Developments in diagnosis and treatment of obstructive sleep apnea

Bosschieter, P.F.N.

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8 Similar effect of hypoglossal nerve stimulation for obstructive sleep apnea in five disease severity categories

Bosschieter PFN, Vries N, Mehra R, Manchanda S, Padhya TA, Vanderveken OM, Ravesloot MJL; ADHERE Registry Investigators

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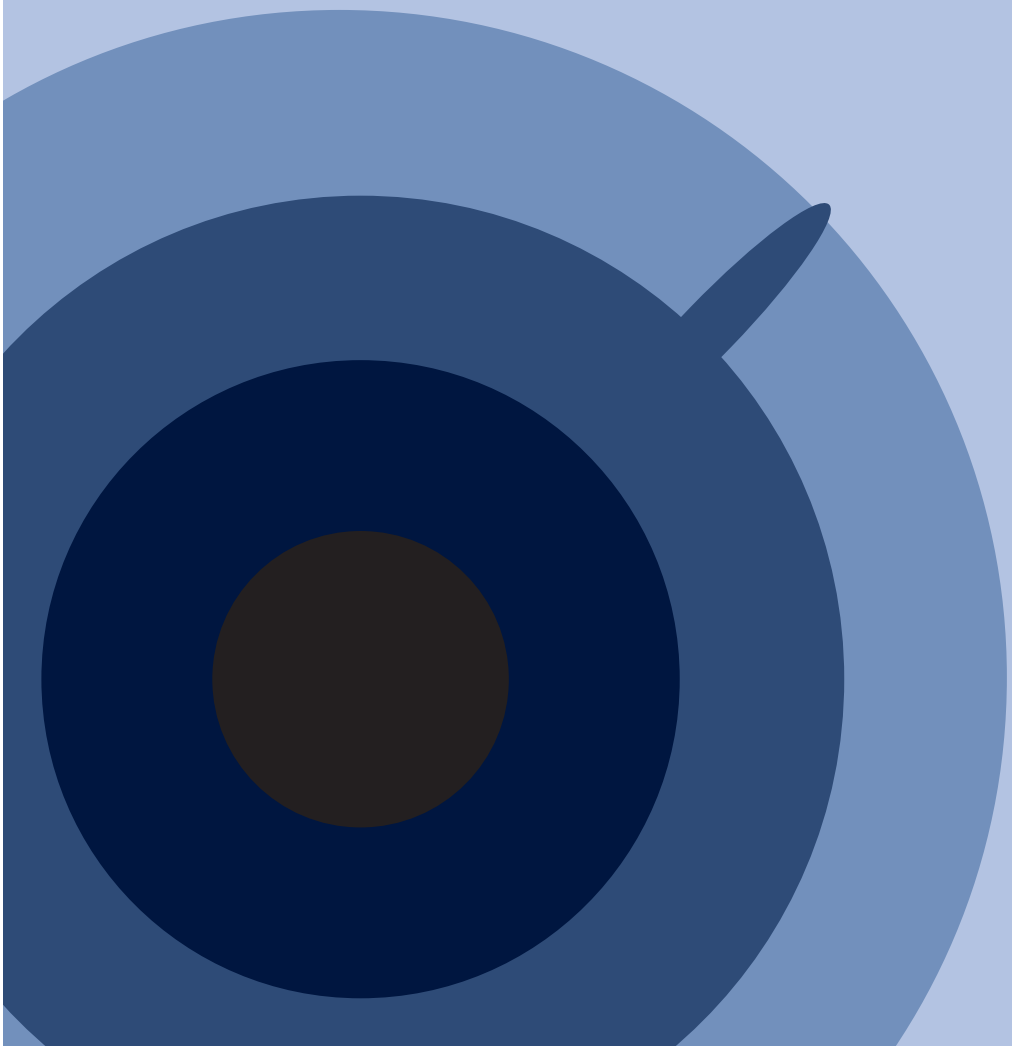


ABSTRACT

Study Objectives: Data on adherence and outcome of Upper Airway Stimulation (UAS) for patients with Obstructive Sleep Apnea (OSA) is collected in an International Registry (ADHERE). Previous publications report significant improvement in self-reported and objective OSA outcomes, durable effectiveness, and high adherence. Debate remains whether the effectiveness of UAS is influenced by pre-operative OSA severity, therefore we aimed to evaluate this, using data from the ADHERE registry.

Methods: ADHERE is a post-market ongoing international, multicenter registry. Adult patients were included if they had undergone UAS implantation and had at least one follow-up visit recorded in the database on June 8th, 2021. We divided the patients into five subgroups, based on OSA severity at baseline (AHI in events/hr): subgroup 1 (0-15), 2 (15-30), 3 (≥30-50), 4 (>50-65), and 5 (>65). We compared results regarding objective and self-reported treatment outcomes.

