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Upper Airway Stimulation for Obstructive Sleep Apnea: Results from the ADHERE Registry

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Abstract

Objective. Upper airway stimulation (UAS) is an alternative treatment option for patients unable to tolerate continuous positive airway pressure (CPAP) for the treatment of obstructive sleep apnea (OSA). Studies support the safety and efficacy of this therapy. The aim of this registry is to collect retrospective and prospective objective and subjective outcome measures across multiple institutions in the United States and Germany. To date, it represents the largest cohort of patients studied with this therapy.

Study Design. Retrospective and prospective registry study.

Setting. Ten tertiary care hospitals in the United States and Germany.

Subjects and Methods. Patients were included who had moderate to severe OSA, were intolerant to CPAP, and were undergoing UAS implantation. Baseline demographic and sleep study data were collected. Objective and subjective treatment outcomes, adverse events, and patient and physician satisfaction were reviewed.

Results. The registry enrolled 301 patients between October 2016 and September 2017. Mean ± SD AHI decreased from 35.6 ± 15.3 to 10.2 ± 12.9 events per hour ($P < .0001$), and Epworth Sleepiness Scale scores decreased from 11.9 ± 5.5 to 7.5 ± 4.7 ($P < .0001$) from baseline to the posttitration visit. Patients utilized therapy for 6.5 hours per night. There were low rates of procedure- and device-related complications. Clinical global impression scores demonstrated that the majority of physicians (94%) saw improvement in their patients' symptoms with therapy. The majority of patients (90%) were more satisfied with UAS than CPAP.

Conclusions. Across a multi-institutional registry, UAS therapy demonstrates significant improvement in subjective and objective OSA outcomes, good therapy adherence, and high patient satisfaction.

Keywords

obstructive sleep apnea, OSA, sleep apnea, upper airway stimulation

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Obstructive sleep apnea (OSA) is a disease characterized by recurrent episodes of upper airway obstruction during sleep. The disruption in airflow caused by OSA has been associated with multiple comorbidities, including hypertension, cardiovascular disease, cardiac arrhythmia, cerebrovascular disease, excessive daytime sleepiness, and mood disorders.[1-3] Continuous positive airway pressure (CPAP) has long been the primary treatment modality of choice for OSA, showing improvements in many comorbidities.[4-7] Unfortunately, despite attempts to improve compliance, many people are unable to tolerate treatment with CPAP. Based on a definition of CPAP use for 4 hours per night, adherence rates were shown to range from 29% to 83% and decrease over the course of a year of use.[8,9] Because of the large percentage of patients not tolerating CPAP, alternative treatment strategies are necessary.

The concept of stimulating the tongue musculature to increase upper airway size and limit the pathophysiologic obstruction leading to OSA was introduced in the late 1980s. A variety of strategies were utilized, including transcutaneous stimulation with placement of electrodes in the submental region, sublingual mucosa, and soft palate.[10-14] However, these studies were limited by their lack of selective stimulation of the primary protrusor of the tongue, the genioglossus muscle. In 2001, Schwartz et al performed a trial in which they selectively stimulated the branches of the hypoglossal nerve, innervating the genioglossus. They noted a significant improvement in the apnea-hypopnea index (AHI) and O_2 desaturation nadir.[15] This technology was subsequently refined, and in 2014 the Stimulation Therapy for Apnea Reduction (STAR) trial was published as the initial clinical trial using upper airway stimulation (UAS) as an alternative therapy to CPAP for treatment of OSA.[16]

As a follow-up to the STAR trial, the ADHERE registry (Adherence and Outcome of Upper Airway Stimulation for OSA International Registry) was designed as a multicenter study to report data among patients undergoing treatment with UAS, with respect to demographics, surgical outcomes, complications, quality of life, and patient-reported outcomes. To date, it represents the largest cohort of patients studied with this therapy.

Methods

Participants

The ADHERE registry is a large multicenter prospective and retrospective observational registry of patients who received an UAS implant in the United States and Germany. The registry is noninterventional; no study-specific procedures or changes to the patient's treatment plan are required for participation. The registry patient cohort includes adults with a history of moderate to severe OSA (AHI, 15-65 events/hour), intolerance or inadequate adherence to CPAP, and favorable anatomic criteria established by previous studies.[16,17] Note that the initial Food and Drug Administration–approved AHI indication for patient selection was between 20 and 65 events per hour. The administration changed the indication in 2017 to 15 to 65 events per hour.

