The effect of renal denervation in patients with advanced heart failure:

OLOMOUC I Study

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Disclosures

☐ MT: honoraria Bayer, Boehringer-Ingelheim, Pfizer, Biotronik

☐ JV: honoraria Servier, Boehringer-Ingelheim, Bayer

☐ ML: honoraria Servier

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Patophysiology of HF

- HF → substantial neurohormonal activation in heart, kidney and skeletal muscle
- Activation of sympatetic NS and RAAS → aggravating HF by increasing ventricular afterload and preload
- Inverse relationship between noradrenaline serum levels and mortality
- Renal sympatetic activation → congestion (release of renin, sodium retention in prox. tubules and elevation of renal vascular resistance)
- Role of renin - angiotensin II on proximal tubulus and vasoconstriction of the efferent renal arteriole

Experimental studies

1. Long-term RD in rats after MI improved LV function and restored natriuresis

2. RD increased renal blood flow in congestive HF rats by 35 % and normalised the autoregulation of renal blood flow

3. RD → normalization of angiotensin II type 1 and 2 receptors expresion in HF rabbits

Study characteristics

- Single center prospective randomized study
- Primary purpose: treatment
- Estimated enrollment: 50 subjects
- Estimated study completion date: VI/2013
- Health authority: MF and UH EC
Inclusion criteria

- Congestive heart failure
- NYHA III(IV)
- Optimal stable medical therapy (>6M)
- Rest heart rate > 70 bpm
- Renal artery anatomy eligible for treatment
- GFR > 50 mL/min/1.73m²
- Not indicated for CRT or other nonpharmacological treatment
Exclusion criteria

- Clinically unstable patient
- Renal/femoral artery anatomy not eligible for treatment
- Pre-existing renal disease, history of prior renal artery intervention
- Valve disease (HS)
- MI, unstable AP, stroke, TIA within 6 M
- Systolic BP < 100 mm Hg
- CRT present or eligible
- Age<18 y, gravidity
- Unable to consent
Study design

Screening (0 – 30 days) + PIC + Randomization
CT scan

RDN
1 M Visit (Doppler or CT)
6 m Visit
12 m Visit

OMT
1 M Visit
6 m Visit
12 m Visit

(7 – 14 days)
Study endpoints

Primary endpoints:
- Ventricular systolic function by echocardiography
- Safety of renal denervation in HF pts.

Secondary endpoints:
- Heart rate
- Renal function
- NT-proBNP levels
- NYHA classification
Patients and follow-up

417 screened
51 randomized

26 to RDN
Deaths: 0
21 analysed

25 to medical therapy (OMT)
Deaths: 2
22 analysed

Median study duration: 10.8 months, maximum: 17.2 months
## Baseline characteristics I

<table>
<thead>
<tr>
<th></th>
<th>RDN</th>
<th>OMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>58</td>
<td>61</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>77</td>
<td>74</td>
</tr>
<tr>
<td>History of HF (m)</td>
<td>41</td>
<td>45</td>
</tr>
<tr>
<td>Ischemic etiology (%)</td>
<td>61</td>
<td>65</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>NYHA II (%)</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>NYHA III/IV (%)</td>
<td>86/7</td>
<td>88/4</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>54</td>
<td>58</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>77</td>
<td>70</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Mean HR (bpm)</td>
<td>84</td>
<td>80</td>
</tr>
<tr>
<td>Mean SBP (mmHg)</td>
<td>112</td>
<td>107</td>
</tr>
<tr>
<td>Mean DBP (mmHg)</td>
<td>70</td>
<td>68</td>
</tr>
</tbody>
</table>
## Baseline characteristics II

<table>
<thead>
<tr>
<th></th>
<th>RDN</th>
<th>OMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEIs or ARBs (%)</td>
<td>93</td>
<td>92</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>86</td>
<td>82</td>
</tr>
<tr>
<td>BB (%)</td>
<td>86</td>
<td>82</td>
</tr>
<tr>
<td>Aldosterone antagonists (%)</td>
<td>58</td>
<td>64</td>
</tr>
<tr>
<td>Digitalis (%)</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>Ivabradine (%)</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>ICD (%)</td>
<td>14</td>
<td>16</td>
</tr>
</tbody>
</table>
Reality of BB therapy

