ERJ Express. Published on November 28, 2018 as doi: 10.1183/13993003.01405-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Post-Approval Upper Airway Stimulation Predictors of Treatment Efficacy in the Adhere Registry

Clemens Heiser, Armin Steffen, Maurits Boon, Benedikt Hofauer, Karl Doghramji, Joachim T. Maurer, J. Ulrich Sommer, Ryan Soose, Patrick J. Strollo, Richard Schwab, Erica Thaler, Kirk Withrow, Alan Kominsky, Christopher Larsen, Eric J. Kezirian, Jennifer Hsia, Stanley Chia, John Harwick, Kingman Strohl, Reena Mehra

Please cite this article as: Heiser C, Steffen A, Boon M, *et al*. Post-Approval Upper Airway Stimulation Predictors of Treatment Efficacy in the Adhere Registry. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.01405-2018).

Post-Approval Upper Airway Stimulation Predictors of Treatment Efficacy in the Adhere Registry

Clemens Heiser MD[1] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Armin Steffen MD[2] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Maurits Boon MD[3] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Benedikt Hofauer MD[1] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Karl Doghramji MD[3] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Joachim T. Maurer MD[4] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

J. Ulrich Sommer MD[4] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Ryan Soose MD[5] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Patrick J. Strollo Jr. MD[5] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Richard Schwab MD[6] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Erica Thaler MD[6] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Kirk Withrow MD[7] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Alan Kominsky MD[8] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Christopher Larsen MD[9] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Eric J. Kezirian MD MPH[10] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Jennifer Hsia MD[11] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Stanley Chia MD[12] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

John Harwick MD[13] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Kingman Strohl MD[14] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

Reena Mehra MD MS[8] (acquisition, analysis, interpretation of the data, drafting manuscript, final approval)

On Behalf of the Adhere Registry Investigators

Institutions:

1. Munich Technical University, Germany
2. University of Lubeck, Germany
3. Thomas Jefferson University
4. University-Hospital Mannheim, Germany
5. University of Pittsburgh, Pittsburgh PA
6. University of Pennsylvania, Philadelphia PA
7. University of Alabama, Birmingham AL
8. Cleveland Clinic
9. Kansas University Medical Center
10. Keck School of Medicine of the University of Southern California, Los Angeles CA
11. University of Minnesota Fairview Hospital
12. MedStar Washington Hospital Center, Washington DC
13. University of Florida Gainesville
14. University Hospital Cleveland Medical Center, Cleveland OH

Corresponding author:

Clemens Heiser, MD
Associate Professor
Department of Otorhinolaryngology, Head and Neck Surgery
Technische Universität München
Ismaninger Str. 22
81675 Munich, Germany
Phone: +49 89 4140-2692
Fax: + 49 89 4140-9583
Email: hno@heiser-online.com
www.schlaf-hno.de

Take-Home Message

In this largest international report to date, we identify a substantial improvement in OSA severity in response to UAS. Increasing age and reduced BMI are predictors of UAS.

Abstract:

Upper airway stimulation (UAS) has been shown to reduce severity of obstructive sleep apnea (OSA). The aim of this registry was to identify predictors of UAS therapy response in an international multicenter registry. Patients who underwent UAS implantation in the US and Germany were enrolled in an observational registry. Data collected included patient characteristics, apnea-hypopnea index (AHI), Epworth Sleepiness Scale, objective adherence, adverse events, and patient satisfaction measures. Post hoc univariate and multiple logistic regression were performed to evaluate factors associated with treatment success. Between October 2016 and January 2018, 508 participants were enrolled from 14 centers. Median AHI was reduced from 34.0 to 7.0 events/h, median ESS reduced from 12 to 7 from baseline to final visit at 12-month post-implant. In post hoc analyses, for each 1-year increase in age, there was a 4% increase in odds of treatment success. For each 1unit increase in BMI, there was 9% reduced odds of treatment success. In the multivariable model, age persisted in serving as statistically significant predictor of treatment success.

In a large multicenter international registry, UAS is an effective treatment option with high patient satisfaction and low adverse events. Increasing age and reduced BMI are predictors of treatment response.

Key words: obstructive sleep apnea, hypoglossal nerve stimulation, upper airway stimulation

Introduction

Obstructive sleep apnea (OSA) is common disorder with an option as a treatment target, to activate the lingual muscles and open the upper airway [1]. A fall in genioglossal electromyography activity (innervated by hypoglossal nerve (CN XII), the motor nerve to the tongue) can result in closure of a vulnerable region of the oropharynx producing the obstructive apnea, and activation reopens the airway. [2, 3] Factors other than airway closure by muscle atonia will influence the frequency of respiratory events and severity of OSA; arousal threshold, loop gain and muscle responsiveness play an important role and could be untouched by hypoglossal nerve stimulation [4]. Repetitive periods of OSA produce nocturnal hypoxemia and sleep fragmentation, and if left untreated, the disorder is associated with cognitive, behavioral and cardiovascular morbidities and increase in all-cause mortality [5]. Current anatomic surgical procedures and mechanical treatments (continuous positive pressure therapy and oral appliances), although effective, are unsatisfactory for many patients, or are accompanied by poor adherence, leaving a significant number of untreated patients with moderate to severe disease [6].

Upper airway stimulation (UAS; Inspire Medical Systems, Inc., Maple Grove, Minnesota, USA) is a system of unilateral hypoglossal nerve stimulation, consisting of an implantable pulse generator, stimulation lead placed on the hypoglossal nerve, and respiratory sensing electrode. The European (2013) and FDA (2014) approvals were based upon demonstration of efficacy and safety for selected patients with moderate to severe OSA who failed or were intolerant to positive airway pressure therapy [7, 8]. Therapy directions from Phase II studies and the Phase III, STAR trial indicate better success for those with an apnea hypopnea index (AHI) between

15-65/hour, a body mass index (BMI) generally less than 35 kg/m^2, and an "appropriate" anatomy [9] [10]. Anatomical evaluation was based largely on the absence of complete concentric collapse at the level of the velopharynx during drug-induced sleep endoscopy (DISE) examination. Surgical training is needed for optimal electrode placement on the distal, and medial branch of CN XII. Following the placement, a period of optimization of home therapy with the stimulator, including follow up verification of its efficacy is accomplished [11, 12].

However, controlled protocols like the STAR trial may not translate well into clinical practice. Deployment beyond the trial centers opens the opportunity for examination of variations in patient referral, financial resources, safety, and adherence. In addition, variations in implantation, management by different specialists, and differences in insurance reimbursement, may influence outcomes. The ADHERE (Adherence and Outcome of Upper Airway Stimulation for OSA International Registry) registry was designed to monitor this transition from trial to clinical practice. The ADHERE platform was created to collect demographic, surgical outcome, complications, quality of life, and patient-reported outcome undergoing treatment with UAS in the United States and Europe. ADHERE is a cumulative cohort, designed to follow the progress of implementation across many centers and across time in the provision of this technology. The primary purpose of this report is to characterize the predictors of responsiveness and adherence of therapy use in this post-approval cohort. We also describe the safety and efficacy in the largest cohort available to date to undergo UAS.

