ORIGINAL ARTICLE

Effect of Obstructive Sleep Apnea Treatment on Renal Function in Patients with Cardiovascular Disease

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Abstract

Rationale: Obstructive sleep apnea (OSA) is associated with impaired renal function, but uncertainty exists over whether OSA treatment can influence renal outcomes.

Objectives: To determine the effects of continuous positive airway pressure (CPAP) on renal function in subjects with coexisting OSA and cardiovascular disease.

Methods: This was a substudy of the international SAVE (Sleep Apnea Cardiovascular Endpoints) trial, in which 2,717 patients with moderate to severe OSA and established coronary or cerebrovascular disease were randomized to receive either CPAP plus usual care or usual care alone. Renal function and adverse renal events were compared between the CPAP (n = 102) and usual care (n = 98) groups. Glomerular filtration rate was estimated at randomization and at the end of follow-up, and the urinary albumin-to-creatinine ratio was measured at study exit.

Measurements and Main Results: In 200 substudy participants (mean age, 64 yr; median, 4% oxygen desaturation index; 20 events/h; mean estimated glomerular filtration rate at baseline, 82 ml/min/1.73 m^2), the median (interquartile range) changes in estimated glomerular filtration rate (ml/min/1.73 m^2/yr) were −1.64 (−3.45 to −0.740) in the CPAP group and −2.30 (−4.53 to −0.71) in the usual care group ($P = 0.21$) after a median of 4.4 years. There were no between-group differences in end-of-study urinary albumin-to-creatinine ratio or in the occurrence of serious renal or urinary adverse events during the trial. The level of CPAP adherence did not influence the findings.

Conclusions: CPAP treatment of OSA in patients with cardiovascular disease does not alter renal function or the occurrence of renal adverse events.

Clinical trial registered with www.clinicaltrials.gov (NCT00738179).

Keywords: obstructive sleep apnea; continuous positive airway pressure; randomized controlled trial; glomerular filtration rate; albuminuria

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At a Glance Commentary

Scientific Knowledge on the Subject: Obstructive sleep apnea (OSA) is a risk factor for developing chronic kidney disease (CKD) and is common in patients with CKD. Animal and clinical studies have indicated that the association between OSA and CKD may be mediated by nocturnal hypoxemia. Observational studies suggest that treatment of OSA with continuous positive airway pressure (CPAP) may improve or mitigate decline in renal function, but this has not been examined in a randomized controlled trial.

What This Study Adds to the Field: To our knowledge, this is the first evaluation of the effects of CPAP treatment for OSA on renal function in a randomized trial. Participants in a large trial of CPAP for the secondary prevention of cardiovascular disease were recruited into a substudy of renal function. Most participants had normal baseline renal function, which showed a gradual decline over several years of follow-up. However, the decline in renal function was not significantly different between those who received CPAP therapy and those who did not.

Obstructive sleep apnea (OSA) is a highly prevalent condition associated with significant morbidity. It is remarkably common among patients with chronic kidney disease (CKD) and may be a risk factor for developing CKD (1–4). An animal model of sleep apnea showed inflammatory and fibrotic changes in the kidney that were attributed to the effects of intermittent hypoxia (5). Nocturnal hypoxemia in patients with OSA is associated with accelerated loss of renal function (3), possibly due to glomerular hypertension and increased activity of the renal renin-angiotensin system (RAS) (6, 7). Patients with OSA are also at increased risk of developing hypertension (8) and diabetes (9), both of which are related to CKD.

Continuous positive airway pressure (CPAP) therapy reduces OSA symptoms and associated hypoxemia (10) and hypertension (11), which may translate into beneficial effects on the kidney. There is support for this hypothesis from some (6, 12), although not all (4), observational CPAP intervention studies, but to date there have been no randomized studies. We report the results of a substudy among participants of the large-scale SAVE (Sleep Apnea Cardiovascular Endpoints) randomized controlled trial (NCT00738179) to determine the effects of CPAP treatment on renal function in a cohort with OSA and cardiovascular disease but without CKD in the majority of patients.

