# OSA and Cardiovascular Disease: Potential Reasons Why RCT Trials failed to show benefit of CPAP Treatment

Shahrokh Javaheri, MD, FCCP, FAASM, FABSM
Division of Pulmonary and Sleep Medicine
Bethesda North Hospital, Cincinnati, OH
Professor Emeritus of Pulmonary and Sleep Medicine
University of Cincinnati, Cincinnati, Ohio
Adjunct Professor of Medicine, Division of Cardiology
The Ohio State University, Columbus Ohio

18th Annual Pulmonary, Critical and Sleep Medicine, 2022

# Recent RCTs on OSA Treatment with CPAP

Treatment of OSA with CPAP is not effective in preventing incident secondary CVD

What have we learned from these trials to guide a future trial?

No COI

# Recent Publications


1. Javaheri S, Martinez-Garcia MA, Campos-Rodriguez F. CPAP treatment and cardiovascular prevention: We need to change our trial designs and implementations. CHEST 2019; 156(3):431-437

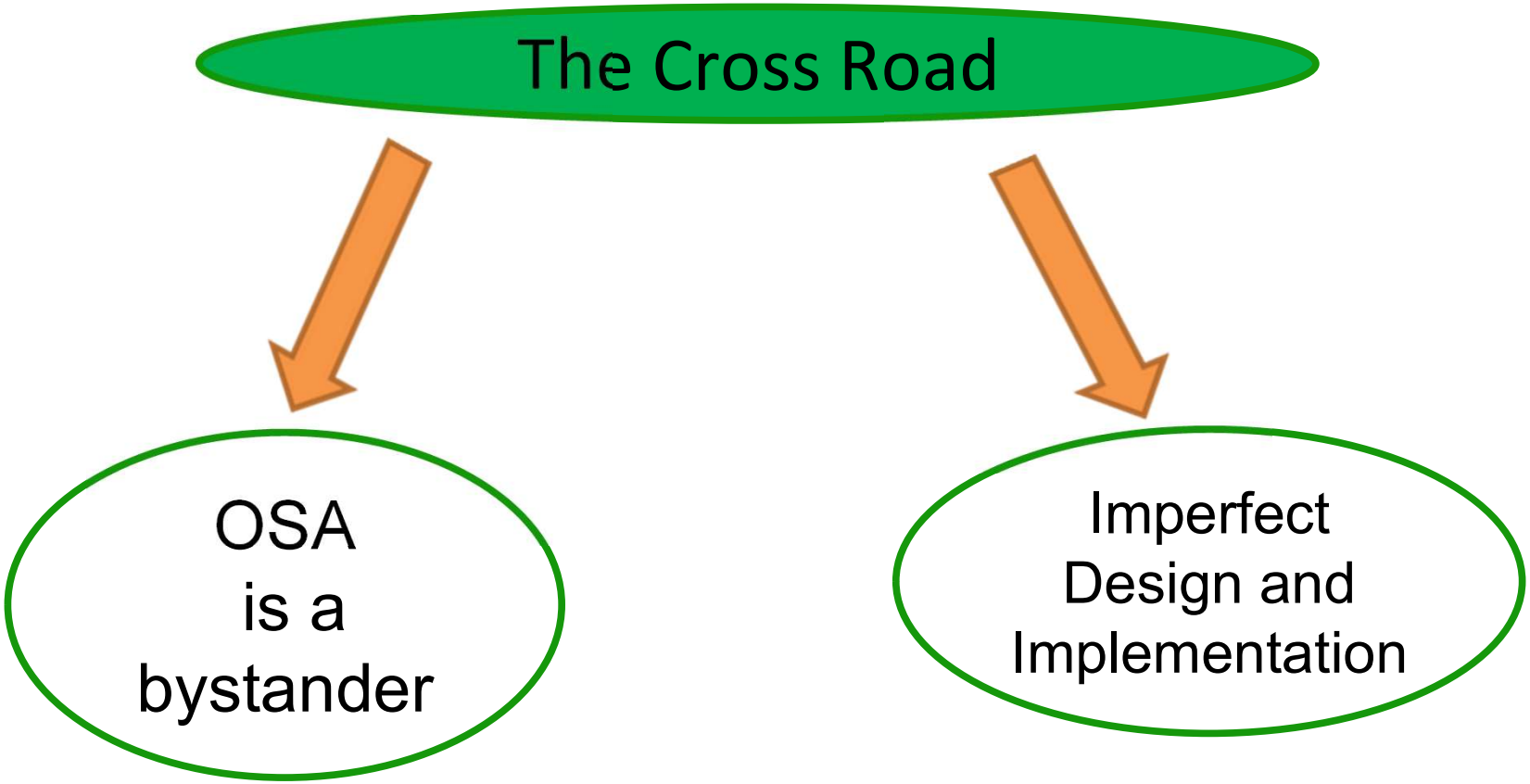
2. Javaheri S, Martinez-Garcia MA, Campos-Rodriguez F, Muriel A, Peker Y. Continuous Positive Airway Pressure Adherence for of Major Adverse Cerebrovascular and Cardiovascular Events in Obstructive Sleep Apnea. Am J Respir Crit Care Med. 2020; 201:607-610.

3. Martinez-García MA, Campos-Rodriguez F, Javaheri S, Gozal, D. PRO: Pro: continuous positive airway pressure and cardiovascular prevention. Eur Respir J 2018; 51: 1702400

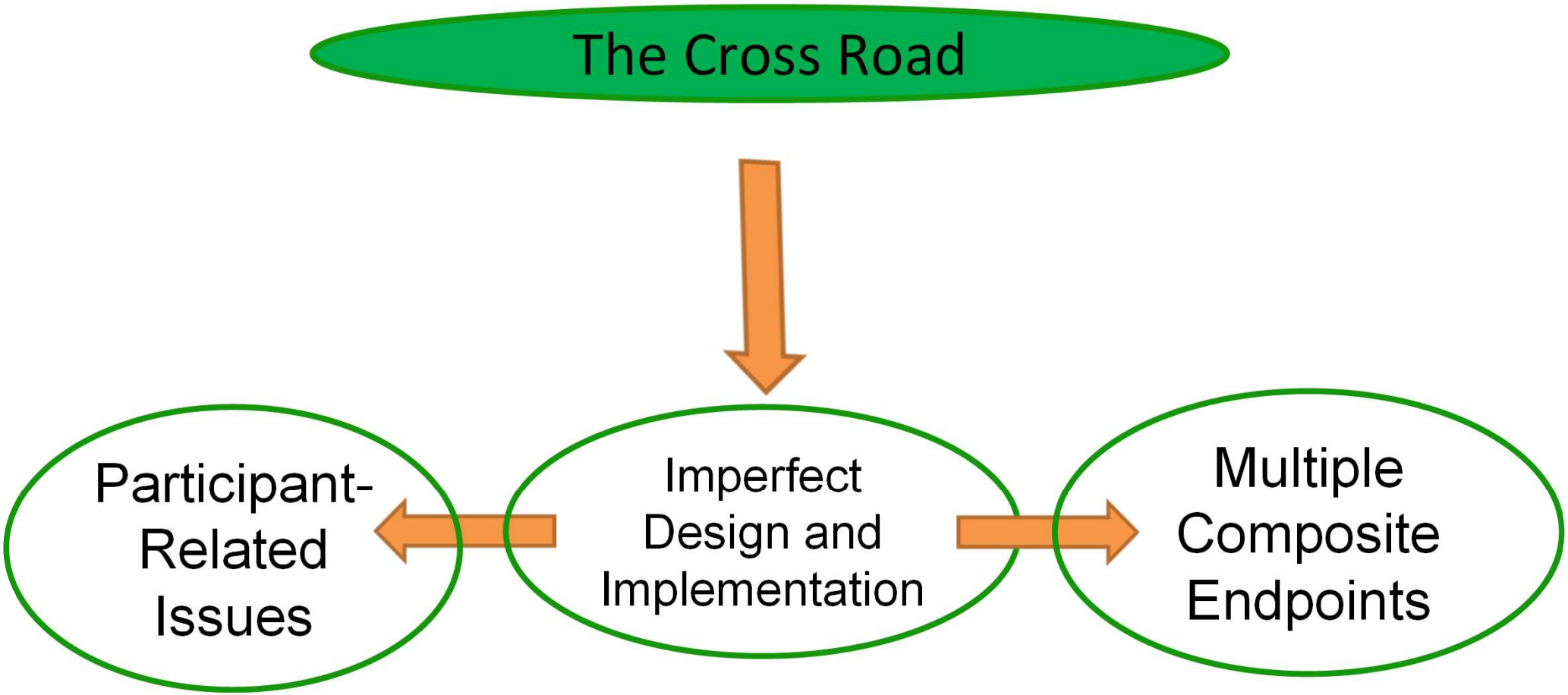
4. Javaheri S, Martinez-Garcia MA, Campos-Rodriguez F. CPAP treatment and cardiovascular prevention: We need to change our trial designs and implementations. CHEST 2020;1047-1048.

