Clinical Outcomes and Cost-effectiveness of Continuous Positive Airway Pressure to Manage Obstructive Sleep Apnea in Patients With Type 2 Diabetes in the U.K.

DOI: 10.2337/dc13-2539

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OBJECTIVE

To assess clinical outcomes and cost-effectiveness of using continuous positive airway pressure (CPAP) to manage obstructive sleep apnea (OSA) in patients with type 2 diabetes (T2D) from the perspective of the U.K.'s National Health Service (NHS).

RESEARCH DESIGN AND METHODS

Using a case-control design, 150 CPAP-treated patients with OSA and T2D were randomly selected from The Health Improvement Network (THIN) database (a nationally representative database of patients registered with general practitioners in the U.K.) and matched with 150 OSA and T2D patients from the same database who were not treated with CPAP. The total NHS cost and outcomes of patient management in both groups over 5 years and the cost-effectiveness of CPAP compared with no CPAP treatment were estimated.

RESULTS

Using CPAP was associated with significantly lower blood pressure at 5 years and increasingly lower HbA_{1c} levels over 5 consecutive years compared with untreated OSA patients. At 5 years, the HbA_{1c} level in the CPAP-treated group was 8.2% (66.0 mmol/mol) vs. 12.1% (108.4 mmol/mol) in the control group ($P < 0.03$). Use of CPAP significantly increased patients' health status by 0.27 quality-adjusted life years (QALYs) per patient over 5 years ($P < 0.001$) and NHS management costs by £4,141 per patient over 5 years; the cost per QALY gained with CPAP was £15,337.

CONCLUSIONS

Initiating treatment with CPAP in OSA patients with T2D leads to significantly lower blood pressure and better controlled diabetes and affords a cost-effective use of NHS resources. These observations have the potential for treatment modification if confirmed in a prospective study.

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Received 30 October 2013 and accepted 16 January 2014.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc13-2539/-/DC1.

Obstructive sleep apnea (OSA) and type 2 diabetes (T2D) are common conditions that often coexist (1). Obesity is a risk factor for both OSA and T2D (2,3); however, OSA has been reported to be associated with increased insulin resistance independently of obesity (4,5). Nevertheless, even just the coexistence of OSA and T2D has important clinical, public health, and economic implications. They are both independently linked to high cardiovascular morbidity and mortality (6–8), and both are potential therapeutic targets for either primary or secondary prevention of cardiovascular disease. OSA is also linked to drug-resistant hypertension (9). Chronic sleep loss, a consequence of OSA, is also associated with decreased glucose tolerance, decreased leptin, and an increase in evening cortisol levels (10,11). Additionally, the daytime sleepiness experienced by patients with OSA can lead to road traffic and occupational accidents (12), as well as impact on their quality of life (13).

The prevalence of moderate OSA in patients with T2D has been reported to be 49% of men and 21% of women (14). This figure is set to rise as the prevalence of obesity and T2D in the population increases (15).

Continuous positive airway pressure (CPAP) is an effective treatment for moderate-to-severe OSA sufferers (16) and affords a cost-effective use of health care resources to the U.K.'s National Health Service (NHS) (17). The short-term effect of CPAP treatment on diabetes is controversial, with some studies reporting an improvement in insulin sensitivity (18–20) and a reduction in HbA_{1c} levels (21,22), while others have reported no effect (23).

It is now impossible to perform an ethical randomized controlled trial of CPAP versus no treatment in patients with OSA over a long period. Therefore, comparing nonrandomly allocated patients, with maximal attempts to control for the inevitable baseline differences, is the best study design that can be used. The effect of CPAP treatment in OSA patients with T2D has been little studied in the real clinical practice setting, especially over periods as long as 5 years. Accordingly, the current study used The Health Improvement Network (THIN) database (a nationally representative database of patients registered with general practitioners [GPs] in the U.K.) (24) to examine the clinical outcomes and cost-effectiveness of using CPAP to manage OSA patients with T2D in clinical practice in the U.K. over 5 years from the perspective of the NHS.

RESEARCH DESIGN AND METHODS

THIN Database

The THIN database (Cegedim, London, U.K.) contains computerized information on >9 million anonymized patients entered by GPs from 500 practices across the U.K. general practices across the U.K. using Vision Practice Management Software are invited to participate in the database and are self-selecting. The patient data within THIN have been shown to be representative of the U.K. population in terms of demographics and disease distribution (24).