Results: A total of 1963 patients were included. Twelve months after implantation, there was a significant (p<0.0001) improvement in objective sleep parameters in all subgroups with an AHI above 15 events/hr. Patients in subgroup 1 had the lowest AHI at final visit and the AHI reduction of patients in subgroup 5 was the largest (p<0.0001). No significant difference was found between the subgroups in overall treatment success (66.6%) and improvement of self-reported outcomes.

Conclusion: Our results suggest that UAS is an effective treatment for patients with an AHI ≥15 events/hr independent of pre-operative OSA severity. Self-reported outcomes and treatment success did not differ significantly between the five subgroups.

These results clearly support that the indication of UAS could be broadened for patients with an AHI above 65 events/hr which to date is not common practice.

Keywords: “Sleep Apnea, Obstructive/therapy”[Mesh]

INTRODUCTION

The ADHERE Registry (Adherence and Outcome of Upper Airway Stimulation for OSA International Registry) is a post-market, multicenter, observational registry which was designed to collect data related to the use and effectiveness of Upper Airway Stimulation (UAS) therapy (Inspire Medical Systems Inc., Minneapolis, MN). The latter is a treatment developed for patients with obstructive sleep apnea (OSA) who are not effectively treated with Positive Airway Pressure (PAP), which has been elaborately described in the literature previously.[1]

All patients who are eligible for Inspire implant may be invited to participated in the ADHERE registry. There are no limitations for the registry for age, gender, BMI, or OSA severity so therefore some patients who are enrolled have been implanted outside of the current indication criteria. Participants who are enrolled in the ADHERE Registry are followed for at least 1-year post-implantation. Information related to demographics, severity of OSA (as measured by polysomnography (PSG) or home sleep test (HST)) and symptoms are collected at baseline. Implant details are collected and recorded at the time of implantation. Follow-up information related to severity of OSA (as measured by PSG or HST), symptoms, surgical outcomes, complications, quality of life, therapy usage, patient improvement and satisfaction with UAS is collected at approximately 6 months (post-titration) and 12 months (final follow-up) post-implantation.

Previous publications on the ADHERE registry report significant improvement in self-reported and objective OSA outcomes, and of greater novelty that the UAS therapy effect is durable and adherence remains high.2-5 These studies suggest that female sex 2, a lower baseline body mass index 2, 3 and increasing age 3, 5 are significant positive predictors of therapeutic outcome. Heiser et al. 2 found that OSA severity was not a predictor for UAS treatment success. Thaler et al. 2, however found that a higher AHI was a negative predictor for success and suggested that this specific predictor bears further investigation.

Bearing this in mind, we specifically aimed to evaluate the effectiveness of UAS in five subgroups stratified by preoperative severity of OSA, using data from the ADHERE registry. A second reason to evaluate whether preoperative OSA severity is a predictor for success, is that in some countries, OSA reimbursement is restricted to certain cut-off values concerning the AHI, due to lack of evidence concerning patients treated with UAS therapy beyond the scope of this range.

We hypothesize that objective and self-reported therapy efficacy, adherence, and patient reported outcomes after UAS implantation are independent of pre-operative OSA severity.

METHODS

We adhered to the STROBE guidelines for reporting of prospective studies.6

Study design, setting and participants

The ADHERE registry, which began enrolment in October 2016 is an ongoing international, multicenter observational study. The registry collects patient and physician reported outcomes before and after UAS implantation at over 50 clinical centers in the United States, Belgium, Germany, Switzerland, and the Netherlands and was approved by the ethics committee or institutional review board at every implantation center. Data is collected once the patient has given informed consent.

The UAS system, indication for implantation and implantation procedure have been described previously.2

The ADHERE Registry collects and reports on real-world data, which may include data on patients who are outside of the current indications for use (at the discretion of the physician). Collection and reporting of this data allow us to determine prevalence and outcomes related to off-label usage. Patients were included in this analysis if they had undergone implantation of the Inspire system and had at least one follow-up visit (post-titration or final visit) recorded in the database on 8 June 2021. For this dataset, a post-titration visit is marked as missed if the patient is more than 9 months past their implant date as of May 2021, 2021. A final visit is marked as missed if the patient is more than 2 years past their implant date.

Variables and data collection

The primary outcome measure of this study was the efficacy of UAS.

Patients were stratified into five subgroups, according to baseline AHI:

- Subgroup 1) Zero to 15 events/hr – non or mild OSA;
- Subgroup 2) Greater than 15 events/hr and less than 30 events/hr – moderate OSA;

- Subgroup 3) Greater than or equal to 30 events/hr and less than or equal to 50 events/hr – severe OSA;
- Subgroup 4) Greater than 50 events/hr and less than or equal to 65 events/hr – severe OSA, not investigated during the original STAR-trial, CE and FDA approved;
- Subgroup 5) Greater than 65 events/hr – severe OSA, no CE and no FDA approval.

Secondary outcomes measures were self-reported therapy efficacy, adherence and patient reported outcomes stratified by preoperative severity of OSA.

