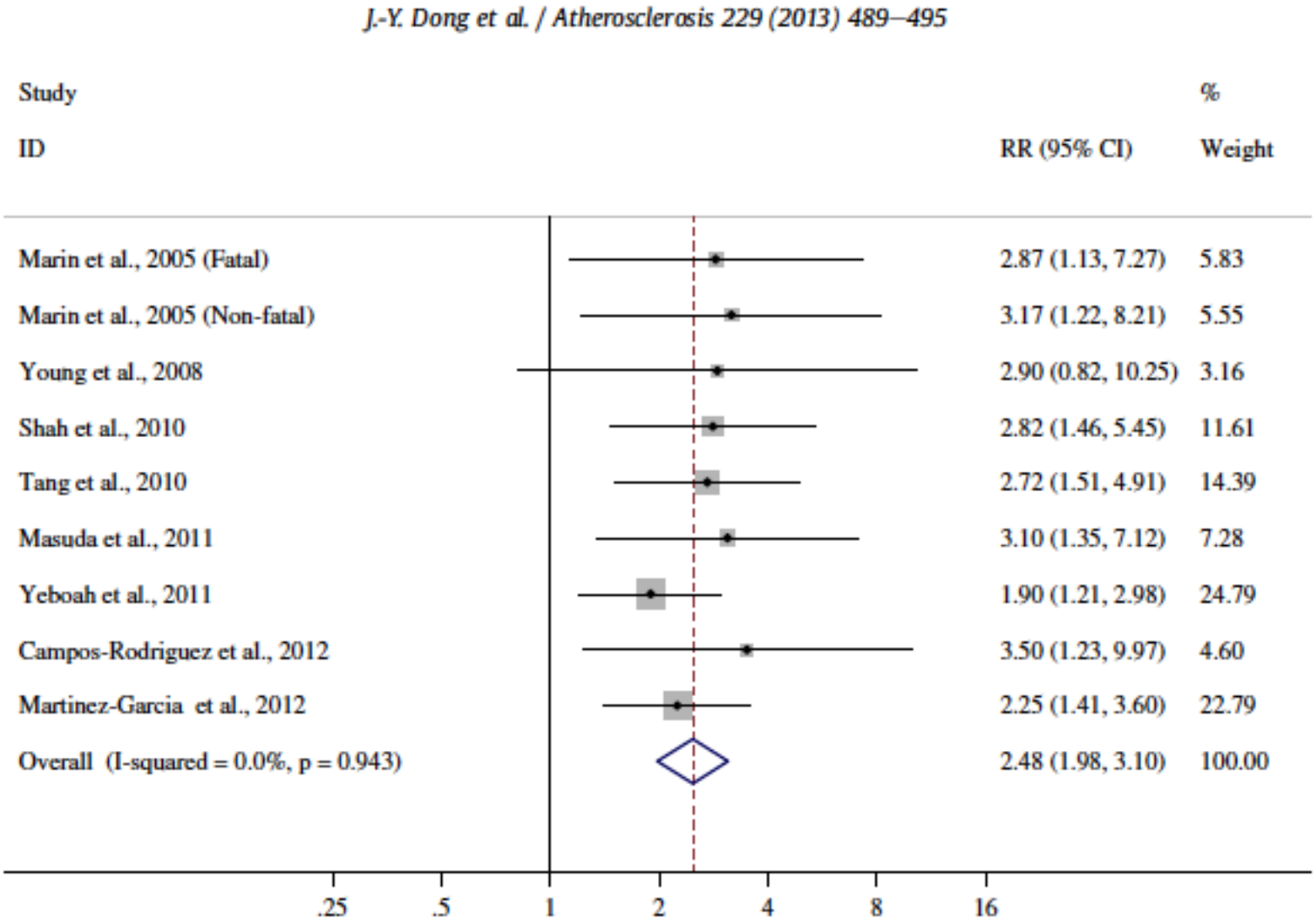
Acc CV fatals et non fatals	ref	prédicteurs
Population clinique	Peker 2002, 2006	IAH, age, H
	Buchner 2007	IAH
	Marin 2005	IAH, age, H, tabac
	Shah 20&0	IAH, age, tabac
Population générale		
	Chami 2011	IAH
	Gottlieb 2010	IAH, H

CONCLUSION (1)
Association du SAOS avec la mortalité:

	Cohorte clinique		**Cohorte de population**	
	Non Ajustée	Ajustée	Non Ajustée	Ajustée
Mortalité (toute cause)	Oui	Oui	Oui	Oui *
Morbi-mortalité CV	Oui	Oui	Oui	Oui #

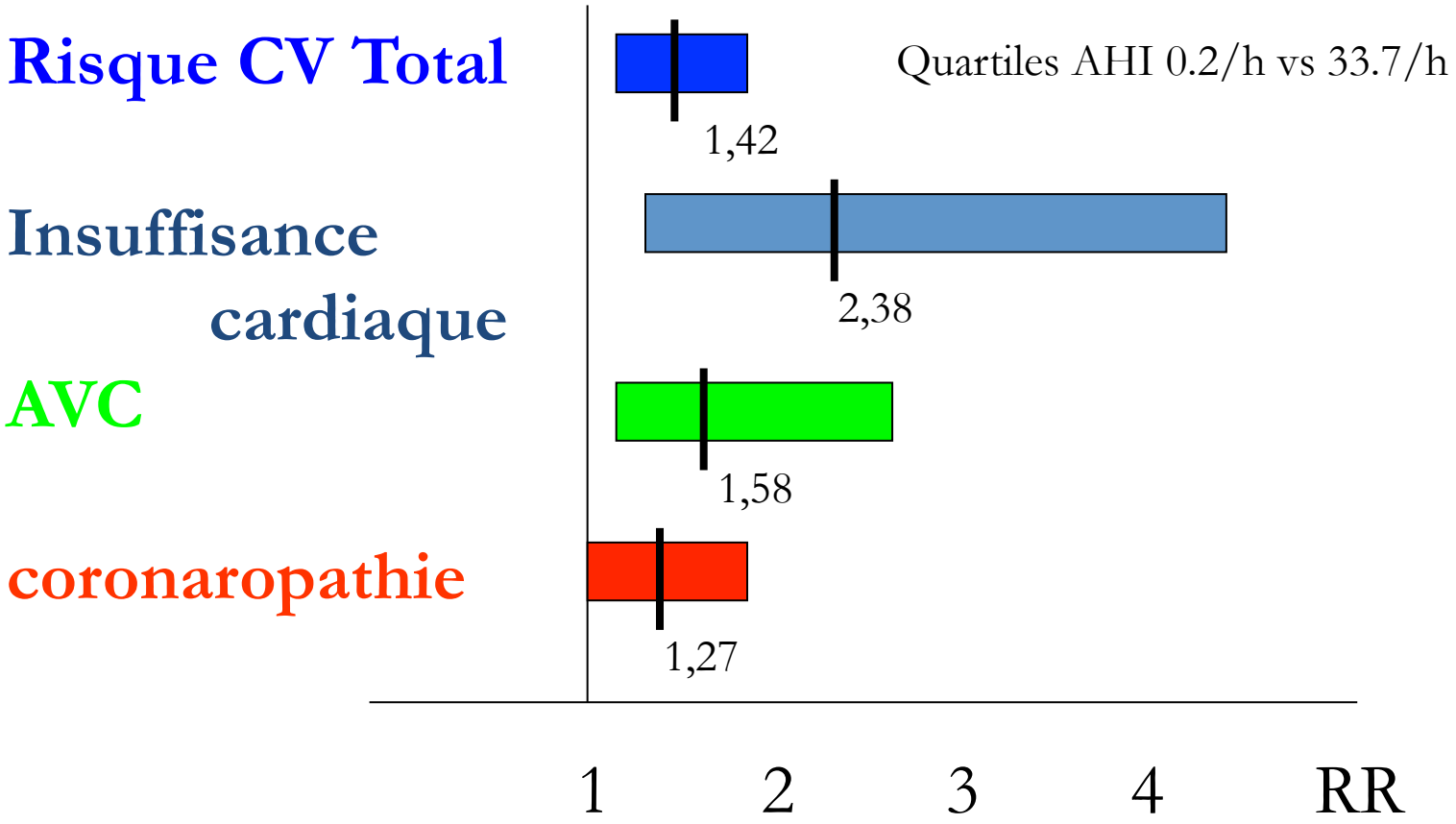
* chez les hommes
# chez les hommes de moins de moins de 70 ans.

Méta-analyse de la relation SAHOS et toutes maladies CV



SAHOS et risque CV

Sleep Heart Health Study n= 6424



SHAHAR E. Am J Respir Crit Care Med Vol 163. pp 19–25, 2001

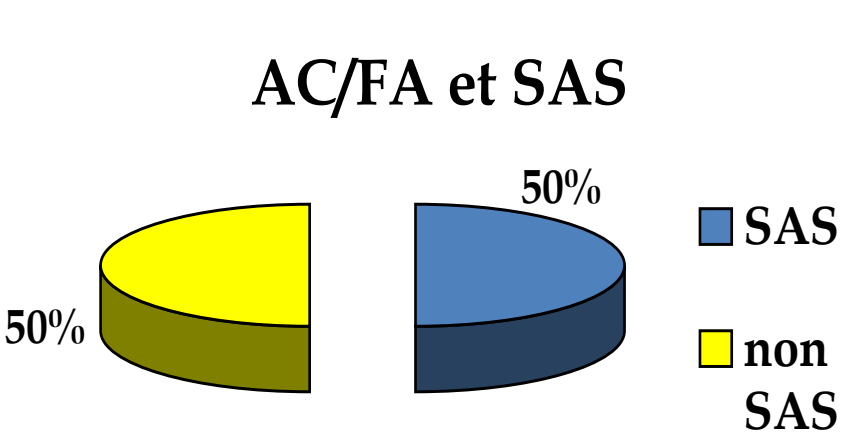
Prévalence du SAS en Population générale

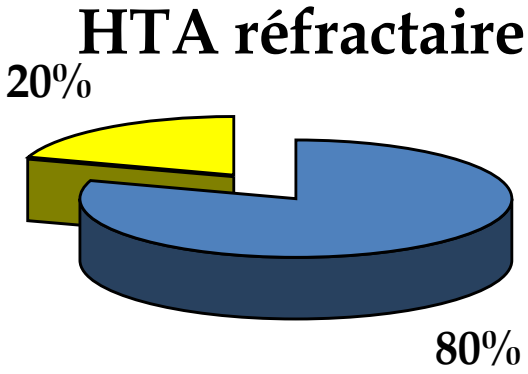
pays	référence	N	ethnie	prevalence homme	femme
USA	Young [105]	602	caucase	4,0%	2,0%
	Bixler [110] [107]	1741$	caucase	3,9%	1,2%
Australie	Bearpak [211]	485*	caucase	3,1%	_
Inde	Udwadia [212]	250	indien	7,5%	4,5%
Chine	Ip [213, 214]	258	chine	4,1%	2,1%
Corée	Kim [215]	457	coréen	4,5%	2,3%
Espagne	Duran [216]	555$	caucase	3,4%	3%

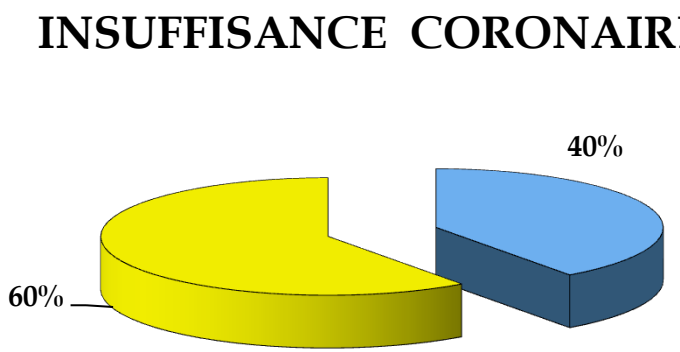
*Polygraphie (polysomnographie pour les autres études)
$ Hypersomnolence et IAH ≥10 (IAH ≥5 pour les autres études)

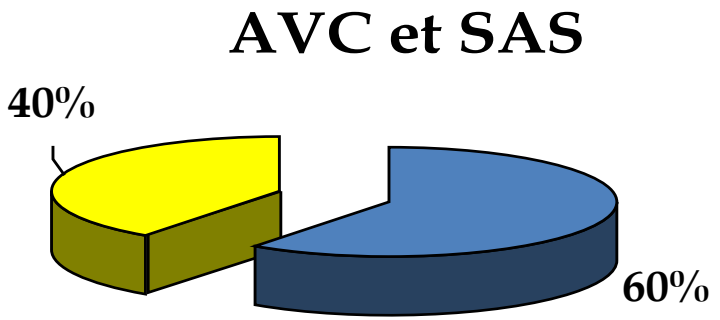
Escourrou P. et al, EMC Pneumologie 2015