Read codes are a coded thesaurus of clinical terms that are used by clinicians in the U.K. to record patient findings and procedures in health and social care information technology systems (25). They have been in use in the NHS since 1985 (25) and have been used to code specific diagnoses in the THIN database. A drug dictionary based on data from the Multilex classification has been used to code drugs in the database. Successive updates of patients' records to the database include any subsequent changes made by GPs.

The computerized information in the THIN database includes patients' demographics, details from GP consultations, specialist referrals, nurse and other clinician visits, hospital admissions, diagnostic and therapeutic procedures, laboratory tests, and prescriptions issued by GPs that are directly generated by the general practice's information technology system. Hence, the information contained in the THIN database reflects real clinical practice, as it is based on actual patient records. Moreover, GPs are the gatekeepers to health care in the U.K., and patients' entire medical history is theoretically stored in their primary care record.

Study Population

At the time of the study, the THIN database contained 1,896 patients with OSA and T2D. With use of data from our previous study in patients with OSA without T2D (17), it was estimated that CPAP-treated patients would have 3.9 QALYS at 5 years and untreated patients would have 3.3 QALYs. Power calculations showed that a sample size of 150 patients in each group would be sufficient to detect this difference with 95% power and a type 1 error of 0.05. Hence, the study population comprised a random sample of 150 patients from the THIN database who were 18 years of age or over, had a Read code for OSA and T2D, and had at least 5 years' follow-up data in their case record (but not necessarily for OSA) after the start of treatment with CPAP unless they died.

The CPAP-treated patients were individually matched with a randomly selected cohort of 150 control patients from the THIN database according to age, sex, their general practice, date of diagnosis of OSA and T2D, never having received CPAP for the treatment of their OSA, and having had at least 5 years' follow-up data in their case record (but not necessarily for OSA) after the start date of CPAP in their matched OSA-treated patient unless they died.

Ethics Approval

Ethics approval to use patients' records from the THIN database for this study was obtained from the Research Ethics Committee that appraises studies using the THIN database.

Study Variables and Statistical Analyses

Information was systematically extracted from the patients' records over the 5-year follow-up period according to the protocol approved by the ethics committee and included age, sex, BMI, smoking status, HbA_{1c} levels, blood pressure, symptoms, morbidities, and CPAP compliance. Patients' Charlson Comorbidity Index Score (CCIS) at baseline was also calculated (26). The CCIS encompasses 19 medical conditions weighted 1–6, which were weighted according to age, and these were used to generate a total comorbidity score ranging from 2 to 14. All information on health care resource use, prescribed medication, and clinical outcomes over a period of 5 years from the start of CPAP treatment, or the matched date in the control patients, was also extracted.

Patients' outcomes and resource use were quantified for both groups.

Differences between the groups were tested for statistical significance using a Mann-Whitney *U* test or χ^2 test and assumed to be attributable to CPAP treatment. Differences within each group were tested for statistical significance using a Wilcoxon matched-pair signed-rank test.

With use of ANCOVA, differences in patients' outcomes and resource use between treatments were adjusted for any heterogeneity in the following covariates: age, sex, baseline comorbidities, baseline blood pressure, baseline BMI, smoking status, and GP visits and hospital admissions in the year before the study start date. Logistic regression was used to investigate relationships between baseline variables and clinical outcomes. Multiple linear regression was also used to assess the impact of patients' baseline variables on resource use and clinical outcomes. All statistical analyses were performed using IBM SPSS Statistics (version 21.0; IBM Corporation).

Health Economic Modeling

A case-control model was constructed and populated with health care resource utilization and clinical outcomes extracted from the THIN data set. The model spans a period of 5 years from the start of CPAP treatment or the matched date among control patients.

