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Upper Airway Stimulation for Obstructive Sleep Apnea: 5-Year Outcomes

B. Tucker Woodson, MD[1], Kingman P. Strohl, MD[2], Ryan J. Soose, MD[3], M. Boyd Gillespie, MD[4], Joachim T. Maurer, MD[5], Nico de Vries, MD[6,7], Tapan A. Padhya, MD[8], M. Safwan Badr, MD[9], Ho-sheng Lin, MD[10], Olivier M. Vanderveken, MD, PhD[7], Sam Mickelson, MD[11], and Patrick J. Strollo Jr, MD[12]

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Abstract

Objective. To present 5-year outcomes from a prospective cohort of patients with obstructive sleep apnea (OSA) who were treated with upper airway stimulation (UAS) via a unilateral hypoglossal nerve implant.

Study Design. A multicenter prospective cohort study.

Setting. Industry-supported multicenter academic and clinical trial.

Methods. From a cohort of 126 patients, 97 completed protocol, and 71 consented to a voluntary polysomnogram. Those having continuous positive airway pressure failure with moderate to severe OSA, body mass index <32 kg/m^2, and no unfavorable collapse on drug-induced sleep endoscopy were enrolled in a phase 3 trial. Prospective outcomes included apnea-hypopnea index (AHI), oxygen desaturation index, and adverse events, as well as measures of sleepiness, quality of life, and snoring.

Results. Patients who did and did not complete the protocol differed in baseline AHI, oxygen desaturation index, and Functional Outcomes of Sleep Questionnaire scores but not in any other demographics or treatment response measures. Improvement in sleepiness (Epworth Sleepiness Scale) and quality of life was observed, with normalization of scores increasing from 33% to 78% and 15% to 67%, respectively. AHI response rate (AHI <20 events per hour and $>50\%$ reduction) was 75% (n = 71). When a last observation carried forward analysis was applied, the responder rate was 63% at 5 years. Serious device-related events all related to lead/device adjustments were reported in 6% of patients.

Conclusions. Improvements in sleepiness, quality of life, and respiratory outcomes are observed with 5 years of UAS. Serious adverse events are uncommon. UAS is a nonanatomic surgical treatment with long-term benefit for individuals with moderate to severe OSA who have failed nasal continuous positive airway pressure.

Keywords

obstructive sleep apnea, cranial nerve, hypoglossal nerve, sleep, device, implant, long term, surgery, polysomnogram, sleepiness, quality of life, device apnea hypopnea index, sleep, quality of life, upper airway stimulation

[1]Department of Otolaryngology and Human Communication, Medical College of Wisconsin, Milwaukee, Wisconsin, USA
[2]Department of Pulmonary, Critical Care and Sleep Medicine, Cleveland VA Medical Center, Cleveland, Ohio, USA
[3]Department of Otolaryngology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[4]Department of Otolaryngology–Head and Neck Surgery, University of Tennessee Health Science Center, Memphis, Tennessee, USA
[5]Department of Otorhinolaryngology–Head and Neck Surgery, Sleep Disorders Center, University Hospital Mannheim, Mannheim, Germany
[6]Department of Otolaryngology, OLVG Hospital and ACTA, Amsterdam, Netherlands
[7]Department of Otorhinolaryngology and Head and Neck Surgery, Multidisciplinary Sleep Disorders Center, University of Antwerp, Antwerp, Belgium
[8]Department of Otolaryngology–Head and Neck Surgery, College of Medicine, University of South Florida, Tampa, Florida, USA
[9]Department of Internal Medicine, Wayne State University Health Center, Detroit, Michigan, USA
[10]Department of Otolaryngology–Head and Neck Surgery, Wayne State University Health Center, Detroit, Michigan, USA
[11]Advanced ENT Associates, Atlanta, Georgia, USA
[12]Division of Pulmonary Allergy and Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

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Corresponding Author:
B. Tucker Woodson, MD, Department of Otolaryngology and Human Communication, Medical College of Wisconsin, 9200 W Wisconsin Ave, Milwaukee, WI 53225, USA.
Email: bwoodson@mcw.edu

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Hypoglossal nerve (CN XII) stimulation for obstructive sleep apnea (OSA) demonstrated safety and efficacy at 12 months in a cohort of participants with moderate to severe OSA who were unable to accept or adhere to positive pressure therapy.[1] In the same cohort, a randomized withdrawal of therapy demonstrated a device-related therapeutic effect and durability, which returned to successful treatment values upon resumption of therapy.[2] Follow-up at 24, 36, and 48 months postimplantation continued to show successful clinical outcomes, low morbidity, and a favorable safety profile.[3-5]

OSA is a chronic disease. Patient-centered outcomes are critical elements of disease management. Hallmark outcomes for success include amelioration of intrusive snoring, excessive daytime sleepiness, impaired cognitive function, and a reduced quality of life.[6,7] While important, the absolute apnea-hypopnea index (AHI) in isolation poorly correlates with these relevant disease outcomes, with differing effects on the quality of life and severity of symptoms among patients having a similar number of events during sleep.[8] Clinicians do not make treatment decisions solely based on an arbitrary AHI threshold. Assessment of successful treatment requires therapy to have not only a meaningful objective improvement but also a successful clinical effect as reported by patients and as combined with effective use by patients for many years.