Prévalence du Syndrome d'Apnées du Sommeil dans la Pathologie Cardiovasculaire

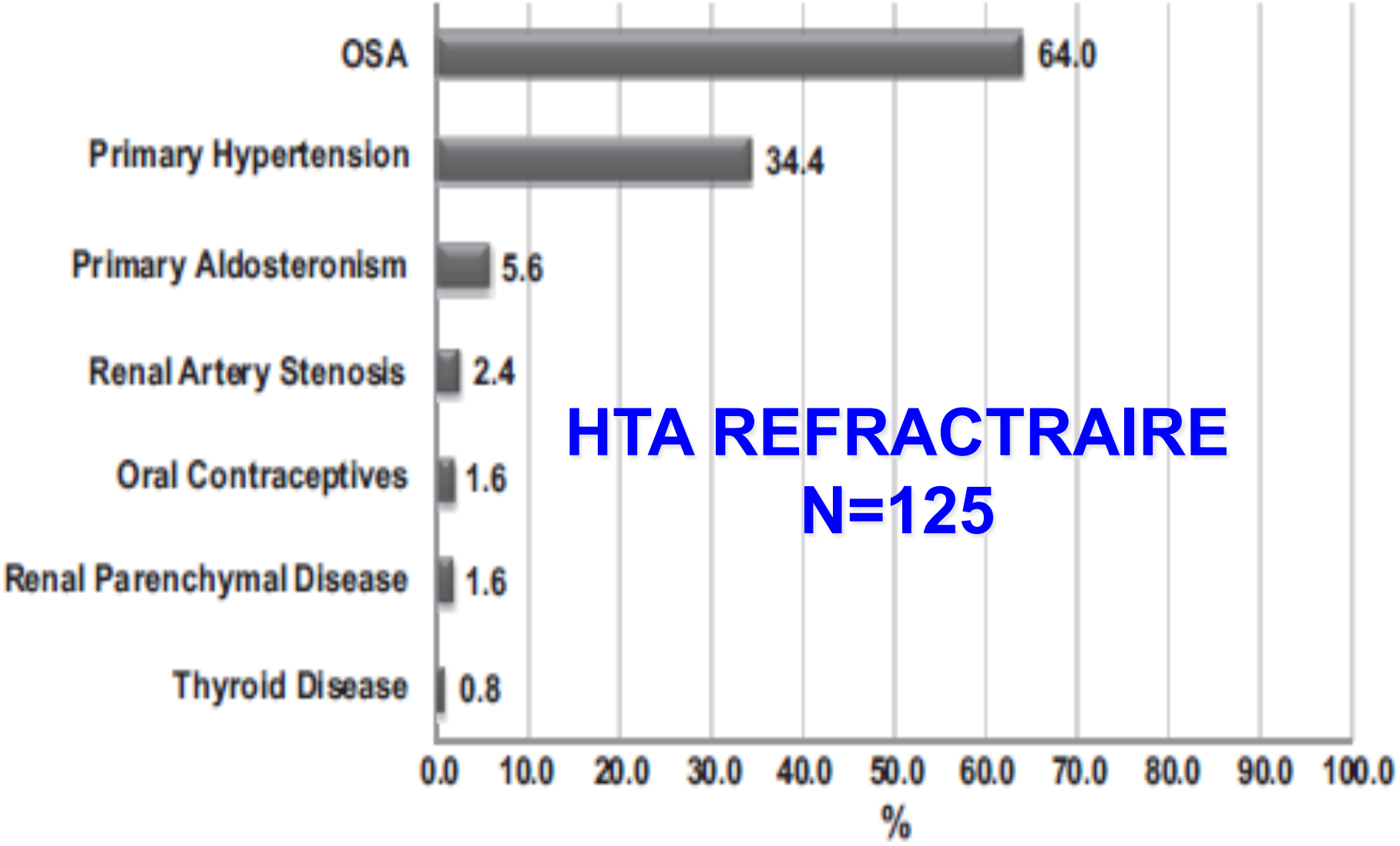








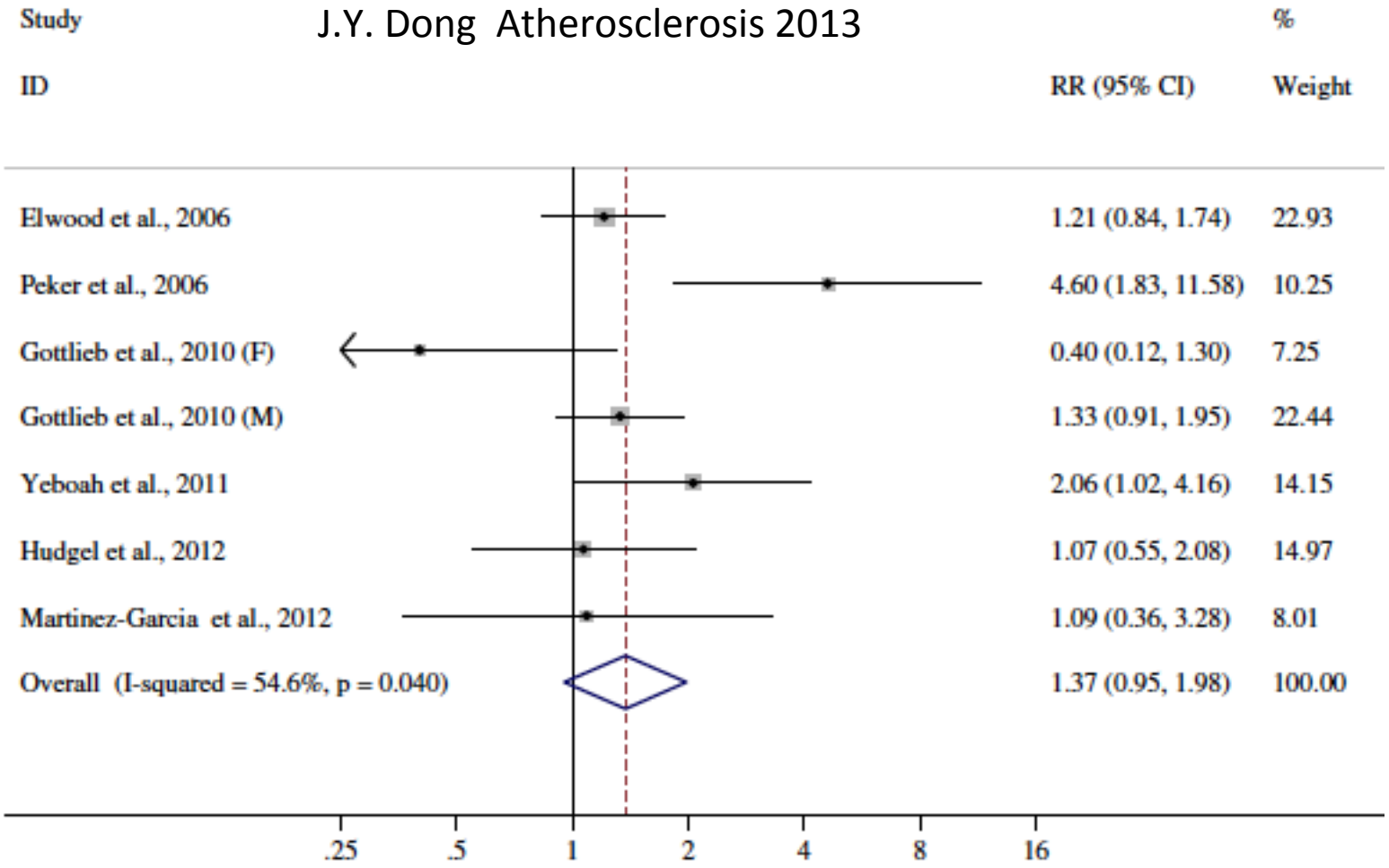
SAHOS et HTA réfractaire



Pedrosa, Hypertension 2012

Méta-analyse de la relation SAOS et coronaropathies

J.Y. Dong Atherosclerosis 2013



Obstructive Sleep Apnea and the Risk of Sudden Cardiac Death

A Longitudinal Study of 10,701 Adults

Apoor S. Gami,

Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation

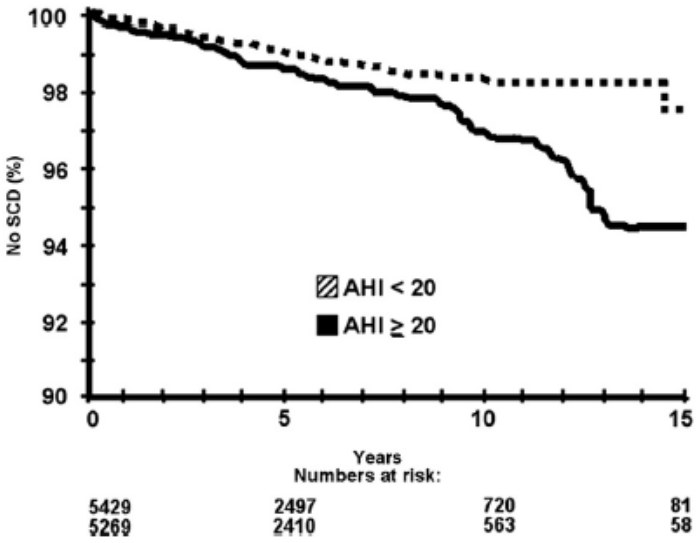


Figure 1 Survival Based on AHI

Survival free of fatal or resuscitated sudden cardiac death (SCD) in the total study population, based on the apnea-hypopnea index (AHI) threshold determined by classification and regression tree analysis (AHI <20 vs. AHI ≥20). Hazard ratio: 1.60, 95% confidence interval: 1.14 to 2.24; p = 0.007.

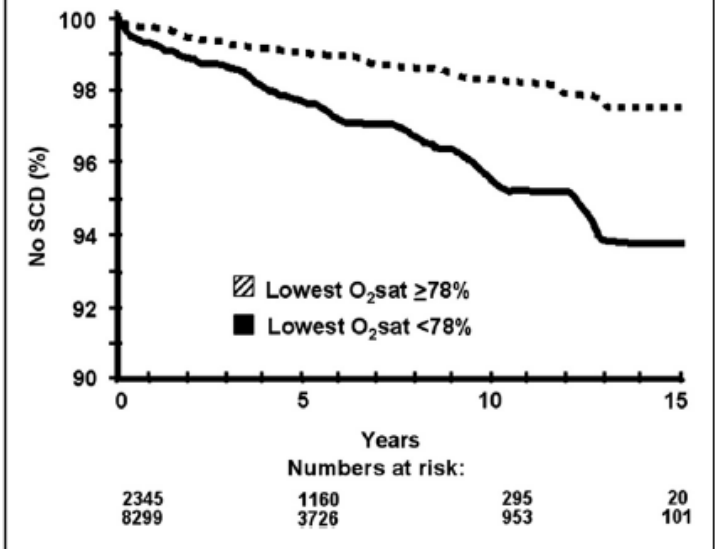


Figure 2 Survival Based on O_2sat

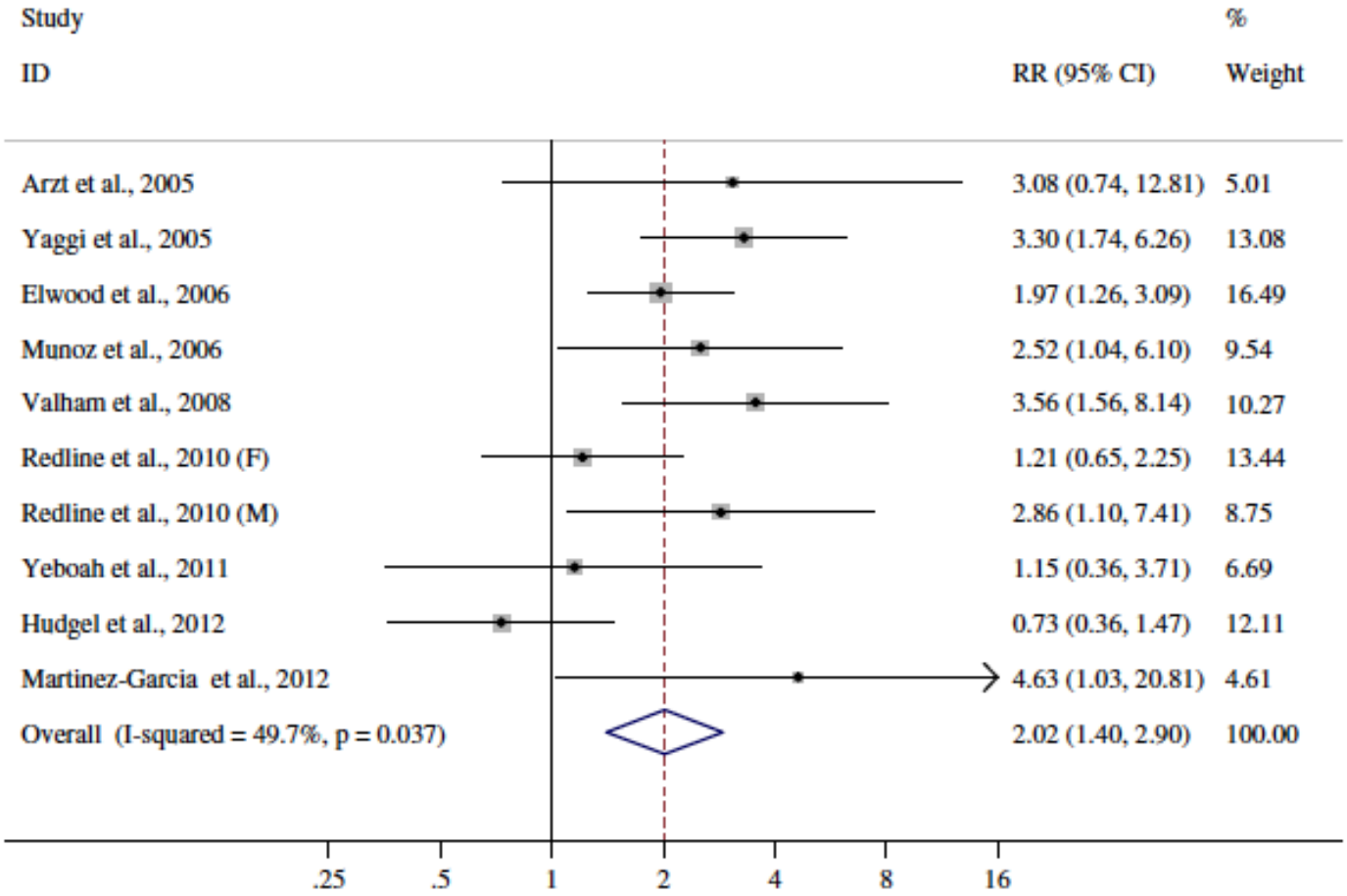
Survival free of fatal or resuscitated sudden cardiac death (SCD) in the total study population, based on the lowest nocturnal oxygen saturation (O_2sat) threshold determined by classification and regression tree analysis (≥78% vs. <78%). In multivariate analysis, hazard ratio = 1.81, 95% confidence interval: 1.28 to 2.56; p = 0.0008.

Etudes épidémiologiques
SAHOS et AVC

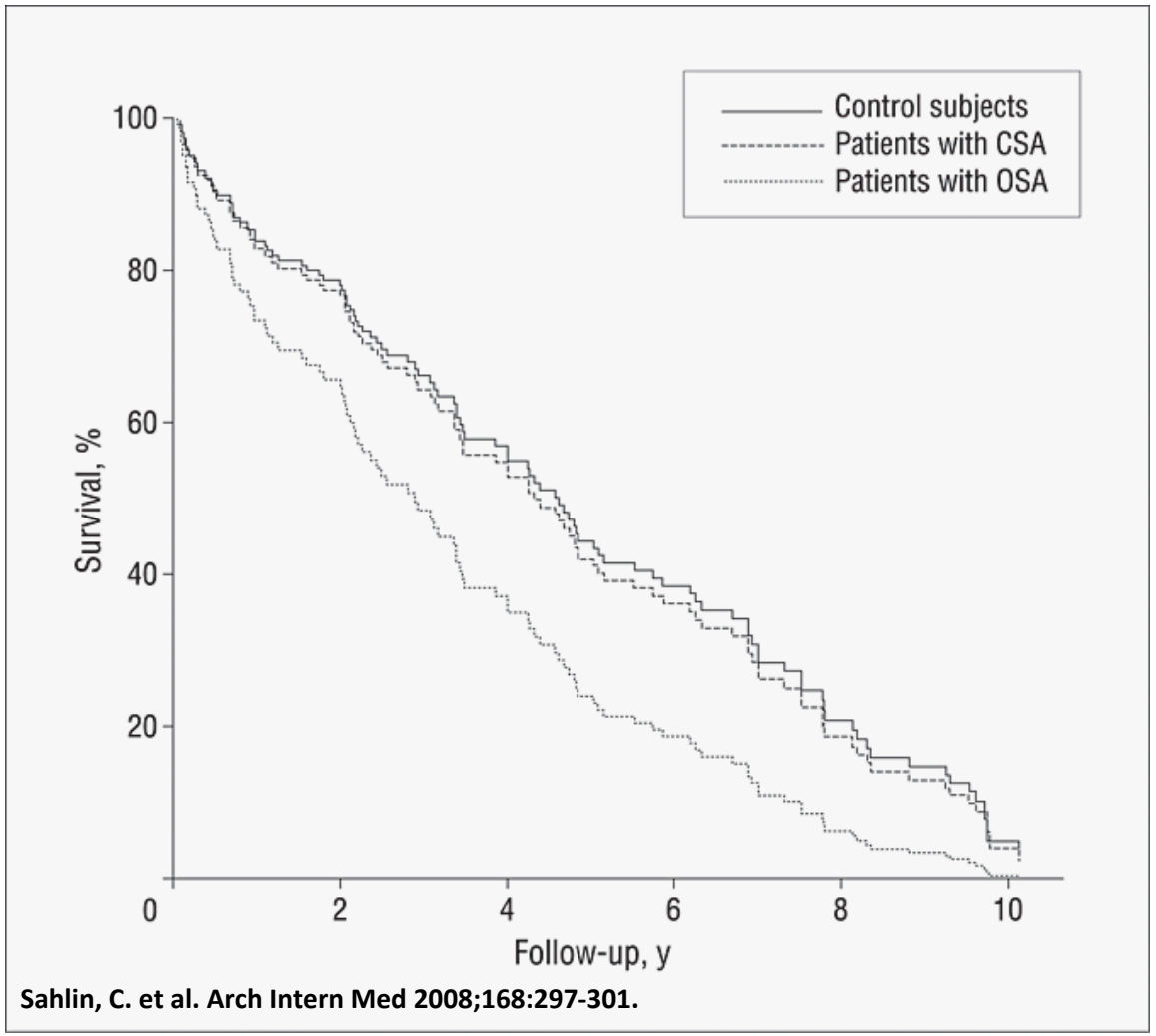
AVC	ref	Facteurs prédictifs
population clinique	Yaggi 2005	AHI, âge
population générale	Artz 2005	ns
	Munoz 2006	AHI, PA
	Redline 2010 (H)	AHI, Age
	Redline 2010 (F)	CV comorbidités, âge, DT2

Méta-analyse de la relation SAHOS et AVC

J.-Y. Dong et al. / Atherosclerosis 229 (2013) 489–495



Survie après AVC et SAS



Sahlin, C. et al. Arch Intern Med 2008;168:297-301.

