Daniel J. Gottlieb, MD, MPH, is Associate Professor of Medicine at Harvard Medical School and faculty in the Program in Sleep and Cardiovascular Medicine at Brigham & Women’s Hospital. He is Director of the Sleep Disorders Center, VA Boston Healthcare System, and plays a leadership role in VA sleep medicine as co-chair of the VA Sleep Network and as a member of the VHA Federal Advisory Committee on Pulmonary, Critical Care and Sleep Medicine. Dr. Gottlieb is a pulmonary and sleep medicine epidemiologist and clinical trialist with 20 years of experience in observational cohort studies and clinical trials focusing on the cardiovascular consequences of sleep apnea. This experience includes a long affiliation with the Framingham Heart Study, where he was an investigator on the Sleep Heart Health Study. Dr. Gottlieb led one of four sites of the Heart Biomarker Evaluation in Apnea Treatment (HeartBEAT) Study, a randomized clinical trial investigating the respective effects of supplemental oxygen and continuous positive airway pressure on hypertension and other markers of vascular risk in patients with obstructive sleep apnea, and is PI of an ongoing VA-funded clinical trial evaluating the cardiovascular benefits of sleep apnea treatment in heart failure. Dr. Gottlieb first visited California in 1980, when he biked the west coast from San Francisco to Vancouver upon college graduation. He has two teenage sons and in his mid-fifties has started playing ice hockey (enthusiastically, although not very well).

OBJECTIVES:
Participants should be better able to:

1. Understand the prevalence of obstructive sleep apnea and its relation to cardiovascular risk;

2. Understand the evidence from recent clinical trials of obstructive sleep apnea treatment for reduction of risk of major cardiovascular and cerebrovascular events;

3. Understand the evidence from recent clinical trials of central sleep apnea treatment in patients with heart failure.
Sleep Apnea and Cardiovascular Risk
What Have We Learned from Recent Clinical Trials?

Daniel J. Gottlieb, MD, MPH
Director, Sleep Disorders Center, VA Boston Healthcare System
Program in Sleep and Cardiovascular Medicine, Brigham & Women’s Hospital
Division of Sleep and Circadian Disorders, Harvard Medical School

No financial conflicts of interest.

“Joe the Fat Boy,” from Dickens’ Posthumous Papers of the Pickwick Club, 1848
Definition of Obstructive Sleep Apnea

Recurrent partial or complete collapse of the upper airway during sleep, usually resulting in:
- intrathoracic pressure swings
- intermittent hypoxemia
- intermittent hypercapnia
- sleep fragmentation

How prevalent is obstructive sleep apnea in the U.S. adult population?

A. 4% of men and 2% of women
B. 14% of men and 5% of women
C. 24% of men and 9% of women
D. 34% of men and 17% of women
How prevalent is obstructive sleep apnea in the U.S. adult population?

A. 4% of men and 2% of women  
B. 14% of men and 5% of women  
C. 24% of men and 9% of women  
D. 34% of men and 17% of women

Prevalence of Obstructive Sleep Apnea

<table>
<thead>
<tr>
<th>Source</th>
<th>Age</th>
<th>Prevalence in Men</th>
<th>Prevalence in Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young, N Engl J Med 1993;328:1230</td>
<td>30-60</td>
<td>24%</td>
<td>9%</td>
</tr>
<tr>
<td>AHI ≥ 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI ≥ 5 with excessive sleepiness</td>
<td></td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Peppard, Am J Epidemiol 2013;177:1006</td>
<td>30-70</td>
<td>34%</td>
<td>17%</td>
</tr>
<tr>
<td>AHI ≥ 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI ≥ 5 with excessive sleepiness (ESS &gt;10)</td>
<td>14%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>
OSA and Sleepiness
Sleep Heart Health Study

[Graph showing the relationship between AHI and percent sleepy, divided into categories: <5, 5 to 15, 15 to 30, and 30+.]

Often sleepy or unrested
ESS >10

Kapur, Sleep 2005;28:472

AHI >30, ESS ≤10, no or mild subjective sleepiness

Epworth

MSLT

Steer-Clear

FOSQ

Is this asymptomatic OSA a problem for the patient?