Utility scores express patient preferences for specific health states on a scale ranging from 0, representing death, to 1, representing perfect health. These scores provide the weights to estimate health-related quality of life (HRQoL) in terms of the number of quality-adjusted life years (QALYs) gained by an intervention or service. HRQoL was not collected in the THIN database. However, it has been reported that the baseline HRQoL of individuals with treated and untreated OSA are 7% and 16% lower than that for average people of the same age, respectively (27). Hence, the baseline utility of each patient in the THIN data set was estimated to be 7% and 16% less than that for average people of the same age in the catalogue of EQ-5D scores for the U.K. (28). Accordingly, the mean baseline utility value was estimated to be 0.747 and 0.676 in the CPAP-treated and untreated group, respectively. These values were consistent with values assigned to treated/untreated OSA patients in other studies using EQ-5D methodology (29,30). The baseline utility value for each patient was then reduced by applying a decrement upon the first occurrence of each chronic condition experienced by a patient during the study period using the values reported in the same catalogue of EQ-5D scores (28). This enabled an estimation of patients' expected health status in terms of the number of QALYs at 5 years from the start of CPAP treatment or the matched date among control patients.

Model Outputs

The primary measure of clinical outcome was patients' health status in terms of the number of QALYs at five years. Secondary measures were a range of outcomes that included BMI and HbA_{1c} levels.

By assignment of unit resource costs at 2011/2012 prices (31–33) to the resource utilization estimates within the model, the health care cost of managing patients in each group over 5 years from the matched start dates was estimated.

Cost-effectiveness Analyses

The cost-effectiveness of CPAP relative to no treatment was calculated as the difference between the expected costs of CPAP-treated patients and control patients divided by the difference in the number of QALYs between the two groups and expressed as the cost per QALY gained.

Sensitivity Analyses

For assessment of uncertainty, bootstrapping was undertaken to estimate the distribution of expected costs, outcomes, and cost-effectiveness ratios. This involved generating 10,000 subsets of the data from each group on the basis of random sampling and replacing the data once sampled. Use of these subsets enabled the construction of a cost-effectiveness acceptability curve showing the probability of CPAP treatment being cost-effective at different thresholds. Additionally, deterministic sensitivity analyses were performed on all of the model's inputs to identify how the incremental cost-effectiveness of CPAP treatment would change by varying the different parameters in the model.

RESULTS

Patients' Characteristics

Patients in both groups were matched by age, sex, and their general practice. Additionally, there was no significant difference in the level of socioeconomic deprivation (using the Townsend Deprivation Index) between the two groups. With use of a χ^2 test, it was found that there were no significant differences between the groups in the percent of patients diagnosed with a comorbidity prior to the study start date. However, prior to the study start date, significantly more CPAP-treated patients were obese and significantly more control patients were smokers (Table 1). Furthermore, 12% of CPAP-treated patients and 17% of control patients stopped smoking during the study period at a mean of 3.7 years after the study start date, and ~80% of nonsmokers in both groups at the study start date were ex-smokers.

Patient Management and Outcomes

From the time of diagnosis of OSA, it took a mean 19.6 $\pm$ 31.2 months to the start of CPAP treatment. Over the 5-year follow-up period, 139 patients remained on CPAP treatment. Hence, adherence ranged from 93% in year 1 to 89% in year 5. Additionally, objective CPAP adherence data were available for only 11 patients. Based on what was written in the medical records of these patients, CPAP adherence was a mean of 5.8 $\pm$ 1.0 h per night (range 4.0–7.2) for these 11 patients.

In both groups, patients' blood pressure declined over the study period. Patients' systolic pressure was not significantly lower than their baseline value until year 3 (P = 0.001) in the CPAP-treated group and year 4 in the control group (P = 0.001). However, patients' diastolic pressure in both groups was significantly lower than their baseline value by year 2 ($P < 0.01$). Additionally, patients' blood pressure in the CPAP-treated group was significantly lower than that of control patients by year 5 (Table 2). Multiple regression showed that patients' blood pressure was only affected by CPAP ($P < 0.05$) and not by any other covariate.

Over the study period, more control patients became obese, thus catching up with the CPAP-treated group where there were no changes in obesity.