The aim of this study was to evaluate the long-term (60-month) safety and effects of upper airway stimulation (UAS) therapy on the propensity for daytime sleepiness, as measured by the Epworth Sleepiness Scale (ESS); daytime functioning, as measured by the Functional Outcomes of Sleep Questionnaire (FOSQ); intrusive snoring, as reported by participant and bed partner; and (4) sleep-disordered breathing, as found in an overnight polysomnography (PSG).

Methods

Participants

The STAR trial is a multicenter Institutional Review Board–approved (see Appendix 1 in the online version of the article) cohort that included adults with a history of moderate to severe OSA and intolerance or inadequate adherence to continuous positive airway pressure (CPAP). Key study exclusion criteria included a body mass index >32 kg/m^2, neuromuscular disease (including hypoglossal nerve palsy or injury), severe cardiopulmonary disorders, active psychiatric disease, and comorbid nonrespiratory sleep disorders that would confound functional assessments related to sleep. Participants who met inclusion/exclusion criteria underwent 3 screening examinations: an in-laboratory attended PSG, a surgical consultation visit, and drug-induced sedated endoscopy. Participants were excluded after the PSG for an AHI <20 or >50 per hour of sleep, central and/or mixed apnea index $>25\%$ of the AHI, or a nonsupine AHI <10. Participants were also excluded after (1) the surgeon's in-office head and neck examination if it identified pronounced anatomic abnormalities (ie, tonsil hypertrophy) that might prevent effective use of the device and (2) the drug-induced sedated endoscopy if complete concentric collapse was observed at the level of the velopharynx.[9]

Study Procedures

Qualified participants who met preimplant screening criteria underwent device implantation. The implanted system (Inspire Medical Systems, Inc, Maple Grove, Minnesota) consists of 3 components: a stimulation cuff electrode that encircles the medial division of the right hypoglossal nerve; a pressure-sensing lead to guide timing of stimulation, placed within the fourth or fifth right intercostal space; and an implantable pulse generator inserted into a right midclavicular subcutaneous pocket. The therapy guides phasic stimulation to the hypoglossal nerve to increase airway muscle tone and luminal diameter prior to the onset of inspiration and to maintain adequate upper airway airflow.

Self-reported outcomes with validated sleep questionnaires, general health status, device metrics, and adverse events were followed at 6-month intervals for 5 years. PSGs per protocol were collected at 12- and 18-month follow-up visits, and voluntary PSGs were performed at 3 and 5 years. The PSG studies were scored by 2 independent core laboratories using standard 2007 scoring criteria,[10] with a hypopnea score based on a 30% airflow reduction and a 4% oxygen desaturation. Sleep states are reported as NREM and REM and arousals as >3-second change in electroencephalographic frequency.[10] Patient-reported outcome measures included subjective sleepiness and sleep-related quality of life with the validated ESS and the FOSQ. Clinical variables, including body mass index (BMI), neck circumference, stimulation parameters, and blood pressure, were measured at scheduled study visits to assess any changes over the course of the study. Subjective self- and bed partner–reported snoring was collected per a categorical scale (no snoring, soft snoring, loud snoring, very intense snoring, or bed partner leaves room). All reported adverse events were reviewed and coded by the Clinical Events Committee. Serious adverse events were defined as any that led to death, life-threatening illness, permanent impairment and related surgery, or a new or prolonged hospitalization. Adverse events were categorized as *procedure related* if related to the surgical procedure or *device related* if secondary to use of the device after therapy activation.

Statistical Analysis

The primary population for analysis comprised participants who were implanted and who completed follow-up at the 5-year visit. We also performed several sensitivity analyses to assess the impact of the missing long-term outcome data of AHI, FOSQ, and ESS at 36 and 60 months. The sensitivity

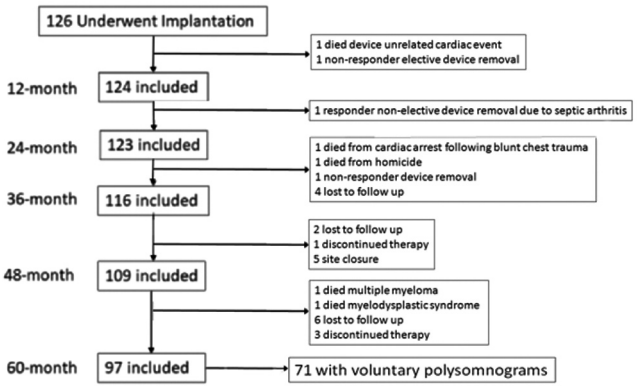

Figure 1. Study flow is shown over 5 years until study completion. Included patients underwent protocol evaluation and follow-up. Nonincluded patients with description are on the right.

