Effect of Shock Wave–Facilitated Intracoronary Cell Therapy on LVEF in Patients With Chronic Heart Failure
The CELLWAVE Randomized Clinical Trial

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EGENERATIVE THERAPIES HAVE emerged as a promising novel approach to improve heart function and prevent the development of end-stage heart failure. Application of various cell types including bone marrow–, heart tissue–, or adipose tissue–derived cell populations were shown to improve cardiac functional recovery. In patients with acute myocardial infarction, recent meta-analyses suggested a moderate but sustained enhancement of left ventricular function and improved clinical outcome following administration of bone marrow–derived mononuclear cells (BMSCs). In contrast, in patients with chronic postinfarction heart failure, BMSC therapy has demonstrated heterogeneous results so far. One possible reason for the impaired efficacy of cell therapy in the chronic setting is that cell retention in the heart is substantially reduced in comparison to acute myocardial infarction. BMSCs are attracted to the target tissue by cytokines such as...

Importance The modest effects of clinical studies using intracoronary administration of autologous bone marrow–derived mononuclear cells (BMSCs) in patients with chronic postinfarction heart failure may be attributed to impaired homing of BMSCs to the target area. Extracorporeal shock wave treatment has been experimentally shown to increase homing factors in the target tissue, resulting in enhanced retention of applied BMSCs.

Objective To test the hypothesis that targeted cardiac shock wave pretreatment with subsequent application of BMSCs improves recovery of left ventricular ejection fraction (LVEF) in patients with chronic heart failure.

Design, Setting, and Participants The CELLWAVE double-blind, randomized, placebo-controlled trial conducted among patients with chronic heart failure treated at Goethe University Frankfurt, Germany, between 2006 and 2011.

Interventions Single-blind low-dose (n=42), high-dose (n=40), or placebo (n=21) shock wave pretreatment targeted to the left ventricular anterior wall. Twenty-four hours later, patients receiving shock wave pretreatment were randomized to receive double-blind intracoronary infusion of BMSCs or placebo, and patients receiving placebo shock wave received intracoronary infusion of BMSCs.

Main Outcomes and Measures Primary end point was change in LVEF from baseline to 4 months in the pooled groups shock wave + placebo infusion vs shock wave + BMSCs; secondary end points included regional left ventricular function assessed by magnetic resonance imaging and clinical events.

Results The primary end point was significantly improved in the shock wave + BMSC group (absolute change in LVEF, 3.2% [95% CI, 2.0% to 4.4%]), compared with the shock wave + placebo infusion group (1.0% [95% CI, −0.3% to 2.2%]) (P=0.02). Regional wall thickening improved significantly in the shock wave + BMSC group (3.6% [95% CI, 2.0% to 5.2%]) but not in the shock wave + placebo infusion group (0.5% [95% CI, −1.2% to 2.1%]) (P=.01). Overall occurrence of major adverse cardiac events was significantly less frequent in the shock wave + BMSC group (n=32 events) compared with the placebo shock wave + BMSCs (n=18) and shock wave + placebo infusion (n=61) groups (hazard ratio, 0.58 [95% CI, 0.40-0.85]; P=.02).

Conclusions and Relevance Among patients with postinfarction chronic heart failure, shock wave–facilitated intracoronary administration of BMSCs vs shock wave treatment alone resulted in a significant, albeit modest, improvement in LVEF at 4 months. Determining whether the increase in contractile function will translate into improved clinical outcomes requires confirmation in larger clinical end point trials.

Trial Registration clinicaltrials.gov Identifier: NCT00326989


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stromal cell–derived factor 1 (SDF-1) and vascular endothelial growth factor. The chemokine SDF-1 is only transiently expressed following acute myocardial infarction, and in chronic ischemic models, expression of these chemoattractants is profoundly reduced, resulting in insufficient cell recruitment to the target area. We have recently shown that extracorporeal application of focused low-energy shock waves increases the tissue expression of chemoattractants such as SDF-1 and vascular endothelial growth factor in the target tissues. Our preclinical studies demonstrated that shock wave–induced local up-regulation of these chemoattractants resulted in significantly enhanced homing of applied cells, which translated into improved neovascularization of chronically ischemic tissue.

Thus, we hypothesized that shock wave–facilitated cell therapy improves the efficacy of intracoronary application of autologous BMCs in patients with chronic postinfarction heart failure.