Methods

Study Design

The registry was approved by ethics committees or institutional review boards of every implant center. The study was registered with www.clinicaltrials.gov (NCT02907398). All procedures

followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revision. Informed consent was signed by every patient. Ongoing patients, who received an UAS implant in all participating implant centers in the USA and Germany and who agreed to participate, were included in this multicenter, prospective and retrospective, observational registry. The aim was not to change the clinical routine of the patient's treatment. The registry is non-interventional, and no study-specific procedures are added. Adult patients with a moderate to severe degree of OSA (AHI between 15-65/hour) and an intolerance to CPAP, who underwent an implantation of an UAS system (Inspire 2 & 4) were included. CPAP intolerance was defined by clinical criteria, namely if the patient was unable or unwilling to use CPAP. In the US and Europe, CPAP intolerance is defined as: 1) inability to use CPAP (greater than 5 nights per week of usage, usage defined as greater than 4 hours of use per night), or 2) unwilling to use CPAP (for example, a patient returns the CPAP system after attempting to use it or has claustrophia on repeated use). As already described in previous studies favorable anatomic criteria were also considered in the decision to implant [9].

Procedures and Sleep Recordings

The UAS system consists of a cuff electrode to stimulate the medial branches of the hypoglossal nerve, that activates the protrusor tongue muscles to open the upper airway; a pressure sensor, that is responsible to detect the breathing cycles, with its lead is placed within the fourth or fifth intercostal space; and an implantable pulse generator inserted into a subcutaneous pocket approximately 4 cm below the clavicle [13]. The details of the surgery are described in prior publications [12-14]. The system and implant are intended to stimulate upper airway opening by

hypoglossal nerve fibers, ideally during inspiration in order to protect the airway from obstruction during expiration.

The system is activated with standard settings programmed approximately one month after the surgical procedure, after an interim surgical follow-up. During the next four weeks or so, patients are asked to gradually increase the stimulation amplitude. This period allows participants to experience therapy and personally optimize comfort and subjective efficacy according to preset limits. Subsequent to this adjustment period, symptoms and comfort with UAS are assessed. In many centers, patients had an in-lab polysomnographic (PSG) titration study between two and six months after implant to optimize therapy. In some centers, for insurance purposes, portable studies were done to confirm settings or determine the need for further adjustments. Following the therapeutic titration, patients were seen in the office for follow-up and symptoms, adverse events and stimulation thresholds were assessed, along with the device settings. The post-titration visit, in many cases, was the first office visit after system set-up and titration. The final ADHERE visit was to occur approximately 12 months post-implantation.

Information that was collected included the baseline AHI prior to UAS implantation, the treatment AHI post-titration and the AHI at final visit. The treatment AHI, or AHI measured under the therapeutic setting, was assessed during a home sleep apnea test (HST), an in-lab PSG, during the initial titration PSG, or during an additional titration PSG. Respiratory event index (REI) for HST and AHI for PSG were summarized under the term "AHI". When the AHI was determined during a PSG, the AHI ("treatment AHI") was collected, which was under therapeutic settings for this time period during the night. The objective outcomes of AHI and

oxygen desaturation index (ODI) were in most of the centers scored using standard 2007 scoring criteria, with hypopnea scored based upon 30% airflow reduction and a 4% oxygen desaturation [15]. The registry actually did not specify AHI scoring criteria to follow, because the aim of the study is to allow collecting how therapy efficacy is being assessed in clinical practices. As in other studies examining surgical success of OSA treatment, we defined effective OSA treatment as a reduction of the apnea hypopnea index (AHI) by at least 50% to an AHI<20 [16]. Also, treatment duration was collected by hours of use per night, provided by interrogation of the implantable pulse generator (IPG) with a programmer at the post-titration visit.

The Epworth Sleepiness Scale (ESS) was administered at baseline, post titration and the final visit. A custom-designed survey for the patients experience with therapy was provided. At every visit, the Clinical Global Impression – Improvement (CGI-I) was completed by the physician to provide an estimate of how much the patient's disease had improved or worsened compared to baseline before initiating treatment.

Adverse events (AE) were monitored from implant until the last follow up visit. This was done to collect data relevant to procedure and device safety. A reportable AE included any event related or possibly related to the implant procedure or stimulation therapy that occurs at a level, intensity or timeframe greater than expected. Adverse event severity was classified as mild (aware of event, but easily tolerated), moderate (discomfort enough to cause interference with usual activity), or severe (inability to carry out usual activity).

Statistical Analysis

Outcome measures of AHI and ESS from the follow-up visit were compared to the baseline measurement. A paired t-test was used to evaluate the difference between baseline and follow-up visit with a type I error rate of 0.05. Results are presented as median and mean ± standard deviation. Post hoc logistic regression analyses include a univariate model of all potential predictors. An additional multivariate model with stepwise selection was used to retain only significant parameters for assessing for predictors of the therapy. Also adherence was performed with data from the final visit. Odds ratios (OR) were calculated for the different parameters with a p-value < 0.05 considered as statistically significant.

Results

Between October, 2016 and January, 2018, a total of 508 participants were enrolled from 14 centers. Three centers had previous experience with UAS in the initial STAR trial, the remaining 11 were new to implementing UAS. The study cohort consisted of a middle-aged, primarily male (79%), Caucasian (97%) and over-weight population. Overall, there was no systolic hypertension in this group. However, diastolic hypertension was present with a mean diastolic blood pressure of 78 ± 9 mmHg **(Table 1)**.

The average surgical time, available from 429 reported implant procedures, was 142 ± 45 minutes. The most common tongue motion accomplished during intra-operative testing was bilateral protrusion (70%), right protrusion (21%) and others (9%, 38 cases of other tongue motion including left-protrusion or retraction). The majority (88%) of United States patients were discharged on the same day; while all patients stayed overnight in the German centers.

Post-titration Outcomes

Post-titration patient outcome was assessed 137 ± 77 days after UAS implant. The mean BMI did not change from baseline to post titration follow-up (29.3 ± 3.9 to 29.2 ± 4.1 kg/m^2, $p > 0.05$). The mean AHI decreased significantly from baseline of 36.3 ± 15.7 to 10.2 ± 13.3 at post-titration ($p < 0.0001$; **Figure 1**) and median AHI decreased from 34.0 to 5.7. The absolute AHI reduction from baseline was -25.7 ± 16.5 and a relative reduction of 72% ± 32% was noted. AHI decreased by at least 50% to less than 20 in 92% of patients. At post-titration, AHI ≤ 5, ≤ 10 or ≤ 15 was achieved in 53%, 79% and 94% of patients. ESS decreased significantly from baseline of 11.8 ± 5.5 to 7.7 ± 4.9 at post-titration ($p < 0.0001$) with median ESS decreasing from 12 to 7 (**Figure 2**). The proportion of Patients with ESS < 10 increased from 37% to 65% from baseline to post-titration.

