Slide 1

AFRICA STEMI LIVE 2018

Heart Failure and Sleep Apnoea

Martin R Cowie MD MSc FRCP FRCP (Ed) FESC
Professor of Cardiology, Imperial College London
m.cowie@imperial.ac.uk

@ProfMartinCowie

Royal Brompton & Harefield NHS Foundation Trust

Imperial College London

Slide 2

Declaration of Interests

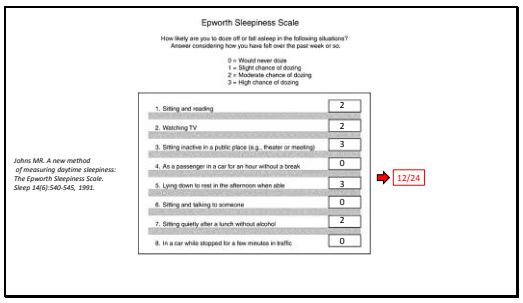
- Research grants administered by Imperial College London from Bayer, Boston Scientific, Abbott, Medtronic, and ResMed
- Consultancy and speaker fees from ResMed, Servier, Novartis, Pfizer, Bayer, Medtronic, Boston Scientific, St Jude Medical, Alere, Daiichi-Sankyo, Bristol Myers Squibb, Roche, Amgen, MSD, Respicardia, Sorin
- Non-Executive Director of the National Institute for Health and Care Excellence (NICE) in England but opinions are my own

Slide 3

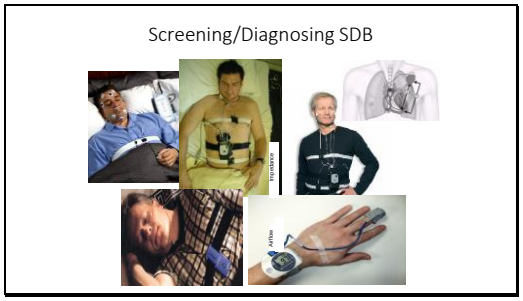
Case study #1

47 year old
BMI 32
Treated HBP
Type 2 DM

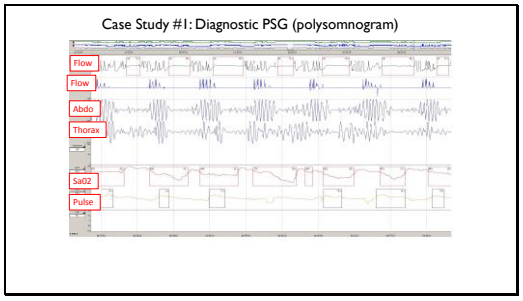
Slide 4



Slide 5



Slide 6



Slide 7

Q1

- What diagnosis would you make?

? A. No abnormality
? B. Central sleep apnoea
? C. Obstructive sleep apnoea
? D. Narcolepsy
? E. Parkinson's Disease

Slide 8

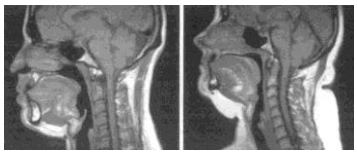
Q1

- What diagnosis would you make?

? A. No abnormality
? B. Central sleep apnoea
? C. Obstructive sleep apnoea
? D. Narcolepsy
? E. Parkinson's Disease

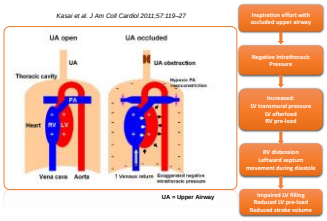
Slide 9

Obstructive sleep apnoea



Slide 10

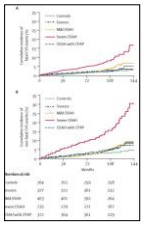
Mechanical Effects of OSA on Heart Function



Slide 11

OSA and CV outcome in patients with CVD

Marin JM et al. Lancet 2005; 365: 1046 – 53



Slide 12

What treatment would you recommend?

? A. Weight loss
? B. Jaw splint
? C. Home oxygen concentrator
? D. CPAP therapy
? E. CPAP therapy and weight loss

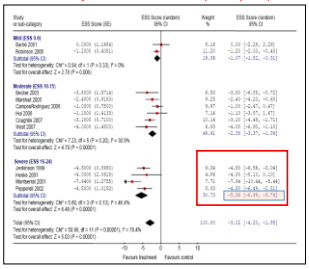
Slide 13

What treatment would you recommend?

