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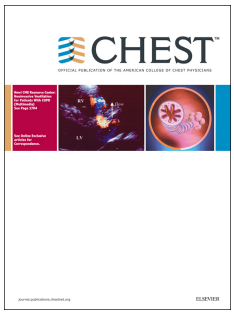

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Fixed but not autoadjusting positive airway pressure attenuates the time-dependent decline in glomerular filtration rate in patients with obstructive sleep apnea

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ABBREVIATIONS LIST

AHI = apnea/hypopnea index

APAP = autoadjusting positive airway pressure

BMI = body mass index

ΔBMI = change in BMI between follow-up and baseline

BP = blood pressure

CKD = chronic kidney disease

CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration

CPAP = continuous positive airway pressure

eGFR = estimated glomerular filtration rate

ΔeGFR= change in GFR between follow-up and baseline

ESADA = European sleep apnea database

fCPAP = fixed CPAP

GFR = glomerular filtration rate

OSA = obstructive sleep apnea

PG = cardiorespiratory polygraphy

PSG = polysomnography

SpO_2 = oxyhemoglobin saturation by pulse oximeter

ABSTRACT

BACKGROUND: The impact of treating obstructive sleep apnea (OSA) on renal function decline is controversial. Previous studies usually included small samples and did not consider specific effects of different continuous positive airway pressure (CPAP) modalities. The aim of this study was to evaluate the respective influence of fixed and auto-adjusting CPAP modes on estimated glomerular filtration rate (eGFR) in a large sample of patients derived from the prospective European Sleep Apnea Database (ESADA) cohort.

METHODS: In patients of the ESADA, eGFR before and after follow-up was calculated using the CKD-EPI equation. Three study groups were investigated, namely untreated patients (n=144), patients receiving fixed continuous positive airway pressure (fCPAP) (n=1,178), and patients on auto-adjusting CPAP (APAP) (n=485).

RESULTS: In the whole sample, eGFR decreased over time. The rate of eGFR decline was significantly higher in the subgroup with eGFR above median [91.42 ml/min/1.73m^2] at baseline ($p<0.0001$ for effect of baseline eGFR). This decline was attenuated or absent ($p<0.0001$ for effect of treatment) in the subgroup of OSA treated by fCPAP. A follow-up duration exceeding the median (541 days), was associated with eGFR decline in the untreated and APAP groups, but not in the fCPAP group ($p <0.0001$ by two-way ANOVA for interaction between treatment and follow-up length). In multiple regression analysis, eGFR decline was accentuated by advanced age, female gender, cardiac failure, higher baseline eGFR and longer follow-up duration, while there was a protective effect of fCPAP.

CONCLUSION: Fixed CPAP but not APAP, may prevent eGFR decline in OSA.

KEY WORDS: obstructive sleep apnea, glomerular filtration rate, therapy, fixed CPAP, automatic CPAP

Obstructive sleep apnea (OSA) is a chronic disorder causing disabling symptoms, such as excessive daytime sleepiness, nonrestorative sleep, and nocturnal choking.[1] The high prevalence of OSA and its cardio-metabolic comorbidities make it a burden for society.[2] Longitudinal observational studies supported a causal association between OSA and cardiovascular or metabolic diseases.[3,4]

A link between OSA and decline in renal function is still debated. Cross-sectional studies reported that glomerular filtration rate (GFR) assessed by estimative equations (eGFR) was,[5,6] or was not,[7-9] related to the apnea/hypopnea index (AHI), or to indices of nocturnal hypoxemia.[9,10] Long-term longitudinal studies provided more consistent results. Two longitudinal studies with polysomnographic documentation of OSA severity demonstrated a faster decline in eGFR in OSA subgroups with the most severe disease.[11,12] Three national database studies showed a higher incidence of chronic kidney disease (CKD) in patients with OSA compared with controls.[13-15] However, little is known about long-term effects of OSA treatment on eGFR.