Study Procedures

All registry centers received institutional review board or ethics committee approval. Qualified participants who met implant criteria underwent device implant (Inspire Medical Systems, Inc, Maple Grove, Minnesota). Details of the surgical technique are described in prior publications.[18-20] The implanted system consists of 3 components: a stimulation cuff electrode that encircles the medial branch of the hypoglossal nerve, a pressure-sensing lead placed within the fourth or fifth intercostal space, and an implantable pulse generator inserted into a subcutaneous pocket beneath the clavicle. The therapy is designed to sense ventilatory effort and provide stimulation to the hypoglossal nerve during inspiration.

The device was activated 1 month after the implant procedure. During the first month of at-home use, participants gradually increased the stimulation amplitude to facilitate therapy acclimatization and to optimize comfort and subjective effectiveness. Between 2 and 6 months following implant, an in-laboratory polysomnography (PSG) titration studies were conducted to optimize therapy. When 1 in-laboratory titration could not establish the therapeutic setting for a patient, the sleep laboratory could conduct additional titration studies. The main reasons for additional studies included lack of therapy response and not enough sleep time for titration. Among 301 patients enrolled, 25 patients had an additional in-office adjustment or in-laboratory titration.

To assess therapy efficacy in the context of clinical practices, the registry collected data from a home sleep apnea test (HST), if it was available after the therapy titration study. Many clinical sites conducted a scheduled HST at 6 and 12 months postimplant as a part of their routine practice. All patients underwent initial in-laboratory titration PSG. Some patients underwent an additional HST (n = 83 of 295) after the titration PSG. The AHI from the HST of these patients was included in the posttitration visit data collection.

The data for this registry report were collected at the posttitration office visit. The posttitration visit occurs after the therapy has been optimally titrated, approximately 2 to 6 months after implant. In general, it is the first office visit after titration. The mean and median follow-up duration was 134 and 123 days after implant, respectively

To accommodate ''real world'' experience with a UAS implant, prospective and retrospective data were collected after patients provided informed consent. Patients receiving a UAS implant were informed and given the option to participate, and patients previously implanted with the UAS system were invited to participate after providing informed consent, at which time their data were collected from medical records. For patients providing consent after the posttitration visit, all data were collected retrospectively; for patients providing consent after the implant but before the posttitration visit, only the posttitration data were collected prospectively; for patients providing consent before the preimplant visit, all data were collected prospectively.

Outcome measures included the baseline AHI collected prior to the UAS implant and the treatment AHI posttitration. The treatment AHI, or AHI measured under the therapeutic setting, was assessed during an HST, an in-laboratory PSG, during the initial titration PSG, or during an additional titration PSG, sometimes called ''advanced'' titration. If the treatment AHI was collected during a titration PSG, it was the AHI from the portion of sleep when the therapy was under the therapeutic setting found for home use.

Therapy use, reported as hours of use per night, was reported by the implanted device and collected upon interrogation of the device in the clinic at the posttitration visit. Patient-reported outcomes were collected at baseline and posttitration visit, which include the Epworth Sleepiness Scale (ESS) and a custom-designed survey for patient experiences with therapy. Clinical Global Impression–Improvement is a common measure of how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention. The measure was recorded by the physician at each follow-up visit.

The occurrence of adverse events was monitored from implant through follow-up visits to assess procedure and device safety. For the registry, a reportable adverse event includes any event related or possibly related to the Inspire procedure or Inspire therapy that occurs at a level, intensity, or time frame greater than expected.

Statistical Analysis

Outcome measures of AHI and ESS from follow-up visits were compared with the baseline measurements. 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 in mean ± SD and 95% CIs.

Results

Between October 2016 and September 2017, a total of 301 participants were enrolled from 10 centers. The study cohort consisted of a middle-aged and primarily male (82%), Caucasian (97%), and overweight population (**Table 1**). Of the 301 participants, 34 had baseline AHI of 15 to 20 events per hour. Based on information provided by the sponsor, approximately 64% of the implanted population at all registry centers provided consent to participate.

The mean surgical time from 270 reported implant procedures was 146 ± 43 (95% CI, 140.5-150.8) minutes. The most common tongue motion observed during the intraoperative testing was bilateral protrusion (69%), right protrusion (23%), and others (2 cases of left protrusion and unknown in 8%).

