This is a "preproof" accepted article for The Journal of Laryngology & Otology
This version may be subject to change during the production process.
10.1017/S0022215125000295

Hypoglossal Nerve Stimulation in Patients Outside the STAR Trial Criteria – A Systematic Review

Lim Tze Xin Pamela[1], Gui Chuan Hao[2], Tan Soon Heng Terry[2]

[1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[2]Department of Otorhinolaryngology, Woodlands Health, Singapore

Author for correspondence:

Lim Tze Xin Pamela

21 Lower Kent Ridge Rd, Singapore 119077

Email: pamlimtx@gmail.com

This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (http://creativecommons.org/licenses/by/4.0), which permits unrestricted re- use, distribution and reproduction, provided the original article is properly cited.

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

Abstract

Objective: To evaluate if there is a role for hypoglossal nerve stimulation outside the original STAR trial criteria.

Methods: This review was conducted using PubMed, Embase and Cochrane Library databases.

Results: Hypoglossal nerve stimulation led to improved outcomes in individuals who fell outside the STAR trial criteria for apnoea-hypopnea index and body mass index. However, this improvement did not extend to patients with complete concentric palatal collapse or those with a significant central apnea component.

Conclusion: Hypoglossal nerve stimulation can be effective in patients outside the original STAR trial criteria for certain parameters. Further research is needed to refine patient selection criteria for optimal outcomes.

Keywords: Hypoglossal Nerve Stimulation, Upper Airway Stimulation, Stimulation Therapy for Apnea Reduction Trial, Food and Drug Administration

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

1. Introduction

Obstructive sleep apnea (OSA) is a condition that affects almost one billion adults worldwide. [1] It is characterised by recurring episodes of partial or complete airway collapse during sleep. In response, the brain is aroused, the sympathetic system is activated and oxygen is desaturated in the blood. [2] Individuals with OSA often report snoring, insomnia, lethargy or excessive daytime sleepiness (EDS). [1 2]

Aside from its repercussions on sleep, it can result in cerebrovascular disorders, cardiovascular disorders, psychological disorders, neurological deficits and decreased work productivity. [3] Severe OSA is a significant independent predictor of cardiovascular and all-cause mortality. [3] The effect on excessive daytime sleepiness has contributed to motor and occupational accidents. Thus, OSA poses a substantial challenge to global health. [3]

The prevalence of OSA has been increasing over time, with a higher prevalence in males compared to females. [2] This increase can be partly attributed to rising obesity rates, which is a significant risk factor for OSA. [2] Other risk factors include higher body mass index (BMI), alcohol and exposure to second-hand smoke. [3]

The severity of OSA is usually determined by apnea-hypopnea index (AHI), which is the number of respiratory events divided by the number of hours of sleep on a polysomnography study. [4 5] Apnea is defined as "a drop in peak signal excursion by ≥90% of pre-event baseline for ≥10s using an oronasal thermal signal (recommended sensor), positive airway pressure (PAP) device flow, or an alternative apnea sensor; without requirement for a desaturation or an arousal". [5] Hypopnea is defined as "a drop in peak signal excursion by ≥30% of pre-event baseline for ≥10 seconds using nasal pressure (recommended sensor), PAP device flow, or an

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

alternative hypopnea sensor, AND a ≥3% oxygen desaturation from the pre-event baseline OR the event is associated with an electroencephalogram (EEG, cortical) arousal." [5] Mild, moderate and severe OSA are defined as ≥5 to <15, ≥15 to <30, and ≥30 (events/h) respectively. [5]

The gold standard treatment modality is a continuous positive airway pressure (CPAP) machine, in which the user wears a nasal mask overnight during sleep to keep the airway open. [4] It is indicated in moderate to severe disease independent of symptoms or in lower AHI accompanied with EDS. [4] Poor tolerance to CPAP has paved the way for the development of alternative treatments. [4]

In terms of other treatment modalities, lifestyle changes and weight loss are recommended for all overweight or obese patients; positional therapy is used in patients whose respiratory events occur nearly exclusively when supine; mandibular advancement devices are indicated in mild to moderate disease, with tongue-base collapse on drug-induced sleep endoscopy (DISE) or CPAP refusal. [4] Surgical management may be indicated for OSA of any severity, which may include procedures such as uvulopalatopharyngoplasty and maxillomandibular advancement surgery. [6] Apart from these, hypoglossal nerve stimulation (HGNS) has also emerged as a surgical option. [4]

HGNS, otherwise known as upper airway stimulation, is a device that is implanted in the chest underneath the skin, it initiates electrical impulses which is transmitted to the hypoglossal nerve. [7] In 1993, Schwartz et al. were the first to introduce the concept of HGNS, testing its effects on upper airway collapsibility in cats. [8] Several companies have produced HGNS systems, including the Apnex device (Apnex Medical, MN USA), the ImThera device

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

(LivaNova, London UK), the Nyxoah Genio device. Thus far, only one company has obtained Food and Drug Administration (FDA) approval for their system: the Inspire II (Inspire Medical Systems, MN, USA). [5]

Compared to the aforementioned other modalities, HGNS has a much more stringent criteria for usage. The initial criteria for HGNS was derived from early feasibility studies and the Stimulation Therapy for Apnea Reduction (STAR) trial, which laid the framework for the FDA to determine their candidacy recommendations for Inspire II (Inspire Medical Systems, MN, USA). [5] In the STAR trial, patients were chosen based on feasibility trials whereby BMI ≤32 kg/m^2 and AHI ≤50 events/h were met with better outcomes, and two small studies (*n* of 7 and 21 patients) which found that HGNS was ineffective if there was palate level complete concentric collapse (CCC) on DISE. [5]

A comparison of the STAR trial criteria and the initial FDA guidelines is presented in Table I. The STAR trial was a multi-institutional single group trial with 126 patients who were not compliant to CPAP with the following: BMI <32kg/m^2, 20<AHI<50, central or mixed apnea events <25% of all apneic events, AHI in non-supine position >10 events/h. [5] Exclusion criteria included individuals with tonsil size 3 or 4 or palate CCC on DISE. [5]

Although the STAR trial only included patients with BMI <32kg/m^2, the FDA indications do not regard BMI as a definitive criterion for candidacy. [5] The initial FDA criteria suggested that HGNS is indicated for individuals ≥18 years old with moderate to severe OSA with failure or intolerance to PAP treatment, <25% events that are central or mixed apneas and no soft palate CCC. [5]

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

The eligibility criteria for HGNS is still being evaluated as new literature continues to emerge. [5] As such, the aim of this study is to evaluate whether there is a role for HGNS in patients that may lie outside the original STAR trial criteria.