Continuous positive airway pressure (CPAP) is the first line therapy for OSA, normalizing symptoms and improving quality of life.[16] Large long-term studies did not demonstrate a positive effect of CPAP therapy on renal function, but lacked information regarding OSA severity, comorbidities and treatment adherence.[13-15] In contrast, better documented but small sample size studies reported a CPAP positive impact in the short-term.[17-20] In a recent substudy from the SAVE trial, 200 severe OSA patients in secondary cardiovascular prevention were randomized to CPAP versus standard medical care for a median 4.4 year period. The sample size was small (200 patients) and likely insufficient to demonstrate an effect of CPAP on either eGFR or albumin excretion.[21] To date, the literature has not addressed the respective impact of different modalities of positive airway pressure therapy [e.g. fixed CPAP (fCPAP) or autoadjusting positive airway pressure (APAP)].

Currently, APAP is widely used for OSA therapy. APAP devices deliver variable pressures adjusted to patient's requirement. Efficacy on symptoms and quality of life, as well as adherence to treatment, are claimed to be similar to fCPAP.[22] However, some data suggest that blood pressure (BP) reduction is greater with fCPAP than with APAP,[23,24] possibly due to a stronger inhibitory effect of fCPAP on sympathetic tone.[25] Such hemodynamic and autonomic effects might have an impact on renal function evolution.[26] Therefore, we hypothesized that an effect on kidney function could be more significant in patients treated with fCPAP compared with those receiving APAP.

The European Sleep Apnea Database (ESADA) prospectively records data from unselected adult patients (age 18-80 years) initially referred to several European sleep centers for suspected OSA.[27] In the present study, we analyzed eGFR in patients of the ESADA who underwent multiple

determinations of serum creatinine with the aim to evaluate longitudinal changes in eGFR in untreated patients and in those receiving different CPAP modalities for OSA treatment.

METHODS

Enrolment in the ESADA started in March 2007. Written informed consent to anonymous use of data was obtained from all patients. Each center obtained approval from the Ethical Committee of its own institution (e-Appendix 1).

The ESADA registry enables entries of clinical and laboratory data from patients seen at baseline and different follow-up visits. Recorded data include anthropometrics, clinical history, daytime somnolence assessed by the Epworth sleepiness scale (ESS), biological parameters and baseline polysomnography (PSG) or level 3 cardiorespiratory polygraphy (PG) data. The methods used for PSG/PG scoring were reported in previous papers.[9,28] The CKD-EPI equation was used for eGFR calculation, as it usually performs better than other equations, like the MDRD.[29,30]

Data recorded between March 2007 and May 2016 were analyzed. The follow-up time ranged between 1 and 100 months. During the follow-up period patients received up to four visits. Baseline data recorded before initiation of OSA treatment and data recorded at the last follow-up visit were analyzed. Data from patients not receiving OSA therapy, or receiving fCPAP or APAP were analyzed separately.

The change in eGFR (ΔeGFR) from baseline to follow-up was computed as the difference in eGFR between the two visits. After initial assessment, each subject received treatment prescriptions relevant to the diagnosed nocturnal breathing disorders and following the principles applied at each clinic. Follow-up visits were planned at variable time points. Clinical and biological data were collected according to the ESADA standard protocol. Information on adherence to therapy (from machine time counter) was recorded.

Statistical analysis

Data are reported as mean ± standard deviation (SD) or median [interquartile range - IQR], as appropriate. Differences in frequency distribution of categorical variables were evaluated by χ^2 test. One-way Analysis of Variance (ANOVA) and Kruskal-Wallis test were used for group comparisons for normally and not normally distributed variables, respectively. Two-way ANOVA was applied to examine the influence of treatment and of its interaction with other categorical variables on ΔeGFR. Fisher's protected least significant difference (PLSD) was used for multiple comparisons in ANOVA models. A multiple linear regression model was built to test the effect of treatment (independent variable) on ΔeGFR (as dependent variable), while adjusting for confounding/effect

modifying variables. In one- and two-way ANOVA and in the multiple model, continuous variables were dichotomized at their 50th percentile (median). All analyses were performed in IBM SPSS Statistics v20. A p-value <0.05 was considered statistically significant.