Safety Summary

The majority (97% of 301) of procedures were completed without a report of an adverse event. There were 2 cases of intraoperative bleeding during tunneling of the stimulation lead, both stopped by application of pressure. Two cases of seroma were noted, and both resolved without sequela. Submandibular swelling, tongue weakness, and dysarthria each developed in 1 patient, which all resolved. One patient had a dislodged stimulation cuff at the activation visit, 1 month postimplant, which required revision to replace the lead (**Table 2**).

At the posttitration visit, 63 adverse events were reported for 54 (18% of 301) patients. No events were perceived to be severe by reporting physicians.

Posttitration Outcome

Posttitration patient outcomes were assessed at a mean 134 ± 76 days (95% CI, 125.4-142.9) and a median 123 days after UAS implant. Mean BMI did not change from baseline to posttitration follow-up (29.2 ± 3.8 to 29.3 ± 4.0 kg/m^2, $P > .05$). Mean AHI decreased from a baseline of 35.6 ±

Table 1. Baseline Characteristics of the Registry Participants.

Demographics	Patients, n (%)
Patients	301
Age, y[a]	59.2 ± 11.2
Sex	
Male	248 (82)
Female	53 (18)
Race	
Caucasian	291 (97)
Other	4 (1)
Black	4 (1)
Asian	1 (<1)
American Indian or Alaska Native	1 (<1)
Body mass index,[a] kg/m^2	29.2 ± 3.8

[a]Mean ± SD.

Table 2. Therapy-Related Adverse Events Reported at the Posttitration Visit.

Type	Events, n	Patients, %
Tongue weakness	1	<1
Swallowing or speech related	2	<1
Discomfort (incision/scar)	3	1
Discomfort (device)	5	2
Infection	—	—
Postoperative (other)[a]	4	1
Stimulation-related discomfort	22	7
Tongue abrasion	6	2
Insomnia/arousal	3	1
Revision interventions (including explant)	1	<1
Other discomfort	3	1
Activation (other)	14	5
Total	64	18[b]

[a]Includes shortness of breath, seroma, numbness of the throat and hoarseness during day, and a mild tongue base and epiglottic obstruction.
[b]A total of 54 patients reported adverse events at the posttitration visit.

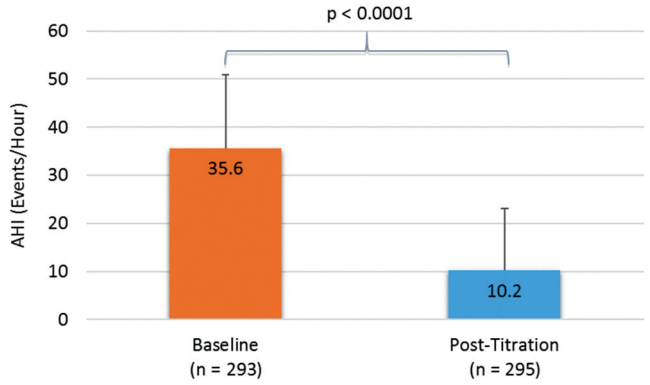

Figure 1. Changes of apnea-hypopnea index (AHI) from baseline to posttitration visit. Results are presented as mean ± SD.

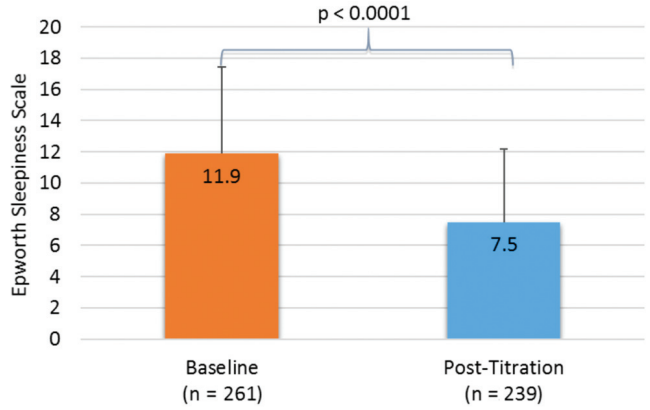

Figure 2. Changes in daytime sleepiness measured by Epworth Sleepiness Scale. Results are presented as mean ± SD.