? A. Weight loss
? B. Jaw splint
? C. Home oxygen concentrator
? D. CPAP therapy
? E. CPAP therapy and weight loss

Slide 14

Meta analysis: CPAP effects on sleepiness (NICE)



Slide 15

SAVE

The Sleep Apnea cardioVascular Endpoints study

Inclusion criteria

- Age 45-75 years
- Coronary or cerebrovascular disease
- Moderate-severe OSA
  - ApneaLink™, ResMed; 4% oxygen desaturation index, ODI, ≥ 12 events/hr[1]
- Able to use CPAP mask
  - Av. >3hrs/night during 1-week sham-CPAP run-in
- Able and willing to give informed consent

1. Ganter D et al. Respirology 2010;15:952–60

Exclusion criteria

- Severe sleepiness or risk of fall-asleep accident
  - Epworth sleepiness score >15; fall-asleep or near miss accident last 12 months; or commercial driver
- Severe oxygen desaturation
  - >10% recording time with SaO_2 <80%
- Heart Failure NYHA Class III-IV
- Cheyne Stokes respiration
- Prior CPAP use
- Other condition which in opinion of investigator made patient unsuitable

McEvoy RD et al. NEJM 2016; 375: 919 – 31

Slide 16

SAVE

Recruitment and Management

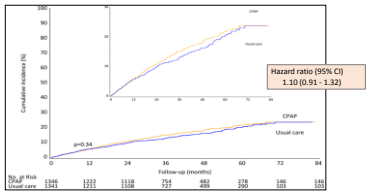
Dec 2008 - Dec 2015

- 2717 patients from 89 centres in 7 countries
- International Coordinating Centre
- Core sleep laboratory

Slide 17

SAVE

Primary endpoint* – neutral



McEvoy RD et al. NEJM 2016; 375: 919 – 31

*Death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack.

Slide 18

Sleepiness, mood, QoL, work and safety

SAVE

CPAP+Usual Care *versus* Usual Care

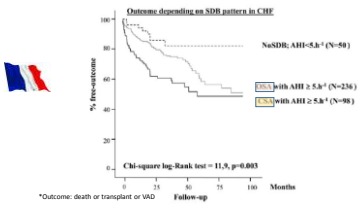
- Improved
  - Epworth sleepiness score (p<0.001)
  - HADS anxiety (p=0.002) and depression (p<0.001) scores
  - SF36 physical (p=0.002) and mental (p<0.001) component scores
  - Work days lost because of ill-health (p<0.001)
- No significant difference
  - Serious adverse events
  - Accidents

McEvoy RD et al. NEJM 2016; 375: 919 – 31

Slide 19

SDB in HF – French registry data

Damy T et al. Eur J Heart Failure 2012; 24: 1009 - 19

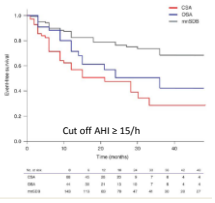


*Outcome: death or transplant or VAD

Slide 20

SDB in HF – risk of malignant ventricular arrhythmia

Bitter T P et al. Eur Heart J 2011; 32: 61-74



Slide 21

ADVENT-HF…

more evidence to come

- RCT: NCT 01128816
- ASV effect on survival and hospital admission in heart failure
- LVEF ≤ 45%; AHI ≥ 15; ESS ≤ 10
- OSA or CSA

- Event driven: 540 endpoints – death, or first hospitalisation, or onset of new Afib/flutter requiring anticoagulation, or appropriate ICD shock not leading to hospitalisation

Lyons et al. Eur J Heart Fail 2017; 19: 579 - 587

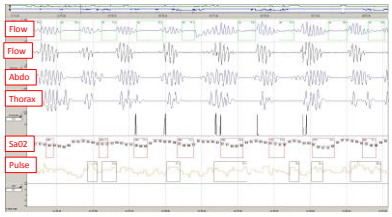
Slide 22

Case study #2

- Patient: AS; male
- Age:78
- BMI: 26.4
- ESS: 7/24 (no daytime sleepiness)
- Fatigue
- Nocturia: 3x
- Nocturnal dyspnoea
- HFrEF (EF 21%), NYHA III
- Recurrent hospitalisations (3 decompensations in the last 12 months despite guideline-based medical therapy)

Slide 23

Case study #2 – diagnostic PSG



Slide 24

What diagnosis do you suspect?