Methods

Background and Study Design

SAVE was an international, multicenter, open, blinded outcome–assessed, randomized trial of CPAP treatment for the secondary prevention of cardiovascular disease, the details of which are outlined elsewhere (13–15). The trial protocol was approved by all appropriate regulatory authorities and ethics committees at participating centers. All participants provided written informed consent to both the main trial and the kidney substudy. Medical history as well as demographic and anthropometric information was collected, and serious adverse events occurring during the study were recorded according to the Medical Dictionary for Regulatory Activities classification system (MedDRA version 14; www.meddra.org). Further details are provided in the Methods section in the online supplement.

Substudy Participants and Samples

Participants enrolled in the SAVE trial at Australian and New Zealand centers between January 2009 and December 2013 were invited to participate in this substudy designed to evaluate the impact of CPAP therapy on renal function. Blood was collected at baseline for separation of serum, which was then frozen and stored at −80°C. Blood and a single 40-ml urine sample were collected from fasting participants at their final follow-up appointments over several months to January 2016 and frozen at −80°C for later analysis. At the conclusion of the trial, all samples were shipped to the Woolcock Institute of Medical Research at the University of Sydney, Australia, with assays centrally batch processed at Sydney South West Pathology Service at Royal Prince Alfred Hospital.

Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine concentrations (automated kinetic, rate-blanked, colorimetric assay, Jaffe method, cobas 8000; Roche Diagnostics, Indianapolis, IN) measured from baseline and end-of-study samples using the CKD Epidemiology Collaboration ("CKD-EPI") equation according to Australian guidelines (16). Because participants were followed for different lengths of time, the annual rate of change in eGFR was calculated by dividing each participant's absolute change in eGFR from baseline to exit by their period of follow-up in years. Kidney function stages (KFSs) were calculated from eGFR (16). Concentrations of creatinine and albumin (automated, solid-phase, competitive chemiluminescence enzyme immunoassay, IMMULITE 2000 XPi system; Siemens Medical Solutions, Malvern, PA) were determined from a urine sample taken at the end-of-study visit and used to calculate the urinary albumin-to-creatinine ratio (UACR), which was categorized in sex-specific ranges as normal, microalbuminuria, or macroalbuminuria (16). These data were then combined with KFS to provide an overall measure of progressive CKD risk category at the conclusion of the trial, as previously described (16).

Statistical Analysis

Initial analyses were undertaken according to randomized group allocation (CPAP vs.

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usual care). In a secondary analysis, the study population was subdivided into three groups: patients allocated to CPAP who had good adherence (average, ⩾4 h/night for the study duration), those allocated to CPAP with poor adherence (average, <4 h/night), and those allocated to usual care who never used CPAP. Twenty-four participants who were randomized to usual care but subsequently reported using CPAP at some point were excluded from this secondary analysis. The Appendix in the online supplement contains details of the analytical methods used. All statistical analyses were undertaken using IBM SPSS Statistics version 23 software (IBM, Armonk, NY).

Results

Of the 200 participants with both baseline and end-of-study blood or urine samples, less than 5% had missing data (*see* Figure E1 for participant flow). Table 1 shows that baseline demographic and anthropometric characteristics were well balanced between groups. Study participants were predominantly middle-aged white men (*see* Table E1 for further details on ethnicity) who were overweight, had moderate to severe OSA, and were representative of Australian and New Zealand participants in the SAVE trial (Table E2). The median (interquartile range [IQR]) periods (yr) of follow-up were 4.3 (2.0–6.2) for the CPAP group and 4.5 (2.0–6.7) for the usual care group. The mean (±SD) use over the duration of the trial for those allocated to CPAP was 4.0 (2.6) hours per night.