analyses included last observation carried forward (LOCF), repeated measures regression, multiple imputation, and maximum likelihood estimation.[11] The LOCF analysis imputed the last available follow-up value for any missing data at months 36 and 60. The repeated measures analysis included all available baseline and follow-up data in a repeated measures regression model and provided least squares estimates of the means at 36 and 60 months. The multiple-imputation analysis created 10 imputed data sets for each parameter, with all available baseline and follow-up data used as predictors. The means at months 36 and 60 were estimated within each imputed data set and combined across imputations. The maximum likelihood estimation analysis provided estimates for the outcomes at months 36 and 60, which maximizes the probability of the observed data. A stepwise multivariable logistic model was used to determine key baseline factors associated with therapy response. Analyses were performed with SAS 9.2 software (SAS Institute).

Results

Participants

Of the 126 participants who underwent implantation, 97 (78%) completed the 5-year follow-up visit (**Figure 1**). Among the 29 participants who did not complete the 5-year assessment, 21 were lost to follow-up within the prespecified time frame; 5 died of unrelated causes (sudden death, cardiac arrest after a fall and blunt chest trauma, homicide, malignant melanoma, and myelodysplastic syndrome); and 3 had the device explanted (implantable pulse generator removal in a nonresponder, system removal in a nonresponder, and nonelective removal in a responder due to septic arthritis). Of the 97 patients meeting the 5-year follow-up protocol, 71 volunteered for an overnight in-laboratory polysomnographic evaluation. The mean ± SD BMI at 5 years was 28.6 ± 2.8, unchanged from baseline.

Among the 97 participants who did complete the protocol as compared with those who did not, baseline age, BMI, and ESS were similar, but subjects who did not complete the month 60 visit had higher AHI, higher ODI, and lower FOSQ scores at baseline. These differences disappeared when evaluation was performed at 12 months while therapy was activated.[1] Among the 71 participants who voluntarily completed a 60-month PSG study, age, AHI, and BMI baseline parameters were not significantly different from those who did not complete the PSG, the 97 patients meeting protocol, or the original cohort (**Table 1**). The AHI treatment response did differ at 12 months (74% vs 52%, $P < .002$), but AHI treatment response at 18 and 36 months, change in sleepiness, and change in quality of life did not differ between groups that did and did not complete the 60-month PSG.

Primary Outcome Measures

The efficacy measures of AHI and ODI decreased from baseline to the 12-month assessment and remained stable at 36 and 60 months (**Table 2**, **Figure 2**). A decrease in AHI >50% and an AHI <20, which were the a priori definition of success, were observed in 75% of participants with 5-year PSG (**Figure 2**).[12] Forty-four percent and 78% of participants had AHIs <5 and <15 at 5-year PSG, respectively. Given the number lost to follow-up over the extended follow-up, an LOCF analysis from the cohort at 12, 18, or 36 months was performed. LOCF demonstrated a mean AHI at 5 years of 15.1 ± 1.5, with a median of 7.6 and a response rate of 63% (5 deaths and 3 explants were counted as nonresponders), which was similar to the responder rate of 66% at 12 months. Based on the LOCF and multiple-imputation methods to account for missing data, the change of AHI from baseline was similar at 36 and 60 months and did not change with different sensitivity analysis (**Table 3**). In addition to sensitivity analysis with the LOCF and multiple-imputation methods, we conducted best- and worst-case analyses, in which the minimal and maximal values from available postoperative AHI at 12, 18, and 36 months were used for all patients who did not complete the 60-month PSG. In the best-case analysis, the mean AHI was 12.3 ± 15.4, with a change of −19.8 ± 15.8 (95% CI, −22.5 to −17.0) at 60 months from baseline. The worst-case analysis demonstrated a mean AHI of 17.0 ± 18.2, with a change of −15.0 ± 16.6 (95% CI, −17.9 to −12.1) at 60 months from baseline. Changes from baseline in best- and worst-case analyses were not significantly different.

When the 5-year AHI responders and nonresponders were compared, univariate analysis demonstrated differences in age and baseline ODI between groups. A multivariable stepwise regression analysis including age, BMI, sex, neck circumference, prior uvulopalatopharyngoplasty, and baseline AHI, ODI, FOSQ, and ESS demonstrated that only a lower ODI was predictive of 5-year AHI responders (**Table 4**).