All data is recorded in an online cloud-based platform (iMEDnet).

OSA severity information including AHI and oxygen desaturation index (ODI), is captured using either in-lab polysomnography (PSG) or a Home Sleep Test (HST) at baseline and follow-up time points. AHI was based on a full-night, we did not use the treatment AHI obtained from the titration.

The Epworth Sleepiness Scale (ESS) was used to acquire information about patient symptoms7. The ESS is a validated, self-report instrument that rates a subject's tendency to fall asleep in eight common daily situations. Scores range from 0 to 24, with a lower score indicating less daytime sleepiness. An ESS score of 10 or less is equivalent to the normalized population.

Therapy usage (hours of active Inspire UAS use per week) was captured by the device when the device is turned ON and is reported during follow-up visits when the device data is downloaded onto the physician programmer.

Patient improvement was recorded using the Clinical Global Impression – Improvement (CGI-I) Scale8. The CGI-I is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened at follow-up, relative to baseline.

Patient satisfaction was collected by questionnaires regarding patients' experience with UAS at follow-up visits.

The mean disease alleviation (MDA) is a measure of therapeutic effectiveness and is the product of therapeutic efficacy and adjusted compliance. Therapeutic efficacy is defined as baseline AHI minus the AHI at 12 months, expressed as the percentage of the baseline AHI. Since we do not know the total sleep time (TST) of the patients, we assumed that patients sleep 7 hours per night. The adjusted compliance was defined as hours of use corrected for TST.

Statistical analysis

Statistical analysis was performed using R (version 4.0.2). Quantitative data was reported as means and standard deviations, or as medians and quartiles 1 and 3, when not normally distributed. Statistical comparisons were made between the subgroups in terms of demographic and outcome variables. Statistical significance testing was done using one of four tests: Wilcoxon Rank Sum Test, paired- t-test, Kruskal-Wallis, Fisher's Exact Test, Chi-square test, or Anova Test. A p -value of less than 0.05 was considered to indicate statistical significance. To investigate the influence of the use of two types of sleep test (HST and PSG) on our outcomes we performed additional analyses. A chi square test was performed with exclusion of patients whereby the type of sleep test was unknown or did not have a final AHI. In addition, we performed two multiple linear regressions (final AHI and change in AHI) and one multiple logistic regression for Sher's response9.

RESULTS

A total of 2824 patients were enrolled in the ADHERE database in May 2021. The baseline AHI was unknown in 91 patients. A total of 1921 participants had completed a post-titration (~6 months post-implant) visit and 1170 participants had completed a final (~12 months post-implant) visit. In this study 1963 participants were analyzed. The average age was 60.2 ± 10.7 years, BMI 29.2 ± 3.8 kg/m2 and 72.8 % were male.

In comparison of the demographic variables between the five subgroups, there was a significant difference in BMI ($p<0.0001$), subgroup 1 had the lowest BMI (28.4 ± 3.5 kg/m2), whilst subgroup 5 had the highest BMI (30.6 ± 3.6 kg/m2). The gender distribution differed significantly ($p=0.01$) between the five subgroups, however in all subgroups the majority of patients were male. Baseline demographic characteristics are shown in Table 1. A comparison of outcome variables is provided in Tables 2A and 2B.

Forty two patients (2.1%) had an AHI of 0-15 events/hr (subgroup 1), 765 patients (39.0%) an AHI of 15-30 events/hr (subgroup 2), 821 patients (41.8%) an AHI of ≥30-50 events/hr (subgroup 3), 258 patients (13.1%) an AHI of ≥50-65 events/hr (subgroup 4) and 77 patients (3.9%) an AHI > 65 events/hr (subgroup 5). There was a statistically significant reduction in AHI between baseline and the final visit in subgroups 2-5. The AHI at final visit and change in AHI significantly differed (both $p<0.000$) between the subgroups, with the lowest AHI at final visit in subgroup 1 and the greatest reduction in AHI in subgroup 5. Figure 1.