? A. No abnormality
? B. Central sleep apnoea
? C. Obstructive sleep apnoea syndrome
? D. Narcolepsy

Slide 25

What diagnosis do you suspect?

? A. No abnormality
? B. Central sleep apnoea
? C. Obstructive sleep apnoea syndrome
? D. Narcolepsy

Slide 26

What treatment would you recommend?

? A. Weight loss
? B. Ensure medication compliance and optimisation only
? C. Home oxygen concentrator
? D. CPAP therapy
? E. Servo-assisted ventilation (ASV)

Slide 27

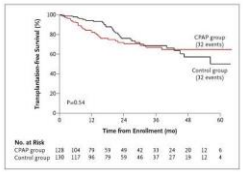
CANPAP

Bradley, T. et al. N Engl J Med 2005;353:2025-2033

- Randomized open label trial at 11 centres
- Adults aged 18-79
- Stable NYHA Class II to IV HF
- LVEF < 40%
- CSA: AHI ≥ 15 (>50% central rather than obstructive)

- 258 patients followed-up for mean of 2 years
- Age 63±10 yrs, EF 24± 8%, AHI 40±16

- Trial stopped early on recommendation of DSMB at first interim analysis
- NEUTRAL result

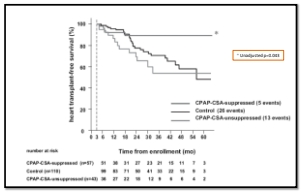


Slide 28

Building the evidence…2007

Arzt et al. Circulation 2007;115:3173-809.

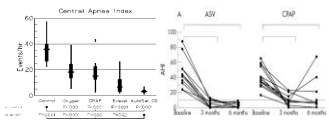
- CANPAP post-hoc analysis suggested that CPAP might improve mortality when CSA was controlled (AHI <15/h) in HF patients with CSA and ejection fraction <40%[1]



Slide 29

Using more modern technologies…?

- ASV is more effective than CPAP for treating CSA/CSR[1,2]



1. Teschler et al. AJRCCM 2001;164:614-9. 2. Philippe et al. Heart 2006;92:337. 3. Kasai et al. Circ Heart Fail 2010;3:560-8.

- HF patients comply better with ASV vs CPAP therapy[2,3]
- Patients prefer ASV over both CPAP and bi-level PAP[3]

Slide 30

Building the evidence…2008 onwards

- Smaller RCTs of ASV treatment in HF patients with CSA/CSR showed:
  - Significant reductions in AHI, NT-pro-BNP levels, urinary catecholamine release, left ventricular dimensions and NYHA class
  - Increases in 6MWD and LVEF
- ASV treatment of CSA/CSR in HF patients has been associated with reduction in mortality on meta-analysis of small randomized trials[1]

Nakamura et al. Clin Res Cardiol 2015;104:208-16.

Slide 31

SERVE HF: Objective

Cowie et al. Eur J Heart Fail 2013;15:937-43; Cowie et al. NEJM 2015; 373: 1095-105

To investigate the effects of adding ASV to guideline-based medical management on survival and cardiovascular outcomes in patients with heart failure with reduced ejection fraction (HFrEF) and predominant CSA

Slide 32

SERVE-HF design

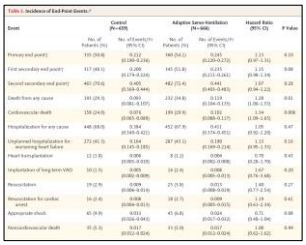
Primary combined endpoint: all cause mortality or life-saving CV intervention or unplanned hospitalisation for worsening HF

- NYHA Class II –IV HF
- Ischaemic, hypertensive or dilated cardiomyopathy
- LVEF < 45%
- Optimal medical therapy (OMT) for ≥ 1 month
- CSA: AHI ≥ 15/hr & > 50% central episodes & central AHI ≥ 10/hr
- 91 centres in 11 countries
- Randomized 1:1 to OMT or OMT + ASV
- ASV initiated over 2-3 nights in-hospital (with check at 2 weeks): starting at EPAP 5 cm H_2O and minimum IPAP 3 cm H_2O, maximum IPAP 10 cm H_2O
- Mask usage monitored

Cowie et al. Eur J Heart Fail 2013;15:937-43; Cowie et al. NEJM 2015; 373: 1095-105

