Morbidity and mortality of chronic heart failure (CHF) patients with central sleep apnoea (CSA) treated by adaptive servoventilation (ASV):

Interim results of FACE cohort study

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Disclosure Statement of Financial Interest

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- Company : Servier
- Company : Servier
- Company : Res Med
- Company : Thoratec
- Company Fifteen : ViforPharma
• SERVE-HF trial including symptomatic Chronic HF (CHF) patients with reduced Left Ventricular Ejection Fraction (LVEF) and predominant CSA treated with ASV compared to control group:

  o No benefit of ASV in this subgroup of HF patient
  o Unexpected increase of cardiovascular mortality

Cowie et al, Adaptive ServoVentilation (ASV) for Central Sleep Apnea (CSA) in Systolic Heart Failure (HF), N Engl J Med. 2015 Sep 17;373(12):1095105)
FACE prospective cohort study

• **AIM**: Provide **long term real-world data** in addition to SERVE-HF trial,

• **Less selective CHF populations** than SERVE-HF
  
  o with reduced (**HFrEF**) or preserved (**HFpEF**) LVEF
  
  o with **predominant CSA** or coexisting CSA and OSA eligible to ASV therapy.

• **Interim long-term morbidity and mortality data** (**1-2 year follow-up**) will be presented:
  
  o To better understand the SERVE-HF results
  
  o **to explore effects of ASV therapy** in CHF patients with different sleep apnea patterns or other types of HF.
• **361 CHF patients** screened from Sept. 2009 to Aug. 2015 eligible for MV-ASV therapy were included depending on whether the patient was **compliant (≥3h/night) with MV-ASV therapy** or not (controls).

• Morbidity and mortality, changes in cardiac function, respiratory/sleep data, are assessed over a period of 2 years.

• The control group included patients who **refused or was not compliant with ASV therapy**.

• Combined **primary outcome** is time for **all-cause death or unplanned hospitalization for worsening HF**.

Event-free survival will be estimated by Kaplan-Meier method and compared using log-rank test.
METHODS

- Median Follow-up duration for analysis: **11 months**

- subgroup populations: **HFrEF: LVEF ≤45% and HFpEF: LVEF > 45%**

- **CSA or coexisting CSA and OSA (CSA-OSA)**

- Baseline cardiac function, respiratory/sleep data, Epworth Sleepiness Scale (ESS) score were assessed.

- **Primary endpoint** is time for all-cause death or unplanned hospitalization for HF worsening

- **Secondary endpoints** are CV death, unplanned all-cause hospitalization or hospitalization for CV cause or worsening HF.
BASELINE GLOBAL CHARACTERISTICS:

- Age: 70.7 ± 11.0
- Male: 87.3%
- BMI: 28.1 ± 5.01
- NYHA III/IV: 43.3%
- Ischemic etiology: 54.9%
- CHF-REF: 64.8%
- CHF-PEF: 35.2%
- ESS score was 7.6 ± 5.2

Comorbidities:
- HTN 72.2%
- Dyslipidemia 59.5%
- AF 41.9%
- Obesity 33.5%
- Diabetes 37.2%
- Cerebrovascular event 25.3%
- Smokers 46%
- Moderate to severe CKD 54.3%
**BASELINE GLOBAL CHARACTERISTICS:**

- **Medical treatment:**
  - β-blockers 77%
  - ACEi or ARBs 81%
  - diuretics 72%
  - Aldosterone antagonists 28%
  - CRT 12%
  - ICD 17%

- **Mean AHI:** 43 ± 18
- **Mean central AHI:** 25 ± 17
- **Severe AHI (>30/h):** 76% of pats
- **Median time with SpO2<90%:** 79 ± 103 min
BASELINE GLOBAL CHARACTERISTICS:

237 pts (66%) were compliant with MV-ASV therapy

Controls were less obese: 17.2% vs 42.2% (p<0.001)

Controls had lower:

- LVEF: 38.8 ± 13.6 vs. 42.9 ± 13.6
- AHI: 38.8 ± 17.4 vs. 45.9 ± 17.1

Controls had a more recent CHF.
BASELINE SUBGROUP CHARACTERISTICS:

- **CHF-REF vs. CHF-PEF:**
  
  CHF-PEF were:
  
  - older (75y vs 68y)
  - less symptomatic (lower NYHA)
  - more often obese (41% vs 28%)
  - higher total and central AHI
  
  less HF drug therapies and **lower rate of cardiac implants** (16% vs 42%) compared to CHF-REF.

