ORIGINAL ARTICLE

Surgery for Drug-Resistant Epilepsy in Children

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ABSTRACT

BACKGROUND

Neurosurgical treatment may improve seizures in children and adolescents with drug-resistant epilepsy, but additional data are needed from randomized trials.

METHODS

In this single-center trial, we randomly assigned 116 patients who were 18 years of age or younger with drug-resistant epilepsy to undergo brain surgery appropriate to the underlying cause of epilepsy along with appropriate medical therapy (surgery group, 57 patients) or to receive medical therapy alone (medical-therapy group, 59 patients). The patients in the medical-therapy group were assigned to a waiting list for surgery. The primary outcome was freedom from seizures at 12 months. Secondary outcomes were the score on the Hague Seizure Severity scale, the Binet–Kamat intelligence quotient, the social quotient on the Vineland Social Maturity Scale, and scores on the Child Behavior Checklist and the Pediatric Quality of Life Inventory.

RESULTS

At 12 months, freedom from seizures occurred in 44 patients (77%) in the surgery group and in 4 (7%) in the medical-therapy group ($P<0.001$). Between-group differences in the change from baseline to 12 months significantly favored surgery with respect to the score on the Hague Seizure Severity scale (difference, 19.4; 95% confidence interval [CI], 15.8 to 23.1; $P<0.001$), on the Child Behavior Checklist (difference, 13.1; 95% CI, 10.7 to 15.6; $P<0.001$), on the Pediatric Quality of Life Inventory (difference, 21.9; 95% CI, 16.4 to 27.6; $P<0.001$), and on the Vineland Social Maturity Scale (difference, 4.7; 95% CI, 0.4 to 9.1; $P=0.03$), but not on the Binet–Kamat intelligence quotient (difference, 2.5; 95% CI, −0.1 to 5.1; $P=0.06$). Serious adverse events occurred in 19 patients (33%) in the surgery group, including hemiparesis in 15 (26%).

CONCLUSIONS

In this single-center trial, children and adolescents with drug-resistant epilepsy who had undergone epilepsy surgery had a significantly higher rate of freedom from seizures and better scores with respect to behavior and quality of life than did those who continued medical therapy alone at 12 months. Surgery resulted in anticipated neurologic deficits related to the region of brain resection. (Funded by the Indian Council of Medical Research and others; Clinical Trial Registry–India number, CTRI/2010/091/000525.)

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Children and adolescents with drug-resistant epilepsy are at increased risk for poor long-term intellectual and psychosocial outcomes, along with a poor health-related quality of life.[1-3] In this form of recalcitrant epilepsy, appropriate surgical management is often undertaken with the goal of reducing or stopping seizures, but there is limited evidence from randomized trials showing the benefit in this age group.

The region of the cerebrum that is subjected to surgery depends on the localization of the origin of seizures in the cerebral cortex and the functional importance of the surrounding brain tissue. These factors are determined on presurgical evaluation, including simultaneously acquired video electroencephalographic (video EEG) recordings and structural and functional imaging of the brain. The type of surgery is dependent on the underlying cause of epilepsy and may include resection of the mesial temporal lobe or other regions of the cerebral cortex, excision of a focal lesion or developmental malformation, sectioning of the corpus callosum (corpus callosotomy), disconnection of a part of the cerebral cortex, or disconnection of an entire hemisphere (hemispherotomy). Some of these procedures necessarily result in neurologic deficits.

Two randomized trials of temporal lobectomy for drug-resistant epilepsy included only adults.[4,5] A Cochrane review of epilepsy surgery included only four trials that had more than 30 participants, and these trials involved patients in all age groups.[6] Three of these trials compared different surgical techniques or compared different extents of surgical resection, but only one[4] randomly assigned patients to surgical and medical groups. A meta-analysis of uncontrolled studies that compared seizure outcomes of surgeries in children showed that 74% of those with brain lesions and 45% of those without lesions had become seizure-free at the 1-year follow-up.[7] In a retrospective analysis involving 142 children who had undergone surgery for drug-resistant epilepsy at a mean age of 9.8 years between 2000 and 2011 at our center, 79.3% were free from disabling seizures after a mean follow-up of approximately 4 years.[8] To follow up on these results, we performed a trial involving children and adolescents with drug-resistant epilepsy to compare epilepsy surgery with continued medical therapy alone in patients on a waiting list for surgery.

Methods

Trial Design and Oversight

The trial was conducted from November 2010 through March 2015 at the All India Institute of Medical Sciences in New Delhi, which is the referral center for epilepsy surgery in northern India. The trial was approved by the institutional ethics committee; written informed consent was provided by parents or legally authorized representatives of the children. An independent data and safety monitoring board reviewed the records of the recruited patients for adverse events at annual meetings. The trial was funded by the Indian Council of Medical Research and the Department of Biotechnology, Government of India. The trial was initiated by the last author, and all the authors contributed to its design. The first and second authors wrote the first draft of the manuscript, and all the authors reviewed the manuscript and vouch for adherence of the trial to the protocol (available with the full text of this article at NEJM.org) and for the completeness and accuracy of the data.

Presurgical Evaluation and Surgical Intervention

Patients were evaluated with long-term video EEG monitoring with the use of scalp electrodes in the standard 10–20 system of electrode placement and with 3-Tesla magnetic resonance imaging (MRI) that included an epilepsy protocol. This protocol involved the use of T_1-weighted sagittal three-dimensional (3D) and 3D FLAIR (fluid-attenuated inversion recovery) sequences with a slice thickness of less than 1 mm without an intervening gap, coronal T_2-weighted and FLAIR sequences with a 2.5-mm slice thickness without a gap (perpendicular to the hippocampus), and axial susceptibility-weighted images.

Drug-resistant epilepsy was defined as the failure of adequate trials of two appropriately chosen antiepileptic drug schedules with acceptable side effects.[9] Patients who had no definite localization of seizures on video EEG, those who had no concordance of the EEG results and a lesion on MRI, and those who had no lesion, more than one lesion, or lesions with poorly defined margins on imaging underwent ictal and interictal single-photon-emission computed tomography (SPECT), positron-emission tomography (PET), or magnetoencephalography (MEG) as part of the presurgical evaluation.[10]

Each patient was discussed at the weekly multidisciplinary epilepsy surgery case conference attended by neurologists, neurosurgeons, neuroradiologists, and nuclear medicine specialists; the assessments of neuropsychologists and psychiatrists were taken into consideration before surgery to evaluate coexisting psychiatric conditions and corroborate the localization of epilepsy and resulting deficits. Patients with concordance of video EEG localization of the region of onset of the seizure (ictal-onset zone) and the location of the lesion on MRI underwent resection of that region of cortex or of the lesion or malformed cortex; those with multiple, subtle, or no lesions underwent resection of the region that was concordant between video EEG results and localization on PET, SPECT, or MEG. Patients who had multiple seizure types (including drop attacks) and multiple bilateral lesions and seizure foci underwent corpus callosotomy. Patients who had extensive lesions confined to one hemisphere with significant weakness of limbs (weak pincer grip or worse) opposite to the involved hemisphere underwent hemispherotomy.

Patients were not included in the trial if there was no consensus regarding the location of an epileptic focus and were excluded if there were metabolic abnormalities (genetic or acquired) or cardiac, renal, or any other systemic illness or a history of status epilepticus. In all the patients in the surgery group, postsurgery MRI was performed with a high-field 1.5 Tesla system in the operating room to ensure the adequacy of the planned excision.

RANDOMIZATION AND BLINDING

Randomization was performed with the use of computer-generated, nonstratified sequences, and assignments were prepared in sequentially numbered, sealed, opaque envelopes by persons not involved in the trial. Patients who were assigned to the surgery group underwent the procedure within a month after randomization; those who were assigned to the medical-therapy group remained on the waiting list, with surgery planned for 1 year or longer after randomization, which represented the standard of care at our center, since the waiting list is typically 12 months or longer. All the patients continued to receive antiepileptic drugs, and changes were made by the treating clinicians as necessary to manage seizures. In the surgery group, patients who became seizure-free underwent tapering of antiepileptic drugs, starting 1 year after surgery.

