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CLINICAL RESEARCH
Ischaemic heart disease

Cardiac shockwave therapy in addition to coronary bypass surgery improves myocardial function in ischaemic heart failure: the CAST-HF trial

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Abstract

Background and Aims In chronic ischaemic heart failure, revascularisation strategies control symptoms but are less effective in improving left ventricular ejection fraction (LVEF). The aim of this trial is to investigate the safety of cardiac shockwave therapy (SWT) as a novel treatment option and its efficacy in increasing cardiac function by inducing angiogenesis and regeneration in hibernating myocardium.

Methods In this single-blind, parallel-group, sham-controlled trial (cardiac shockwave therapy for ischemic heart failure, CAST-HF; NCT03859466) patients with LVEF ≤40% requiring surgical revascularisation were enrolled. Patients were randomly assigned to undergo direct cardiac SWT or sham treatment in addition to coronary bypass surgery. The primary efficacy endpoint was the improvement in LVEF measured by cardiac magnetic resonance imaging from baseline to 360 days.

Results Overall, 63 patients were randomized, out of which 30 patients of the SWT group and 28 patients of the Sham group attained 1-year follow-up of the primary endpoint. Greater improvement in LVEF was observed in the SWT group (Δ from baseline to 360 days: SWT 11.3%, SD 8.8; Sham 6.3%, SD 7.4, $P = .0146$). Secondary endpoints included the 6-minute walking test, where patients randomized in the SWT group showed a greater Δ from baseline to 360 days (127.5 m, SD 110.6) than patients in the Sham group (43.6 m, SD 172.1) ($P = .028$) and Minnesota Living with Heart Failure Questionnaire score on day 360, which was 11.0 points (SD 19.1) for the SWT group and 17.3 points (SD 15.1) for the Sham group ($P = .15$). Two patients in the treatment group died for non-device-related reasons.

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Conclusions In conclusion, the CAST-HF trial indicates that direct cardiac SWT, in addition to coronary bypass surgery improves LVEF and physical capacity in patients with ischaemic heart failure.

Structured Graphical Abstract

Key Question

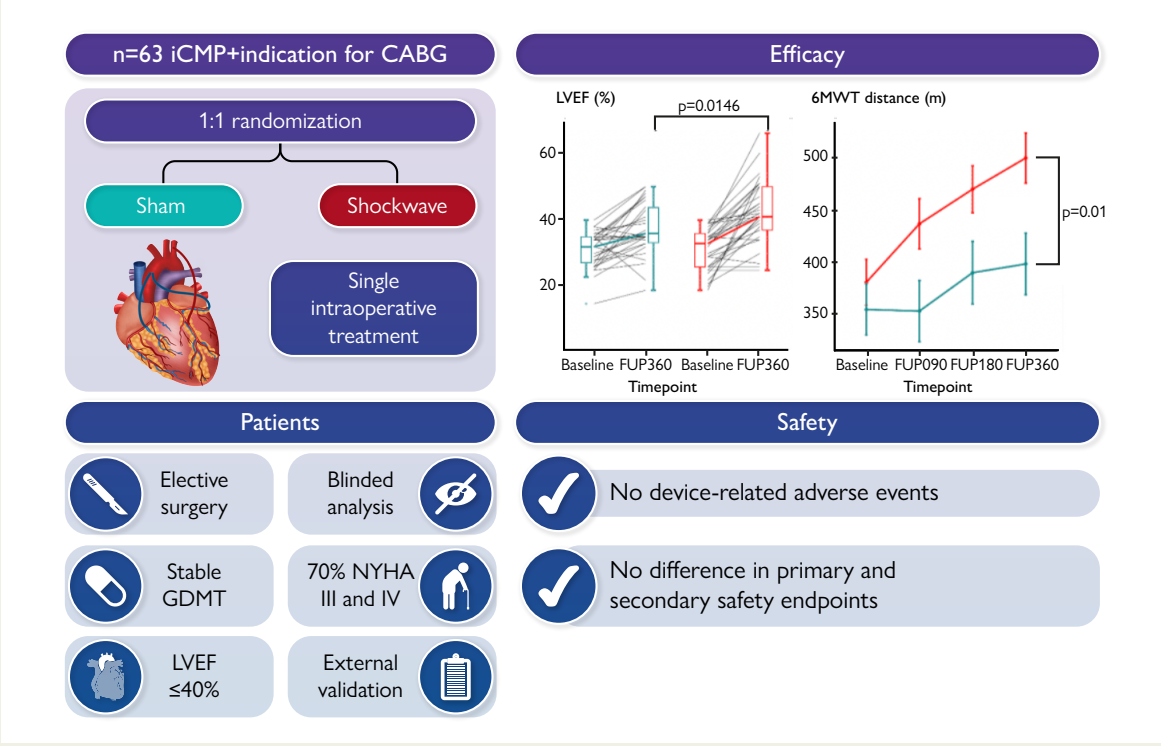
Is direct epicardial shockwave therapy (SWT) safe and effective in addition to coronary artery bypass graft (CABG) surgery in patients suffering from ischaemic cardiomyopathy (iCMP)?