Table 1. Demographic Information

Demographic Variables		All Patients	Subgroups					
			Subgroup 1 AHI < 15	Subgroup 2 15 ≥ AHI <30/hr	Subgroup 3 30 ≥ AHI ≤ 50/hr	Subgroup 4 50 > AHI ≤ 65/hr	Subgroup 5 AHI > 65/hr	
		(N=1963)	(N=42)	(N=765)	(N=821)	(N=258)	(N=77)	*p*-value~
Age (years)		N=1957 60.2 ± 10.7	N=42 59.6 ± 10.8	N=763 60.3 ± 10.7	N=817 60.2 ± 10.7	N=258 60.1 ± 11.2	N=77 59.0 ± 10.8	0.89*
Body Mass Index (*kg/m2)		N=1918 29.2± 3.8	N=41 28.4 ± 3.5	N=748 28.9 ± 3.9	N=796 29.1 ± 3.6	N=257 29.8 ± 4.2	N=76 30.6 ± 3.6	<0.0001*
Sex	Male	1423 (72.8 %)	27 (64.3%)	527 (69.2%)	613 (75.0%)	194 (75.5%)	62 (81.6%)	0.01**
Race∞	White	1860 (94.0%)	39 (90.7%)	722 (93.4%)	785 (95.0%)	244 (94.6%)	70 (88.6%)	0.47**
	Black	36 (1.8%)	1 (2.3%)	15 (1.9%)	11 (1.3%)	6 (2.3%)	3 (3.8%)	
	Asian	15 (0.76%)	1 (2.3%)	6 (0.8%)	6 (0.7%)	2 (0.8%)	0 (0.0%)	
	American Indian or Alaska Native	5 (0.25%)	0 (0.0%)	3 (0.39%)	2 (0.24%)	0(0%)	0 (0%)	
	Other	40 (2.0%)	1 (2.3%)	17 (2.2%)	14 (1.7%)	4 (1.6%)	4 (5.1%)	
	Unknown	23 (1.2%)	1 (2.3%)	10 (1.3%)	8 (0.97%)	2 (0.78%)	2 (2.5%)	

Data is presented as mean ± SD, median (min, max) or count (%)
~p-values compare 5 subgroups, * Anova; ** Chi-square test
∞ Chi-square compared, white versus non-white patients, some patients selected multiple races which is why the cumulative number is higher than the total amount of patients

Table 2A. Outcome Variables

Outcome Variables	All patients (n=1963)			
	Baseline	***6M (Post-Titration)***	***12M (Final)***	***p-values***[2]
AHI (evens/ hour)	N=1963 33.0 (0.60, 118.7)	N=1852 7.8 (0.0, 103.0)	N=890 10.2 (0.0, 96.2)	<0.0001*
Change in AHI (events/hr)		N=1852 23.0 ± 18.3	N=890 20.7 ± 18.4	See above
ODI (events/ hr)	N=461 22.9 (0.0, 242.0)	N=930 8.4 (0,126.0)	N=557 9.4 (0.0, 198.0)	<0.0001*
ESS	N=1712 11.0 (0.0, 24.0)	N=1528 7 (0.0, 24.0)	N=994 6.0 (0.0, 23.0)	<0.0001*
Therapy Usage (hours/ night)		N=1573 6.4 ± 2.1	N=913 5.7 ± 2.2	<0.00014

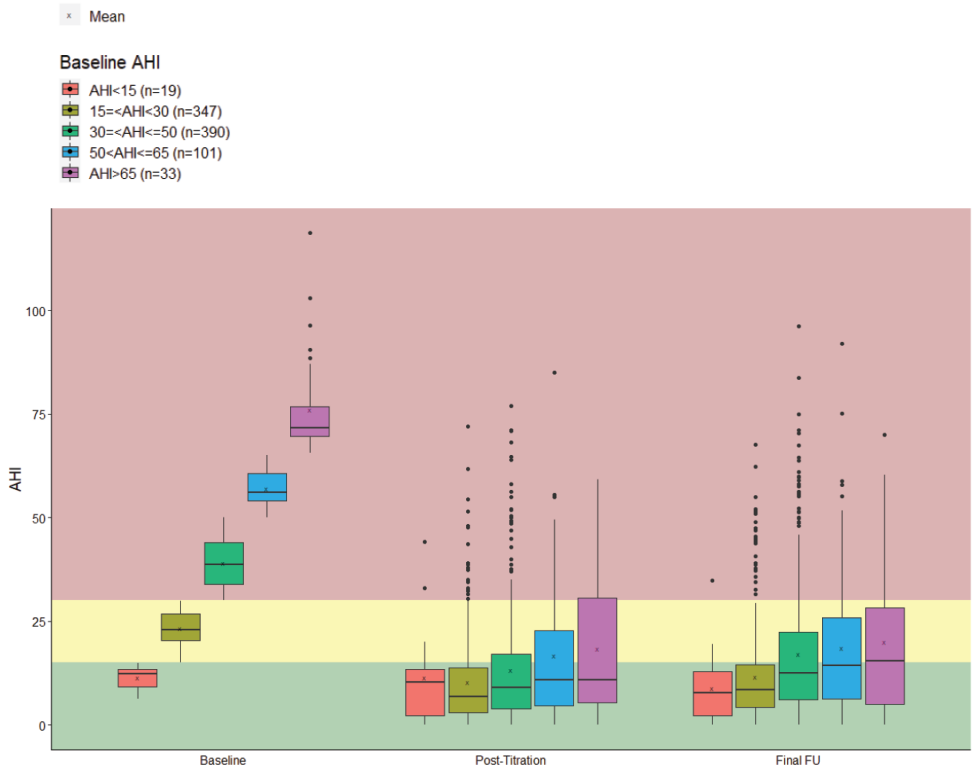
Apnea-hypopnea Index (AHI), Change in AHI, Oxygen Desaturation Index (ODI) , Epworth Sleepiness Scale (ESS)
Data is presented as mean ± SD or median (min, max) 2p-values compare baseline and final visit using a paired t-test, 4compared to Post-Titration