- BB at randomization: 86% (RDN) vs. 82% (OMT)
- At least 50% target daily dose: 51% (RDN) vs. 49% (OMT)
- Target daily dose: 25% (RDN) vs. 24% (OMT)
Renal denervation protocol

- Definition of anatomy – CT scan + 3D reconstruction
- Analgosedation
- Direct BP monitoring, $O_2$ sat, ACT
- RF energy – 6F catheter and RF generator
  (Symplicity Renal Denervation System, Medtronic, Inc., Mountain View, CA)
- RF energy applications in a helical fashion (>5 mm distance), pullback (periphery $\rightarrow$ ostium)
- Using AP, LAO and RAO projections

<table>
<thead>
<tr>
<th></th>
<th>R RA</th>
<th>L RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr. of RF applications</td>
<td>5.2 ± 1.3</td>
<td>5.4 ± 2.0</td>
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</tbody>
</table>
Variability in renal artery anatomy
Change in LVEF

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>12 months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDN</td>
<td>25±12</td>
<td>31±14</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>OMT</td>
<td>26±11</td>
<td>28±12</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Left ventricular ejection fraction (%)
Change in LVESVI

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDN (n=21)</td>
<td>70±28</td>
<td>59±27</td>
</tr>
<tr>
<td>OMT (n=22)</td>
<td>68±30</td>
<td>62±28</td>
</tr>
</tbody>
</table>

p < 0.01

p = 0.15
Change in LVEDV (mL/m²)

Baseline 12 months

RDN (n=21) 96±32 85±28

OMT (n=22) 91±30 89±28

p < 0.01

p = 0.28
Change in NT-proBNP

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDN (n=21)</td>
<td>5897 ±3558</td>
<td>1852 ±1247</td>
</tr>
<tr>
<td>OMT (n=22)</td>
<td>6292 ±2903</td>
<td>5836 ±1470</td>
</tr>
</tbody>
</table>

- **p < 0.01** for both RDN and OMT between baseline and 12 months.
- **p = 0.12** for OMT between baseline and 12 months.

NT-proBNP (pmol/l)
Hospitalization for heart failure

Cumulative frequency (%) vs. Months

- RDN
- OMT
Heart rate reduction

Heart rate (bpm)

Months

RDN
OMT
## Renal function development

<table>
<thead>
<tr>
<th>Δ Renal function (baseline x 6 M)</th>
<th>RDN (mean ±SD)</th>
<th>OMT (mean ±SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGRF (MDRD) (mL/min/1.73m²)</td>
<td>-5±12</td>
<td>1±10</td>
<td>0.55</td>
</tr>
</tbody>
</table>
NYHA Class changes

- Improvement: 42% RDN, 22% OMT
- Worsening: 5% RDN, 8% OMT
- Stability: 53% RDN, 70% OMT
## Complications

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>RDN</th>
<th>OMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV fistula with surgical revision</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Thrombus formation during procedure (ACT 283)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>AP requiring coronary stenting</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Death during FU</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
Conclusion

- HF and systolic dysfunction are associated with poor prognosis.
- RDN increased the LV systolic function and reduced the mean heart rate ($p<0.01$).
- RDN in a pilot study with HFLEF patients is a safe procedure, no significant BP decrease.
- RDN did not change the renal function.
- Trend in to more (repeated) hospitalizations for HF in OMT and to decrease in NYHA class in RDN.
Discussion

- Role of ivabradin – ESC HF Guidelines 2012
- Substrate: ischemic x non-ischemic → difference in outcome?
- Definition of substrate: MRI – LA
Patients with HF and LV aneurysm: Contraindication for RDN?
Discussion

- Role of ivabradin – ESC HF Guidelines 2012
- Substrate: ischemic x non-ischemic → difference in outcome?
- Definition of substrate: MRI – LA
- Role of current and future technology for RDN
- Effect of RDN on RAAS and HF must be verified → large international prospective study