5. Javaheri et al. Sleep Med Reviews,2022

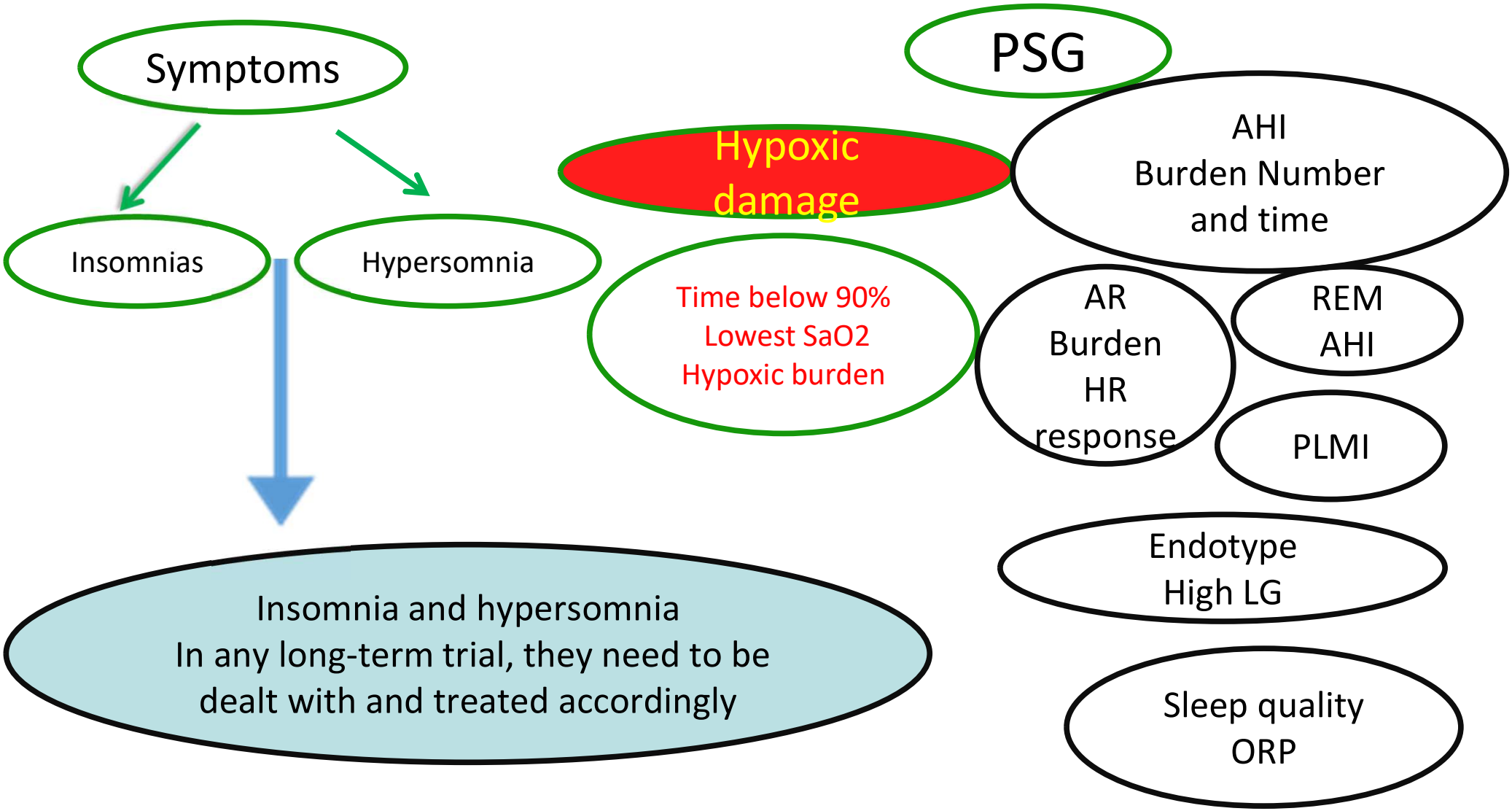
# Null Results of RCTs



# Null Results of RCTs



# The pheo-endotypes of OSA



# SAVE Trial

The largest RCT in OSA: 2700 subjects enrolled

Conclusion

Therapy with CPAP plus usual care, as compared with usual care alone, did not prevent cardiovascular events in patients with ***moderate-to-severe obstructive sleep apnea*** *and* ***established cardiovascular disease***

**What have we learned to guide future trials???**

# Exclusion criteria

- Pattern of Cheyne–Stokes respiration on the ***Apnea Link***
- Nasal pressure recording patients excluded if >50% of nasal pressure, defined apneas and hypopneas judged to be due to CSR
- Apnea Link: 2 channels, pressure probe+ oximetry
- Pressure probe is not the appropriate probe for apneas
- Pressure probe does not pick up mouth breathing
- SDB may have not been accurately identified
- Central apneas missed?

# Exclusion criteria
Pattern of CSB

## Inclusion criteria

- Stroke
- Hypertension
- Any heart disease
- Myocardial infarction
- Coronary stent insertion
- CABG
- NYHA categories III-IV of heart failure

## High prevalence of CSA

| | |
|---|---|
| 44% | |
| 80 % | |
| 40% | LVS/D dysfunction |
| 33% | Hidden CSA |
| 34% | **not suppressed by CPAP** |
| 12% | |

# Issues in RCT trials which may have resulted in negative results

1. Enrollment of subjects with CCeVD and with CSA
2. Exclusion of sleepy subjects
3. Exclusion of subjects with severe OSA and hypoxemia
4. Short duration of treatment
5. Poor adherence and limited use of CPAP
6. Composite endpoints ( stroke vs. cardiac)
7. Small number of subjects and the power of the trial
8. Age ( inadequate number of young subjects)

# Future Trials

**Polygraphy with a type III device allows the best minimal opportunity to exclude those with CSA which may not be suppressed by CPAP**

**Minimal number of channels**

1. **Thermocouple**
2. **Pressure probe**
3. **Rib cage**
4. **Abdominal**
5. **$Sao_2$**

# Issues in RCT trials which may have resulted in negative results

1. Enrollment of subjects with CCeVD and with CSA
2. Exclusion of sleepy subjects
3. Exclusion of subjects with severe OSA and hypoxemia
4. Short duration of treatment
5. Poor adherence and limited use of CPAP
6. Composite endpoints ( stroke vs. cardiac)
7. Small number of subjects and the power of the trial
8. Age ( inadequate number of young subjects)

# All Recent Randomized Trials of Effect of CPAP on Cardiovascular Events Had a Shared e Bias

| Study | Exclusion Criteria | Epworth Sleepiness Score |
|---|---|---|
| SAVE[1] | Epworth >15 | 7.3±3.6 / 7.5±3.6 |
| ISAACC[2] | Epworth >10 | 5.4±2.5 / 5.3±2.5 |
| RICCADSA[3] | Epworth ≥10 | 5.5±2.4 / 5.5±2.2 |

## THESE ARE NOT OUR PATIENTS

1McEvoy RD, et al, NEJM 375:919,2016
2Sanchez-de-la Torre M, et al, Lancet Respir Med 8:359, 2020
3Peker Y, et al, AJRCCM 194:613,2016

# Symptom Subtypes of Obstructive Sleep Apnea Predict Incidence of Cardiovascular Outcomes (BJ,2020)

**N=1,207 OSA (spectrum of sleepiness: minimal to severe**

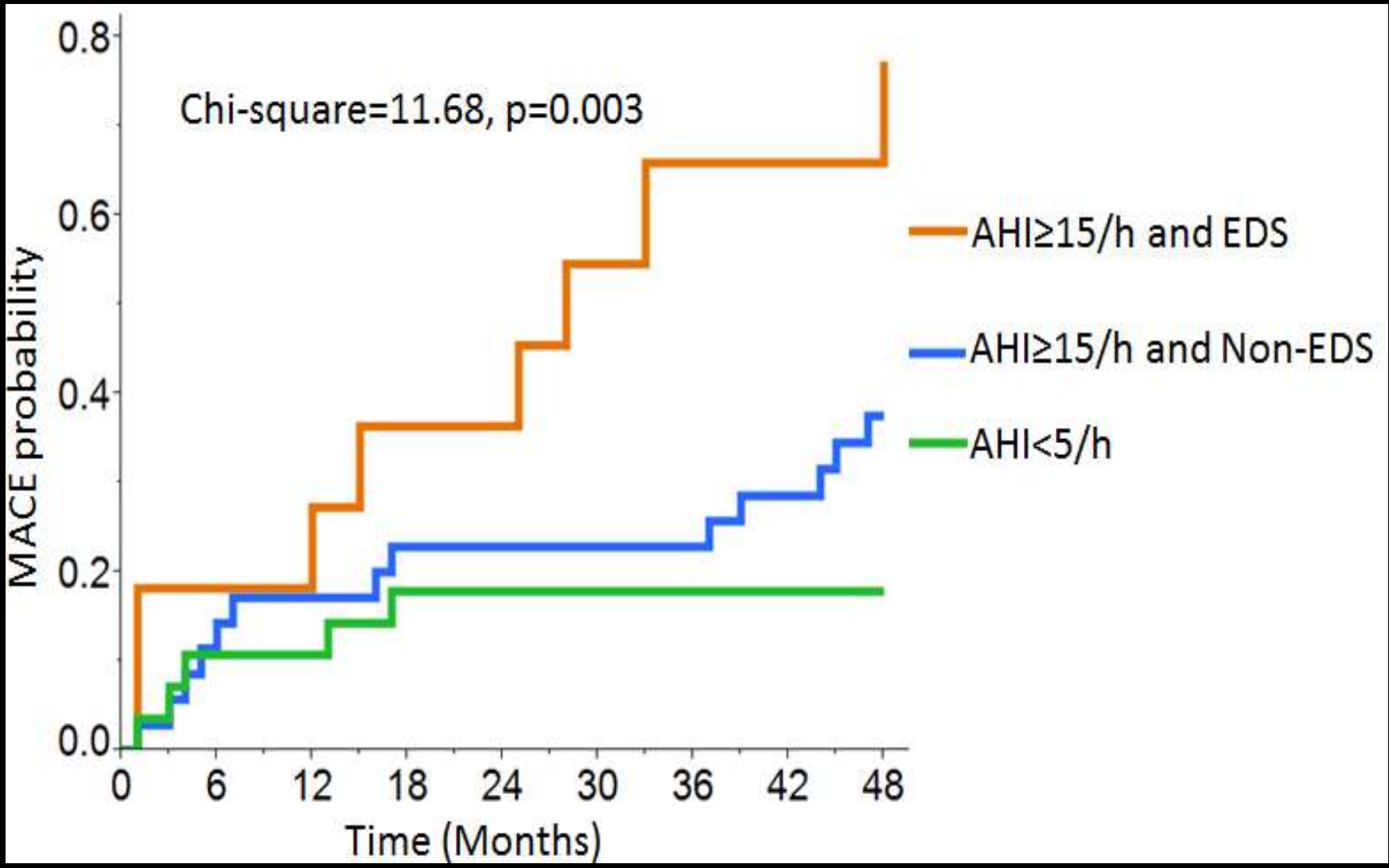
**Patients symptom subtype was associated with incident CVD (p<0.001),**

**CHD (p=0.015) and HF (p=0.018), with the Excessively Sleepy phenotype**

**demonstrating increased risk (HR= 1.7-2.4) compared to other subtypes**

Mazzotti, Keenan BT, Lim DC, Gottlieb DJ, Jinyoung Kim J, Pack AI.