RESULTS

At the time of analysis, the database included 19,665 subjects. Among them, 1,807 subjects had creatinine determinations both at baseline and at a follow-up visit. These patients were classified according to the assigned OSA treatment: 144 patients were assigned to no OSA therapy or were recommended to lose weight (untreated group), 485 were assigned to APAP, and 1,178 to fCPAP. Compared with the 17,858 excluded subjects, the study sample had more severe OSA at baseline, but differences in demographic characteristics and comorbidities between samples, although statistically significant, were small (e-Table 2). In the fCPAP group, mean therapy pressure was 8.9±2.4 cmH_2O. In the APAP group, lowest pressure was set at 4.6±1.1 cm H_2O, and highest at 15.1±2.1 cmH_2O.

Table 1 shows the main characteristics of the included subjects. OSA was less severe, and percentage of subjects with comorbidities was lower, in the untreated than in the APAP or fCPAP groups. Systematic differences in AHI values obtained by PG and PSG respectively were in line with those previously reported.[28] Most patients had normal or slightly diminished eGFR.

The follow-up period and change in BMI were similar in all groups. The ESS reduction was more pronounced in the APAP and fCPAP groups compared with the untreated control group without significant differences between the two CPAP modes. CPAP adherence was high and similar in the APAP and fCPAP groups (Table 2).

Median follow-up duration in the whole sample was 541 [220-1,255] days. During the follow-up period, eGFR decreased, although the inter-individual variability was high. In unadjusted analyses, eGFR decreased more in older patients and in those with chronic heart failure, lower baseline eGFR, and milder oxyhemoglobin saturation (SpO_2) falls during the baseline night (Table 3); however, among the patients with milder nocturnal hypoxemia, more untreated subjects were represented (12.6% vs 3.5%). Gender, arterial hypertension, diabetes mellitus, BMI, and subjective sleepiness did not significantly influence ΔeGFR (Table 3).

Unadjusted analysis showed a slight increase of eGFR in the fCPAP group (0.60±11.13, p<0.004 vs untreated, and p<0.003 vs APAP), whereas eGFR decreased in untreated (-2.80±8.81 ml/min/1.73m^2) and in APAP (-1.12±10.03) treated patients.

Figure 1 shows ΔeGFR for each type of therapy after allocation of baseline eGFR into below or above the median value. The strongest reduction in eGFR over time was observed in untreated subjects. In addition, eGFR was reduced among subjects with baseline eGFR above the median ($p<0.0001$ both for effect of therapy and of baseline eGFR). The effect of baseline eGFR did not change with type of therapy ($p=0.107$ for interaction). Pairwise comparisons between treatment groups showed that ΔeGFR in the untreated patients differed from ΔeGFR in the fCPAP (Fisher's PLSD test, $p=0.0003$), but not from ΔeGFR in the APAP group ($p=0.104$).

Figure 2 shows ΔeGFR according to type of treatment and length of follow-up (below or above the median). Overall, the strongest reduction in eGFR was found in untreated subjects and in those with a longer follow-up ($p<0.0001$ both for effect of therapy and of follow-up length). This analysis showed a significant interaction between treatment and follow-up duration ($p<0.0001$): in fact, while in the untreated and in the APAP groups a more pronounced decrease in eGFR occurred in the subjects with longer follow-up, in the fCPAP group eGFR remained substantially unchanged irrespective of treatment duration. Similar to results of the previous analysis, ΔeGFR differed between the untreated and the fCPAP group ($p=0.0004$), but not between the untreated and the APAP group ($p=0.111$).