Table 1. Baseline Characteristics of Allocated Treatment Groups (Intention to Treat)

	CPAP	Usual Care
Total, n = 200	102	98
Male sex, n (%)	90 (88)	92 (94)
Caucasian/European ethnicity, n (%)	94 (92)	87 (89)
Never smoker, n (%)	29 (28)	29 (30)
Past smoker, n (%)	64 (63)	66 (67)
Current smoker, n (%)	9 (9)	3 (3)
Cardiac disease history only, n (%)	90 (88)	82 (84)
Cerebrovascular disease history only, n (%)	9 (9)	13 (13)
Both cardiac and cerebrovascular disease history, n (%)	3 (3)	3 (3)
Diabetes, n (%)	22 (22)	26 (27)
ESS score ⩾11, n (%)	32 (31)	23 (23)
Blood pressure–lowering drugs, n (%)	96 (94)	88 (90)
ACE inhibitor/ARB, n (%)	72 (71)	71 (72)
Lipid-modifying agents, n (%)	94 (92)	89 (91)
Insulin, n (%)	5 (5)	7 (7)
Oral antidiabetic agents, n (%)	15 (15)	22 (22)
Antiplatelet/antithrombotic agents, n (%)	100 (98)	90 (92)
Organic nitrates, n (%)	28 (28)	22 (22)
Age, yr, mean ± SD	63 ± 7	65 ± 7
Weight, kg, mean ± SD	93 ± 14	93 ± 15
BMI, kg/m^2, median (IQR)	30.7 (28.1–34.5)	30.7 (27.3–34.3)
Waist-to-hip ratio, mean ± SD	0.99 ± 0.06	1.00 ± 0.07
Systolic blood pressure, mm Hg, mean ± SD	131 ± 19	133 ± 20
Diastolic blood pressure, mm Hg, mean ± SD	79 ± 10	79 ± 11
Heart rate, beats/min, mean ± SD	65 ± 10	66 ± 11
Apnea–hypopnea index, events/h, median (IQR)	21 (15–29)	20 (15–29)
Oxygen desaturation index, events/h, median (IQR)	20 (16–28)	21 (16–30)
Time <90% O_2 saturation, % of recording time, median (IQR)	8.52 (3.84–16.11)	8.84 (3.69–17.81)
Time <85% O_2 saturation, % of recording time, median (IQR)	0.69 (0.21–1.84)	0.75 (0.20–3.29)
Time <80% O_2 saturation, % of recording time, median (IQR)	0.00 (0.00–0.24)	0.00 (0.00–0.45)
Baseline eGFR, ml/min/1.73 m^2, mean ± SD	82.9 ± 18.3	81.6 ± 15.9
CPAP nightly adherence for duration of trial, h, mean ± SD	4.04 ± 2.59	—

Definition of abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; CPAP = continuous positive airway pressure; eGFR = estimated glomerular filtration rate; ESS = Epworth Sleepiness Scale; IQR = interquartile range.

Effects of CPAP on Renal Function

Figure 1 shows that there was no significant difference in eGFR values between the CPAP and usual care groups at baseline or at the end of the study. The median (IQR) annual rates of change in eGFR (ml/min/1.73 m^2/yr) were −1.64 (−3.45 to −0.74) in the CPAP group and −2.30 (−4.53 to −0.71) in the usual care group ($P = 0.21$).

Most participants had normal or near-normal renal function at study baseline, though the distribution of participants across KFSs 1 and 2 (i.e., normal and mildly impaired function, respectively) between the CPAP and usual care groups bordered on significance (Table 2). There was no between-group difference in the distribution of participants across KFS categories at study exit (Table 2) ($P = 0.92$), with an overall decline in eGFR and a shift toward higher KFS categories observed in both groups.

