Upper Airway Stimulation for OSA 2018

Patrick J Strollo, Jr, MD, FACP, FCCP, FAASM
Professor of Medicine and Clinical and Translational Science
Vice Chair of Medicine for Veterans Affairs, University of Pittsburgh

Disclosure: Patrick J Strollo, Jr., MD

Research Support
• Federal
  – R01 HL107370
  – R01 DK096028-02
  – RO1 HL120354-01A1
  – 1UH2HL125103-01
  – 5UL1TR000005-09
• Industry
  – Research Grant Philips-Respironics, Inc.
  – Research Grant ResMed, Corp.
  – Inspire Medical Systems
  – National Football League
  – PinMed
• Industry Advisory:
  - ResMed
  - Emmi Solutions
  - Jazz Pharmaceuticals
  - Itamar Medical
  - Inspire Medical Systems
  - Separation Design Group
Outline

• Upper Airway Stimulation
• STAR Trial
• Adhere Registry
• Conclusions
Upper Airway Stimulation: A new class of therapy

- Anatomy (small, collapsible upper airway)
- CPAP
- OAT
- UPPP / MMA
- Sleep (arousal threshold)
- Loop gain (Unstable ventilatory control)
- Low UA Drive and Poor Reflex (inadequate muscle activation)
- Recurrent Apnea and Hypopnea
- Obstructive Sleep Apnea Hypopnea Syndrome


Upper Airway Stimulation

- Implanted System
- Physician Programmer
- Patient Remote

The Distal Hypoglossal Nerve

- Hypoglossal Nerve (CN XII)
- Genioglossus Muscle
- Geniohyoid Muscle
- Styloglossus Muscle
- Hyoglossus Muscle
- Mild stimulation

Basic Therapy Parameters

- **Amplitude** (V) – primary stimulation strength adjustment
- **Rate** (Hz) – default 33 Hz
- **Pulse Width** (μsec) – default 90 μsec

Heiser et al Sleep and Breathing 2016
Increases in retropalatal and retrolingual area comparing no stimulation with progressively higher levels of stimulation during DISE

| No stimulation | First sensation | Bulk movement | Titrated therapeutic | Sub-discomfort |


**PSG: Effect of Stimulation**

- EEG
- EMG
- Nasal Pressure
- Thermo
- Chest
- Abdomen
- SpO₂

30 seconds

Therapy OFF

Therapy ON
Outline

- Upper Airway Stimulation
- STAR Trial
- Adhere Registry
- Conclusions

Stimulation Therapy for Apnea Reduction (STAR Trial)  ClinicalTrials.gov NCT01161420

Hypothesis: Unilateral Stimulation of the Hypoglossal Nerve during sleep will safely and effectively treat Obstructive Sleep Apnea

Strollo et al, NEJM 2014 370:139-49
Outcome Measures: Baseline vs. 12-Months

- **Co-Primary**
  - Apnea Hypopnea Index
  - Oxygen desaturation index (ODI4%)

- **Secondary**
  - Epworth Sleepiness Scale
  - Functional Outcomes of Sleep Questionnaire
  - SaO2 < 90%

Strollo et al, NEJM 2014 370:139-49

Methods

- Prospective, multicenter trial with a randomized therapy withdrawal arm in participants with moderate to severe OSA who had not accepted or had not tolerated CPAP.

- All underwent a screening polysomnographic (PSG) study, surgical consultation, and drug-induced sedation endoscopy (DISE).

Strollo et al, NEJM 2014 370:139-49
## Inclusion / Exclusion Criteria

### Inclusion
- AHI between 20 and 50
- Have not accepted or not tolerated CPAP
- Central and mixed sleep apnea accounted for < 25% of all AHI events
- Absence of significant apnea when sleeping in a non-supine position (AHI\textsubscript{non-supine} > 10)

### Exclusion
- BMI > 32
- Neuromuscular diseases
- Severe Co-Morbid Cardiopulmonary Disease
- Other chronic sleep disorders
- Complete concentric collapse at the level of soft palate during drug-induced sedation endoscopy (DISE)

Strollo et al, NEJM 2014 370:139-49

## Examples collapse at the level of the palate during DISE

<table>
<thead>
<tr>
<th>Anteroposterior collapse</th>
<th>Concentric collapse</th>
</tr>
</thead>
</table>

JCSM 2013 9 (5) 433-438
Primary Outcome Measures: AHI and ODI (n = 124)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>29.3</td>
<td>9.0</td>
</tr>
<tr>
<td>ODI</td>
<td>25.4</td>
<td>7.4</td>
</tr>
</tbody>
</table>

* 68% reduction in AHI from baseline to Month-12

* 70% reduction in ODI from baseline to Month-12

*Median and error bar in standard error

Strollo et al, NEJM 2014 370:139-49

Secondary Outcome Measures: FOSQ & ESS (n = 123)