Table 2B. Outcome Variables

Outcome Variables	Subgroup 1 AHI < 15 (n=42)				Subgroup 2 15 ≥ AHI < 30/hr (n=765)				Subgroup 3 30 ≥ AHI ≤ 50/hr (n=821)				Subgroup 4 50 < AHI ≤ 65/hr (n=258)				Subgroup 5 *AHI > 65/hr (n=77)*				
	Baseline	*6M (Post-Titration)*	*12M (Final)*	*p-values*[2]	*Baseline*	*6M (Post-Titration)*	*12M (Final)*	*p-values*[2]	*Baseline*	*6M (Post-Titration)*	*12M (Final)*	*p-values*[2]	*Baseline*	*6M (Post-Titration)*	*12M (Final)*	*p-values*[2]	*Baseline*	*6M (Post-Titration)*	*12M (Final)*	*p-values*[2]	*p-values*[3]
Apnea-hypopnea Index (AHI)	N=42 11.2 (0.6, 14.9)	N=39 6.1 (0.0, 44.2)	N=19 7.8 (0.0, 34.8)	0.17*	N=765 22.3 (15.0, 29.9)	N=723 6.0 (0.0, 72.0)	N=347 8.5 (0.0, 67.6)	<0.0001*	N=821 38.2 (30, 50.0)	N=773 8.7 (0.0, 80.0)	N=390 12.6 (0.0, 96.2)	<0.0001*	N=258 56.3 (50.1, 65.0)	N=242 10.4 (0.0, 85.0)	N=101 14.4 (0.0, 92.0)	<0.0001*	N=77 72.4 (65.5, 118.7)	N=75 17.9 (0.0, 103)	N=33 15.5 (0.0, 70.0)	<0.0001*	<0.0001**
Change in AHI		N=39 0.28 ± 10.19	N=19 2.57 ± 7.9	See above		N=723 13.0 ± 11.0	N=347 11.6 ± 11.7	See above		N=773 25.5 ± 15.0	N=390 22.1 ± 16.0	See Above		N=242 40.4 ± 18.4	N=101 38.4 ± 17.4	See Above		N=75 50.3 ± 24.8	N=33 56.0 ± 21.1	See above	<0.0001***
Oxygen Desa-turation Index (ODI)	N=12 4.75 (0.0, 29.2)	N=21 6.15 (0.0, 126.0)	N=11 8.45 (0.5, 74.5)	0.63*	N=192 16.8 (0.2,92)	N=370 6.4 (0,66.7)	N=217 7.8 (0.0, 198)	0.01*	N=205 28.2 (1.0, 94.0)	N=410 9.0 (0.0, 96.0)	N=251 10.7 (0.0, 61.5)	<0.0001*	N=35 45.9 (15.2, 242.0)	N=98 14.6 (0.2, 87.0)	N=63 13.2 (0.0, 89.0)	NA	N=17 53.9 (4.0, 90.4)	N=31 18.7 (0.0, 62.4)	N=15 21.5 (0.0, 70.0)	NA	<0.0001**
Epworth Sleepiness Scale (ESS)	N=37 11.0 (0.0, 20.0)	N=26 5.5 (0.0, 16.0)	N=24 4.0 (0.0, 14.0)	<0.0001*	N=664 11.0 (0.0, 24.0)	N=598 7.0 (0.0, 24.0)	N=371 6.0 (0.0, 21.0)	<0.0001*	N=726 11.0 (0.0, 24.0)	N=647 7.0 (0.0, 23.0)	N=442 6.0 (0.0, 23.0)	<0.0001*	N=215 12.0 (0, 24.0)	N=200 8.0 (0.0, 24.0)	N=116 7.0 (0.0, 22.0)	<0.0001*	N=70 11.0 (0.0, 22.0)	N=57 9.0 (0.0, 21.0)	N=41 6.0 (0.0, 20.0)	<0.0001*	0.21**
Therapy Usage (hours/ night)		N=30 6.55 ± 1.61	N=20 5.67 ± 2.21	0.454		N=609 6.5 ± 2.0	N=343 6.0 ± 2.1	<0.00014		N=670 6.5 ± 2.0	N=398 5.7 ± 2.2	<0.00014		N=206 6.1 ± 2.3	N=115 5.4 ± 2.4	<0.00014		N=58 5.7 ± 2.1	N=37 4.7 ± 2.6	0.0544	0.005***

Data is presented as mean ± SD or median (min, max)
2p-values compare baseline and final visit; 3p-values compare groups at final visit; 4p-values compare post-titration to final visit; *paired t-test, **Kruskal-Wallis, ***Anova; NA = not enough data to run statistical test