OUTCOMES

The primary outcome was freedom from seizures, which was defined as class 1 (no seizures or auras) on the International League Against Epilepsy scale[11] at 12 months. Other categories on the scale are as follows: auras only with no other seizures (class 2), 1 to 3 seizure days per year (class 3), from 4 seizure days per year to a number of seizure days that represents a 50% reduction in the number of days from baseline (class 4), from less than a 50% reduction in the number of seizure days to a 100% increase in the number of seizure days from baseline (class 5), and more than a 100% increase in the number of seizure days from baseline (class 6).

Secondary outcomes, which were evaluated at 12 months after the date of surgery or randomization and were compared with baseline scores, included any occurrence of seizures, the score on the Hague Seizure Severity scale (ranging from 13 to 54, with higher scores indicating greater severity), the Binet–Kamat intelligence quotient or the social quotient on the Vineland Social Maturity Scale (normal range, 85 to 110 on both scales, with higher scores indicating higher levels of function), the T score on the Child Behavior Checklist (normal score, <60; borderline, 60 to 63; and clinically impaired, >63), and the score on the Pediatric Quality of Life Inventory (ranging from 0 to 100, with higher scores indicating a better quality of life). The Binet–Kamat test was administered to children with adequate verbal responses, and the Vineland Social Maturity Scale was administered to children younger than 2 years of age and to older children whose verbal response was inadequate for the completion of the Binet–Kamat test. (Details regarding the evaluation scales and testing procedures are provided in Section 1 in the Supplementary Appendix, available at NEJM.org.)

The primary outcome measure of freedom from seizures was assessed in a blinded manner on the basis of seizure diaries, as reported by telephone at 6 months and 12 months (see Section 2 in the Supplementary Appendix) and verified from seizure diaries. Diaries were coded with unique identification numbers and sent to the assessor by a person uninvolved in the trial. Secondary outcomes of seizure occurrence during the 12-month period and psychosocial measures

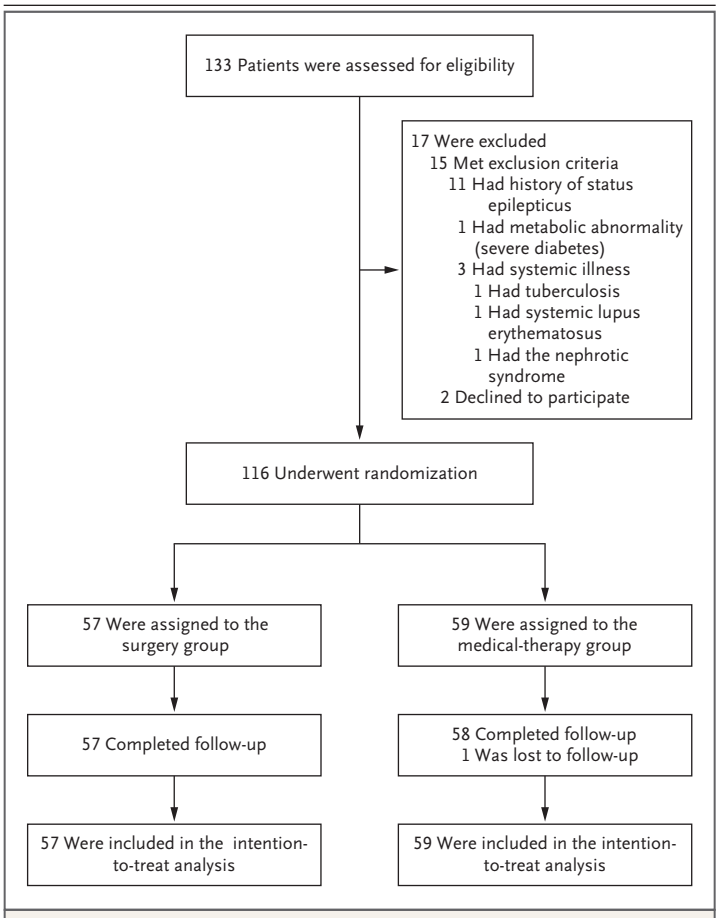

Figure 1. Enrollment and Outcomes.

were assessed by the treating epileptologist and psychologist (both of whom were aware of study-group assignments) during clinical visits and with the use of the seizure diary. All the patients were seen at the epilepsy clinic every 3 months or more frequently as required for clinical care.

ADVERSE EVENTS

Adverse events that were classified as serious were assessed in a blinded manner during a telephone checklist discussion. (Details are provided in Section 2 in the Supplementary Appendix.) Serious adverse events included death, hospital admission or prolongation of an existing hospital stay, and events that resulted in persistent or substantial disability or incapacity or that were considered to be life-threatening.[12] All other adverse events were recorded as nonserious.

STATISTICAL ANALYSIS

Power calculations were based on the results of the study by Widjaja et al., in which the seizure-free rate after surgery was 60%.[13] We calculated that the enrollment of 116 patients would provide a power of 90% to determine an absolute between-group difference of 40 percentage points in the rate of freedom from seizures (and a superiority margin of 15% in the surgery group) at 12 months at a two-sided alpha level of 5% and assuming that 5% of the patients would be lost to follow-up.

We used the chi-square test and Fisher's exact test to compare categorical characteristics at baseline; we used Student's t-test to compare normally distributed continuous variables and the Wilcoxon rank-sum test to compare nonparametric continuous data. Intention-to-treat analyses were performed for both primary and secondary outcomes. Patients who did not complete follow-up at 12 months were not considered to be seizure-free in the primary analysis; for the secondary outcomes, the last observation was carried forward.

The primary outcome of complete freedom from seizures at 12 months was analyzed with the use of the z-test and was reported as the difference in proportions and relative risk with 95% confidence intervals. We used the Kaplan–Meier method and log-rank test to analyze the secondary outcome of seizure during the 12-month period and a Cox proportional-hazards model to calculate hazard ratios and 95% confidence intervals. We used Student's t-test to analyze other secondary outcomes and the paired t-test to analyze the change from baseline to last follow-up. A P value of less than 0.05 was considered to indicate statistical significance. All the statistical analyses were performed with the use of Stata software, version 11.0.

RESULTS

PATIENTS

A total of 133 children underwent screening; 2 of the children were eligible but did not provide informed consent and 116 met the inclusion criteria (57 in the surgery group and 59 in the medical-therapy group) (Fig. 1). One patient in the medical-therapy group did not return for the last follow-up visit. There were no significant

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Surgery Group (N=57)	Medical-Therapy Group (N=59)
Median age (range) — yr	9.0 (0.8–17.0)	10.0 (2.0–17.0)
Female sex — no. (%)	23 (40)	19 (32)
Family history of epilepsy — no. (%)	3 (5)	6 (10)
Median age at onset of seizures (range) — yr†	1.5 (0.1–9.0)	3.0 (0.1–10.0)
Median duration of epilepsy (range) — yr	4.9 (0.4–16.3)	5.0 (0.5–16.0)
Type of seizures — no. (%)		
Focal	43 (75)	43 (73)
Secondary generalized	14 (25)	16 (27)
Frequency of seizures 6 mo before randomization		
≥1 Per day	48 (84)	40 (68)
≥1 Per week	5 (9)	10 (17)
≥1 Per mo	4 (7)	6 (10)
≥1 Per 3 mo	0	3 (5)
Median number of previous antiepileptic medications (range)	3 (2–6)	3 (2–6)
Score on Hague Seizure Severity scale‡	37.9±4.2	37.4±4.3
Intelligence quotient on Binet–Kamat test§	63.9±19.3	62.8±21.4
Social quotient on Vineland Social Maturity Scale§	38.6±24.2	41.8±20.9
Total score on Child Behavior Checklist¶	69.5±6.3	67.8±5.1
Total score on Pediatric Quality of Life Inventory‖	53.4±15.4	53.2±16.4

* Plus–minus values are means ±SD. There were no significant differences between the groups.
† The earliest onset was between 2 and 4 days after birth.
‡ Scores on the Hague Seizure Severity scale range from 13 to 54, with higher scores indicating greater seizure severity.
§ Average scores on the tests of intelligence quotient and social quotient range from 85 to 110, with higher scores indicating higher levels. Intelligence quotient was tested in 30 patients in the surgery group and 33 in the medical-therapy group; social quotient was tested in 27 patients in the surgery group and 26 in the medical-therapy group.
¶ The normal T score on the Child Behavior Checklist is less than 60, with higher scores indicating greater behavioral problems.
‖ Scores on the Pediatric Quality of Life Inventory range from 0 to 100, with higher scores indicating a better quality of life.

differences in the baseline characteristics between the two groups (Table 1). The following surgical procedures were carried out: temporal lobe resections in 14 patients, resection of lesion in a lobe other than temporal in 12, hemispherotomy in 15, corpus callosotomy in 10, and disconnection or resection of hypothalamic hamartoma in 6. (Details regarding the surgical procedures are provided in the Supplementary Appendix, Section 1, Tables S7 and S8.)