“The presence of 15 or more obstructive respiratory events per hour of sleep in the absence of sleep related symptoms is also sufficient for the diagnosis of OSA due to the greater association of this severity of obstruction with important consequences such as increased cardiovascular disease risk.”
How much is risk of heart attack or stroke increased in the presence of severe OSA, compared to similar individuals without OSA?

A. 1.5- to 2-fold increased risk
B. 2- to 3-fold increased risk
C. 4- to 6-fold increased risk
D. 7- to 10-fold increased risk
Severe untreated OSA is associated with increased risk of stroke and myocardial infarction

![Graph showing the increased risk over time for untreated OSA compared to controls and snorers without OSA.]

Men, mean age 49.9 years

OR 2.4 for incident non-fatal CVD after multiple risk factor adjustment, compared to snorers without OSA

Multiple clinic-based observational studies find increased CVD risk in untreated OSA

<table>
<thead>
<tr>
<th>Study</th>
<th>Exposure</th>
<th>Outcome</th>
<th>N</th>
<th>M</th>
<th>F</th>
<th>Adjusted HR (untreated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marin 2005</td>
<td>AHI &gt;30</td>
<td>CV death</td>
<td>1651</td>
<td></td>
<td></td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-fatal MI, stroke</td>
<td>1651</td>
<td></td>
<td></td>
<td>2.4</td>
</tr>
<tr>
<td>Campos-Rodriguez 2012</td>
<td>AHI &gt;30</td>
<td>CV death</td>
<td>1116</td>
<td></td>
<td></td>
<td>3.5</td>
</tr>
<tr>
<td>Peker 2002</td>
<td>AI &gt;5</td>
<td>MI, stroke, CV death</td>
<td>174</td>
<td></td>
<td></td>
<td>7.7</td>
</tr>
<tr>
<td>Mooe 2001</td>
<td>AHI &gt;10</td>
<td>MI, stroke, death</td>
<td>264</td>
<td>128</td>
<td></td>
<td>1.6</td>
</tr>
<tr>
<td>Campos-Rodriguez 2014</td>
<td>AHI &gt;10</td>
<td>Incident MI, stroke</td>
<td>967</td>
<td></td>
<td></td>
<td>2.8</td>
</tr>
<tr>
<td>Garcia-Rio 2013</td>
<td>AHI &gt;5</td>
<td>Recurrent MI</td>
<td>160</td>
<td>26</td>
<td></td>
<td>3.2</td>
</tr>
</tbody>
</table>

Mooe, AJRCCM 2001; 164:1910
Peker, AJRCCM 2002;166:159
Marin, Lancet 2005;365:1046
Campos-Rodriguez, Ann Internal Med 2012;156:115
Garcia-Rio, Int J Cardiol 2013;168:1328
Campos-Rodriguez, AJRCCM 2014;189:1544
Population-based observational studies also find increased CVD risk in OSA

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort</th>
<th>Adjusted HR Stroke</th>
<th>Adjusted HR CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gottlieb 2010</td>
<td>Sleep Heart Health Study (men)</td>
<td>2.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Redline 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arzt 2005</td>
<td>Wisconsin Sleep Cohort Study</td>
<td>3.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Hla 2015</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gottlieb, Circulation 2010;122:352
Redline, AJRCCM 2010; 182:269
Arzt, AJRCCM 2005; 172:1447
Hla, Sleep 2015;38:677

Significant after adjustment for age, race, BMI, smoking, SBP, DBP, and prevalent HTN, DM, CVD

Punjabi, PLoS Medicine 2009;e1000132
Are these associations causal or due to unmeasured confounding?
(e.g., by adiposity, diet, exercise, or other lifestyle factors)
Does treatment of OSA improve outcome?

No increased risk of stroke/MI in treated severe OSA

Marin, Lancet 2005;365:1046
Clinic-based observational studies suggest the OSA-related CVD risk is eliminated by CPAP

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>OR (untreated)</th>
<th>OR (treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peker 2002</td>
<td>AHI &gt;5 MI, stroke, CV death</td>
<td>7.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Marin 2005</td>
<td>AHI &gt;30 CV death</td>
<td>2.8</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Non-fatal MI, stroke</td>
<td>2.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Campos-Rodriguez 2012</td>
<td>AHI &gt;30 CV death</td>
<td>3.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Garcia-Rio 2013</td>
<td>AHI &gt;5 Recurrent MI</td>
<td>3.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Campos-Rodriguez 2014</td>
<td>AHI &gt;10 Incident MI</td>
<td>2.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Peker, AJRCCM 2002;166.159
Marin, Lancet 2005;365:1046
Campos-Rodriguez, Ann Internal Med 2012;156:115
Garcia-Rio, Int J Cardiol 2013;168:1328
Campos-Rodriguez, AJRCCM 2014;189:1544