Finally, a multiple regression analysis was performed, with ΔeGFR as dependent variable, and variables that were significant in univariate analysis (table 3) together with treatment by APAP, treatment by fCPAP, gender, change in BMI and main comorbidities as independent variables. We identified older age, female gender, chronic heart failure, higher baseline eGFR and follow-up time as independent predictors of a reduction in eGFR. Conversely, only treatment with fCPAP was identified as a significant and independent predictor for an increase in eGFR at follow up, whereas treatment with APAP was possibly associated with only a modest improvement in eGFR (trend $p=0.087$) (Table 4). When corrected for other confounders/modifiers, subjects treated by fCPAP presented an overall increase of 3.6 ml/min/1.73m^2 in eGFR by comparison with untreated subjects.

In a sensitivity analysis, the multiple regression model was run after excluding hypertensive patients. The effect of treatment remained unchanged: fCPAP was still significant ($B=3.710$, $p<0.0001$) compared to untreated, and APAP did not demonstrate a significant impact ($B=1.401$, $p=0.232$).

DISCUSSION

It has been shown that eGFR progressively declines in OSA at a rate proportional to nocturnal hypoxemia.[11] Few studies addressed the effects of CPAP treatment on renal function. Existing

studies have been performed on rather small samples of subjects,[17-21] and, with one exception,[21] were based on short-term follow-up. Besides, no study yet has separately analyzed fCPAP and APAP effects. The main result of this study was that in adult OSA patients a progressive reduction in eGFR was attenuated by fCPAP, whereas APAP had no significant impact. In addition, advanced age, female gender and chronic heart failure, accelerated the eGFR decline.

fCPAP and APAP have been mostly compared regarding their respective effects on adherence, symptoms and quality of life. As only marginal non-clinically relevant differences were found for adherence,[22,31] with similar effects in the correction of sleep respiratory disorders and symptoms,[22,32] the two treatment modalities are usually considered equivalent. In agreement with previous experiences, we observed similar changes in ESS after fCPAP and APAP. So far, less attention has been paid to possible differences between the two treatment modalities on cardiovascular, metabolic or renal outcomes. Two studies reported a greater reduction in BP after fCPAP than APAP,[23-24] which was attributed to a persistent higher sympathetic activity with APAP compared to fCPAP.[25] We hypothesized that the smaller reduction in sympathetic activity under APAP might translate into smaller BP reduction, endothelial dysfunction and then a limited effect on eGFR. This was confirmed by our data showing that fCPAP, but not APAP, could attenuate the spontaneous decline of eGFR observed in untreated subjects. We did not find differences in BP changes between fCPAP and APAP therapy, but our database only included office BP measurements. In fact, only measurements by ambulatory BP monitoring were statistically different between fCPAP and APAP in a previous study.[24] The superiority of fCPAP for maintaining renal function might be clinically relevant in OSA patients at risk for renal function decline.

Another important finding was that baseline eGFR affected subsequent eGFR changes in all treatment groups. On average, eGFR decreased in the subjects with higher baseline values, while it decreased less, or increased, in those with a lower value. Likewise, in the SAVE study the rate of change in eGFR was lower in patients with reduced compared to those with normal baseline eGFR.[21] Previous investigations on eGFR changes after CPAP in small samples of patients reported different findings depending on the characteristics of the studied patients. Two studies in patients with a mean baseline GFR >120 ml/min/1.73m^2 found that GFR decreased after a one-month treatment period, which was interpreted as improved renal function due to decreased hyperfiltration.[17,19] Instead, in patients with slightly reduced eGFR (77±12 ml/min/1.73m^2), an increase in eGFR was observed after three months with CPAP.[18] In patients with stage 3-5 CKD, a slower decrease in eGFR was reported after 0.6-3.5 years if compliance to CPAP was >4 hours/day.[20] Therefore, CPAP in OSA may have different beneficial influences on renal function that are not fully revealed by eGFR changes alone.

A progressive reduction in GFR occurs in the general population after the age of 30-40 years,[33] but whether gender influences the progression of eGFR decline is controversial.[34-36] In the present study, an independent detrimental effect of female gender on renal function in OSA was found. In our ESADA cross-sectional study, we also found a significant association between female gender and CKD in OSA.[9] Thus, our data support that OSA can be more harmful to kidney function in women than in men. Further studies may clarify the mechanisms through which gender may influence renal function in OSA.