**METHODS**

The study was a randomized, placebo-controlled, clinical phase 1/2 trial approved by the ethics committee and the Paul-Ehrlich-Institut, Langen, Germany (ID 183/01) and registered with clinicaltrials.gov. All patients provided written informed consent.

Patients were eligible for inclusion if they were aged 18 to 80 years with an anterior myocardial infarction occurring 3 months or more prior to inclusion and stable chronic postinfarction heart failure, defined as left ventricular ejection fraction (LVEF) less than 50% or symptoms of New York Heart Association (NYHA) class II or greater. Patients were also required to have a patent vessel supplying the target region. Major exclusion criteria were the presence of a ventricular thrombus and a baseline serum creatinine level greater than 2 mg/dL (176.8 μmol/L) in addition to poor ultrasound access to the heart. Detailed inclusion and exclusion criteria are listed in the eMethods at www.jama.com.

Randomization was performed in 2 steps for the entire study cohort at the cell processing center (German Red Cross Blood Service, Frankfurt) by a simple random allocation with known N (N=100) using a computer list. Because of dropout after the first randomization step, 3 patients were added to the randomization list. Included patients were first randomized (2:2:1; single-blind) to receive echocardiographically guided low-dose, high-dose, or placebo shock wave targeted to the left ventricular anterior wall 24 hours prior to cell administration. Patients receiving shock wave pretreatment were then randomized in a second step (1:1; double-blind) to receive intracoronary infusion of either BMCs or cell-free medium (placebo), whereas patients receiving placebo shock wave received intracoronary infusion of BMCs (Figure 1). There was no blockwise randomization.

The primary efficacy end point was improvement of global LVEF on quantitative left ventricular angiography at 4 months’ follow-up. The absolute change in LVEF was compared between the pooled groups receiving shock wave + placebo infusion vs shock wave + BMCs.

Secondary end points included changes in left ventricular volumes and in NYHA class as well as regional left ventricular function and late enhancement volume assessed by magnetic resonance imaging (MRI). The clinical events death and mode of death, rehospitalization for worsening heart failure, recurrent myocardial infarction, ventricular tachycardia, revascularization, and stroke (major adverse cardiac events [MACEs]) were prospectively collected by study nurses.

Safety end points comprised the tolerance of shock wave application, occurrence of ventricular arrhythmias, and increases in troponin T levels after shock wave application, as well as in-hospital MACEs.

**Shock Wave Application**

Patients randomized to receive shock wave treatment received single-blind low-energy shock wave under continuous electrocardiographic trigger at either high dose (0.051 mJ/mm²) or low dose (0.014 mJ/mm²) to 4 separate spots in the target region (750 shots per spot; total, 3000 shots) under 2-dimensional echocardiographic guidance by a custom-built shock wave generator (Biotripter, Dornier Med Tech Systems). The shock waves were focused to the anterior, lateral, and apical left ventricular segments demonstrating severe wall motion impairment attributable to the previous myocardial infarction using modified parasternal long-axis and apical 4-chamber echocardiographic views. Figure 1 illustrates the setup and principles of shock wave delivery. Placebo shock wave treatment was administered by placing an airfoam cushion between the shock wave applicator and the patient’s chest wall, thus preventing shock wave penetration.

**Cell and Placebo Preparation and Administration**

Preparation of BMC and placebo infusions, and administration protocols were identical to those of the REPAIR-AMI trial. Details are reported in the eMethods.

**Statistics**

Distributions of categorical variables were tested by χ² test or Fisher exact test. Continuous variables are reported as means and 95% CIs, if not stated otherwise. All variables were tested for homogeneity of variance by Levene test. Groups were compared using analysis of variance. Paired variables were analyzed using t test. The primary statistical plan called for comparing absolute change in LVEF at 4 months between the shock wave + BMCs and shock wave + placebo infusion groups with a paired t test and α = 5%. The absolute improvement of 3% on the left ventricular function measurement scale at 4 months with an SD of 3 was the assumed effect size for our sample size calculation. Power analysis was conducted in STATA 11.2. A total of 20 patients ensured a statistical power of 80% based on our assumption, when comparing the treatment groups.