# EDS predicts MACE in MI patients




**N=104**

**Xie et al, 2017**

MAYO CLINIC

# Sleepy OSA Phenotype

In patients with history of MI, a major determinant of lack of reinfarction and MACE is absence of EDS

*In the SAVE trial, 33% of the 2687 subjects recruited had history of MI and in average did not have EDS*

These subject may not have benefited from use of CPAP

# IL and TNF as the cause of EDS and CVD

- Injection of either IL-1 or TNF into brain or intraperitoneally enhances the amount of time spent in NREMS

- IL-1 and TNF have been somnogenic in every species thus far tested

KRUEGER, J.M. et al. 1999. Humoral regulation of physiological sleep: cytokines and

GHRH. J. Sleep Res. 8(suppl. 1): 53–59

**OSA-related cardiovascular disordered could be in part mediated by upregulation of inflammatory cascades**

# The Sleepy OSA Phenotype

1. **In OSA, there may be common biopathophysiological mechanisms linking EDS to HTN, CVD, and insulin resistance**
2. **TNF and IL6 are somnogenic and inflammatory**
3. **Nonsleepy subjects may not respond to CPAP as sleepy subjects do**

**Javaheri and Javaheri ,CHEST 2020**

# OSA phenotype with EDS

Future trial

Sleepy patients should not be excluded with some exceptions

(Truck drivers)

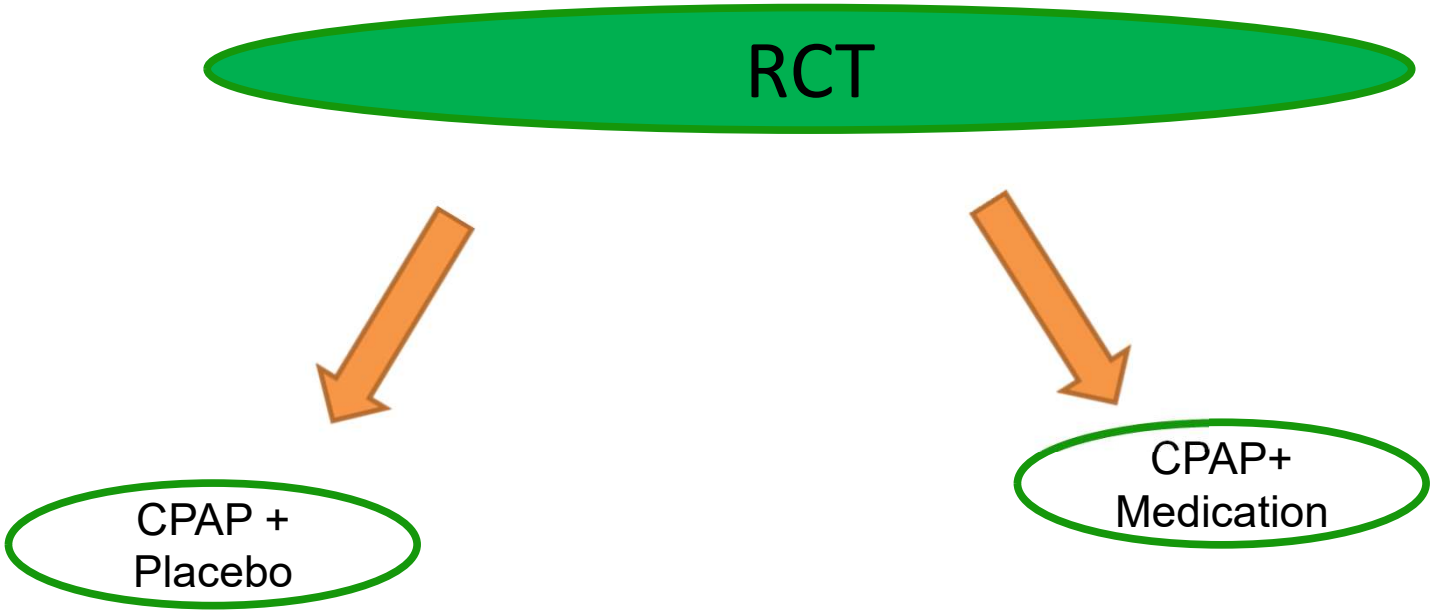
Pharmacotherapy of EDS in both arms

Many patients with severe OSA remain sleepy on CPAP

and need pharmacological therapy

( Javaheri, Chest 2020)

# Sleepy  OSA Phenotype

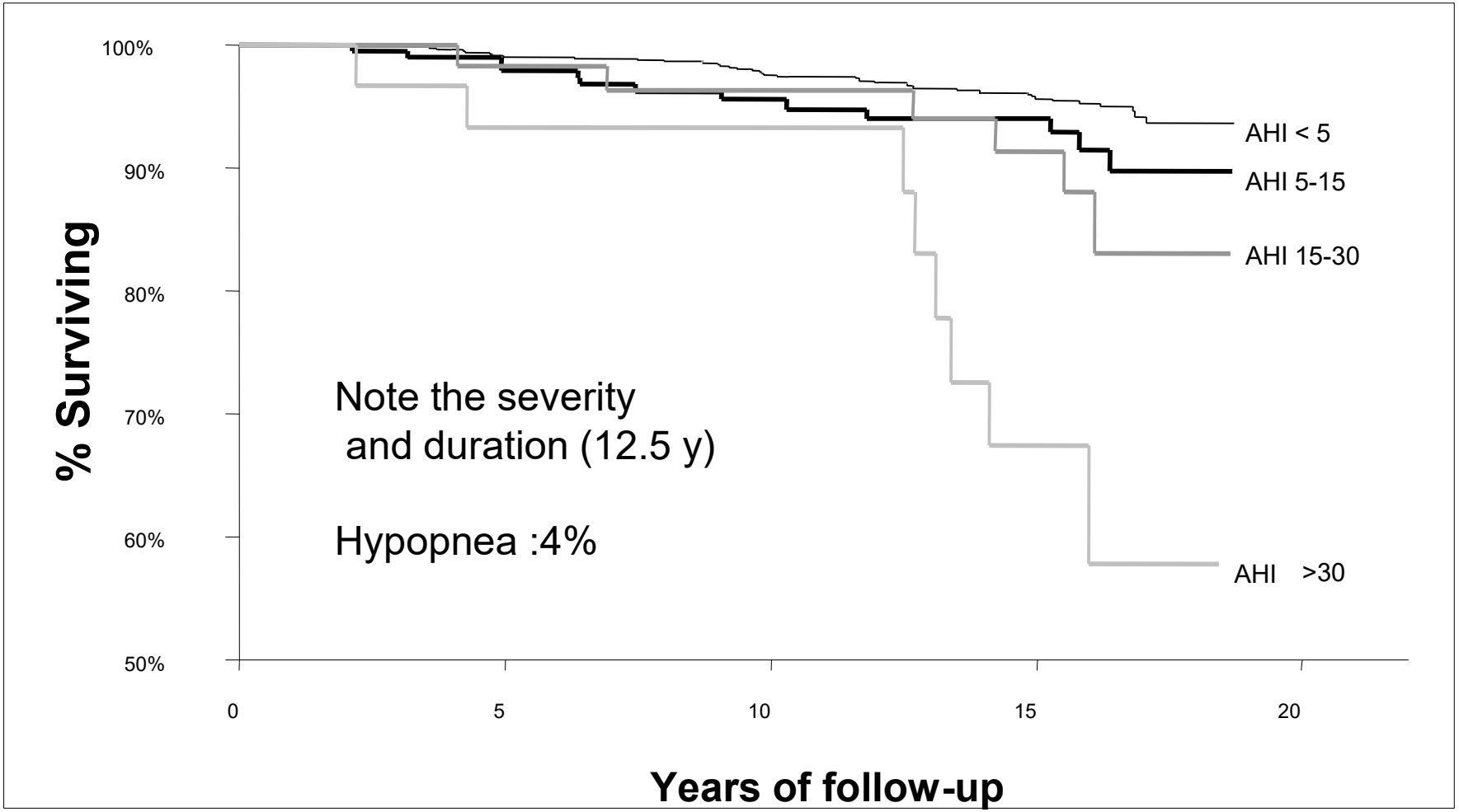



Modafinil; Solriamfetol; Pitolisant

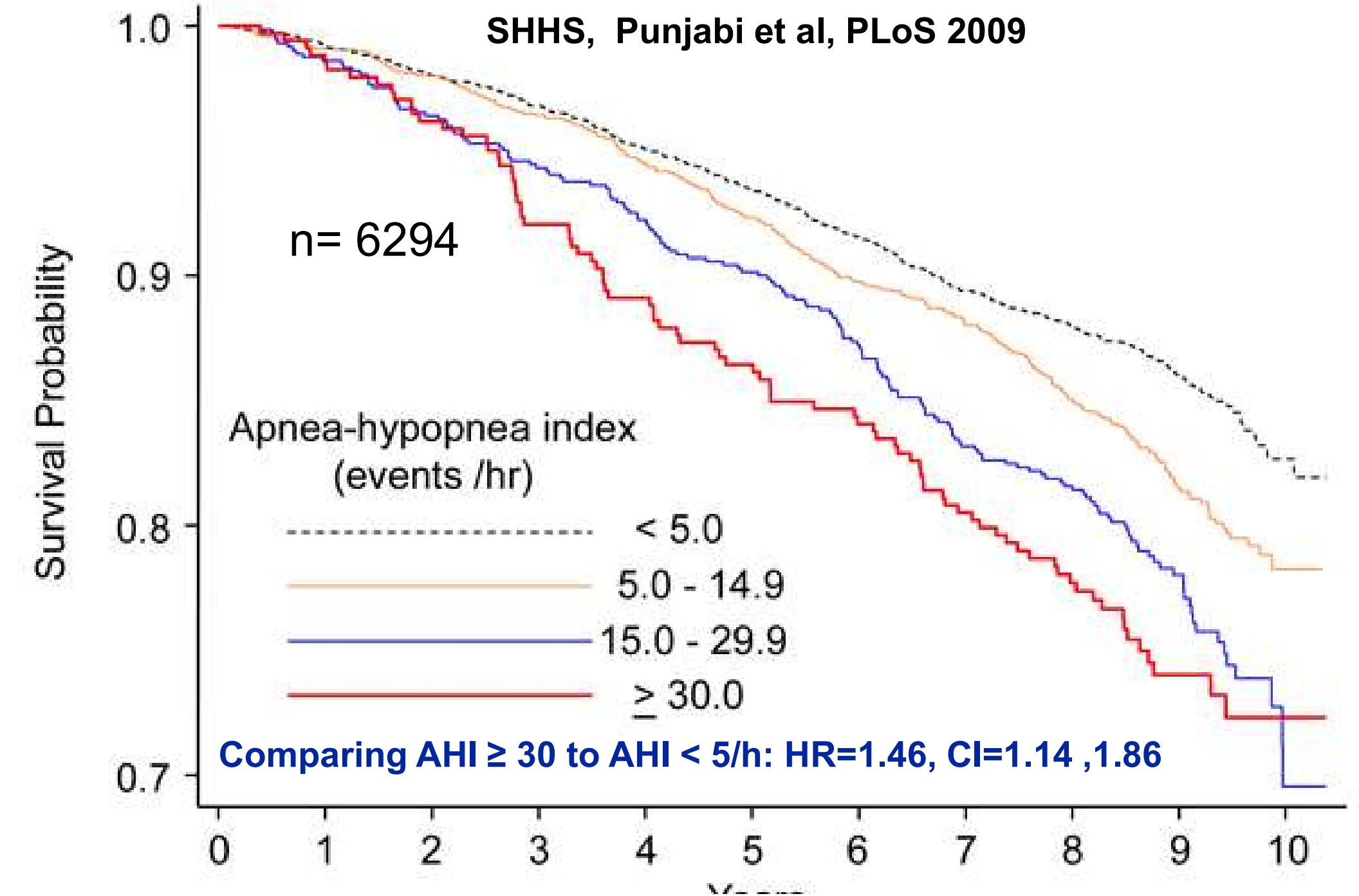
# Issues in RCT trials which may have resulted in negative results