The other significant determinants of eGFR changes in our sample were age and chronic heart failure, both of which are well-known important determinants of kidney function loss.[33,37] Lowest nocturnal SpO_2 was the only parameter of severity of OSA independently related to CKD in our previous cross-sectional analysis.[9] In this study, baseline SpO_2 was not significant in multivariate analysis as only a small number of subjects, mainly with mild-to-moderate OSA, did not receive any treatment for their respiratory disorders during the follow-up. In univariate analysis, mild hypoxemia was associated with a more marked decrease in eGFR. Subjects with milder hypoxemia also had lower AHI and were more often untreated. That could suggest that even mild to moderate OSA, when left untreated, may be harmful to renal function.

Unexpectedly, no effect of CPAP adherence on ΔeGFR could be demonstrated. Mean compliance to treatment was high, possibly because our sample represented a self-selected population where the patients more compliant to treatment were more likely to return for follow-up evaluations. Possibly, a higher number of patients poorly compliant to treatment would be necessary for a more reliable evaluation of the potential compliance effects.

Among hypertensive subjects, either treated by APAP or fCPAP, the most common antihypertensive treatment included drugs acting on the renin-angiotensin system (respectively 68.7% and 62.7% of subjects), either alone or in association with other drugs. The large variety of pharmacological treatments in the whole sample made the analysis of effects of medical therapy extremely complex. However, the respective effects of fCPAP and APAP were confirmed in normotensive subjects, without the confounding effect of antihypertensive medications.

This study has important strengths. It is the first study that evaluated eGFR in response to OSA treatment on a large number of subjects and in the long-term. In addition, it may have important clinical implications on the therapeutic management of OSA, as it adds some knowledge to the so far poorly explored field of differential impact of fCPAP and APAP treatment. This study has also limitations. The study population exhibited a higher rate of comorbidities including hypertension and type 2 diabetes and more severe sleep apnea syndrome compared to ESADA patients not included in the analysis. Thus our results may not perfectly fit the whole clinically

suspected OSA population. Besides, since more than 90% of the subjects were of Caucasian origin, our results may not apply to other ethnic groups. Some factors that could influence eGFR evolution, like inflammatory markers,[38] or residual sleep fragmentation during positive pressure application,[26] were not evaluated. Furthermore, the study lacks additional information on kidney damage such as albuminuria. Finally, we are not aware whether GFR estimates were influenced by methods used for creatinine determination in some patients, as measurement techniques were not recorded.

In conclusion, eGFR progressively decreases in patients with OSA. Although fCPAP and APAP may be similarly effective on daytime sleepiness, only fCPAP may attenuate eGFR decline. This finding, taken together with the previously reported lesser effectiveness of APAP in reducing BP, supports greater benefits of fCPAP on general health status in OSA. That should not discourage treatment with APAP in all OSA patients, but suggests that APAP should not be the first choice for treatment, especially in patients with some comorbidities, like arterial hypertension or CKD. Further studies are needed to explore if other health aspects that are known to be influenced by OSA, e.g. metabolic dysfunction or inflammatory activation, may be also differently affected by fCPAP and APAP, or to verify if different software or settings of APAP may impact on long-term APAP effects.

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TABLE 1. Baseline characteristics of the subjects included in the study