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

2. Materials and Methods

2.1 Study Design and Search Strategy

This systematic review was conducted in accordance with the latest 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. [9] To identify relevant studies, a comprehensive search was performed on PubMed, Embase and Cochrane Library databases on 1 July 2024. The search strategy used the following combination of terms "hypoglossal nerve stimulation" or “HGNS” or “HNS” or “upper airway stimulation” or “UAS”, and “Food and Drug Administration” or "FDA" or “Stimulation Therapy for Apnea Reduction” or “Stimulation Therapy for Apnea Reduction Trial” or "STAR" or "STAR Trial". Only studies published in English were included. Shortlisted studies were reviewed thereafter to assess the suitability for inclusion. To allow for a comprehensive search, we also reviewed the references of all relevant articles.

2.2 Inclusion Criteria

Both prospective and retrospective studies were included. Only studies investigating HGNS in patients outside the original STAR trial criteria and those investigating HGNS in a subgroup of such patients were included. Studies were required to report demographic and clinical details, such as patient age, gender, baseline apnea-hypopnea index (AHI), body mass index (BMI), upper airway collapse pattern on DISE and surgical technique. For duplicated studies, the most comprehensive and recent report was chosen.

2.3 Exclusion Criteria

Our review excluded studies about OSA in the Paediatric Down Syndrome population and studies exclusively reporting on patients within the STAR trial criteria.

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

3. Results

The initial systematic search identified 334 studies (Figure I). After removing duplicates, 306 studies remained. Two independent researchers (Lim and Gui) then screened the titles and abstracts of these studies, eventually identifying 21 full-text articles that were relevant to this study. Upon review of the full-texts, 7 studies were included in this systematic review. [10-16] A flowchart illustrating the study selection process, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, is presented in Figure I.

These 7 studies consisted of 5 case series (3 prospective, 2 retrospective), 1 retrospective case-control and 1 case report. A total of 88 participants were included in this systematic review. Regarding the level of evidence, one study was classified as level 3, five studies as level 4 and one study as level 5. The characteristics of the included studies are detailed in Table II.

3.1 Technical Specifications of Hypoglossal Nerve Stimulation Systems

The following HGNS systems were used: Inspire I stimulating system (Medtronic Inc, Minneapolis, Minn), Inspire II Upper Airway Stimulation (UAS) system (Inspire Medical Systems, Maple Grove, MN). The Inspire I system has an implantable intrathoracic pressure sensor, a programmable pulse generator and a stimulating electrode. [10] In contrast, the Inspire II system has a respiration sensor, programmable implanted pulse generator (IPG) and a stimulating electrode. [11] Similarly, both systems use electrodes to deliver an electrical current to the hypoglossal nerve before and during the inspiratory phase, which is detected by their respective sensors. External programming devices are used in both systems to adjust parameters. The key differences are in the electrode design (Inspire I uses a platinum

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

electrode while Inspire II uses a platinum/iridium electrode) and how respiratory signals are detected (Inspire I uses a intrathoracic pressure sensor whereas Inspire II uses the IPG). [10, 11]

3.2 Factors Outside the STAR Trial Criteria

Of the seven studies, three investigated patients with an elevated AHI [10, 11, 15] and one evaluated patients with both an elevated and reduced AHI [12]. Three studies assessed patients with elevated BMI. [11, 12, 14] Two reported on CCC at the soft palate. [11, 16] Two investigated the effects when the contribution of central apnea to AHI was greater than 25%. [12, 13]

3.3 Outcomes

The majority of the studies did not focus exclusively on patients outside the STAR trial criteria. Consequently, some data could not be extracted as the information was not categorised into subgroups.

The objective outcomes evaluated were AHI, obstructive AHI (oAHI), oxygen desaturation index (ODI), arterial oxygen saturation (SaO2), oxygen nadir (O2 nadir), oxyhemoglobin nadir, central apnea index (CAI), arousal index, stimulation parameters, breathing parameters and sleep architecture. It is worthwhile to recognise that AHI measurement serves two purposes: the baseline AHI is a factor that can affect the efficacy of HGNS and the post-operative AHI is measured to assess the effectiveness of HGNS. All of the studies used AHI for the latter purpose. All included studies reported the baseline AHI.

The subjective outcomes assessed included the Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ). Additionally, the treatment success rate was also reported, defined as the criteria established by Sher et al (≥50% reduction in AHI from baseline and post-treatment AHI <20). [17]

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

3.3.1 Elevated or reduced AHI as a factor

Of the seven included studies, four [10-12, 15] included patients whose baseline AHI fell outside the STAR trial criteria, which is defined as AHI of >20 and <50. All four studies [10-12, 15] included patients with a pre-operative AHI greater than 50, while only one study [12] included patients with a pre-operative AHI below 20.

Two out of the four studies [10, 15] concluded that elevated pre-operative AHI levels, even those outside the STAR criteria, are associated with favourable post-operative outcomes. Thaler et al. [15] described how patients with AHI > 50 had significant improvements, with mean postoperative AHI of ≤10. With a baseline mean AHI of 67.2 ± 26.1, AHI was reduced to 5.7 ± 3.9 post-implant, achieving a 91.39% ± 4.46 reduction. Schwartz et al. [10] reported a mean reduction in NREM AHI of 58.1% ± 26.1 following the implantation of HGNS in a subgroup of patients with a baseline AHI of 124.5 ± 25.3. However, data on the total AHI (the sum of NREM AHI and REM AHI) were not reported, and no information regarding treatment success according to Sher's Criteria is available. One study by Sarber et al. [12] reported mixed results, concluding that patients with an AHI ≥ 65 experienced a 50% surgical success rate. A study by Van de Heyning et al. [11] showed contrasting results. In this two-part study design, participants in the first group were initially enrolled using broad selection criteria and evaluated for factors affecting treatment success after HGNS insertion. These factors were then applied in the second group to assess their impact on response. In the first group, patients with an AHI > 50 (baseline AHI of 51.1 ± 16.8) experienced poorer outcomes following HGNS insertion compared to those with an AHI between 20 and 50 (baseline AHI of 26.1 ± 5.0).