Figure 1: Therapy outcomes (AHI)

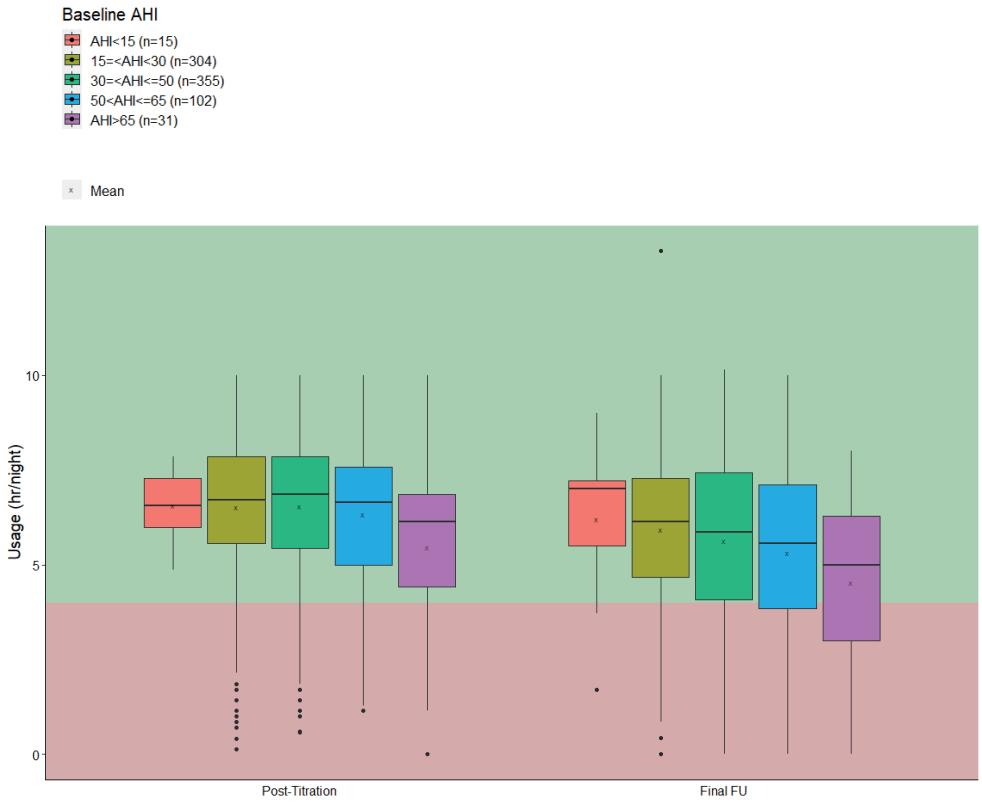


AHI: apnea-hypopnea index

Excessive daytime sleepiness (ESS) significantly improved in all subgroups from baseline to final visit. There was no significant difference (p = 0.21) in ESS score between the five subgroups at final follow-up.

Overall, therapy usage decreased between 6 and 12 months post-implant, this was not significant in subgroup 1 and 5.Subgroup 5 had the lowest therapy usage of 4.7 hours/night at final visit ., which exceeds the commonly used criteria for CPAP tolerance of 4 hours per night.10 Adherence differed significantly (p=0.005) between all subgroups, with the highest adherence in subgroup 2. Figure 2. The MDA was 24.6% for subgroup 1, 53.0% for subgroup 2, 54.5% for subgroup 3, 57.4% for subgroup 4 and 52.7% for subgroup 5.

Figure 2: Therapy usage



AHI: apnea-hypopnea index

Treatment success was calculated according to Sher's criteria: at least 50% decrease in AHI and treatment AHI≤20 events/hr9. Overall treatment success for all patients was 66.6%. Treatment success as determined by Sher's Criteria ranged from 42.1% (subgroup 1) to 68.3% (subgroup 2), but did not differ significantly between the subgroups (Table 3).

For subgroup 5 patient improvement (CGI-I) was rated slightly less positive, although this outcome was not significantly different compared to the other subgroups (p=0.58) (Table 4). Patient satisfaction was impressive in all subgroups without significant differences between the subgroups. At least 90% of all participants rating UAS better than CPAP (Table 5).