STROKE: Survival curves after adjustments for age, sex, body mass index, current smoking, hypertension, diabetes mellitus, atrial fibrillation, Mini-Mental State Examination score, and Barthel index of activities of daily living

CONCLUSION
Association SAS et morbidité CV

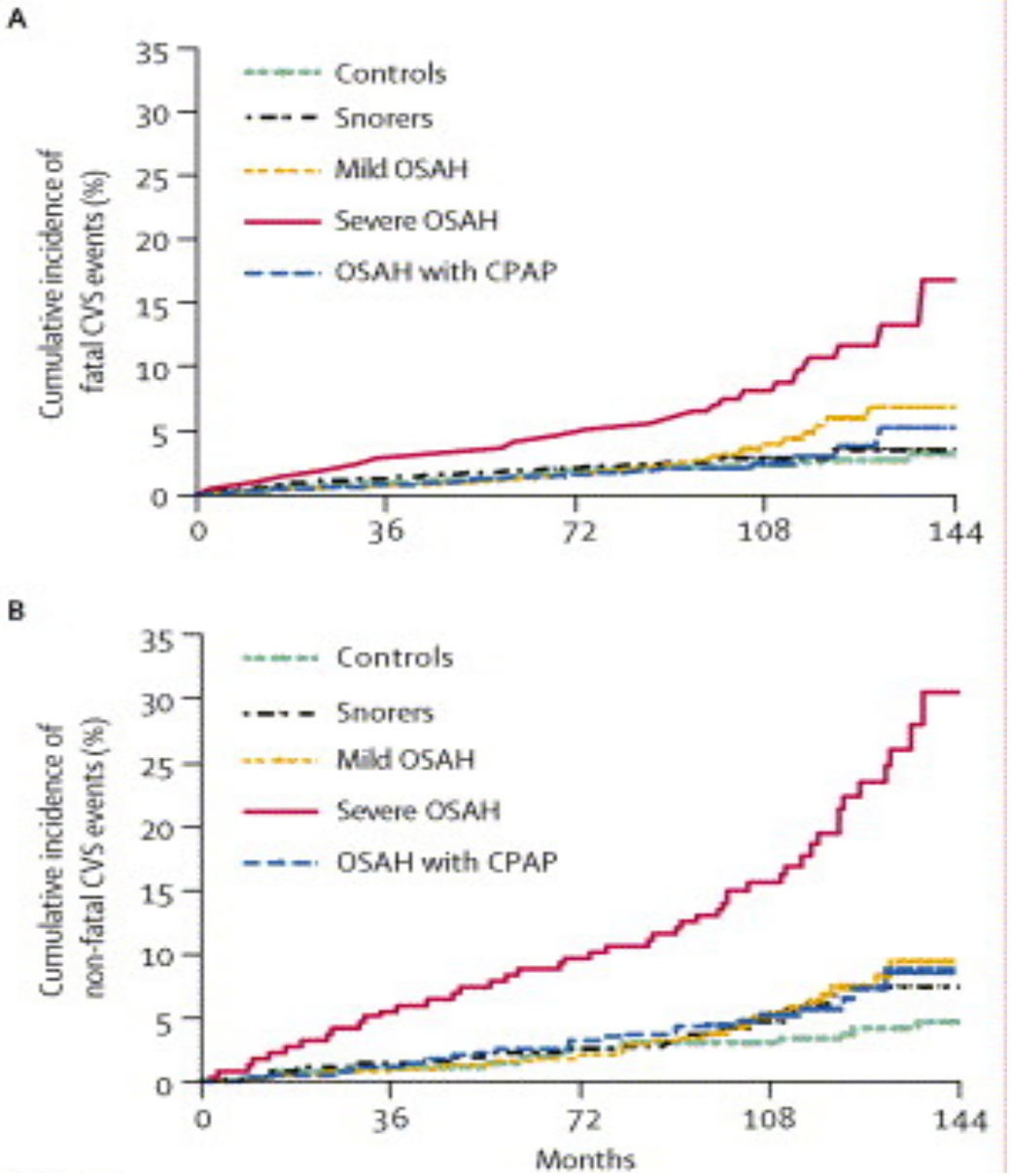
	Étude transversale (Prévalence)		Étude prospective (Incidence)	
	Non Ajustée	Ajustée	Non Ajustée	Ajustée
AVC	Oui	Oui	Oui	Oui *
Coronaropathie	Oui	Oui	Oui	Oui #
FA	Oui	Oui	Oui	Oui
Morbi-mortalité CV	-	-	Oui+++	discuté

* chez les hommes
# chez les hommes de moins de moins de 70 ans.

Effet de la PPC sur les complications CV

	Outcomes	Treatment	Patient population	Duration of follow-up	Key findings	
Hypertension*						
Durán-Cantolla et al (2010)[56]	Blood pressure	Therapeutic CPAP vs sham CPAP	340 patients with untreated hypertension and AHI at least 15/h	3 months	1·5 mm Hg decrease in mean ABPM, 2·1 mm Hg decrease in systolic ABPM, and 1·3 mm Hg decrease in diastolic ABPM	+/-
Barbé et al (2010)[57]	Blood pressure	Therapeutic CPAP vs conservative treatment	359 hypertensive patients with AHI at least 20/h, without daytime sleepiness (Epworth Sleepiness Scale score <11)	1 year	Significant decrease in clinic diastolic blood pressure of 2·19 mm Hg. A decrease of 3·5 mm Hg was observed in patients who used CPAP more than 5·6 h per night	+
Lozano et al (2010)[58]	Blood pressure	Therapeutic CPAP vs conservative treatment	75 patients with resistant hypertension and AHI at least 15/h	3 months	4·9 mm Hg decrease in diastolic ABPM in the CPAP group. Decrease of 6·9 mm Hg in diastolic ABPM and 9·7 mm Hg in systolic ABPM noted in patients adherent to CPAP longer than 5·8 h per night	+
Martínez-García et al (2012)[59]	Blood pressure	Therapeutic CPAP vs conservative treatment	210 patients with resistant hypertension and AHI at least 15/h	3 months	No changes in ABPM. More patients with CPAP recovered a dipper pattern. Patients with adherence longer than 4 h showed a significant decrease of 5·5 mm Hg in systolic ABPM and 4·2 mm Hg in diastolic ABPM	+
Stroke						
Hsu et al (2006)[60]	Neurological function	Therapeutic CPAP vs conservative treatment	30 patients with AHI at least 15/h and acute stroke	6 months	No change in neurological function, sleepiness, or health status in the CPAP group. Patients allocated to CPAP had very low adherence (average 1·4 h per night)	0 (obs)
Ryan et al (2011)[61]	Neurological function	Therapeutic CPAP vs rehabilitation	48 patients with AHI at least 15/h admitted for rehabilitation within 3 weeks of stroke onset	1 month	CPAP treatment improved functional and motor, but not neurocognitive outcomes	+
Parra et al (2011)[62]	Neurological function	Therapeutic CPAP vs conservative treatment	140 patients with AHI at least 20/h and acute, first-ever ischaemic stroke	2 years	Cardiovascular event-free survival and neurological recovery was similar in both groups	0
Heart failure						
Kaneko et al (2003)[63]	LVEF	Therapeutic CPAP vs conservative treatment	24 patients with AHI at least 20/h and LVEF less than 45%	1 month	LVEF increased from 25·0% to 33·8% with CPAP	+
Egea et al (2008)[64]	LVEF	Therapeutic CPAP vs sham CPAP	60 patients with AHI higher than 10/h and chronic heart failure with LVEF less than 45%	3 months	LVEF increased from 28·8% to 31·0% with CPAP	+/-
Arias et al (2005)[65]	Cardiac function	Therapeutic CPAP vs sham CPAP	27 patients with AHI at least 10/h and LVEF less than 50%, and 15 healthy controls	Crossover design, 12 weeks on CPAP and 12 weeks on sham CPAP	At baseline, an abnormal left ventricular filling pattern was present in 15 of 27 patients with OSA and only 3 of 15 in the control group. CPAP significantly improved several diastolic abnormalities	+
Smith et al (2007)[66]	LVEF and exercise capacity	Auto-titrating CPAP vs sham CPAP	26 patients with AHI at least 15/h and LVEF less than 45%	Crossover design, 6 weeks on autotitrating CPAP and 6 weeks on sham CPAP	Autotitrating CPAP did not improve cardiac function, exercise capacity, or neurohormonal activation. CPAP compliance was low (3·5 h per night)	0 (obs)
Mansfield et al (2004)[67]	LVEF, overnight UNE excretion, and quality of life	Therapeutic CPAP vs conservative treatment	55 patients with AHI greater than 5/h and LVEF less than 55%	3 months	CPAP treatment was associated with significant improvements in LVEF (1·5 [SD 1·4%] vs 5·0 [1·0%], p=0·04), and with reductions in overnight UNE excretion and improvements in quality of life	
Composite						
Barbé et al (2012)[68]	Incidence at a composite endpoint (hypertension or cardiovascular events)	Therapeutic CPAP vs conservative treatment	725 patients with AHI at least 20/h, without daytime sleepiness (Epworth score <11)	4 years	Incidence of the composite endpoint was similar in both groups (9·20 vs 11·02 per 100 person-years). In a post-hoc analysis, patients who used CPAP longer than 4 h per night showed a significant decrease in the incidence of the composite endpoint	+ (>4H)

PPC et évènements CV



-1600 sujets
-suivie de cohorte observationnelle
-suivie de 10 ans +/- 1.6

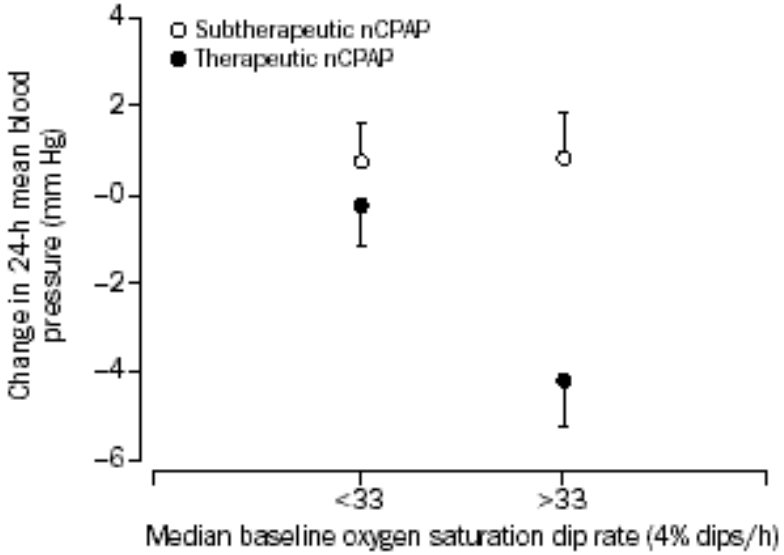
OR 2,87 (CI 1,17-7,51)
OR 3,17 (1,12-7,51)

Marin et al, Lancet 2005

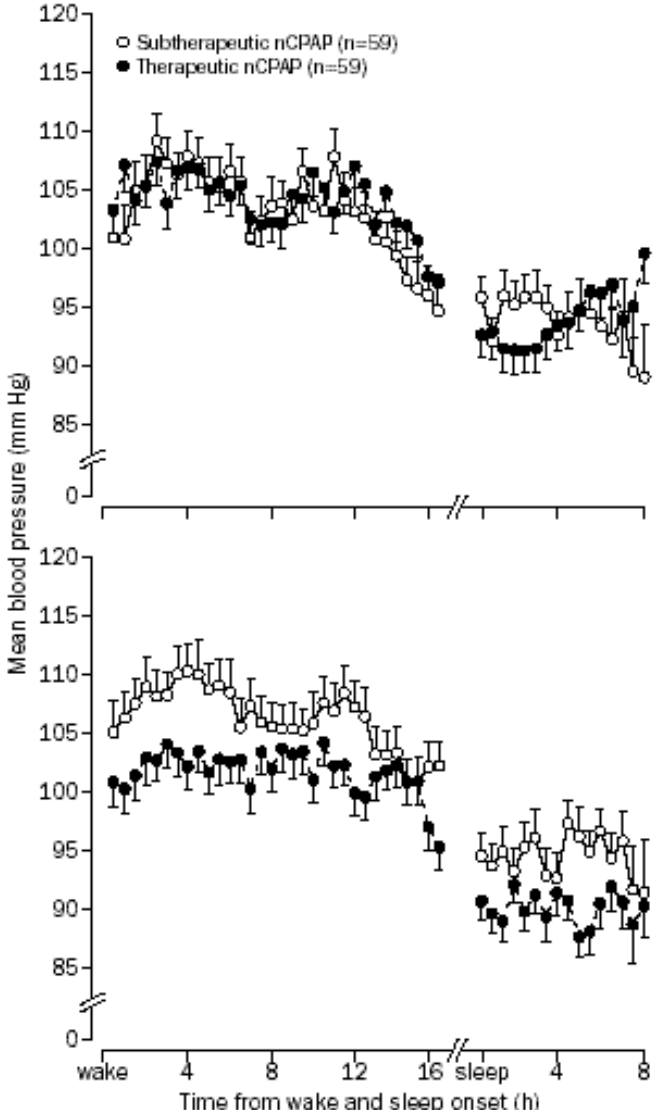
Effet du traitement du SAS sur la Pression artérielle