Key Finding

In a single-center, randomized, single-blind, parallel-group, sham-controlled trial, direct cardiac SWT in addition to CABG resulted in an improvement of left ventricular ejection fraction, physical capacity and quality of life at one-year follow-up in the intervention group in the absence of adverse events.

Take Home Message

The findings of the CAST-HF trial suggest that SWT in addition to CABG is a promising novel therapeutic option for patients suffering from iCMP.



Direct cardiac shockwave therapy (SWT) in addition to coronary artery bypass graft (CABG) surgery improves left ventricular ejection fraction (LVEF), physical capacity and quality of life in patients with ischaemic heart failure. 6MWT, 6-min walking test; FUP, follow-up; GDMT, guideline-directed medical therapy; NYHA, New York Heart Association; iCMP, ischaemic cardiomyopathy

Keywords Ischaemic cardiomyopathy • Heart Failure • Shockwave Therapy • Surgical Revascularization

Introduction

Ischaemic heart failure is the most frequent underlying cause of heart failure. Coronary artery bypass graft surgery (CABG) is a class I indication for patients with ischaemic heart failure.[1,2] Surgical revascularisation controls symptoms but is less effective in improving left ventricular ejection fraction (LVEF). Morbidity and mortality remain high in those patients.[2] Strategies for myocardial regeneration adjunctive to revascularisation failed to show a substantial benefit and are not yet routinely used in clinical practice.[3,4]

Shockwave therapy (SWT) has been shown to trigger regenerative effects on soft tissues including tendinopathies and wound healing disturbances.[5–8] Driven by the clinical need and the lack of regenerative therapies in routine clinical practice, we investigated the biological effects of direct cardiac SWT on myocardial regeneration. In preclinical studies on small- and large-animal models, we could show that it is effective to induce the regeneration of ischaemic myocardium.[9–11]

Shock waves are specific sonic pressure waves that can propagate through tissue, thereby generating a physical stimulus activating the innate immune system of treated cells, leading to increased DNA

accessibility and cellular plasticity, together with the secretion of angiogenic cytokines and growth factors.[8,9] SWT thus induces angiogenesis in the hibernating myocardium.[10–12] Newly formed vessels then support the recruitment of chronically undersupplied myocardium.[9,10]

Percutaneous cardiac SWT in observational studies has shown to exert beneficial effects in patients with stable angina.[13] Lung tissue covering the heart absorbs waves and percutaneous SWT therefore is limited to small areas of the heart. We therefore developed a system for SWT in direct contact with the myocardium during CABG surgery to reach all areas of the heart.

CAST-HF was the first randomized, single-blind, parallel-group, sham-controlled trial to evaluate the safety and efficacy of direct cardiac SWT in addition to CABG surgery in patients presenting with multivessel disease and a severely reduced LVEF.

Methods

Study design

CAST-HF was a randomized, single-blind, parallel-group, sham-controlled trial undertaken in a single centre at the Medical University of Innsbruck, Austria. The trial was sponsored by the Medical University of Innsbruck and the protocol was approved by the institutional ethics committee.[14] The sponsor was responsible for study management, data collection, and data analysis; analyses were performed by an independent statistician from the Institute of Medical Statistics and Informatics, Medical University of Innsbruck.