Table 1—Patients' characteristics at baseline

	CPAP-treated group	Control group	*P*
Patients (*n*)	150	150	ns
Age (years)	53.9 ± 0.9	53.6 ± 1.0	ns
Male (%)	82	83	ns
Body weight (kg)	114.0 ± 1.9	109.5 ± 2.0	ns
BMI (kg/m^2)	38.9 ± 0.6	35.4 ± 0.5	<0.001
Smokers (%)	51	68	<0.02
CCIS (comorbidity index)	2.3 ± 0.1	2.3 ± 0.1	ns
Systolic blood pressure (mmHg)	137.5 ± 1.7	140.3 ± 1.7	ns
Diastolic blood pressure (mmHg)	82.0 ± 1.0	84.3 ± 1.1	ns
Patients with blood pressure >140/90 mmHg (%)	12	19	ns
Patients with blood pressure >140/≤90 mmHg (%)	22	31	ns
Patients with blood pressure ≤140/>90 mmHg (%)	5	<1	ns
HbA_{1c} levels, % (mmol/mol)	7.5 ± 2.4 (58.1 ± 2.9)	7.4 ± 2.4 (56.9 ± 2.7)	ns
GP visits in the year before the study start date	15.7 ± 1.2	12.3 ± 0.8	ns
Hospital admissions in the year before the study start date	0.2 ± 0.1	0.1 ± 0.1	ns
Patients diagnosed with specific symptoms in the year before the study start date (%)			
Obesity or morbid obesity	88	75	<0.02
Hypertension	56	50	ns
Gastrointestinal disorder	37	37	ns
Respiratory disorder	37	25	ns
Breathless disorder	32	24	ns
Depression	23	24	ns
Cardiac arrhythmias	9	5	ns
Arthritis	8	10	ns
Angina	8	10	ns
Endocrine disorder	8	9	ns
Anxiety	4	2	ns
Ophthalmological disorder	3	3	ns
Gout	2	2	ns
Myocardial infarction	1	2	ns
Retinopathy	0	2	ns
Stroke	0	1	ns

Data are means ± SE per patient unless otherwise indicated. ns, not significant.

Hence, at 5 years there was no significant difference between the two groups in terms of the percentage of obese patients (Table 2). However, CPAP-treated patients had significantly better controlled diabetes than the control patients (Fig. 1 and Table 2) and a significantly better HRQoL (Table 2). Two percent of CPAP-treated patients, and 11% of control patients, had no diagnosed symptoms in the year before the study start date. During the study period, significantly more CPAP-treated patients were diagnosed with a cardiac arrhythmia, and significantly more control patients were diagnosed with diabetic retinopathy (Table 2). Additionally, 3% of CPAP-treated patients and 3% of control patients experienced no new symptoms during the study period.

Logistic regression showed that sex was an independent predictor of having controlled diabetes. Female patients were four times more likely than males to have normal HbA_{1c} levels at 5 years (odds ratio 4.78; $P < 0.02$). Multiple regression showed that patients' HRQoL over the five years was higher among females (0.11 more QALYs among females than males [$P < 0.03$]).

Health Care Resource Use Associated With Patient Management

Patients in both groups were predominantly managed by their GPs, having a mean of ~140 visits per patient during the study period (Table 3). These visits were for the management of their comorbidities, shown in Tables 1 and 2, as well as their T2D and OSA. Additionally, patients in both groups had a mean of 13–14 hospital outpatient visits per patient (Table 3). However, there were no statistically significant differences between the groups in their use of health care resources over the study period. CPAP-treated patients received significantly more prescriptions for respiratory drugs ($P < 0.02$) and neurological drugs ($P < 0.03$), and patients in the control group received significantly more prescriptions for antidiabetes medication (Table 3). Moreover, 7% of CPAP-treated patients and 5% of control patients started to use insulin a mean 11.9 months and 4.6 months, respectively, after the study start date. These patients continued to receive insulin prescriptions continuously for the rest of the study period.

Multiple regression showed the following over the 5 years:

1. The number of GP visits per patient increased with higher comorbidity scores (31.3 more visits for each unit increase in CCIS at baseline [$P < 0.001$]), number of GP visits in the year