PRIMARY OUTCOME

At 12 months, complete freedom from seizures was reported in 44 patients (77%) in the surgery group and in 4 (7%) in the medical-therapy group (absolute difference, 70.4 percentage points; 95% confidence interval [CI], 57.8 to 83.1; P<0.001) (Table 2). The relative risk of seizure recurrence was 4.09 (95% CI, 2.52 to 6.62) in the medical-therapy group as compared with the surgery group.

At the last follow-up, all the patients who had undergone temporal lobectomy or hypothalamic hamartoma surgeries were seizure-free. Of those who had undergone extratemporal resection or hemispherotomy, 11 of 12 patients (92%) and 13 of 15 (87%), respectively, had complete freedom from seizures (Supplementary Appendix, Section 1, Table S2). In the medical-therapy group, 2 of 15 patients (13%) who were on the waiting list for a temporal lobectomy were seizure-free at 12 months, along with 1 of 19 patients (5%) who were on a waiting list for an extratemporal resection and 1 of 16 (6%) who were waiting

Table 2. Primary and Secondary Outcomes at 1 Year.*

Outcome	Surgery Group (N=57)	Medical-Therapy Group (N=59)	Absolute Difference		Difference in Change from Baseline	
			Value (95% CI)	P Value	Value (95% CI)	P Value
Primary outcome: freedom from seizures — no. (%)	44 (77)	4 (7)	70.4 (57.8 to 83.1)†	<0.001	NA	NA
Secondary outcomes						
Score on Hague Seizure Severity scale	15.4±5.5	34.3±11.8	18.9 (15.5 to 22.3)	<0.001	19.4 (15.8 to 23.1)	<0.001
Intelligence quotient on Binet–Kamat test	62.7±18.5	58.9±22.1	3.7 (−6.6 to 14.0)	0.47	2.5 (−0.1 to 5.1)	0.06
Social quotient on Vineland Social Maturity Scale	41.5±23.1	39.9±19.7	1.6 (−10.3 to 13.4)	0.79	4.7 (0.4 to 9.1)	0.03
Total score on Child Behavior Checklist	57.2±6.7	68.6±7.6	11.4 (8.8 to 14.0)	<0.001	13.1 (10.7 to 15.6)	<0.001
Total score on Pediatric Quality of Life Inventory	76.1±13.1	53.9±18.5	22.1 (16.2 to 28.1)	<0.001	21.9 (16.4 to 27.6)	<0.001

* Plus–minus values are means ±SD. NA denotes not applicable.
† The absolute between-group difference for the primary outcome is provided in percentage points.

for a corpus callosotomy; among those with a planned hemispherotomy or intervention for hypothalamic hamartoma, none of the patients were seizure-free (Supplementary Appendix, Section 1, Table S3).

SECONDARY OUTCOMES

Estimates of the probability of being seizure-free at 12 months on Kaplan–Meier analysis were 36.7% in the surgery group and zero in the medical-therapy group (hazard ratio for freedom from seizures in the surgery group, 6.2; 95% CI, 4.6 to 8.2; P<0.001) (Fig. 2). (Although 77% of the patients in the surgery group were seizure-free at the 12-month follow-up, the postoperative seizures that had occurred during the first 6 months were included in the Kaplan–Meier analysis.) The reduction from baseline in the score on the Hague Seizure Severity scale at 1 year was significantly greater in the surgery group than in the medical-therapy group (between-group difference in the change from baseline, 19.4; 95% CI, 15.8 to 23.1; P<0.001) (Table 2). The Binet–Kamat test was administered to 63 patients (30 in the surgery group and 33 in the medical-therapy group). The reduction from baseline in the mean (±SD) intelligence quotient was not significant in the surgery group (–1.3±6.5, P=0.29) and was significant in the medical-therapy group (–3.8±3.6, P<0.001); however, the between-group difference in change from baseline to 12 months was not significant (difference, 2.5; 95% CI, −0.1 to 5.1; P=0.06). The Vineland Social Maturity Scale test was administered to 53 children (27 in the surgery group and 26 in the medical-therapy group). There was no significant change from baseline in the mean social quotient in either group (2.9±7.9 in the surgery group, P=0.07; and –1.8±7.7 in the medical-therapy group, P=0.24), but the between-group difference in the change from baseline significantly favored the surgery group (difference, 4.7; 95% CI, 0.4 to 9.1; P=0.03) (Table 2).

At 12 months, the change from baseline in the mean T score on the Child Behavior Checklist was significant in the surgery group (–12.3±6.2, P<0.001) but not in the medical-therapy group (–0.86±7.2, P=0.36), which resulted in a significant between-group difference that favored the surgery group (difference, 13.1; 95% CI, 10.7 to 15.6; P<0.001). On the Pediatric Quality of Life Inventory, the mean total score increased sig-

nificantly in the surgery group (22.7±14.3; 95% CI, 18.9 to 26.5; P<0.001) but not in the medical-therapy group (0.70±16.0; 95% CI, 3.5 to 4.9; P=0.74), which also resulted in a significant between-group difference in the change from baseline that favored the surgery group (difference, 21.9; 95% CI, 16.4 to 27.6; P<0.001). (Details regarding the subscales on the Child Behavior Checklist and Pediatric Quality of Life Inventory at baseline and 12 months are provided in the Supplementary Appendix, Section 1, Tables S5 and S6.)

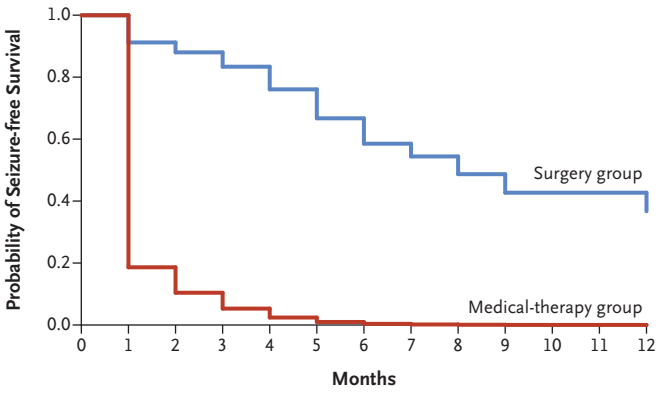

Figure 2. Probability of Seizure-free Survival at 1 Year.
Shown are Kaplan–Meier estimates of the probability of being seizure-free at 1 year in the two study groups. The rate of seizure-free survival was 36.7% in the surgery group and zero in the medical-therapy group (hazard ratio for freedom from seizures in the surgery group, 6.2; 95% confidence interval, 4.6 to 8.2; P<0.001).

ADVERSE EVENTS

There were no deaths in either group. Serious adverse events occurred in 19 patients (33%) in the surgery group and none in the medical-therapy group. These events included monoparesis in 2 patients who had undergone temporal lobectomy or resection of parietal focal cortical dysplasia, hemiparesis in 15 patients who had undergone hemispherotomy, and generalized hypotonia and language deficits in 1 patient each who had undergone frontal lobectomy. Of the 17 patients with monoparesis or hemiparesis, 15 (with the exclusion of 2 of those with hemiparesis) were able to move all major joints against gravity or better at 12 months. In the child with generalized hypotonia and the one with language deficits after surgery, both reached baseline levels of motor and language functions, respectively, at 12 months. In the medical-therapy group, 10 had physical injuries associated with seizures (cuts, burns, and fractures), 1 had an adverse event associated with an antiepileptic drug, and autistic features developed in another. (Details regarding adverse events are provided in the Supplementary Appendix, Section 1, Tables S7 and S9.)