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Preliminary data analyses suggested that patients with missing left ventricular angiography assessments tended to have a more severe disease course. We did not find any indication that the likelihood of missing data depends on unknown or unobserved variables. The exclusion of patients with no data on left ventricular angiography may result in biased effect estimates by a possible selection bias. We applied multivariate multiple imputation by an iterative Markov chain Monte Carlo approach for estimating the missing data in left ventricular angiography. Predictor variables for missing values in LVEF, end-diastolic volume index, end-systolic volume index, and stroke volume index were any available left ventricular angiography assessment, age, sex, NYHA class, levels of creatinine and the N-terminal fragment of the precursor to B-type natriuretic peptide (NT-proBNP), and the Seattle Heart Failure Model score.

The results from the 5 imputed data sets were combined by the Rubin

Figure 1. Trial Design of CELLWAVE

![Trial Design of CELLWAVE](image-url)
A random-effects model was applied for modeling the change in LVEF. For assessment of the primary end point, the high-dose and low-dose shock wave groups for patients receiving either BMCs or placebo infusion were combined. Analysis of the absolute change in LVEF from baseline to 4 months revealed that treatment with shock wave + BMCs was associated with a significant improvement in global LVEF (absolute change in LVEF, 3.2% [95% CI, 2.0% to 4.4%]; n=41) compared with shock wave + placebo infusion (absolute change in LVEF, 1.0% [95% CI, −0.3% to 2.2%]; n=38) (P=.02). Using only data obtained from quantitative angiography revealed identical results (absolute change in LVEF, 1.3% [95% CI, 0.03% to 2.5%]; n=31 for shock wave + placebo infusion vs 3.2% [95% CI, 2.1% to 4.3%]; n=33 for shock wave + BMCs [P=.02]). As illustrated in Figure 2B, changes in LVEF in the prespecified subgroup of patients with a baseline LVEF of 40% were combined.

**Effects on Left Ventricular Function by Quantitative Left Ventricular Angiography**

Quantitative left ventricular angiography was performed in all but 2 patients at baseline. At 4 months' follow-up, left ventricular angiography data could not be obtained because of emergency intervention for non-ST-segment elevation myocardial infarction at follow-up (n=1), psychiatric disease (n=1), different heart rhythms at baseline and follow-up (n=2), unwillingness to repeat cardiac catheterization (n=3), and loss to follow-up (n=1). In addition, in 13 patients, the quality of the paired left ventricular angiography data was insufficient for analysis. In 9 of these patients, paired MRI data were available and used instead. Thus, in patients with missing left ventricular functional data at baseline or follow-up, values were estimated using multiple imputations. Thus, a total of 100 paired data sets (97%) for assessment of the primary and secondary end points were available (Figure 1).

As illustrated in Table 2, baseline LVEF did not significantly differ between the 5 groups. In the low-dose and high-dose shock wave + placebo infusion groups, there was no change in LVEF at 4 months. Likewise, there was also no significant change in LVEF in the placebo shock wave + BMCs group. In contrast, patients receiving intracoronary infusion of BMCs 24 hours after targeted low-dose or high-dose shock wave application demonstrated a significant improvement in LVEF at 4 months (Table 2 and Figure 2A).

For assessment of the primary end point, the high-dose and low-dose shock wave groups for patients receiving either BMCs or placebo infusion were combined. Analysis of the absolute change in LVEF from baseline to 4 months revealed that treatment with shock wave + BMCs was associated with a significant improvement in global LVEF (absolute change in LVEF, 3.2% [95% CI, 2.0% to 4.4%]; n=41) compared with shock wave + placebo infusion (absolute change in LVEF, 1.0% [95% CI, −0.3% to 2.2%]; n=38) (P=.02). Using only data obtained from quantitative angiography revealed identical results (absolute change in LVEF, 1.3% [95% CI, 0.03% to 2.5%]; n=31 for shock wave + placebo infusion vs 3.2% [95% CI, 2.1% to 4.3%]; n=33 for shock wave + BMCs [P=.02]). As illustrated in Figure 2B, changes in LVEF in the prespecified subgroup of patients with a baseline LVEF of 40%...
or less revealed a dose-response effect (P = .03 for trend) from low-dose to high-dose shock wave pretreatment followed by BMC infusion. Moreover, LVEF improved in 27 of 29 patients receiving shock wave + BMCs, compared with only 18 of 28 patients in the shock wave + placebo infusion group (P = .008) and 9 of 14 patients in the placebo shock wave + BMCs group (P = .02).

In line with the results for LVEF, left ventricular stroke volumes demonstrated a significant increase in the high-dose shock wave + BMCs group but did not show a significant increase in the low-dose shock wave + BMCs group (Table 2). There were no significant changes in end-diastolic or endsystolic volumes at 4 months.