The trial was conducted and reported in accordance with the protocol and the statistical analysis plan, both of which are available in the Supplementary data online, appendix.

The inclusion and safety of patients in the trial were overseen by an independent data safety monitoring board (DSMB).

Participants

All patients provided written informed consent and were screened for eligibility. Inclusion criteria included age ≥21 years, ischaemic heart failure requiring surgical revascularization, as assessed by the institutional heart team of interventional cardiologists and cardiac surgeons, LVEF) ≤40%, as determined by cardiac magnetic resonance imaging (MRI), and regional left ventricular (LV) wall motion abnormalities.

Medical treatment for heart failure was individually tailored prior to enrolment, in accordance with guidelines.[15] During follow-up visits to assess LVEF, patients had to have been on stable guideline-directed medical therapy for at least 30 days prior to each visit (detailed description of medication use in the Supplementary data online, appendix).

The exclusion criteria consisted of significant concomitant aortic valve disease requiring surgical treatment, serious radiographic contrast allergy, cardiogenic shock or acute myocardial infarction (MI) (ST-elevation or non-ST-elevation MI), a contraindication for cardiac MRI, history of significant ventricular arrhythmias (other than MI-associated arrhythmia), a concomitant comorbid condition decreasing life expectancy to less than one year, ventricular thrombus, cardiac tumour and pregnancy.

Before the enrolment of a patient in the study, a DSMB validated the enrolment criteria for the patient concerned. The study was conducted as an all-comers trial and the DSMB gave its permission for each patient enrolment to rule out the possibility of any patient selection bias by the investigators. This was performed prior to the intra-operative randomization and the DSMB therefore was blinded to the later patient allocation.

Randomization and masking

Patients were randomly assigned to the SWT or Sham group in a 1:1 ratio. The randomization process was executed independently of the clinical investigators with the use of opaque envelopes. The envelopes were opened by an assistant at the beginning of the surgical procedure. To further avoid any bias of the surgeons, an amendment to the study protocol was filed and became effective on 13 October 2021 after the enrolment of 27 patients. From this date onwards, envelopes were opened at the end of the CABG procedure, after the aortic cross-clamp had been released (bypasses fully established). A comparison of outcomes between patients enrolled before and after this amendment showed no relevant effect of the protocol change (see Supplementary data online, *Table S9*).

None of the participants were aware of the group to which they had been assigned throughout the study. The surgeons responsible for performing the intervention were aware of the group assignment, but the investigators responsible for follow-up assessments, all core laboratory staff, the biostatisticians performing the analysis, and the members of the DSMB were masked to group assignment.

Procedures

Cardiac MRI examinations were performed at baseline, at day 180 and at day 360 on a 1.5 Tesla clinical MRI unit (AVANTO^{fit}; Siemens, Erlangen, Germany). The baseline MRI confirmed the inclusion criteria. MRI examinations were performed according to a multiparametric protocol. The details are presented in the Supplementary data online, appendix. Briefly, LV function and volumes were assessed on short-axis cine images using standard software (cvi42; Circle Cardiovascular Inc, Calgary, Canada) for post-processing analyses with semi-automatic detection of LV endo- and epicardial borders. Papillary muscles were excluded from myocardial mass and included in the LV volume.

If present, infarction scars were quantified on late gadolinium enhancement (LGE) images using Circle analyses software and the results were expressed as a percentage of myocardial LV mass. Late gadolinium enhancement was defined as an image intensity level ≥5 standard deviations above the mean of remote myocardium.[16]

Baseline physical examinations (6-minute walk test [6MWT] and New York Heart Association [NYHA] functional class), health status (Minnesota Living with Heart Failure Questionnaire [MLHFQ], SF-36 test, Seattle Angina Pectoris Questionnaire [SAQ]), ECG recording and blood sampling were performed.