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

In the only study evaluating the effect of reduced AHI, Sarber et al. [12] reported a 100% surgical success rate in patients with an AHI < 15.

3.3.2 Elevated BMI as a factor

Two studies [12, 14] evaluated patients with a BMI ≥32, which falls outside of the STAR trial criteria.

Both studies demonstrated that an elevated BMI has positive post-operative outcomes. A case-control study by Huntley et al. [14] reported no difference in post-operative AHI between patients with elevated and non-elevated BMI (6.51 ± 8.26 vs. 5.60 ± 8.95, P = 0.441). Success rates were comparable, with 92.30% in the elevated BMI group and 95.40% in the non-elevated BMI group (P = 0.345). Additionally, outcomes such as oxygen desaturation nadir and ESS scores did not differ significantly between groups. Sarber et al. [12] presented similar findings, noting a 91.7% surgical success rate among patients with a BMI >32 and a post-operative AHI of 3.4 ± 3.4.

3.3.3 Complete concentric collapse as a factor

Two studies [11, 16] described patients with CCC, which was excluded in the original STAR trial criteria.

Both concluded that CCC is associated with poor post-operative outcomes. Van de Heyning et al. [11] presented the impact of soft palate CCC in four patients, reporting that they were non-responders at six months post-implantation, with AHI increasing from 39.4 ± 14.9 at baseline to 45.2 ± 20.2. In contrast, three patients without CCC responded well, showing a reduction in AHI from 24.9 ± 5.6 to 5.8 ± 4.8. Likewise, Vanderveken et al. [16] found that patients with

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

CCC experienced no significant AHI improvement six months after HGNS, with AHI increasing from 41.5 ± 13.8 to 48.1 ± 18.7 (P = 0.44).

3.3.4 Central apnea as a factor

Two studies [12, 13] reported on patients with elevated central apnea contributions exceeding the STAR trial criteria (>25%), where total AHI combines both central and obstructive events, represented by the central apnea index (CAI) and obstructive AHI (oAHI). [5]

The outcomes were mixed, with unclear effects of HGNS on central apnea. Although HGNS did not meet the criteria for overall treatment success, it effectively reduced oAHI in both patients, but its impact on CAI varied, decreasing in one patient and increasing in the other. Both patients continued to experience central events post-operatively and developed Cheyne-Stokes breathing.

For the first patient [12], AHI decreased from 102.9 (CAI of 35.5, oAHI of 67.4) to 30.8 (CAI of 5.4, oAHI of 25.4) over six months. This patient had both central and obstructive respiratory events at baseline, suggesting a phenotype of OSA with high loop gain and sleep instability. The second patient [13] initially used continuous positive airway pressure therapy, which was complicated by treatment-emergent central sleep apnea (TESCA). After subsequently undergoing supraglottoplasty and hyoid suspension, his AHI increased from 44.4 (CAI of 12.5, oAHI of 31.9) to 83.8 (CAI of 78.9, oAHI of 4.9) post-HGNS, while his ESS score improved from 11 to 7, and oxygen saturation nadir rose from 78 to 87.

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

3.3.5 Elevated AHI and elevated BMI as a factor

One study [11] studied both elevated AHI (>20) and elevated BMI (≥32), which are outside of the STAR trial criteria. It showed that simultaneously elevated AHI and elevated BMI has worse post-operative objective outcomes, but equivocal subjective outcomes.

Van de Heyning et al. [11] conducted a subgroup analysis demonstrating that patients with a baseline AHI ≤50 and BMI ≤32 were significantly more likely to achieve successful outcomes (P = 0.01), while those not meeting these criteria were less successful. Baseline ESS and FOSQ scores did not differ between groups.

3.3.6 Reduced AHI and complete concentric collapse as a factor

One study [16] evaluated both reduced AHI (<15) and CCC, which are outside of the STAR trial criteria. A concurrently reduced AHI and CCC was associated with poorer post-operative outcomes.

Vanderveken et al. [16] assessed HGNS outcomes in patients with reduced AHI <15, finding a 0% success rate among patients with concurrent palatal CCC, compared to 68.8% among those without CCC. Since AHI <15 falls outside the STAR trial criteria, these results suggest that while HGNS may succeed in cases with reduced AHI alone, the addition of CCC significantly reduces success.

3.4 HGNS device malfunction

Only one study [10] documented instances of device malfunction. These malfunctions were attributed to pulse generator failure, intermittent sensor shutdown, transient asynchronous stimulation due to sensor signal artifact and electrode breakage. It should be noted that this

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

study used the Inspire I device, though it is not specified whether these malfunctions occurred in patients outside the STAR trial criteria.

3.5 HGNS complications

Adverse effects of HGNS were reported in two studies. However, it remains unclear whether these effects occurred in patients outside the STAR trial criteria.

Van De Heyning et al. [11] detailed a case of neck pain and swelling at the incision site post-implantation, which resolved with antibiotics. Another subject required device explantation due to delayed device-related infection. Other minor complications included postoperative pain, stiffness, sore throat, cutaneous stitch abscess, local swelling, fever and lack of tongue response to stimulation within the allowable amplitude range. These all resolved with no intervention. Notably, there was no hypoglossal nerve palsy or pneumothorax.

Sarber et al. [12] described a herpes zoster outbreak on post-operative day 10 and a neck incision skin infection which was treated with oral antibiotics.