Table 2—Patients' outcomes over the study period

	CPAP-treated group	Control group	*P*
Conditions with which patients were newly diagnosed (%)			
Obesity or morbid obesity	0	6	ns
Depression	57	53	ns
Breathless disorder	40	40	ns
Hypertension	39	38	ns
Gastrointestinal disorder	49	50	ns
Ophthalmological disorder	47	42	ns
Cardiac arrhythmias	27	14	<0.03
Respiratory disorder	30	43	ns
Arthritis	21	27	ns
Endocrine disorder	20	11	ns
Angina	16	21	ns
Anxiety	6	12	ns
Gout	11	7	ns
Stroke	4	6	ns
Retinopathy	2	11	<0.02
Myocardial infarction	4	5	ns
BMI (kg/m^2)	38.6 ± 0.6	36.8 ± 0.6	ns
Systolic blood pressure (mmHg)			
Year 1	139.0 ± 2.1	137.5 ± 1.9	ns
Year 2	136.2 ± 2.3	140.4 ± 2.1	ns
Year 3	133.7 ± 1.9	138.2 ± 1.9	ns
Year 4	134.1 ± 1.9	136.0 ± 1.8	ns
Year 5	131.0 ± 2.1	135.4 ± 2.0	0.02
Diastolic blood pressure (mmHg)			
Year 1	81.5 ± 1.3	81.8 ± 1.2	ns
Year 2	79.4 ± 1.1	81.6 ± 1.1	ns
Year 3	79.4 ± 1.3	81.8 ± 1.2	ns
Year 4	79.9 ± 1.2	80.1 ± 1.1	ns
Year 5	78.1 ± 1.2	80.7 ± 1.2	<0.02
HbA_{1c}, % (mmol/mol)			
Year 1	7.5 ± 2.6 (58.1 ± 5.4)	7.9 ± 2.6 (62.3 ± 4.8)	ns
Year 2	8.8 ± 4.0 (72.6 ± 19.7)	13.1 ± 4.3 (119.7 ± 23.5)	<0.05
Year 3	8.1 ± 3.9 (65.4 ± 18.8)	12.2 ± 4.2 (109.9 ± 22.5)	<0.05
Year 4	7.8 ± 3.9 (61.6 ± 18.7)	13.3 ± 4.3 (121.9 ± 23.8)	<0.03
Year 5	8.2 ± 3.5 (66.0 ± 15.0)	12.1 ± 3.8 (108.4 ± 17.9)	<0.03
QALYs	2.5 ± 0.04	2.26 ± 0.03	<0.001

Data are means ± SE per patient unless otherwise indicated. ns, not significant.

before the study start date (2.3 more visits for each GP visit in the year before the study start date [$P < 0.001$]), and by sex (females had 31.9 more visits than males [$P < 0.01$]).

2. The number of outpatient visits per patient increased with the number of hospital admissions in the year before the study start date (6.6 more visits for each admission in the year before the study start date [$P < 0.005$]) and by sex (females had 5.6 more visits than males [$P < 0.03$]).
3. The number of hospital admissions per patient increased with the number of hospital admissions in the year before the study start date (0.8 more admissions for each admission in the year before the study start date [$P < 0.01$]).

Health Care Cost of Patient Management

The 5-yearly NHS cost of managing patients in the CPAP-treated group was £18,234 ± 1,033 per patient compared with £14,092 ± 1,029 per patient in the control group. Hence, the incremental cost associated with CPAP treatment was £4,141 ± 1,588 per patient over 5 years (Table 4). GP visits were the principal cost driver in both groups, accounting for 41% and 54% of the total NHS management cost of CPAP-treated patients and control patients, respectively.

Cost-effectiveness Analyses

Use of CPAP led to an increase in patients' health status of 0.27 QALYs and an increase in the total NHS cost of patient management of £4,141. Hence, the cost per QALY gained with CPAP was estimated to be £15,337 (i.e., 4,141 ÷ 0.27).

Sensitivity Analyses

Bootstrapping demonstrated the distribution in NHS costs and QALYs at 5 years (Supplementary Fig. 1) from which it was seen that, while there is some overlap in the costs of the two patient cohorts, the distribution of QALYs is distinct. A cost-effectiveness acceptability curve was generated from the bootstrapped subsets (Supplementary Fig. 2), demonstrating that at a cost-effectiveness threshold of £20,000 per QALY, up to 87% of a cohort is expected to be cost-effectively treated with CPAP compared with no CPAP treatment.