Justin C T Pepperell , Lancet 2001; 359: 204–10

étude randomisée, parallèle avec PPC
thérapeutique ■ *et subthérapeutique (placebo)* □
4 semaines de traitement
Effet maximum lorsque l'index de désaturation est >33/h

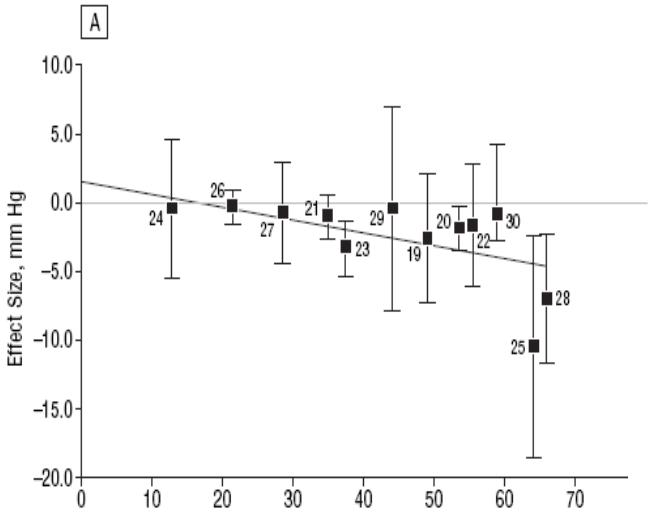


Modification de la PA moyenne sur 24/h selon l'index de désaturation



PA moyenne avant traitement (haut) et aprés traitement (bas) actif et placébo

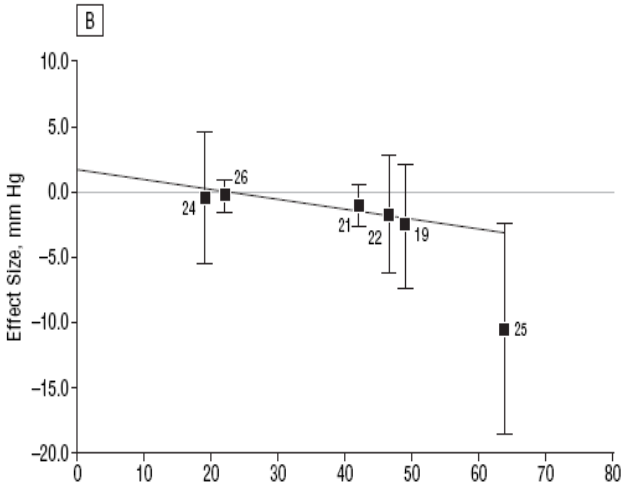
Impact de la PPC sur la PA dans le SAOS: méta-analyse



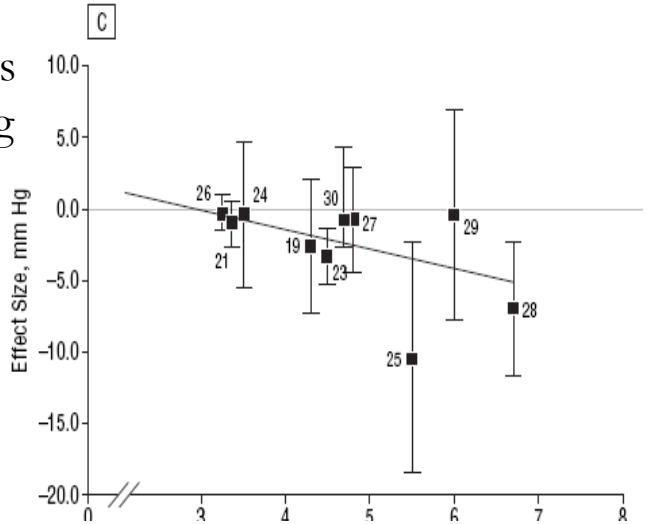
IAH /h

572 pts de 12 essais contrôlés
Baisse de PAM = 1,69mmHg
Dépend:

- sévérité IAH
- observance
- micro-éveils



Index de micro-éveils



Utilisation de la PPC h/nuit

Haentjens,
Arch Int Med 2007

Pronostic:
La baisse de 1à 2 mmHg a un effet favorable sur le risque CV: AVC, IDM et IC

CHEST 2014 Original Research

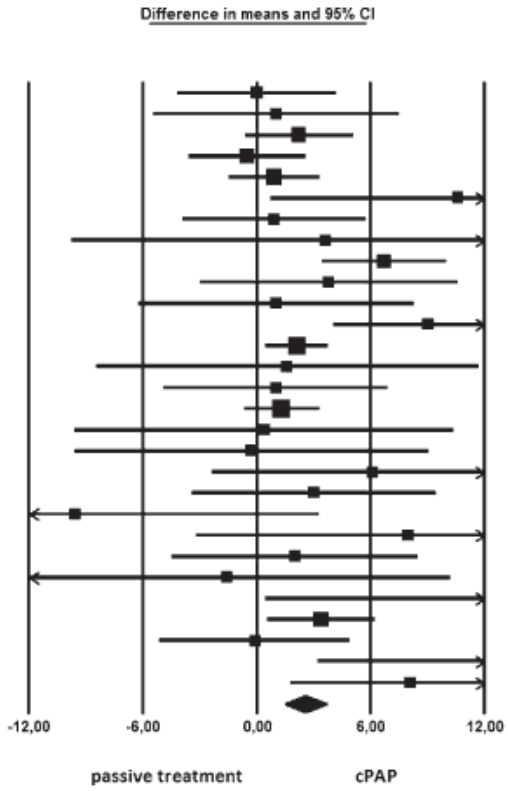
SLEEP DISORDERS

Effect of CPAP on Blood Pressure in Patients With OSA/Hypopnea

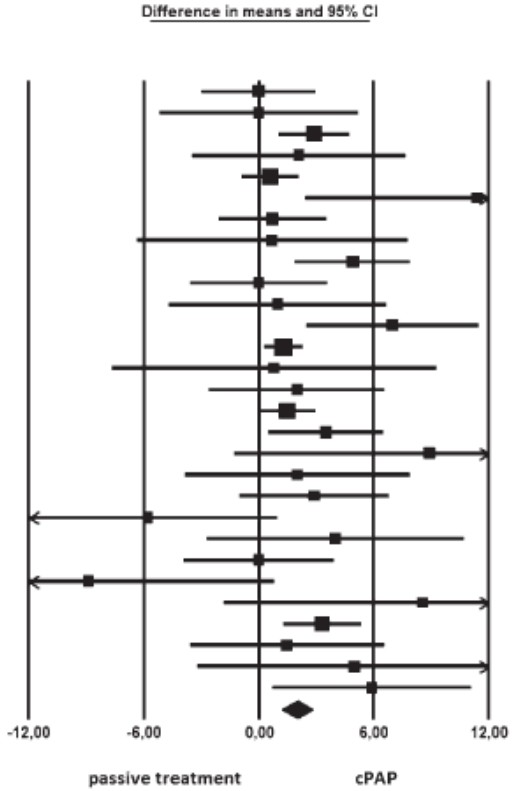
A Systematic Review and Meta-analysis

Cristiano Fava, MD, PhD; Stefania Dorigoni, MD; Francesco Dalle Vedove, MD;

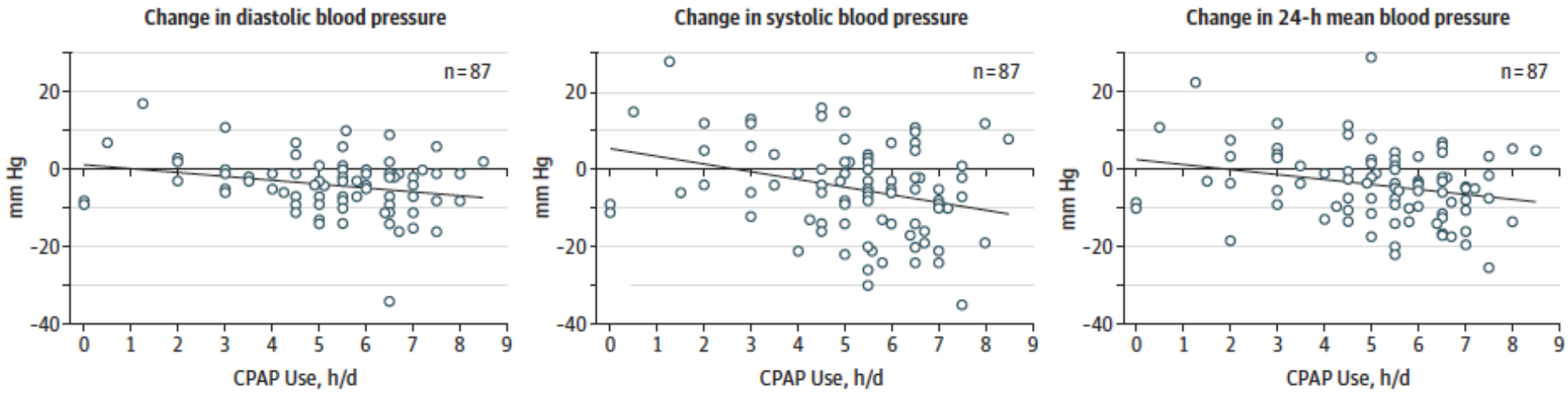
P systolique



P diastolique



Effect of CPAP on Blood Pressure in Patients With Obstructive Sleep Apnea and Resistant Hypertension
The HIPARCO Randomized Clinical Trial
Miguel-Angel Martinez-Garcia JAMA 2013



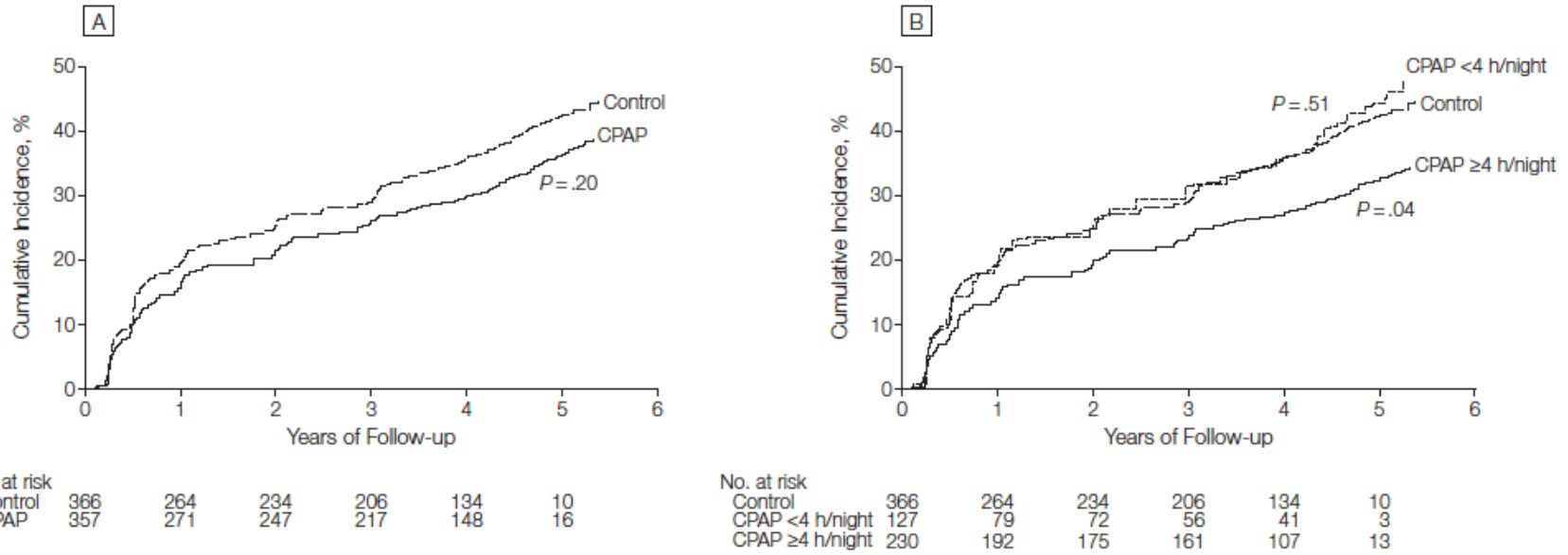
Correlation between continuous positive airway pressure (CPAP) use and change in blood pressure in the patients of the CPAP group who finished the follow-up.

Effet de la PPC sur l'HTA résistante - 5 à -10mmHg

- Lozano L, Tovar JL, Sampol G, et al. Continuous positive airway pressure treatment in sleep apnea patients with resistant hypertension: a randomized, controlled trial. J Hypertens 2010;28:2161–8.
- Pedrosa RP, Drager LF, LK GdP, et al. Effects of obstructive sleep apnea treatment on blood pressure in patients with resistant hypertension: a randomized trial. Chest2013;144:1487–94.

SAHOS non somnolent: la PPC diminue l'incidence de l'HT si l'observance est >4H/nuit (RCT)

Figure 2. Cumulative Incidence of Hypertension or Cardiovascular Events During Follow-up



A, Cumulative incidence of hypertension or cardiovascular events for the intervention groups during follow-up and the *P* value for the incidence density ratio of continuous positive airway pressure (CPAP) vs control (Wald test). B, Panel A with CPAP group stratified according to adherence (<4 vs ≥4 h/night) and the *P* values for their incidence density ratios in reference to the control group.