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

4. Discussion

The aim of our review was to assess whether HGNS could be beneficial for patients beyond the criteria established in the STAR trial. Published in 2014, the STAR trial cohort showed substantial improvements in objective (AHI, ODI, percentage of sleep spent below 90% saturation) and subjective (daytime sleepiness measured by ESS, snoring levels assessed via bed partner visual analog scores, sleep-related quality of life based on FOSQ) measures of OSA over a five-year period. [16, 18, 19] At the five-year follow-up mark, 75% of the remaining cohort satisfied Sher's criteria for treatment success. The success rate was 63% after accounting for those lost to follow-up. [18]

Since then, the landscape of OSA treatment has evolved, with an increasing body of literature supporting the effectiveness of HGNS in broader patient populations. Recent post-approval single-centre and multi-institutional cohort studies have further validated HGNS as a modality which allows for significant improvements in objective and subjective measures. At the 3-year mark, the Phase IV German Post-Market Study (GPMS) demonstrated a decrease in median AHI from 28.6 to 10, with 67% of the original cohort reporting an AHI <10. [20-22] The ADHERE registry, an ongoing prospective observational study, serves as a database of Inspire patients worldwide. It has reported notable improvements in AHI and ESS, and higher treatment compliance compared to positive airway pressure therapy. The mean AHI reduced from 35.6 to 10.2 while ESS decreased from 11.9 to 7.5. [23] At the 12 month mark, 69% met Sher's criteria. [24] Along with other studies, the ADHERE registry suggested that HGNS is effective in a larger AHI range (>15 and <65), BMI <35 and absent palatal CCC on DISE. [5]

This has informed the latest 2023 FDA guidelines, which has expanded the indications for HGNS. The updated criteria now allow for the treatment of individuals ≥22 years old with

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

moderate to severe OSA (15≤ AHI ≤100) who are intolerant to PAP and do not have soft palate CCC. Furthermore, the new guidelines extend eligibility to the following groups provided they meet the above criteria and additionally, are not adenotonsillectomy candidates and they have been previously considered for other standard alternative treatments. This includes younger patients aged 18 to 21 years old with moderate to severe OSA (15≤ AHI ≤100) and individuals with Down syndrome aged 13 to 18 years old with severe OSA (10≤ AHI ≤50). Additionally, this criteria applies to all individuals: central or mixed events must comprise <25% of all apneic events. The update also specifies a maximum BMI limit of ≤40. [25]

The success rate of the STAR trial was 63% at the five-year follow-up while the ADHERE registry reported a success rate of 69% at the 12-month follow-up. [18, 24] In light of the evolving literature and the updated FDA guidelines, this further reinforces the importance of this study, which aims to evaluate whether HGNS can offer benefits to a wider range of patients beyond those initially included in the STAR trial.

Overall, our review found that HGNS led to improved outcomes in individuals who fell outside the STAR trial criteria for AHI and BMI. However, this improvement did not extend to patients with CCC or those with a significant central apnea component.

4.1 AHI

Determining the likelihood of success with HGNS implantation in patients with an elevated AHI remains challenging. While Schwartz et al. and Thaler et al. [10, 15] suggested that HGNS can still be effective in such cases, Sarber et al. reported mixed outcomes [12] and Van de Heyning et al. [11] found it to be ineffective.

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

It is essential to acknowledge that the study by Schwartz et al. [10] used the NREM AHI as the outcome measure for OSA following implantation. OSA can occur during both rapid eye movement (REM) and non-REM (NREM) sleep, with respiratory events distributed between REM and NREM sleep. Individuals may present with REM-predominant or NREM-predominant OSA. [26-28] REM sleep accounts for approximately only 25% of the total sleep duration. [29] During REM, muscle atonia causes the upper airway to be the most vulnerable to collapse. [26] It is also characterised by prolonged respiratory events, higher oxygen desaturation and lower respiratory effort compared to NREM sleep. [29] AHI is calculated as the total number of apneas and hypopneas per hour during total sleep time. Similarly, the NREM AHI and REM AHI are calculated by the number of events in the respective stages of sleep divided by the duration of NREM and REM time. [30] In reference to the Schwartz et al. study, the total AHI could not be determined because the REM AHI was not reported. Consequently, the NREM AHI alone may not accurately reflect the overall OSA control after implantation as it excludes the REM stage AHI. Moreover, this representation would be further distorted if the patient had REM or NREM-predominant OSA, which would disproportionately elevate the AHI during REM or NREM sleep, rendering NREM an even less reliable metric.

Among studies evaluating elevated AHI, those with higher baseline AHI values [10, 15] were associated with greater treatment success when compared to the study by Van de Heyning et al. [11]. In the first two studies, Schwartz et al. [10] and Thaler et al. [15] reported baseline AHI values of 124.5 ± 25.3 and 67.2 ± 26.1 respectively. Comparatively, Van de Heyning et al. [11] assessed individuals with baseline AHI values of 51.1 ± 16.8, this lower baseline AHI value could have contributed to the poor outcomes following HGNS in these patients. Similar

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

findings were observed in studies by Kent et al. and Renslo et al., where a higher AHI baseline was associated with an increased AHI reduction or treatment response. [30-33] However, it is important to note that Kent et al. reported a mean baseline AHI of 33.8 ± 15.5, which falls within the STAR trial criteria. Therefore, this finding may not be directly applicable to our study, which involves baseline AHI levels exceeding the STAR trial criteria. In contrast, Renslo et al. did not publish their baseline AHI data, making direct comparison challenging.

Overall, the findings suggest that using HGNS may be beneficial for individuals with elevated AHI, further supporting the FDA's decision to expand the guidelines to include a broader range of AHI values.