Final Visit Outcomes

The final visit adherence outcome was assessed 386 ± 136 days after UAS implant. The mean BMI did not significantly change from baseline to the final visit (29.3 ± 3.9 to 28.9 ± 4.2 kg/m^2, $p > 0.05$). The mean AHI decreased significantly from baseline of 36.3 ± 15.7 to 10.3 ± 11.5 at final visit ($p < 0.0001$) with the median AHI reduced from 34.0 to 7.0 (**Figure 1**). The absolute AHI reduction from baseline was -24.3 ± 17.3 and a relative reduction of 68% ± 34%. AHI reduced by at least 50% to less than 20 in 81% of patients. At post-titration, AHI ≤ 5, ≤ 10 or ≤ 15 was achieved in 41%, 65% and 78% of patients. ESS decreased significantly from baseline of 11.8 ± 5.5 to 6.7 ± 4.7 at final visit ($p < 0.0001$) with median ESS reduced from 12 to 6. Patients with ESS < 10 was increased from 37% to 76% from baseline to final visit (**Figure 2**).

94% physicians rated syndromic improvement on the CGI-I relative to baseline prior to UAS implant at post-titration, that persisted at 93% at final visit. Of note, 48% of physician noted a high degree of improvement post-titration that increased at the final visit to 57% (**Figure 3**). Regarding patient-reported response to therapy experience, 96% of patients reported that UAS is better than as remembered CPAP therapy at post-titration and at the final visit with 95% stating that they would undergo UAS again at the post-titration visit, and 94% at the final visit. At the post-titration visit, 93% of patients reported that they would recommend UAS to family and friends which increased to 96% at the final visit. At the post-titration visit, 91% of patients reported that they were overall satisfied with UAS therapy; at the final visit it was 94%.

Overview of Safety Outcomes

The majority (98%) of the 508 implanting procedures were completed without a report of an adverse event. There were two cases of intra-operative bleeding during the tunneling of the stimulation lead; both stopped with applying pressure. Two cases of seroma both resolved without sequelae. One patient was found with submandibular swelling, two patients with transient tongue weakness, and three patients with transient dysarthria. One patient was found with a dislodged stimulation cuff at the activation visit one-month post-implant, which was repositioned without complications. At the post-titration visit, a total of 87 adverse events were reported in 23% patients. At the final visit, a total of 61 adverse events were reported in 23% patients (**Table 4**). One patient underwent a revision procedure to reposition the cuff electrode due to inadequate therapy response. The revision procedure was completed without

complications. The AHI of the patients was 28.3, 24 and 14 at the baseline, post-titration and final visit. The definitions of ratings of mild, moderate and severe adverse events varied across sites. The details of events across category and those categorized as severe are provided in **Tables S2 and S3** respectively.

Primary Results: Predictors of Upper Airway Stimulation Effective Treatment and Adherence

In the univariate logistic regression analysis, age and body mass index were significantly associated with OSA treatment success. Specifically, for each 1-year increase in age, there was a 4% increase in odds of OSA treatment success. Alternatively, for each 1unit increase in BMI, there was 9% reduced odds of OSA treatment success **(Table 2)**. In the multivariable model, only age persisted in serving as a statistically significant predictor of UAS OSA treatment success. The degree of OSA at baseline and hours of usage were not significant predictors of success (**Table 2**). That means, that patients, who used their device more than other patients, did not show a better chance of a successful treatment. Interestingly, although not statistically significant, women had a point estimate reflecting a nearly 3-fold higher odds of OSA treatment success with UAS compared to men.

The objective adherence monitoring was interrogated from the IPG and showed an average home device use of 6.4 ± 2.0 hours per night at post-titration (n=344) and 5.7 ± 2.2 at final visit (n=229). In terms of examination of predictors of UAS adherence,

this was defined as usage for >4 hours per sleep period and alternatively defined as hourly average usage (**Table 3**). Age was associated with increased adherence such that for each year increase, there was a 9% increased odd s ratio of UAS usage. Similar to the UAS success findings, BMI was a predictor of lower UAS adherence such that for each unit increase in BMI, the odds of UAS adherence was 10% lower. Similarly, for each unit increase in baseline AHI, there was a 2% lower odds of UAS adherence. None of the parameters at the post-titration visit (such as tongue protrusion parameters) other than therapy use was associated with adherence at the final visit. A multivariable model using stepwise selection was fit with all parameters with univariable $p<0.20$ retaining only those with $p<0.05$. The final model included baseline AHI ($p=0.03$) and therapy hours at final visit ($p<0.0001$). With therapy hours, higher therapy hours at post-titration are associated with adherence at the final visit while higher baseline AHI is associated with less adherence at the final visit. Furthermore, there was no statistically-significant association between participant gender and treatment adherence.

Discussion

In this largest assembled cohort to date of patients undergoing UAS therapy, we identified a positive association for age, and an inverse association for BMI, as predictors of UAS therapy effectiveness as well as a trend towards women having an increased odd of UAS therapy effectiveness. Objective adherence was high with an average usage of 5.7 ± 2.2 hours per day at the final visit. Age and BMI were positive

and negative predictors, respectively, of final visit adherence [17]. These findings were no longer statistically significant in the multivariable model for BMI. The baseline AHI demonstrated a somewhat unanticipated inverse association with final visit adherence. The post-titration adherence (a marker of early adherence) was predictive of final visit adherence. These findings persisted in the multivariable model. Overall, these findings are of clinical significance to inform risk stratification and adherence optimization strategies in those being considered for UAS.

UAS therapy resulted in an improvement in OSA severity (AHI: 36.3/h ± 15.7 to 10.3 ± 11.5), comparable to STAR trial AHI outcomes. This was paralleled by improvement in daytime sleepiness. Physician clinical global impression scores were very high (>90%) and patients rated UAS therapy higher than CPAP, (i.e. would recommend to family and friends and were overall satisfied with therapy) with many of these measures increasing from post-titration to the final visit. The percentage of adverse events were low (2%) and although some adverse events were rated as severe (n=9, 6% of AEs) by the individual sites, these did not meet criteria of serious adverse events as defined by the overall study.