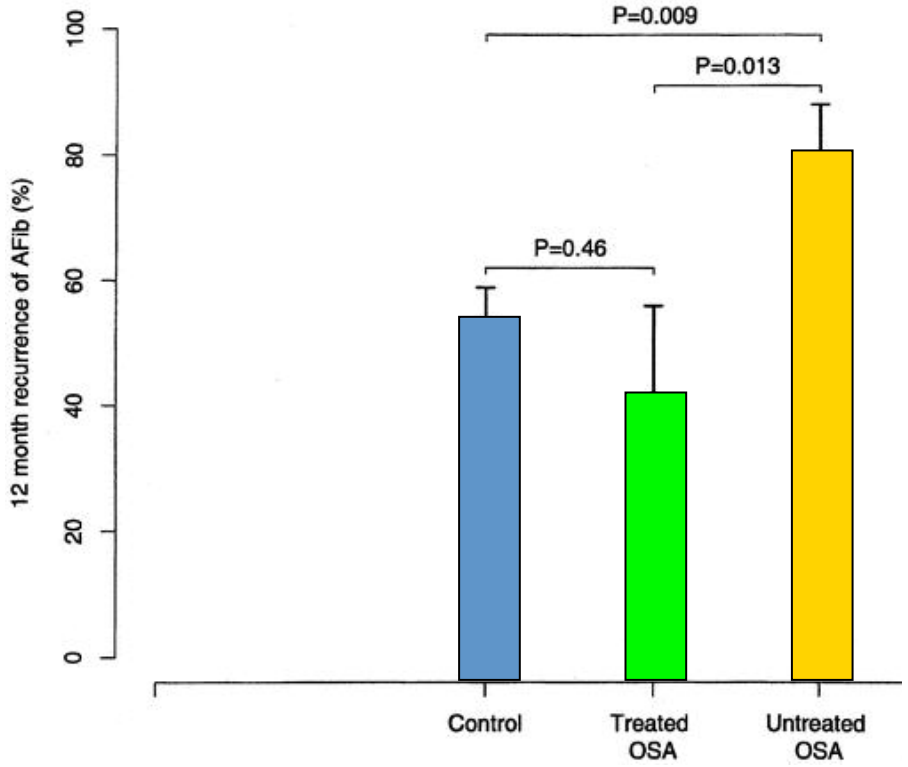
Barbe et al JAMA 2012

Effet de la PPC sur l'HTA

- L'efficacité du traitement par PPC sur la pression artérielle a été démontrée au cours de nombreux essais randomisés (niveau de preuve A).
- L'amplitude de l'effet (- 1,69 mmHg) est modeste mais cliniquement significative car elle correspond à une réduction importante du risque de survenue de nouveaux accidents cardio-vasculaires. (niveau de preuve A)
- l'effet de réduction de la pression artérielle est d'autant plus important: (niveau de preuve A)
  - que le SAHOS est sévère
  - Et que l'observance est importante

Le traitement du SAS par CPAP diminue le risque de récidive de FA après Cardioversion

- 53% de récidive à 1 an chez 79 **contrôles**
- 42% de récidive chez les 12 **SAS traités**
- 82% chez 27 **SAS non traités**



Kanagala, Circulation 2003

Cardiovascular Mortality in Obstructive Sleep Apnea in the Elderly: Role of Long-Term Continuous Positive Airway Pressure Treatment

A Prospective Observational Study

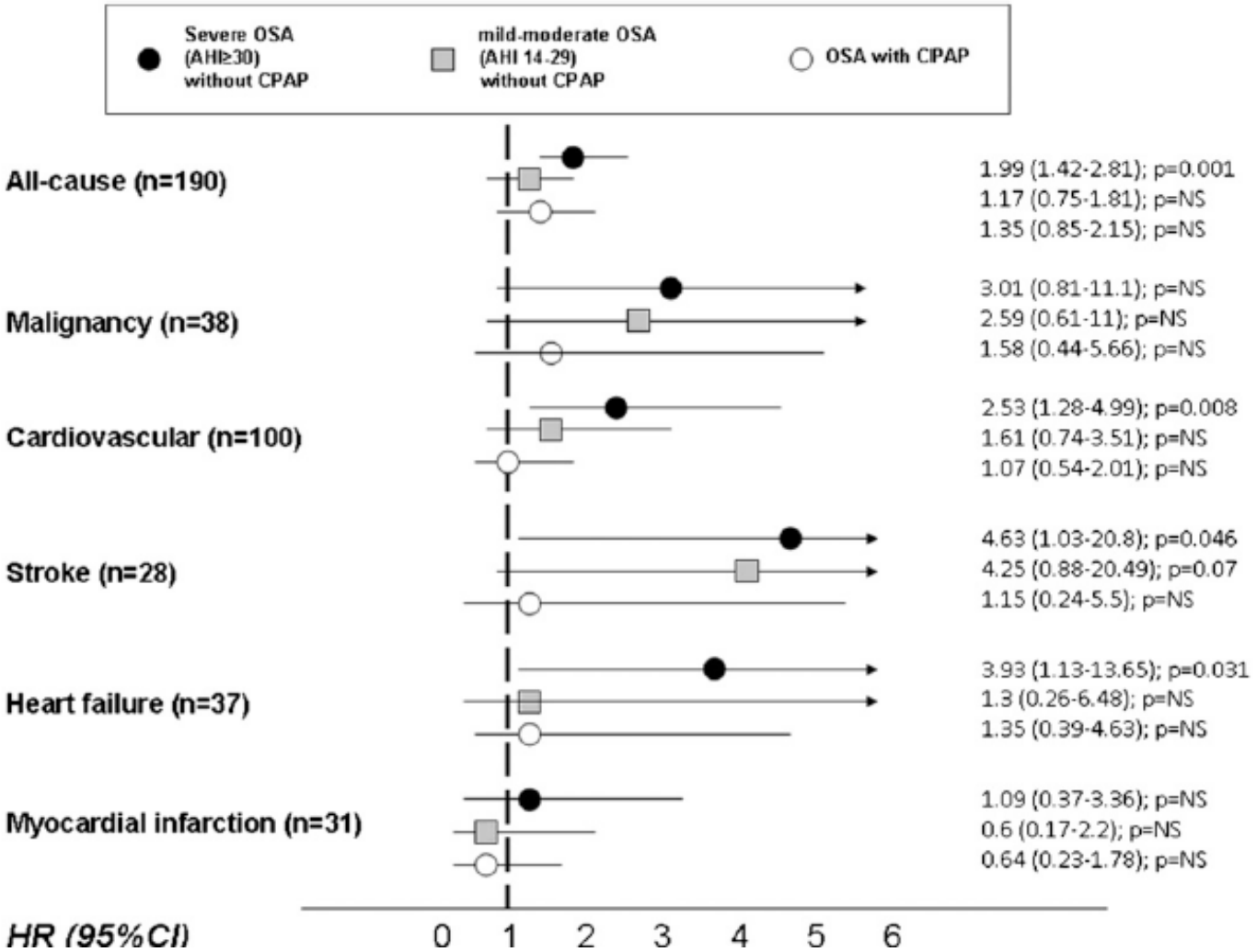
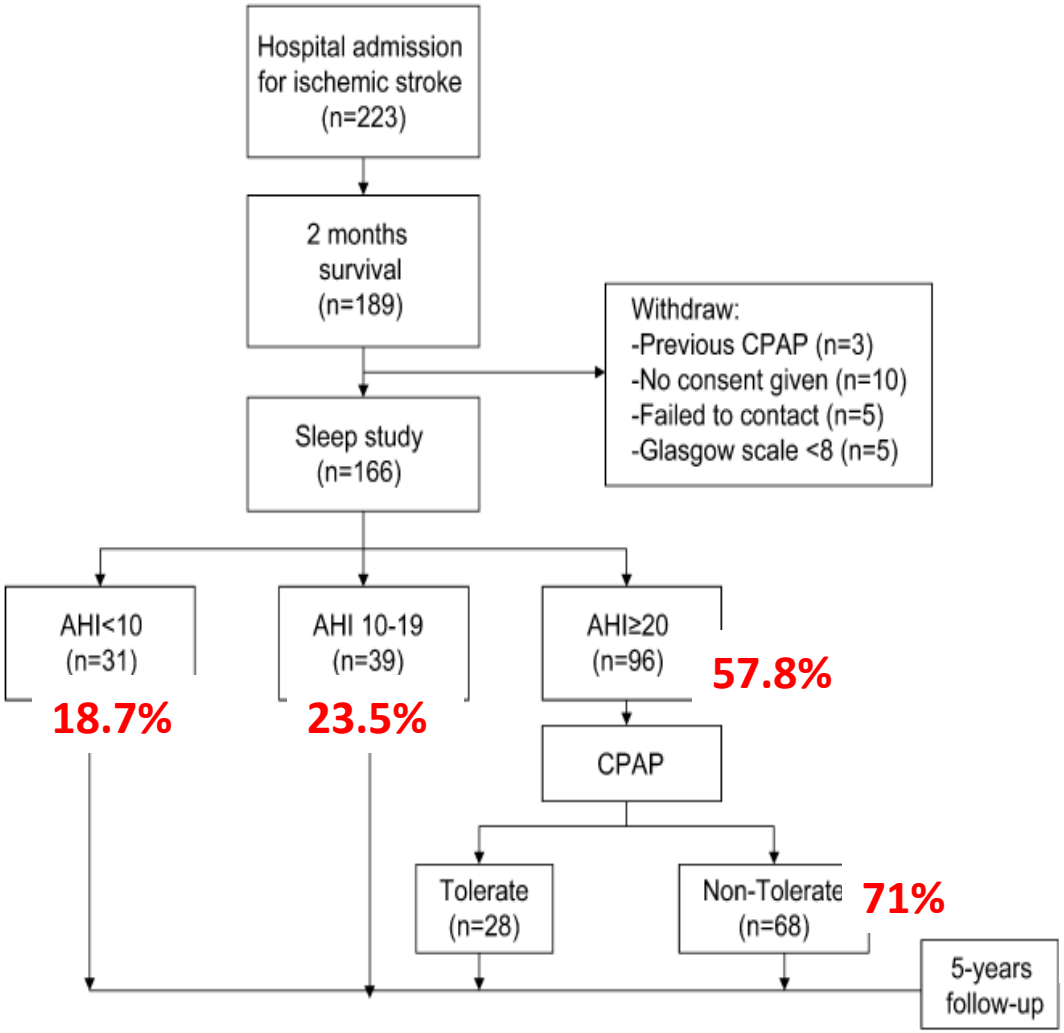
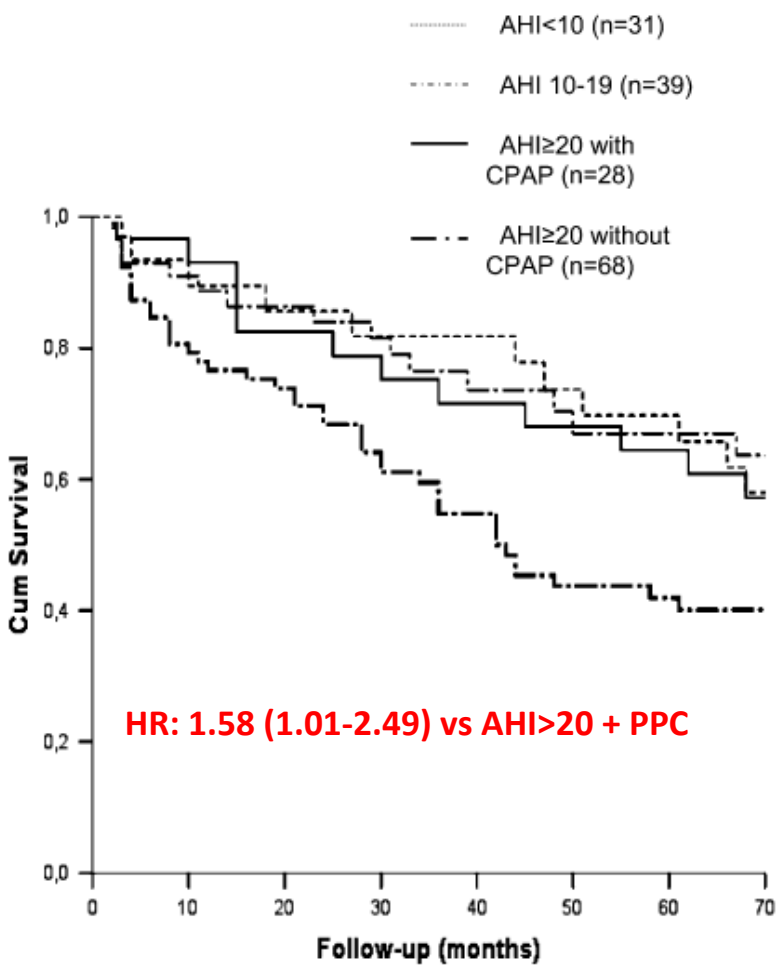


Figure 3. Hazard ratio (95% confidence interval) of the various analyses of general mortality, cardiovascular mortality, and types of cardiovascular and noncardiovascular events studied with respect to the control group without OSA. *Note*: The risk of death from stroke has also been adjusted for the presence of atrial fibrillation. Three patients experienced sudden death. AHI = apnea–hypopnea index; CI = confidence interval; CPAP = continuous positive airway pressure; HR = hazard ratio; NS = not significant; OSA = obstructive sleep apnea.

Augmentation de la survie chez les patients avec SAHOS post AVC acceptant la PPC comparés aux patients intolérants



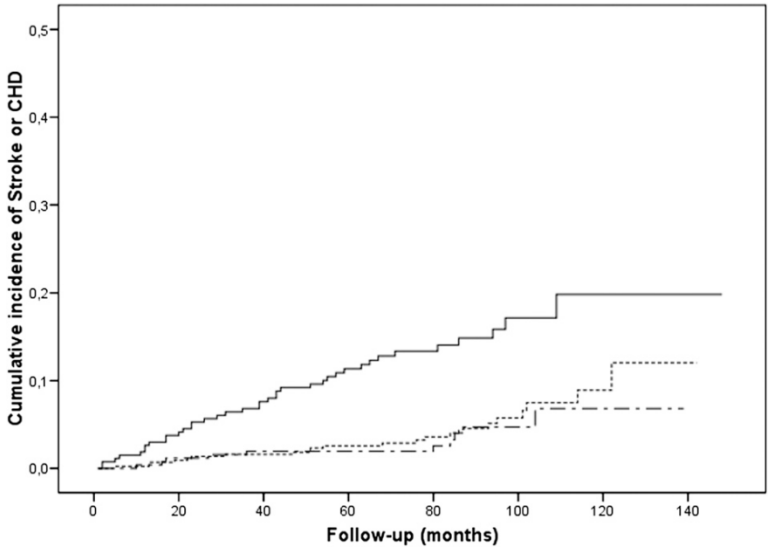


Martinez Garcia AJRCCM 2009

Role of Sleep Apnea and Continuous Positive Airway Pressure Therapy in the Incidence of Stroke or Coronary Heart Disease in Women

Francisco Campos-Rodriguez[1], Miguel A. Martinez-Garcia[2,3], Nuria Reyes-Nuñez[1], Isabel Caballero-Martinez[1], Pablo Catalan-Serra[4], and Carmen V. Almeida-Gonzalez[5]

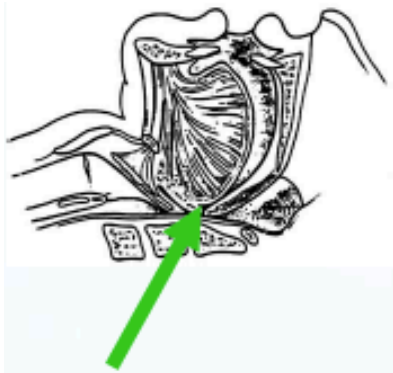
Etude observationnelle prospective sur 2 centres, 967 femmes sans atcd CV.
SAS traité si obs ≥ 4h. Non SAS IAH< 10/h.
Suivi moyen= 6,8 ans.
=>Le SAS non traité multiplie par 6 le risque d'incidence des AVC chez les femmes, particulièrement de < de 65 ans.
=> La PPC semble annuler cette augmentation de risque.