- **Predominant CSA versus CSA-OSA:**
  
  Patient characteristics, severity of cardiac parameters and medical HF treatment were similar between both groups.

**Differences:** CSA-OSA patients were more often obese (43.7% vs 29%, p<0.01) had a higher **obstructive AHI** (med 19 (9-29) vs. 7 (2-18) p<0.001), and a lower **central AHI** (13 (6-21) vs. 28 (17-40); p<0.001).
## RESULTS: Morbidity and mortality incidence at 1-2 year FU

**No difference**

<table>
<thead>
<tr>
<th>Primary criteria</th>
<th>MV-ASV Group</th>
<th>Control group</th>
<th>HR [CI 95]</th>
<th>p</th>
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<tbody>
<tr>
<td><strong>All-cause death OR Unplanned hospitalization for worsening HF</strong></td>
<td>N (%)</td>
<td>Nb ev./yr [IC95]</td>
<td>N (%)</td>
<td>Nb ev./yr [IC95]</td>
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<tr>
<td>54 (22.8)</td>
<td>0.245 [0.179-0.310]</td>
<td>29 (23.4)</td>
<td>0.257 [0.163-0.351]</td>
<td>0.96 [0.61-1.51]</td>
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<tr>
<td><strong>CV death OR Unplanned hospitalization for worsening HF</strong></td>
<td>N (%)</td>
<td>Nb ev./yr [IC95]</td>
<td>N (%)</td>
<td>Nb ev./yr [IC95]</td>
</tr>
<tr>
<td>48 (20.3)</td>
<td>0.217 [0.156-0.279]</td>
<td>29 (23.4)</td>
<td>0.257 [0.163-0.351]</td>
<td>0.84 [0.53-1.34]</td>
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<tr>
<td><strong>All-cause death OR Unplanned all-cause hospitalization</strong></td>
<td>N (%)</td>
<td>Nb ev./yr [IC95]</td>
<td>N (%)</td>
<td>Nb ev./yr [IC95]</td>
</tr>
<tr>
<td>92 (38.8)</td>
<td>0.478 [0.380-0.575]</td>
<td>53 (42.7)</td>
<td>0.594 [0.434-0.754]</td>
<td>0.81 [0.58-1.13]</td>
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</tbody>
</table>
RESULTS: KM survival curve: Primary Endpoint at 1-2 year FU “MV-ASV group” vs “Control group”

No difference
## RESULTS: Morbidity and mortality incidence at 1-2 year FU – “HFrEF group” vs “HFpEF group”

### No difference

<table>
<thead>
<tr>
<th>Primary criteria</th>
<th>HFrEF</th>
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<th>HFpEF</th>
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<tr>
<td></td>
<td>N (% )</td>
<td>Nb ev/an [IC95]</td>
<td>N (% )</td>
<td>Nb ev/an [IC95]</td>
<td></td>
<td>p</td>
</tr>
<tr>
<td>All-cause death OR Unplanned hospitalization for worsening HF</td>
<td>58 (27.9)</td>
<td>0.293 [0.218-0.368]</td>
<td>21 (18.6)</td>
<td>0.202 [0.116-0.288]</td>
<td>1.46</td>
<td>0.14</td>
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<tr>
<td>CV death OR Unplanned hospitalization for worsening HF</td>
<td>55 (26.4)</td>
<td>0.278 [0.204-0.351]</td>
<td>18 (15.9)</td>
<td>0.173 [0.093-0.253]</td>
<td>1.62</td>
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<tr>
<td>All-cause death OR Unplanned all-cause hospitalization</td>
<td>92 (44.2)</td>
<td>0.544 [0.433-0.656]</td>
<td>42 (37.2)</td>
<td>0.479 [0.334-0.624]</td>
<td>1.15</td>
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</table>
RESULTS: KM survival curve: primary endpoint at 1-2 year FU
“HFrEF” vs ”HFpEF” patient subgroup

No difference
RESULTS: KM survival curve: primary endpoint at 1-2 year FU “Serve-HF like subgroup” vs ” Non-Serve-hf like subgroup”

<table>
<thead>
<tr>
<th>Test</th>
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<tr>
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<td>0.1402</td>
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Product-Limit Survival Estimates With Number of Subjects at Risk