Based upon findings from this post-approval registry, age and BMI were positive and negative predictors of UAS efficacy in OSA defined as a reduction of the AHI by at least 50% and AHI<20 [16]. Upper airway surgical success predictors have been limited to pharyngeal classification, e.g. different rates of uvulopalatopharyngoplasty (UPPP) success, i.e. 52% for Type 1 (retropalatal obstruction alone) versus 5% for

Types II (both retropalatal and hypopharyngeal obstruction) and III (hypopharyngeal obstruction alone) with little data on predictiveness of subject characteristics on success mainly due to limited sample size. [16] In regard to the age effect, we cannot understand the new finding that UAS effectiveness is greater in those who are older, and more information will be needed to address this issue. There may be ascertainment and referral bias. But it is interesting to speculate about mechanisms if one can assume that these factors are similar in older and younger patients who meet inclusion criteria. There are aging-related decreased collagen and elastin composition in the hyoepiglottic ligament [18, 19], so that nerve-muscular activation could have an enhanced effect. These aging-related changes may enhance laxity of the ligament thereby predisposing to posterior displacement, i.e. anteroposterior epiglottis-related obstruction [19]. Aging can influence upper airway tissue structural integrity conferring an increased risk of anteroposterior airway collapse. If tongue strength of older people is decreased, due to the fact that ageing leads to neuromuscular alterations of the tongue [20], one can image that hypoglossal stimulation might be useful in CPAP intolerant patients. Other possibilities include aging-related behavioral factors, for instance seeking a technologic innovation. The finding of increasing BMI associated with decrements in UAS efficacy in OSA is consistent with initial feasibility studies [21, 22]. DISE plays a crucial part in the inclusion criteria of UAS. It is known, that with a higher BMI a higher probability of complete concentric palatal collapse occurs [23]. There is a grey zone, where the evaluating physician needs to decide if the collapse patterns during DISE are complete concentric or not. In

advanced specialized centers a careful selection of patients even with a BMI higher than 35 kg/m^2, can still respond to therapy with good clinical outcomes [24].

The adherence in UAS at the final visit is highly favorable relative to adherence rates for continuous positive airway pressure therapy (CPAP). CPAP non-adherence estimates range between 29-83% mainly from clinic-based studies.[25, 26] The most consistent predictors of PAP adherence include increasing age [25], early PAP adherence[17], self-reported daytime sleepiness[27], and certain psychological factors [28]. Although the prevalence of OSA is 2-4 fold higher in men, data focused upon the influence of sex on PAP adherence in OSA has been somewhat inconsistent.[29, 30] Consistent with existing data on CPAP adherence data, increasing age was associated with increased odds of UAS adherence suggesting factors inherent to the aging process which transcend OSA therapy type contribute to enhanced usage. These findings demonstrate anticipated parallels of UAS success and adherence relative to increasing age. Conversely, increasing BMI was associated with reduction in UAS adherence - again consistent with UAS efficacy findings. It is possible that the more limited impact on OSA treatment control in those who are more obese may result in a negative impact on adherence. Given the Caucasian predominance, we are limited in examination of race-specific differences of adherence. Although there was suggestion that UAS adherence may be greater in women than men, the smaller number of women in the registry may have precluded sufficient power to examine statistical significance. Given the borderline significant (albeit high magnitude of point estimate) findings showing increasing UAS responsiveness of women versus men, we cannot exclude the

possibility of post-menopausal status with increased age as a potential explanatory factor. Although the 21% representation of women in this cohort is higher in the FDA studies and is an area to examine more carefully as this registry increases in numbers and granularity of outcomes. Finally, similar to CPAP adherence, post-titration UAS adherence predicted final visit adherence suggesting that early adopters are more likely to have durability in adherence.

The major strength of this study is the large sample size of individuals undergoing UAS therapy (n=508 compared to the STAR trial [7] with n=126) to date that allows the ability to more effectively examine predictors of treatment success and adherence. Other strengths include the multicenter and multinational (United States and Europe) representation of patients included in the registry and clinic-based nature which allows for ability to examine real world effectiveness of UAS therapy implementation. The limitations include the use of post hoc analysis to identify predictors of treatment success and adherence, which need validation in prospective studies. Another limitation is that therapeutic AHI was gathered by different methods for the post titration outcome visit including PSG and HST, and titration studies, where AHI may not represent the entire night value. Also, the final visit adherence data were limited to a subsample given the ingoing nature of registry data collection. Furthermore, there are constraints in terms of limited gender and race diversity and distribution which precludes effective examination of these specific attributes in terms of UAS efficacy and adherence. The lack of standardization of scoring of the hypopnea events across patients represents another limitation, albeit observed findings are likely to be similar

even with uniformity in hypopnea scoring because the same criteria were used at each center for scoring the studies before and after UAS implantation. Future investigation should be focused on elucidation of the mechanistic underpinnings underlying the age-related tissue and physiologic upper airway alterations predisposing to enhanced amenability of UAS therapeutic benefit. A better understanding of how adiposity influences upper airway function and responsiveness to neurostimulation might lead to a reappraisal of BMI inclusion criteria to one more based on anatomy. Finally, existing knowledge gaps of sex- and race-specific differences in UAS treatment responsiveness and adherence should be better characterized by intentional augmentation of the registry with a more diverse sample of participants.

Conclusion

The international ADHERE registry reveals the efficacy of UAS in a clinical setting in patients with OSA, who are non-compliant to CPAP. Furthermore, we identified a positive association for age, and an inverse association for BMI, as predictors of UAS therapy efficacy and a trend towards women having an increased odd of UAS therapy efficacy.

Acknowledgements: We are in debt to all participants in the ADHERE registry for supporting data collection in all study visits.

References.

1. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013: 177(9): 1006-1014.
2. Remmers JE, deGroot WJ, Sauerland EK, Anch AM. Pathogenesis of upper airway occlusion during sleep. *Journal of applied physiology: respiratory, environmental and exercise physiology* 1978: 44(6): 931-938.
3. Strohl KP, Saunders NA, Feldman NT, Hallett M. Obstructive sleep apnea in family members. *N Engl J Med* 1978: 299(18): 969-973.
4. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea - New pathways for targeted therapy. *Sleep Med Rev* 2016.
5. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev* 2010: 90(1): 47-112.
6. Verse T, Dreher A, Heiser C, Herzog M, Maurer JT, Pirsig W, Rohde K, Rothmeier N, Sauter A, Steffen A, Wenzel S, Stuck BA. [S2e-guideline: "ENT-specific therapy of obstructive sleep apnea in adults" short version : Sleep Medicine Task Force of the German Society for Otorhinolaryngology, Head and Neck Surgery]. *HNO* 2016: 64(5): 310-319.
7. Strollo PJ, Jr., Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, Hanson RD, Padhya TA, Steward DL, Gillespie MB, Woodson BT, Van de Heyning PH, Goetting MG, Vanderveken OM, Feldman N, Knaack L, Strohl KP, Group ST. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014: 370(2): 139-149.
8. Woodson BT, Gillespie MB, Soose RJ, Maurer JT, de Vries N, Steward DL, Baskin JZ, Padhya TA, Lin HS, Mickelson S, Badr SM, Strohl KP, Strollo PJ, Jr., Investigators ST, Investigators ST. Randomized controlled withdrawal study of upper airway stimulation on OSA: short- and long-term effect. *Otolaryngol Head Neck Surg* 2014: 151(5): 880-887.
9. Heiser C, Hofauer B. Predictive Success Factors in Selective Upper Airway Stimulation. *ORL J Otorhinolaryngol Relat Spec* 2017: 79(1-2): 121-128.
10. Steffen A, Sommer JU, Hofauer B, Maurer JT, Hasselbacher K, Heiser C. Outcome after one year of upper airway stimulation for obstructive sleep apnea in a multicenter German post-market study. *Laryngoscope* 2018: 128(2): 509-515.
11. Heiser C, Thaler E, Boon M, Soose RJ, Woodson BT. Updates of operative techniques for upper airway stimulation. *Laryngoscope* 2016: 126 Suppl 7: S12-16.
12. Heiser C, Thaler E, Soose RJ, Woodson BT, Boon M. Technical tips during implantation of selective upper airway stimulation. *Laryngoscope* 2017.
13. Heiser C, Thaler ER, Boon M, Soose RJ, Woodson BT. Updates of operative techniques for upper airway stimulation. *Laryngoscope* 2016.
14. Heiser C, Knopf A, Hofauer B. Surgical anatomy of the hypoglossal nerve: A new classification system for selective upper airway stimulation. *Head Neck* 2017: 39(12): 2371-2380.
15. Iber C, Ancoli-Israel S, Chessonn A, Quan SF. In the AASM Manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL, 2007.
16. Sher AE, Schechtman KB, Piccirillo JF. The efficacy of surgical modifications of the upper airway in adults with obstructive sleep apnea syndrome. *Sleep* 1996: 19(2): 156-177.
17. Budhiraja R, Parthasarathy S, Drake CL, Roth T, Sharief I, Budhiraja P, Saunders V, Hudgel DW. Early CPAP use identifies subsequent adherence to CPAP therapy. *Sleep* 2007: 30(3): 320-324.
18. Ancoli-Israel S, Kripke DF, Klauber MR, Mason WJ, Fell R, Kaplan O. Sleep-disordered breathing in community-dwelling elderly. *Sleep* 1991: 14(6): 486-495.
19. Irvine LE, Yang Z, Kezirian EJ, Nimni ME, Han B. Hyoepiglottic ligament collagen and elastin fiber composition and changes associated with aging. *Laryngoscope* 2018.

