

Mortality of sleep apnoea patients treated by nasal continuous positive airway pressure registered in the ANTADIR observatory

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ABSTRACT: The aim of this study was to examine risk factors for and causes of mortality in patients with obstructive sleep apnoea syndrome (OSAS) treated by nasal continuous positive airway pressure (CPAP).

Univariate and multivariate analyses of the data on patients registered in the Association Nationale pour le Traitement À Domicile de l'Insuffisance Respiratoire chronique (ANTADIR) Observatory between January 1, 1985 and December 31, 1993 and followed to January 1, 1996. Survival ratios were compared to those of the French population. A case control study compared patients who died with patients of the same age and sex, in the same Regional Association, who were equipped with CPAP at the same time. Five-thousand-six-hundred-and-sixty-nine patients had CPAP treatment. Two-hundred-and-seventy-six had died. One-hundred-and-twenty-four deaths were examined and compared to 123 control subjects.

Overall mortality was the same as the general French population. Independent risk factors for death were age, oxygen tension in arterial blood (P_{a,O_2}) and forced expiratory volume in one second (FEV₁) (per cent predicted). In the case-control study independent risk factors for death in the past history were cardiac arrhythmia with an odds ratio (OR) of 2.8 (95% confidence interval (CI) 1.1–7.2), respiratory disorders (OR 2.8; CI 1.6–4.9) ischaemic events (OR 2.2; CI 1.2–4.2), neurological and psychiatric disorders (OR 2.4; CI 1.1–5.4). A significant excess of cardiovascular deaths and an excess of deaths from accidents and poisonings was found.

In conclusion, patients die on therapy predominantly from cardiovascular causes but many have a past history of cardiovascular conditions. Compliance with treatment may be important for survival. Continuous positive airway pressure is an effective therapy for obstructive sleep apnoea syndrome but older patients with reduced spirometry and hypoxaemia may need more attention paid to these aspects of their condition.

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Obstructive sleep apnoea syndrome (OSAS) is a common condition [1, 2] affecting 1–4% of the adult population. Thus there are large consequences for public health because of the associated morbidity and mortality [3–7]. Nasal continuous positive airway pressure (CPAP) is now a well-established treatment for the management of OSAS [8] with a major benefit in improving sleepiness. CPAP treatment may also improve some of the consequences of OSAS such as hypertension [9, 10] and autonomic dysfunction [11], but a recent review concluded that stronger evidence is needed to prove the effectiveness of this treatment [12].

Few studies have been performed to assess the effectiveness of CPAP treatment on mortality and all studies to date have focused on patients from one centre. Thus the number of deceased subjects in these studies is small, as the mortality rate of treated OSAS is low. LAVIE *et al.* [5] followed 1,620 patients diagnosed with OSAS between

1976–1988. Fifty-seven had died by 1991 but only 25 of the total number had been treated by CPAP. Risk factors for mortality were age, body mass index (BMI), apnoea/hypopnoea index (AHI) and hypertension.

In 1996 in France there were 13,900 patients on CPAP registered with Association Nationale pour le Traitement À Domicile de l'Insuffisance Respiratoire chronique (ANTADIR) (the federated National Association for respiratory home care). ANTADIR is a national observatory with large numbers of patients registered and is thus an ideal structure for epidemiological study of the treated population [13]. The authors have been able to calculate survival rates and prognostic factors of CPAP treated patients. In order to assess risk factors and causes of death in treated patients a case control study of patients who died on CPAP treatment over a 10-yr period between 1985 and the end of 1995 was conducted.

Patients and methods

Mortality study of overall population treated by continuous positive airway pressure

Data collection. ANTADIR was set up in France in the 1970s as a nonprofit network for home treatment of patients with chronic respiratory insufficiency (CRI). ANTADIR collects clinical data on treated patients in an "Observatory" and data is available from 25/33 associations in the network covering 79% of the patients in ANTADIR. At treatment initiation data is collected from the Social Security form that is filled in by the prescriber concerning the patient's age, sex, height, weight, forced expiratory volume in one second (FEV₁), vital capacity (VC) and arterial blood gases (ABG) in room air. Subsequent treatment modification or withdrawal and death are registered. The anonymous registration of patients was approved by the "Commission Nationale de l'Informatique et des Libertés" (CNIL).