Conversely, one study found that a lower baseline AHI (<15) was met with successful HGNS implantation. [12] This suggests that patients with mild OSA can benefit from HGNS. However, the high cost, invasiveness and potential discomfort associated with the procedure may not warrant its use. To prevent overtreatment, it is essential to have a comprehensive discussion with patients about the risks and benefits. [34]

4.2 BMI

Two studies [12, 14] reported successful HGNS implantation in patients with elevated BMI. Contrastingly, the ADHERE registry data has suggested an inverse association between BMI and the effectiveness of HGNS, with a 8.5% decrease in the odds of treatment success for every unit of increase in BMI. However, the cutoff for BMI level has not been well-established. [5, 24] Kezirian et al. showed that patients with a BMI <35 experienced a greater reduction in AHI with HGNS. This study employed the use of the Apnex device (Apnex

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

Medical, MN USA) while our research involved the Inspire device, making direct comparisons less applicable. [35] Further data is needed to resolve this inconsistency. Nonetheless, BMI >32 appears to be an indirect predictor of the HGNS response. [36] BMI has a positive correlation with the probability of palatal CCC. [37] Thus, if CCC is excluded on DISE, a higher BMI has minimal effect on the success of HGNS. [34] As such, BMI should be evaluated in tandem with the presence or absence of CCC. Current evidence supports the use of HGNS with BMI <40. [5]

Although current FDA guidelines do not include BMI as a definitive candidacy criterion, some insurance policies continue to adhere to the original STAR trial guidelines, which set a BMI threshold of <32 for coverage eligibility. [5] In view of this, cost has emerged as a significant barrier to the widespread adoption of HGNS. The high cost is primarily due to the cost of the device and the cost of the procedure. [38] The cost of HGNS has been quoted to be approximately 30,000 dollars per individual. [34] The Inspire system has been demonstrated to be cost-effective, lifetime incremental cost-effectiveness ratio (ICER) of $39,471 per quality-adjusted life year (QALY) for patients meeting the STAR trial inclusion criteria. This is below the commonly accepted cost-effectiveness threshold of $40-50K per QALY. However, it is still significantly less cost-effective than CPAP, which has an ICER of $15,915 per QALY. [38] More research should be done to determine the cost-effectiveness of HGNS in patients outside the STAR trial criteria. This would help to inform public health policies and insurance coverage, potentially enabling more individuals to access this treatment modality, particularly those with a high BMI who are currently excluded from coverage. In cases where CCC is absent, these individuals may still benefit from the treatment, as it could prove effective despite their BMI.

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

4.3 Complete concentric collapse

Our findings suggest that HGNS is ineffective for patients with CCC and may even exacerbate OSA. [11, 16] On DISE, CCC is the strongest contraindication to HGNS. Therefore, even when other criteria for HGNS are satisfied, an anatomical pattern of complete concentric collapse is a strong indicator of potential treatment failure. [34] This pattern of collapse is widespread, affecting 20 to 25% of patients who cannot tolerate CPAP and may be candidates for HGNS. [34, 39] There are currently no multi-institutional studies that have showed HGNS success in patients with CCC. [5] Of note, the absence of CCC has been a common requirement in the STAR trial criteria, the original FDA guidelines and the latest 2023 FDA guidelines. In conjunction with our findings, we conclude that CCC is a significant factor that renders HGNS ineffective.

4.4 Central apnea

The requirement that central or mixed events comprise less than 25% of all apneic events has been consistently applied in the STAR trial criteria, the original FDA guidelines and the latest 2023 FDA guidelines. The two studies by Sarber et al. [12, 13] highlighted instances where HGNS failed in patients with a significant central apnea contribution to their total AHI. The effects of HGNS on these patients varies. In one case, the CAI increased while in the other, it decreased. Furthermore, one patient developed central sleep apnea after implantation, which was hypothesised to be due to treatment-emergent central sleep apnea (TECSA). However, both patients showed a reduction in oAHI after implantation. [12] [13] Yan Wang et al. hypothesised that OSA patients with severe daytime sleepiness might be more susceptible to developing TESCA, with an ESS score of 16 or more associated with severe sleepiness. [40] [41] In contrast, the patient who developed TESCA in the Sarber et al. study had an ESS of 11. The ESS score of the other patient who did not develop TESCA was not reported. [13] This

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

suggests that severe daytime sleepiness may not fully explain the risk of developing TESCA. Further research is required to understand the mechanisms behind these variable outcomes.

4.5 Use of HGNS in Paediatric Down Syndrome Population

Our study excluded articles on HGNS in paediatric Down syndrome patients due to the lower prevalence of OSA in children compared to adults, which is estimated to be 1-3%. [5] Although recent FDA guidelines has extended the use of HGNS to individuals with Down syndrome aged 13 to 18 years old with severe OSA ($10 \leq$ AHI ≤ 50), this is a relatively new and specific subgroup. By focusing our study on adult populations, in which OSA is more prevalent, we endeavoured to generate findings that are more broadly applicable to the larger OSA adult population. Further studies on paediatric Down syndrome patients is warranted but were beyond the scope of our current investigation.

4.6 Limitations

In terms of limitations, only one study included was classified as level 3 evidence, which compared two study arms. The remaining studies were predominantly level 4, with one being level 5. This reflects the current state of research in this field, where high-level randomised controlled rials and large cohort studies are limited. However, this study still provides valuable insights, contributing to the expanding body of literature about this topic. Moreover, the majority of studies had a follow-up duration of 6 months. While this provides an understanding on the short-term effects of HGNS, a longer follow-up durations necessary to fully evaluate its long-term efficacy, safety and sustainability of outcomes. Additionally, our

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

review predominantly included male adults, with fewer female patients represented. This is reflective of the known demographic trends of OSA, where males are consistently reported to have a higher prevalence. Furthermore, up to a certain age, the severity of OSA tends to be higher in males when matched with females for BMI. [42] However, the underrepresentation of females may limit the generalisability of these findings to both genders. More studies with a balanced gender distribution will help to evaluate HGNS outcomes across different demographic groups.

4.7 Conclusion

In conclusion, this review suggests the potential of HGNS as an effective treatment for OSA in patients outside the original STAR trial parameters. While these results are promising for patients with AHI and BMI values outside the initial STAR criteria range, caution is warranted in cases involving CCC or a significant central apnea component as the findings related to these factors remain inconclusive. This underscores the need for further research to evaluate the use of HGNS across a wider range of patient demographics and OSA phenotypes. To optimise outcomes, further refinement of patient selection criteria will be crucial. In this regard, the ADHERE registry holds great potential in fulfilling this purpose.