	All subjects n=1,807	Untreated n=144	APAP n=485	fCPAP n=1,178	p value
Age (yrs)	53.5±11.0	50.5±11.8	55.3±11.0	53.1±10.8	<0.0001[#]
Gender (F, %)	25.2	34.7	25.8	23.9	0.018[§]
BMI (kg/m^2)	31.9±6.3	28.8±4.7	31.9±6.4	32.3±6.2	<0.0001[#]
ESS	10.1±5.1	9.2±5.3	11.0±5.2	9.9±5.1	<0.0001[#]
Arterial hypertension (%)	46.0	32.9	51.9	45.2	0.0003[§]
Diabetes mellitus (%)	17.9	7.0	16.6	19.8	0.0008[§]
Chronic heart failure (%)	3.1	0.7	1.9	3.9	0.022[§]
COPD (%)	5.1	5.0	5.4	5.0	0.949[§]
eGFR (ml/min/1.73 m^2)	89.4 ±17.2	92.6±15.7	87.1±16.3	89.9±17.6	0.0006[#]
PSG (%)	51.0	49.6	15.3	65.9	<0.0001[§]
AHI_{PG}	22.9 [12.2-44.6]	8.5 [3.7-14-7]	23.8 [13.7-44.1]	26.7 [13.9-47.2]	<0.0001[†]
AHI_{PSG}	38.9 [24.3-60.3]	16.4 [10.5-27.5]	37.0 [23.0-54.8]	40.6 [26.8-61.6]	<0.0001[†]
Lowest SpO_2 (%)	81 [75-85]	86 [82-89]	80 [73-85]	81 [74-85]	<0.0001[†]

Data are expressed as mean±standard deviation or as median [interquartile range].

BMI=body mass index; ESS=Epworth Sleepiness Scale; COPD=Chronic Obstructive Pulmonary Disease; eGFR=estimated glomerular filtration rate; PSG=patients studied by polysomnography; AHI_{PG}=apnea/hypopnea index measured at cardiorespiratory polygraphy; AHI_{PSG}=apnea/hypopnea index measured at polysomnography; SpO_2=oxyhemoglobin saturation.

[#]One-way ANOVA; [§]χ^2 test; [†]Kruskal-Wallis test

TABLE 2. Follow-up duration, compliance to treatment and changes in body mass index and in subjective sleepiness in each therapy group

	Untreated	APAP	fCPAP
Follow-up duration (days)	420 [194-999]	614 [303-1203]	522 [202-1277]
Compliance to therapy (h/day)	--	5.4±2.1	5.3±2.0
ΔBMI (kg/m^2)	-0.35±2.24	-0.25±3.50	-0.03±2.41
ΔESS	-1.68±3.64	-5.16±5.11*	-4.91±5.29*

ΔBMI=difference in body mass index between follow-up and baseline; ΔESS=difference in Epworth Sleepiness Scale score between follow-up and baseline.

* $p<0.0001$ vs untreated (One-way ANOVA and Fisher's protected least significant difference)

TABLE 3. Change in estimated glomerular filtration rate (follow-up minus baseline value) (ΔeGFR) evaluated on the basis of patients' baseline and treatment characteristics.

		ΔeGFR		ΔeGFR	p value
Baseline characteristics					
Age (years)	≤54	0.61±10.29	>54	-0.89±11.09	0.0029
Gender	F	0.08±10.40	M	-0.75±11.58	0.15
Baseline BMI (kg/m^2)	≤31.14	-0.25±10.25	>31.14	-0.01±11.16	0.64
Baseline ESS	≤10	-0.34±10.58	>10	0.02±10.85	0.48
Arterial hypertension	absent	0.12±10.17	present	-0.42±11.36	0.28
Diabetes mellitus	absent	-0.06±10.15	present	-0.43±13.10	0.58
Chronic heart failure	absent	-0.02±10.56	present	-3.39±14.89	0.021
COPD	absent	-0.12±10.69	present	-0.26±11.80	0.903
Baseline eGFR (ml/min/1.73 m^2)	≤91.42	2.22±11.67	>91.42	-2.48±9.08	<0.0001
Baseline lowest SpO_2 (%)	≤81	0.57±10.86	>81	-0.80±10.38	0.0065
Treatment characteristics					
Follow-up (days)	≤541	0.69±9.93	>541	-0.95±11.40	0.0011
ΔBMI (kg/m^2)	≤0	0.18±10.78	>0	-0.56±10.64	0.15
fCPAP compliance (h/day)	≤4	1.09±11.14	>4	0.42±10.89	0.423
APAP compliance (h/day)	≤4	-0.24±11.01	>4	-1.00±9.76	0.553

COPD=Chronic Obstructive Pulmonary Disease; eGFR=estimated glomerular filtration rate; SpO_2=oxyhemoglobin saturation; BMI= body mass; fCPAP=fixed continuous positive airway pressure; APAP=autoadjusting continuous positive airway pressure.