20. Fei T, Polacco RC, Hori SE, Molfenter SM, Peladeau-Pigeon M, Tsang C, Steele CM. Age-related differences in tongue-palate pressures for strength and swallowing tasks. *Dysphagia* 2013: 28(4): 575-581.
21. Van de Heyning PH, Badr MS, Baskin JZ, Cramer Bornemann MA, De Backer WA, Dotan Y, Hohenhorst W, Knaack L, Lin HS, Maurer JT, Netzer A, Odland RM, Oliven A, Strohl KP, Vanderveken OM, Verbraecken J, Woodson BT. Implanted upper airway stimulation device for obstructive sleep apnea. *Laryngoscope* 2012: 122(7): 1626-1633.
22. Vanderveken OM, Maurer JT, Hohenhorst W, Hamans E, Lin HS, Vroegop AV, Anders C, de Vries N, Van de Heyning PH. Evaluation of drug-induced sleep endoscopy as a patient selection tool for implanted upper airway stimulation for obstructive sleep apnea. *J Clin Sleep Med* 2013: 9(5): 433-438.
23. Vroegop AV, Vanderveken OM, Boudewyns AN, Scholman J, Saldien V, Wouters K, Braem MJ, Van de Heyning PH, Hamans E. Drug-induced sleep endoscopy in sleep-disordered breathing: Report on 1,249 cases. *Laryngoscope* 2014: 124(3): 797-802.
24. Heiser C, Knopf A, Bas M, Gahleitner C, Hofauer B. Selective upper airway stimulation for obstructive sleep apnea: a single center clinical experience. *Eur Arch Otorhinolaryngol* 2017: 274(3): 1727-1734.
25. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev* 2011: 15(6): 343-356.
26. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008: 5(2): 173-178.
27. Shapiro GK, Shapiro CM. Factors that influence CPAP adherence: an overview. *Sleep Breath* 2010: 14(4): 323-335.
28. Poulet C, Veale D, Arnol N, Levy P, Pepin JL, Tyrrell J. Psychological variables as predictors of adherence to treatment by continuous positive airway pressure. *Sleep Med* 2009: 10(9): 993-999.
29. Chai-Coetzer CL, Luo YM, Antic NA, Zhang XL, Chen BY, He QY, Heeley E, Huang SG, Anderson C, Zhong NS, McEvoy RD. Predictors of long-term adherence to continuous positive airway pressure therapy in patients with obstructive sleep apnea and cardiovascular disease in the SAVE study. *Sleep* 2013: 36(12): 1929-1937.
30. Woehrle H, Graml A, Weinreich G. Age- and gender-dependent adherence with continuous positive airway pressure therapy. *Sleep Med* 2011: 12(10): 1034-1036.

Figure legends:

Figure 1: Changes of Apnea Hypopnea Index (AHI) from Baseline to Post-Titration and Final Visit Results

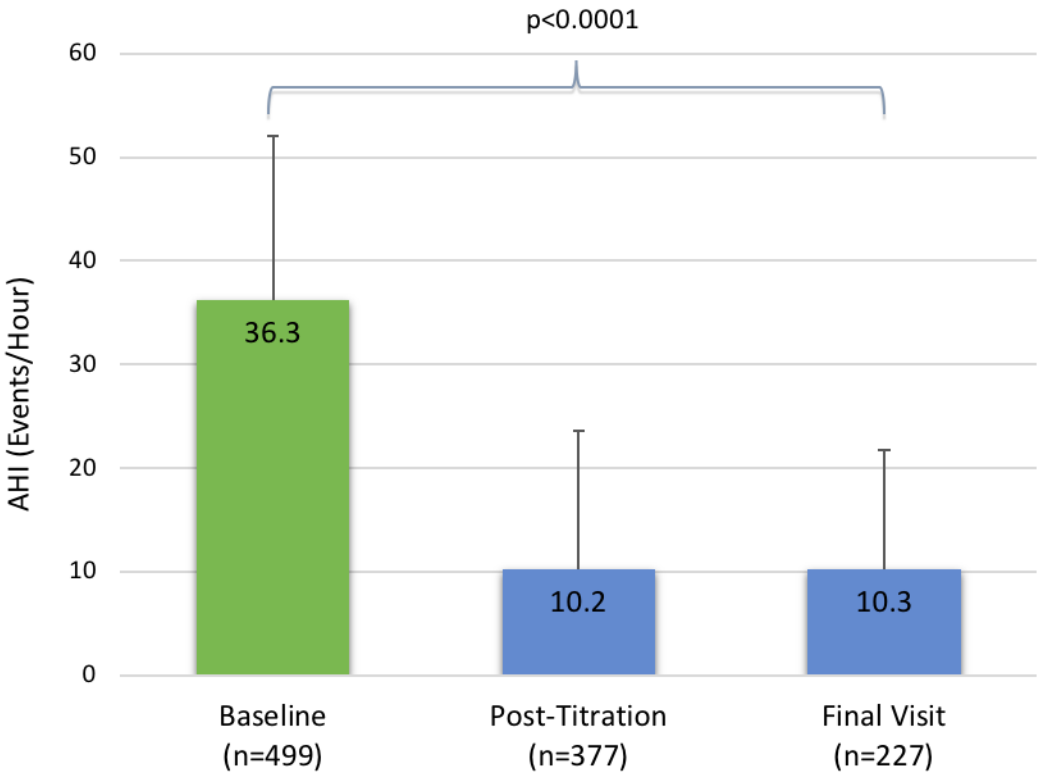

Figure 2: Changes of Epworth Sleepiness Scale (ESS) from Baseline to Post-Titration and Final Visit Results.