Competing interests. None declared

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

References

1 McNicholas WT, Korkalainen H. Translation of obstructive sleep apnea pathophysiology and phenotypes to personalized treatment: a narrative review. *Frontiers in Neurology* 2023;**14**

2 Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Medicine Reviews* 2017;**34:**70-81

3 Qian Y, Dharmage SC, Hamilton GS, Lodge CJ, Lowe AJ, Zhang J, et al. Longitudinal risk factors for obstructive sleep apnea: A systematic review. *Sleep Medicine Reviews* 2023;**71:**101838

4 Gambino F, Zammuto MM, Virzì A, Conti G, Bonsignore MR. Treatment options in obstructive sleep apnea. *Intern Emerg Med* 2022;**17:**971-8

5 Chang JL, Goldberg AN, Alt JA, Mohammed A, Ashbrook L, Auckley D, et al. International Consensus Statement on Obstructive Sleep Apnea. *International Forum of Allergy & Rhinology* 2023;**13:**1061-482

6 Chang H-P, Chen Y-F, Du J-K. Obstructive sleep apnea treatment in adults. *The Kaohsiung Journal of Medical Sciences* 2020;**36:**7-12

7 Mashaqi S, Patel SI, Combs D, Estep L, Helmick S, Machamer J, et al. The Hypoglossal Nerve Stimulation as a Novel Therapy for Treating Obstructive Sleep Apnea-A Literature Review. *Int J Environ Res Public Health* 2021;**18**

8 Schwartz AR, Thut DC, Russ B, Seelagy M, Yuan X, Brower RG, et al. Effect of electrical stimulation of the hypoglossal nerve on airflow mechanics in the isolated upper airway. *Am Rev Respir Dis* 1993;**147:**1144-50

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

9 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj* 2021;**372:**n71

10 Schwartz AR, Bennett ML, Smith PL, De Backer W, Hedner J, Boudewyns A, et al. Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg* 2001;**127:**1216-23

11 Van de Heyning PH, Badr MS, Baskin JZ, Cramer Bornemann MA, De Backer WA, Dotan Y, et al. Implanted upper airway stimulation device for obstructive sleep apnea. *Laryngoscope* 2012;**122:**1626-33

12 Sarber KM, Chang KW, Ishman SL, Epperson MV, Dhanda Patil R. Hypoglossal Nerve Stimulator Outcomes for Patients Outside the U.S. FDA Recommendations. *Laryngoscope* 2020;**130:**866-72

13 Sarber KM, Ishman SL, Patil RD. Emergence of Cheyne-Stokes Breathing After Hypoglossal Nerve Stimulator Implant in a Patient With Mixed Sleep Apnea. *JAMA Otolaryngol Head Neck Surg* 2019;**145:**389-90

14 Huntley C, Steffen A, Doghramji K, Hofauer B, Heiser C, Boon M. Upper Airway Stimulation in Patients With Obstructive Sleep Apnea and an Elevated Body Mass Index: A Multi-institutional Review. *Laryngoscope* 2018;**128:**2425-8

15 Thaler ER, Schwab RJ. Single-institution experience and learning curve with upper airway stimulation. *Laryngoscope* 2016;**126 Suppl 7:**S17-9

16 Vanderveken OM, Maurer JT, Hohenhorst W, Hamans E, Lin HS, Vroegop AV, et al. 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:**433-8

17 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:**156-77

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

18 Woodson BT, Strohl KP, Soose RJ, Gillespie MB, Maurer JT, de Vries N, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: 5-Year Outcomes. *Otolaryngol Head Neck Surg* 2018;**159:**194-202

19 Strollo PJ, Jr., Gillespie MB, Soose RJ, Maurer JT, de Vries N, Cornelius J, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: Durability of the Treatment Effect at 18 Months. *Sleep* 2015;**38:**1593-8

20 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:**509-15

21 Heiser C, Maurer JT, Hofauer B, Sommer JU, Seitz A, Steffen A. Outcomes of Upper Airway Stimulation for Obstructive Sleep Apnea in a Multicenter German Postmarket Study. *Otolaryngol Head Neck Surg* 2017;**156:**378-84

22 Steffen A, Sommer UJ, Maurer JT, Abrams N, Hofauer B, Heiser C. Long-term follow-up of the German post-market study for upper airway stimulation for obstructive sleep apnea. *Sleep Breath* 2020;**24:**979-84

23 Boon M, Huntley C, Steffen A, Maurer JT, Sommer JU, Schwab R, et al. Upper Airway Stimulation for Obstructive Sleep Apnea: Results from the ADHERE Registry. *Otolaryngol Head Neck Surg* 2018;**159:**379-85

24 Thaler E, Schwab R, Maurer J, Soose R, Larsen C, Stevens S, et al. Results of the ADHERE upper airway stimulation registry and predictors of therapy efficacy. *The Laryngoscope* 2020;**130:**1333-8

25 Inspire Upper Airway Stimulation – P130008/S090. In: https://www.fda.gov/medical-devices/recently-approved-devices/inspire-upper-airway-stimulation-p130008s090

26 Bonsignore MR, Mazzuca E, Baiamonte P, Bouckaert B, Verbeke W, Pevernagie DA. REM sleep obstructive sleep apnoea. *European Respiratory Review* 2024;**33:**230166

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

27 Yamauchi M, Fujita Y, Kumamoto M, Yoshikawa M, Ohnishi Y, Nakano H, et al. Nonrapid Eye Movement-Predominant Obstructive Sleep Apnea: Detection and Mechanism. *J Clin Sleep Med* 2015;**11:**987-93

28 Sattaratpaijit N, Kulalert P, Wongpradit W. Characteristics of rapid eye movement-related obstructive sleep apnea in Thai patients. *Scientific Reports* 2022;**12:**11360

29 Zou J, Liu Y, Xu H, Meng L, Zou J, Qian Y, et al. Association of apnea-hypopnea index during rapid eye movement sleep with insulin resistance in patients with suspected obstructive sleep apnea: a cross-sectional study. *Annals of Translational Medicine* 2020;**9:**243

30 Al Oweidat K, AlRyalat SA, Al-Essa M, Obeidat N. Comparing REM- and NREM-Related Obstructive Sleep Apnea in Jordan: A Cross-Sectional Study. *Can Respir J* 2018;**2018:**9270329

31 Renslo B, Hobelmann K, Sagalow ES, Ananth A, Boon M, Huntley C. Palatal Coupling Maneuvers Do Not Predict Hypoglossal Nerve Stimulator Treatment Efficacy. *The Laryngoscope* 2023;**133:**431-6