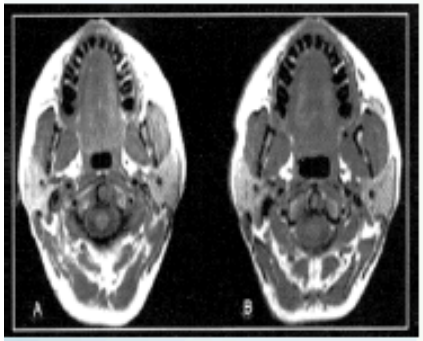


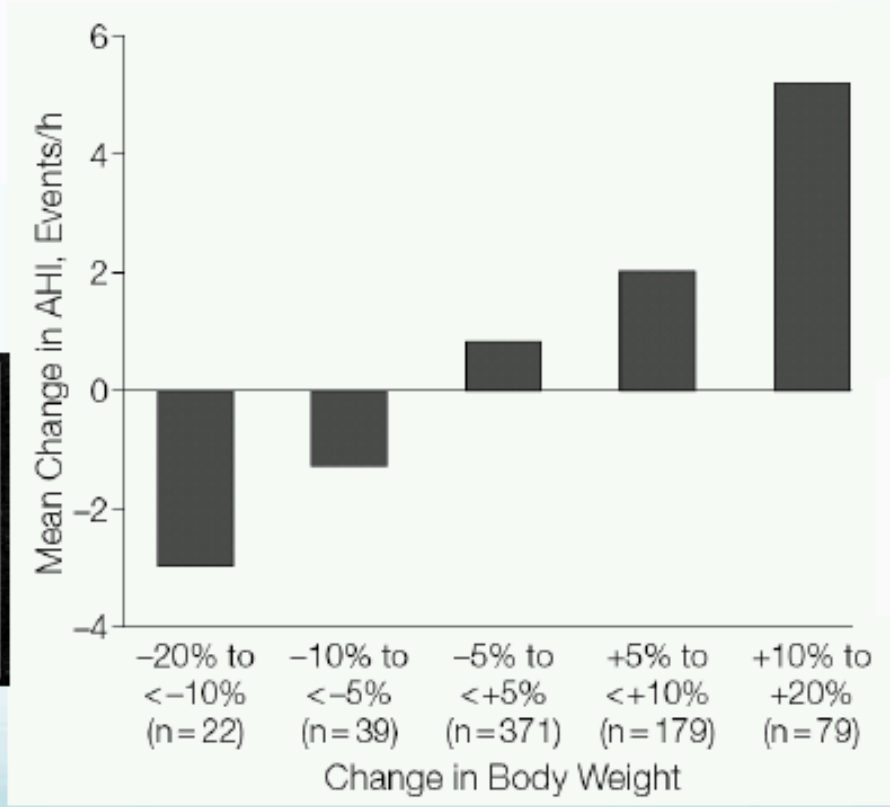
OSA Groups	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Incidence of stroke (n = 25)			
AHI < 10 (control group) (n = 258, 2 events)	1	1	1
AHI ≥ 10, untreated (n = 268, 17 events)	8.94 (2.06–38.7)	6.90 (1.57–30.22)	6.44 (1.46–28.34) ←
AHI ≥ 10 treated with CPAP (n = 441, 6 events)	1.79 (0.36–8.87)	1.40 (0.28–7.03)	1.31 (0.26–6.59)
Incidence of CHD (n = 46)			
AHI < 10 (control group) (n = 258, 8 events)	1	1	1
AHI ≥ 10, untreated (n = 268, 21 events)	2.69 (1.19–6.11)	1.90 (0.82–4.37)	1.77 (0.76–4.09) ←
AHI ≥ 10 treated with CPAP (n = 441, 17 events)	1.22 (0.52–2.85)	0.73 (0.30–1.76)	0.70 (0.29–1.70)

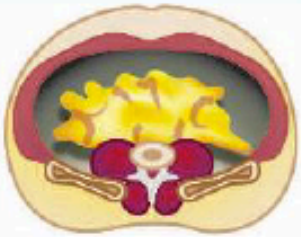
AJRCCM 2014

Variation de Poids et SAHOS









Peppard PE et al. JAMA 2000

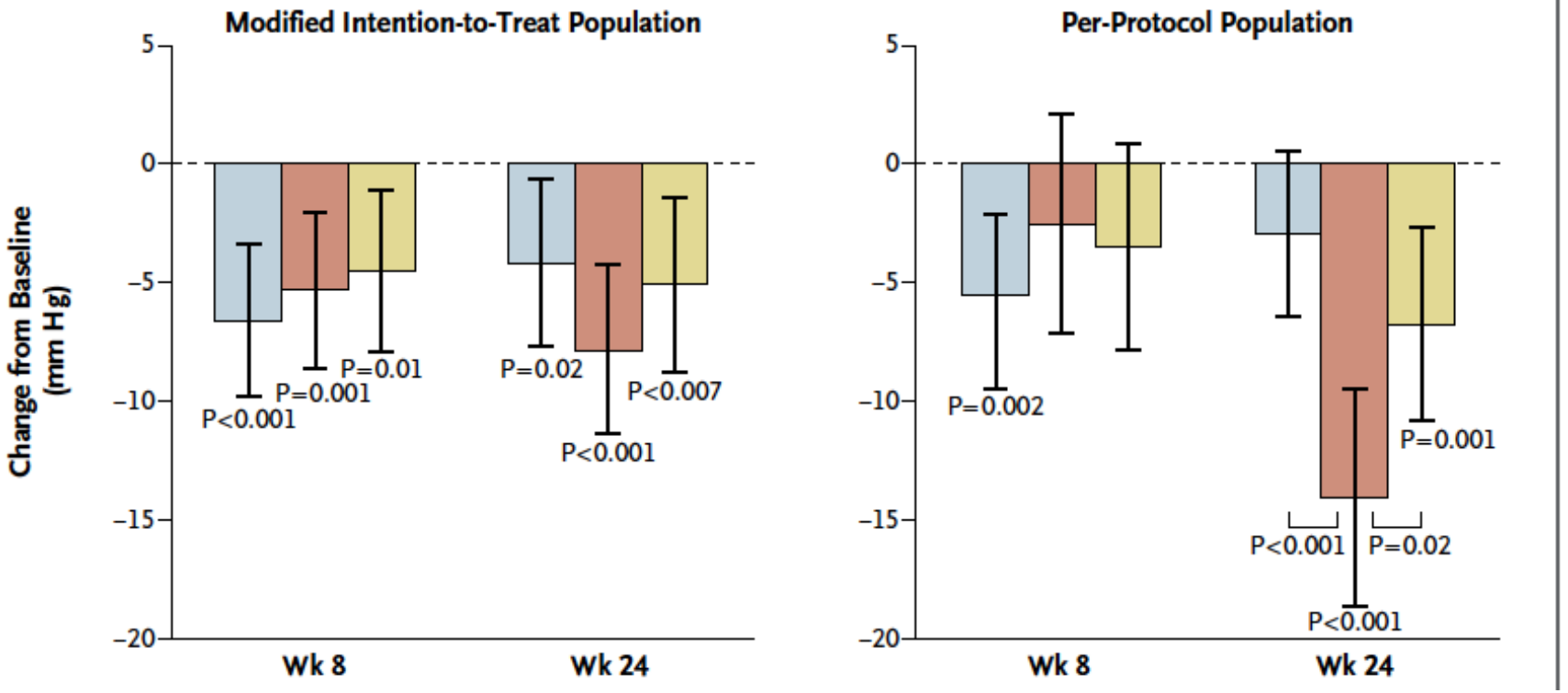
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 12, 2014 VOL. 370 NO. 24

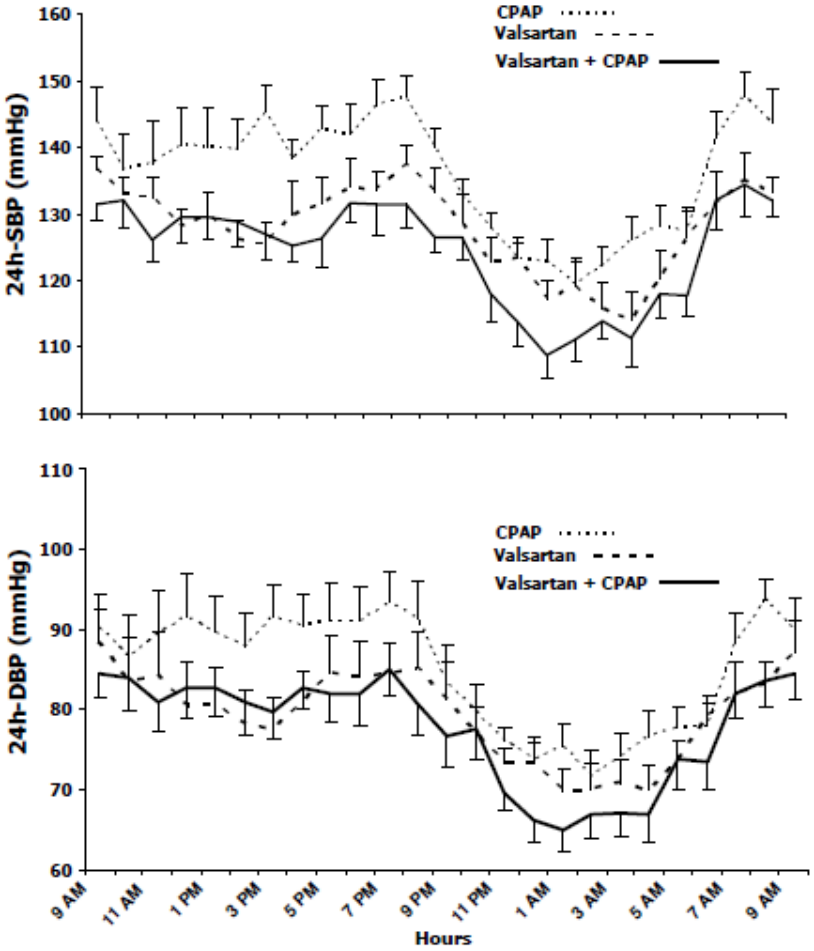
CPAP, Weight Loss, or Both for Obstructive Sleep Apnea

Julio A. Chirinos, M.D., Ph.D., Indira Gurubhagavatula, M.D., Karen Teff, Ph.D., Daniel J. Rader, M.D.,