Self-reported Outcome Measures

FOSQ and ESS improvements observed at prior evaluation periods persisted at 5 years. The average increase of FOSQ was 3.2 units, as observed and unchanged with the

Table 1. Characteristics of Cohort, Protocol, and Voluntary Polysomnogram Patients Followed and Not Followed at 60 Months.[a]

		Month 60 Completed			Month 60 PSG		
Parameter	Original Cohort (N = 126)	Yes (n = 97)	No (n = 29)	*P* Value[b]	Yes (n = 71)	No (n = 55)	*P* Value[c]
Baseline							
Age	54.5 ± 10.2	54.4 ± 10.3	55.1 ± 10.2	.73	54.5 ± 9.9	54.6 ± 10.7	.98
BMI	28.4 ± 28.5	28.6 ± 2.5	27.8 ± 2.8	.16	28.6 ± 2.5	28.1 ± 2.8	.30
AHI	32.0 ± 11.8	30.5 ± 10.8	37.2 ± 13.5	.01	30.4 ± 9.4	34.1 ± 14.1	.09
ODI	28.9 ± 9.6	27.5 ± 10.8	33.5 ± 14.4	.02	27.2 ± 10.0	31.0 ± 13.9	.09
FOSQ	14.3 (3.2)	14.7 ± 2.9	13.52 ± 3.9	.03	14.8 ± 2.6	13.7 ± 3.8	.07
ESS	11.6 (5.2)	11.3 ± 5.2	12.4 ± 4.0	.33	11.6 ± 5.0	11.5 ± 5.0	.86
Outcomes							
Change AHI							
Month 12		−16.0 ± 16.3	−17.8 ± 18.4	.63			
Month 36		−19.9 ± 12.5	−13.9 ± 17.8	.13			
Responder							
Month 12					79 (56 of 71)	54 (28 of 53)	.003
Month 18					70 (50 of 71)	60 (30 of 50)	.25
Month 36					80 (53 of 66)	65 (20 of 31)	.13
Change FOSQ							
Month 12		−3.0 ± 2.9	−2.8 ± 3.9	.82	−2.7 ± 2.7[d]	−3.2 ± 3.6[e]	.43
Month 36		−2.9 ± 3.6	−1.7 ± 4.7	.22	−2.7 ± 3.0[d]	−2.6 ± 4.8[f]	.89
Change ESS							
Month 12		4.7 ± 5.1	4.0 ± 4.9	.53	5.0 ± 5.1[d]	4.3 ± 4.8[e]	.46
Month 36		4.4 ± 5.6	4.0 ± 4.6	.72	4.3 ± 5.8[d]	4.6 ± 5.1[f]	.84

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; FOSQ, Epworth Sleepiness Scale; ODI, oxygen desaturation index; PSG, polysomnography.
[a]Values are presented as mean ± SD or % (n).
[b]Complete vs noncomplete.
[c]PSG vs no PSG.
[d]n = 70.
[e]n = 53.
[f]n = 43.

Table 2. Primary and Secondary Outcomes.

Outcome Measure	Baseline	Month 12	Month 36	Month 60
AHI				
n	126	124	98	71
Mean ± SD	32.0 ± 11.8	15.3 ± 16.1	11.5 ± 14.0	12.4 ± 16.3
Median	29.3	9.0	6.0	6.2
ODI (4%)				
n	126	124	98	71
Mean ± SD	28.9 ± 18.2	14.0 ± 15.6	9.1 ± 11.7	9.9 ± 14.5
Median	25.4	7.4	4.8	4.6
FOSQ				
n	126	123	113	92
Mean ± SD	14.3 ± 3.2	17.3 ± 2.9	17.4 ± 3.5	18.0 ± 2.2
Median	14.6	18.2	18.8	18.7
ESS				
n	126	123	113	92
Mean ± SD	11.6 ± 5.0	7.0 ± 4.3	7.0 ± 5.0	6.9 ± 4.7
Median	11	6	6	6

Abbreviations: AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; FOSQ, Epworth Sleepiness Scale; ODI, oxygen desaturation index.