DISCUSSION

In this single-center, randomized, controlled trial, seizure outcomes 1 year after epilepsy surgery were significantly better than after continued medical therapy alone. Of the 57 patients who underwent surgery, 44 (77%) became seizure-free and 13 (23%) had ongoing seizures of varying degrees (class 2 to class 5 on the International League Against Epilepsy scale) (Supplementary Appendix, Section 1, Tables S1 and S2). In comparison, 93% of those receiving medical therapy alone continued to have seizures. In the surgery group, 21 patients (37%) were completely seizure-free during the entire 12-month period, whereas during the first weeks after surgery, the other 23 patients continued to have seizures; these episodes subsequently decreased in frequency, a feature that has been observed in other series of epilepsy surgery.[14] A substantial proportion of the children in the surgery group had anticipated major postoperative motor, sensory, or cognitive deficits that were related to the area of the brain that was resected or disconnected.

Complete freedom from seizures occurred in all the patients in our trial who had undergone temporal lobectomy, as compared with only 38% of those who had undergone the same surgery in another randomized trial of epilepsy surgery that included only adults with a longer duration of epilepsy than the children in our trial. The difference in ages and duration of epilepsy between the two trials may explain the difference in results.[4]

The between-group difference in the change from baseline to 12 months in the mean intelligence quotient was not significant in our trial, and it is possible that the 12-month interval of observation was too brief to observe a change in this measure. The improvements that were observed in other cognitive, behavioral, and quality-of-life scores in the surgery group may have been due to a reduction in the frequency of

seizures; conversely, the deterioration in these measures in the medical-therapy group may be attributed to a continuation of seizures, which has been associated with poor cognitive functioning in children.[15-24] In two nonrandomized trials, overall quality-of-life scores were significantly better among children who had undergone epilepsy surgery than among those who had received only medical therapy after 2 years or more of follow-up.[25,26] An observational study comparing surgical versus medical treatment in children with epileptic encephalopathy in infancy and early childhood showed that surgery resulted in better seizure control and a better developmental quotient than did medical therapy.[27]

Our trial has some limitations. First, we included patients undergoing many types of epilepsy surgeries that were directed at several underlying pathological causes of seizures. However, the patients who were included in the trial reflect the populations encountered at a referral center for pediatric epilepsy. Second, there was an overrepresentation of hypothalamic hamartomas in our trial as compared with some other series. And third, our statistical analysis plan called for an outdated approach of last observation carried forward for missing data of secondary outcomes, although the effect was relatively minor, since information was missing in only one patient.

Serious adverse events due to the surgery included major motor, sensory, and cognitive deficits that were related to the area of the brain that was resected or disconnected. Despite these deficits, quality-of-life measures were significantly better in the surgery group, possibly because of better seizure control.

In conclusion, surgery in children with drug-resistant epilepsy resulted in higher rates of cessation of seizures at 1 year and better scores on some measures of behavior and quality of life than continued medical therapy alone. Some patients in the surgery group had anticipated serious neurologic consequences, including hemiparesis, some of which improved over time.

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No potential conflict of interest relevant to this article was reported.

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CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

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ABSTRACT

BACKGROUND

Obstructive sleep apnea is associated with an increased risk of cardiovascular events; whether treatment with continuous positive airway pressure (CPAP) prevents major cardiovascular events is uncertain.

METHODS

After a 1-week run-in period during which the participants used sham CPAP, we randomly assigned 2717 eligible adults between 45 and 75 years of age who had moderate-to-severe obstructive sleep apnea and coronary or cerebrovascular disease to receive CPAP treatment plus usual care (CPAP group) or usual care alone (usual-care group). The primary composite end point was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack. Secondary end points included other cardiovascular outcomes, health-related quality of life, snoring symptoms, daytime sleepiness, and mood.

RESULTS

Most of the participants were men who had moderate-to-severe obstructive sleep apnea and minimal sleepiness. In the CPAP group, the mean duration of adherence to CPAP therapy was 3.3 hours per night, and the mean apnea–hypopnea index (the number of apnea or hypopnea events per hour of recording) decreased from 29.0 events per hour at baseline to 3.7 events per hour during follow-up. After a mean follow-up of 3.7 years, a primary end-point event had occurred in 229 participants in the CPAP group (17.0%) and in 207 participants in the usual-care group (15.4%) (hazard ratio with CPAP, 1.10; 95% confidence interval, 0.91 to 1.32; P=0.34). No significant effect on any individual or other composite cardiovascular end point was observed. CPAP significantly reduced snoring and daytime sleepiness and improved health-related quality of life and mood.

CONCLUSIONS

Therapy with CPAP plus usual care, as compared with usual care alone, did not prevent cardiovascular events in patients with moderate-to-severe obstructive sleep apnea and established cardiovascular disease. (Funded by the National Health and Medical Research Council of Australia and others; SAVE ClinicalTrials.gov number, NCT00738179; Australian New Zealand Clinical Trials Registry number, ACTRN12608000409370.)

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*A complete list of sites and trial investigators and coordinators in the Sleep Apnea Cardiovascular Endpoints (SAVE) study is provided in the Supplementary Appendix, available at NEJM.org.

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Obstructive sleep apnea causes episodic hypoxemia and nocturnal sympathetic nervous system activation[1] and elevates blood pressure[2] and markers of oxidative stress, inflammation, and hypercoagulation.[3,4] Large negative intrathoracic pressure swings also impose mechanical stress on the heart and great vessels.[5-7] Population-based and sleep-clinic–based cohort studies have shown an association between obstructive sleep apnea and cardiovascular events,[8-16] particularly stroke.[17] Randomized, controlled trials have shown that treatment with continuous positive airway pressure (CPAP) lowers systolic blood pressure by 2 to 3 mm Hg in patients with normotensive obstructive sleep apnea[18] and by 6 to 7 mm Hg in patients with resistant hypertension,[19] improves endothelial function,[20] and increases insulin sensitivity.[21] Observational clinical studies have shown that the use of CPAP is associated with lower rates of cardiovascular complications and of death from cardiovascular causes, especially among patients who are adherent to treatment.[10,13]

Obstructive sleep apnea is a common condition among patients with cardiovascular disease, affecting 40 to 60% of such patients.[12,16,22,23] Because the risks of recurrent cardiovascular events among these patients remain high despite contemporary therapies, CPAP could be a useful additional treatment for the prevention of these events. We describe the main results of the Sleep Apnea Cardiovascular Endpoints (SAVE) study, a secondary prevention trial that was designed to evaluate the effectiveness of CPAP in reducing the rate of cardiovascular events among patients with obstructive sleep apnea.[24]

METHODS

STUDY DESIGN AND OVERSIGHT

The SAVE study was an international, multicenter, randomized, parallel-group, open-label trial, with blinded end-point assessment. Details of the design and analysis plan of the trial have been published previously.[24,25] An executive committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed the study and supervised the conduct of the trial and the collection of the data. The Adelaide Institute for Sleep Health of Flinders University of South Australia was responsible for the overall management of the trial and provided the core sleep laboratory analysis and monitoring of the CPAP data and treatment at the sites. Investigators at the George Institute for Global Health coordinated the trial, managed the database, and performed the statistical analyses. All the authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol, available at NEJM.org. An independent data and safety monitoring board monitored unblinded trial results and safety events. The trial protocol was approved by all appropriate regulatory authorities and ethics committees at the participating centers. All participants provided written informed consent.

The National Health and Medical Research Council of Australia and Philips Respironics provided the main funding for the trial. In-kind donations were provided by Respironics for the CPAP equipment and by ResMed for the sleep apnea diagnostic devices. None of the funding agencies contributed to the design of the trial, the collection or analysis of the data, the writing of the manuscript, or the decision to submit the manuscript for publication.