15.3 events per hour (33.8-37.3) to 10.2 ± 12.9 (8.7-11.7) at posttitration ($P < .0001$) with a median AHI decreasing from 32.5 to 5.5 events per hour (**Figure 1**). The absolute AHI reduction from baseline was –25.3 ± 16.4 events per hour (–27.2 to –23.4) and a relative reduction of 71% ± 34% (67%-75%). AHI reduced by at least 50% to <20 in 78% of patients. At posttitration, AHI ≤5, ≤10, or ≤15 events per hour was achieved in 48%, 67%, and 81% of patients, respectively.

ESS decreased from 11.9 ± 5.5 (95% CI, 11.2-12.6) at baseline to 7.5 ± 4.7 (6.9-8.1) at posttitration ($P < .0001$) with a median reduced from 12 to 7. Patients with ESS <10 increased from 38% to 67% at baseline to posttitration (**Figure 2**).

There was no difference between the AHI and ESS data collected retrospectively from the medical record versus those collected prospectively. The AHI was 10.3 ± 13.5 (95% CI, 8.4-12.2) among 98 patients with retrospective data and 10.0 ± 11.5 (7.7-12.3) from 197 with prospective data collection. ESS was 7.5 ± 4.5 (6.8-8.2) among 84 patients with retrospective data and 7.4 ± 5.9 (6.3-8.5) from 155 patients with prospective data collection.

The AHI at the posttitration visit was collected from an HST or a PSG. If the AHI was collected during a titration

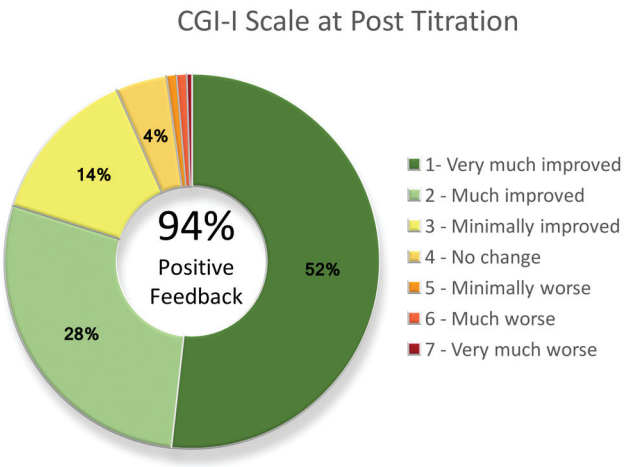

Figure 3. Clinical Global Impression–Improvement (CGI-I) rated by the physician at the posttitration visit.

PSG, the AHI was used from the portion of sleep when therapy was under therapeutic settings for home use. The AHI was 9.1 ± 12.4 (95% CI, 7.4-10.8) among 212 patients with PSG, which is lower than the AHI of 12.9 ± 13.8 (10.0-15.9) among 83 patients with HST ($P = .02$).

The objective adherence monitoring was interrogated from device registration and showed an average home device use of 6.5 ± 2.3 hours per night (95% CI, 6.1-6.9). The median use was 46 hours per week. The therapy use was reported as the cumulative hours of use since last device check, and 96% of patients had therapy use >20 hours per week

For clinical global impression, 94% physicians rated patients' OSA as having improved relative to baseline prior to UAS implant (**Figure 3**).

For patient-reported response to therapy experience, 90% of patients reported a better experience than CPAP; 96% would choose the procedure again; 94% would recommend the procedure to a friend or family member; and overall 92% were satisfied with the UAS therapy (**Figure 4**).

Discussion

UAS therapy takes advantage of the branching and innervation pattern of the hypoglossal nerve, to selectively stimulate the protrusor and stiffening muscles of the tongue. During implantation, the stimulation lead is placed distally along the hypoglossal nerve to selectively stimulate the genioglossus and the transverse and vertical intrinsic muscles of the tongue. Stimulation is linked to respiration, to alleviate upper airway obstruction with each breath. The initial publication of the STAR trial cohort in 2014 showed a significant improvement in AHI, oxygen desaturation index, ESS, and Functional Outcomes of Sleep Questionnaire (FOSQ) scores after 12 months of therapy (vs baseline).[16] This cohort has been followed, and data reviewed at 18-, 24-, 36-, and 48-month publications showed endurance of the improvement in objective PSG measures and subjective ESS and FOSQ scores.[21-24]