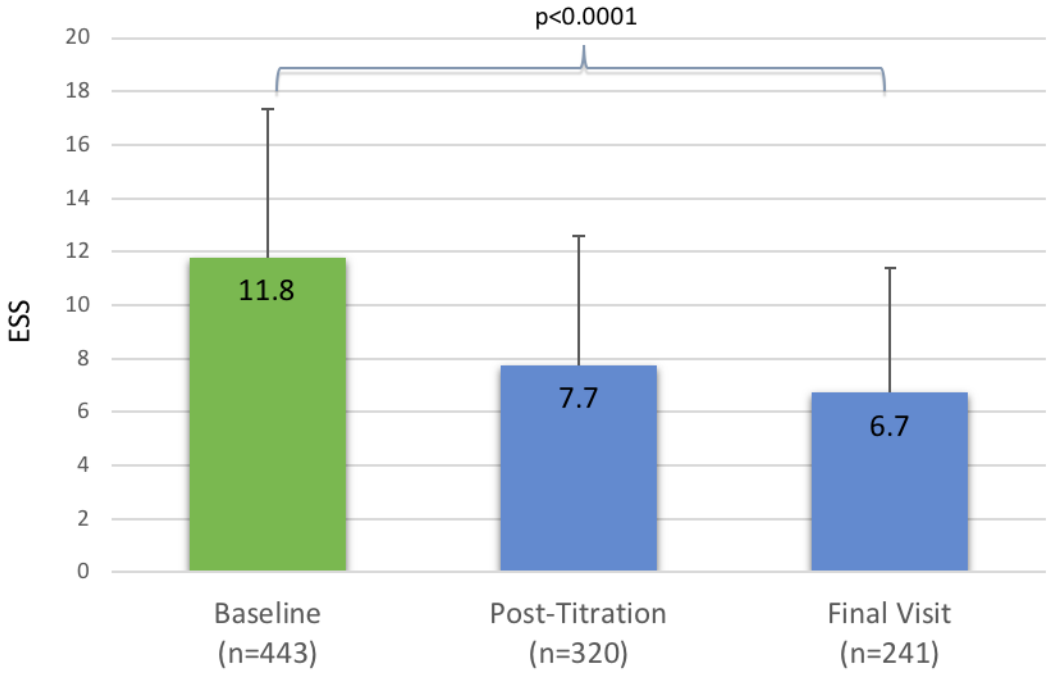

Figure 3: Clinical Global Impression of the Intervention (CGI-I) Rated by the Physician at the Post-titration and Final Visit.

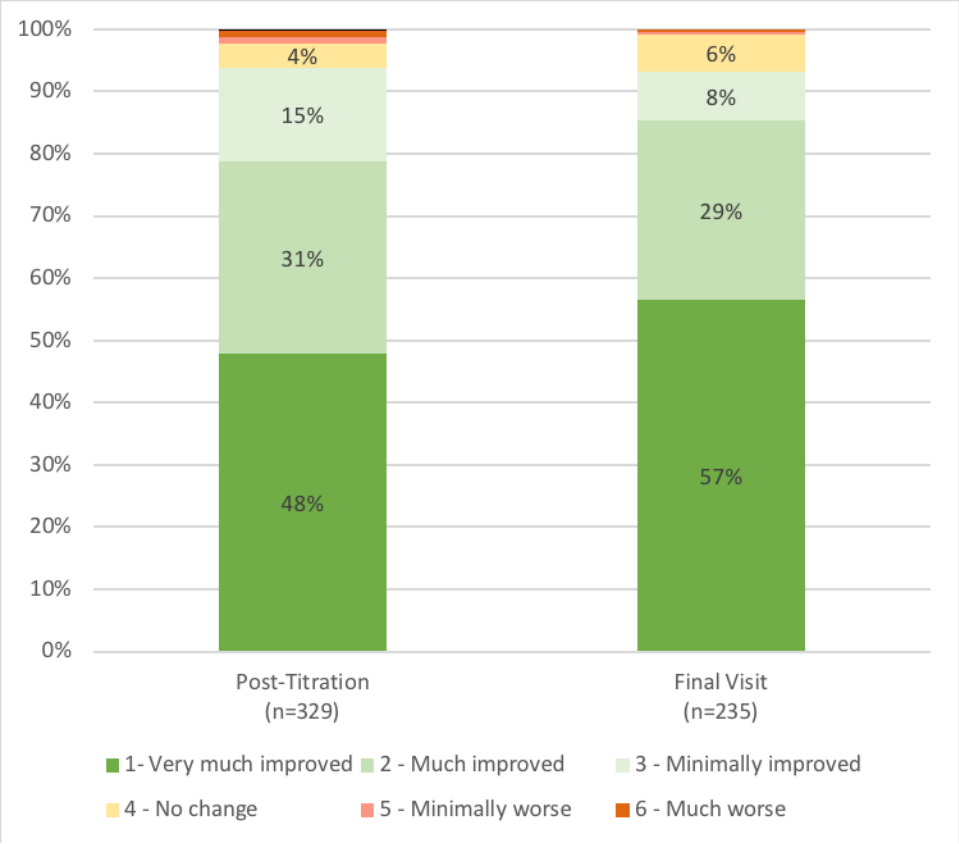

Figure 4: Patient Experience with Upper Airway Stimulation at the Post-titration and Final Visit.