Mortality rates were calculated on patients diagnosed as having OSAS alone and equipped with nasal CPAP but not oxygen therapy between January 1, 1985 and December 31, 1993. Three-hundred-and-eleven patients who had oxygen therapy as well as CPAP were excluded in order to avoid a sampling bias towards an overlap syndrome.

Statistical analysis

Survival was estimated by the actuarial method from the first day of home treatment and compared to that of the general population of similar age and sex distribution derived from the French National statistics (INSEE) [14]. Prognostic factors were analysed by the log rank test with quantitative variables being divided into predefined groups. Multivariate analysis used the semi-parametric model of Cox with stepwise regression to define the association of significant factors. The variables studied were age, sex, BMI, FEV₁ and VC as per cent predicted [15], and the oxygen tension in arterial blood (P_{a,O_2}) plus carbon dioxide tension in arterial blood (P_{a,CO_2}) in ambient air. These variables compared survivors and patients who died using the Chi-squared test and Student t-test. Data on patients who were lost to view or stopped CPAP were also examined.

Case control study on a sample of patients

A case-control study was carried out in 7/25 associations in order to find past medical history, cause of death and the role of OSAS. The roles of disease severity and the level of compliance were also examined. The participating centres identified from their files patients who died while on nasal CPAP therapy up to January 1, 1996 and who did not have additional oxygen therapy. Matched control subjects of the same sex and age and equipped with CPAP within 6 months of the index case were chosen. Written instructions were given to the doctors searching the data to find patients of the same sex, within a 5 yr age band and then within the shortest time difference of installation of CPAP. Demographic and clinical data were sought for case subjects and control subjects and the prescribing doctor or general practitioner or the family were contacted to seek the cause

of death. Compliance as hours per night of CPAP use was sought from records of the technicians from the clock counters in the machines during home visits.

The characteristics of the patients who died were compared with those of the control subjects by the Chi-squared test and Student's t-test. Multivariate analysis by logistic regression was performed in order to find the best association of prognostic factors. Significance was recognized at $p < 0.05$.

Results

Mortality data for overall population

Five-thousand-six-hundred-and-sixty-nine patients were equipped with CPAP between January 1, 1985 and December 12, 1993. At the date of analysis (January 1, 1996) 3,906 (69%) were still being treated with CPAP, 276 (4.9%) patients had died and 1,487 (26%) had been lost to follow-up having had treatment stopped mainly due to noncompliance. These patients were included in the study up to the date of last information which was, for the most part, the date of discontinuation of therapy, as is usual in this type of study. There were no differences as regards sex or BMI ($\text{kg}\cdot\text{m}^{-2}$) between deceased and survivors (table 1). The patients who died were older and had reduced respiratory function (FEV₁, VC and FEV₁/VC) with a lower P_{a,O_2} and a slight but significant increase in P_{a,CO_2} . Patients lost to follow-up were similar to those still on CPAP as regards age, sex and spirometry but had a clinically insignificant BMI difference (mean \pm SD 34.3 ± 7.3 versus 34.6 ± 7.5 $\text{kg}\cdot\text{m}^{-2}$). Similarly the differences in

Table 1. – Demographic data for continuous positive airway pressure treated subjects alive, lost to follow-up and dead (Association Nationale pour le Traitement À Domicile de l'Insuffisance Respiratoire chronique (ANTADIR) Observatory)

	Alive (n=3906)	Lost* (n=1487)	Dead (n=276)	Alive versus lost*	Alive +lost* versus dead
Sex					
% male	85.6	86.8	86.7	NS	NS
Age	55.6 \pm 10.8	55.5 \pm 11.7	61.5 \pm 10.2	NS	<0.001
BMI $\text{kg}\cdot\text{m}^{-2}$	34.6 \pm 7.5	32.8 \pm 6.9	34.3 \pm 7.3	<0.001	NS
FEV ₁	84.0 \pm 20.9	84.9 \pm 21.6	73.5 \pm 21.8	NS	<0.001
% pred					
VC	88.3 \pm 18.3	90.0 \pm 18.8	78.4 \pm 19.4	<0.05	<0.001
% pred					
FEV ₁ /VC %	73.8 \pm 10.8	73.9 \pm 11.0	71.1 \pm 12.3	NS	<0.01
P_{a,O_2} mmHg	75.5 \pm 11.5	77.2 \pm 11.6	69.7 \pm 10.8	<0.001	<0.001
P_{a,CO_2} mmHg	42.4 \pm 5.1	41.9 \pm 4.7	43.6 \pm 5.0	<0.01	<0.001

Data are presented as absolute numbers or as mean \pm SD. *: to follow-up. BMI: body mass index; FEV₁: forced expiratory volume in one second; VC: vital capacity; P_{a,O_2} : oxygen tension in arterial blood; P_{a,CO_2} : carbon dioxide tension in arterial blood.

blood gases between these two groups of patients were not of clinical importance (table 1).

