Three-year outcomes of cranial nerve stimulation for obstructive sleep apnea : the STAR Trial

3 Year Long Term Outcomes of Cranial Nerve Stimulation for OSA: The STAR TRIAL

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Abstract

Objective:

To describe the long term (36 month) clinical and polysomnographic outcomes in an OSA cohort treated with cranial nerve upper airway stimulation.

Methods:

126 participants were enrolled in a prospective phase III trial evaluating the efficacy of Inspire II (Inspire Medical Systems, Minnesota, USA). Prospective outcomes included AHI, ODI, side effects and self-reported measures including sleepiness (ESS), sleep related quality of life (FOSQ), and snoring, .Data was collected at baseline and t select time points post-device activation. .

Results:

116 of 126 enrolled patients completed 36 month follow up evaluation per protocol. 98 patients additionally agreed to an interval 36 month PSG. Daily device usage was 81%. In the interim PSG group, 74% met the *a priori* definition of success with the primary outcomes of AHI and ODI improved from baseline to 12 and 36 months (32.0±11.8 to 15.3±16.1 and 11.5±13.9 and 28.9±18.2 to 14.0±15.6 and 9.1±11.7, all $p<0.01$). Similarly, self- reported outcomes improved from baseline to 12 months and were maintained at 36 months. Soft or no snoring was reported in 86% at 36 months follow up. From 12 to 36 months, serious device related adverse events were rare with one device related explantion for ineffectiveness.

Conclusion:

Long term 3 year improvements in objective respiratory, self reported sleep, and sleep related quality of life measures are maintained. Adverse events are rare. Cranial nerve stimulation for

the treatment of moderate to severe OSA is a successful and appropriate long term treatment of CPAP intolerant individuals with moderate to severe sleep apnea.

Introduction

Obstructive sleep apnea is a prevalent chronic disease impacting quality of life and sleep and associated with increasing risks of hypertension, cardiovascular disease, metabolic abnormalities, traffic accidents, and mortality.[1,2] Successful treatment improves quality of life reduces associated disease morbidity and is associated with major reductions in downstream health care costs.[3,4] Treatment is a major public health care concern.

The most widely accepted treatment is nasal continuous positive pressure (CPAP). CPAP use improves PSG outcomes, quality of life, and medical morbidities including new onset cardiovascular disease and hypertension.[5,6] Although CPAP is first line treatment of moderate and severe sleep apnea, long term use for many patients is suboptimal. Adherence in several large cohort studies over a time period of 6 months or less is only 39 to 50%.[6,7,8]

Cranial nerve stimulation of the hypoglossal nerve (CNXII) was FDA approved in 2014 for the treatment of moderate and severe OSA in adults. Favorable selection criteria included a BMI < 32, lack of central apnea, and the exclusion of complete concentric palatal collapse during drug induced sedated endoscopy (DISE). Short term results of feasibility trials were favorable and a major prospective trial (STAR Trial) demonstrated a 66% success based on primary outcome measures of AHI and ODI at one year with normalization of many secondary outcome measures.[9] A therapy withdrawal study supported effectiveness at 13 months and treatment durability at 18 months.[10] Self-reported clinical outcomes demonstrate large effects at 24

months.[11] Treatment with upper airway stimulation compared to no treatment is a cost-effective therapy in the U.S. healthcare system.[12]

The current study assesses the long term outcomes and durability of the therapy at 36 months.

Methods

Participants

The STAR trial multicenter cohort included adults with a history of moderate to severe OSA, and intolerance or inadequate adherence to CPAP. Key study exclusion criteria included body mass index > 32 kg/m^2, neuromuscular disease including hypoglossal nerve palsy or injury, severe cardio-pulmonary disorders (chronic obstructive pulmonary disease, pulmonary arterial hypertension, heart failure, persistent uncontrolled hypertension despite medications, a recent myocardial infarction (within 6 months), or severe cardiac arrhythmias, active psychiatric disease, and co-morbid non-respiratory sleep disorders that would confound functional assessments related to sleep.