Table 3. Therapy Response

Therapy Response	All Patients	Subgroups					
		Subgroup 1 AHI < 15	Subgroup 2 15 ≥ AHI <30/hr	Subgroup 3 30 ≥ AHI ≤ 50/hr	Subgroup 4 50 > AHI ≤ 65/hr	Subgroup 5 AHI > 65/hr	p-value
Sher response9	N=593 (66.6%)	N=8 (42.1%)	N=237 (68.3%)	N=260 (66.7%)	N=66 (65.4%)	N=22 (66.7%)	0.23*
AHI<21	N=678 (76.2%)	N=18 (94.7%)	N=295 (85.0%)	N=277 (71.0%)	N=66 (65.4%)	N=22 (66.7%)	<0.0001**
50% reduction AHI	N=618 (69.4%)	N=8 (42.1%)	N=237 (68.3%)	N=267 (68.5%)	N=80 (79.2%)	N=26 (78.8%)	0.01*

p-value (chi-square test) compares the response rates between the five subgroups, *Chi-square test ,**Fisher's exact test

Table 4. Clinical Global Impression – Improvement (CGI-I) Scale

CGI-I	All Patients N=917	Subgroups					
		Subgroup 1 AHI < 15 N=21	Subgroup 2 15 ≥ AHI < 30 N=349	Subgroup 330 ≥ AHI ≤ 50 N=399	Subgroup 4 50 < AHI ≤ 65 N=109	Subgroup 5 AHI > 65 N=39	p-value*
Very much improved	41.4%	33.3%	45.0%	40.1%	43.1%	23.1%	0.58
Much improved	36.1%	47.6%	35.0%	37.3%	33.0%	35.9%	
Minimally improved	13.1%	9.5%	12.0%	12.8%	13.8%	25.6%	
No change	6.2%	4.8%	5.7%	5.5%	8.3%	12.8%	
Minimally worse	2.0%	4.8%	1.4%	2.8%	0.9%	0%	
Much worse	1.1%	0.0%	0.86%	1.3%	0.9%	2.6%	
Very much worse	0.11%	0.0%	0.0%	0.25%	0.0%	0.0%	

* p-value (Chi-square test) compares subgroups at final visit; improved versus not improved (including no change)

Table 5. Patient Satisfaction with Therapy

Patient Satisfaction	All Patients	Subgroups					
		Subgroup 1 AHI < 15	Subgroup 2 15 ≥ AHI <30/hr	Subgroup 3 30 ≥ AHI ≤ 50/hr	Subgroup 4 50 > AHI ≤ 65/hr	Subgroup 5 AHI > 65/hr	p-value*
Subject rated Inspire as better than CPAP	90.5%	89.5%	92.5%	90.2%	84.3%	92.3%	0.16
Subject would choose Inspire again	91.5%	89.5%	92.7%	90.9%	90.9%	88.5%	0.41
Subject would recommend Inspire to friends or family	92.8%	89.5%	94.9%	91.7%	92.1%	88.5%	0.47
Subject is satisfied with Inspire	89.8%	89.5%	91.2%	89.3%	90.0%	80.8%	0.44

* p-value (Fisher's exact) compares subgroups at final visit

DISCUSSION

Not only is this the largest cohort study of patients with UAS therapy to date, it is also the first to focus on the efficacy of treatment on both objective and self-reported values, as well as adherence of therapy stratified by baseline AHI severity. After 12 months, there was a significant improvement in objective sleep parameters in all subgroups with a baseline AHI of 15 events/hr and above. The AHI at the final visit was the lowest in the subgroup with the lowest pre-operative AHI. The subgroup with the highest pre-operative AHI had the greatest reduction in AHI at final visit. There was significant improvement regarding symptoms of excessive daytime sleepiness (ESS) and patient improvement as measured by the CGI-I at 12 months after implantation, without differences between the five subgroups. Overall treatment success was 66.6% without significant differences between the subgroups.

Despite the increasing baseline AHI, objective sleep parameters were significantly improved in subgroups 2-5 at final visit. This is particularly interesting when considering that it is generally easier to reach surgical success in patients with a low AHI.10 Whether preoperative OSA severity is a predictor for success is not reserved for UAS therapy alone, it remains a question of debate in all types of upper airway surgery for OSA. For example in a meta-analysis performed to assess the effects of isolated uvulopalatopharyngoplasty and tonsillectomy in patients with OSA, the authors conclude that it may be hypothesized that clinical anatomy is of higher relevance than disease severity.11 In another meta-analysis, surgical success rate of maxillomandibular advancement (MMA) was greater in a lower mean preoperative AHI.12 For most surgical treatment modalities it remains unclear. A possible explanation for the found equality between the severity subgroups is that due to the strict inclusion criteria only perfectly suitable patients are included. Patients with a higher baseline AHI often have a higher BMI (>35) and a complete concentric collapse of the soft palate. Both are negative predictors for surgical success and in case of UAS exclusion criteria. In addition, recent studies found that UAS not only resolves obstruction at tongue base level but also at epiglottic level as well as isolated palatal obstruction (palatal coupling and tethering). Due to its multi-level effect, UAS is in particular suitable for patients with multi-level collapse, which is more often associated with a higher baseline AHI.13 Compared to other surgical treatment options, UAS is dynamic. In general, surgical treatment success depends on wound healing and fibrotic tissue. In the case of UAS, treatment is adjustable (titration) to the patients' need, synchronized with the respiration and surgery does

not cause fibrotic tissue in the upper airway. A recent study suggest that patients with a BMI up to 35 kg/m2 have a positive treatment response with UAS therapy14; these recent findings together with the results of the present analysis, suggest that the current indications for Inspire could be broadened.