Patients underwent on-pump, single cross-clamp CABG surgery according to the institutional standard. Complete revascularization of all vessels at least 1.5 mm in diameter with ≥50% stenosis was aimed for in all patients as defined in the SYNTAX trial.[17] After complete revascularisation, while still on cardiopulmonary bypass, shockwaves were applied in direct contact to the ischaemic myocardium of the left ventricle (300 impulses per coronary supply territory, 0.38 mJ/mm^2, 3 Hz) in the treatment group. The optimal dosage had been determined in a prior large-animal trial.[9] An identical manipulation of the heart was performed with an inactive applicator for the Sham group.

The cardiac shockwave system consisted of a table-top device (Nonvasiv Medical GmbH, Konstanz, Germany) and a sterile single-use applicator releasing electrohydraulic shockwaves (Heart Regeneration Technologies GmbH, Innsbruck, Austria) (see Supplementary data online, *Figure S1*). The applicator was inserted into a sterile cover containing ultrasound gel. Continuous saline rinsing was applied throughout the procedure, to ensure acoustic coupling between the applicator and the myocardium. In the CAST-HF study, 300 impulses per coronary supply territory were applied at an energy flux density (EFD) of 0.38 mJ/mm^2 and a frequency of 3 Hz. These parameters were defined based on the results of preclinical trials in small and large animal models as well as from an unpublished in-human pilot trial. To treat the periinfarction zone with SWT to induce angiogenesis and to recruit hibernating myocardium, areas with wall motion abnormalities were identified in the preoperative MRI and treated during surgery. More information about the trial device and its use are provided in the Supplementary data online, appendix.

Post-procedural follow-up visits were performed on days 0, 1, and 2 and on discharge from the hospital. ECG recording and blood tests were performed during these consultations. Long-term follow-up visits on days 90,

180, and 360 included physical examinations (6MWT and NYHA functional class), health status analysis (MLHFQ, SF-36 test, SAQ), ECG recording, blood sampling and echocardiography. A cardiac MRI was performed on days 180 and 360.

Outcomes

The primary efficacy endpoint was the improvement in LVEF measured on cardiac MRI from baseline to day 360 after the procedure. All MRI measurements were performed at our institution by independent investigators masked to the group assignment. The primary safety endpoint was the occurrence of device-related adverse or serious adverse effects during the study period.

The secondary endpoints for efficacy were improvement in 6MWT distance, change in NYHA functional class, change in serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration (Elecsys®, Roche Diagnostics, Mannheim, Germany), change in renal function (glomerular filtration rate, GFR) and improvement in quality of life, as assessed with the MLHFQ, the SF-36 Questionnaire and the SAQ).

The secondary safety endpoints included the occurrence of ventricular arrhythmia, periprocedural myocardial injury, assessed by measuring levels of the cardiac biomarkers creatine kinase (CK)-MB (Cobas®, Roche Diagnostics, Mannheim, Germany), troponin T (hs-TropT test, Elecsys®, Roche Diagnostics, Mannheim, Germany), and signs of infection, assessed by determining the increase in C-reactive protein (CRP) concentration or leukocytosis during hospital stay. All events were adjudicated by the independent DSMB, masked to the group assignment.

The primary efficacy endpoint—improvement of LEVF from baseline to day 360—was validated by an independent, external MRI core laboratory (ImaCor AB, Lund, Sweden) at the timepoint of recruitment halt. The core laboratory was masked to the group assignment and the follow-up time point.

Statistical analysis

Two power calculations were performed to define the number of recruited patients for an early analysis (interim analysis) and the final analysis. The required sample size had been determined for the primary endpoint using results from an unpublished first-in-human pilot study (including 10 patients) for the treatment group, and from a meta-analysis on CABG patients with a reduced ejection fraction for the sham group using a two sample *t*-test.[18]

For the first power calculation (pragmatic method) we used the lowest standard deviation from both cohorts (intervention: LVEF 10.4 ± 7.22, control: LVEF 4.5 ± 5.76). Assuming an effect size (Cohen's *d*) of 0.903 between groups 32 participants (16 intervention/16 sham) were required for statistical analysis with adequate power, assuming an alpha risk of 0.05 (one-tailed) and a beta risk of 0.20.

For the second power calculation (conservative method) we used the highest standard deviation from both cohorts (intervention: LVEF 10.4 ± 8.7, control LVEF 4.5 ± 8.7). Assuming an effect size (Cohen's *d*) of 0.678 between groups 72 participants (36 intervention/36 sham) would be required for statistical analysis with adequate power, assuming an alpha risk of 0.05 (two-tailed) and a beta risk of 0.20.