1. Enrollment of subjects with CCeVD and with CSA
2. Exclusion of sleepy subjects
3. Exclusion of subjects with severe OSA and hypoxemia
4. Short duration of treatment
5. Poor adherence and limited use of CPAP
6. Composite endpoints ( stroke vs. cardiac)
7. Small number of subjects and the power of the trial
8. Age ( inadequate number of young subjects)

# Hard CV outcomes have been associated with severe OSA




All-cause mortality with untreated SDB,
(Sample excludes 126 CPAP users )(Young,Sleep,2008)


SHHS, Punjabi et al, PLoS 2009
n= 6294
Survival Probability
1.0
0.9
0.8
0.7
0
1
2
3
4
5
6
7
8
9
10
Apnea-hypopnea index
(events /hr)
< 5.0
5.0 - 14.9
15.0 - 29.9
≥ 30.0
Comparing AHI ≥ 30 to AHI < 5/h: HR=1.46, CI=1.14 ,1.86

## Hypoxemia burden in OSA ( *duration and severity*)
## Duration

- In the SHHS, among men, less than 70 y in age, TST < 90% was a significant predictor of mortality

Compared to the first three quartiles (TST90 ≤2.7%),
the fourth quartile (TST90 >2.7%)
had an adjusted HR of 1.83 (95% CI: 1.31–2.52) for mortality

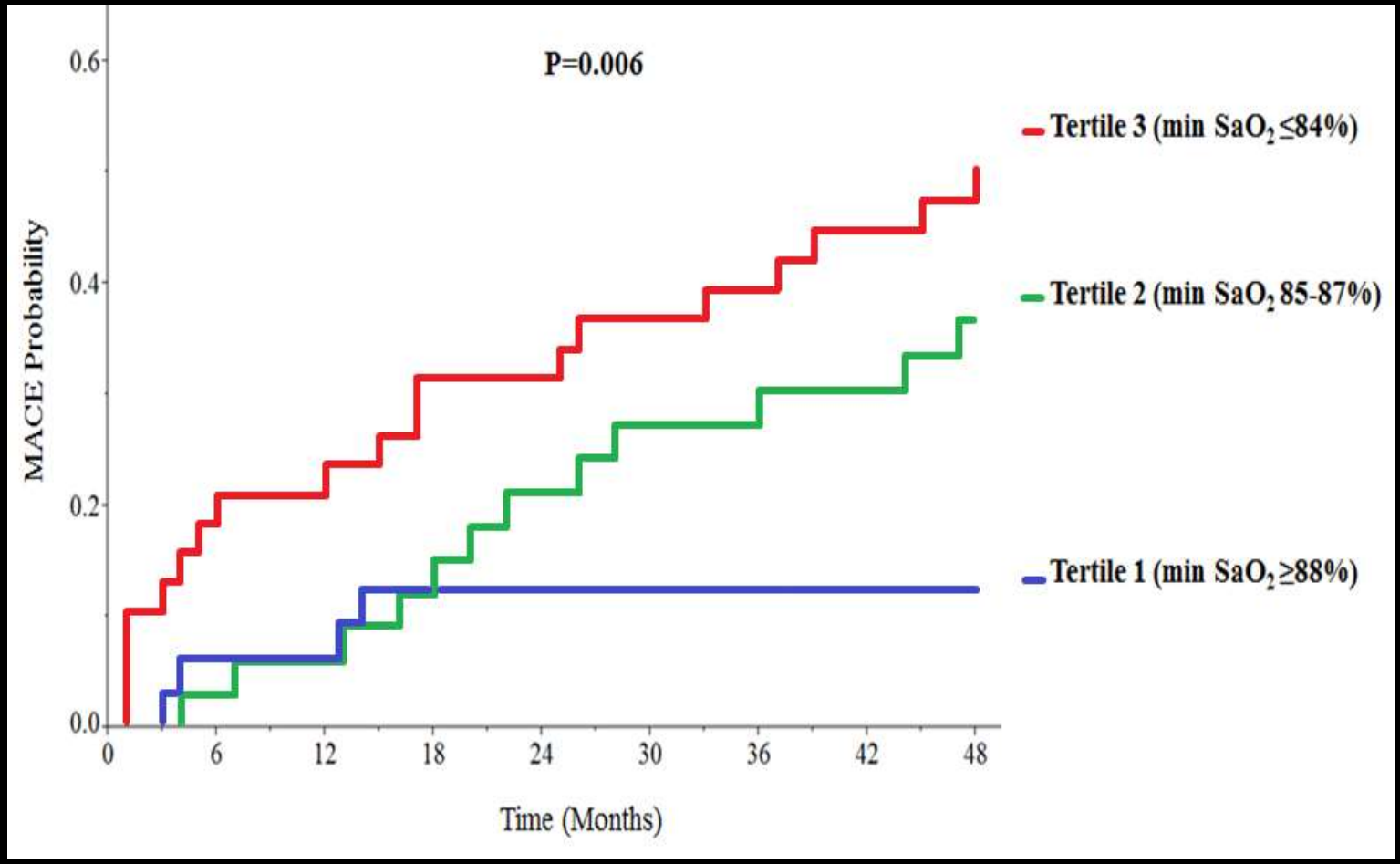
Adjustments: age, race, smoking status, BMI, SBP, DBP, AHI, prevalent hypertension, diabetes, and CVD

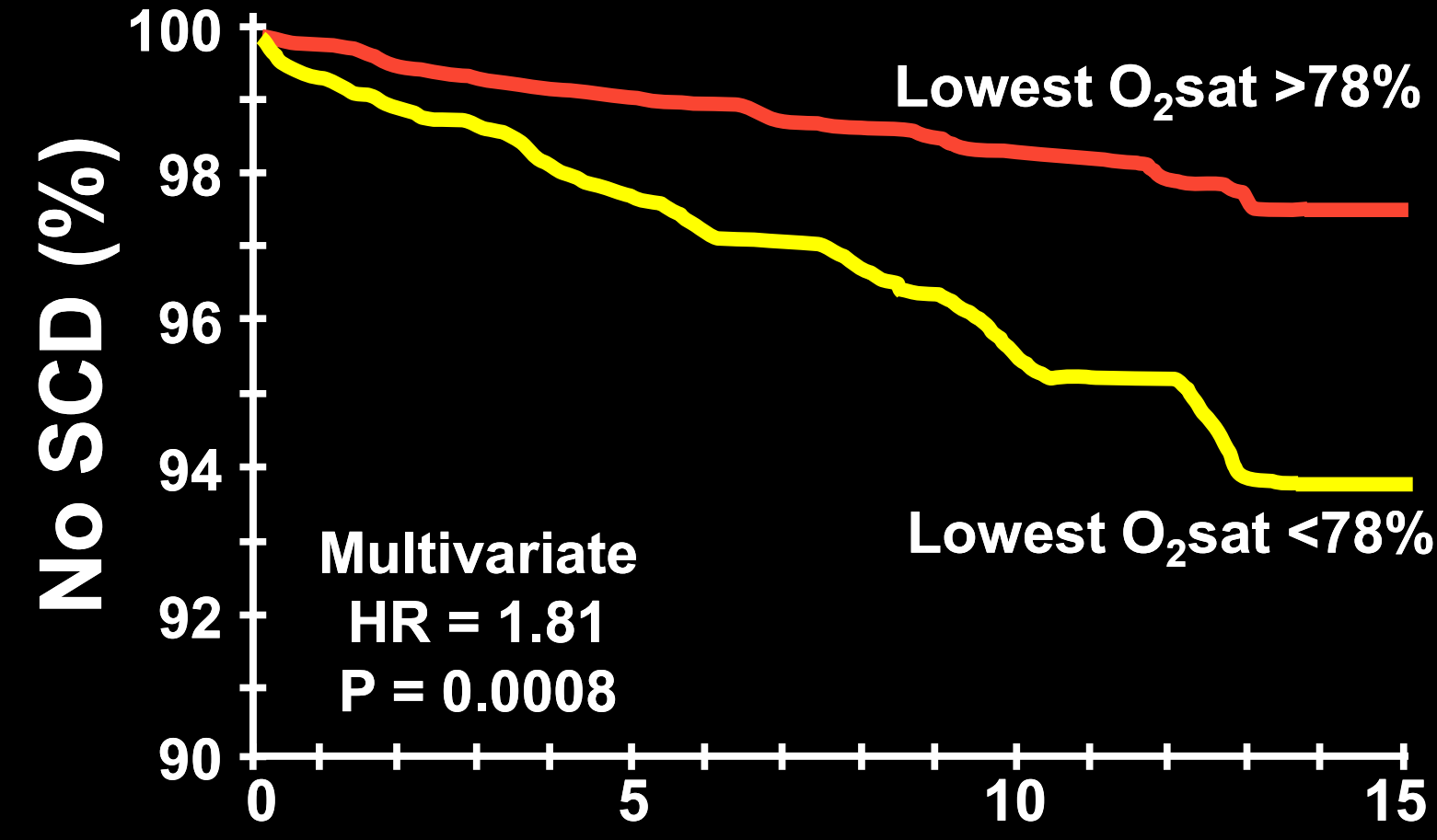
Punjabi et al. Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med 2009; 6: e1000132