Because CPAP treatment of OSA might affect renal function differently in those with and those without preexisting renal impairment, we assessed the annual rate of change of eGFR for participants allocated to CPAP or usual care, categorized as those with normal (stage 1; eGFR, ⩾90 ml/min/1.73 m^2) and impaired (stage 2 or worse; eGFR, <90 ml/min/1.73 m^2) kidney function at baseline (Figure 2). The median annual rate of change in eGFR was lower in those with a reduced baseline eGFR compared with those with a normal baseline eGFR (−1.57 [IQR, −4.18 to −0.33] vs. −2.40 [−4.14 to −1.34] ml/min/1.73 m^2/yr, respectively; $P = 0.035$). However, analysis of covariance indicated that treatment allocation did not predict annual change in eGFR after adjustment for baseline eGFR (CPAP vs. usual care, $B = 2.828$ ml/min/1.73 m^2/yr; 95% confidence interval [CI], −1.969 to 7.624; $P = 0.25$), and there was no significant interaction of baseline eGFR with treatment allocation ($B = -0.027$ ml/min/1.73 m^2/yr; 95% CI, −0.084 to 0.031; $P = 0.36$). Further analysis restricted to individuals (n = 22) with more severely reduced baseline eGFR (KFS 3A or worse; eGFR, <60 ml/min/1.73 m^2),

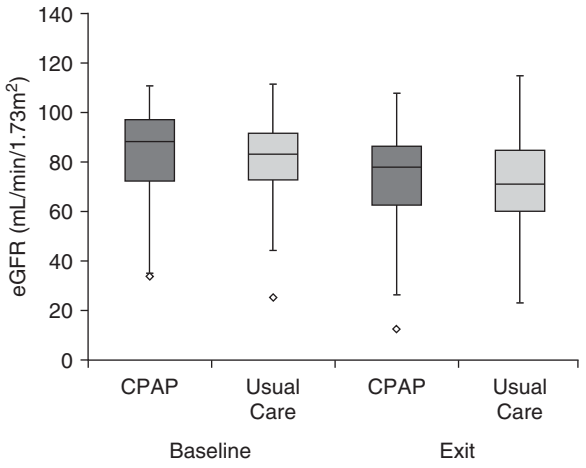

Figure 1. Estimated glomerular filtration rate (eGFR) among participants allocated to continuous positive airway pressure (CPAP) plus usual care or to usual care alone at baseline and exit time points. *Boxes* represent interquartile range with median as a *bar*; *whiskers* are 1.5 times the interquartile range; and *diamonds* represent outliers. Between-group comparisons were not significant at either time point (Mann-Whitney *U* test).

showed comparable rates of decline in eGFR between treatment groups (-0.87 ± 4.40 vs. -1.05 ± 2.62 ml/min/1.73 m^2 in CPAP and usual care groups, respectively; $P = 0.50$). Use of medications targeting the RAS, such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, was also not a significant predictor of the rate of change of eGFR, nor was there any significant interaction between medication status for these drugs and CPAP treatment (data not shown).

The end-of-study UACR was not different between the CPAP and usual care groups (median [IQR], 1.45 [0.70 to 5.95] vs. 1.30 [0.65 to 3.55] mg/mmol; $P = 0.43$). In the subgroup of participants who had baseline eGFR less than 60 ml/min/1.73 m^2 and who were therefore at higher risk of CKD, UACR was also not significantly different between the CPAP and usual care groups (11.2 [2.6 to 73.0] vs. 15.6 [1.6 to 34.4] mg/mmol; $P = 1.00$). Combining UACR and eGFR data, the proportions of patients in various categories of risk for progressive CKD at study exit were also not different (Figure 3) ($P = 0.71$). Regression analyses indicated that adjustment for RAS medication status did not significantly alter these outcomes (data not shown).

A total of 406 serious adverse events in participants in this substudy were reported, 244 (68 individuals) in the CPAP group and 162 (52 individuals) in the usual care group, including 7 in each group classified as MedDRA category "renal and urinary disorders" ($P = 1.00$). There was no statistically significant difference between the CPAP and usual care groups in the incidence of individual event types coded within this category, but the low number precluded further analysis.