Participants who met inclusion/exclusion criteria underwent three screening tests: an in-lab attended polysomnography (PSG), a surgical consultation visit, and drug induced sedated endoscopy (DISE). Participants were excluded after the PSG for an AHI less than 20 or greater than 50; central and/or mixed apnea index > 25% of the AHI; or a non-supine AHI < 10. Participants were excluded during surgical consultation if pronounced anatomical abnormalities would prevent effective use or assessment of the device (e.g. tonsil size 3 or 4). During DISE the site and pattern of upper airway collapse under sedation (e.g., propofol), was analyzed and participants were excluded if they had complete concentric collapse at the level of the velopharynx.

Study Procedures

Qualified participants who met pre-implant screening criteria underwent device implantation. Details of the surgical technique are described in a prior publication[13]. The implanted system consists of three components: a stimulation cuff electrode which encircles a distal branch of the right hypoglossal nerve; a pressure sensing lead placed within the fourth or fifth right intercostal space; and an implantable pulse generator inserted into a subcutaneous pocket beneath right mid-clavicle contralateral to the region commonly used in cardiac pacemaker implantation. The therapy is designed to sense ventilator effort and synchronize stimulation to the hypoglossal nerve with inspiration in order to increase airway muscle tone and luminal diameter.

All participants had their device activated one month after the implant procedure. During the first month of home use following device activation, participants gradually increased the stimulation strength for acclimatization tofunctional stimulation. Between two to six months, one or more titration studies were conducted for each participant during in-lab PSG. Additional titration studies were performed in some participants after six months based on previous titration results and participant feedback.

All participants self reported outcomes are followed at 6 month intervals for 5 years. PSGs were collected at both 12 and 18-month follow-up visits per the protocol. In addition, all participants were invited to complete a non-scheduled interval PSG at 36 months. The primary outcomes of AHI and ODI were scored by an independent core lab, using standard 2007 scoring criteria [14,Iber, 2007], with hypopnea scored based on a 30% airflow reduction and a 4% oxygen desaturation. Secondary outcome measures included subjective sleepiness and sleep-related quality of life using the validated Epworth Sleepiness Scale (ESS) and the Functional Outcomes of Sleep

Questionnaire (FOSQ) , respectively. Clinical variables including BMI, neck circumference, and blood pressure were measured at scheduled study visits in order to assess for any changes over the course of the study. Subjective reports of snoring were collected from participants and bed partner on a categorical scale (no snoring, soft snoring, loud snoring, very intense snoring, or bed partner leaves room).

All reported adverse events were reviewed and coded by the Clinical Events Committee. Serious adverse events were defined as any events that led to death, life-threatening illness, permanent impairment, or new or prolonged hospitalization. Adverse events were categorized as procedure-related if related to the surgical procedure or device-related if secondary to use of the device after therapy activation.

Statistical Analysis

The sample size was calculated on the basis of previous studies [15,Van de Heyning PH, 2012]. Approximately 108 participants were required for the primary endpoint evaluation using the exact one-sided binomial test at a significant level of 2.5% with 80% power. For primary outcome, the AHI and ODI at the 12, 18 and 36 month follow-ups were compared to the baseline measurement which was the average of the pre-implant and 1 month pre-activation measurements. A paired t-test was used to evaluate the difference between baseline and 12 months, baseline and 36 months, and between 12 months and 36 months at the 5% significant level.

Results

After enrollment and screening, the original cohort consisted of 126 participants, a total of 124, 123, and 116 completed follow up at the 12, 24, and 36 month visit post-implant, respectively (Table 1). Baseline characteristics and measures did not differ between the follow up cohort patients to the original (baseline) cohort. The mean BMI in the follow up cohort was unchanged from baseline, 12, and 36 months.

Ninety eight participants voluntarily completed an interval PSG study at 36 months. The data collected at this time point did not differ in key baseline and sleep characteristics from the original or 12 month data (Table 1). The primary efficacy outcome measures of AHI and ODI decreased from baseline to the 12 month assessment and these remained stable at 36 months. Mean AHI for the cohort decreased from baseline to 12 months and remained stable at 36 months (32.0±11.8 to 15.3±16.1 and 11.5±13.9 events/hr). ODI demonstrated a small further reduction at 36 months compared to 12 months (Figure 1 and Table 2). Using the Sher criteria (an AHI decrease of $\geq$ 50% to < 20), which was the *a priori* definition of success, 74% of the interim- PSG group achieved a response to treatment. An AHI of less than 5 or 10 events/hr. was observed in 44% and 69% respectively. A total of 51 (52%) showed consistently favorable response at 12, 18 and 36 months while nine (9%) participants did not meet response status at any time period (see appendix). In the 17 non-interim PSG patients, 54% were non-responders at the 12 month evaluation. Using a last visit carried forward (LCVF) analysis from the cohort at 12 months (n=124), the average AHI at 36 months was 14.2 ± 15.9, with median AHI of 7.3, and response rate of 65% (two withdrawn participants are counted as non-responders).