Slide 33

8x more events than CANPAP



425 deaths

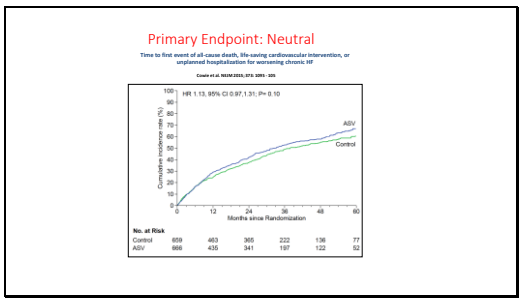
357 CV deaths

559 pts WHF hosp

20 heart tx

26 VAD

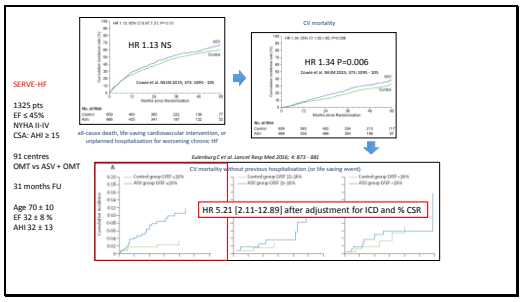
Slide 34



The incidence of the primary endpoint did not differ significantly between the ASV and control groups (event rates 54.1% and 50.8%, respectively).

Because the first and second secondary end points were pre-specified to be analyzed hierarchically only if the null hypothesis for the primary end point was rejected, the results of those analyses are considered exploratory; there was however also no significant difference between the two groups for either of these end points.

Slide 35



Slide 36

Imaging and biomarker sub-study

Baseline and 12 month data

- No between-group differences over 12 months in:
  - LVEF
  - LVEDD/ESD
  - LA size
  - IVRT; E/e'; DT etc
  - RV dimensions or TAPSE
  - Estimated PA pressure
  - BNP
  - hsTnT, hsTnI, ST2, galactin
  - Cystatin C, creatinine, NGAL
  - Hs-CRP, TNF-α

Eur J Heart Failure 2018; 20: 536 – 544

Slide 37

ADVENT-HF…

more evidence to come

- RCT: NCT 01128816
- ASV effect on survival and hospital admission in heart failure
- LVEF ≤ 45%; AHI ≥ 15; ESS ≤ 10
- OSA or CSA

- Event driven: 540 endpoints
  - death, or first hospitalisation, or onset of new Afib/flutter requiring anticoagulation, or appropriate ICD shock not leading to hospitalisation

Lyons et al. Eur J Heart Fail 2017; 19: 579 - 587

Slide 38

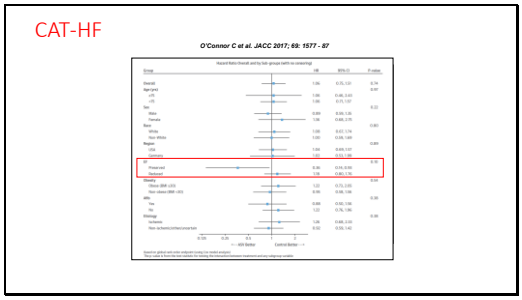
CAT-HF: SDB in acute heart failure

METHODS Eligible patients hospitalized with HF and moderate-to-severe sleep apnea were randomized to ASV plus optimized medical therapy (OMT) or OMT alone (control). The primary endpoint was a composite global rank score (hierarchy of death, cardiovascular hospitalizations, and percent changes in 6-min walk distance) at 6 months.

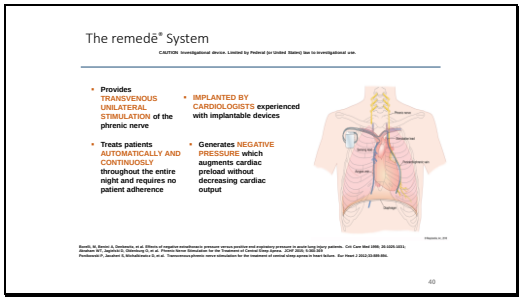
RESULTS 126 of 215 planned patients were randomized; enrollment was stopped early following release of the SERVE-HF (Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure) trial results. Average device usage was 2.7 h/night. Mean number of events measured by the apnea-hypopnea index decreased from 35.7/h to 2.1/h at 6 months in the ASV group versus 35.1/h to 19.0/h in the control group ($p < 0.0001$). The primary endpoint did not differ significantly between the ASV and control groups ($p = 0.92$ Wilcoxon). Changes in composite endpoint components were not significantly different between ASV and control. There was no significant interaction between treatment and ejection fraction ($p = 0.10$ Cox model); however, pre-specified subgroup analysis suggested a positive effect of ASV in patients with HF with preserved ejection fraction ($p = 0.036$).