The mean age at death of the 276 patients who died was 61.5 ± 10.2 yrs (mean \pm SD). Survival was 90% at 6 yrs and identical to that of the general population (fig. 1). Comparison of observed *versus* expected survival with the programme of HAKULINEN and ABEYICKRAMA [16] showed no significant difference in the expected survival of the age groups 18–49 yrs and 50–69 yrs. In contrast, older patients (70–90 yrs) had a greater survival than the general population (fig. 2). Comparison of the survival curves (fig. 2) confirmed the significance of age, spirometric data and diurnal blood gases. Sex and BMI do not appear to be predictive factors. Multivariate analysis showed that independent risk factors for death were age, P_{a,O_2} , and FEV₁ (per cent predicted; table 2).

Case-control study on 124 patients

In the case-control study 124 patients who died were matched with 123 control subjects. There was no difference as regards age, duration of treatment or BMI (table 3). There were slightly more smokers in the group of deceased patients ($p=0.07$). Risk factors, for dying on CPAP were FEV₁, VC (per cent predicted) and diurnal P_{a,O_2} . The P_{a,CO_2} was slightly higher in the deceased group. There was no difference as regards AHI on the polygraphic study and the minimum saturation overnight was similar between the groups. However, the percentage of time spent with a $P_{a,O_2} < 90\%$ was much greater in the patients who died. By logistic regression the best predictors of subsequent death were the FEV₁ (per cent predicted) and percentage of time spent with an arterial saturation (S_{a,O_2}) $< 90\%$. When this factor is introduced into the logistic regression the significance of diurnal P_{a,O_2} disappears. The level of CPAP pressure was slightly higher in the patients who died. Compliance with treat-

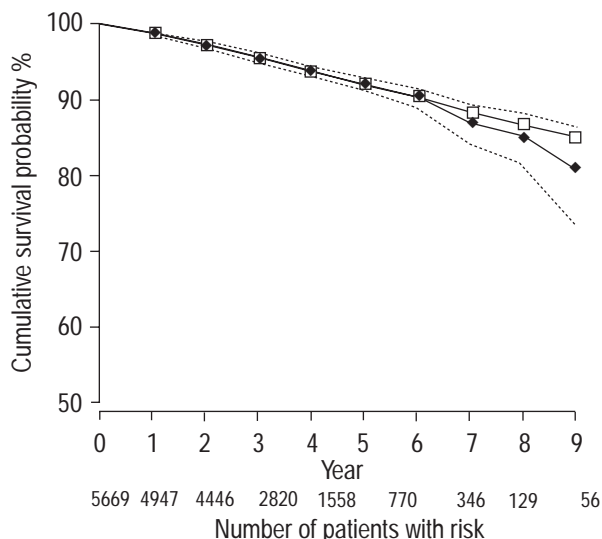


Fig. 1. – Cumulative survival (◆) for patients treated with nasal continuous positive airway pressure in the Association Nationale pour le Traitement A Domicile de l'Insuffisance Respiratoire chronique (ANTADIR) Observatory with 95% confidence intervals (– –) and expected survival curve for the French population of the same age and sex distribution (□).

ment was worse among deceased patients but these data were not available for 22 patients and two control subjects. When the patients for whom no compliance data were available are excluded, 57% of the deceased patients used CPAP for ≥ 5 h while 77% of the control subjects had this level of compliance, the difference being highly significant (Chi-squared=10, $p<0.002$). The median duration of treatment for the patients who died was 2 yrs and for their control subjects equipped at the same time it was 4 yrs reflecting their continuation in the study.