When long term responders and non-responders were compared, univariate analysis demonstrated differences in AHI, ODI, and prior UPPP between groups, however, in a stepwise

logistic model, only AHI remained significantly associated. BMI was not associated with therapy success. (Table 4).

Secondary Outcomes

113 participants completed self-reported outcomes at 36 months. Improvements observed at 12 months persisted at 36 months (Table 3). At baseline, only 33% reported a normal ESS (ESS< 10) and 15% reported a normal FOSQ score (FOSQ > 17.9). At 36 months, this was increased to 76% and 64%, respectively. Improvements in the percent time of SaO2 <90% at 12 months were maintained at 36 months. However, similar to other time point assessments, no changes in sleep stages or sleep efficiency were observed at 36 months.

Long term bedpartner and patient reported subjective snoring reports demonstrated improvement from baseline and were stable at 36 months compared to 12 months. The percentage of no or soft snoring increased from 22% at baseline to 86% at 12 and remained stable at 86% at 36 months (Figure 2). Self-reports of "partner leaving the room due to snoring" were reduced from 30% at baseline to 5% at 12 months and 3% at 36 months. Participants' subjective report of nightly therapy use was at 86% at 12 months and 81%, both at 24- and 36-months. Among the 21 participants who reported not using therapy every night at 36 months, ten reported therapy use for at least four nights each week. Reasons listed by the other 11 participants, who reported less than 4 nights use per week included discomfort related to stimulation (5), forgetting to turn device on (2), other sleep disorders (2), and others (2), onelost his remote and one returned to CPAP.

Adverse Events

The largest number of non-serious adverse events were related to implant procedure and were reported within the first month of implantation and have been previously reported. After 12 months the only serious adverse event were elective device removal due to non-effectiveness (n=1) and due to device unrelated septic arthritis (n=1). Three patients continued to report numbness at the incisional sites after 12 months. Discomfort due to electrical stimulation was reported 80 times in the first year, and 23 and 24 times in the second and third year of the follow-up, respectively. Tongue abrasions caused by movement of the tongue over mandibular dentition decreased from 28 events at the first year to 4 events at the third year. In 12 patients recurrent tongue abrasions or discomfort related to tongue movement along the teeth were successfully treated with plastic dental guards. After an average follow up of 40 ± 6 months (range 10 to 51 months), there two additional device or disease unrelated deaths (1 cardiac arrest after a fall, and 1 homicide). Three participants were lost to follow up. A detailed list of adverse events is provided in the supplemental appendix.

Discussion

The objective of the current study was to assess the long term clinical effectiveness of cranial nerve stimulation of the hypoglossal nerve using the Inspire^{TM} Implant System (Inspire Medical Systems, Minneapolis, MN, USA). In a prospectively followed cohort, improvements at 36 months were observed in both objective primary metrics (AHI and ODI) and in secondary outcomes. Improvements observed at 12 months were sustained at 3 years follow up. 116 subjects completed the scheduled 36 month follow up. An additional 98 patients also

volunteered for an interval 36 month PSG. For the group having a 36 month PSG, mean AHI decreased from 30.4 ± 10.4 events/hr at baseline to 13.5 ± 14.3 at 12 months and 11.5 ± 13.9 at 36 months. The data support an ongoing long term clinical effectiveness of the device.