Healthy User Effect

CHARM Study

HR candesartan: 0.90
HR compliance: 0.65

Granger, Lancet 2005;366:2005
Despite the findings from observational and quasi-experimental studies, we still need randomized clinical trials to prove effectiveness of OSA treatment for prevention of coronary and cerebral vascular disease and death.

Recent Clinical Trials

- CPAP for treatment of hypertension
- CPAP for prevention of MI, stroke and death
- Treatment of central sleep apnea in heart failure
Recent Clinical Trials

- CPAP for treatment of hypertension
  - Spanish Sleep & Breathing Network
  - HIPARCO
  - HeartBEAT
- CPAP for prevention of MI, stroke and death
- Treatment of central sleep apnea in heart failure

How much is mean blood pressure reduced by treatment with CPAP in patients with OSA?

A. None
B. 1 to 2 mmHg
C. 2 to 4 mmHg
D. 6 to 10 mmHg
How much is mean blood pressure reduced by treatment with CPAP in patients with OSA?

A. None  
B. 1 to 2 mmHg  
C. 2 to 4 mmHg  
D. 6 to 10 mmHg

CPAP lowers BP in patients with newly diagnosed, untreated hypertension and unsuspected OSA

Durán-Cantolla, BMJ 2010;341:bmj.c5991
CPAP vs. valsartan for untreated hypertension

Pépin, Am J Respir Crit Care Med 2010;182:954

CPAP lowers BP in Patients with Resistant Hypertension
The HIPARCO Study

<table>
<thead>
<tr>
<th>BP variables, mm Hg</th>
<th>Mean (SD)</th>
<th></th>
<th></th>
<th></th>
<th>Intergrup Differences (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h mean BP</td>
<td>103.9 (9.6)</td>
<td>99.8 (14.6)</td>
<td>102.9 (9.6)</td>
<td>102.1 (18.2)</td>
<td>3.9 (1.3 to 6.6)</td>
<td>.004</td>
</tr>
<tr>
<td>24-h SBP</td>
<td>144.9 (11.7)</td>
<td>140.2 (13.1)</td>
<td>143.5 (13.2)</td>
<td>142.3 (17.1)</td>
<td>4.2 (0.4 to 8.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Diurnal</td>
<td>147.2 (12.1)</td>
<td>144.0 (13.7)</td>
<td>145.1 (13.3)</td>
<td>142.5 (16.2)</td>
<td>1.1 (-2.9 to 5.2)</td>
<td>.59</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>141.2 (15.8)</td>
<td>134.6 (16.4)</td>
<td>140.4 (16.8)</td>
<td>137.8 (19.4)</td>
<td>5.8 (1.1 to 10.5)</td>
<td>.02</td>
</tr>
<tr>
<td>24-h DBP</td>
<td>83.4 (11.1)</td>
<td>79.5 (11.5)</td>
<td>82.6 (10.0)</td>
<td>82.1 (12.7)</td>
<td>3.8 (1.4 to 6.1)</td>
<td>.002</td>
</tr>
<tr>
<td>Diurnal</td>
<td>85.7 (11.6)</td>
<td>82.7 (12.5)</td>
<td>84.6 (10.4)</td>
<td>83.2 (13.2)</td>
<td>2.1 (-0.1 to 4.8)</td>
<td>.07</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>78.5 (12.4)</td>
<td>75.4 (11.7)</td>
<td>78.6 (11.1)</td>
<td>77.5 (13.5)</td>
<td>1.3 (0.5 to 6.1)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Mean ESS 9.1
Mean AHI 40.4
12 weeks
N=194
Mean 3.8 BP meds

Martinez-Garcia, JAMA 2013;310:2407
CPAP lowers BP in patients with well-controlled hypertension
The HeartBEAT Study