In the past medical histories (table 4) the incidence of arterial hypertension was similar in the two groups. In

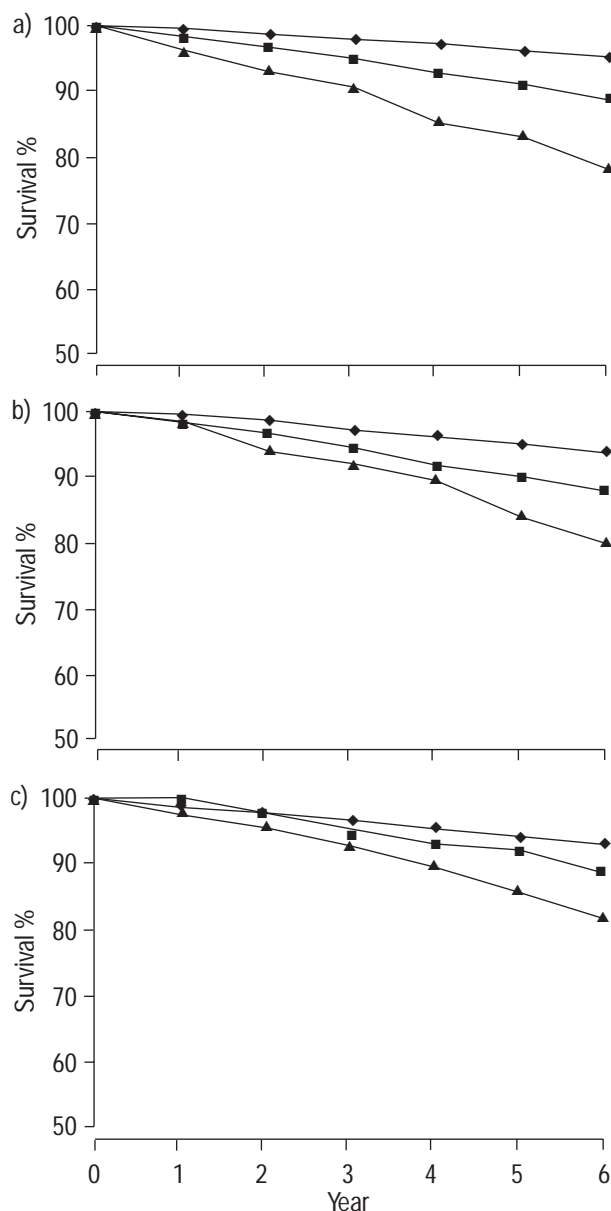


Fig. 2. – Survival curves for patients treated by nasal continuous positive airway pressure in the Association Nationale pour le Traitement A Domicile de l'Insuffisance Respiratoire chronique (ANTADIR) Observatory for different ranges of age (a), oxygen tension in arterial blood (b) and forced expiratory volume in one second (per cent predicted; (c)). a) ◆: 18–49 yrs; ■: 50–69 yrs; ▲: 70–90 yrs; $p<0.001$. b) ◆: ≥ 75 mmHg; ■: 60–74 mmHg; ▲: 50–59 mmHg; $p<0.001$. c) ◆: ≥ 80 L; ■: 65–79 L; ▲: < 65 L; $p<0.001$.

Table 2. – Multivariate analysis of prognostic factors by Cox model (n=3055)

	Mean±SD	p-value	Hazard ratio (95% CI)
Age for 10 yrs	0.59±0.08	<0.001	1.80 (1.52–2.13)
P_{a,O_2} for 10 mmHg	-0.27±0.08	0.001	1.31 (1.11–1.54)
FEV1 (% pred) for 10%	-0.13±0.04	0.001	1.14 (1.06–1.22)

CI: confidence interval; P_{a,O_2} : oxygen tension in arterial blood; FEV1: forced expiratory volume in one second.

contrast patients who died had significantly greater incidence of cardiac dysrhythmia, ischaemic events (coronary events, and cerebrovascular and peripheral vascular events), left or right ventricular insufficiency, respiratory illnesses, neurological and psychiatric events and diabetes. The incidence of cancer was slightly but nonsignificantly increased in the deceased group. Using multivariate analysis significant risk factors for death were dysrhythmia with an odds ratio (OR) of 2.8 (95% confidence interval (CI) 1.1–7.2) ischaemic events (OR 2.2, CI 1.2–4.2), respiratory events (OR 2.8, CI 1.6–4.9) and neuropsychiatric events (OR 2.4, CI 1.1–5.4).