PATIENTS AND PROCEDURES

Patients were recruited at 89 clinical centers in 7 countries; eligibility criteria included an age between 45 and 75 years, a diagnosis of coronary artery disease or cerebrovascular disease, and a diagnosis of moderate-to-severe obstructive sleep apnea. The diagnosis of moderate-to-severe obstructive sleep apnea, which was defined as an oxygen desaturation index (the number of times per hour during the oximetry recording that the blood oxygen saturation level drops by ≥4 percentage points from baseline) of at least 12, was established with the use of a home sleep-study screening device (ApneaLink, ResMed) and was confirmed by review of the data at a central core sleep laboratory. Patients were excluded from the study if they reported severe daytime sleepiness (Epworth Sleepiness Scale score >15; scores range from 0 to 24, with higher scores indicating greater severity) or were considered to have an increased risk of an accident from falling asleep, if they had very severe hypoxemia (oxygen saturation <80% for >10% of recording time), or if they had a pattern of Cheyne–Stokes respiration on the ApneaLink nasal pressure recording.

Potential participants were required to have a minimum level of adherence to CPAP therapy,

which was defined as an average of 3 hours per night, during a 1-week run-in period in which sham CPAP was used (i.e., CPAP at subtherapeutic pressure). Further details of the inclusion and exclusion criteria and of the procedures performed at the core sleep laboratory are provided in the Supplementary Appendix.

RANDOMIZATION AND INTERVENTIONS

After eligibility was confirmed, the patients were randomly assigned, at a central location, to receive either CPAP therapy plus usual care (CPAP group) or usual care alone (usual-care group). Randomization was performed with the use of a minimization procedure to balance the group assignments according to site, type of cardiovascular disease (cardiac, cerebrovascular, or both), and severity of daytime sleepiness (Epworth Sleepiness Scale score <11 vs. ≥11).

The patients who were assigned to receive mask-delivered CPAP treatment were provided with an automated positive airway pressure machine (REMstar Auto, M or PR series, Philips Respironics) that was initially set in automatic mode for 1 week and thereafter fixed to the 90th percentile of pressure that was calculated by the automated positive airway pressure device from the recorded data. The core sleep laboratory monitored trends in adherence to CPAP therapy and provided corrective advice to investigators (further details are provided in the Supplementary Appendix). Concomitant management of cardiovascular risk factors was performed in accordance with national guidelines. All participants were given advice on healthful sleep habits and lifestyle changes to minimize obstructive sleep apnea. Clinic visits were scheduled for all participants at 1, 3, 6, and 12 months and annually thereafter; the participants were contacted by telephone at 6 months between annual clinic visits.

STUDY MEASUREMENTS

At randomization and at each follow-up visit, participants had resting blood pressure and heart rate measured at the clinic, and details of current medication use and health behaviors were documented through a structured interview. Among the participants in the CPAP group, data on adherence to the use of the CPAP device were recorded. At randomization, at 6 months, and at 2 and 4 years, anthropometric measurements were obtained in all participants, and all participants completed several questionnaires: questionnaires that assessed symptoms of obstructive sleep apnea (snoring, witnessed episodes of apnea, and degree of sleepiness according to the Epworth Sleepiness Scale score), the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36; scores range from 0 to 100, with higher scores indicating better quality of life) for assessment of health-related quality of life, and the Hospital Anxiety and Depression Scale (on which anxiety and depression scores range from 0 to 21, with higher scores indicating more symptoms) for assessment of mood. Electrocardiography was performed in all participants at the time of randomization and at 2 years. The European Quality of Life–5 Dimensions questionnaire (EQ-5D; scores range from 1 to 3, with higher scores indicating more problems across five categories of quality of life) was administered only at the end-of-study visit.

The end-of-study visits were conducted from September 2015 through January 2016 (except in India, where they were conducted from July through October 2013). In addition to performing a regular central review of data quality, research staff visited the participating sites to monitor and verify the completeness and authenticity of source documents and adverse-event reporting. Additional details on study measurements and monitoring procedures are provided in the Supplementary Appendix.

STUDY END POINTS

A committee whose members were unaware of the study-group assignments adjudicated the major cardiovascular outcomes specified in the protocol. The primary end point was a composite of death from any cardiovascular cause, myocardial infarction (including silent myocardial infarction), stroke, or hospitalization for heart failure, acute coronary syndrome (including unstable angina), or transient ischemic attack. Prespecified secondary cardiovascular end points included the individual components of the primary composite end point, other composites of cardiovascular events, revascularization procedures, new-onset atrial fibrillation, new-onset diabetes mellitus, and death from any cause. Other secondary end points included symptoms of obstructive sleep apnea, health-related quality of life, and mood.

Prespecified safety end points were assessed each time the participant was contacted; these

end points included all serious adverse events, self-reported accidents causing personal injury that occurred while the participant was driving or while at work, and any accidents or near-miss accidents that occurred as a result of the participant falling asleep. Two safety end points that were not prespecified — the number of self-reported road-traffic accidents from any cause and the number of days off from work because of poor health — were also assessed. Descriptions of the study end points and of the procedures used by the data and safety monitoring board and end-point adjudicators are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Our original plan was to recruit 5000 patients. In 2012, challenges in achieving recruitment targets prompted us to review the accumulated blinded study data and an updated meta-regression of studies of cardiovascular events and severity of obstructive sleep apnea. The meta-regression showed that cardiovascular risk increased by 25 to 32% for every increase of 10 events per hour in the apnea–hypopnea index (the number of occurrences of apnea or hypopnea per hour of sleep), which was a stronger relationship than we had originally assumed.[24] In consideration of this information, together with interim blinded trial data showing an annual event rate of 6.86% and better-than-expected adherence to CPAP therapy, we revised our sample size to 2500 patients; we estimated that with this sample size, the study would have 90% statistical power (at an alpha level of 0.05) to detect a 25% lower incidence with CPAP plus usual care than with usual care alone of the primary composite cardiovascular end point, which was anticipated to occur in 533 patients overall over a mean follow-up of 4.5 years.

The primary analysis was an unadjusted survival analysis performed according to the intention-to-treat principle with the use of Cox proportional-hazards regression modeling that was based on positively adjudicated events. We performed a series of sensitivity analyses, including an analysis with adjustment for stratification variables, region, and severity of obstructive sleep apnea; an analysis with Poisson regression to account for participants with multiple events; and an analysis that included all events that were reported by the investigators and not just those that were positively adjudicated. To estimate the effect in patients who were adherent to CPAP therapy, which was defined as an average of 4 hours or more of treatment per night over the first 2 years, we used prespecified propensity-score matching to match adherent patients one-to-one with participants selected from the usual-care (control) group who never used CPAP. The change in clinical variables from baseline to 48 months or to the end-of-study visit (whichever came first) was assessed with the use of analysis of covariance with adjustment for baseline values. All P values are two-sided and were not adjusted for multiple testing. Statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute). (Additional details regarding the sample-size calculations and other aspects of the statistical analysis are provided in the Supplementary Appendix.)

RESULTS

STUDY PARTICIPANTS

A total of 15,325 patients were assessed for eligibility; 5844 met the initial eligibility criteria and underwent ApneaLink testing, and 3246 entered the 1-week run-in phase (Fig. 1). The 2717 patients who were eligible for participation after the run-in phase were enrolled in the study from December 2008 through November 2013 and were randomly assigned to receive CPAP plus usual care (1359 patients) or usual care alone (1358 patients).

All 21 participants from one site were excluded from the study because it was determined during site monitoring that the required standard for conducting clinical trials was not met; in addition, 9 other participants withdrew consent at the time of randomization or did not adhere to the trial protocol from the time of randomization. Thus, 2687 participants were included in the primary analysis (Fig. 1 and Table 1). The mean age of the participants was 61 years, and 81% were men. The mean body-mass index (the weight in kilograms divided by the square of the height in meters) of the participants was 29; the mean oxygen desaturation index, 28 events per hour; and the mean Epworth Sleepiness Scale score, 7.4. Participants were evenly divided between those with coronary artery disease and those with cerebrovascular disease.