Effects according to Levels of CPAP Adherence

Except for significantly more smokers in the poor CPAP adherence group, the baseline characteristics were similar between the three groups included in the per-protocol secondary analysis (Table E3). The three groups had similar baseline and end-of-study eGFR values (Figure E2). The annual rate of change in eGFR was not different between groups (median [IQR], good CPAP use, -2.06 [-3.49 to -0.92] ml/min/1.73 m^2/yr; poor CPAP use, -1.45 [-3.16 to -0.49] ml/min/1.73 m^2/yr; usual care with no CPAP use, -2.45 [-4.72 to -0.71] ml/min/1.73 m^2/yr; $P = 0.33$). Further, no significant relationship was found between annual change in eGFR and average hours of CPAP use (Figure E3). Analysis of covariance indicated that the relationship between annual change in eGFR and CPAP adherence remained nonsignificant ($B = -0.040$ ml/min/1.73 m^2/yr; 95% CI, -0.286 to 0.205; $P = 0.75$) after adjustment for baseline eGFR, which was a significant predictor of the rate of change ($\geq$90 ml/min/1.73 m^2; $B = -1.956$ ml/min/1.73 m^2/yr; 95% CI, -3.223 to -0.689; $P = 0.003$). There was no difference between the three protocol adherence groups in KFS at baseline or at the end of the study, in UACR at the end of the study, or in progressive CKD risk categories at the end of the study (Tables E4 and E5 and Figure E4, respectively).

Factors Influencing Progressive CKD Risk

In ordinal regression analysis, neither allocation to receive CPAP nor adherence with CPAP therapy during the trial was significantly associated with category of progressive CKD risk at study exit (Table E6).

Table 2. Kidney Function Stage of Participants according to Treatment Allocation

eGFR (*ml/min/1.73 m²*)	Kidney Function Stage	CPAP		Usual Care	
		Baseline (*n = 102*)	Exit (*n = 102*)	Baseline (*n = 98*)	Exit (*n = 97*)
≥90	1	47 (46%)*	15 (15%)	31 (32%)*	11 (11%)
60–89	2	43 (42%)*	64 (63%)	57 (58%)*	62 (64%)
45–59	3A	7 (7%)	13 (13%)	8 (8%)	12 (12%)
30–44	3B	5 (5%)	8 (8%)	1 (1%)	8 (8%)
15–29	4	0	1 (1%)	1 (1%)	3 (3%)
<15 or dialysis	5	0	1 (1%)	0	1 (1%)

Definition of abbreviations: CPAP = continuous positive airway pressure; eGFR = estimated glomerular filtration rate.
*Proportions of participants with kidney function stages 1 and 2 between CPAP and usual care groups at baseline ($P = 0.048$ by Fisher's exact test).