The goal of OSA treatment is not only to improve surrogate sleep study metrics but also to improve clinical outcomes. At 36 months, improvements in self-reported quality of life and validated sleep outcomes, which were abnormal at baseline and markedly improved at 12 months, demonstrated durability of clinical response. The clinical outcomes of the therapy continue to be robust. Of the 36 month follow up group (n=116), 81% use the device regularly. When accounting for individuals that use the device at least 4 nights a week, 84% of the initial implanted cohort (n=126) still are (4 nights or more) reporting frequently activating the device. A large percentage of individuals also report normalization of clinical outcomes at 3 years. The proportion of people reporting not being excessively sleepy during the day (ESS) increased from 32.5% to 76% while the percent of patients reporting a normal quality of life (FOSQ) increased from 15.1% to 64%.

The number of adverse events associated with the therapy continue to be acceptable. The majority of device related events occurred in association with device implantation and have been discussed in earlier publications. The rate of device related events continues to decrease with time. Most events are minor and related to sensation of tongue stimulation and tongue abrasions. These have been managed with adjustment of stimulation parameters and dental adjustments. The only serious device related adverse effects have included three device explantations. Two were at patients' request due to ineffectiveness and one was in a device responder due an

unrelated systemic septic arthritis. For the group, there have been no changes in stimulation thresholds (sensation, functional, or sub-discomfort (see appendix)). Based on these data, device harm or risk is low at three years.

The data from this study provides additional important evidence supporting neuromodulation as a method of treatment of OSA. In contrast to other surgical procedures with directly alter the upper airway to prevent upper airway obstruction, upper airway stimulation using the Inspire implant reduces upper airway obstruction by phasically increasing muscle tone to selected upper airway muscles innervated by the hypoglossal nerve. Given the accepted multilevel obstructive pathophysiology of OSA, the current long term effectiveness of the procedure supports that it is a pharyngeal procedure and not a "tongue base" procedure. Activation of tongue musculature not only mechanically opens the oral and oropharyngeal airway directly associated with the tongue but also has effects on the retropalatal airway.(ref) The presence of this tongue palate mechanical linkage has been previously observed experimentally and the current data supports that activation of the tongue protrusor muscles maintains a sustained clinical effect.

The nature of the mechanical linkage of the tongue and palate remains uncertain. Fluoroscopy and drug induced sedated endoscopy (DISE) demonstrate that unilateral hypoglossal nerve stimulation mechanically effects the entire pharynx. Selection criteria support that success is ultimately determined by the impact the device has on the palatal associated airway. Factors that worsen or improve palatal collapsibility (especially of the lateral retropalatal pharyngeal wall) are likely those that affect clinical outcomes of UAS. Mechanistically, it appears likely that lateral pharyngeal wall collapse, which is known to be associated with both BMI and AHI, is closely linked with device outcomes.

Multiple independent studies using several devices now provide data to support cranial nerve upper airway stimulation for the treatment of OSA. Eastwood, Van de Heyning, and Mwenge published data demonstrating improvement in sleep apnea. A cost benefit analysis using surrogate cost metrics shows the device compares favorably to many therapies. The STAR trial provides the strongest data supporting neuromodulation therapy for OSA. Although a single study, data at one year and a randomized withdrawal effect at 12 and 18 months has been published. The current study provides prospective results at 3 years strongly supporting the therapy for individuals who have moderate to severe OSA, who have failed conventional therapy, and who meet favorable inclusion criteria. The duration of this trial is unique in sleep apnea treatment literature where long term data is often considered months not years of therapy.

In conclusion, a long term prospective trial of cranial nerve upper airway stimulation using the Inspire implant system for the treatment of sleep apnea continues to demonstrate a high level of both objective and self reported quality of life and sleepiness improvements. A large percentage of individuals continue to use the device at three years with a majority reporting a normalization of sleepiness and sleep related quality of life measures.