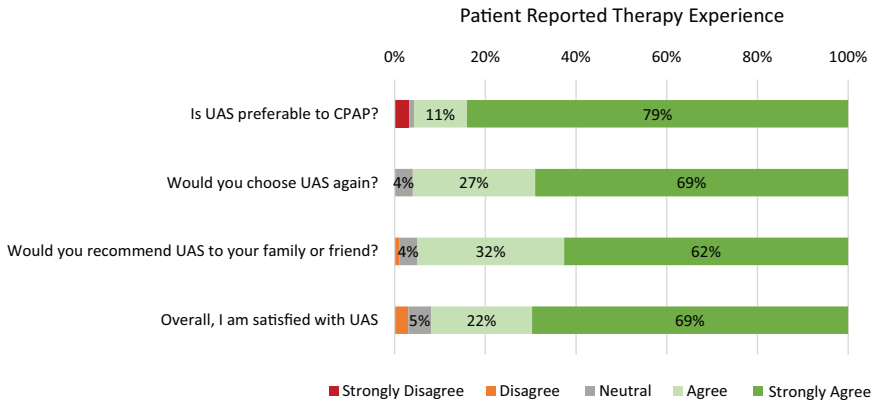

Figure 4. Patient report on therapy experience: 5% reported an insufficient experience with continuous positive airway pressure (CPAP) as compared with upper airway stimulation (UAS).

As a follow-up to the STAR trial data, single- and multicenter clinical data have been published. These studies corroborated the STAR trial findings, with improvements in apnea burden and low rates of device- and procedure-related complications. Kent et al evaluated 20 patients undergoing UAS implantation and found a significant improvement in AHI and ESS with treatment.[25] Heiser et al reviewed a cohort of 31 patients and found the mean AHI to decline from a baseline of 32.9 to 11.5 events per hour at the whole-night titration PSG. This was followed by HST at 6 and 12 months showing treatment AHIs of 7.6 and 7.1 events per hour, respectively.[26] The German postmarket study evaluated patients at 3 centers with baseline HST and again at 6 months after therapy. It revealed significant improvement in ESS and FOSQ scores with a drop in median AHI from 28.6 to 8.3 events per hour. There were minimal procedural and device-related adverse events, all of which resolved.[27] A follow-up to this study, evaluating the same cohort of patients at 12 months after therapy, showed maintenance of treatment benefit with a median AHI of 9.5 events per hour.[28] Huntley et al reviewed and compared the outcomes at 2 high-volume academic centers and found a significant improvement in AHI and ESS at both institutions with comparable results.[29]

In this study, we evaluated surgical variables, adverse events, usage of therapy, outcomes, and patient satisfaction on a large scale across multiple centers. The cohort of patients undergoing implantation consisted largely of overweight Caucasian men. Surgical time was approximately 2.5 hours, with only 3% having an adverse event during surgery. Only 1 patient required repeat intervention to replace a dislodged stimulation cuff. None of the events resulted in any long-term or permanent sequelae.

Very few patients suffered procedure- or device-related adverse events. There were no infections and a very low rate of serious procedure-related adverse events, such as nerve paresis/paralysis, dysphagia, or dysarthria. The majority of these occurrences were classified as mild and resolved by the final visit. Device-related adverse events were also a rare occurrence, consisting mainly of discomfort related to stimulation or tongue abrasions. These were largely classified as mild to moderate in severity and had a high resolution rate by follow-up.

By and large, UAS therapy showed objective success and satisfaction according to the surgeons and patients. There was a significant improvement in AHI and ESS at the 6-month visit as compared with baseline values. The elevated respiratory event index during HST versus titration PSG may be a representation of the full-night evaluation of therapy as opposed to a limited amount of time at therapeutic voltage.

Patients were also found to be utilizing therapy, with a mean nightly usage of 6.5 hours. When surgeons were queried, the majority considered their patients to be significantly improved with therapy. Most patients thought that UAS was a better option than CPAP, would choose UAS again, would recommend it to their family or friends, and were overall very satisfied.

This study further supports the already published evidence showing improvement in objective PSG variables, subjective symptoms, and low complication rates. These findings are even more notable when considering that each of the patients included in all UAS publications have failed therapy with CPAP, the gold standard. By having a successful alternative treatment option for patients with OSA, we are able to reach a large proportion of patients currently going untreated.