Continuous variables were dichotomized at the level of their 50th percentile (median), with he exception of compliance. All comparisons were done by one-way ANOVA.

TABLE 4. Parameters estimated by multiple linear regression analysis model for ΔeGFR (difference in estimated glomerular filtration rate between follow-up and baseline) as dependent variable and therapy as independent variable (APAP and fCPAP with Untreated as reference), corrected for age, sex, gender, ΔBMI, presence of arterial hypertension, diabetes mellitus, chronic heart failure, and COPD at baseline, eGFR at baseline, lowest SaO_2 at baseline, and follow-up duration.

	B	95% C.I.	p value
Age (years)	-0.226	-0.280 to -0.171	<0.0001
Baseline eGFR (ml/min/1.73m^2)	-0.248	-0.282 to -0.215	<0.0001
fCPAP (ref. Untreated)	3.604	1.791 to 5.416	<0.0001
Follow-up duration (ln days)	-0.768	-1.280 to -0.255	0.003
Chronic heart failure (ref. absence)	-4.349	-7.113 to -1.584	0.002
Gender (ref. M)	-1.299	-2.395 to -0.203	0.020
APAP (ref. Untreated)	1.707	-0.250 to 3.665	0.087
ΔBMI (kg/m^2)	-0.140	-0.314 to 0.035	0.116
Arterial hypertension (ref. absence)	-0.663	-1.696 to 0.371	0.209
Diabetes mellitus (ref. absence)	-0.742	-2.039 to 0.554	0.262
Baseline lowest SpO_2 (%)	-0.024	-0.076 to 0.028	0.361
COPD (ref. absence)	0.668	-1.468 to 2.804	0.540

eGFR=estimated glomerular filtration rate; fCPAP=fixed continuous positive airway pressure; APAP=autoadjusting continuous positive airway pressure. ΔBMI=difference in body mass index between follow-up and baseline. SpO_2=oxyhemoglobin saturation; COPD=Chronic Obstructive Pulmonary Disease.

B coefficients with 95% confidence intervals and p values are shown

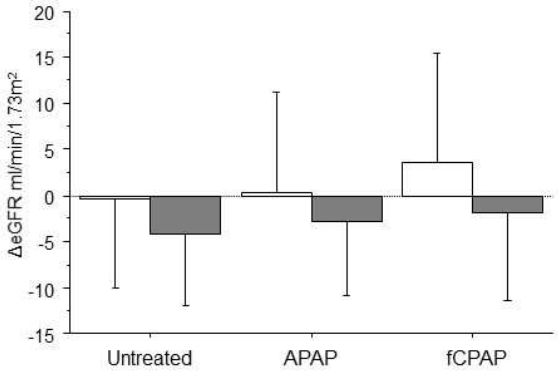
FIGURES LEGENDS

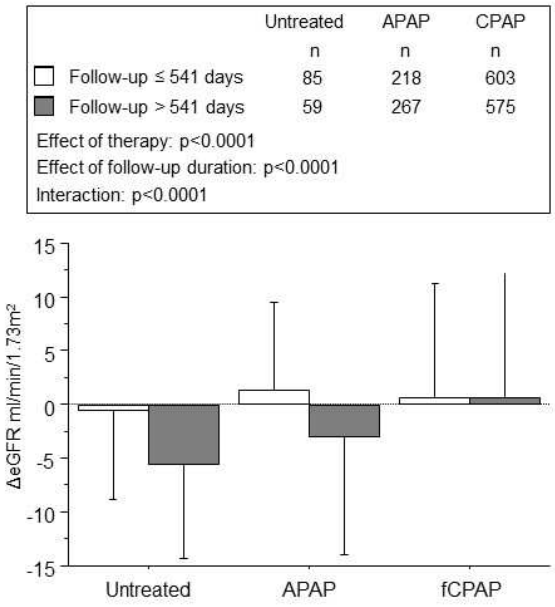
Figure 1. Changes in estimated glomerular filtration rate (ΔeGFR) between last follow-up visit and baseline in patients with baseline eGFR below (white columns) and above (grey columns) median, separately for treatment groups.
$p<0.0001$ for both effects of therapy and of baseline eGFR (two-way ANOVA).