Bibliography

298 Table 1

Characteristics of the Study Population at Enrollment			
	Baseline (N = 126)	Completed 12 month (N = 124)	Completed 36 month (N = 116)
Characteristics	Mean ± SD or N (%)		
Age, year	54.5 ± 10.2	54.3 ± 10.2	54.3 ± 10.3
Body Mass Index, kg/m^2	28.4 ± 2.6	28.5 ± 2.6	28.6 ± 2.6
AHI events/hr.	32.0 ± 11.8	31.7 ± 11.6	31.1 ± 10.9
Male sex, no. (%)	83%		
Caucasian race, no. (%)	97%		
Neck size, cm	41.2 ± 3.2		
Systolic BP, mmHg	128.7 ±16.1		
Diastolic BP, mmHg	81.5 ± 9.7		
Hypertension, no. (%)	38%		
Diabetes	9%		
Asthma	5%		
Congestive heart failure	2%		
Prior UPPP, no. (%)	18%		

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302 Table 2

	Baseline N=126	12 Months N=124	36 Months N=98	Change (Baseline-12M) (95% CI)	Change (Baseline-36M) (95% CI)	Change (12M-36M) (95 %CI)
AHI	32.0±11.8	15.3±16.1	11.5±13.9	16.4 (13.4,19.4)*	18.8 (16.1,21.6)*	2.0 (-1.0,4.9)
Median (N)	29.3	9.0	6.2	17.3	19.4	0.6
ODI	28.9±18.2	14.0±15.6	9.1±11.7	14.6 (11.8,17.4)*	18.0 (15.5,20.4)*	2.9 (0.4,5.3)*
Median (N)	25.4	7.4	4.8	15.7	17.2	1.1

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305 Table 3
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	Baseline	**12 Months**	**36 Months**	**Change (Baseline-12M) (95% CI)**	**Change (Baseline-36M) (95% CI)**	**Change (12M-36M) (95 %CI)**
FOSQ	14.3±3.2 **N=126**	17.3±2.9 **N=123**	17.4±3.5 **N=113**	-2.9 (-3.5,-2.4)*	-2.7 (-3.4,-1.9)*	0.2(-0.3,0.8)
Median (N)	14.6	18.2	18.8	-2.4	-2.6	-0.02
ESS	11.6±5.0 **N=126**	7.0±4.3 **N=123**	7.0±5.0 **N=113**	4.7 (3.8,5.6)*	4.3 (3.3,5.4)*	-0.1 (-0.7,0.6)
Median (N)	11	6	6	4	4	0
%SaO2<90%	8.7±10.2 **N=126**	5.9±12.4 (n=124)	5.7±10.2 (n=98)	2.5 (0.6,4.5)*	2.2 (-0.1,4.5)	-0.7 (-2.7,1.2)
Median	5.4	0.9	1.0	2.2	1.5	-0.0

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309 Table 4

Baseline Characteristics	Month 36 Responders N = 73 Mean (SD) or % (N)	Month 36 Non-responders N = 25 Mean (SD) or % (N)	Odds Ratio	95% confidence limits (*p*-value)
Age	56.4 (10.4)	51.6 (10.2)	1.05	1.00, 1.10 (0.0496)
Gender (% Male)	82% (59)	92% (23)	0.37	0.08, 1.74 (0.21)
BMI	28.5 (2.8)	29.2 (2.0)	0.88	0.72, 1.08 (0.22)
Neck Size	41.1 (3.5)	41.6 (2.5)	0.95	0.82, 1.10 (0.48)
Baseline AHI	28.8 (9.3)	35.0 (12.4)	0.95	0.91, 0.99 (0.01)
Baseline ODI	25.6 (9.5)	31.5 (13.0)	0.95	0.91, 0.99 (0.02)
Prior UPPP (%)	25% (18)	4% (1)	0.13	0.02, 1.01 (0.05)
Baseline FOSQ	14.6 (3.2)	15.3 (2.6)	0.92	0.79, 1.07 (0.28)
Baseline ESS	11.1 (4.8)	11.1 (4.3)	1.01	0.91, 1.11 (0.92)

310 Using a logistic regression analysis with the 3 significant covariates, AHI remained statistically significant
311 with p=0.01, with odds ratio of 0.95, and 95% confidence limits of 0.93 to 0.99.