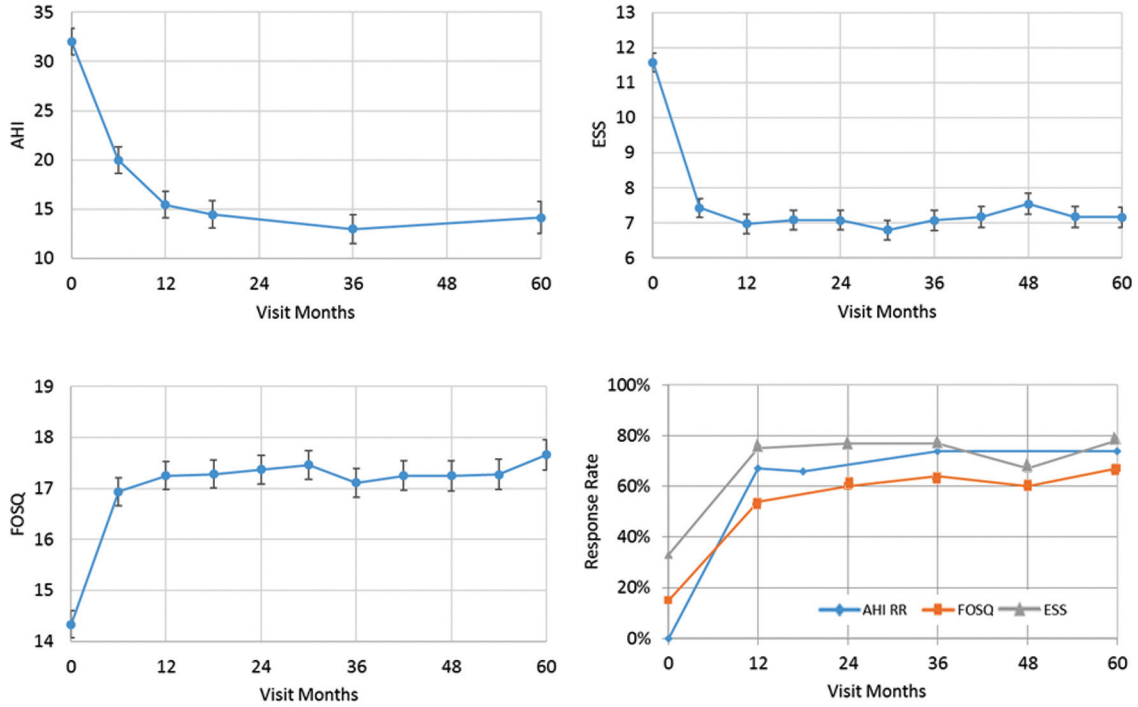

Figure 2. Sixty-month outcome of AHI, sleep quality of life (FOSQ), and daytime sleepiness (ESS). Values are presented as mean ± SD. Response rates (in percentages) are based on the following parameters: AHI >50% reduction to <20 events/hour, ESS score <10, and FOSQ score >17.9. AHI, apnea hypopnea index; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire.

sensitivity analysis. At baseline, only 15% reported a normal FOSQ score (>17.9); this increased to 67% at 5 years. The average reduction of ESS was 4.4 units. The percentage of participants who reported a normal ESS score (<10) increased from 33% at baseline to 78% at 5 years (**Figure 2**).

Long-term bed partner–reported (**Figure 3**) and self-reported snoring reports demonstrated improvement from baseline and remained relatively stable from 12 to 60 months. Based on partner report, intrusive snoring (very intense snoring or bed partner leaves room) was reduced from 54% at baseline to 2% at 60 months; no snoring or soft snoring increased from 17% to 90%. Participant self-reports of nightly device use were 86%, 81%, and 80% at years 1, 3, and 5, respectively.

Other Measures

As at other time points, the cohort demonstrated no changes in sleep stage distribution. Arousal index was significantly reduced (27.8 ± 117 to 7.8 ± 9.7 events per hour, $P < .0001$). Percentage time with oxygen desaturation <90% was unchanged (8.0% ± 10.1% to 7.4% ± 13.3%). For patients who completed protocol follow-up, stimulation parameters changed. Sensory thresholds, functional thresholds, and subdiscomfort thresholds decreased.

Adverse Events

After 5 years, 8 participants (6% of 126) had a total of 9 serious device-related adverse events requiring surgical repositioning or replacement of the neurostimulator or implanted leads. One participant had 2 revision procedures to reposition the neurostimulator and the sensing lead to resolve discomfort. One participant underwent stimulation lead repositioning due to unfavorable tongue movement pattern and to improve therapy response. Four participants had insulation failure with the sensing lead and underwent replacement of both the neurostimulator and the sensing lead. For 1 participant, the stimulation lead was inadvertently cut and then required replacement.

Discomfort due to electrical stimulation was the most common nonserious adverse-reported event, occurring 81 times during the first year. For most subjects, this complaint was resolved by reprogramming the stimulus levels and was reported only 5 times during the fifth year. Tongue abrasion from tongue movement was reported 28 times the first year and was reduced to 2 times during the fifth year. **Table 5** provides a detailed list of adverse events.

Discussion

The durability of the treatment effect of upper airway muscle stimulation therapy by the Inspire System was addressed with a 5-year follow-up of participants in the STAR trial. Voluntary PSG measures of 71 of the original 126 participants and data from protocol visits of 97 patients demonstrated long-term resolution of objective measures of sleep-disordered breathing, daytime symptoms, and quality-of-life components of the disease. The major findings of the study are as follows: (1) UAS therapy provides clinically

Table 3. Change from Baseline at 36 and 60 Months as Observed and Estimated with LOCF and Multiple Imputation.