# Hypoxemia and prognosis after MI

- 103 MI patients, 44% with SDB (AHI ≥15 event/h)
- 4 yr follow-up

***Xie et al., 2016***



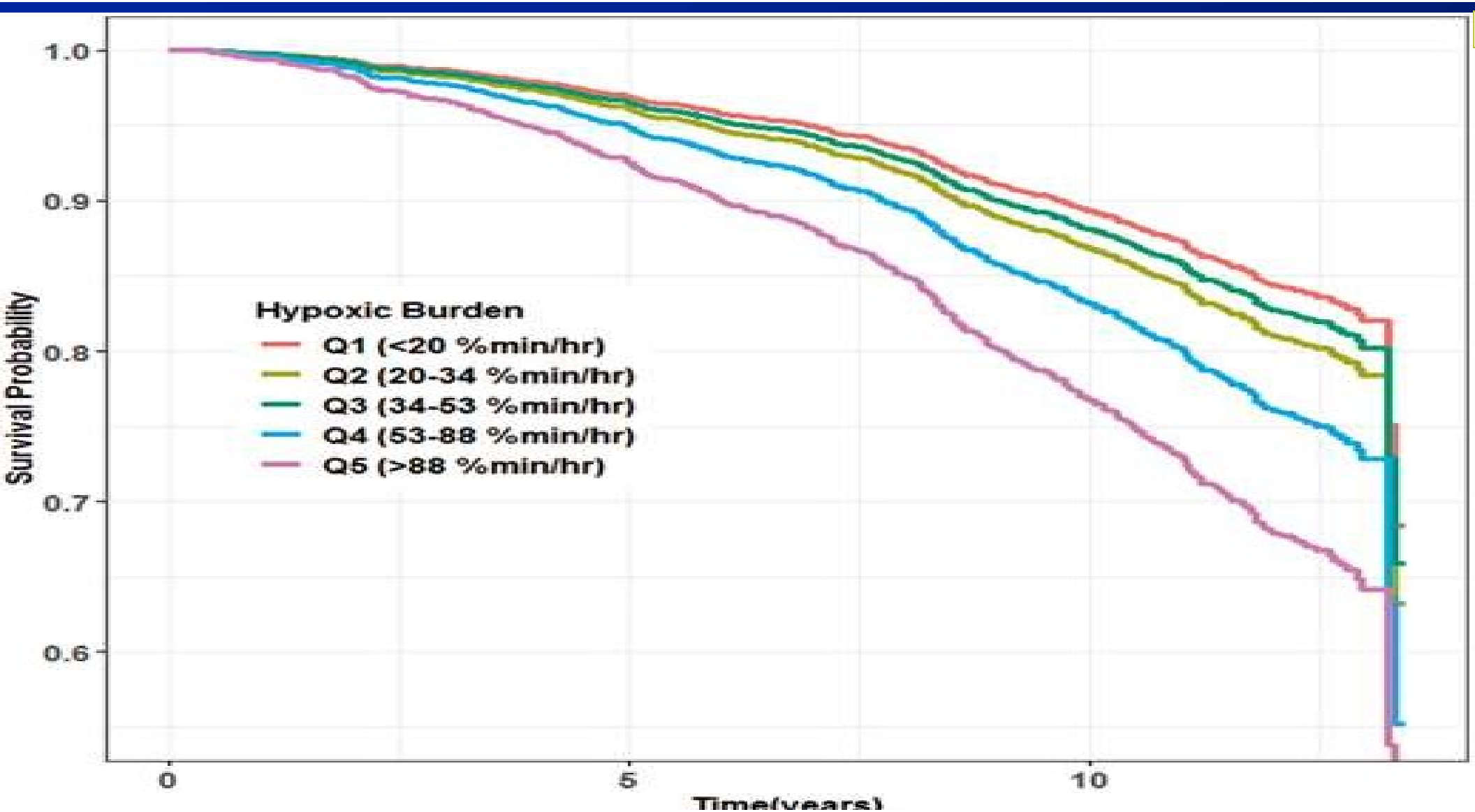



(Gami, Somers et al)

| Numbers at risk: | | | |
|---|---|---|---|
| 2345 | 1160 | 295 | 20 |
| 8299 | 3726 | 953 | 101 |

MAYO CLINIC

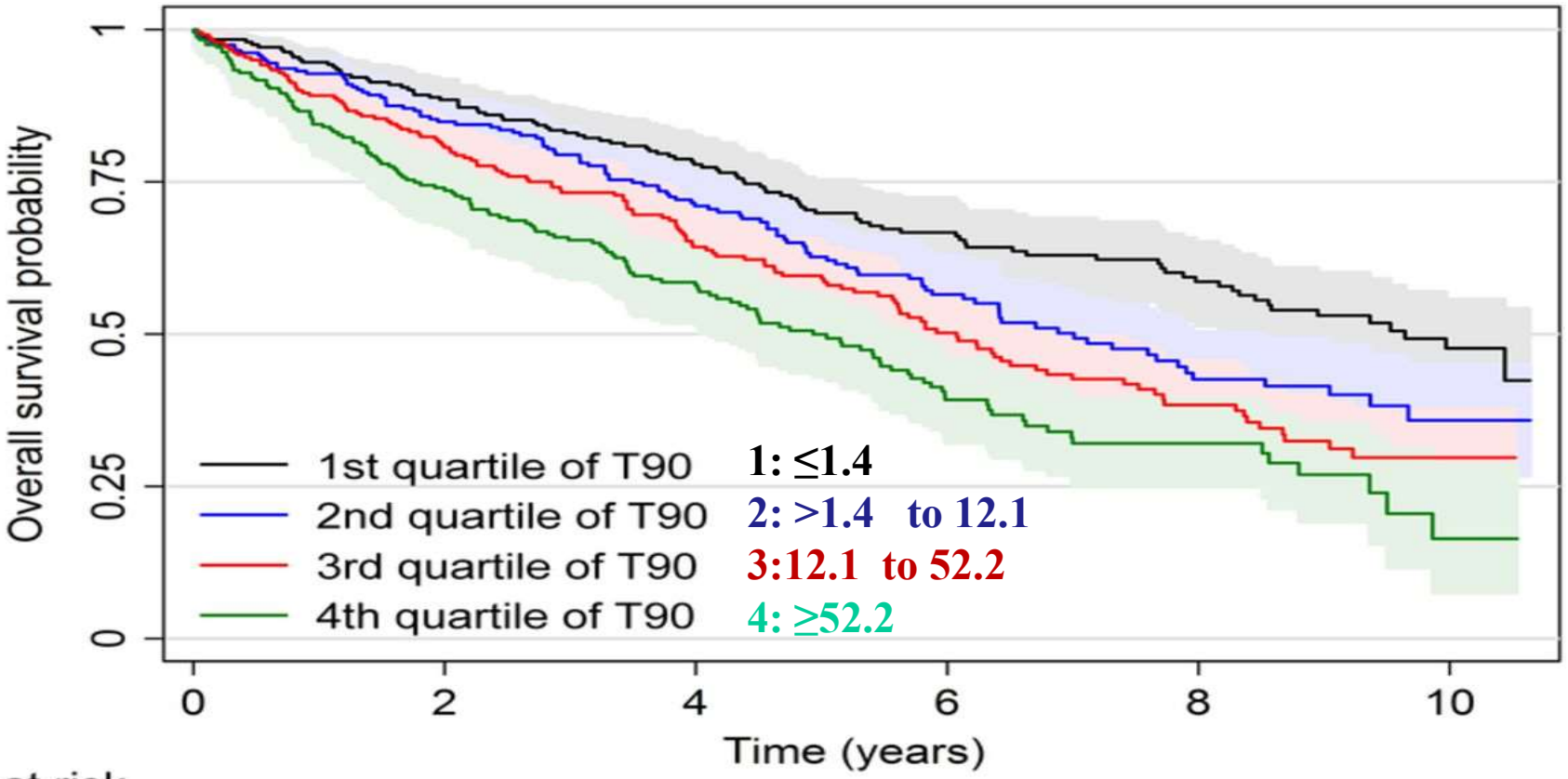
**The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. Azarbarzin et al. EHJ (2019) 40, 1149–1157**



## Slide 27

**SJ1** Shahrokh Javaheri, 9/16/2020

Kaplan–Meier survival curves by quartile of time with nocturnal oxygen saturation below 90% (T90, min) in patients with HF




Number at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| 1st quartile | 244 | 214 | 173 | 115 | 79 | 30 |
| 2nd quartile | 237 | 191 | 141 | 82 | 42 | 11 |
| 3rd quartile | 241 | 188 | 127 | 78 | 43 | 12 |
| 4th quartile | 241 | 167 | 107 | 55 | 23 | 3 |

**Oldenburg et al. Eur Heart J 2015**

## Excusion of subjects with severe hypoxemia

| | ISAACC | SAVE |
|---|---|---|
| ODI >4%, per h | 31 (24 ) | 28 (15) |
| Mean SaO2 | 92 (9) | ? |
| Minimum $SaO_2$ | 82 (7) | ? |
| Time with $SaO_2$ <90% | 12 (18) | <80% for >10% excluded |

ISAACC study (Lancet Respir Med 2020; 8: 359–67

| | SAVE | ISAACC CPAP (629) |
|---|---|---|
| ODI >4%, per h | 28 (15) Minimum ODI=12 | 31 (24 ) |
| Mean SaO2 | | 92 (9) |
| Minimum SaO2 | | 82 (7) |
| Time with SaO2 <90% | >10%< 80% (excluded) | 12 (18) |

# AHI in OSA and mortality

In subjects with OSA , an AHI of ≥ 30/hour, and severe desaturation are associated with excess mortality

Subjects with AHI ≤ 30and less sever hypoxemia may not benefit fromthe use of CPAP