Final follow-up visits were completed by January 2016; a total of 147 patients discontinued their participation in the study before the intended

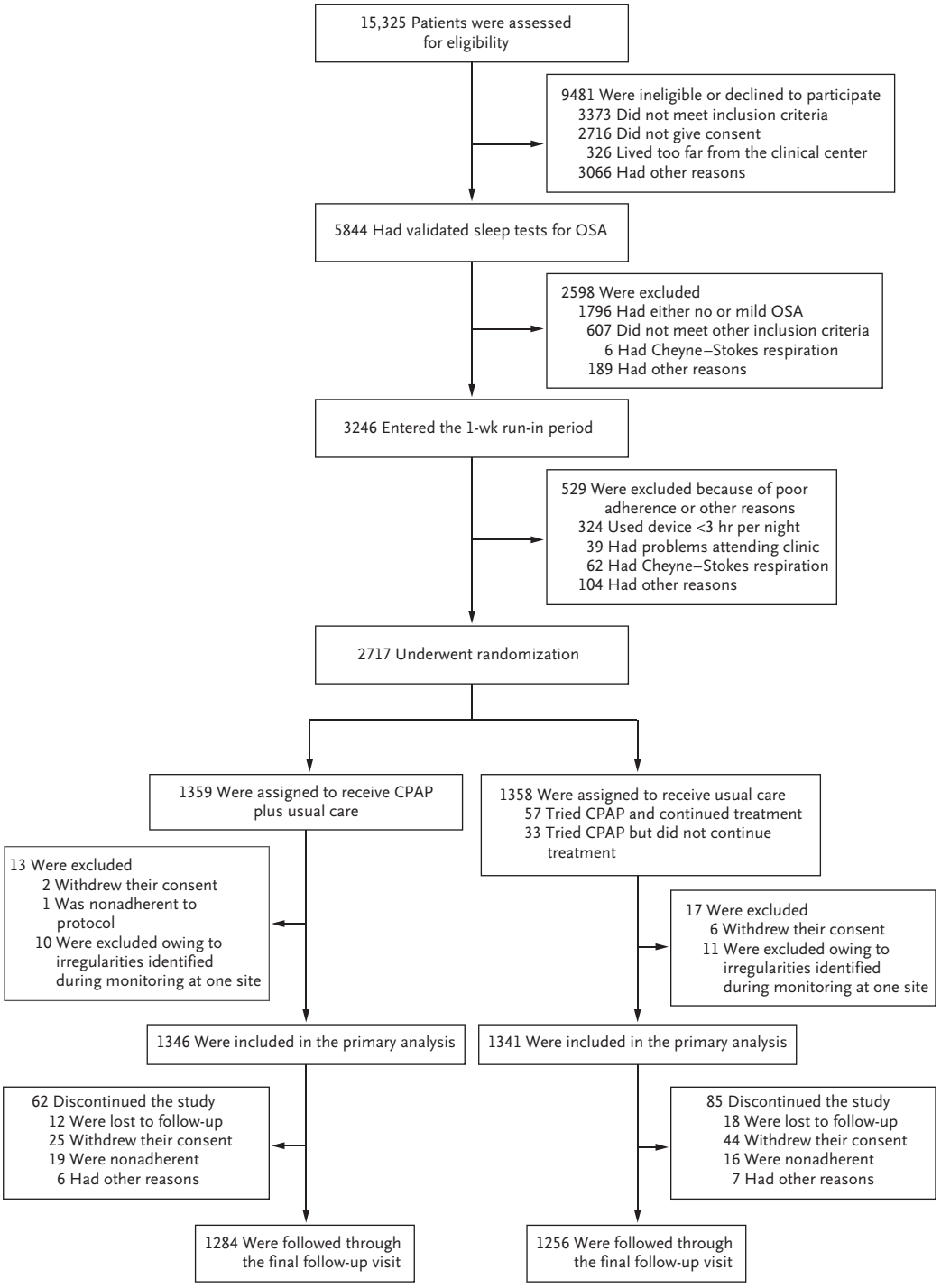

Figure 1. Screening, Randomization, and Follow-up Analyses.

Testing for obstructive sleep apnea (OSA) involved the use a home sleep-study screening device (ApneaLink [ResMed]). During the 1-week run-in period, the participants received sham continuous positive airway pressure (CPAP) and were educated on the use of the equipment. In the case of participants who discontinued the study, only data that were acquired before discontinuation were included in the analysis.

Table 1. Baseline Characteristics of the Study Participants*

Characteristic	CPAP Group (N=1346)	Usual-Care Group (N=1341)
Age — yr	61.3±7.7	61.2±7.91
Male sex — no./total no. (%)	1092/1346 (81.1)	1082/1341 (80.7)
Race — no./total no. (%)†		
Asian	857/1346 (63.7)	843/1340 (62.9)
White	336/1346 (25.0)	341/1340 (25.4)
Other	153/1346 (11.4)	156/1340 (11.6)
Type of cardiovascular disease — no./total no. (%)		
Coronary artery disease	682/1346 (50.7)	681/1341 (50.8)
Cerebrovascular disease	664/1346 (49.3)	660/1341 (49.2)
Both	50/1346 (3.7)	58/1341 (4.3)
Medical history — no./total no. (%)‡		
Hypertension	1057/1343 (78.7)	1046/1338 (78.2)
Any stroke	589/1343 (43.9)	594/1338 (44.4)
Any transient ischemic attack	135/1343 (10.1)	130/1338 (9.7)
Any heart disease	556/1343 (41.4)	534/1338 (39.9)
Myocardial infarction	434/1343 (32.3)	465/1338 (34.8)
Coronary stent insertion	451/1343 (33.6)	462/1338 (34.5)
Coronary-artery bypass surgery	160/1343 (11.9)	159/1338 (11.9)
Diabetes mellitus	405/1343 (30.2)	393/1338 (29.4)
Tobacco use§	213/1343 (15.9)	194/1338 (14.5)
Medications — no./total no. (%)		
Antihypertensive agent	1049/1346 (77.9)	1040/1341 (77.6)
Statin or other lipid-lowering agent	762/1346 (56.6)	800/1341 (59.7)
Antidiabetic oral medication	291/1346 (21.6)	291/1341 (21.7)
Insulin	80/1346 (5.9)	83/1341 (6.2)
Aspirin or other antithrombotic agent	1009/1346 (75.0)	1009/1341 (75.2)
Anthropometric measurements		
Body-mass index¶	28.8±4.6	28.5±4.4
Waist-to-hip ratio	0.96±0.08	0.95±0.08
Neck circumference — cm	40.8±4.0	40.6±4.2
Obstructive sleep apnea characteristics		
Oxygen desaturation index‖	28.1±14.1	28.4±14.5
Apnea–hypopnea index**	29.0±15.9	29.6±16.4
Epworth Sleepiness Scale score††	7.3±3.6	7.5±3.6
Reported snoring almost every day — no./total no. (%)‡‡	1091/1305 (83.6)	1049/1288 (81.4)
Adherence to sham CPAP device use during the run-in phase — hr per night	5.2±1.4	5.2±1.4

* Plus–minus values are means ±SD. There was no significant differences in baseline values between the participants assigned to receive continuous positive airway pressure plus usual care (CPAP group) and the participants assigned to received usual care alone (usual-care group).
† Race was self-reported.
‡ Medical history was self-reported or determined though a review of medical records.
§ Values reflect current use of tobacco.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.
‖ The oxygen desaturation index is the number of times per hour during the oximetry recording that the blood oxygen saturation level drops by at least 4 percentage points from baseline.
** The apnea–hypopnea index is the number of apnea and hypopnea events per hour of recording.
†† The Epworth Sleepiness Scale ranges from 0 to 24, with higher scores indicating greater sleepiness; a score higher than 10 indicates pathologic sleepiness.
‡‡ Snoring was reported by the patient on a questionnaire.

final visit, but their data up to the time of withdrawal were included in the primary analysis performed in the intention-to-treat population (Fig. 1). The mean duration of follow-up was 3.7 years. (Further details on the study participants are provided in Tables S1, S2, and S3 in the Supplementary Appendix.)