	Change from Baseline		
Parameter: Visit	As Observed	LOCF	Multiple Imputation
AHI			
36 mo			
n	97	126	
Mean ± SE	−19.1 ± 1.4	−17.8 ± 1.3	−18.2 ± 1.5
95% CI	−21.8 to −16.4	−20.4 to −15.1	−21.1 to −15.3
60 mo			
n	71	126	
Mean ± SE	−18.0 ± 1.7	−17.0 ± 1.4	−17.1 ± 1.7
95% CI	−21.4 to −14.6	−19.7 to −14.3	−20.5 to −13.6
FOSQ			
36 mo			
n	113	126	
Mean ± SE	2.7 ± 0.4	2.7 ± 0.3	2.7 ± 0.4
95% CI	2.0 to 3.4	2.0 to 3.4	2.0 to 3.5
60 mo			
n	92	126	
Mean ± SE	3.2 ± 0.3	3.0 ± 0.3	3.2 ± 0.3
95% CI	2.6 to 3.8	2.4 to 3.6	2.6 to 3.8
ESS			
36 mo			
n	113	126	
Mean ± SE	−4.4 ± 0.5	−4.3 ± 0.5	−4.4 ± 0.5
95% CI	−5.5 to −3.4	−5.3 to −3.3	−5.4 to −3.4
60 mo			
n	92	126	
Mean ± SE	−4.4 ± 0.6	−4.2 ± 0.5	−4.3 ± 0.6
95% CI	−5.5 to −3.2	−5.2 to −3.2	−5.4 to −3.2

Abbreviations: AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; FOSQ, Epworth Sleepiness Scale; LOCF, last observation carried forward.

meaningful and statistically significant improvements in PSG measures of OSA; (2) clinically meaningful and statistically significant improvements in key patient-centered outcomes in snoring, daytime sleepiness, and sleep-related quality of life were achieved; and (3) there was a very low incidence of device-related adverse outcomes beyond the implant period.

Sustained effectiveness is critical in a chronic condition such as OSA, which requires long-term management. The detrimental effect of OSA on activities of daily living and quality of life was mitigated by this therapy for a significant number of participants at 5 years. Untreated moderate to severe OSA has been associated with increased health care costs and physician visits, motor vehicle accidents, and workplace errors, as well as loss of productivity. CPAP via a mask is the standard first-line therapy.[13] It is highly effective when used consistently. Unfortunately, many individuals cannot or do not adjust to this therapy. Challenges with CPAP acceptance and adherence among patients with moderate to severe disease have been identified as an impediment to the ability to mitigate comorbid cardiovascular sequelae.[14] This report indicates that multiyear control of OSA hypopnea syndrome can be achieved by a non-CPAP and nonanatomic surgical approach.

Patient-reported outcome measures capture the subjective aspects of the sleep apnea syndrome, and these self-reported symptoms often drive patients to be evaluated for sleep apnea.[15] PSG measures correlate loosely with OSA disease burden as well as symptom expression. These symptoms may contribute significantly to personal morbidity, as well as the direct and indirect health care costs of untreated OSA.[16,17] Improvements in several aspects of quality of life accompanied by use of UAS result in objective and subjective recidivism if the therapy is interrupted, as shown in the withdrawal study.[2] Other common consequences of OSA are spousal complaints related to snoring. There is currently no accepted standard objective measure of snoring. Although the reliability of self-report and bed partner report

Table 4. Predictors of 60-Month AHI Responders.

	Month 60, Mean ± SD or % (n)			
Characteristic	Responders (n = 53)	Nonresponders (n = 18)	Odds Ratio	95% Confidence Limits (*P* Value)
Age	56.0 ± 9.3	50.1 ± 10.4	1.07	1.01, 1.13 (.03)
Male	81 (43)	83 (15)	0.86	0.21, 3.55 (.83)
BMI	28.6 ± 2.5	28.8 ± 2.3	0.97	0.77, 1.21 (.76)
Neck size	40.8 ± 3.5	41.5 ± 2.9	0.93	0.79, 1.11 (.43)
AHI	29.3 ± 7.6	33.7 ± 13.1	0.95	0.90, 1.01 (.09)
ODI	25.5 ± 8.5	32.2 ± 12.4	0.94	0.88, 0.99 (.02)
Prior UPPP	32 (17)	6 (1)	0.13	0.02, 1.02 (.052)
FOSQ	14.8 ± 2.7	15.0 ± 2.3	0.96	0.78, 1.19 (.73)
ESS	11.3 ± 4.9	12.7 ± 5.3	0.95	0.85, 1.06 (.32)

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; FOSQ, Epworth Sleepiness Scale; ODI, oxygen desaturation index; UPPP, uvulopalatopharyngoplasty.