Future Trial

As a start: an RCT of subjects with severe OSA

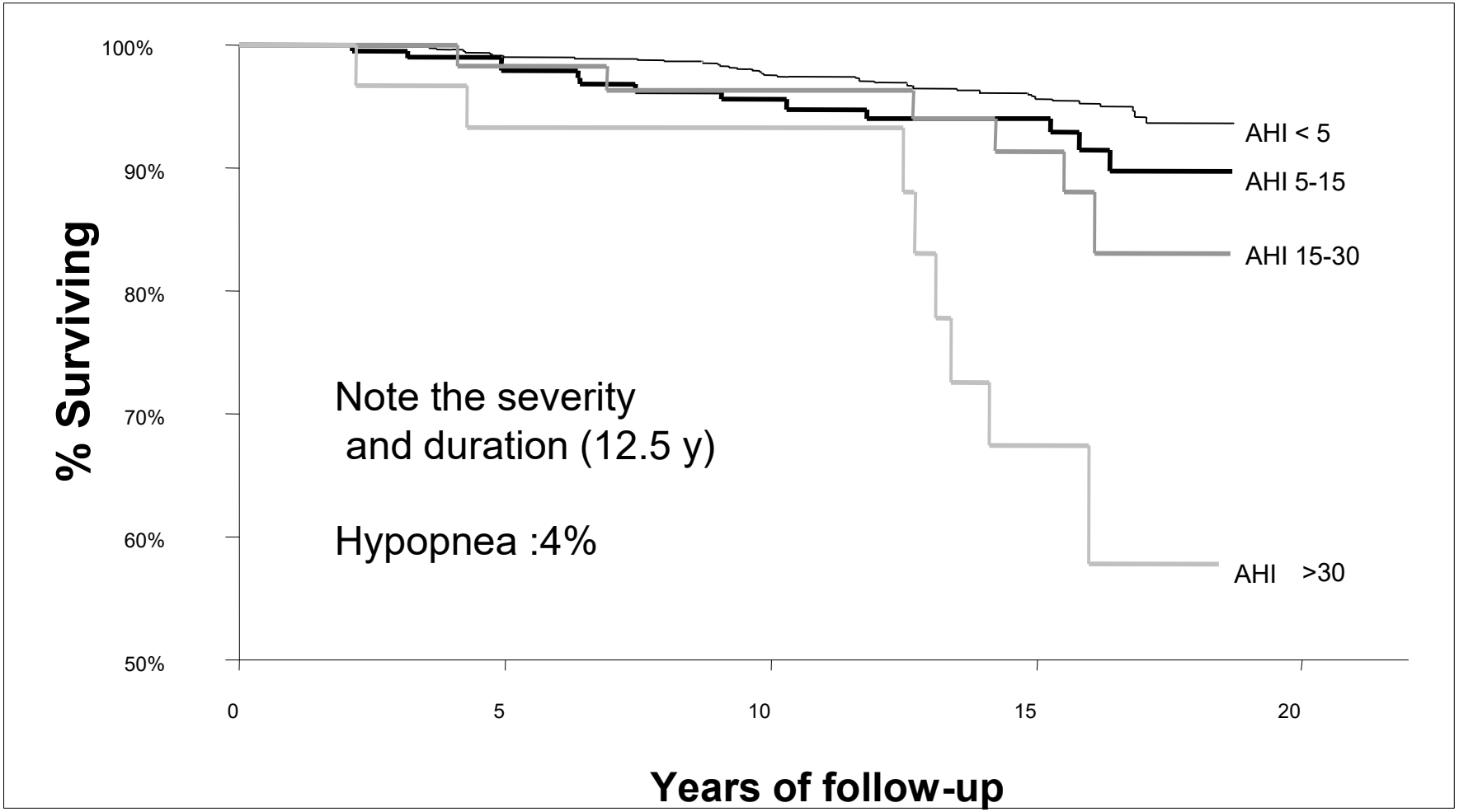
# Issues in RCT trials which may have resulted in negative results

1. Enrollment of subjects with CCeVD and with CSA
2. Exclusion of sleepy subjects
3. Exclusion of subjects with severe OSA and hypoxemia
4. Short duration of treatment
5. Poor adherence and limited use of CPAP
6. Composite endpoints ( stroke vs. cardiac)
7. Small number of subjects and the power of the trial
8. Age ( inadequate number of young subjects)

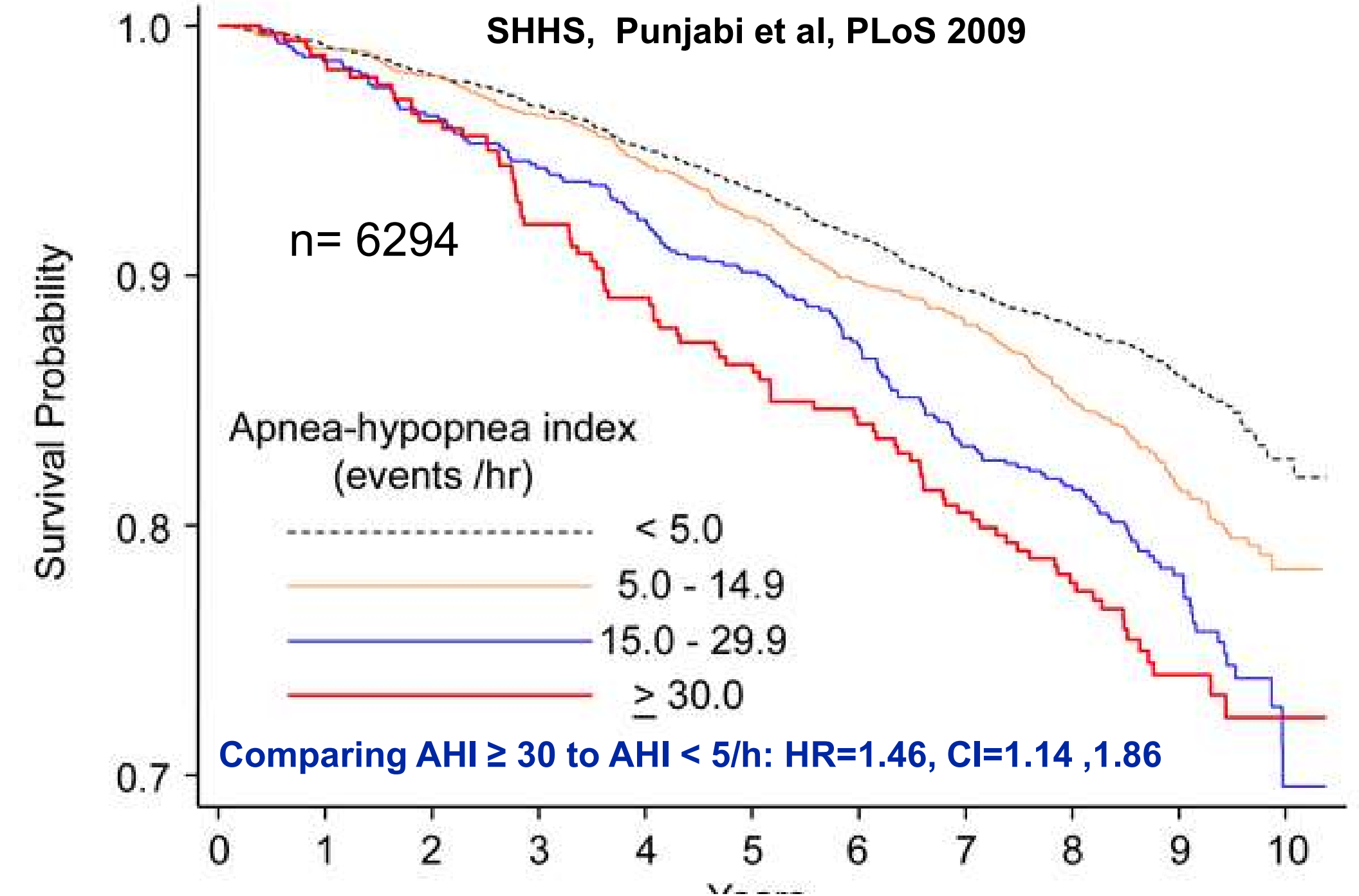
Short Duration

| SAVE trial | Duration(years) | Median( years) |
|---|---|---|
| | 7 | 3.7 |
| ISAACC | 6 | 3·35 |

# Hard CV outcomes have been associated with severe OSA




All-cause mortality with untreated SDB,
(Sample excludes 126 CPAP users )(Young,Sleep,2008)


SHHS, Punjabi et al, PLoS 2009
n= 6294
Survival Probability
1.0
0.9
0.8
0.7
0
1
2
3
4
5
6
7
8
9
10
Apnea-hypopnea index
(events /hr)
< 5.0
5.0 - 14.9
15.0 - 29.9
≥ 30.0
Comparing AHI ≥ 30 to AHI < 5/h: HR=1.46, CI=1.14 ,1.86

Short Duration

| SAVE trial | Duration(years) | Median( years) |
|---|---|---|
| | 7 | 3.7 |
| ISAACC | 6 | 3·35 |

I believe that subjects with less severe OSA ( as recruited in the SAVE trail) need to be followed longer than those with severe OSA, and with god adherence to CPAP

# Issues in RCT trials which may have resulted in negative results

1. Enrollment of subjects with CCeVD and with CSA
2. Exclusion of sleepy subjects
3. Exclusion of subjects with severe OSA and hypoxemia
4. Short duration of treatment
5. Poor adherence and limited use of CPAP
6. Composite endpoints ( stroke vs. cardiac)
7. Small number of subjects and the power of the trial
8. Age ( inadequate number of young subjects)

# Poor PAP adherence

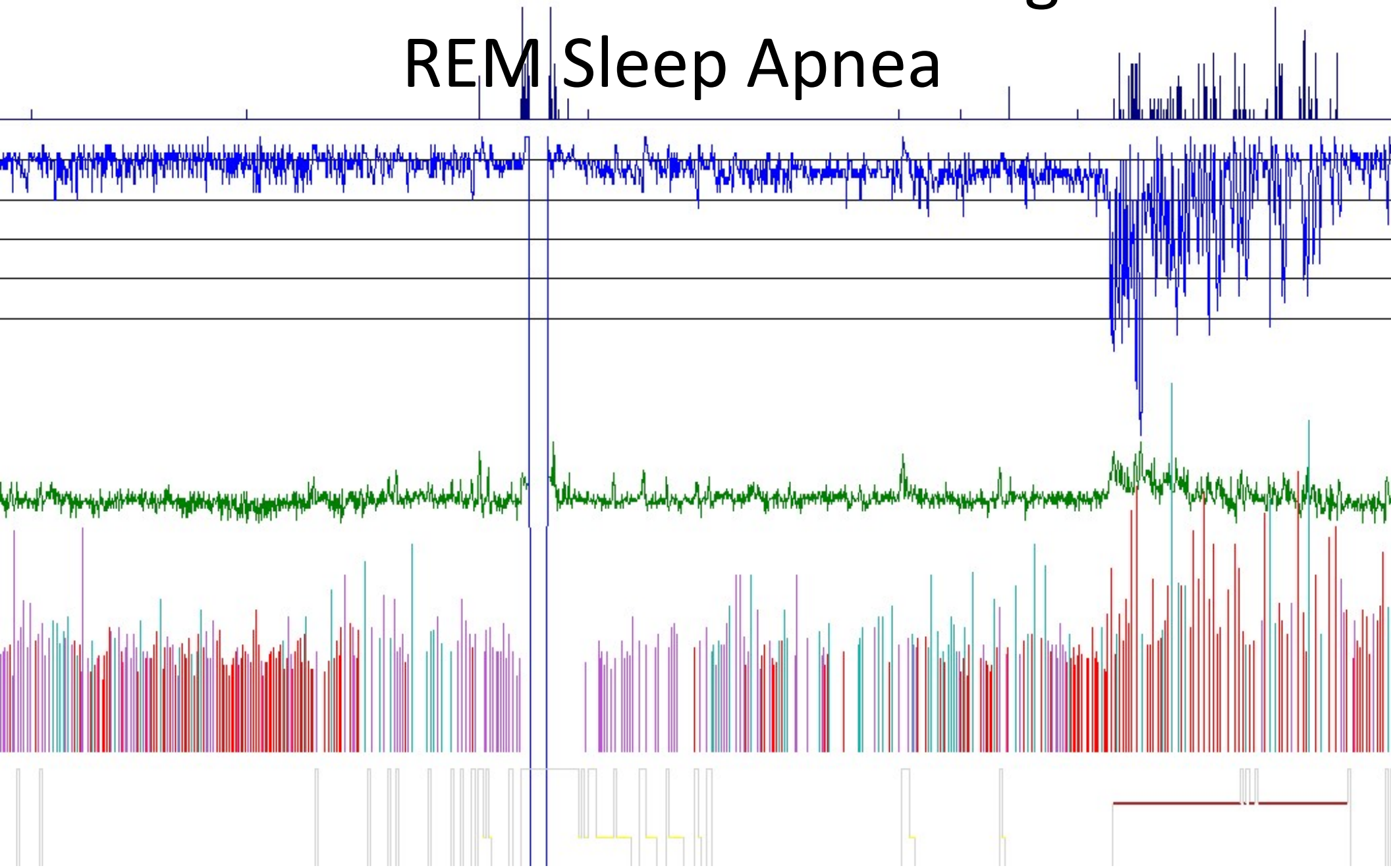
- 1. studies consistently show that only adherent subjects benefit from beneficial effect of CPAP