C Change in Systolic Blood Pressure

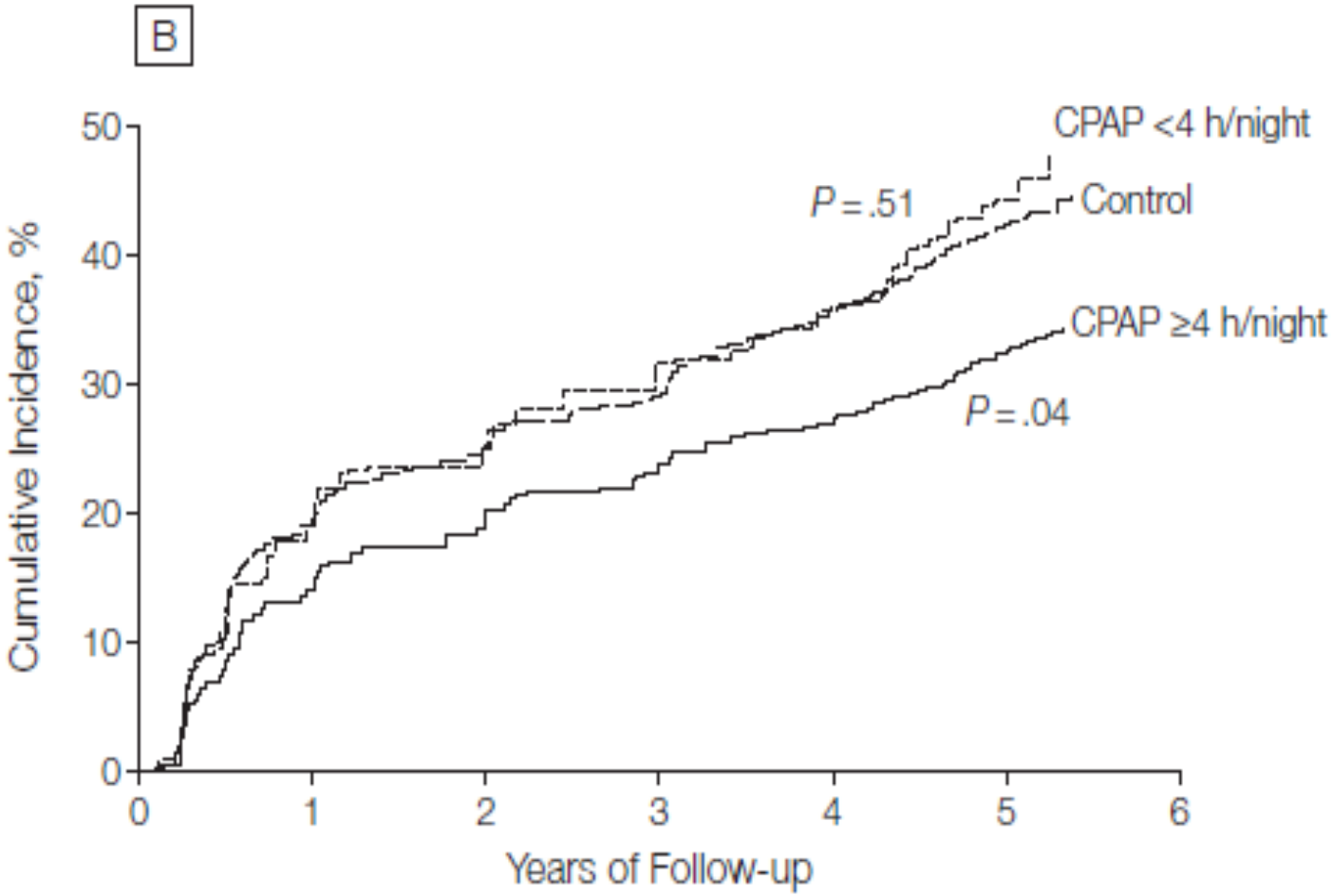


Effet cumulatif des anti-HT et de la PPC



Pépin et al AJRCCM 2010

Moins d'évènements CV sous traitement régulier par PPC

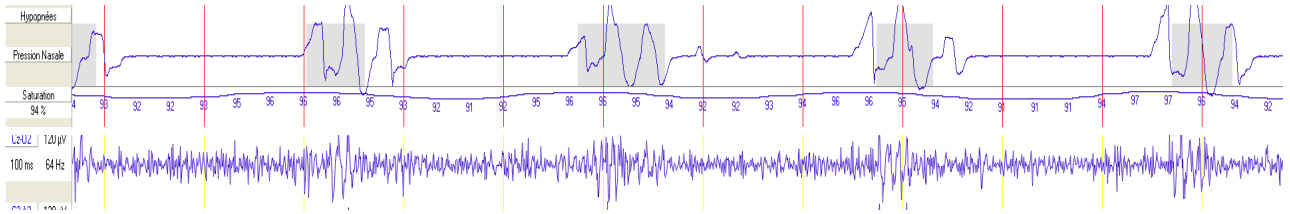


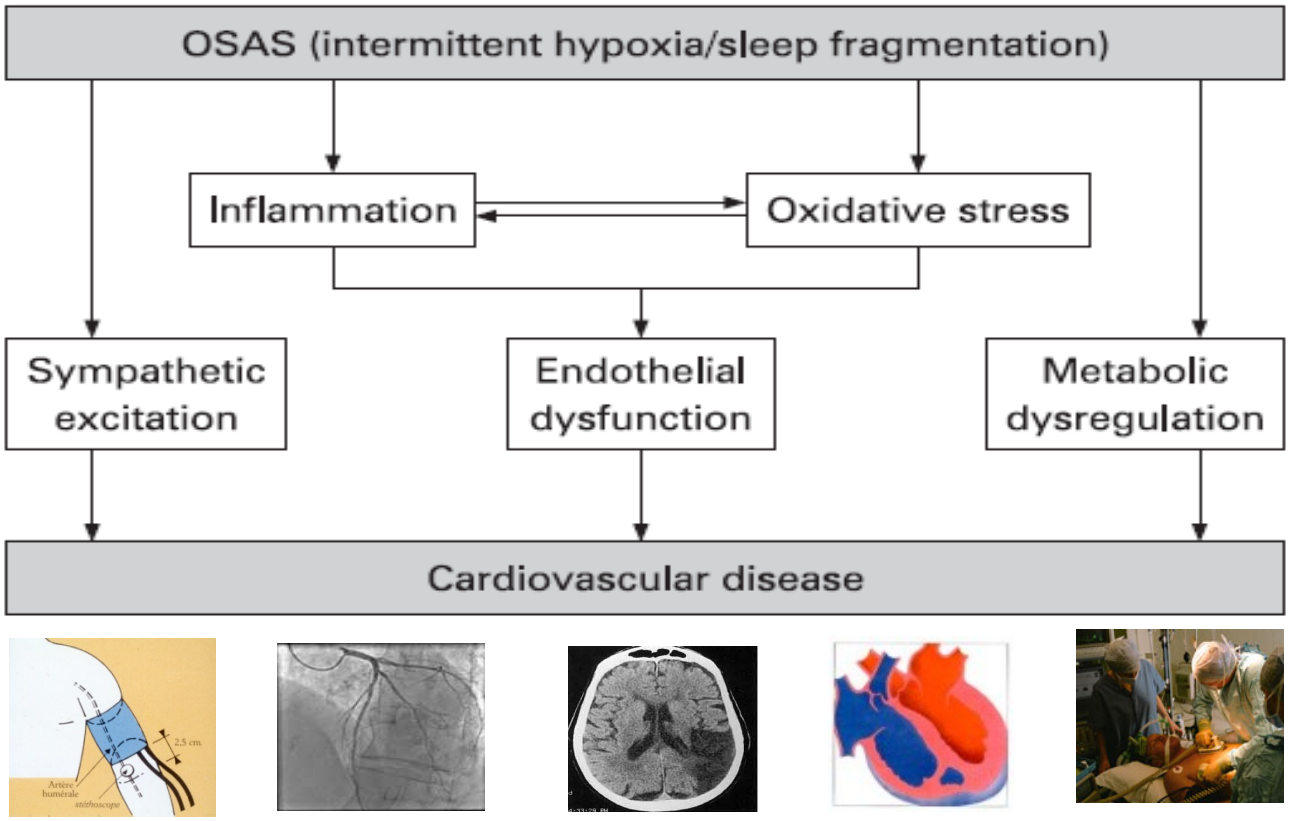
Barbé, JAMA 2012

Conséquences CV du SAHOS

1. Quelle est la mortalité du SAHOS?
    1. Mortalité globale
    2. Mortalité cardiovasculaire
2. Le SAHOS est-il un facteur de risque CV?
    1. Hypertension artérielle
    2. Maladie coronaire
    3. Troubles du rythme
    4. AVC
    5. Artériopathies et Anévrysme aortique
    6. Insuffisance cardiaque
3. La PPC diminue-t-elle le risque CV?
4. Quelle est la physiopathologie des conséquences CV du SAOS

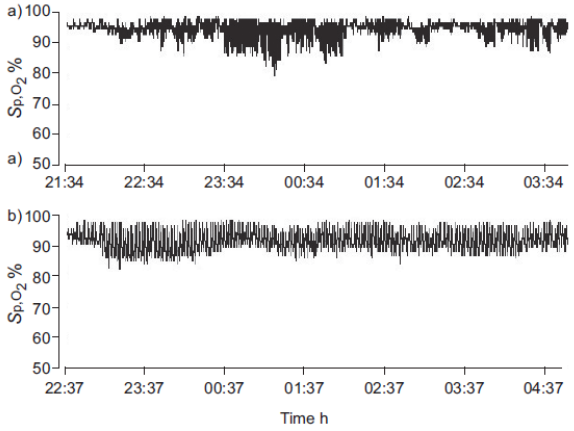
Conséquences cardiovasculaires du SAHOS: de la physiopathologie aux maladies