O'Connor C et al. JACC 2017; 69: 1577 - 87

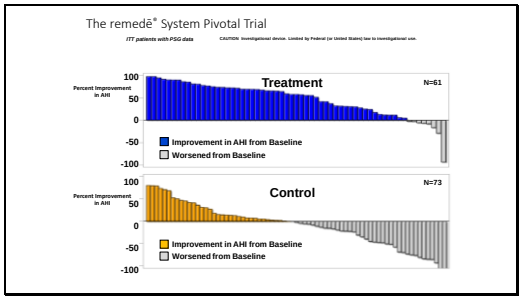
Slide 39



Slide 40



Slide 41



This slide shows the distribution of changes in AHI by randomized group.

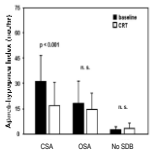
As you can see in the control group, with no treatment, over half of the patients demonstrated no change or deteriorated. However, 87% of the treatment group demonstrated an improvement, which ranged from 5.1% to 98%. **These are clinically meaningful changes for this respiratory disease.**

These graphs show the relative benefit of remede vs control beyond the data summarized in the primary endpoint.

Slide 42

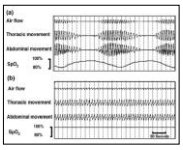
Improving HF improves CSA

CRT improves CSA



Oldenburg et al. Eur J Heart Fail. 2007;9:820-6

LVAD improves CSA



Vazir et al. Int J Cardiol 2010; 138: 317-9

Slide 43

What treatment would you recommend for CSA?

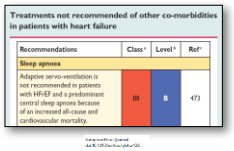
? A. Weight loss
? B. Ensure medication compliance and optimisation only
? C. Home oxygen concentrator
? D. CPAP therapy
? E. Servo-assisted ventilation (ASV)

Slide 44

What treatment would you recommend for CSA?

? A. Weight loss
? B. Ensure medication compliance and optimisation only
? C. Home oxygen concentrator
? D. CPAP therapy
? E. Servo-assisted ventilation (ASV)

Slide 45


Treatments not recommended of other co-morbidities in patients with heart failure

Recommendations	Class	Level	Ref
Sleep apnoea			
Adaptive servo-ventilation is not recommended in patients with HFrEF and a predominant central sleep apnoea because of an increased all-cause and cardiovascular mortality.	III	B	473

What the guidelines say

III: Harm	**B-R**	**In patients with NYHA class II–IV HFrEF and central sleep apnea, adaptive servo-ventilation causes harm (203).**	**NEW**: New data demonstrate a signal of harm when adaptive servo-ventilation is used for central sleep apnea.
See Online Data Supplement G.			

Yancy CW et al. JACC 2017 doi 10.1016/j.jacc.2017.04.025

Slide 46

What the guidelines say

IIb	**B-R**	**In patients with cardiovascular disease and obstructive sleep apnea, CPAP may be reasonable to improve sleep quality and daytime sleepiness (204).**	**NEW**: New data demonstrate the limited scope of benefit expected from CPAP for obstructive sleep apnea.
See Online Data Supplement G.			

Recommendations for Treatment of Sleep Disorders			
COR	**LOE**	**Recommendations**	**Comment/Rationale**
IIa	**C-LD**	**In patients with NYHA class II–IV HF and suspicion of sleep disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable (200, 201).**	**NEW**: Recommendation reflects clinical necessity to distinguish obstructive versus central sleep apnea.
See Online Data Supplement G.			

Yancy CW et al. JACC 2017 doi 10.1016/j.jacc.2017.04.025

Slide 47

‘Take home’ messages

- OSA is common in obese, hypertensive, diabetic, CHD patients with no heart failure
- If daytime sleepiness – think OSA - and offer CPAP

- For HFrEF patients NO randomised trial evidence of improvement in outcome with treating SDB *as yet* – and possibility of harm from treating CSA
- Little known about HFpEF; Acute HF; or OSA in HFrEF, but

- Watch this space!