  (HTN, Insulin restance and inflammatory cascade)

- 2. Nonselective users of CPAP may not benefit from beneficial effect of CPAP ( REM-protective effect)

Javaheri et al: State of the art review: JACC 2017

# OSA worsens across the night
# REM Sleep Apnea



# Future trial

Inclusion of running-in period with low pressure sham CPAP and enrollment of only adherent subjects , similar to drug therapy of CHF.

Minimum 6 w and 5 hours to satisfy eligibility for randomization

# Issues in RCT trials which may have resulted in negative results

1. Enrollment of subjects with CCeVD and with CSA
2. Exclusion of sleepy subjects
3. Exclusion of subjects with severe OSA and hypoxemia
4. Short duration of treatment
5. Poor adherence and limited use of CPAP
6. Composite endpoints ( stroke vs. cardiac)
7. Small number of subjects and the power of the trial
8. Age ( inadequate number of young subjects)

# Composite end point

| SAVE | ISAACC |
| --- | --- |
| Cardiovascular death | Cardiovascular death |
| MI(including silent MI) | MI |
| Hospitalization for | Hospitalization for |
| Heart failure | Heart failure |
| Acute coronary syndrome | |
| Unstable angina | Unstable angina |
| TIA | TIA |
| Stroke | Non-fatal stroke |

## Advantages and disadvantages of composite endpoints

### Advantages

1. Decreased sample size

2. Assessment of treatment effects in the presence of competing risks

### Disadvantages

1. Diminishes the possibility of detecting an important treatment effect on individual components of the endpoint

2. Applicability of the results to individual patients becomes less certain

There is considerable evidence showing that OSA is an important risk factor for incident stroke

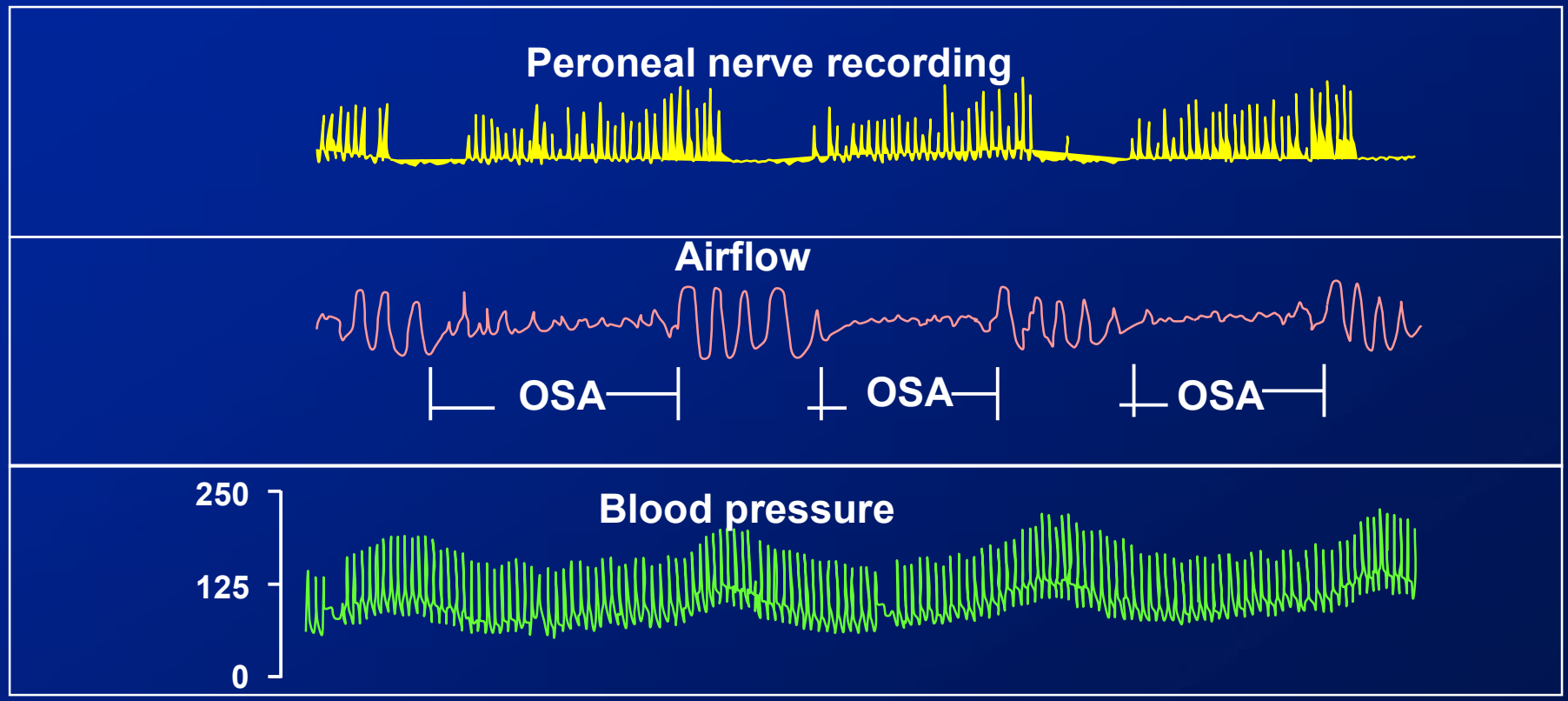
The association between OSA and CHD is not as strong as with stroke

In the cross sectional SHHS, coronary heart disease and stroke were prevalent the point estimates for stroke were significantly higher than those of coronary heart disease or heart failure

Several reasons may explain these findings:
The different pathophysiologic pathways of blood flow regulation:

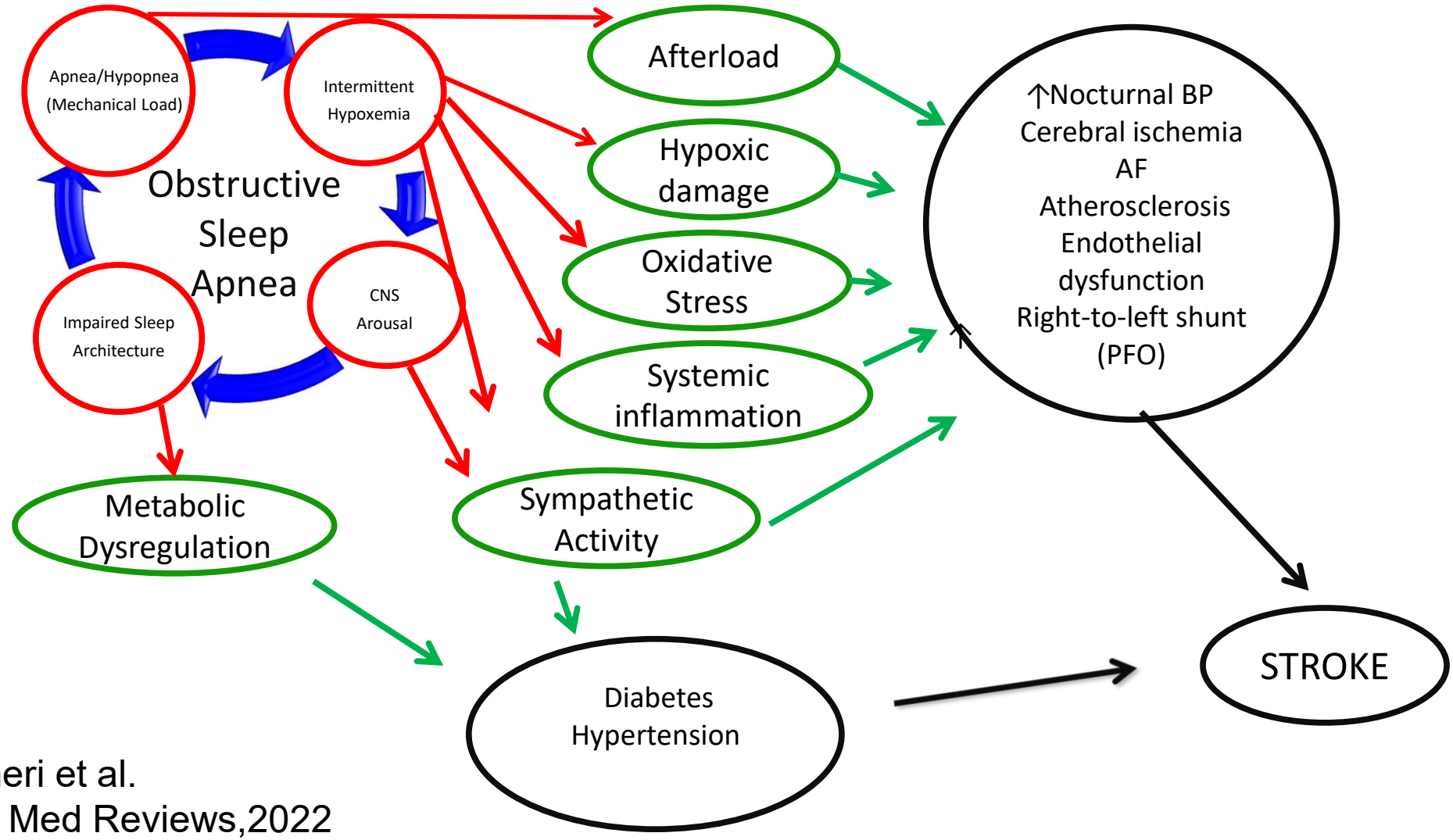
Due to unsteady dynamic cycles of OSA, autoregulatory mechanisms to maintain homeostasis are ineffective and cerebral vascular bed is exposed to apnea-related fluctuations in SBP and DBP, whereas blood flow to the heart occurs only in diastole with overall much less coronary vascular stress

# Fig 7. Cyclic increases in sympathetic nerve activity, BP and HR in parallel to episodes of OSA




Somers VK et al. J Clin Invest. 1995;96:1897.