**Regional Left Ventricular Function Assessed by MRI**

Serial MRI analysis could be performed in 38 patients without implanted devices and free of claustrophobia. Overall analysis of left ventricular function confirmed the results of quantitative angiography for the primary end point (absolute change in LVEF from baseline to 4 months: −1.1% [95% CI, −5% to 3%]; n = 12 for shock wave + placebo infusion; 1.9% [95% CI, 0% to 4%]; n = 15 for shock wave + BMCs [P = .13]).

Wall thickening of infarcted segments improved significantly (P = .01 for trend) in patients receiving shock wave + BMCs (8.3% [95% CI, 5.7% to 10.9%] to 11.9% [95% CI, 8.9% to 14.9%]; P < .001) (FIGURE 3A Com).
Table 2. Results From Quantitative Left Ventricular Angiography

<table>
<thead>
<tr>
<th></th>
<th>Low-Dose Shock Wave + BMCs (n = 21)</th>
<th>Low-Dose Shock Wave + Placebo Infusion (n = 19)</th>
<th>High-Dose Shock Wave + BMCs (n = 50)</th>
<th>Placebo Shock Wave + BMCs (n = 51)</th>
<th>P Value from ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>37.2 (31.7 to 42.7)</td>
<td>29.9 (24.0 to 35.7)</td>
<td>32.4 (26.9 to 37.9)</td>
<td>32.3 (26.5 to 38.1)</td>
<td>.47</td>
</tr>
<tr>
<td>4 mo</td>
<td>39.9 (34.1 to 45.7)</td>
<td>30.2 (24.1 to 36.3)</td>
<td>35.5 (29.7 to 41.3)</td>
<td>34.0 (28.0 to 40.1)</td>
<td>.24</td>
</tr>
<tr>
<td>Absolute change</td>
<td>2.9 (1.2 to 4.6)</td>
<td>0.5 (~1.3 to 2.3)</td>
<td>3.5 (1.9 to 5.2)</td>
<td>1.5 (~0.4 to 3.3)</td>
<td>.06</td>
</tr>
<tr>
<td>P value, baseline vs 4 mo</td>
<td>.001</td>
<td>.59</td>
<td>&lt;.001</td>
<td>.12</td>
<td>.34</td>
</tr>
<tr>
<td>Stroke volume index, mL/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>93 (75 to 111)</td>
<td>123 (104 to 141)</td>
<td>105 (86 to 123)</td>
<td>111 (92 to 130)</td>
<td>.11</td>
</tr>
<tr>
<td>4 mo</td>
<td>96 (80 to 112)</td>
<td>118 (101 to 134)</td>
<td>102 (86 to 117)</td>
<td>114 (98 to 131)</td>
<td>.15</td>
</tr>
<tr>
<td>Absolute change</td>
<td>4 (~6 to 14)</td>
<td>~6 (~16 to 24)</td>
<td>~1 (~10 to 8)</td>
<td>6 (~4 to 15)</td>
<td>.48</td>
</tr>
<tr>
<td>P value, baseline vs 4 mo</td>
<td>.40</td>
<td>.25</td>
<td>.78</td>
<td>.25</td>
<td>.56</td>
</tr>
</tbody>
</table>

Abbreviations: ANOVA, analysis of variance; BMC, bone marrow–derived mononuclear cells; LVEF, left ventricular ejection fraction.

Compared with those receiving shock wave + placebo infusion (8.5% [95% CI, 5.8% to 11.1%] to 8.9% [95% CI, 6.1% to 11.8%]; P = .55) and placebo shock wave + BMCs (5.1% [95% CI, 1.2% to 9.0%] to 7.0% [95% CI, 3.0% to 11.1%]; P = .02). Changes in regional wall thickening were paralleled by a significant (P = .001 for trend) decrease in global infarct size as measured by late enhancement volume (LEV) (5.1% [95% CI, 0.9% to 9.3%] for shock wave + placebo infusion; 1.1% [95% CI, −2.7% to 5.0%] for placebo shock wave + BMCs; −3.4% [−5.6% to −1.1%] for shock wave + BMCs) at 4 months. Even after exclusion of 1 patient experiencing a silent myocardial infarction in a area different than that treated in the left ventricle in the shock wave + placebo infusion group, there was a significant (P = .002 for trend) reduction in LEV in the shock wave + BMCs group compared with the shock wave + placebo infusion group (Figure 3B, eFigure 2).