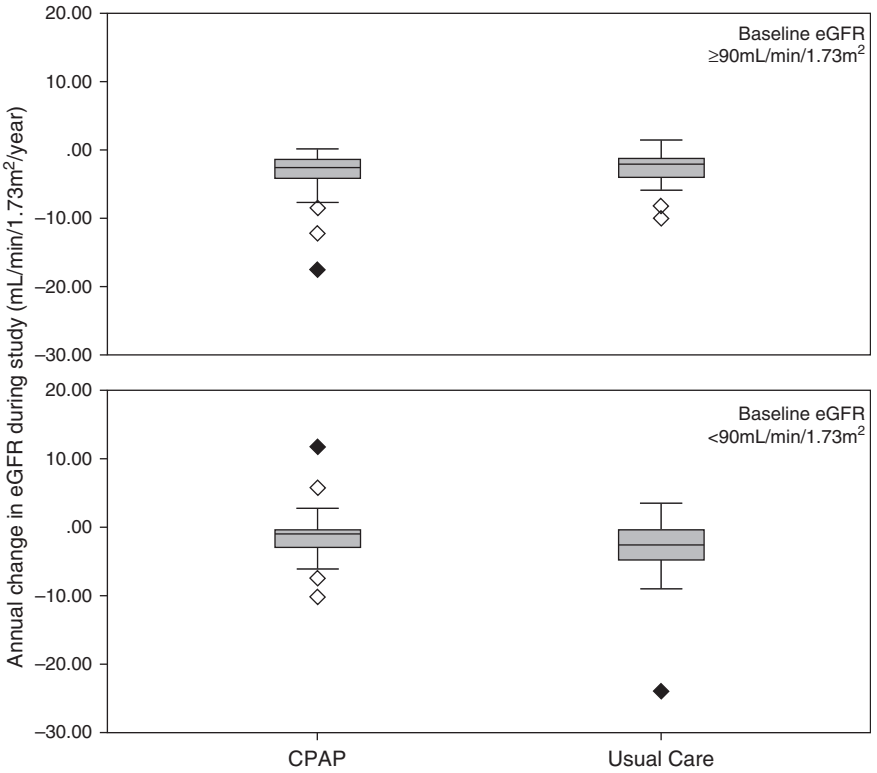

Figure 2. Change in estimated glomerular filtration rate (eGFR) per trial year, according to treatment allocation. The *top panel* shows participants with baseline eGFR greater than or equal to 90 ml/min/1.73 m^2, and the *bottom panel* shows participants with baseline eGFR less than 90 ml/min/1.73 m^2. *Boxes* represent interquartile range with median as a *bar*; *whiskers* are at 1.5 times the interquartile range; and *diamonds* represent outliers. No significant difference between treatment groups was found (Mann-Whitney *U* test). CPAP = continuous positive airway pressure.

Preexisting diagnosis of diabetes as well as higher baseline waist-to-hip ratio, systolic blood pressure, and percentage of nocturnal time spent with oxygen saturation less than 85% were all significantly associated with CKD risk at study exit, but neither CPAP allocation nor adherence predicted CKD risk category at study exit in adjusted models (Table E6).

Discussion

This subgroup analysis of the SAVE study among patients with moderate to severe OSA and a history of cardiovascular disease with generally preserved renal function shows that CPAP treatment over several years had no effect on several measures of renal function. Moreover, there was no benefit of CPAP according to baseline levels of renal function or according to levels of CPAP treatment adherence. Comorbid conditions such as diabetes, central obesity, and hypertension, as well as severity of nocturnal oxygen desaturation, were the strongest predictors of CKD risk.

Several cross-sectional (1, 2) and longitudinal studies (4, 17) have shown an association between CKD and OSA. Using a large Taiwanese administrative health insurance database, Lee and coworkers (17) showed that a diagnosis of sleep apnea was associated with a nearly twofold increase in the risk of developing CKD, whereas researchers in a long-term U.S. cohort study of ex–service personnel with OSA reported a greater risk of incident CKD and a faster decline in renal function than among those without a diagnosis of OSA (4). The rate of decline in eGFR in the veterans cohort study was greatest in those individuals with treated OSA (4). However, these studies were limited by an inability to fully control for various confounding factors, such as hypertension, diabetes mellitus, and other cardiovascular risk factors, as well as biases related to sleep assessment referrals, prescriptions, and adherence to CPAP.

Authors of a metaanalysis of eight observational studies totaling 240 patients with OSA in whom eGFR was assessed before and after positive airway pressure interventions found a neutral or negative association with most outcomes, with any potential benefit regarding renal function being confined to older people using treatment for longer than 3 months (18). A more recent retrospective study of 42 patients with moderate to severe CKD and OSA suggests that the influence of CPAP on renal function is related to the level of adherence (19). Most of this patient cohort had stages 3–5 kidney disease and severe sleep apnea (apnea–hypopnea index, >30) at the time of enrollment, which contrasts with the patients in the present study, most of whom had preserved renal function (i.e., eGFR >60).

Our randomized assessment showed no effect of CPAP treatment for OSA on renal function in a high cardiovascular risk group in which the rate of decline in eGFR (2.57 mg/ml/1.73 m^2/yr) was more than three times greater than has been reported in the general population (20). A very high proportion of our study participants had hypertension, and approximately one-fourth were diabetic, both of which are known risk factors for the development and progression of kidney disease (21, 22). Although the level of adherence to CPAP (average, 4 h/night) in those allocated to the treatment is reflective of clinical practice, it is possible that this level was still insufficient to impact renal function.