<table>
<thead>
<tr>
<th></th>
<th>FOSQ Score</th>
<th>ESS Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>11.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Month-12</td>
<td>6.0</td>
<td>6.0</td>
</tr>
</tbody>
</table>

*Median and error bar in standard error

Strollo et al, NEJM 2014 370:139-49
### 5 Year F/U: Summary of Outcome Measures

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline N</th>
<th>Baseline Mean ± SD</th>
<th>Baseline Median</th>
<th>Month 12 N</th>
<th>Month 12 Mean ± SD</th>
<th>Month 12 Median</th>
<th>Month 36 N</th>
<th>Month 36 Mean ± SD</th>
<th>Month 36 Median</th>
<th>Month 60 N</th>
<th>Month 60 Mean ± SD</th>
<th>Month 60 Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI</td>
<td>126</td>
<td>32.0 ± 11.8</td>
<td>29.3</td>
<td>124</td>
<td>15.3 ± 16.1</td>
<td>9.0</td>
<td>98</td>
<td>11.5 ± 14.0</td>
<td>6.0</td>
<td>71</td>
<td>12.4 ± 16.3</td>
<td>6.2</td>
</tr>
<tr>
<td>ODI</td>
<td>126</td>
<td>28.9 ± 18.2</td>
<td>25.4</td>
<td>124</td>
<td>14.0 ± 15.6</td>
<td>7.4</td>
<td>98</td>
<td>9.1 ± 11.7</td>
<td>4.8</td>
<td>71</td>
<td>9.9 ± 14.5</td>
<td>4.6</td>
</tr>
<tr>
<td>FOSQ</td>
<td>126</td>
<td>14.3 ± 3.2</td>
<td>14.6</td>
<td>123</td>
<td>17.3 ± 2.9</td>
<td>18.2</td>
<td>113</td>
<td>17.4 ± 3.5</td>
<td>18.8</td>
<td>92</td>
<td>18.0 ± 2.2</td>
<td>18.7</td>
</tr>
<tr>
<td>ESS</td>
<td>126</td>
<td>11.6 ± 5.0</td>
<td>11</td>
<td>123</td>
<td>7.0 ± 4.3</td>
<td>6</td>
<td>113</td>
<td>7.0 ± 5.0</td>
<td>6</td>
<td>92</td>
<td>6.9 ± 4.7</td>
<td>6</td>
</tr>
</tbody>
</table>


### Study Flow

5 Year F/U: Sensitivity Analyses

Sustained therapeutic effects on AHI, FOSQ and ESS during the 5-year follow-up using a repeated measure model for estimated mean using all available data


UAS Self-reported Nightly Device Use

<table>
<thead>
<tr>
<th>Patients Reported Nightly Use (%)</th>
<th>Month 12 (N = 124)</th>
<th>Month 24 (N = 117)</th>
<th>Month 36 (N = 108)</th>
<th>Month 60 (N = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hours of use per night (mean ± SD)</th>
<th>≥ 4 hours of use/night n (%)</th>
<th>≥ 20 hours of use/week n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.7 ± 1.9</td>
<td>60 (67%)</td>
<td>72 (80%)</td>
</tr>
</tbody>
</table>

Outline

• Upper Airway Stimulation
• STAR Trial
• Adhere Registry
• Conclusions
Adherence and Outcomes of UAS in OSA Registry (ADHERE Registry)

• **Study design:** International, multi-center registry of consecutive patients who have received an implanted UAS system (Inspire II, Inspire Medical Systems, Maple Grove MN).
• **Sample size:** Enrollment goal is a total of 2500 patients
• **Follow-up interval:** Implant through 12-months post-implant

www.clinicaltrials.gov NCT02907398

14 Centers enrolled 508 patients

<table>
<thead>
<tr>
<th>ID</th>
<th>Enrolling Center</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Munich Technical University</td>
</tr>
<tr>
<td>2</td>
<td>University of Lubeck</td>
</tr>
<tr>
<td>3</td>
<td>Thomas Jefferson University</td>
</tr>
<tr>
<td>4</td>
<td>University-Hospital Mannheim*</td>
</tr>
<tr>
<td>5</td>
<td>University of Pittsburgh*</td>
</tr>
<tr>
<td>6</td>
<td>University of Pennsylvania</td>
</tr>
<tr>
<td>7</td>
<td>University of Alabama</td>
</tr>
<tr>
<td>8</td>
<td>Cleveland Clinic</td>
</tr>
<tr>
<td>9</td>
<td>Kansas University Medical Center</td>
</tr>
<tr>
<td>10</td>
<td>Keck School of Medicine of the University of Southern California</td>
</tr>
<tr>
<td>11</td>
<td>University of Minnesota Fairview Hospital</td>
</tr>
<tr>
<td>12</td>
<td>MedStar Washington Hospital Center</td>
</tr>
<tr>
<td>13</td>
<td>University of Florida Gainesville</td>
</tr>
<tr>
<td>14</td>
<td>University Hospital Cleveland*</td>
</tr>
</tbody>
</table>