Deterministic sensitivity analyses were performed on all the model's

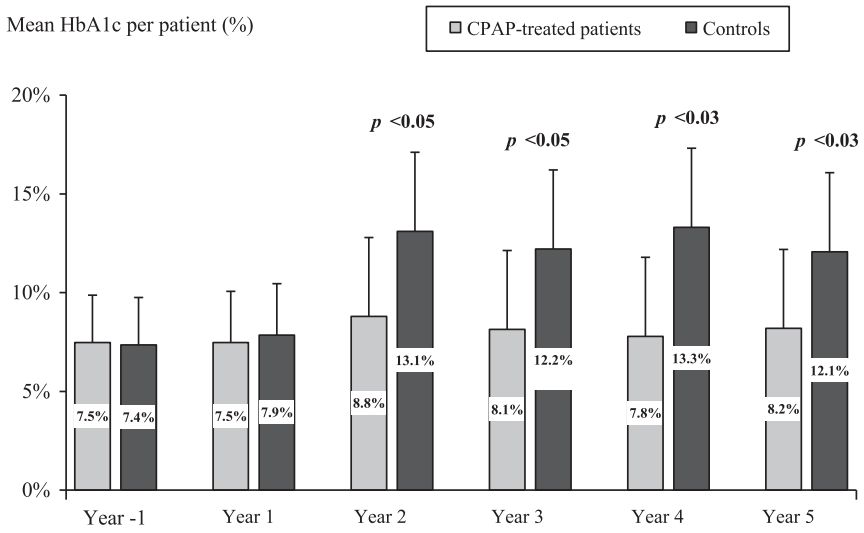

Figure 1—Patients' mean (±SE bars) HbA_{1c} levels over the study period.

inputs, but only the main findings have been presented (Supplementary Table 1). These analyses showed that for plausible changes in the model's inputs, CPAP remains a cost-effective intervention for OSA patients with T2D.

CONCLUSIONS

This comparative study aimed to determine the relative clinical outcomes and cost-effectiveness of using CPAP to treat OSA patients with T2D in clinical practice in the U.K. Accordingly, a random sample of patients in the THIN database who had a diagnosis of OSA and T2D and were treated with CPAP was compared with matched OSA and T2D patients who were not treated with CPAP and who had a clinical history for at least 5 years unless they died in order to exclude patients who had moved or changed their general practice. The advantage of using the THIN database is that the patient pathways and associated resource use are based on actual clinical practice rather than trial protocol–driven resource use. However, this naturalistic approach does have its limitations. Patients were not randomized to the treatment they received. Hence, there would have been differences between the groups resulting in the hospital physician's decision whether to offer CPAP and the patient's willingness to accept after the diagnosis of OSA. Every attempt was made to account for these differences and to overcome the nonrandomized study design. Differences in patients' outcomes and resource use between treatments were adjusted for any heterogeneity in age, sex, baseline comorbidities, baseline blood pressure, baseline BMI, smoking status, and number of GP visits and hospital admissions in the year before the study start date. Moreover, 300 patients have been included in the analysis, which should have been a sufficiently large sample to allow for relevant baseline differences to be apparent. Nevertheless, there will have been some differences that have not been accounted for. Additionally, power calculations showed that the

Table 3—Mean health care resource use per patient over the study period

Resource	CPAP-treated group	Control group	*P*
GP office visits	138.4 ± 6.9	140.5 ± 6.7	ns
GP home visits	0.5 ± 0.1	0.5 ± 0.1	ns
Nurse visits	0.9 ± 0.3	1.0 ± 0.2	ns
Hospital outpatient visits	13.3 ± 1.9	14.5 ± 1.8	ns
Accident and emergency attendances	1.0 ± 0.3	0.4 ± 0.2	ns
Day case attendances	0.3 ± 0.2	0.2 ± 0.1	ns
Hospital admissions	1.3 ± 0.2	0.8 ± 0.2	ns
Surgical procedures	0.8 ± 0.1	1.0 ± 0.1	ns
Therapeutic procedures	0.8 ± 0.1	0.4 ± 0.1	ns
Laboratory tests	25.8 ± 0.1	22.6 ± 0.1	ns
Diagnostic tests	11.7 ± 0.1	9.2 ± 0.1	ns
Number of drug prescriptions			
Analgesics	15.1 ± 2.8	8.7 ± 2.2	0.05
Antidiabetes drugs for T2D	16.8 ± 4.0	27.1 ± 3.7	<0.02
Anti-infectives	7.7 ± 1.0	4.1 ± 0.9	<0.01
Cardiovascular drugs	87.9 ± 8.6	84.5 ± 8.3	ns
Dermatological preparations	5.9 ± 1.5	3.3 ± 1.4	ns
Endocrine drugs	5.6 ± 1.1	4.9 ± 1.4	ns
Gastrointestinal drugs	15.1 ± 2.1	10.6 ± 2.2	ns
Genito urinary drugs	5.2 ± 1.7	4.8 ± 1.5	ns
Insulin	2.8 ± 1.6	1.4 ± 1.4	ns
Musculoskeletal drugs	9.9 ± 1.9	8.9 ± 2.1	ns
Neurological drugs	21.6 ± 3.7	11.3 ± 4.0	<0.03
Ophthalmological drugs	4.1 ± 1.1	0.7 ± 1.2	ns
Otolaryngeal drugs	5.0 ± 1.2	2.4 ± 1.3	ns
Respiratory drugs	30.7 ± 5.8	14.1 ± 5.4	<0.02
Wound care products	4.6 ± 1.9	1.9 ± 1.7	ns

Data are means ± SE resource per patient unless otherwise indicated. ns, not significant.