Figure 2. Changes in estimated glomerular filtration rate (ΔeGFR) between last follow-up visit and baseline in patients with follow-up below (white columns) and above (grey columns) median, separately for treatment groups.
$p<0.0001$ for both effects of therapy and of follow-up duration. A significant interaction between treatment and follow-up duration was also found ($p<0.0001$, two-way ANOVA).

	Untreated	APAP	CPAP
	n	n	n
Baseline eGFR ≤ 91.42 ml/min/1.73m²	65	277	561
Baseline eGFR > 91.42 ml/min/1.73m²	79	208	616

Effect of therapy: p<0.0001
Effect of baseline eGFR: p<0.0001





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e-Appendix 1. Institutional review board data

IRB University of Palermo, Policlinico P. Giaccone, Palermo, Italy: approval no. 2102, September 21st, 2007

CNIL DR-2010-158 n°910289 and IRB n°5891/2009-6, Grenoble, France

Regional Ethical Review Board, University of Gothenburg, Sweden: Application 386-09, approved Oct 22nd, 2009

Ethics committee, Antwerp University Hospital, Belgium : EC7/33/184

Ethics Committee of the Hospital District of Southwest Finland; May 22nd, 2007 §204

Ethical Committee of the University of Bergen, Norway, ref. number 2008/2570-ANØL, March 10th, 2008.

Ethical Committee of Ege University Faculty of Medicine, Turkey, approval number 12-1.1/7, February 2nd, 2012

Ethical Committee of the Istituto Auxologico Italiano IRCCS, Milan, Italy, Prot. 368, June 12th, 2007

Research ethics committee St Vincent's University Hospital, Dublin, Ireland: McNicholas, August 2007

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e-Table 1. Characteristics of excluded and included subjects from the complete ESADA data base.

	Excluded (n=17,858)	Included (n=1,807)	p value
Age (yrs)	52.3±12.8	53.5±11.0	<0.0001*
Gender (F, No., %)	5,366 (30.1)	456 (25.2)	<0.0001§
BMI (kg/m^2)	31.3±6.7	31.9±6.3	0.0001*
ESS	9.5 [6.0-14.0]	10.0 [6.0-14.0]	0.04†
Hypertension (No., %)	7,486 (42.0)	827 (46.0)	0.0009§
Diabetes (No., %)	2,263 (12.7)	322 (17.9)	<0.0001§
Heart failure (No., %)	5,050 (2.9)	56 (3.1)	0.49§
Creatinine (mg/dl)	0.91 [0.80-1.04]	0.89 [0.79-1.01]	<0.0001†
AHI_{PG} (No./h)	12.0 [3.8-30.6]	22.9 [12.2-44.6]	<0.0001†
AHI_{PSG} (No./h)	23.3 [10.0-47.0]	38.9 [24.3-60.4]	<0.0001†
Mean SpO_2 (%)	94.0 [92.0-95.0]	93.4 [91.9-95.0]	<0.0001†
Lowest SpO_2 (%)	83.0 [77.0-88.0]	81.0 [75.0-85.0]	<0.0001†

BMI=body mass index; ESS=Epworth Sleepiness Scale; AHI_{PG}=apnea/hypopnea index measured at cardiorespiratory polygraphy; AHI_{PSG}=apnea/hypopnea index measured at polysomnography; SpO_2=oxyhemoglobin saturation.

Continuous variables: mean±SD or median [interquartile range] for normally and not normally distributed variables, respectively. Categorical variables: number (percentage).

*one-way ANOVA; §χ^2 test; †Mann-Whitney U-test