Calculating global left ventricular scar mass from LEV and total left ventricular mass revealed that scar mass significantly decreased by an absolute −4.0 g (−6.6 to −1.3) in the shock wave + BMCs group but remained essentially unchanged in the shock wave + placebo infusion group (+4.5 g [95% CI, −0.7 to 9.8]) and in the placebo shock wave + BMCs group (0.1 g [−4.4 to 4.6]) (P = .006 for trend). The alterations in scar mass were paralleled by reciprocal changes in left ventricular viable mass (−5 g [95% CI, −10 to 1]) for shock wave + placebo infusion, −3 g [95% CI, −5 to 0] for placebo shock wave + BMCs, and 2 g [95% CI, −1 to 5] for shock wave + BMCs (P = .007 for trend).

The absolute 3.4% reduction in LEV translated into a relative 10% smaller infarct size at 4 months in patients receiving low-dose or high-dose shock wave + placebo infusion (absolute change in NYHA class, 0.1 [95% CI, 0.4 to 0.5] in both groups), as well as in patients receiving placebo shock wave + BMCs (absolute change in NYHA class, −0.2 [95% CI, −0.6 to −0.1]). In contrast, patients receiving low-dose shock wave + BMCs showed a modest improvement in symptomatic status (absolute change in NYHA class, −0.3 [95% CI, −0.6 to 0]) and patients receiving high-dose shock wave + BMCs demonstrated a significant reduction in NYHA class (absolute change, −0.4 [95% CI, −0.8 to −0.1]) (Figure 4), driven by reductions in NYHA class III and corresponding increases in NYHA class I.

Baseline levels of NT-proBNP did not show statistically significant differ-
erences between the 3 pooled groups. Se-
rial assessment of NT-proBNP serum
levels was confined to patients with
stable kidney function, defined as a cre-
tinine level at 4 months lower than
125% of the baseline level. In the 29 pa-
tients receiving shock wave + placebo
infusion, serum levels of NT-proBNP
remained unchanged at 4 months’ fol-
low-up (1368 [95% CI, 780 to 1956]
pg/mL at baseline vs 1174 [95% CI, 715
to 1633] pg/mL at 4 months) (P = .18).

Likewise, there was no change in NT-
proBNP level in the 18 patients receiv-
ing placebo shock wave + BMCs (669
[95% CI, 468 to 870] pg/mL at baseline vs 646 [95% CI, 433 to 858] pg/mL
at 4 months) (P = .64). In contrast, in
the 34 patients receiving shock
wave + BMCs, NT-proBNP serum lev-
els were significantly reduced from
1384 (95% CI, 847 to 1920) pg/mL at
baseline to 1095 (95% CI, 662 to 1529)
pg/mL at 4 months’ follow-up (P = .04).

Clinical Outcome
As shown in the analysis of multiple and
recurrent clinical events (eFigure 3), the
overall frequency of MACEs was sig-
nificantly reduced in patients receiv-
ing placebo shock wave + BMCs (18
events) compared with patients receiv-
ing shock wave + placebo infusion
(61 events) or shock wave + BMCs (32
events) (hazard ratio, 0.58 [95% CI,
0.40-0.85]; P = .02). FIGURE 5 illus-
trates the hazard ratios for the indi-
vidual clinical end points and pre-
defined combined end points
comparing the shock wave + placebo
infusion vs shock wave + BMCs groups.
These data illustrate that the observed
improvements in contractile left ven-
tricular function and heart failure symp-
toms are paralleled by a decrease in the
overall frequency of individual clinical end points.

DISCUSSION
The present clinical trial investigated
the effects of combining target-tissue
preconditioning by extracorporeal
shock wave application with intracoro-
nary infusion of autologous BMCs on
left ventricular function in patients with
chronic postinfarction heart-failure. The
results demonstrate that shock wave–
facilitated infusion of BMCs benefi-
cially affects global and regional left
ventricular contractile function and may
reduce adverse clinical events in these
chronically ill patients.