<table>
<thead>
<tr>
<th>Variable</th>
<th>CPAP (N=90)</th>
<th>HLSE (N=97)</th>
<th>CPAP vs. HLSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-Hr mean arterial blood pressure</td>
<td>89.5±8.6</td>
<td>87.7±9.3</td>
<td>-2.4 (P=0.04)</td>
</tr>
<tr>
<td>Baseline</td>
<td>87.8±8.1</td>
<td>89.0±11.2</td>
<td></td>
</tr>
<tr>
<td>12 Wk</td>
<td>124.7±13.5</td>
<td>123.6±14.3</td>
<td>-1.9 (P=0.25)</td>
</tr>
<tr>
<td>24-Hr mean systolic blood pressure</td>
<td>123.4±12.8</td>
<td>124.7±16.4</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>72.0±7.7</td>
<td>69.6±8.6</td>
<td>-2.8 (P=0.005)</td>
</tr>
<tr>
<td>12 Wk</td>
<td>69.8±7.5</td>
<td>70.9±10.1</td>
<td></td>
</tr>
</tbody>
</table>

Mean ESS 8.4
Mean AHI 25.5
12 weeks
N=187
Mean 2.4 BP meds

CPAP but not supplemental O$_2$ reduces BP


Recent Clinical Trials

- CPAP for treatment of hypertension
- CPAP for prevention of MI, stroke and death
  - Spanish Sleep & Breathing Network
  - RICCADSA
  - SAVE
- Treatment of central sleep apnea in heart failure
Effect of Continuous Positive Airway Pressure on the Incidence of Hypertension and Cardiovascular Events in Nonsleepy Patients With Obstructive Sleep Apnea
A Randomized Controlled Trial

Barbé, JAMA 2012;307:2161

Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea (RICCADSA): A secondary Prevention Trial

Peker, AJRCCM 2016;194:613
**Sleep Apnea Vascular Endpoints (SAVE) Trial**

Secondary prevention trial

- 5844 sleep tests
- 3246 eligible for run-in
- 2717 randomized
- AHI 28/hour
- ESS 7.4

Mean f/u 3.7 years

Mean CPAP use 3.3 hours/night

Primary outcome:
- CV death, MI, stroke, or hospitalization for heart failure, unstable angina or TIA

Antic, Sleep 2014; Nov 24. pii: sp-00540-14
McEvoy, NEJM 2016;375:919

---

**SAVE Trial Results**

HR 1.10 favoring usual care

McEvoy, NEJM 2016;375:919
Why was no benefit of CPAP observed?

- Perhaps OSA treatment does not reduce CVD risk
- Inadequate CPAP adherence
- Different ancestry of participants
- Treatment of mediators of OSA effect (hypertension, diabetes) may mitigate OSA-related risk
- Secondary prevention may be too late to see impact
- Inability adequately stratify risk

Summary

- Observational studies are suggestive of increased cardio- and cerebrovascular risk from OSA
- Reductions in blood pressure have been clearly demonstrated with CPAP treatment
  - This may be beneficial in resistant hypertension
- Randomized clinical trials do not demonstrate reduction in risk of MI, stroke or death with CPAP
  - No clear rationale for treatment of OSA to reduce CVD risk
Which of the following is an acceptable treatment for Cheyne-Stokes respiration in patients with heart failure and reduced LVEF?

A. Adaptive servo-ventilation (ASV)
B. Nocturnal oxygen therapy
C. Metoprolol plus lisinopril
D. Both B and C
Which of the following is an acceptable treatment for Cheyne-Stokes respiration in patients with heart failure and reduced LVEF?

A. Adaptive servo-ventilation (ASV)  
B. Nocturnal oxygen therapy  
C. Metoprolol plus Lisinopril  
D. Both B and C

Recent Clinical Trials

- CPAP for treatment of hypertension
- CPAP for prevention of MI, stroke and death
- Treatment of central sleep apnea in heart failure
  - CANPAP
  - SERVE-HF
Cheyne J. *A case of apoplexy in which the fleshy part of the heart was converted into fat.* Dublin Hospital Report 1818;2:216.

Stokes W. *The Diseases of the Heart and Aorta.* Dublin 1854.