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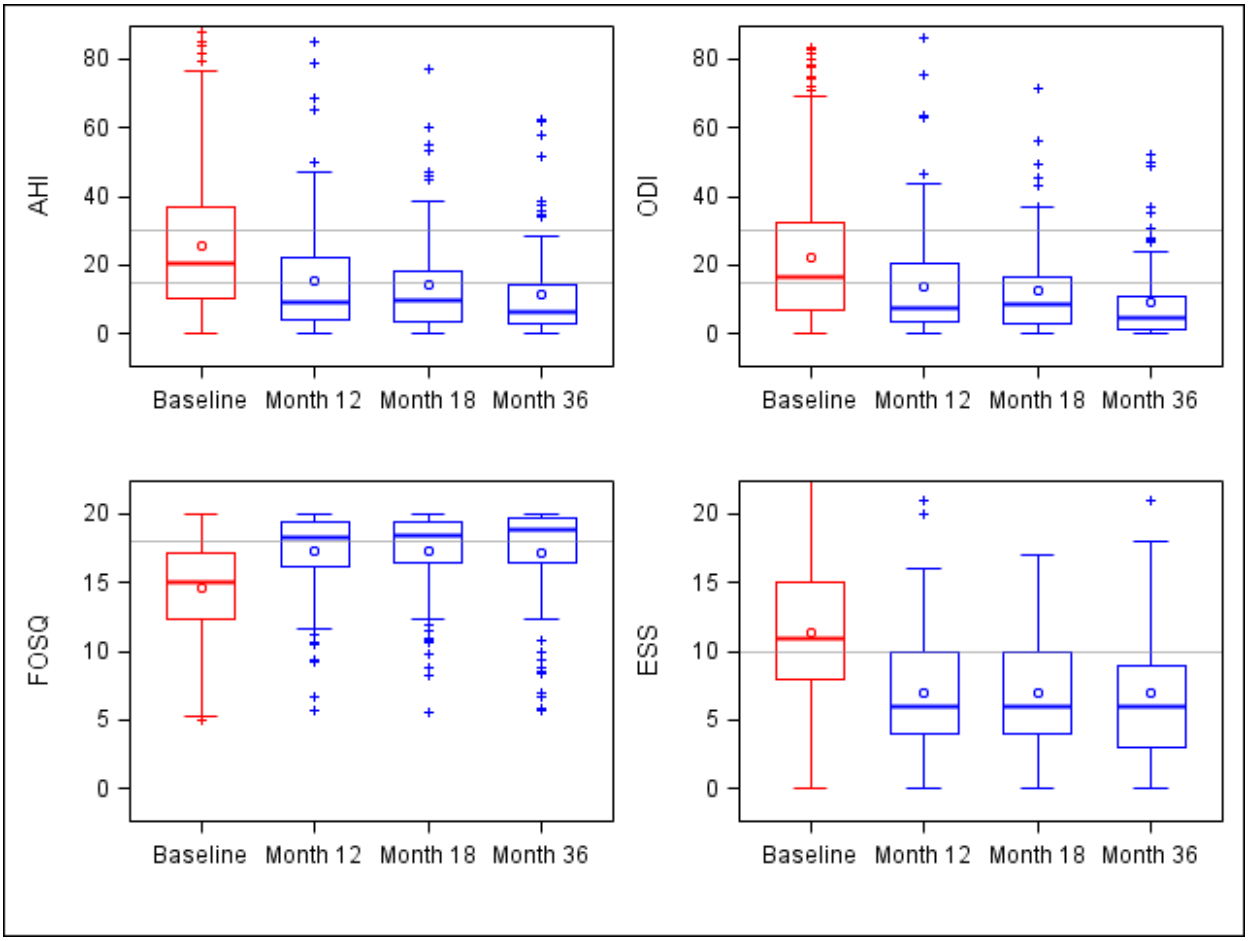
Figure 1