Table 4—Mean 5-yearly NHS cost (at 2011/2012 prices) of resource use per patient

Resource	CPAP-treated group	Control group	Incremental cost associated with CPAP treatment
GP visits	7,428.33 (41)	7,541.04 (54)	−112.71 (−3)
Hospitalization	2,466.04 (14)	1,517.56 (11)	948.48 (23)
Prescribed drugs	3,714.65 (20)	2,140.47 (15)	1,574.19 (38)
CPAP	1,696.00 (9)	0.00 (0)	1,696.00 (41)
Outpatient visits	1,786.51 (10)	1,947.70 (14)	−161.19 (−4)
Tests and procedures	518.06 (3)	402.55 (3)	115.52 (3)
Diagnosis of OSA	343.14 (2)	343.14 (2)	0.00 (0)
Day case attendances	51.30 (<1)	34.20 (<1)	17.10 (<1)
Nurse visits	53.77 (<1)	59.75 (<1)	−5.97 (<−1)
Accident and emergency attendances	116.12 (1)	46.45 (<1)	69.67 (2)
Community care	59.56 (<1)	59.56 (<1)	0.00 (0)
Total	18,233.50 (100)	14,092.42 (100)	4,141.08 (100)

Data are mean cost (£) of resource per patient (% of total cost).

sample size was sufficiently large to detect any significant differences with 95% power and a type I (α) error of 0.05 between the two groups, had they occurred, as well as large enough to accurately assess treatment patterns and health care resource use attributable to managing OSA and T2D in actual clinical practice.

For patients to be included in the data set, they had to have received CPAP for their OSA or be matched to these patients on the basis of their age, sex, the same general practice, date of diagnosis of their OSA and T2D and not received CPAP. Severity of OSA was not included as a matching criteria, since this was not documented in the patients' records. All the patients in this data set had their OSA diagnosed by a respiratory physician. However, patients in both groups were subsequently managed primarily by their GP, who saw them on average every 2 weeks, but not necessarily for OSA, and they only saw a hospital physician about twice a year. Moreover, it took a mean 20 months to the start of CPAP treatment after a diagnosis of OSA. The THIN data set in this study covers the period from 2007 to 2011, so this is a reflection of how most patients with OSA and T2D were managed in the community in the U.K. at that time. Nevertheless, this study found that once started, compliance with CPAP ranged from 93% in year 1 to 89% in year 5. This compliance rate reflects "real-world" practice and is much higher than those reported in other studies (34). Our study does not address the question of who should diagnose and manage OSA or how it should be done or the more complex question of integrated care pathways.

After adjustment for baseline differences, this study estimated that over the first 5 years after the study start date, the incremental cost of initiating CPAP treatment was a mean £4,141 and leads to a 12% improvement in patients' HRQoL (of 0.27 QALYs), resulting in a cost per QALY gain of £15,337. This value is concordant with the cost-effectiveness of using CPAP over 5 years, based on a simulated modeled cohort of patients with severe OSA (17). Additionally, use of CPAP led to significantly lower blood pressure by year 5 and significantly lower HbA_{1c} levels progressively over the 5 years compared with untreated patients. Regression analyses found that there was no relationship between the number of antidiabetes medication prescriptions and HbA_{1c} levels. These observations reinforce the findings of others that use of CPAP can reduce hypertension (35) and possibly reduce insulin resistance (18–20), leading to lower serum glucose levels and HbA_{1c} levels (21,22,36). However, this is the first time a study, based on the management of patients in actual clinical practice, has shown that use of CPAP leads to lower HbA_{1c} levels over five consecutive years compared with untreated patients. This difference was due to the HbA_{1c} levels having only increased by 0.7% over 5 years among CPAP-treated patients compared with 4.7% over the same period in the untreated patients. As HbA_{1c} is a surrogate measure of glycemic control, this study's findings support the notion that in some way the use of CPAP facilitates glycemic control in OSA patients with T2D. Moreover, the untreated patients required significantly more prescriptions for antidiabetes drugs. Hence, it could be postulated that CPAP treatment reduces insulin resistance in these patients. Conversely, it may just be that those who accept CPAP also comply better with their medication. Also, CPAP-treated patients may be less sleepy and more inclined to look after their diabetes better. Clearly, these observations warrant further investigation.