The cause of death was found for 112/124 patients (table 5). This information was from the general practitioner or prescribing doctor in 86% and in 15 cases directly from the family. In comparison to the general French population of the same age and sex a significant excess of

Table 3. – Case control study: characteristics of patients

	Cases (dead)	Control subjects (alive)	p-value
Sex			
Female	15	18	0.56
Male	109	105	
Age yrs	63.2±10.0	62.9±11.1	0.78
BMI kg·m ⁻²	34.9±7.7	34.2±7.0	0.4
Smoking history %			
Nonsmoker	21	29	0.07
Exsmoker	63	71	
Smoker	30	17	
FEV1 % pred	68.0±20.6	80.8±22.2	<0.001
VC % pred	76.3±18.0	84.4±19.4	0.002
FEV1/VC %	68.1±12.2	73.3±10.2	<0.001
P_{a,O_2} mmHg daytime	68.4±12.6	74.2±12.4	<0.001
P_{a,CO_2} mmHg daytime	42.8±7.0	41.5±5.0	0.084
AHI	46.6±19.7	49.6±19.5	0.26
S_{a,O_2} min, night	66.8±14.7	67.7±16.9	0.72
Percentage nights with S_{a,O_2} <90%	54.5±32.2	36.9±28.5	<0.001
CPAP pressure cmH ₂ O	10.3±2.4	9.7±2.2	0.05
Compliance with CPAP			
≥5 h	55 (44%)	93 (75%)	<0.001
2–5 h	21 (17%)	16 (13%)	
<2 h	21 (17%)	12 (10%)	
Unknown	27 (22%)	2 (2%)	

Data are presented as mean±SD unless indicated otherwise. BMI: body mass index; FEV1: forced expiratory volume in one second; VC: vital capacity; P_{a,O_2} : oxygen tension in arterial blood; P_{a,CO_2} : carbon dioxide tension in arterial blood; AHI: apnoea/hypopnoea index; S_{a,O_2} : arterial oxygen saturation; CPAP: continuous positive airway pressure.

Table 4. – Case control study: past medical history

	Dead cases	Control subjects	p-value
Hypertension	70 (56)	68 (55)	0.111
Cardiac dysrhythmia	20 (16)	8 (7)	0.016
Ischaemia (coronary, cerebral, peripheral)	45 (36)	24 (20)	0.003
Cardiac failure	16 (13)	6 (5)	0.025
Respiratory function	68 (55)	34 (28)	<0.001
Neurological/psychiatric history	25 (20)	12 (10)	0.021
Diabetes	35 (28)	18 (23)	0.009
Cancer	23 (19)	13 (11)	0.072

Data are presented as absolute numbers with percentages in parentheses.

cardiovascular deaths was found with a large number of sudden deaths and cardiac arrests. In contrast the proportion of respiratory deaths was as in the general population. There was an excess of deaths from accidents and poisonings with an increase in suicide and postoperative deaths.

Discussion

This study has shown that patients with OSAS treated with nasal CPAP alone have a similar mortality rate to the general French population despite substantial numbers having significant past histories of cardiovascular disease. The patients who died on CPAP, however, had increased cardiovascular mortality. These patients were less compliant with treatment than a matched group of survivors and had more severe nocturnal hypoxaemia. These are important points for clinicians managing these patients.

Previous studies have found an increased mortality in the untreated OSAS population [3, 5]. HE *et al.* [3] showed an increased mortality in patients with AHI >20 in a questionnaire study of 706 males with 385 responses. Eight year survival ratio was 0.96 for AHI <20 compared to 0.63 for those with AHI >20. Like LAVIE *et al.* [5] the current authors found a survival advantage for elderly patients but it is thought that this may reflect the choice of fitter elderly patients for the demands of CPAP therapy. The authors cannot claim a survival benefit for CPAP, as this would require a prospective randomized study.

It has been found that increasing age and low FEV1 were predictive of poor survival in a CPAP treated population and in the case-control study. HOLE *et al.* [17] have shown that FEV1 is an independent risk factor for mortality of all causes. In addition diurnal P_{a,O_2} was a prognostic factor and the amount of time spent asleep

Table 5. – Case control study: cause of death

Cause of death	n	Observed	Expected	p-value
Cardiovascular disease	55	49.1	27.5	<0.001
Cancers	29	25.9	41.4	<0.001
Respiratory system	6	5.4	5.4	NS
Infectious diseases	2	1.8	2.0	NS
Gastrointestinal	1	0.9	6.6	<0.01
Trauma, poisoning	19	17.0	9.7	<0.001

Data are presented as absolute numbers.

with arterial oxygen saturation under 90% during the initial sleep study. Patients were excluded if they were treated with oxygen and CPAP in order to avoid a confounding effect. Oxygen saturation declines with age but we matched patients for age in the case-control study and the patients who died had lower daytime oxygenation.