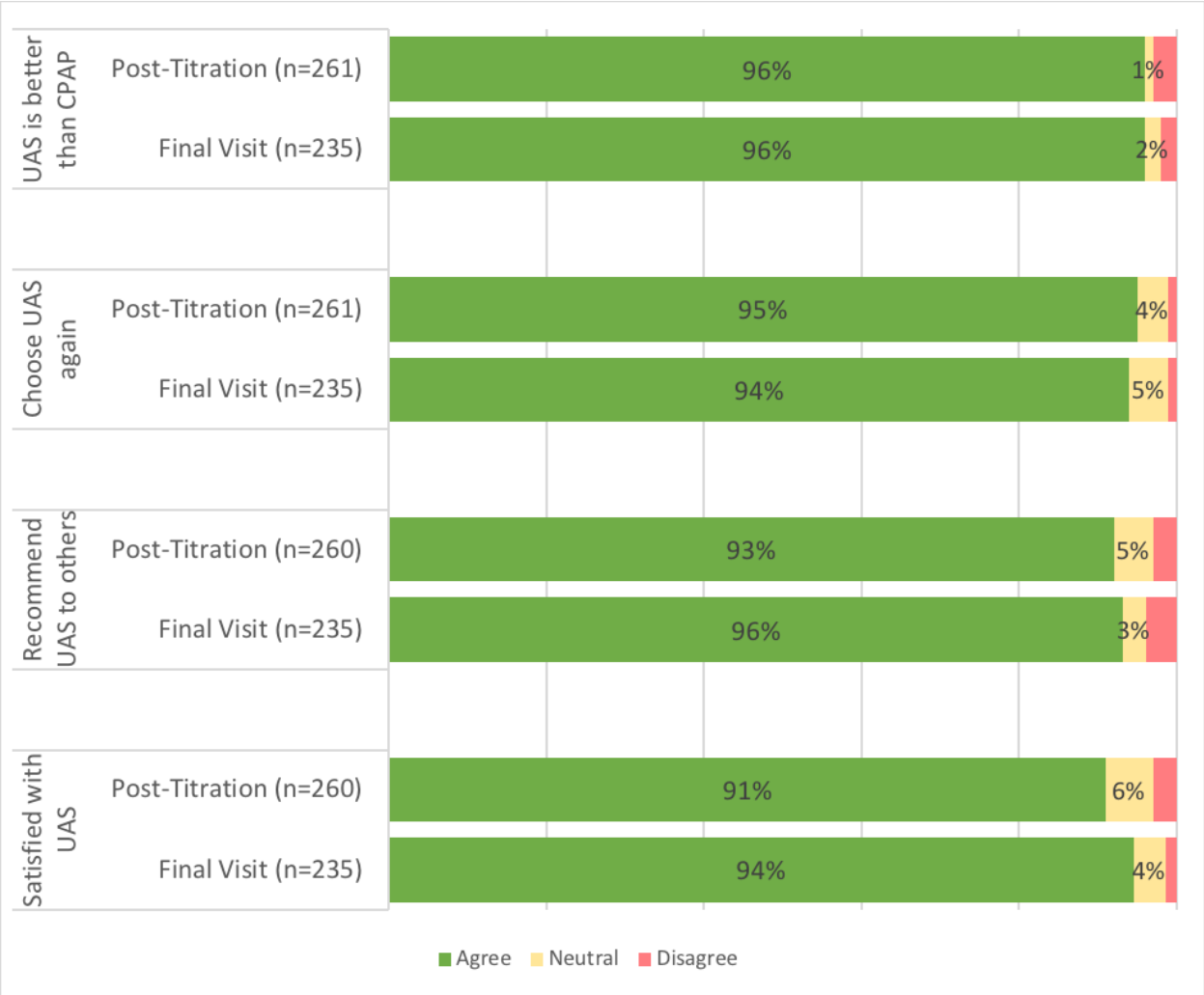

Table 1. Baseline Characteristics of the Registry Participants.

Demographics	
Number of patients	508
Age (in years)	59.4 ± 11.2
Gender	Male: n=399 (79%) Female: n=109 (21%)
Race • *Caucasian* • *Other* • *Black* • *Asian* • *American Indian or Alaska Native*	 n=491 (97%) n=7 (1%) n=6 (1%) n=2 (<1%) n=2 (<1%)
Body mass index (BMI), kg/m^2	29.3 ± 3.9
Systolic Blood Pressure, mmHg, N = 499	130 ± 13
Diastolic BP, mmHg, N = 499	78 ± 9
AHI, events/hour	36.3 ± 15.7
ESS	11.8 ± 5.5
Hypertension	46.5%
Depression	21.3%
Diabetes Mellitus	11.2%
Atrial Fibrillation	5.4%
Myocardial Infarction	3.8%
Stroke	2.5%

N = numbers; mmHg = millimeters of mercury; BP = blood pressure; AHI = Apnea-Hypopnea Index; ESS = Epworth Sleepiness Scale

Table 2. Logistic Regression Univariate Analysis of Predictors of Obstructive Sleep Apnea Treatment Success at the Final Visit (median time: 373 days).

Parameter	OR (p-value)	95% CI for OR
Age (baseline, in years)	1.04 (0.01)	1.01, 1.08
Gender (Female vs Male)	2.62 (0.08)	0.88, 7.78
BMI (baseline, in kg/m^2)	0.91 (0.027)	0.83, 0.99
AHI (Baseline, in /hour)	1.00 (0.88)	0.98, 1.03
Therapy hours per week at post-titration visit	1.04 (0.25)	0.99, 1.67
Therapy hours per week at final visit	1.02 (0.219)	0.99, 1.04
Bilateral protrusion vs. Right protrusion	2.08 (0.37)	0.96, 4.51
Other vs. Right protrusion	2.03 (0.61)	0.50, 8.21

OR = odds ratio, AHI = apnea-hypopnea index; BMI = body mass index; CI = confidence interval.

A multivariable model was fit with stepwise selection used to reduce the model to retain only significant parameters (age and BMI) and only age was retained.

Table 3. Logistic Regression of Univariate Analysis to Assess for Predictors of Upper Airway Stimulation Adherence (greater than 28 hours per week) at the Final Visit.

	Univariable Results	
Parameter	**OR (p-value)**	**95% CI for OR**
Age at consent	1.04 (0.01)	1.01, 1.07
Gender (Female vs Male)	2.14 (0.14)	0.79, 5.77
BMI at baseline	0.90 (0.009)	0.83, 0.97
Baseline AHI	0.98 (0.04)	0.96, 0.999
Bilateral protrusion vs. Right protrusion	0.92 (0.59)	0.41, 2.11
Other vs. Right protrusion	1.33 (0.62)	0.32, 5.59
Change in AHI at post-titration visit	1.01 (0.19)	0.99, 1.04
Change in ESS at post-titration visit	0.98 (0.57)	0.91, 1.05
AHI Success at post-titration visit	0.99 (0.98)	0.42, 2.34
Improvement by CGI at post-titration visit	0.67 (0.33)	0.30, 1.51
Patient satisfied or strongly satisfied at post-titration	0.60 (0.48)	0.15, 2.47
Therapy use at post-titration	1.08 (<0.0001)	1.05, 1.11
Therapy use ≥ 28 hours/week at post-titration	0.19 (0.0004)	0.07, 0.48

OR = odds ratio; CI = confidence interval; BMI = Body Mass Index; AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale.

A multivariable model was fit with stepwise selection used to reduce the model to retain only significant parameters (age, BMI, AHI, and therapy at post-titration) and only BMI and therapy use at post-titration visit was retained.

Table 4. Summary of Post-Operative Adverse Events.

	Post-Titration		Final Visit	
Type	**Number of Events**	**% of Patients**	**Number of Events**	**% of Patients**
Tongue Weakness	2	<1%	0	-
Swallowing or speech related	3	<1%	0	-
Discomfort (incision/scar)	5	1%	5	2%
Discomfort (device)	7	2%	3	1%
Infection	0	-	0	-
*Post-Op – Other**	8	2%	3	1%
Stimulation related discomfort	26	8%	15	6%
Tongue abrasion	7	2%	7	3%
Insomnia/Arousal	6	2%	9	3%
Revision interventions (including explant)	0	-	1	<1%
Other Discomfort	5	1%	2	<1%
Activation - Other	18	5%	16	6%
Total	87	23%	61	23%

**Post-op other include shortness of breath, seroma, numbness of the throat and hoarseness during day and a mild tongue-base and epiglottic obstruction. A total of 72 patients reported adverse events at the post-titration visit and 50 at the final visit (not mutually exclusive). Some patients reported multiple AEs. Percentage of patients was calculated based on the number of patients at each visit who completed the Visit form, which contains Adverse Event information.*

Supplementary Data

Table S1: Summary of Comparison between Patients with Greater or Less Than 4 hours/night Therapy Use at the Final Visit.