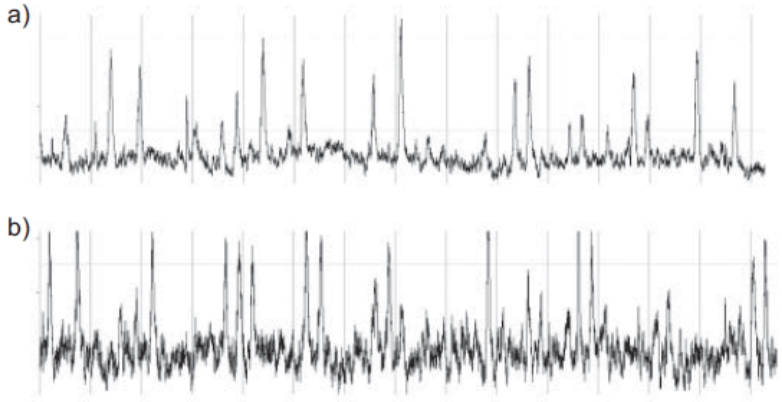


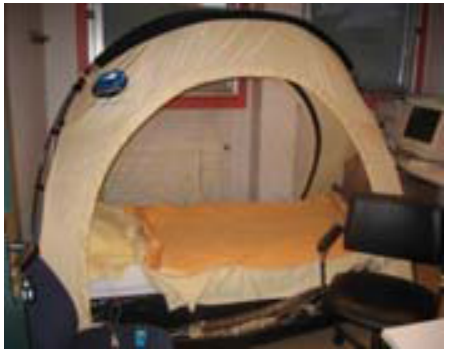


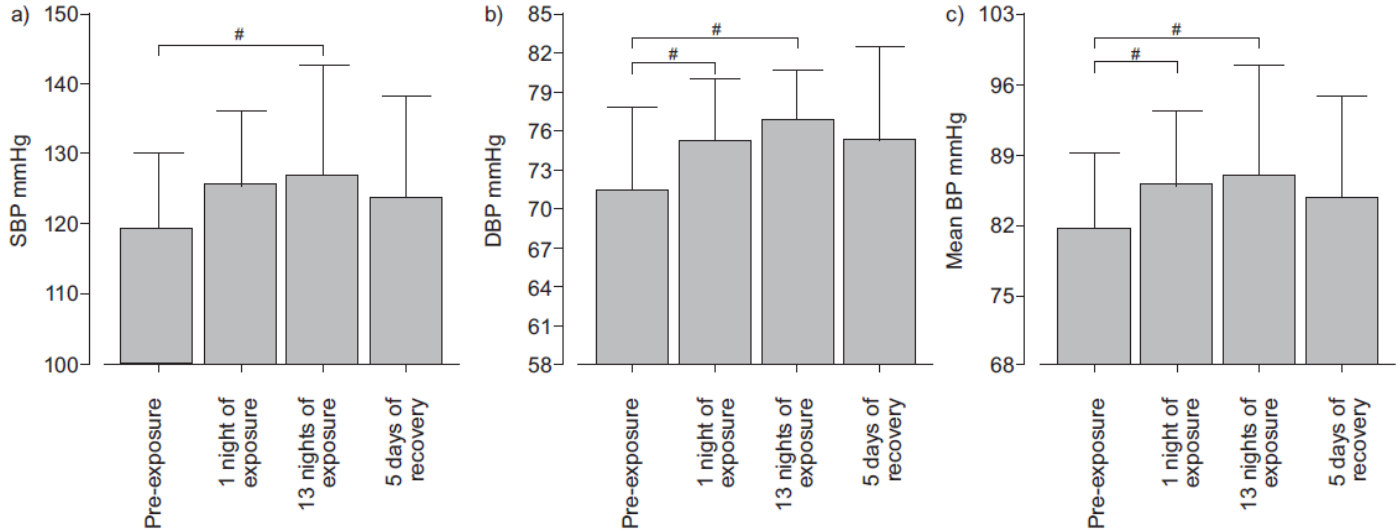
Ryan, Thorax 2009

SAHOS et HTA
Approche expérimentale



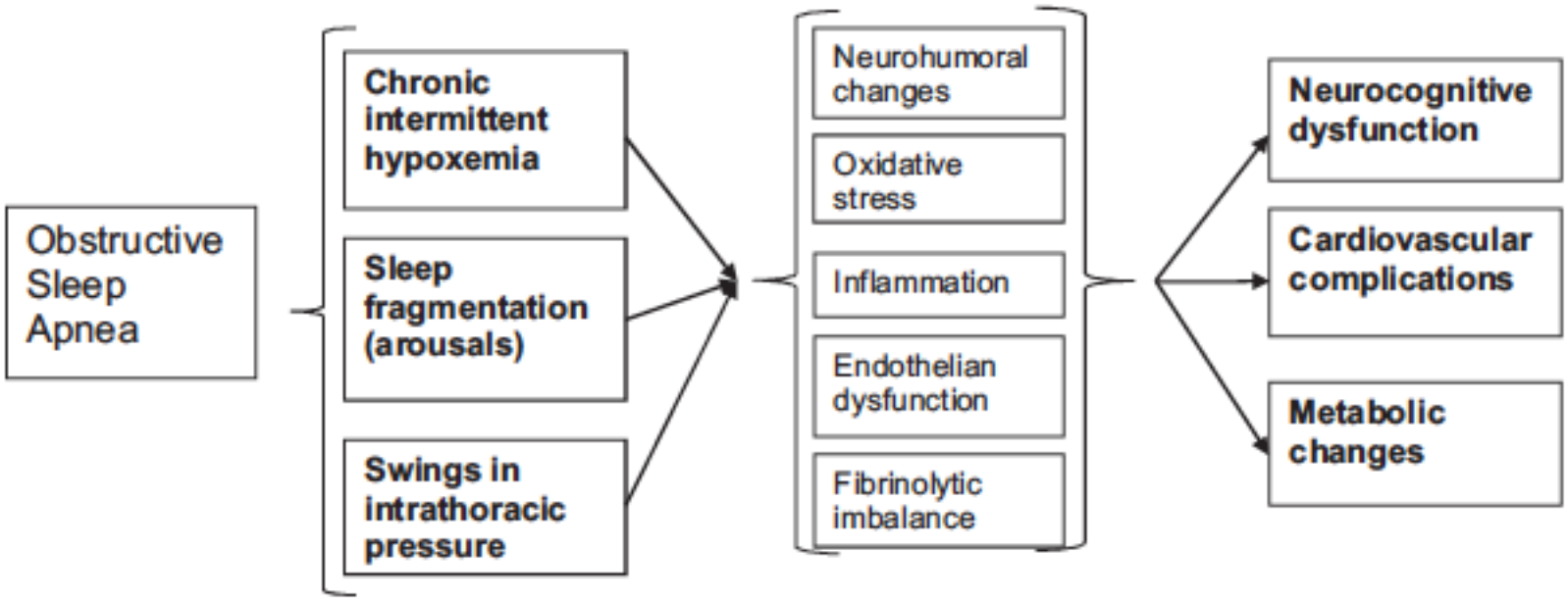




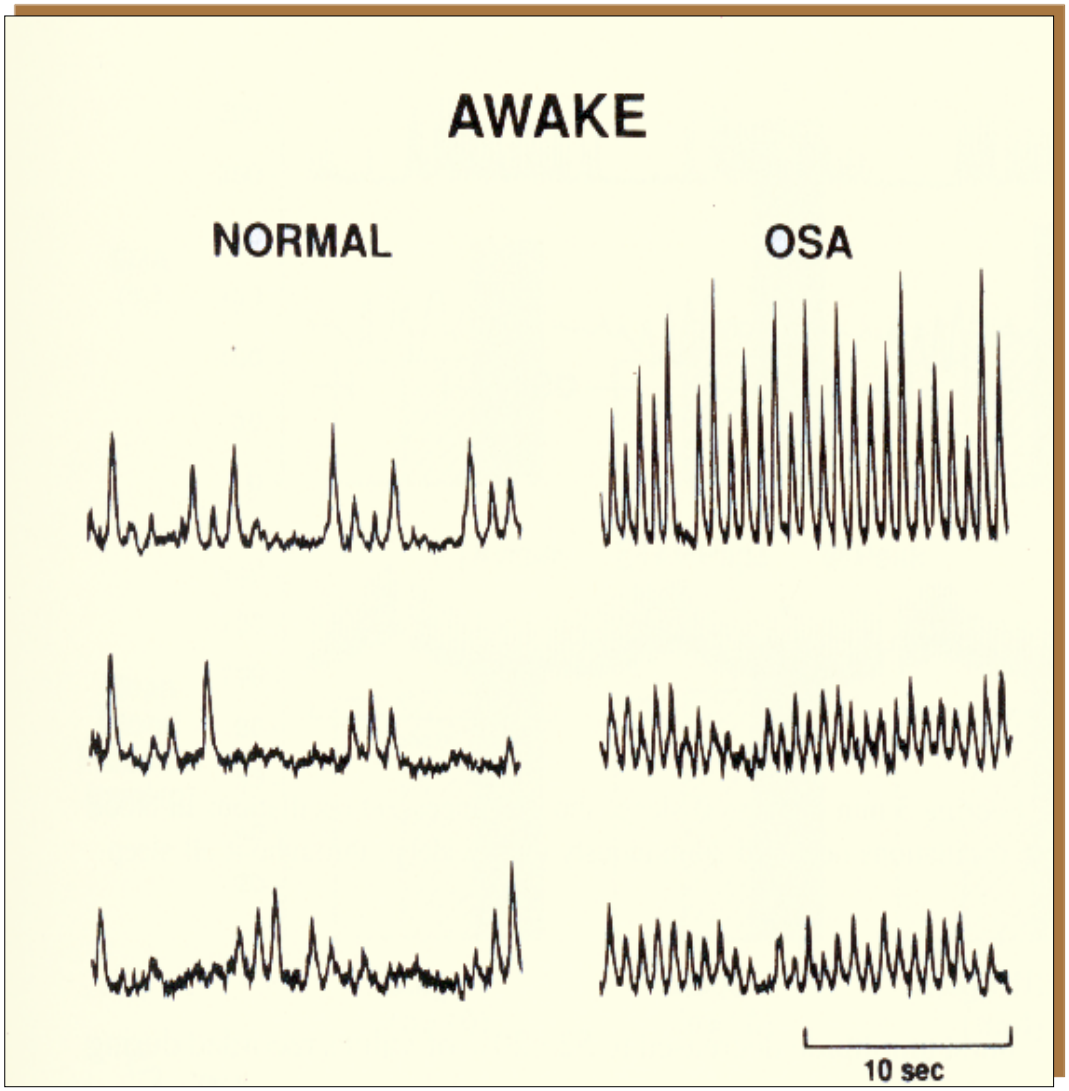


Tamisier et col. ERJ 2011

Pathophysiology of OSAS consequences

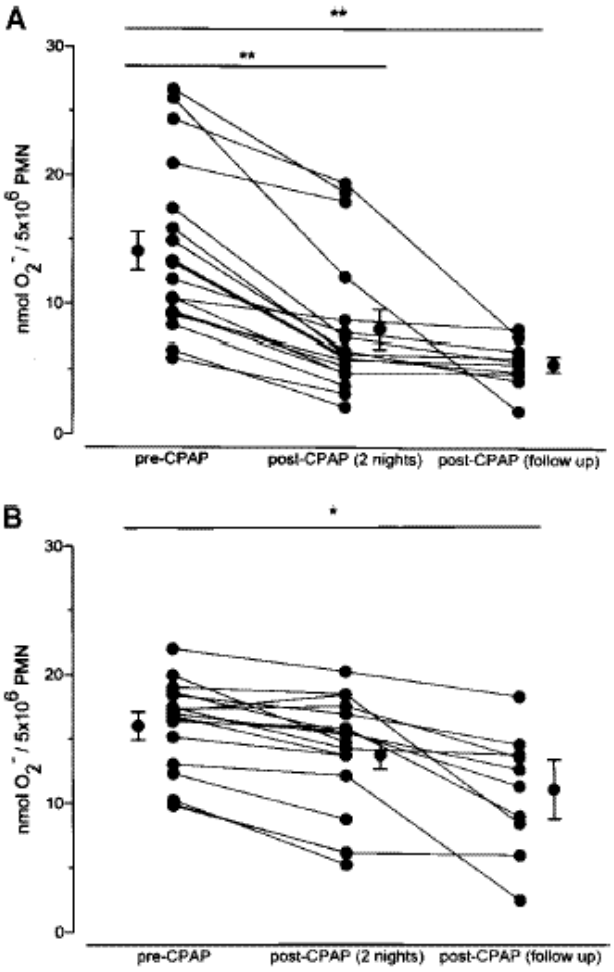


Microneurographie sympathique périphérique



SOMERS, 1996

Enhanced Release of Superoxide from Polymorphonuclear Neutrophils in Obst. Sleep Apnea



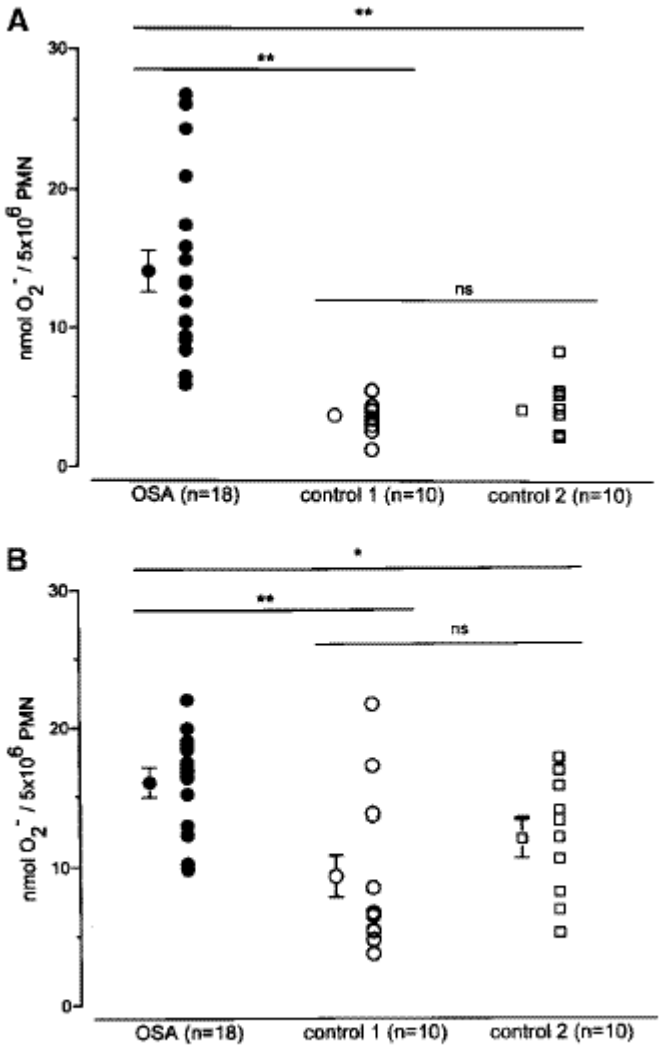
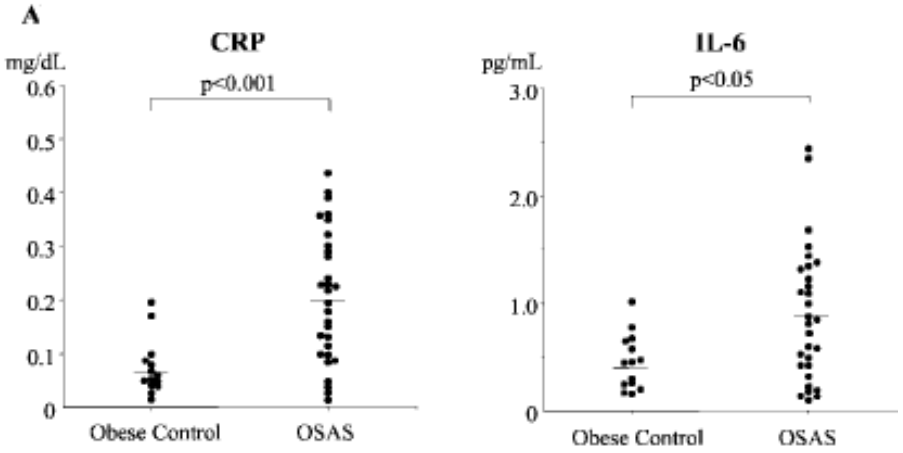


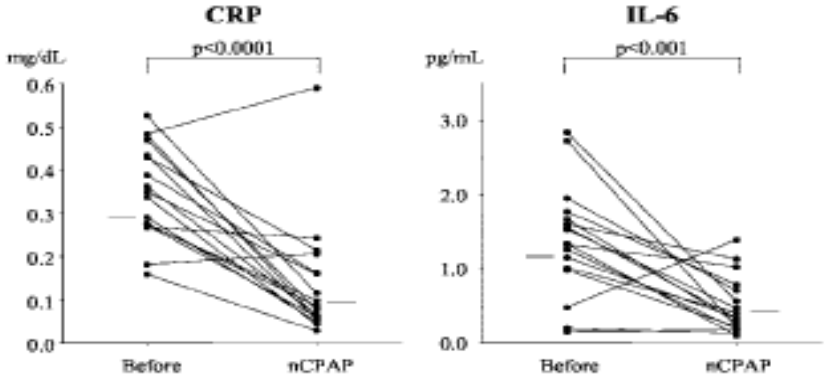
Figure 1. Superoxide release from polymorphonuclear neutrophils (expressed as nanomoles of O_2^- per 5×10^6 PMNs) after stimulation with fMLP (*A*) and A23 (*B*) in patients with untreated OSA (*closed circles*) and the control groups (control group 1: healthy volunteers, *open circles*; control group 2: patients without OSA, *rectangles*). All data are

R.Scuhlz, Am J Respir Crit Care Med Vol 162. pp 566–570, 2000

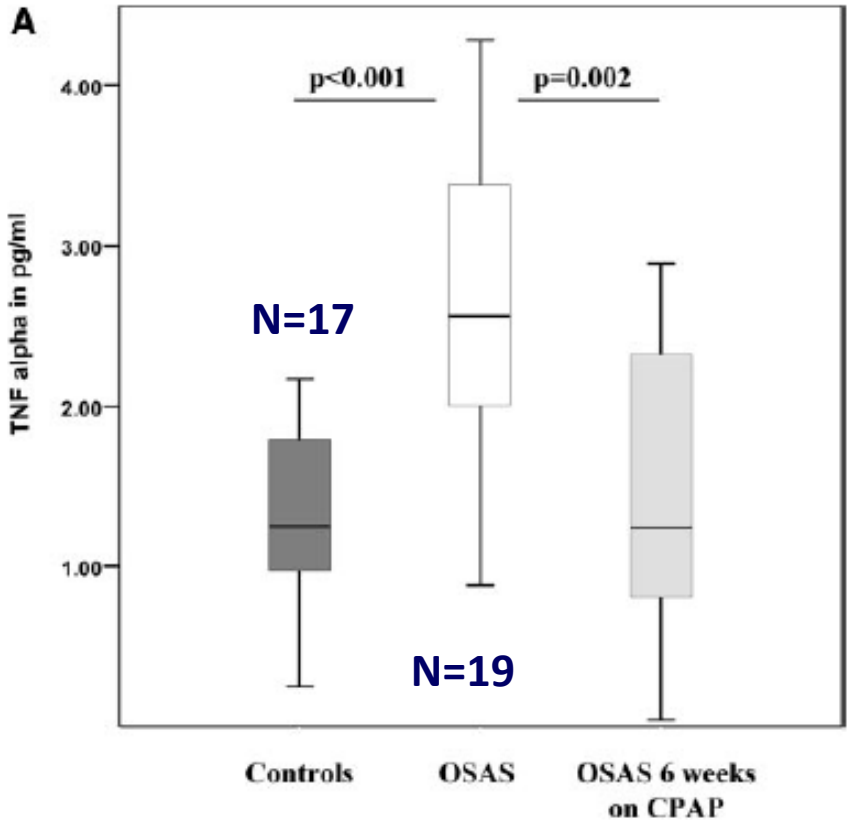
Amélioration des marqueurs biologiques d'inflammation systémique sous PPC



N=30 patients SAHOS et 14 obèses contrôles

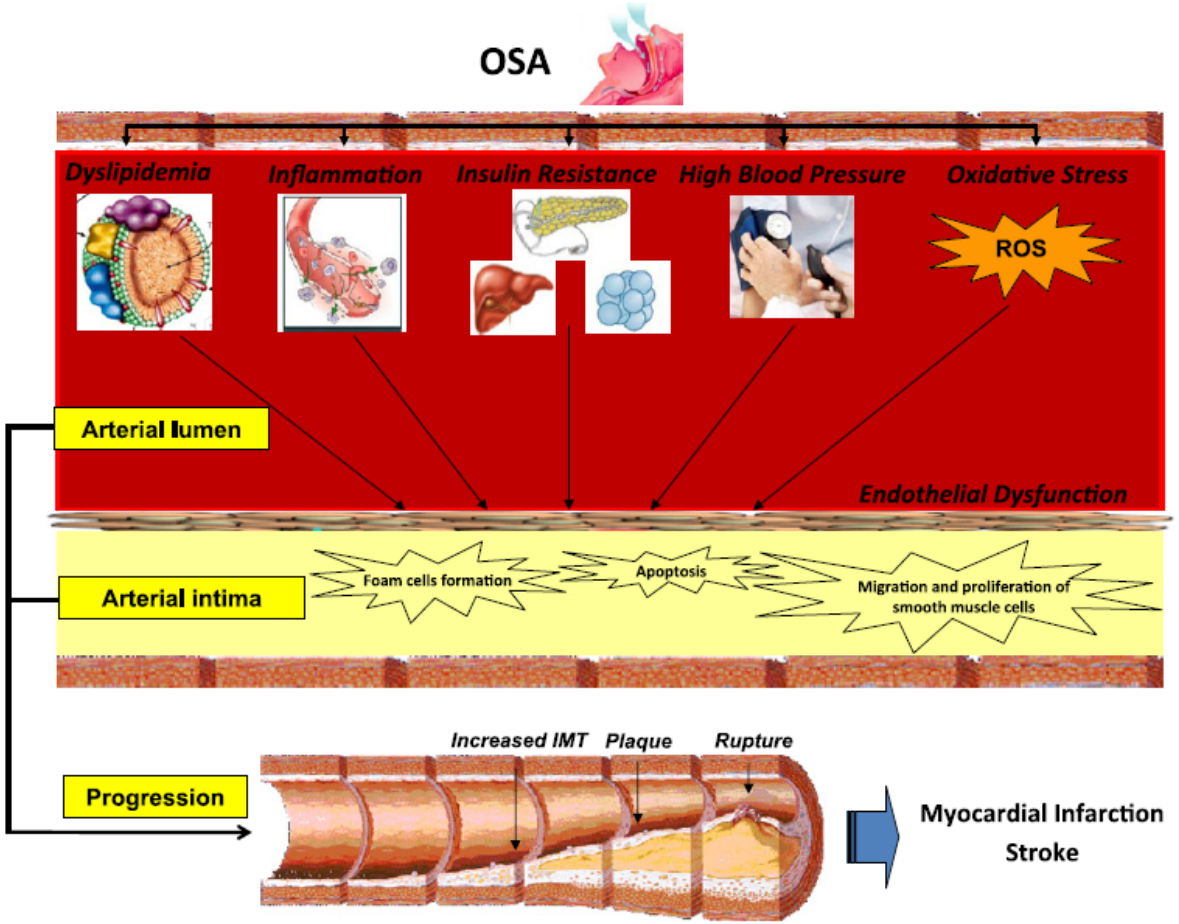


N=17 patients avec SAHOS modérés à sévères avant et après 1 mois de PPC



Yokoe, Circulation 2003 Ryan, Circulation 2005

Voies possibles de l'athérogenèse liée au SAOS



Drager, Chest 2012

Conclusions

Le SAS représente un facteur de risque majeur supplémentaire et indépendant pour les pathologies cardiovasculaires.

La recherche de signes cliniques de SAS (ronflement habituel, hypersomnolence diurne, apnées observées …) est indispensable en cas de :

1. Troubles du rythme ou de la conduction cardiaque à prédominance nocturne,
2. Une hypertension artérielle « essentielle » ou réfractaire,
3. Une insuffisance coronaire, d'autant plus si le patient est jeune et que les autres facteurs de risque sont absents ou minimes

Nécessité de traiter le SAHOS mais aussi les autres facteurs de risque CV

Conclusions

4. Un accident vasculaire cérébral en raison du pronostic qui peut être amélioré par la PPC (lorsqu'elle est tolérée)

5. D'une insuffisance cardiaque pour l'amélioration du pronostic vital envisageable (non encore prouvé) par le traitement des apnées centrales ou obstructives.

Futures directions

- Evaluer l'effet des modificateurs du risque (sexe, age, somnolence diurne, BMI…) sur la valeur prédictive de l'IAH
- Prédictivité CV des différents seuils d'IAH?
- Les maladies CV ou les Facteurs de risque CV augmentent-ils les risques du SAHOS? Nécessité d'un traitement pour des seuils d'AHI plus faibles?
- Effets des différentes définitions d'hypopnées dans la prédiction du risque de maladie CV
- Nécessité de stratification du risque du SAHOS à partir des données démographiques, cliniques, polysomnographiques…pour guider le traitement du SAOS.

Sleep disordered breathing and enlargement of the right heart after myocardial infarction Buchner ERJ 2015