32 Tukanov E, Van Loo D, Dieltjens M, Verbraecken J, Vanderveken OM, Op de Beeck S. Baseline Characteristics Associated with Hypoglossal Nerve Stimulation Treatment Outcomes in Patients with Obstructive Sleep Apnea: A Systematic Review. *Life* 2024;**14:**1129

33 Kent DT, Carden KA, Wang L, Lindsell CJ, Ishman SL. Evaluation of Hypoglossal Nerve Stimulation Treatment in Obstructive Sleep Apnea. *JAMA Otolaryngol Head Neck Surg* 2019;**145:**1044-52

34 Baptista PM, Costantino A, Moffa A, Rinaldi V, Casale M. Hypoglossal Nerve Stimulation in the Treatment of Obstructive Sleep Apnea: Patient Selection and New Perspectives. *Nature and Science of Sleep* 2020;**12:**151-9

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

35 Kezirian EJ, Goding GS, Jr., Malhotra A, O'Donoghue FJ, Zammit G, Wheatley JR, et al. Hypoglossal nerve stimulation improves obstructive sleep apnea: 12-month outcomes. *J Sleep Res* 2014;**23:**77-83

36 Steffen A. What makes the responder to upper airway stimulation in obstructive sleep apnea patients with positive airway pressure failure? *Journal of Thoracic Disease* 2018**:**S3131-S4

37 Vroegop AV, Vanderveken OM, Boudewyns AN, Scholman J, Saldien V, Wouters K, et al. Drug-induced sleep endoscopy in sleep-disordered breathing: Report on 1,249 cases. *The Laryngoscope* 2014;**124:**797-802

38 Wray CM, Thaler ER, Gao J. Hypoglossal nerve stimulation for obstructive sleep apnea: A review of the literature. *World Journal of Otorhinolaryngology- Head and Neck Surgery* 2016;**02:**230-3

39 Steffen A, Frenzel H, Wollenberg B, König IR. Patient selection for upper airway stimulation: is concentric collapse in sleep endoscopy predictable? *Sleep and Breathing* 2015;**19:**1373-6

40 Wang Y, Penzel T, Salanitro M, Arens P. Persistent Treatment-Emergent Central Sleep Apnea (TECSA) Following Hypoglossal Nerve Stimulation. *Nat Sci Sleep* 2022;**14:**2227-36

41 Berry RB, Wagner MH. Introduction. In: Berry RB, Wagner MH, eds. *Sleep Medicine Pearls (Third Edition)*. Philadelphia: W.B. Saunders, 2015;181-7

42 Kim SW, Taranto-Montemurro L. When do gender differences begin in obstructive sleep apnea patients? *J Thorac Dis* 2019;**11:**S1147-s9

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

Tables and Figures

Table I: Comparison of the STAR trial criteria and initial FDA guidelines

	Age	AHI	AHI in non-supine position	CPAP	% of central or mixed apneas of all apneic events	Palate CCC	Tonsil size	BMI
STAR trial criteria [1]	NS	>20 and <50	>10	Non-compliance	<25%	None	Excluded if size 3 or 4	<32
Initial FDA guidelines [1]	≥18	≥15	NS	Non-compliance	<25%	None	NS	NS*

AHI = Apnea-Hypopnea Index, CPAP = Continuous Positive Airway Pressure, CCC = Complete Concentric Collapse, BMI = Body Mass Index, NS = Not Specified, FDA = Food and Drug Administration