	Therapy ≥ 4 hours/night at Final Visit	**Therapy < 4 hours/night at Final Visit**
Parameter	**Mean ± SD (N) Or % (n/N)**	**Mean ± SD (N) Or % (n/N)**
Age at consent	60.6 ± 10.3 (180)	56.2 ± 12.5 (48)
Gender (% Female)	19.9% (36/181)	10.4% (5/48)
BMI at baseline	28.7 ± 3.8 (178)	30.5 ± 4.6 (47)
Baseline AHI	33.8 ± 14.1 (180)	38.8 ± 17.6 (48)
Baseline ESS	12.0 ± 5.4 (163)	11.9 ± 5.7 (42)
Tongue motion		
Right protrusion	20.7% (36/174)	20.0% (9/45)
Bilateral protrusion	70.1% (122/174)	73.3% (33/45)
Other	9.2% (16/174)	6.7% (3/45)
Change in AHI at post-titration visit	-23.7 ± 14.9 (167)	-29.1 ± 22.0 (46)
Change in ESS at post-titration visit	-5.7 ± 5.3 (156)	-4.2 ± 5.7 (40)
AHI Success at post-titration visit	82.4% (145/176)	80.4% (37/46)
Change in AHI at Final	-24.4 ± 16.7 (186)	-27.5 ± 18.4 (19)
Change in ESS at Final	-5.5 ± 5.4 (176)	-4.3 ± 6.1 (40)
AHI Success at Final	83.3% (155/186)	73.7% (14/19)
Improvement by CGI at post-titration visit	83.1% (138/166)	76.7% (33/43)
Patient satisfied or strongly satisfied at post-titration	94.5% (120/127)	91.2% (31/34)
Therapy use at post-titration	47.3 ± 11.6 (170)	34.9 ± 14.1 (44)
Therapy use ≥ 28 hours at post-titration	94.1% (160/170)	75.0% (33/44)

SD = standard deviation; N = numbers; AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; CGI = clinical global impression; BMI = Body Mass Index (in kg/m^2).

Table S2. Adverse Events at the Post-Titration and Final Visits in Severity.

Type	Post-Titration	Final Visit	Severity			Total
			Mild	Moderate	Severe	
Tongue Weakness	2	0	1	1	0	2
Swallowing or speech related	3	0	2	1	0	3
Discomfort (incision/scar)	5	5	6	3	1	10
Discomfort (device)	7	3	7	2	1	10
Infection	0	0	0	0	0	0
Post-Op – Other	8	3	11	0	0	11
Stimulation related discomfort	26	15	21	19	1	41
Tongue abrasion	7	7	9	4	1	14
Insomnia/Arousal	6	9	8	5	2	15
Revision interventions (including explant)	0	1	0	0	1	1
Other Discomfort	5	2	5	1	1	7
Activation - Other	18	16	23	10	1	34
Total	87	61	93	46	9	149

The table lists the number of patients for each event type at the different visits as well as the severity.

Table S3. List of All Reported Severe Adverse Events during the Post-Titration and Final Visit.

Visit	Event	Event - Specify	Severity
Post-Titration	Discomfort (incision/scar)	Right shoulder pain (Scarring)	Severe
Post-Titration	Discomfort (device)	Strain at stimulation electrode	Severe
Post-Titration	Insomnia/Arousal	Can't fall asleep again during therapy pauses if wakes up at night	Severe
Post-Titration	Other Discomfort	Strong electric shock	Severe
Post-Titration	Activation - Other	Hospitalized for bilateral pulmonary embolus felt unrelated to device	Severe
Final Follow-up	Stimulation related discomfort	Too strong at therapeutic level from last reprogram; therefore, not using it	Severe
Final Follow-up	Tongue abrasion	Tongue rubs on teeth	Severe
Final Follow-up	Insomnia/Arousal	Wakes up from tongue rubbing	Severe
Final Follow-up	Revision interventions	Inadequate therapeutic response, lack of tongue protrusion, revision cuff	Severe

Supplemental Table 1. Registry Centers, enrollment and investigators:

Registry Centers, Germany	**Patient Enrolled**	**Investigators**
Technical University of Munich	96	Clemens Heiser, MD Benedikt Hofauer, MD Sabrina Wenzel, RN Katharina Eckbauer, RN
University Hospital of Schleswig-Holstein, Lubeck	87	Armin Steffen, MD Nicole Behn, RN
University ENT Clinic Mannheim	57	Joachim T Maurer, MD J Ulrich Sommer, MD Oliver Schmidt, RN
Registry Centers, United States		
Thomas Jefferson University and Hospital	74	Maurits Boon, MD Colin Huntley, MD Karl Doghramji, MD Beth Duddy, RN
University of Pittsburgh Medical Center	50	Ryan Soose, MD Patrick J. Strollo Jr., MD Courtney Chou, MD Tina Harrison, RN
University of Pennsylvania	41	Richard Schwab, MD Erica Thaler, MD Sarah Leinwand, BS Nadia Azad, BS
University of Alabama at Birmingham	24	Kirk Withrow, MD Lisa Clemons, RN
Cleveland Clinic Foundation	23	Tina Waters, MD Reena Mehra, MD Alan Kominsky, MD Douglas Trask, MD Harneet Walia, MD Joan Aylor, RN
University of Kansas Medical Center	16	Christopher Larsen, MD Suzanne Stevens, MD Damien Stevens, MD Jill Tuschhoff, RN Bryan Humphrey, RRT-NPS
University of Southern California	14	Eric Kezirian, MD Yeini Colombia Guardia, RN
University Hospital Cleveland	10	Kingman Strohl, MD Mark Weidenbecher, MD Mary Andrew, RN

		Stacey Pot, RN
University of Minnesota Fairview	8	Conrad Iber, MD Jennifer Hsia, MD Liz Silbernick, RN
MedStar Health Research Institute	7	Stanley Chia, MD Tricia Moriarty, RN
University of Florida Gainesville	1	John Harwick, MD Richard Barnett Berry, MD Alexis Lovelace, RN

Supplemental Table 2: Surgical Times. There were 5 sites that participated in previous studies, which had surgical time on 290 patients, and 9 sites that were offering UAS for the first time, with data on 139 patients. There was no significant difference in the surgical time between the two groups. (p=0.65)

	# entries with surgical time	Average Surgical Time (minutes)
Centers with previous UAS experience (n=5)	290	142.7 ± 41.9
Centers without previous UAS experience (n=9)	139	140.6 ± 50.7
p-value		0.65