AHI
ODI
FOSQ
ESS
0
20
40
60
80
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5
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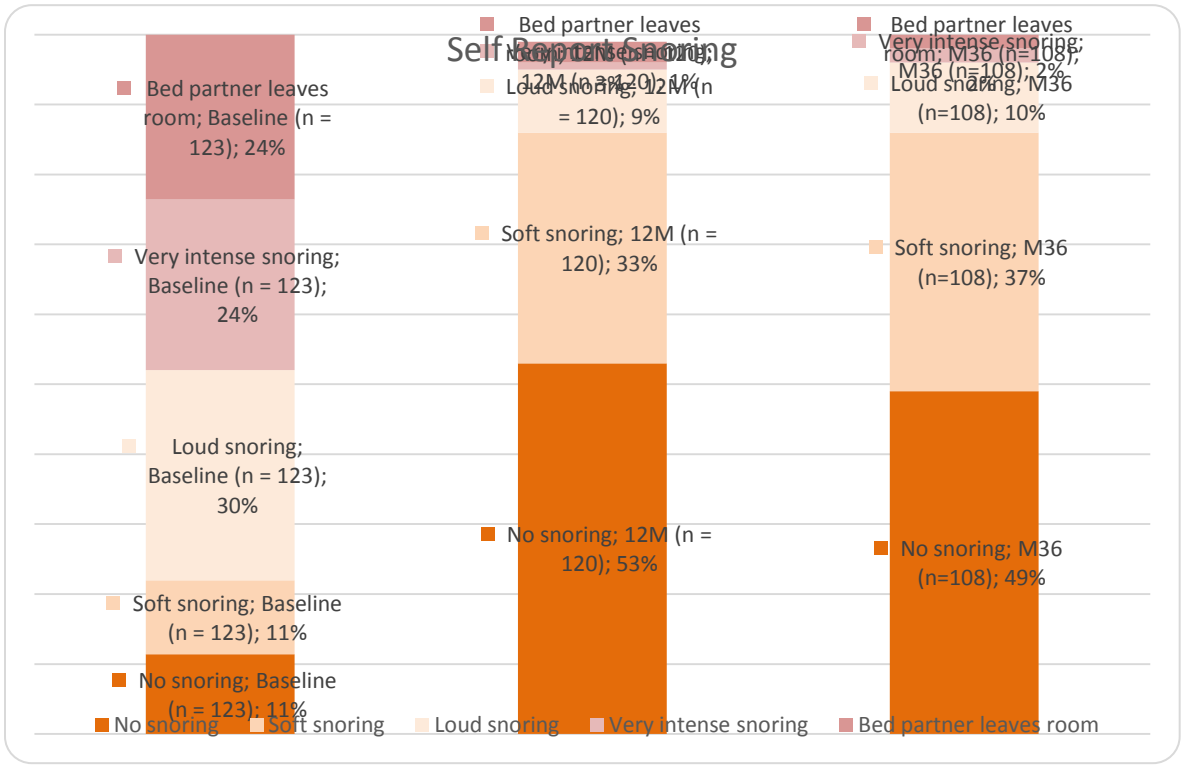
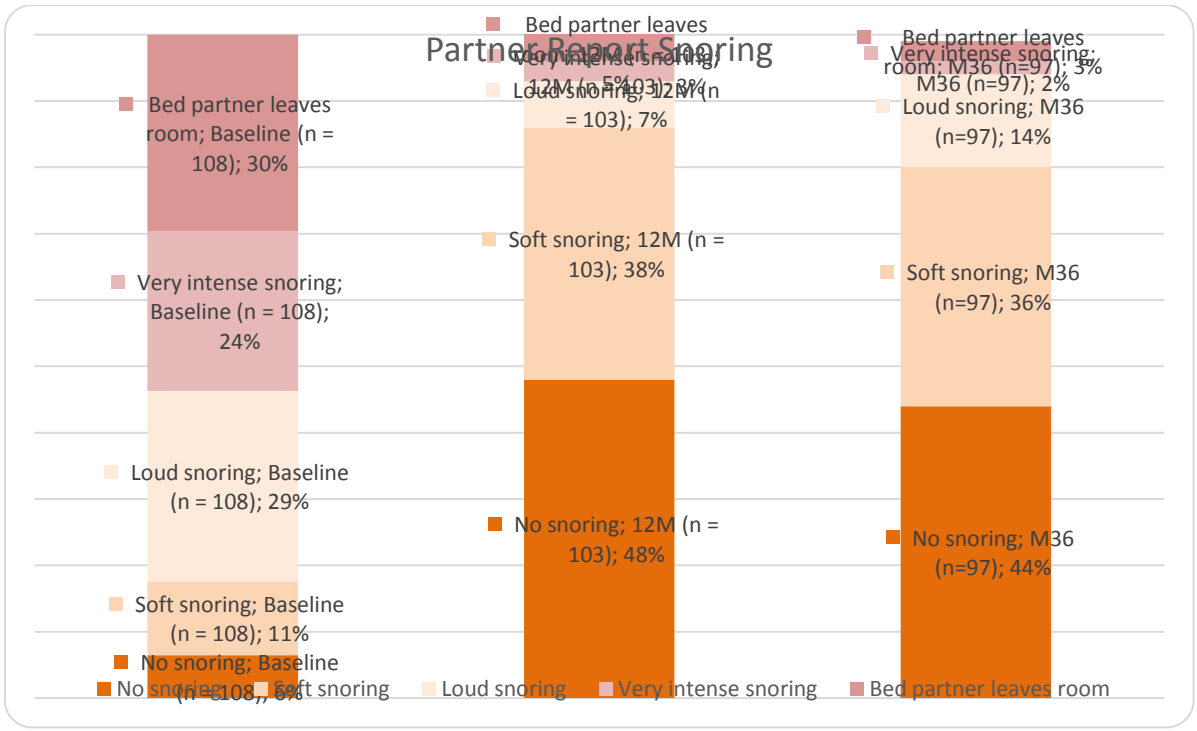
Baseline
Month 12
Month 18
Month 36