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

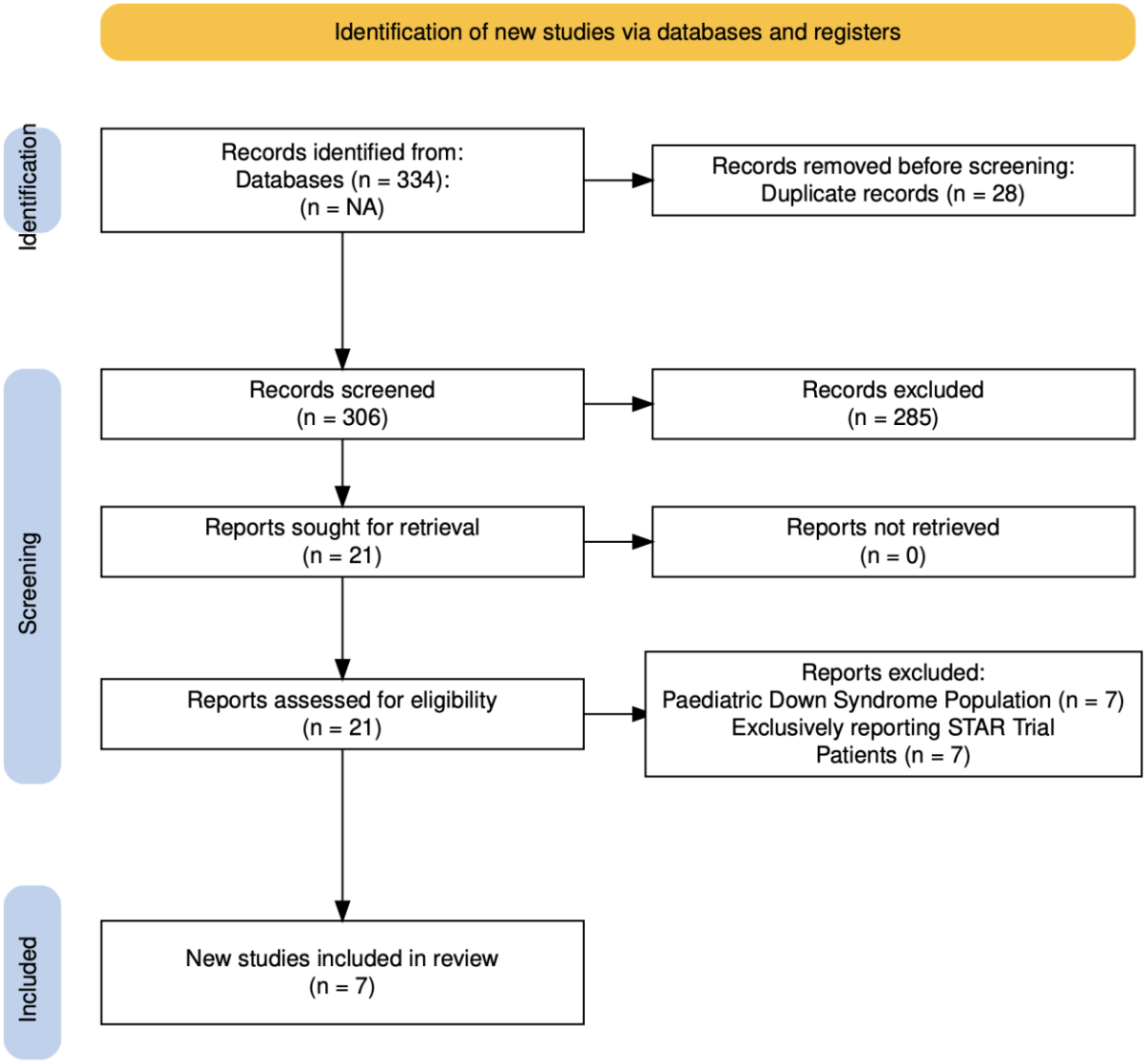

Figure I: Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') 2020 flow diagram [2]

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

Table II: Characteristics of Included Studies

Author, year	Study design	Number of patients outside STAR trial criteria	Number of controls	Mean age	Gender	Follow-up after implantation	Device	Inclusion criteria	Exclusion criteria	Measured outcome	Level of evidence
Sarber et al., 2020 [3]	Retrospective case series	18 1. 4 with AHI <15 2. 4 with AHI >65 3. 12	NA	63 (range of 44 - 82) The median age	17 M, 1F	6 months	Inspire****	AHI ≤15 or >65, BMI ≥32, CAI >25% of total AHI, palatal	-	AHI, ESS, oxyhemoglobin nadir, arousal index, sleep architecture*****	4

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

		with BMI ≥32 4. 2 with CAI >25 % of total AHI		was repo rted.				CCC			
Sarbe r et al., 2019 [4]	Case report	1 with CAI >25 % of total AHI This patie nt was alrea dy	NA	Age with in rang e of 60-69 The actu al age was not	1M	3 mont hs	Inspi re**** *	-	-	AHI, oAHI, CAI, ESS, O2 nadir	5

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

		included in the study by Sarber and was not counted again in the total number of patients.		specified.							
Huntley et	Retrospectiv	40 with	113	59.97 ±	Not spe	2 - 2.5	Inspire***	Intolerant to	No postop	AHI, ESS, O2	3

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

al., 2018 [5]	e case-control	BMI >32		11.50	cified	months	*	CPAP, AHI ≥15, UAS implantation, underwent postoperative sleep study	erative sleep study	nadir	
Thaler et al., 2016 [6]	Retrospective case series	9 with AHI >50 Data was only reported for 7 patie	NA	51.8 ± 13.4	8M, 1F	>2 months***	Inspire****	AHI within and above FDA criteria	-	AHI	4

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

		nts.									
Vandervekeen et al., 2013[7]	Prospective case series	5 with soft palate CCC	NA	55 ± 9	5M	6 months	Inspire II	Intolerant to CPAP, AHI ≥15, BMI <35	COPD, NYHA class III or IV CHF, neuromuscular diseases, prior upper airway surgeries unrelated to OSA	AHI, ESS	4
Van de Heyning et al.,	Prospective case series	Part 1: 9 1. 9 with BMI	NA	Part 1: 55.7 ± 8.1*	Part 1: 9M	6 months	Inspire II	Intolerant to CPAP, BMI <35,	COPD, NYHA class III or IV	AHI, ODI, ESS, FOSQ, sleep	4

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

2012 [8]		>32 or AHI >50 2. 4 with soft palate CCC An overlap was assumed to obtain a total of 9 patie						AHI ≥25	CHF, neuro-muscular diseases, prior upper airway surgeries unrelated to OSA	architecture*****	

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

		nts as the study did not specify whether the 9 patients with a BMI >32 or AHI >50 overlapped with									

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

		the 4 patients with CCC.									
		Part 2: 1 with AHI >50 This patient met all inclusion criteria except for		Part 2: 53.6 ± 11.9 *	Part 2: 7M, 1F**			Intolerant to CPAP, BMI ≤32, 20<AHI<50, no CCC			

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

		AHI.									
Schwartz et al., 2001 [9]	Prospective case series	6 with AHI >50	NA	49.9 ± 8.1*	6M	>6 months***	Inspire I	NREM AI >10, predominantly obstructive apneas	Medical, neuromuscular, otolaryngologic disease	AHI, SaO2, stimulation parameters (amplitude, frequency, pulse width), breathing patterns, sleep architecture****	4

AHI = Apnea-Hypopnea Index (events/hour); AI = Apnea Index (events/hour); oAHI = Obstructive Apnea-Hypopnea Index; BMI = Body Mass Index (kg/m^2); CAI = Central Apnea Index; CCC = Complete Concentric Collapse; CHF = Congestive Heart Failure; COPD =

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press

Chronic Obstructive Pulmonary Disease; CPAP = Continuous Positive Airway Pressure; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; NA = Not Applicable; NREM = Non–Rapid Eye Movement; NYHA = New York Heart Association; ODI = Oxygen Desaturation Index; o2 nadir = Oxygen Saturation Nadir; SaO2 = Arterial Oxygen Saturation; UAS = Upper Airway Stimulation

*The age of patients outside the FDA criteria was not specified. Thus, the mean age reported encompasses all patients, including those within the FDA criteria.

**The gender of the patient was not specified. Thus, the gender described encompasses all patients, including those within the FDA criteria.

***A final follow-up appointment was scheduled after this time period, timing was not specified.

****Not specified whether Inspire I or II was used.

*****Sleep architecture refers to the following parameters: total sleep time, sleep efficiency, % of time in different stages of sleep

https://doi.org/10.1017/S0022215125000295 Published online by Cambridge University Press