A reduction in HbA_{1c} level has been shown to be associated with a reduction in the risk of macrovascular and microvascular complications associated with T2D (7,37). This is consistent with the findings from this study, since the relative risks of developing angina, myocardial infarction, stroke, and diabetic retinopathy are all reduced in the CPAP-treated group (Table 2). Moreover, the increased rate of diabetic retinopathy in the untreated control patients is compatible with the findings of others (38).

This study found that significantly more CPAP-treated than control patients had a diagnosis of cardiac arrhythmias. This is difficult to explain, since use of CPAP has been shown to reduce cardiac arrhythmias (39). We have attempted to account for any differences between the groups, but severity of some patients' symptoms remains unknown, as not all of this information was recorded in their records. Hence, the CPAP-treated patients may have had more severe OSA than the control patients, which we have not been able to address. Notwithstanding this, the CPAP-treated patients had better glycemic control of their diabetes over 5 years and there were no significant differences in baseline symptoms between the groups. Nevertheless, regression analyses found no relationship between CPAP adherence and the study's outcomes, but this may reflect the fact that adherence data were only available for 11 patients.

This study has a number of other limitations. The results were censored at 5 years and excluded the costs and

consequences of managing patients beyond this period. The THIN database may have underrecorded use of some health care resources outside the GP's surgery, such as some home visits made by clinicians, outpatient visits, attendance at accident and emergency departments, and hospital admissions if not documented in the GP records. The analysis excluded hospital-based prescribing, but this should have minimal impact on the results, since most prescribing is undertaken by GPs in the community.

The analysis only considered the cost of NHS resource use for the "average patient," and no attempt was made to stratify resource use and costs according to sex, comorbidities, suitability of patients for different treatments, and other disease-related factors. Also excluded were the costs incurred by patients and indirect costs incurred by society as a result of patients taking time off work.

This evaluation provided an estimate of the clinical outcomes, resource implications, and associated costs attributable to managing OSA patients with T2D. While the study results are compelling, the analyses of clinical outcomes were based on clinicians' entries into their patients' records and inevitably subject to a certain amount of imprecision and lack of detail. Moreover, the computerized information in the THIN database is collected by GPs for clinical care purposes and not for research. Prescriptions issued by GPs and practice nurses are recorded in the database, but it does not specify whether the prescriptions were dispensed or patient compliance with the product. Consequently, this study's findings should provide a framework for a randomized controlled trial comparing the use of CPAP in the management of OSA patients with T2D to prospectively measure a range of clinical outcomes and HRQoL in combination with cost-effectiveness metrics. However, as discussed earlier, this will be almost impossible if patients with OSA-related symptoms are considered for recruitment, as most physicians and patients would not be prepared to wait 5 years for treatment with CPAP after allocation to a control arm.

In conclusion, within the limitations of the data set, first-line CPAP treatment in OSA patients with T2D leads to significantly lower blood pressure and significantly better controlled diabetes and affords a cost-effective use of NHS resources. This study also demonstrates that use of CPAP can potentially facilitate glycemic control in OSA patients with T2D over the longer term. This observation has the potential to alter treatment decisions, particularly if confirmed in a prospective trial.

Duality of Interest. This study was funded with an unrestricted research grant from ResMed, Martinsried, Germany. No other potential conflicts of interest relevant to this article were reported.

ResMed did not have any control of the methodology, conduct, results, or conclusion of this study or editorial involvement in the manuscript.

Author Contributions. J.F.G. designed the study, managed the analyses, performed some analyses, checked all the other analyses, and wrote the manuscript. M.P. conducted much of the analyses and edited the manuscript. E.S. conducted much of the analyses. S.T. and J.S. scrutinized the analyses, suggested further analyses, helped interpret some of the findings, and edited the manuscript. J.F.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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