Figure 2


Self Report Snoring
Bed partner leaves room; Baseline (n = 123); 24%
Very intense snoring; Baseline (n = 123); 24%
Loud snoring; Baseline (n = 123); 30%
Soft snoring; Baseline (n = 123); 11%
No snoring; Baseline (n = 123); 11%
Bed partner leaves room; M36 (n=108); 2%
Very intense snoring; M36 (n=108); 2%
Loud snoring; M36 (n=108); 10%
Soft snoring; M36 (n=108); 37%
No snoring; M36 (n=108); 49%
No snoring
Soft snoring
Loud snoring
Very intense snoring
Bed partner leaves room


Partner Report Snoring
Bed partner leaves room; Baseline (n = 108); 30%
Very intense snoring; Baseline (n = 108); 24%
Loud snoring; Baseline (n = 108); 29%
Soft snoring; Baseline (n = 108); 11%
No snoring; Baseline (n = 108); 6%
Bed partner leaves room; M36 (n=97); 3%
Very intense snoring; M36 (n=97); 2%
Loud snoring; M36 (n=97); 14%
Soft snoring; M36 (n=97); 36%
No snoring; M36 (n=97); 44%
No snoring
Soft snoring
Loud snoring
Very intense snoring
Bed partner leaves room

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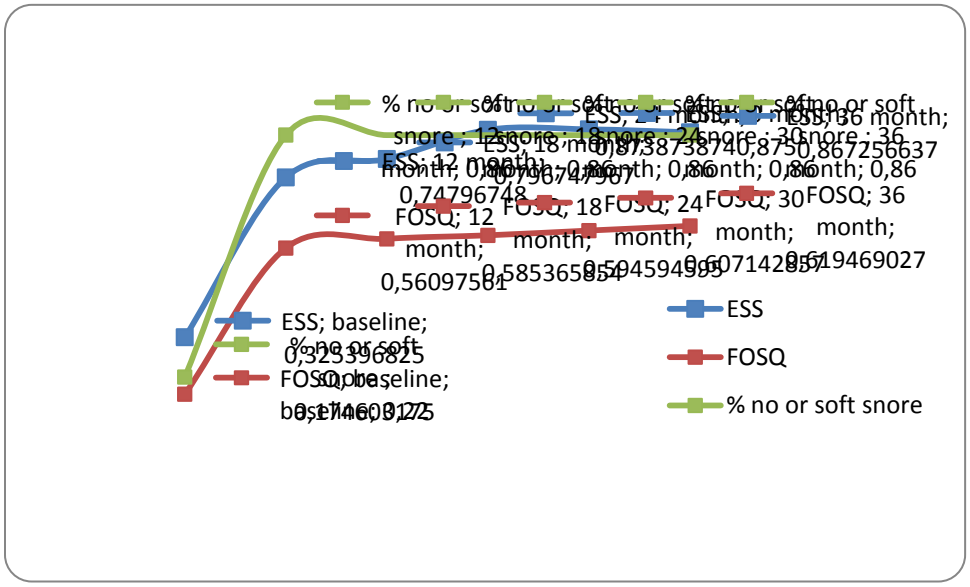

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