Preconditioning the target tissue by
shock wave offers a novel approach to
redirect intra-arterially applied cells to
the region of interest by up-regulation of
chemoattractant cytokines.13 Local
shock wave–induced up-regulation of SDF-1 is expected to improve homing and retention of C-X-C chemokine receptor type 4 (CXCR4)–expressing cells in the hearts of patients when the cells are delivered via the intracoronary route. Recently, Wu et al20 demonstrated that early recruitment and retention of intramyocardially injected cardiac progenitor cells did predict subsequent contractile recovery in mouse models of myocardial infarction. Thus, attempts to increase recruitment and homing of applied cells should translate into improved efficacy. Indeed, the results of our study demonstrate that treatment with shock wave + BMCs was associated with a significant, albeit modest increase in LVEF attributable to improved wall thickening in the shock wave–treated region. Importantly, in the patients with the most severely reduced LVEF, treatment with shock wave + BMCs resulted in a homogeneous response, with improved LVEF observed in 93%, suggesting that target-region preconditioning reduces the heterogeneity in individual responses to intracoronary infusion of BMCs observed in the placebo shock wave + BMCs group of the present and in previous studies.7 CXCR4, the SDF-1 receptor, is expressed in subpopulations of BMCs,10,11,21 mesenchymal stem cells, very small embryonic-like cells, adult cardiac stem cells under hypoxic conditions, and in adipose tissue–derived stem cells.22–24 Thus, preconditioning the target tissue by noninvasive application of shock waves may also improve the efficacy of other cell therapeutic approaches.

The 3.2% absolute improvement in global LVEF with shock wave–facilitated infusion of BMCs appears to be rather modest. However, as summarized in a recently published meta-analysis quantitatively assessing the relationship between short-term (4-6 months) therapy–induced changes in left ventricular remodeling analyzed in controlled trials and long-term outcomes in patients with heart failure attributable to left ventricular systolic dysfunction,22 mean placebo-subtracted increases in LVEF range from 1.3% for valsartan in the VAL-HeFT (Valsartan Heart Failure Trial) including more than 5000 patients,26 to 2.0% for aldosterone blockade,27 2.7% for cardiac re-synchronization therapy,25 and 2.9% for carvedilol in patients with stable heart failure and nonhibernating myocardium—yet all of these therapies are well established to improve clinical outcomes in patients with chronic heart failure. These numbers compare favorably with the results of the present study showing a placebo-subtracted increase in LVEF of 2.0% for the entire study cohort and of 3.0% for the patients with LVEF less than 40%, which occurred in addition to comprehensive conventional pharmacological therapy for heart failure. Moreover, MRI revealed a selective increase in infarct wall thickening and a measurable reduction in infarct size in the shock wave + BMCs group. It is possible that, with time, these improvements could contribute to reversal of the adverse remodeling that commonly follows myocardial infarction. Nevertheless, the observed beneficial effects on MACEs during follow-up require confirmation in larger studies, because the

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sample size of the present study was not powered to demonstrate significant differences in clinical outcome.

Whereas treatment with shock wave + BMCs was associated with an increase in global and regional myocardial contractility, there was no significant improvement with shock wave + placebo infusion. Thus, in the setting of chronic postinfarction heart failure without ongoing ischemia, shock wave-mediated preconditioning alone does not appear to mediate contractile recovery by attracting endogenously circulating progenitor cells, which may be rationalized by the profound functional impairment of the cells in this patient cohort.29

Some limitations of our study merit further discussion. First and most importantly, the effects of BMC administration in the placebo shock wave group was considerably smaller than in the BMCs group of our previously published TOPCARE-CHD (Transplantation of Progenitor Cells and Regeneration Enhancement in Coronary Heart Disease) trial.7 Side-by-side comparison of the 2 patient cohorts revealed that the patients in the present CELLWAVE trial had significantly more advanced heart failure and coronary artery disease compared with the TOPCARE-CHD patient cohort. In line with more advanced cardiac disease, the patients in the present study received significantly lower numbers of BMCs, and the administered cells had profoundly impaired colony-forming unit capacity, indicating severe functional impairment. Our previous studies demonstrated that the number of applied BMCs giving rise to colony-forming units is a major determinant of the efficacy of intracoronary infusion of BMCs in patients with chronic heart failure.30 Thus, we believe that the more advanced cardiac disease has contributed to the lack of effect observed in the placebo shock wave + BMCs group of the present study.