---

Central sleep apnea associated with a doubling of mortality in HF

![Graph showing survival rates](image)

Figure 1 **CSA is a Predictor of Mortality in Systolic HF**

Javaheri, JACC 2007;49:2028
Effect of CPAP on LVEF in Heart Failure with Cheyne-Stokes Respiration

29 patients with Cheyne-Stokes respiration, mean LVEF 22%

Sin, Circulation 2000;102:61

CANPAP Trial

Adaptive servo-ventilation

- Baseline low EPAP
- Modest minimum inspiratory pressure support
- Inspiratory support increases when ventilation (or flow) fall below 90% of long-term moving average

Teschler, AJRCCM 2001;164:614

ASV vs. CPAP in Heart Failure

CSA

Mixed CSA and OSA

Philippe, Heart 2006;92:337
Kasai, Circulation 2010;3:140
Treatment of Predominant Central Sleep Apnoea by Adaptive SERvo VEntilation in Patients with Heart Failure (SERVE-HF)

Participants
- Heart failure with LVEF ≤45%
- AHI ≥15, central AHI ≥10, central > obstructive

Intervention
- ASV (VPAP Adapt SV - lab titration) vs. usual care

Primary Outcome
- Death (any cause)
- Lifesaving cardiovascular intervention
  - Transplant, VAD, cardiac arrest, appropriate shock
  - Hospitalization for decompensated heart failure

SERVE-HF Participants (n=1325)

Heart failure
- NYHA Class: 2* (30%), 3 (69%), 4 (1%)
- Mean LVEF: 32%
- ICD or CRT-D: 48%

Sleep apnea
- Mean AHI 31: events/hr
- Central apneas + hypopneas: 81% of total events
- Epworth Sleepiness Scale score: 7
SERVE-HF Results

A Primary End Point (death, lifesaving CV intervention, ADHF hospitalization)

Hazard ratio, 1.13 (95% CI, 0.97–1.31)
P = 0.10

Deaths were out-of-hospital sudden death
ICD protective against ASV-associated death
Deaths were not on-device

C Death from Cardiovascular Causes

Hazard ratio, 1.34 (95% CI, 1.09–1.65)
P = 0.006

Deaths were out-of-hospital sudden death
ICD protective against ASV-associated death
Deaths were not on-device

Cowie, NEJM 2015; 373:1095
SERVE-HF: Who is at risk of death?

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients</th>
<th>ASV</th>
<th>Control</th>
<th>p-value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDB (AHI events/hour)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>697</td>
<td>0.252</td>
<td>0.214</td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>527</td>
<td>0.230</td>
<td>0.210</td>
<td></td>
</tr>
<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>= II</td>
<td>389</td>
<td>0.180</td>
<td>0.144</td>
<td></td>
</tr>
<tr>
<td>≥ III</td>
<td>927</td>
<td>0.277</td>
<td>0.246</td>
<td></td>
</tr>
<tr>
<td>CSR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50%</td>
<td>237</td>
<td>0.174</td>
<td>0.270</td>
<td></td>
</tr>
<tr>
<td>50-70%</td>
<td>439</td>
<td>0.239</td>
<td>0.172</td>
<td></td>
</tr>
<tr>
<td>&gt; 70%</td>
<td>460</td>
<td>0.304</td>
<td>0.224</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td>560</td>
<td>0.215</td>
<td>0.173</td>
<td></td>
</tr>
<tr>
<td>≥ 70</td>
<td>735</td>
<td>0.272</td>
<td>0.247</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>1168</td>
<td>0.250</td>
<td>0.233</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>127</td>
<td>0.305</td>
<td>0.121</td>
<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>526</td>
<td>0.459</td>
<td>0.313</td>
<td>0.06</td>
</tr>
<tr>
<td>≥ 30</td>
<td>742</td>
<td>0.178</td>
<td>0.177</td>
<td></td>
</tr>
</tbody>
</table>

Cowie, NEJM 2015; 373:1095

Recommendations

Asymptomatic CSA
- Optimize HF treatment
- No CSA-specific treatment indicated

Symptomatic CSA
- Optimize HF treatment
- Consider treatment with CPAP, O₂ or both
- Before using ASV, document normal LVEF
  - Or at least >30%
- If ineffective, could consider phrenic pacing, exogenous CO₂, acetazolamide
“No, I don’t need an alarm clock—
anxiety is my alarm clock.”