Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.
**eMethods**

- Complete inclusion and exclusion criteria of the CELLWAVE trial
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- Cell Preparation and administration
- LV angiography
- Magnetic resonance imaging and analysis
- Supplemental references

**Complete inclusion and exclusion criteria of the CELLWAVE trial**

Inclusion Criteria: Chronic ischemic heart disease; previous anterior myocardial infarction > 3 months; LVEF < 50% or NYHA II-IV; age 18-80 years; written informed consent.

Exclusion Criteria: Ventricular thrombus; myocardial infarction < 3 months; active infection or fever; chronic inflammatory disease (e.g. Crohn’s disease, rheumatoid arthritis); HIV infection or active hepatitis; neoplastic disease w/o complete remission within 5 years; stroke < 3 months; creatinine > 2 mg/dl; relevant liver disease (GOT > twice the upper limit); anemia (hemoglobin <10 mg/dl); thrombocytopenia < 100,000/µl; allergies to aspirin, clopidogrel, heparin; history of bleeding disorder; history of coagulopathy; gastrointestinal bleeding < 3 months; surgery or trauma < 2 months; pregnancy; mental retardation; participation in other clinical study < 1 month.

**Randomization and blinding**

The randomization was performed in two steps for the entire study cohort at the cell processing center (Red Cross Blood Service, Frankfurt) by a simple random allocation with known N (N=100) using a computer list. In case of drop-out cases after the first randomization step, 3 patients were added on the randomization list. Included patients were first randomized (2:2:1; single-blind) to receive echo-guided low-dose, high-dose or placebo shock wave targeted to the LV anterior wall 24 hours prior to cell administration. The investigator applying SW (DHW) was not blinded to the treatment modality.
Following bone marrow aspiration, the aspirate was sent to the central cell processing unit, where further simple randomization (1:1; random number generator) to BMC or Placebo infusion was performed for patients being treated with LD- or HD-SW. Patients and investigators were blinded for the intracoronary infusion of the study medication.

Cell Preparation and administration

Cell and placebo preparation and administration protocols were identical to the protocols used in the REPAIR-AMI trial. Briefly, a total of 50 ml of bone marrow was aspirated into heparin-containing syringes from the iliac crest under local anesthesia. Mononuclear cells were isolated and enriched with the use of Ficoll–Hypaque centrifugation procedures. The cell suspension consisted of a heterogeneous cell population including hematopoietic, mesenchymal, and other progenitor cells. The cells were suspended in 10 ml of X VIVO 10 medium (a serum-free medium containing pharmaceutical-grade human components, Cambrex), including 2 ml of the patient’s own serum. The placebo medium consisted of the 10 ml of X VIVO 10 medium, including 2 ml of the patient’s own serum (without BMC). Frequencies of BMC within the applied cellular product were assessed according to the guidelines of the International Society of Hematotherapy and Graft Engineering. Functionality of the applied cell was assessed as previously described.

After arterial canulation, all patients received 7500 to 10,000 U of heparin. Cells were infused using the stop-flow technique through an over-the-wire balloon catheter (Opensail, Guidant, or Voyager OTW, Abbott) positioned in a native coronary artery or bypass graft supplying the left ventricular segments of the previous anterior myocardial infarction, as described previously.

LV angiography

Left ventricular angiograms were obtained in identical standard projections at the baseline procedure (immediately prior to intracoronary study infusion) and at 4 months follow-up. Quantitative analysis of monoplane left ventricular angiograms (30° RAO projection) was performed by an experienced investigator (BA) in a central core lab, blinded to the treatment
modality of the individual patients, using the software CMS 6.0 (Medis, Leiden, Netherlands), as previously described 1.