Because the present study is to our knowledge the first to clinically apply focused shock wave therapy to the hearts of patients with postinfarction heart failure, it was designed to detect potential dose-dependent unwanted effects of shock wave application, such as minor myocardial injury or destabilization of coronary plaques, leading to acute coronary syndromes. Therefore, we purposely selected 2 doses of shock wave, corresponding to the medium and high doses of our experimental validation studies.13 However, the prespecified analysis plan called for comparing the results of the combined low-dose and high-dose shock wave + BMCs vs shock wave + placebo infusion. The trial design also precluded a definite answer to the question of whether shock waves alone affected left ventricular contractile recovery, because we did not include a group of patients receiving both placebo shock wave and placebo infusion. Last, we used quantitative left ventricular angiography for the assessment of the primary end point of the study, although MRI would be superior. However, MRI is impossible in patients with implanted devices, so use of MRI would have precluded left ventricular analysis in almost half of our patient population. Nevertheless, MRI of suitable patients corroborated the findings obtained from left ventricular angiography and also provided important mechanistic insights.

In conclusion, shock wave-mediated preconditioning of the target tissue prior to intracoronary administration of autologous BMCs is associated with significant, albeit modest absolute improvements in global and regional left ventricular contractile function in patients with chronic postinfarction heart failure. However, the observed beneficial effects on clinical outcome require confirmation in larger clinical end point trials.

Author Contributions: Drs Assmus and Zeiher had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy

<table>
<thead>
<tr>
<th>No.</th>
<th>Shock Wave + BMCs (n = 43)</th>
<th>Shock Wave + Placebo Infusion (n = 39)</th>
<th>Hazard Ratio (Hazard Ratio 95% CI)</th>
<th>Favors Shock Wave + BMCs</th>
<th>Favors Shock Wave + Placebo Infusion</th>
<th>P Value</th>
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</thead>
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<td>All-cause death</td>
<td>5</td>
<td>6</td>
<td>0.9 (0.3-3.1)</td>
<td>0.01</td>
<td>0.9 (0.3-2.7)</td>
<td>0.09</td>
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<td>4</td>
<td>5</td>
<td>0.9 (0.2-3.4)</td>
<td>0.88</td>
<td>0.9 (0.1-0.9)</td>
<td>0.3</td>
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<td>Repeat AMI</td>
<td>1</td>
<td>4</td>
<td>0.9 (0.03-2.7)</td>
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<td>0.6 (0.3-1.2)</td>
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<td>9</td>
<td>20</td>
<td>0.5 (0.2-1.1)</td>
<td>0.09</td>
<td>0.6 (0.3-1.0)</td>
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<td>Ventricular tachycardia</td>
<td>5</td>
<td>16</td>
<td>0.3 (0.1-0.9)</td>
<td>0.03</td>
<td>0.5 (0.3-0.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>Cardiac death and rehospitalization for heart failure</td>
<td>13</td>
<td>25</td>
<td>0.6 (0.3-1.2)</td>
<td>0.12</td>
<td>0.5 (0.3-0.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>Cardiac death, rehospitalization for heart failure, and repeat AMI</td>
<td>14</td>
<td>29</td>
<td>0.6 (0.3-1.0)</td>
<td>0.06</td>
<td>0.5 (0.3-0.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>Cardiac death, rehospitalization for heart failure, repeat AMI and ventricular tachycardia</td>
<td>19</td>
<td>45</td>
<td>0.5 (0.3-0.8)</td>
<td>0.006</td>
<td>0.5 (0.3-0.8)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Hazard ratios and 95% CIs for the individual and combined clinical major adverse cardiac events estimated by an Anderson and Gill model for multiple and ordered recurrent time-to-event data. BMCs indicates bone marrow–derived mononuclear cells.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Dimmeler and Dr Zeiher report that they are cofounders of t2cure; a for-profit company focused on regenerative therapies for cardiovascular disease, and for which they serve as scientific advisers and are shareholders. Dr Dimmeler reported serving on a scientific advisory board for Miragen; serving as a consultant to Merck; receiving grants or grants pending from the German Research Foundation (DFG) and the European Union; receiving payment for lectures from various entities; holding patents or patents pending (mir-29, mir-92); and receiving travel expenses from various entities. Dr Zeiher reported serving as a consultant to sanofi-aventis, Capricor, and Baxter Healthcare; receiving a grant from the DFG; receiving grants or grants pending from the German Ministry of Health and Education; receiving payment for lectures from Bayer, Berlin Chemie, Orbis Neich, and AstraZeneca; and holding patents or patents pending from Siemens Healthcare. No other authors reported disclosures.

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Online-Only Material: eMethods, eTable, and efigures 1 and 2 are available at www.jama.com.

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REFERENCES


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