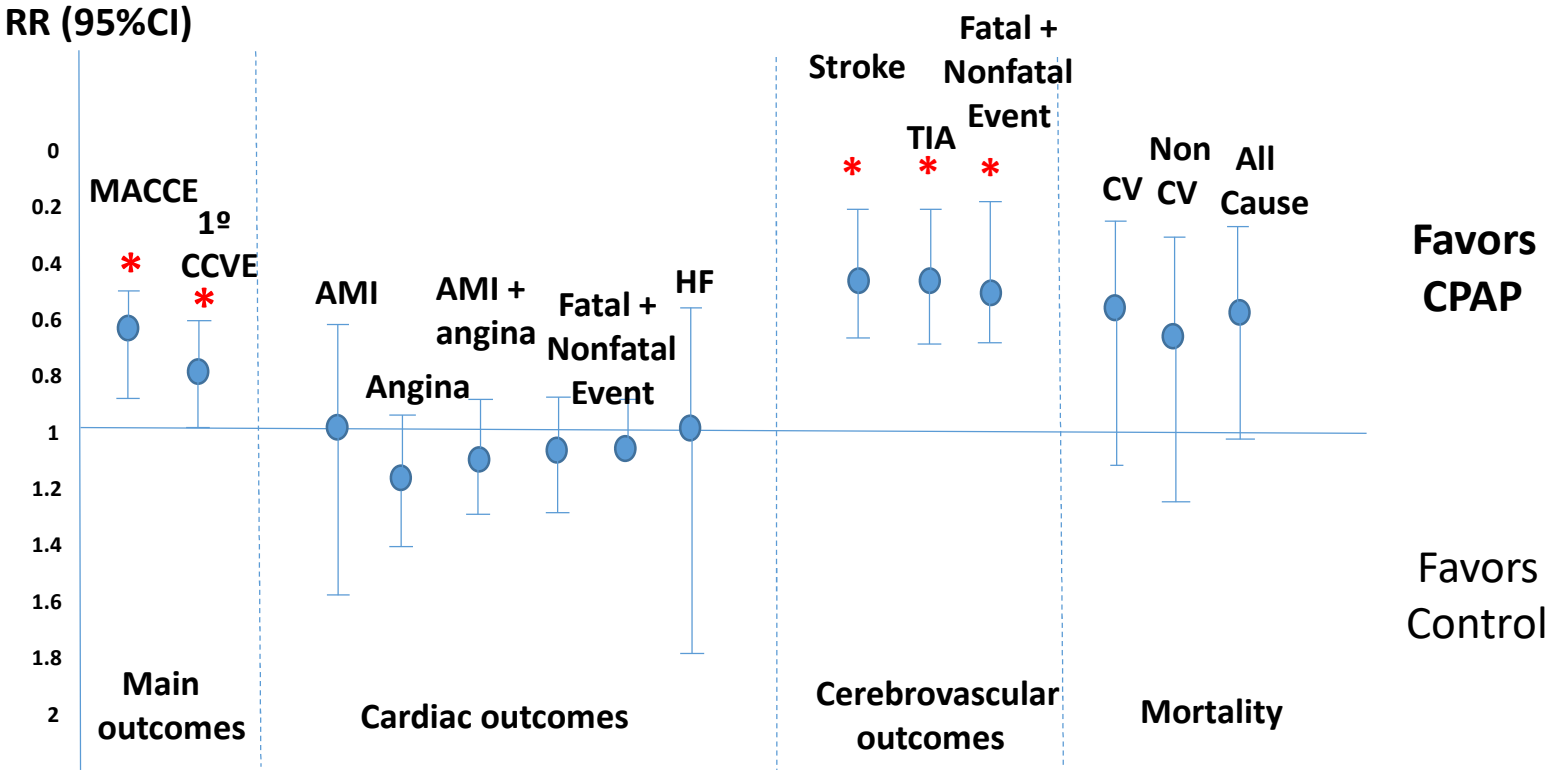
# Mechanisms of Stroke Risk in Sleep Apnea




Javaheri et al.
Sleep Med Reviews,2022

Effective Use of CPAP Improves cerebrocardiovascular outcomes

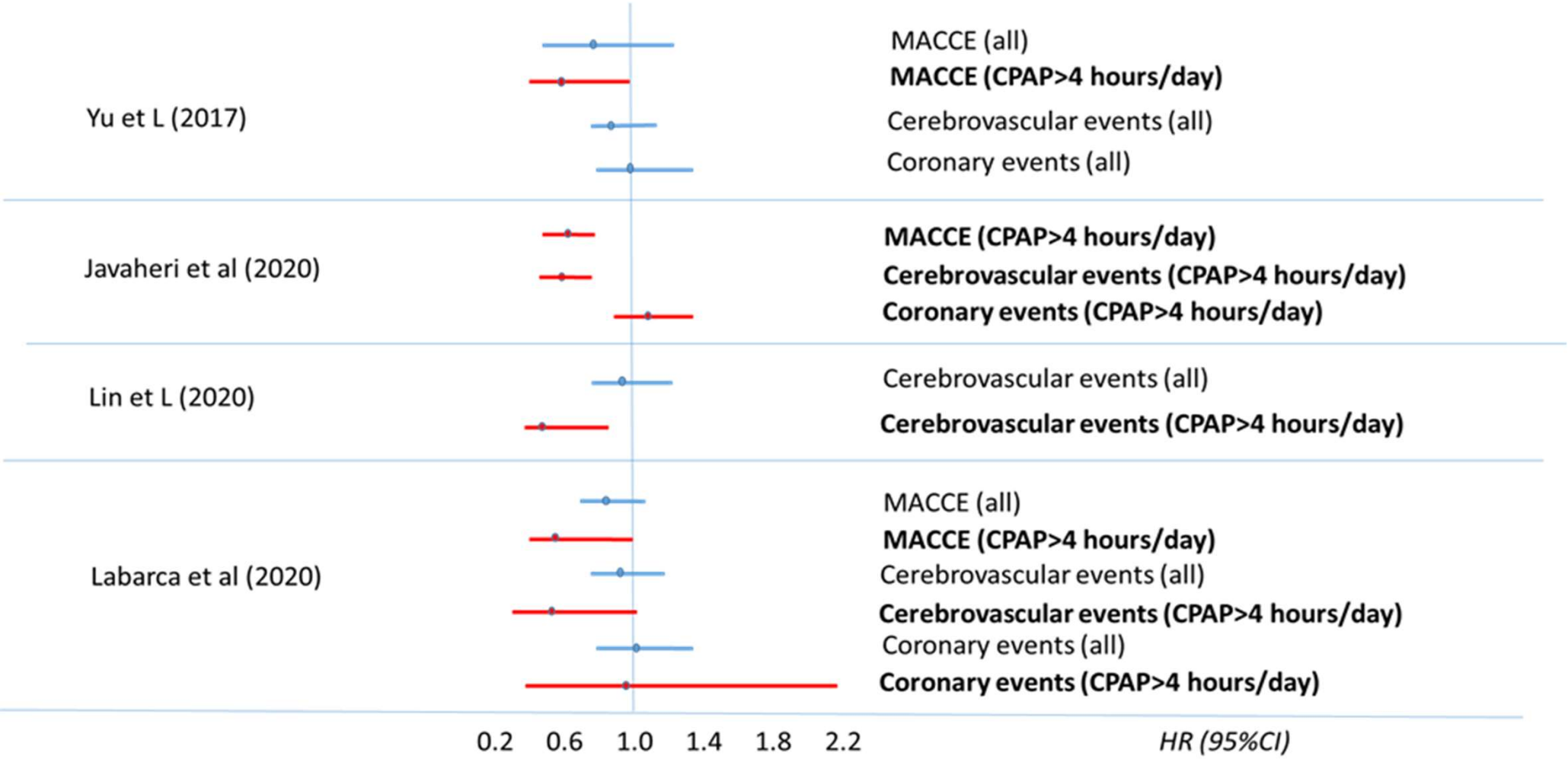
NO = 1141, Control  NO = 943, CPAP use ≥4 hr/day




*p<0.05

Javaheri et al,  Am J Respir Crit Care Med,  2020

# OSA, Stroke and Cardiac Diseases



# FOUR META-ANALYSIS


- Yu J, Zhou Z, McEvoy RD, Anderson CS, Rodgers A, Perkovic V, et al. Association of positive airway pressure with cardiovascular events and death in adults with sleep apnea: a systematic review and meta-analysis. J Am Med Assoc 2017;318(2):156e66

- Javaheri S, Martinez-Garcia MA, Campos-Rodriguez F, Muriel A, Peker Y. CPAP adherence for prevention of major adverse cerebrovascular and cardiovascular events in obstructive sleep apnea. Am J Respir Crit Care Med 2020 Mar 1;201(5):607e10

- Lin HJ, Yeh JH, Hsieh MT, Hsu CY. Continuous positive airway pressure with good adherence can reduce risk of stroke in patients with moderate to severe obstructive sleep apnea: An updated systematic review and meta-analysis. Sleep Med Reviews 2020; 54. 101354.

- Labarca G, Dreyse J, Drake L, Jorquera J, Barbe F. Efficacy of continuous positive airway pressure (CPAP) in th prevention of cardiovascular events in patients with obstructive sleep apnea: Systematic review and meta-analysis. 2020; 52: 10131

# The equipoise

The Best chance to a home run

1. Severe OSA, sleepy and hypoxemic not excluded, unless there is contraindications

2. CNS composite endpoint (Stroke, TIA and cerebrovascular death )

3.Long running-in perioid and exclusion of CPAP- nonadherents

4. Power calculations and inclusion of younger individuals

# Future Trial

The power and number of participants of the trial depends on the primary outcome

***For Cerebrovascular outcome:***

***Total 2000 participants***

***For composite outcome***

***Total 16,000 to 24000 participants***

**Javaheri S, Martinez-Garcia MA, Campos-Rodriguez F. CPAP treatment and cardiovascular prevention: We need to change our trial designs and implementations. CHEST 2020;1047-1048**