INTERVENTION ADHERENCE, MEDICATIONS, AND LIFESTYLE FACTORS

The mean duration of use of the sham CPAP device during the 1-week run-in phase was 5.2 hours per night (Table 1). Among the participants in the CPAP group, the mean (±SD) duration of adherence to CPAP therapy in the first month of treatment was 4.4±2.2 hours per night, which decreased to 3.5±2.4 hours per night by 12 months and remained relatively stable thereafter (mean adherence during follow-up, 3.3±2.3 hours). The residual apnea–hypopnea index during CPAP use, as measured by the CPAP machine, averaged 3.7 events per hour, which indicated good control of obstructive sleep apnea with CPAP. Of the 1346 patients in the CPAP group, 566 (42%) had good adherence to treatment (≥4 hours per night) during follow-up. Of the 1341 patients who were followed in the usual-care group, 90 (6.7%) tried CPAP but only 57 (4.3%) continued the treatment. No significant differences were observed between the CPAP group and the usual-care group in the use of medications for diabetes mellitus and cardiovascular conditions, in lifestyle factors including diet and smoking, and in body-mass index from baseline to the end of the study. (Further details are provided in Fig. S1 and Tables S4 through S6 in the Supplementary Appendix.)

PRIMARY END POINT

A primary end-point event was confirmed in 436 participants — 229 (17.0%) in the CPAP group and 207 (15.4%) in the usual-care group (hazard ratio with CPAP, 1.10; 95% confidence interval [CI], 0.91 to 1.32; P=0.34) (Table 2 and Fig. 2). No significant effect of CPAP was found in the adjusted analysis or in the analyses that were based on total event rates and on primary end-point events reported by the investigators. No significant heterogeneity was observed for the primary end point across subgroups defined according to region (China vs. outside China), age group (>60 years vs. ≤60 years), sex, severity of obstructive sleep apnea, body-mass index (<30 vs. ≥30), daytime sleepiness, type of cardiovascular disease, and presence or absence of diabetes mellitus.

Anthropometric and disease characteristics of patients with good adherence to CPAP therapy (≥4 hours per night) differed from those of patients with lower adherence and from the patients in the usual-care group as a whole. One-to-one propensity-score matching was performed to compare 561 patients who were adherent to CPAP therapy with 561 patients in the usual-care group. Among these propensity-score–matched patients, 184 primary end-point events occurred — 86 (15.3%) in the CPAP group and 98 (17.5%) in the usual-care group (hazard ratio, 0.80; 95% CI, 0.60 to 1.07; P=0.13). The adjusted Cox regression model (adjusted for the baseline factors used in the propensity-score–matching comparison) that compared patients with good adherence and those with poor adherence in the CPAP group with the patients in the usual-care group showed a similar result. (Further details on the results for the primary end point are provided in Tables S7 through S12 and Figs. S2 and S3 in the Supplementary Appendix.)

SECONDARY AND OTHER END POINTS

No significant between-group differences were observed in any of the cause-specific or composite secondary cardiovascular end points in the primary analysis (Table 2) or in the subsidiary analyses, except for a higher rate of total hospital admissions for transient ischemic attack among the patients in the CPAP group (relative risk, 2.29; 95% CI, 1.05 to 4.99; P=0.04). The propensity score–matched analyses showed that the patients who were adherent to CPAP therapy had a lower risk of stroke than those in the usual-care group (hazard ratio, 0.56; 95% CI, 0.32 to 1.00; P=0.05), as well as a lower risk of the nonprespecified composite end point of cerebral events (hazard ratio, 0.52; 95% CI, 0.30 to 0.90; P=0.02), but these results were not adjusted for multiple testing. A post hoc CPAP dose–response analysis of the primary and secondary cardiovascular end points showed no significant association.

The reductions from baseline in sleepiness and other symptoms of obstructive sleep apnea

Table 2. Primary and Secondary Cardiovascular End Points

End Point	CPAP Group (N=1346)	Usual-Care Group (N=1341)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Primary composite end point*	229 (17.0)	207 (15.4)	1.10 (0.91–1.32)	0.34
Secondary end points				
Components of primary end point				
Death from cardiovascular causes	25 (1.9)	20 (1.5)	1.22 (0.68–2.20)	0.50
Myocardial infarction	42 (3.1)	39 (2.9)	1.06 (0.68–1.64)	0.80
Stroke	67 (5.0)	68 (5.1)	0.97 (0.69–1.35)	0.84
Hospitalization for heart failure	17 (1.3)	17 (1.3)	0.98 (0.50–1.92)	0.96
Hospitalization for unstable angina	99 (7.4)	90 (6.7)	1.09 (0.82–1.45)	0.56
Hospitalization for transient ischemic attack	16 (1.2)	9 (0.7)	1.75 (0.77–3.95)	0.18
Other vascular end points				
Composite of ischemic cardiovascular events†	207 (15.4)	191 (14.2)	1.07 (0.88–1.31)	0.49
Composite of major cardiovascular events‡	117 (8.7)	120 (8.9)	0.96 (0.74–1.23)	0.72
Composite of cerebral events§	80 (5.9)	74 (5.5)	1.06 (0.77–1.45)	0.72
Composite of cardiac events¶	167 (12.4)	157 (11.7)	1.06 (0.85–1.31)	0.62
Revascularization procedures	99 (7.4)	74 (5.5)	1.33 (0.98–1.79)	0.07
Death from any cause	40 (3.0)	43 (3.2)	0.91 (0.59–1.40)	0.67
New-onset atrial fibrillation‖	22 (1.6)	15 (1.1)	1.46 (0.76–2.81)	0.26
Newly diagnosed diabetes	66 (4.9)	76 (5.7)	0.85 (0.61–1.19)	0.35

* The primary composite end point included death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure, unstable angina, and transient ischemic attack.
† The composite end point of ischemic cardiovascular events included cardiovascular death, myocardial infarction, ischemic stroke, and hospitalization for either an ischemic coronary (angina) or cerebral (transient ischemic attack) event.
‡ The composite end point of major cardiovascular events included cardiovascular death, myocardial infarction, and stroke.
§ The composite end point of cerebral events included any stroke and hospitalization for transient ischemic attack, including fatal events; this composite end point was not prespecified in the trial protocol.
¶ The composite end point of cardiac events included any myocardial infarction and hospitalization for unstable angina, atrial fibrillation, or heart failure, including fatal events; this composite end point was not prespecified in the trial protocol.
‖ New-onset atrial fibrillation was confirmed through electrocardiography.

were greater in the CPAP group than in the usual-care group (estimated mean between-group difference in the change from baseline in Epworth Sleepiness Scale score, –2.5; 95% CI, –2.8 to –2.2; P<0.001) (Table 3). Greater reductions from baseline in the anxiety and depression subscale scores of the Hospital Anxiety and Depression Scale were also observed in the CPAP group than in the usual-care group (Table 3), and the percentage of patients with clinically relevant depression scores was 25 to 30% lower in the CPAP group than in the usual-care group at the end of follow-up. The CPAP group had greater improvement in scores on the physical and mental subscales of the SF-36 than the usual-care group (Table 3), as well as fewer days off from work because of poor health (a nonprespecified end point) than the usual-care group (Table 4). The number of serious adverse events and the rate of road-traffic accidents and accidents causing injury did not differ significantly between the two groups (Table 4). (Further de-

tails on the results for the secondary and other end points are provided in Figs. S4 and S5 and Tables S8 and S12 through S16 in the Supplementary Appendix.)

DISCUSSION

This secondary prevention trial in adults with cardiovascular disease and obstructive sleep apnea showed that the risk of serious cardiovascular events was not lower among patients who received treatment with CPAP in addition to usual care than among those who received usual care alone. Treatment with CPAP was associated with a greater reduction in symptoms of daytime sleepiness and with improved health-related quality of life, mood, and attendance at work. This study was not powered to provide definitive answers regarding the effects of CPAP on secondary cardiovascular end points, but there was no indication of a significant benefit with respect to any cause-specific cardiovascular outcome.