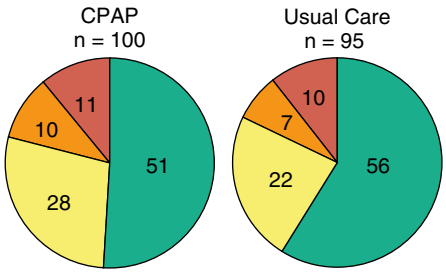

Figure 3. Chronic kidney disease risk categories based on combined estimated glomerular filtration rate and urinary albumin/creatinine ratio. Risk of progressive disease was as defined elsewhere (16). *Green* = low; *yellow* = moderate; *orange* = high; *red* = very high. Participants are grouped according to treatment allocation (either continuous positive airway pressure [CPAP] plus usual care or usual care alone). No significant difference between treatment groups was found (Fisher's exact test).

However, the secondary per-protocol analyses showed no effects among those who used CPAP for an average of 6 hours per night, which should have provided excellent control of their OSA and associated hypoxemia.

It is also possible that the neutral result may have been influenced by the enrollment criteria for the SAVE study, where patients with very severe nocturnal hypoxemia, who potentially have the most to gain from CPAP treatment, were excluded. It is interesting to note that regression analysis showed that the time spent below 85% oxygen saturation as measured by pulse oximetry in the baseline screening sleep study was predictive of a higher CKD risk category after several years of follow-up. However, because less than 5% of patients screened for enrollment in the SAVE trial were excluded on this basis, our results are still likely to be relevant to the great majority of people with OSA and cardiovascular disease.

We recognize several limitations of our study. First, our *post hoc* power calculations revealed that we would have required a difference between groups in eGFR decline of at least 50% to have ruled out a treatment effect in the rate of change of eGFR. Effects on GFR of this magnitude have been observed with some modern renoprotective agents (e.g., canagliflozin) in patients with type 2 diabetes and preserved renal function (23) and after blood pressure reduction from approximately 140/90 to 130/85 mm Hg in patients with existing renal disease (24). Similarly, captopril reduces the annual increase in serum creatinine in patients with diabetic nephropathy by 60% (25). However, effects on GFR attributed to some other interventions, such as sodium restriction (26) and angiotensin II receptor antagonist treatment in diabetic nephropathy (27, 28), are smaller. The relative reduction in time-normalized change in eGFR that we observed with CPAP was only 21% and highly variable. Calculations using the observed values indicate that this study had only 23% power to detect these differences at a nominal type I error rate of $\alpha = 0.05$. A small renoprotective effect on GFR similar to that observed with angiotensin II receptor antagonists therefore cannot be excluded. However, beneficial effects of CPAP on renal function were not supported by per-protocol analyses or regression analyses, further reinforced by the lack of difference in proteinuria at the end of the study and in renal adverse events during the trial.

Second, although the two treatment groups appeared well balanced at baseline, there is still the potential for confounding of known and unknown factors on the outcomes. Third, approximately 90% of participants were male, precluding an assessment of the impact of sex on clinical outcomes. Finally, because urine was collected only at the conclusion of the trial, we cannot exclude the possibility that CPAP treatment influenced the development of micro- or macroalbuminuria, which may have altered the classification of CKD risk category.

In summary, in a subgroup of a large secondary prevention trial of individuals with OSA and cardiovascular disease but generally normal kidney function, CPAP treatment for OSA had no significant effect on common measures of renal function or on the participants' risk of progressive kidney disease. In view of the limitations of our study, larger randomized trials may be required to determine if CPAP is renoprotective or if CPAP improves renal function in patients with established CKD, particularly in those with very severe nocturnal hypoxemia. Because proven cardiovascular risk factors such as diabetes, hypertension, and central obesity are stronger predictors of CKD risk than OSA or its treatment, these should continue to be the focus of efforts to preserve renal function and prevent other serious cardiovascular events in this high cardiovascular risk patient group. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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