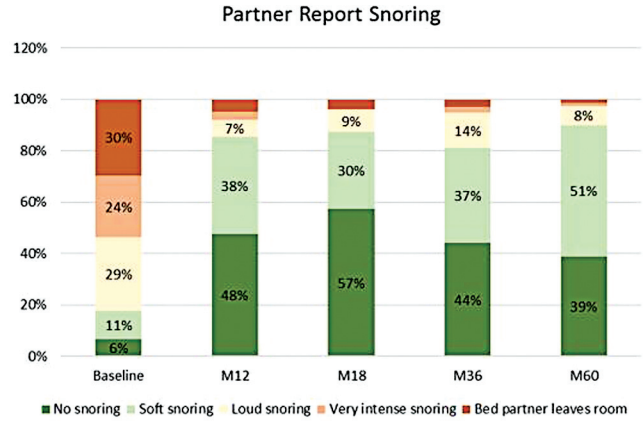

Figure 3. Bed partner report of snoring intensity over time.

of snoring intensity may be questioned, most participants in this cohort achieved a successful reduction in their snoring from loud or disruptive levels to soft or no snoring.

Cranial nerve stimulation with Inspire is an innovative first-in-class therapy. In contrast to other surgical approaches, this therapy does not directly modify the pharynx or surrounding structures. Instead, it addresses pharyngeal collapse with a more physiologic approach. This study is noteworthy in demonstrating a high level of durable effect but also a low rate of complication and morbidity. Several recent independent single-center cohort studies reported additional safety, efficacy, and therapy adherence data in the real-world clinical practice setting subsequent to Food and Drug Administration approval in 2014. Kent et al[18] reported a case series of 21 patients consecutively implanted. After a mean 7.8 months of follow-up, the AHI was reduced from 33.3 to 5.1 ($P < .01$), and ESS improved from 10.3 to 6.0 ($P < .01$). Objective device adherence was 7.0 ± 2.2 hours of use per night. Heiser et al[19] reported a case series of 31 consecutive patients. After 12 months, the mean AHI was reduced from 32.9 to 7.1, and ESS improved from 12.6 to 5.9. All participants demonstrated high rates of therapy adherence, with 6.6 ± 2.7 hours per night at 12 months according to objective device reporting. In addition to these single-center studies, a multicenter postmarket study of 60 patients recently reported consistent improvements in patient outcomes after 6- and 12-month follow-up[20,21] in AHI, ESS, and FOSQ, as observed in the STAR trial. These single- and multicenter postapproval studies demonstrated that hypoglossal nerve stimulation can be effectively implemented in the routine clinical practice for treating patients with OSA who could not adhere to CPAP.

The size of this prospective cohort and the high number of patients with long-term follow-up data are considerable strengths of this surgical study. The assessments were consistently collected in US and European sites so that intra- and interindividual comparisons could be objectively and statistically addressed. The clinical management among

Table 5. Nonserious Adverse Events.

Adverse Event	No. of Events						Participants With Event, % (n of 126)
	0-12 mo	12-24 mo	24-36 mo	36-48 mo	>48 mo	Total	
Procedure related							
Postoperative discomfort related to incisions	47	1	2	1	1	52	30.2 (38)
Postoperative discomfort independent of incisions	41	0	1	0	0	42	27.0 (34)
Temporary tongue weakness	34	0	0	0	0	34	18.3 (23)
Intubation effects	18	0	0	0	0	18	11.9 (15)
Headache	8	0	0	0	0	8	6.3 (8)
Other postoperative symptoms	22	0	0	0	0	22	11.1 (14)
Mild infection	1	0	0	0	0	1	0.8 (1)
Device related							
Discomfort due to electrical stimulation	81	23	26	7	5	142	60.3 (76)
Tongue abrasion	28	12	4	3	2	49	27.0 (34)
Dry mouth	10	5	2	0	3	20	15.1 (19)
Mechanical pain associated with presence of the device	7	2	3	1	1	14	11.1 (14)
Temporary internal device usability or functionality complaint	12	8	1	3	1	25	16.7 (21)
Temporary external device usability or functionality complaint	11	11	8	9	6	45	26.2 (33)
Other acute symptoms	21	14	1	2	1	39	24.6 (31)
Mild infection	1	0	0	0	0	1	0.8 (1)

surgeons and sleep medicine practitioners and data integrity were maintained over 5 years.

The biggest limitations are related to the lack of a control group and the assessment of treatment effects other than withdrawal of stimulation at 12 months. However, the effect sizes of objective and subjective responses are large—of the order of other evidence-based therapies. Since the study group was predominantly male, obese, CPAP intolerant, and of European descent, conclusions about generalizability to women and other ethnic groups may require additional study. The inclusion and exclusion criteria (AHI range, BMI limit, and anatomic configuration of airway collapse) were consensus based, and additional studies will likely address these issues. Also, note that the current study evaluated a novel treatment and, as such, appropriately excluded participants with active cardiovascular disease. Thus, although the current data adequately address AHI, ODI, snoring, quality of life, and behavioral sleepiness, they are insufficient to address blood pressure and cardiac effects of long-term therapy.