**Magnetic resonance imaging and analysis**

MRI images were acquired with a 1.5-Tesla MRI system (Magnetom sonata, Siemens Medical Solutions Erlangen, Germany) and use of a phased-array body surface coil with 4 to 12 elements during breath-hold (maximum 12 seconds) with ECG triggering, as previously described 5. Cine images with a slice thickness of 6 mm were detected throughout the entire left ventricle in long- and short axis views by use of contiguous 2D True-FISP sequences. The typical in-plane resolution was 2.2 x 1.3 mm². 12 to 15 minutes after intravenous application of Gadolinum-DTPA (0.2 mmol/kg body weight, Magnevist, Bayer Vital, Leverkusen, Germany), “delayed enhancement” (LE) technique was performed by using a 2D True-FISP sequence after adjustment for the individually optimized inversion time between 170 ms to 280 ms.

All images were analyzed offline using a QMass MR (Medis, Leiden, Netherlands) workstation by two experienced readers blinded to treatment allocation. Global and regional functional analyses were performed after manually tracing endocardial and epicardial borders. Regional left ventricular function was assessed for 20 automatically divided, evenly spaced myocardial segments. Late enhancement volumes were quantified by using the semi-automatic segmentation based on signal intensity (SI) thresholds with a cut-off of 50 SI for myocardial scar as recently described 6. The percentage of LE extent as well the transmural extent of LE were scored manually for each individual segment. Wall thickening in infarcted segments was quantified as % wall thickening at endsystole in segments with > 50% signal intensity of late enhancement.
eReferences


**eTable.** Complete List of Exclusion Criteria for Screened Patients

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor ultrasound access to the heart</td>
<td>137</td>
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<tr>
<td>Impaired kidney function</td>
<td>65</td>
</tr>
<tr>
<td>Previous myocardial infarction &lt; 3 months</td>
<td>28</td>
</tr>
<tr>
<td>Unknown left ventricular thrombus</td>
<td>9</td>
</tr>
<tr>
<td>Anaemia (Hb &lt; 10 mg/dl)</td>
<td>8</td>
</tr>
<tr>
<td>Participation in other clinical trial &lt; 1 months</td>
<td>8</td>
</tr>
<tr>
<td>Neoplastic disease w/o complete remission within 5 years</td>
<td>7</td>
</tr>
<tr>
<td>Previous surgery &lt; 2 months</td>
<td>5</td>
</tr>
<tr>
<td>GI bleeding &lt; 3 months</td>
<td>5</td>
</tr>
<tr>
<td>Recent TIA / Stroke &lt; 3 months</td>
<td>3</td>
</tr>
<tr>
<td>Active hepatitis (unknown)</td>
<td>3</td>
</tr>
<tr>
<td>Intolerance to aspirin</td>
<td>1</td>
</tr>
</tbody>
</table>
Supplemental figure 1: Schematic illustration of shockwave application

- Coil High Voltage pulse
- Membrane (Magnetic field)
- Rapid membrane movement
- Shock wave produced in water bellow
- Shockwave focused by acoustic lens

Shock wave generator

Power generator with Energy level control unit and ECG synchronization

ECG R-wave triggered shock wave application

Shock wave source
- Flat coil
- Membrane
- Acoustic lens
- Bellow
- Shockwave path

Patient

SW target area

Apical 4-chamber view by echocardiography
(LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle)
Supplemental figure 2: Representative image of scar size in a patient receiving shock wave + BMC
(The red area represents the scar as analyzed by semiautomatic segmentation based on signal intensity (SI) thresholds with a cut-off of 50 SI for myocardial scar; green line epicardial contour, red line endocardial contour.)
**eFigure 3. Occurrence of Multiple Events per Patient**

Each horizontal line indicates an individual patient, with the total length indicating duration of follow-up. Each vertical line illustrates an event. In the case of more than 1 event at the same point, lines were minimally separated manually to remain visible. Statistical comparison of multiple and ordered recurrent events is performed using an Anderson and Gill model. $P = .02$ across all 3 groups. BMC indicates bone marrow–derived mononuclear cells.