Three other randomized trials have investigated the effect of CPAP on cardiovascular end points in patients with obstructive sleep apnea.[26-28] Two studies — a multicenter study conducted in Spain that compared CPAP with usual care in 725 patients with obstructive sleep apnea who did not have prior cardiovascular disease[26] and a single-center study involving 224 patients with obstructive sleep apnea and coronary artery disease who had just undergone revascularization[28] — showed no difference in composite cardiovascular end points over several years of follow-up, although in adjusted analyses, both studies reported better outcomes among patients who were adherent to CPAP therapy (≥4 hours per night) than among patients who did not receive CPAP or who used CPAP less than 4 hours per night. The third study involving 140 patients with recent ischemic stroke showed no effect of CPAP on event-free survival over 2 years.[27]

One important potential limitation of our trial is that, for several of the participating countries, the diagnosis and treatment of sleep apnea were not well established in clinical practice when the trial began. However, before trial recruitment, we expended substantial time and effort in conducting training workshops for investigators and study coordinators. In addition, extensive site monitoring was conducted throughout the trial to ensure a high standard of study conduct.

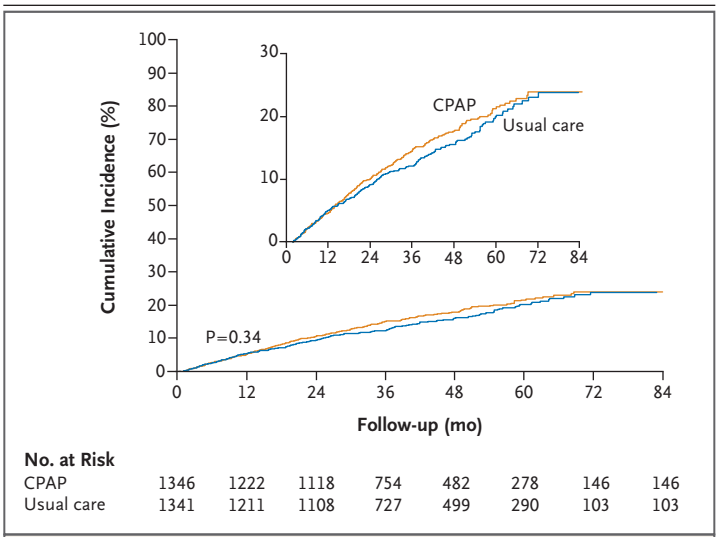

Figure 2. Cumulative Event Curve of the Primary End Point.

Shown is the cumulative incidence of a first primary end point (a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure, unstable angina, or transient ischemic attack) in the group that received CPAP plus usual care (CPAP group) and in the group that received usual care alone (usual-care group). The inset shows the same data on an enlarged y axis.

Participants in the SAVE study who were assigned to CPAP adhered to the treatment for a mean of 3.3 hours per night over several years, which is similar to the mean adherence in other reports of CPAP use in patients who had no or minimal daytime sleepiness[29,30] and which is consistent with CPAP use in clinical practice.[31] However, although this overall level of adherence to CPAP therapy exceeded the estimates in our power calculations, it may still have been insufficient to provide the level of effect on cardiovascular outcomes that had been hypothesized. For practical reasons and to ensure efficient recruitment and consistency of data across multiple sites, we used a simple screening device (ApneaLink) that was based on oximetry and nasal pressure recordings and used automated algorithms to analyze signals, rather than the conventional standard test for obstructive sleep apnea in which polysomnographic data from an overnight stay in a hospital or clinic are scored manually. The ApneaLink screening device has been shown to be a reliable method for diagnosing moderate-to-severe obstructive sleep apnea.[32,33] To mitigate

Table 3. Other Outcomes.*

Outcome	CPAP Group (N=1346)					Usual-Care Group (N=1341)					Adjusted Difference in Change from Baseline (95% CI)†	P Value
	Baseline		End of Study		Change from Baseline	Baseline		End of Study		Change from Baseline		
	no. of patients with data	*value*	*no. of patients with data*	*value*		*no. of patients with data*	*value*	*no. of patients with data*	*value*			
Blood pressure — mm Hg												
Systolic	1341	132±16	1166	132±16	0.7±17‡	1333	131±16	1158	132±16	1.5±17	−0.4 (−1.5 to 0.8)	0.55
Diastolic	1341	80±11	1166	79±16	−0.9±11	1333	79±11	1158	79±10	−0.1±11	−0.7 (−1.4 to 0.0)	0.05
Epworth Sleepiness Scale score	1346	7.3±3.6	1221	4.2±3.5	−3.1±4.1	1341	7.5±3.6	1188	6.8±4.4	−0.7±4.3	−2.5 (−2.8 to −2.2)	<0.001
Hospital Anxiety and Depression Scale												
Anxiety score	1341	4.6±3.7	1220	3.8±3.6	−0.8±3.6	1336	4.6±3.6	1190	4.2±3.6	−0.4±3.5	−0.4 (−0.6 to −0.2)	0.002
Depression score	1341	5.1±3.9	1220	4.3±3.6	−0.8±4.0	1336	5.2±3.9	1190	5.1±3.8	−0.1±3.8	−0.8 (−1.0 to −0.5)	<0.001
SF-36§												
Physical-component summary score	1335	45.4±7.7	1218	46.9±8.0	1.3±7.5	1332	45.1±7.8	1189	45.9±8.1	0.6±7.6	0.9 (0.3 to 1.4)	0.002
Mental-component summary score	1332	52.6±8.6	1218	53.6±8.0	1.0±8.9	1332	52.3±8.7	1189	52.4±8.8	0.0±8.9	1.2 (0.6 to 1.8)	<0.001
EQ-5D utility score¶	—	—	1252	0.8±0.3	—	—	—	1229	0.8±0.3	—	0.02 (0.00 to 0.05)	0.03

* Plus–minus values are means ±SD.
† Analysis of covariance was used to compare the change from baseline in the CPAP group with that of the usual-care group; the analysis was adjusted for the baseline value.
‡ The change in systolic blood pressure from baseline to the end of the study is not apparent because mean blood pressure values were rounded to the nearest integer value.
§ Scores on the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) range from 0 to 100, with higher scores indicating better quality of life with respect to either the physical or mental component.
¶ Utility scores on the European Quality of Life–5 Dimensions questionnaire (EQ-5D) are described in the Supplementary Appendix. The EQ-5D was administered only at the end of the study.

Table 4. Serious Adverse Events and Other Conditions of Interest.

Variable	CPAP Group (N=1346)			Usual-Care Group (N=1341)			Rate Ratio (95% CI)*	P Value
	Participants	Events	Annual Rate	Participants	Events	Annual Rate		
	no. (%)	*no.*	%	*no. (%)*	*no.*	%		
Serious adverse events	498 (37)	1031	—	469 (35)	1025	—	—	0.27†
Road-traffic accidents‡	41 (3.0)	56	1.1	47 (3.5)	70	1.4	0.78 (0.55–1.11)	0.17
Accident causing injury	99 (7.4)	219	4.4	118 (8.8)	255	5.2	0.84 (0.70–1.00)	0.06
Accidents and near-miss accidents from falling asleep§	16 (1.2)	—	—	25 (1.9)	—	—	—	—
Days off from work because of poor health‡	306 (22.7)	6543	130¶	317 (23.6)	7796	159¶	0.82 (0.80–0.85)	<0.001

* Poisson regression was used to calculate the rate ratio between the CPAP group and the usual-care group.
† The chi-square test was used to compare the difference in the proportions of participants experiencing a serious adverse event.
‡ The end points of road-traffic accidents and days off from work because of poor health were not prespecified.
§ The participants were asked whether they had had an episode of falling asleep while driving or working that resulted in an accident or near-miss accident since their last review. The number of such events was not recorded.
¶ The annual rate is given as the number of days off from work because of poor health per 100 participants in 1 year.

the risk of recruiting patients with predominantly central apnea rather than obstructive sleep apnea, we excluded patients with overt heart failure and patients in whom the nasal pressure signals showed a predominant pattern of Cheyne–Stokes respiration.

In conclusion, in a large group of adults with both cardiovascular disease and moderate-to-severe obstructive sleep apnea, the use of CPAP therapy had no significant effect on the prevention of recurrent serious cardiovascular events, despite significantly reduced sleepiness and other symptoms of obstructive sleep apnea and improved quality-of-life measures.

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APPENDIX

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