We recognize that this study is limited by certain aspects of its design. The study consists largely of overweight Caucasian men, which is likely due to a design issue with the study. Although this represents a large proportion of patients with OSA, many demographic groups are not included our cohort. The AHI outcome data are obtained from a mix of posttitration home sleep apnea testing and titration PSG values scored without a central core laboratory. In addition, the scoring for hypopnea was not standardized in the AHI data collection. This is a clear limitation of a registry. However, it is a representation of real-world clinical practice data. Furthermore, patients in the study consisted of those willing to participate from multiple centers across the United States and Europe. Even though the

registry is intended to enroll consecutive patients, not all patients undergoing implantation were included, introducing an element of selection bias. A prospective study utilizing a core sleep laboratory and enrolling consecutive patients would support our findings.

Conclusions

The ADHERE registry is the largest study of its kind to use UAS. The study demonstrates strong clinical results supporting UAS for treating patients with OSA. Given the continued limitation of CPAP therapy based on adherence, the success of this therapy represents a tremendous advance in the treatment of OSA.

Author Contributions

Maurits Boon, conception, acquisition and analysis of data, drafting and final approval of manuscript; **Colin Huntley,** conception, acquisition and analysis of data, drafting and final approval of manuscript; **Armin Steffen,** acquisition and analysis of data, revising and final approval of manuscript; **Joachim T. Maurer,** acquisition and analysis of data, revising and final approval of manuscript; **J. Ulrich Sommer,** acquisition and analysis of data, revising and final approval of manuscript; **Richard Schwab,** conception, acquisition and analysis of data, revising and final approval of manuscript; **Erica Thaler,** acquisition and analysis of data, revising and final approval of manuscript; **Ryan Soose,** conception, acquisition and analysis of data, revising and final approval of manuscript; **Courtney Chou,** acquisition and analysis of data, revising and final approval of manuscript; **Patrick Strollo,** conception, acquisition and analysis of data, revising and final approval of manuscript; **Eric J. Kezirian**, acquisition and analysis of data, revising and final approval of manuscript; **Stanley Chia,** acquisition and analysis of data, revising and final approval of manuscript; **Kirk Withrow,** acquisition and analysis of data, revising and final approval of manuscript; **Mark Weidenbecher,** acquisition and analysis of data, revising and final approval of manuscript; **Kingman Strohl,** conception, acquisition and analysis of data, revising and final approval of manuscript; **Karl Doghramji,** conception, acquisition and analysis of data, revising and final approval of manuscript; **Benedikt Hofauer,** acquisition and analysis of data, revising and final approval of manuscript; **Clemens Heiser,** conception, acquisition and analysis of data, drafting and final approval of manuscript.

Disclosures

Competing interests: Maurits Boon, Inspire Medical Systems (honoraria, consultancy); Armin Steffen, Inspire Medical Systems (travel costs, speaker's royalties, study funding), ResMed (travel costs, study funding); Joachim T. Maurer, Inspire Medical Systems (consultant, research funding, invited speaker), Nyxoah (consultant), ImThera (research funding, invited speaker), MED-EL (research funding); J. Ulrich Sommer, Inspire Medical Systems, ImThera Medical, Nyxoah (consultant, grants); Richard Schwab, Inspire Medical Systems (honoraria, research grant); Erica Thaler, Inspire Medical Systems (honoraria, consultant); Ryan Soose, Inspire Medical Systems (honoraria, consultant), STAR (trial investigator), Galvani Bioelectronics (consultancy); Patrick Strollo, Inspire Medical Systems (consultant, honoraria), Jazz Pharmaceuticals (advisory board, research grant), Emmi Solutions (advisory board), Belluscura (consultant); Eric J. Kezirian, Inspire Medical Systems (honoraria), Nyxoah, Berando Scientific, Cognition Life Science, Split Rock Scientific, Gerard Scientific, ReVENT Medical (consultant, equity), Magnep (patent ownership); Kirk Withrow, Inspire Medical Systems (honoraria, consultant); Karl Doghramji, Inspire Medical Systems (honoraria, consultant); Benedikt Hofauer, Inspire Medical Systems (travel expenses, conference fees); Clemens Heiser, Inspire Medical Systems (honoraria, consultant).

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