Test 1: SERVE HF-like Controls
Test 3: Non-SERVE HF-like Controls
Test 2: SERVE HF-like ASV subgroup
Test 4: Non-SERVE HF-like ASV subgroup

<table>
<thead>
<tr>
<th>Time</th>
<th>SERVE HF-like Controls</th>
<th>Non-SERVE HF-like Controls</th>
<th>SERVE HF-like ASV subgroup</th>
<th>Non-SERVE HF-like ASV subgroup</th>
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</thead>
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<tr>
<td>1</td>
<td>60</td>
<td>44</td>
<td>23</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>52</td>
<td>31</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>52</td>
<td>25</td>
<td>13</td>
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<tr>
<td>4</td>
<td>169</td>
<td>136</td>
<td>79</td>
<td>23</td>
</tr>
</tbody>
</table>

RESULTS: KM survival curve: primary endpoint at 1-2 year FU
“Serve-HF like subgroup” vs ” Non-Serve-hf like subgroup”

SERVE HF-like subgroup (symptomatic HFrEF with predominant CSA) treated with ASV (red) had the worst prognosis.

Other HF patients (HFrEF with no predominant CSA or HFpEF) treated with ASV (brown) seem to have better prognosis.
RESULTS: KM survival curve: Primary endpoint at 1 – 2 years
Quartile subgroup analysis of Baseline Time with SpO2<90%

<table>
<thead>
<tr>
<th>Test</th>
<th>Khi-2</th>
<th>DDL</th>
<th>Pr &gt; khi-2</th>
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<tbody>
<tr>
<td>Log-Rank</td>
<td>9.3245</td>
<td>3</td>
<td>0.0253</td>
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</table>

Product-Limit Survival Estimates
With Number of Subjects at Risk

<table>
<thead>
<tr>
<th></th>
<th>1: 1st quartile</th>
<th>2: 2nd quartile</th>
<th>3: 3rd quartile</th>
<th>4: 4th quartile</th>
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<tr>
<td>1</td>
<td>79</td>
<td>68</td>
<td>38</td>
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<tr>
<td>2</td>
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</tr>
<tr>
<td>4</td>
<td>80</td>
<td>65</td>
<td>35</td>
<td>12</td>
</tr>
</tbody>
</table>
time spent with a SpO2<90% have a negative impact on survival:
the percentage of time spent with an SPO2<90% at the baseline visit is correlated to morbidity and mortality during the 2 year FACE follow-up. Patients in the 4th quartile (>75% time spent at baseline with a SPO2<90%) have the worst prognosis
RESULTS:

Other interesting results:

**Pulse pressure (PP)** is significantly lower at 2 yr FU in the control group compared to the MV-ASV group: **45.7 mmHg (24-73) vs 57.2 mmHg (16-129)**, p=0.001.

A reduction of the PP is a factor of bad prognosis.

**Multivariate analysis** of predictive factors for primary endpoint in the global study population show that

- **BMI** (0.44 [0.19-0.99] p=0.049)
- **Heart Rhythm** (1.03 [1.01-1.04] p=0.011)
- **diuretics** (5.65 [1.34-23.79] p=0.018) are independent predictive factors of morbidity and mortality

- **COPD** (6.65 [1.59-27.65] p=0.009)
- **Pulse Pressure** (0.93 [0.89-0.97] p=0.0008)
- **beta-blockers** (0.16 [0.03-0.79] p=0.025)
- **antiarrhythmic** (4.61 [1.32-16.09] p=0.0167) are independent predictive factors of cardiovascular mortality
CONCLUSION & PERSPECTIVES:

**CHF patients** eligible for ASV therapy have severe CSA and multiple cardiac and metabolic comorbidities.

Adjusted multivariate analysis **did not confirm at this stage any benefits nor deleterious effect of ASV therapy on morbidity and mortality in the global CHF population and subgroups.**

However, **HFrEF patients with predominant CSA may have a poorer prognosis under ASV therapy than other CHF populations (CSA-OSA or CHF-PEF)**

The multicentre FACE cohort study may be a useful tool after SERVE HF results, to understand better the impact of ASV therapy in different categories of CHF populations with central SDB, especially CHF with preserved LVEF.

Long-term FU is expected for additional analysis of the FACE study.
Thank you for your attention