A case control study was performed in order to make a more detailed search by seeking severity and compliance data. The data for AHI were likely to be tainted by the diversity of diagnostic methods particularly in the early years of CPAP therapy and thus the authors did not find the AHI to be significantly different between case subjects and control subjects. The question arises as to whether AHI is the best estimate of severity of OSA [18]. Perhaps the severity of nocturnal oxygen desaturation may be more relevant.

The duration of sleep apnoea may be relevant but the authors cannot determine whether the patients who died had a longer prediagnosis history of sleep related breathing difficulties than the survivors. Smoking and obesity are recognized as major risk factors for cardiovascular mortality and a multivariate analysis was performed including these factors and found that compliance with CPAP and untreated nocturnal desaturation level remain of prognostic significance.

Compliance with treatment was better in the surviving control group but there was less compliance data in the deceased group. This may be because earlier machines did not facilitate recording of compliance data. Compliance may thus be an important issue for the prognosis of sleep apnoea syndrome (SAS) patients. The critical level of compliance is not known [19] but some studies have shown benefit from only 3 or 4 h of treatment per night [20, 21]. Prospective studies are needed to clarify what patterns of compliance are of significance.

An excess of cardiovascular deaths were found in this population compared to the general French population of the same age and sex structure. Nocturnal hypoxaemia and increased sympathetic activity could theoretically promote the development of atherosclerosis [22]. The population who died tended to contain more smokers than the surviving population but this did not reach statistical significance. The proportion of known hypertensive patients was similar in both groups. The evidence that SAS causes hypertension is controversial [12] but more recent studies [23–25] found a consistent independent correlation of AHI and blood pressure (BP). PANKOW *et al.* [26] have recently shown that OSA is associated with hypertension independently of the confounding factors of age and obesity.

The proportion of patients with other cardiovascular diagnoses such as dysrhythmia; ischaemic diseases and cardiac failure was higher in the group dying on CPAP. The authors cannot be certain that OSA causes these conditions but the results do show that patients with such conditions are at increased risk when found to have OSA and this should be taken into consideration in therapeutic decisions. Twenty per cent of the patients who died had a past history of cardiac arrhythmia. Cardiac arrhythmias are known to occur in OSA patients [27] and this is related to the mean nocturnal S_{a,O_2} being <90%. Also, OSA patients have abnormal cardiac autonomic stress tests [28]. The patients who died had lower levels of daytime and night-time

oxygenation and an increased level of ischaemic heart disease. GILLIS *et al.* [29] showed that Q-T interval corrected for heart rate (QTc) prolongation occurred during apnoeas and QTc prolongation is associated with ventricular arrhythmia and sudden death in myocardial ischaemia [30]. Thus all these compounding factors may have played a role in the demise of these patients despite treatment of their sleep apnoea. A recent study showed that 5/14 patients with OSA and known coronary heart disease had frequent ischaemic events during sleep compared to only one of seven patients with OSA who did not have coronary heart disease [31]. Thus cardiovascular risk factors should be addressed in patient management.

Sleep disordered breathing can be associated with psychiatric disease such as depression and psychosis [32] and these syndromes can be improved with effective treatment [33]. It was found that eight of the patients had committed suicide, which is higher than the general population. Likewise the proportion of patients dying from traumatic causes was elevated. Nonetheless, a recent report has shown that CPAP may reduce the number of accidents and near-miss accidents [34].

While continuous positive airway pressure treatment in obstructive sleep apnoea is primarily for the relief of symptoms, particularly daytime sleepiness, this study indirectly shows the benefits of continuous positive airway pressure on survival. The authors have identified risk factors for mortality which are relevant even when the patient is treated. Thus in considering patients for treatment of obstructive sleep apnoea clinicians should pay special attention to those with cardiovascular conditions or indicators of resting hypoxaemia. Aspects of compliance may merit special attention in this group of patients since low compliance seems a risk factor for mortality in this population.

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