* STAR Trial sites

Heiser et al under review
AHI Reduced at follow up visits

Daytime Sleepiness Reduced
Patient Experience with UAS at the Post-titration & Final Visit

<table>
<thead>
<tr>
<th></th>
<th>Post-Titration (n=261)</th>
<th>Final Visit (n=235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAS is better than CPAP</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>Choose UAS again</td>
<td>95%</td>
<td>94%</td>
</tr>
<tr>
<td>Recommend UAS to others</td>
<td>93%</td>
<td>96%</td>
</tr>
<tr>
<td>Satisfied with UAS</td>
<td>91%</td>
<td>94%</td>
</tr>
</tbody>
</table>

Heiser et al under review

Additional observations

Therapy use was high at 12 months

<table>
<thead>
<tr>
<th></th>
<th>Post Titration</th>
<th>Final Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.4 ± 2.0 hours per night</td>
<td>n = 344</td>
</tr>
<tr>
<td></td>
<td>5.7 ± 2.2 hours per night</td>
<td>n = 229</td>
</tr>
</tbody>
</table>

Post Hoc Analysis

- 4% increase in treatment success for each 1-year increase in age
- 9% reduced odds of treatment success for each one unit increase in BMI
- 3-fold higher odds of OSA treatment success in women vs men

Heiser et al under review
CPAP adherence – SAVE trial

Pre-randomization sham CPAP run-in
Potential participants were required to have at least 3 hr/day CPAP use during a 1-week run-in period using sham CPAP

<table>
<thead>
<tr>
<th>Month</th>
<th>1</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1284</td>
<td>1277</td>
<td>1260</td>
<td>1219</td>
<td>1035</td>
<td>710</td>
<td>481</td>
</tr>
<tr>
<td>Mean hr/day (SD)</td>
<td>4.4 (2.2)</td>
<td>4.1 (2.3)</td>
<td>3.9 (2.4)</td>
<td>3.5 (2.4)</td>
<td>3.4 (2.6)</td>
<td>3.3 (2.7)</td>
<td>3.2 (2.7)</td>
</tr>
<tr>
<td>Median (iqr)</td>
<td>4.8 (3.0-6.0)</td>
<td>4.5 (2.5-5.8)</td>
<td>4.2 (2.0-5.6)</td>
<td>3.6 (1.3-5.4)</td>
<td>3.4 (0.7-5.6)</td>
<td>3.5 (0.3-5.5)</td>
<td>3.3 (0.1-5.6)</td>
</tr>
</tbody>
</table>


PAP use for 3-4 Hours may be Inadequate

Babak Mokhlesi, MD, MSc (with permission)
The Inspire Cloud™ System Patient Outcomes & Practice Efficiency

USB
Data exported via flash drive

Inspire Cloud™ App

Full implementation in 2017

Therapy Parameters & Utilization Dashboard

Patient Adherence Report

Energy Level Histogram

Sensing and Stimulation Settings

Night to Night Adherence and Sleep History Analysis (on, pause, off times)

Full implementation in 2018
Impact of Age on OSA is not fully explained by BMI

- Decrease in Negative Pressure with Age
- Increase in Fat Pad Thickness with Age
- OSA Prevalence

Response to Upper Airway Stimulation in Older Adults with Moderate to Severe Obstructive Sleep Apnea

- Strollo et al APSS 2018

AJRCCM 2002 165:1217-1239
Am J Med 2006 119:9-14
ASSOCIATION BETWEEN ADHERENCE TO CPAP TREATMENT & COST AMONG MEDICARE ENROLLEES

- We identified 22,361 Medicare enrollees (mean age=67.2 years, sd=12.2) with a diagnosis of sleep apnea during 2007-2008.
- A diagnosis of sleep apnea was associated with higher costs (Odds Ratio (OR) =1.60; 95% Confidence Interval (CI)=1.58, 1.63) compared to those without a sleep apnea diagnosis after controlling for demographic characteristics and comorbidities.
- Almost half (47%) of those with a sleep apnea diagnosis were treated for sleep apnea using CPAP.
- We defined an episode of CPAP as at least one DME claim for CPAP in a 6-month period. Those who had four such episodes in the two year period since diagnosis were ‘continuously adherent’, and those with three episodes were ‘partially adherent’.
- Continuous adherence with CPAP for two years was associated with 4-8% lower cost compared to those sleep apnea patients who did not receive CPAP treatment.

Chhatre et al under review
Conclusions

- Upper Airway Stimulation is an additional tool for the management of properly selected “at risk” patients who do not accept or adhere to positive pressure therapy
- The STAR Trial has provided robust evidence that upper airway stimulation is safe and effective in participants with moderate to severe OSA
- The treatment effect is maintained beyond the 12 month endpoint
- Preliminary data from the ADHERE Registry reveals favorable UAS adherence
FROM STEEL TO SCIENCE

NATURE 2010 463: 258-259

Thank You

University of Pittsburgh / CTSI / Clinical + Translational Science Institute