Extracorporeal Shockwave Myocardial Revascularization (ESMR) Treatment for Refractory Angina – Review

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Shockwaves - Background

• Shockwaves are special acoustics waves that can be targeted and focused non-invasively to a selected area inside the patient body.

• Shock wave therapies have been used in the last decades in Nephrology (kidney stone lithotripsy), Orthopedics (plantar facilities) and Urology (erectile dysfunction) applications.

Cavitation bubble imploding close to a membrane generation a jet
Shockwaves - Background

• *In-vitro* and animal data indicated an increase of angiogenic factor production and signs of neo-vascularization following treatment with low intensity shock waves (10% of the energy used for lithotripsy). → Basis for feasibility testing in regional myocardial ischemia.

• Therapeutic effect is *localized* (<2 mm precision) and *controlled*.
• Meta-analysis of Extracorporeal Shockwave Myocardial Revascularization (ESMR) trials (Cardiospec™) presented between 2006 and 2012

• 494 patients in 17 medical centers across Europe and Asia
Elements of the Meta-Analysis

• Feasibility studies, uncontrolled
  – ETT – Exercise Tolerance Time
  – CCS class
  – SPECT analysis
  – Nitrate use
• All received the same treatment protocol
  – Energy level
  – Number of shocks
  – Treatment strategy
**Treatment Protocol**

**Scheme:**
- 3 sessions per week
- up to 10 spots per session
- 100 shocks per spot

**Evaluation after 3 months follow-up**
At each treatment session, shock waves should be delivered to the border of the ischemic area for triggering angiogenesis etc. within the viable tissue

**Scheme:**

♥ 3 sessions per week
♥ up to 10 spots per session
♥ 100 shocks per spot
Energy Level: 0.09 mJ/mm²; ~1000 shocks per Tx
SPECT Analysis

• Typical patient
<table>
<thead>
<tr>
<th>Investigator</th>
<th>Institution</th>
<th>City</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naber CK</td>
<td>Essen University Hospital</td>
<td>Essen</td>
<td>Germany</td>
</tr>
<tr>
<td>Vainer J</td>
<td>Maastricht University Medical Center</td>
<td>Maastricht</td>
<td>Netherlands</td>
</tr>
<tr>
<td>Vasyuk Y</td>
<td>Moscow University of Medicine and Dentistry</td>
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<tr>
<td>Takayama T</td>
<td>Nighon School of Medicine</td>
<td>Tokyo</td>
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<td>Faber L</td>
<td>Heart and Diabetes Center, NRW</td>
<td>Bad Oeynhausen</td>
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<td>Lyadov K</td>
<td>Medical and Rehabilitation Center</td>
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<tr>
<td>Ge J</td>
<td>Zhongshan Hospital</td>
<td>Shanghai</td>
<td>China</td>
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<td>Zuoziene G</td>
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<td>Lithuania</td>
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<td>Leibowitz D</td>
<td>Hadassah Medical Center</td>
<td>Jerusalem</td>
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<tr>
<td>Samad A</td>
<td>Karachi Institute of Heart Diseases</td>
<td>Karachi</td>
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<td>Nikonenko I</td>
<td>Institute of Cardiovascular Surgery</td>
<td>Zaporozhie</td>
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<tr>
<td>Fu M</td>
<td>Chang Gung Memorial Hospital</td>
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<tr>
<td>Alunni G</td>
<td>Molinette Hospital</td>
<td>Torino</td>
<td>Italy</td>
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<tr>
<td>Yaakob Z, Zuhdi A,</td>
<td>University Malaya Medical Center</td>
<td>Kuala Lumpur</td>
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<tr>
<td>Ismail M</td>
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<tr>
<td>Koltunov I</td>
<td>Center of Prophylactic Medicine</td>
<td>Moscow</td>
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</table>
Patient selections

Inclusion criteria

• Viable myocardial segments with reversible ischemia and/or hibernation
• Optimum medical therapy (least 6 weeks)
• Absence of acute clinical events (for > 1 months)
• Unsuitable for invasive revascularization

Exclusion criteria

• Active coronary inflammatory process
• Acute MI < 3 months prior to treatment
• Intra-ventricular thrombus
• Pregnancy.
• Malignancy in the area of treatment.
• Inability of adequate echocardiography window
Improvement in CCS class (n=451)

Mean improvement 42%

Zuoziene G, 2012: 69%
Vainer J, 2012: 56%
Ismail M, 2012: 80%
Yaakob Z, 2011: 20%
Alunni G, 2011: 54%
Panaeva S, 2010: 40%
Fu M, 2010: 31%
Vasyuk Y, 2010: 47%
Zuoziene G, 2010: 49%
Vainer J, 2010: 48%
Nikonenko A, 2010: 37%
Ge J, 2009: 31%
Koltunov I, 2008: 23%
Samad A, 2008: 31%
Faber L, 2008: 33%
Lyadov K, 2006: 32%
Naber CK, 2008: 33%
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Mean Improvement (%)</th>
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</thead>
<tbody>
<tr>
<td>Ismail M, 2012</td>
<td>2012</td>
<td>32%</td>
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<tr>
<td>Vainer J, 2012</td>
<td>2012</td>
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<td>Yaakob Z, 2011</td>
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<td>Panaeva S, 2010</td>
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<td>Leibovitz D, 2010</td>
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<td>Lyadov K, 2006</td>
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<td>Naber CK, 2008</td>
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<td>64%</td>
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</table>

(*) Different analysis methods
Decrease of Weekly Nitrate Intake (n=275)

Mean improvement 82%

- Vainer J, 2012: 85%
- Zuoziene G, 2012: 94%
- Panaeva S, 2010: 86%
- Nikonenko A, 2010: 71%
- Zuoziene G, 2010: 92%
- Vasyuk Y, 2010: 64%
- Vainer J, 2010: 82%
### Increase in Left Ventricular Ejection Fraction (n=250)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Improvement</th>
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<tr>
<td>Koltunov I, 2008</td>
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<td>10%</td>
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<td>Alunni G, 2010</td>
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<td>Nikonenko A, 2010</td>
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<td>Zuoziene G, 2010</td>
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<td>Panaeva S, 2010</td>
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<tr>
<td>Zuoziene G, 2012</td>
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</table>

Mean improvement 11%
Improvement of Myocardial Perfusion (n=114)

Mean improvement (*)33%

- Yaakob Z, 2011: 39.43%
- Alunni G, 2010: 21%
- Vasyuk Y, 2010: 43%
- Faber L, 2008: 20%
- Takayama T, 2008: 19.5%
- Naber CK, 2008: 53%

(*) Different analysis methods
Summary

• The data from the current meta-analysis demonstrate that Extracorporeal Shockwave Myocardial Revascularization (ESMR)
  – improves symptoms
  – delays the ischemic threshold
  – increases exercise tolerance.

• No side effects were reported and no ESMR-related myocardial damage was observed.
Conclusion

• ESMR is a non-invasive therapy that is safe and appears to be efficacious in the treatment of Refractory Angina Pectoris.

• Extracorporeal Shockwave Myocardial Revascularization (ESMR) may therefore be regarded as an effective non-invasive method of treatment for myocardial ischemia in end-stage CAD patients.

• Randomized, double-blind studies will represent the next milestone for further validation of the clinical effectiveness of ESMR therapy.