This is the first report of a medical or surgical device intervention for OSA that systematically followed participants with PSG measures and quality-of-life outcomes over a 5-year period. UAS therapy can provide clinically and statistically significant improvements in disease-defining PSG values, self-reported quality of life, daytime alertness, and snoring. Results indicate that in a selected group of participants with moderate to severe OSA who are unable to accept or adhere to CPAP, hypoglossal nerve stimulation therapy can provide significant improvement in objective measures of sleep-disordered breathing and important sleep-related quality-of-life outcome measures. The effect is maintained across a 5-year follow-up period.

Author Contributions

B. Tucker Woodson, substantial contributions to conception, design, acquisition, analysis, or interpretation of data, significant drafting/revising intellectual content, final approval, accountable for all aspects of the work; **Kingman P. Strohl**, substantial contributions to conception, design, acquisition, analysis, or interpretation of data, significant drafting/revising intellectual content, final approval, accountable for all aspects of the work; **Ryan J. Soose**, substantial contributions to conception, design, acquisition, analysis, or interpretation of data, significant drafting/revising intellectual content, final approval, accountable for all aspects of the work; **M. Boyd Gillespie**, substantial contributions to conception, design, acquisition, analysis, or interpretation of data, significant drafting/revising intellectual content, final approval, accountable for all aspects of the work; **Joachim T. Maurer**, substantial contributions to conception, design, acquisition, analysis, or interpretation of data, significant drafting/revising intellectual content, final approval, accountable for all aspects of the work; **Nico de Vries**, substantial contributions to conception, design, acquisition, analysis, or interpretation of data, significant drafting/revising intellectual content, final approval, accountable for all aspects of the work; **Tapan A. Padhya**, substantial contributions to conception, design, acquisition, analysis, or interpretation of data, significant drafting/revising intellectual content, final approval, accountable for all aspects of the work; **M. Safwan Badr**, substantial contributions to conception, design, acquisition, analysis, or interpretation of data, significant drafting/revising intellectual content, final approval, accountable for all aspects of the work; **Ho-sheng Lin**, substantial contributions to conception, design, acquisition, analysis, or interpretation of data, significant drafting/revising intellectual content, final approval, accountable for all aspects of the work; **Olivier M. Vanderveken**, substantial contributions to conception, design, acquisition, analysis, or interpretation of data, significant drafting/revising intellectual content, final approval, accountable for all aspects of the work; **Sam Mickelson**, substantial contributions to conception, design, acquisition, analysis, or interpretation of data, significant drafting/revising intellectual content, final approval, accountable for all aspects of the work; **Patrick J. Strollo Jr**, substantial contributions to conception, design, acquisition, analysis, or interpretation of data, significant drafting/revising intellectual content, final approval, accountable for all aspects of the work.

Disclosures

Competing interests: B. Tucker Woodson, Inspire Medical Systems—study investigator, consultant; Medtronic—consultant, royalty; Siesta Medical—consultant; Cryosa—consultant, stock option; Zelegant—consultant; LinguaFlex—consultant; Kingman P. Strohl, Inspire Medical Systems—study investigator, consultant; Sommetrics—consultant; Seven Dreamers—consultant; Galvani Bioelectronics—consultant; Jazz Pharmaceuticals—site principal investigator and consultant; Medscape—speaker; Up-to-Date—speaker; Ryan J. Soose, Inspire Medical Systems—study investigator, consultant; Philips Respironics—consultant; Galvani Bioelectronics—advisory board, consultant; M. Boyd Gillespie, Inspire Medical Systems—study investigator, consultant, research support; Medtronic, Olympus, Arthrocare—consultant; Surgical Specialties—consultant, research support; Joachim T. Maurer, Inspire Medical Systems—study investigator, consultant; personal fees from GlaxoSmithKline, Weinmann, Olympus, ResMed, Neuwirth, Medtronic, and Heinen & Löwenstein, outside the submitted work; Nyxoah—consultant; ReVent—invited speaker; ImThera—invited speaker; Nico de Vries, Inspire Medical Systems—study investigator, consultant; Philips, Olympus—consultant; Night Balance/ReVent—medical advisor, shareholder, funding from company; Tapan A. Padhya, Inspire Medical Systems—study investigator, consultant; M. Safwan Badr, Inspire Medical Systems—study investigator; Intuitive Surgical—proctor; Ho-sheng Lin, Inspire Medical Systems—study investigator; Intuitive Surgical—consultant, proctor; Checkpoint Medical—consultant; Olivier M Vanderveken, Inspire Medical Systems—study investigator, consultant; Philips Electronics B.V.-consultant, research grant; SomnoMed—research grant; GlaxoSmithKline—consultant; NightBalance—research support; Sam Mickelson, Inspire Medical Systems—study investigator; ImThera Medical—research support; Patrick J. Strollo Jr, Inspire Medical Systems—study investigator, consultant, research grant; ResMed—scientific advisory board, research grant; Philips Respironics—research grant; Jazz Pharmaceuticals—advisory board, research grant; Emmi Solutions—advisory board; Belluscura—consultant.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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