One remarkable finding was that treatment adherence was significantly lower in patients with an AHI>65. In general, adults with severe disease tend to be more adherent to treatment due to a combination of relatively more self-reported improvement and the understanding of long-term consequences of untreated severe disease.15 In CPAP use, severe disease is a predictor for adherence.16, 17 We hypothesize that this is related to therapy response and airway collapsibility. We experienced that patients with a higher baseline AHI require higher stimulation levels, potentially leading to treatment discomfort. The functional higher amplitudes are likely due to greater collapsibility of the airway. A recent study of Op de Beeck et al18 illustrated that higher Arousal Threshold leads to an increased tolerability for stimulation and vice versa. Taking this into account, patients with an AHI higher than 65 events/hr in combination with high enough arousal threshold should certainly be good candidates for UAS in the future. Another possible explanation is a slightly higher residual AHI adversely affecting compliance with therapy. Nevertheless, even in the highest disease severity subgroup, treatment use was high (4.7 hours/night) and exceeds the commonly used arbitrary criteria for CPAP adherence of 4 hours per night. Effectiveness of conservative treatment regarding the reduction in AHI depends both on the impact on the airway obstruction and compliance.19 Bearing this in mind we calculated the MDA, representing therapeutic effectiveness, which showed no differences between the subgroups 2-5, the calculated MDA was similar for subgroup 2 and 5 (53.0% and 52.7% respectively). Subgroup 1 had a lower MDA (24%) due to the small change in AHI.

We did not have actual data on usage of the device as percentage of TST and assumed patients sleep seven hours per night.

The positive effect of UAS in patients with an AHI above 50 has important clinical consequences. For one, the findings from this study suggest that patients with an AHI greater than 50 events/hr are suitable candidates for UAS therapy and the chance of improvement of objective and self-reported parameters remains parallel to patients with less severe OSA. The findings are in line with the indications for UAS according to CE mark and FDA approval. This is indeed an avenue that should be

pursued for the patients with AHI>50/hr. This is of particular importance, since these patients need alternative treatment when CPAP is not tolerated, due to the health and functional risks associated with untreated severe OSA.

In subgroup 1 the AHI did not decrease significantly but subjective outcomes significantly improved and did not differ significantly from the other subgroups. However, it remains debatable if patients with an AHI below 15 events/hr and in general less disease burden should be treated in this manner since many other less invasive treatment options are available.

There are limitations to be noted. The ADHERE registry does not record patients who refused participation. The distribution amongst the severity subgroups was not equal. Additionally, the majority of subjects were Caucasian males, which does not represent the general population, influencing external validation. However, it must be noted that due to the strict privacy laws in Europe, documentation of race is not performed as standard of care, it may only be documented when specifically agreed on by the patient. Since the ADHERE registry only collects standard of care date, information on race in Europa remains missing, thereby further influencing report of race of the registry. The chosen stratification is based on OSA severity, reimbursement and FDA approval. While the original STAR trial was a randomized controlled trial with a treatment withdrawal arm after 12 months, the present study is a cohort study. As described previously, both home and in-laboratory studies were used in the analysis, with potential lack of uniformity of AHI recording. Home sleep studies may underestimate AHI—this may have affected both the pre- and post-implantation studies. Therefore, we performed additional analysis, the type of sleep test (HST vs PSG) done at the final visit was significantly different between the five subgroups (p=0.01). However, when controlling for the type of sleep test, change in AHI remains highest in subgroup 5 and final AHI remains lowest in subgroup 1 and there is still no significant difference in response rates between the subgroups. So, while the type of sleep test at final indeed differs between the five AHI groups, it is not the reason why the subgroup's results differ. When interpreting the self-reported results on satisfaction with therapy regarding CPAP versus UAS, one must consider that patients are candidates for UAS if they had CPAP intolerance or failure. Therefore, the chance that they prefer UAS more than CPAP is likely to be higher. There are multiple reasons why a patient may not tolerate CPAP and if not addressed may affect the adherence with UAS treatment. The greatest strength of this study is that the ADHERE registry has a large sample size and is an ongoing international effort.

CONCLUSION

UAS is a safe and effective treatment for moderate to severe OSA, independent of the degree of severity (AHI). This analysis demonstrates that there are no significant differences between the subgroups based on pre-operative disease severity regarding treatment success, excessive daytime sleepiness symptoms (ESS) or self-reported improvement (CGI-I). Mean therapy usage in each subgroup is at least 4.7 hours per night. Patient satisfaction remains high in all subgroups. These results support the broader indication for UAS therapy, in patients with an AHI above 50 and even above 65 per hour sleep. These are the patients with the highest burden of disease, wherefore no other effective treatment options are available in case of CPAP failure.

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