Based on these calculations we pre-defined to perform the early analysis (interim analysis) when 20 patients per group attained one-year follow-up for the primary endpoint. If the trial had not been positive for its primary endpoint in the interim analysis, further patient enrolment would have been performed for up to 80 patients in total. For both the interim and final analysis, the alpha risk was corrected for multiple testing and set at 0.0294 according to the alpha spending plan proposed by Pocock.[19] We used the Pocock rule instead of a flexible approach because the interim analysis was performed at a pre-specified time point and was not intended to lead to a new power-calculation.[20]

Change in LVEF from baseline to 360-day follow-up, defined as the primary endpoint for efficacy, was evaluated in an analysis of covariance (ANCOVA) adjusted for LVEF at baseline, taking into account regression to the mean in repeated continuous measurements, as suggested by the European Medicines Agency guideline on adjustment for baseline covariates in clinical trials.[21] All assumptions for ANCOVA (linearity, homogeneity and normality) were met. The baseline endpoint for safety, the occurrence of adverse events, was compared between treatment groups in χ^2 tests and Fisher's exact tests, as appropriate. Secondary endpoints were analysed through descriptive statistics in paired and unpaired *t*-tests and in Mann–Whitney *U*-tests. The intention-to-treat (ITT) population was the primary analysis population. In cases of missing data, the last-observation-carried-forward (LOCF) method was applied as an imputation technique. In addition, a multiple imputation technique was performed to substantiate the validity of the results from the earlier defined LOCF imputation. A multiple imputation using chained equations with 50 imputations was applied. Predictive mean matching with 20 iterations was used. To derive an overall estimate and confidence interval, we performed linear regression across all imputed datasets and pooled coefficients and standard errors across all models according to Rubin's rules.[22]

The per-protocol and sensitivity analyses are presented in the Supplementary data online, appendix. All analyses were performed with the use of CRAN RStudio, version 2022.7.1.554 (R Foundation for Statistical Computing, Vienna, Austria). The trial is registered at ClinicalTrials.gov (NCT03859466).

Results

Between 29 November 2018 and 4 April 2022, 87 patients were assessed for eligibility, 63 of whom met the inclusion criteria. Thirty-three patients were allocated to the SWT group, and 30 patients were allocated to the Sham group. As pre-specified in the study protocol, an interim analysis was performed when 20 patients per arm had attained 1-year follow-up. On 1 June 2022 this interim analysis was conducted and showed a significant difference of the primary endpoint between groups. The DSMB therefore decided to halt further patient recruitment as pre-defined in the study protocol.

Thirty patients of the SWT group and 28 patients of the Sham group form the ITT population for the analysis of the primary endpoint (*Figure 1*). Three patients in the SWT group and 2 patients in the Sham group were lost to follow-up or died (see Supplementary data online, *Table S1*). Those missing values were imputed by the LOCF method.

In the SWT group, two patients had died from causes unrelated to the procedure (detailed description in the Supplementary data online, appendix) and one patient refused cardiac MRI on day 360. In the Sham group, one patient missed the day 180 follow-up visit due to recurrent pneumonia, one patient refused cardiac MRI on day 360, and one patient had moved abroad before day 360. The patients with incomplete follow-ups are listed in Supplementary data online, *Table S1*.

Patients' characteristics at baseline were balanced between groups. The patients had a mean age of 64 years (SD 8.52), 11% were female, 70% had an NYHA class III–IV disease, and mean LVEF was 31% (SD 5.88). Blood pressure was well-balanced between groups (mean: 130/75 mmHg). Baseline NT-proBNP concentration was increased in both groups (median: 1099 ng/L, IQR: 631.5–2031.0). SYNTAX score was intermediate or high in 75% of patients, and the mean EuroSCORE II score was 2.93 (SD 2.04) (*Table 1*). Myocardial scar sizes were comparable between groups with a relative mass of 12.7% (SD 7.0) from the left ventricle (see Supplementary data online, *Table S2*). Baseline medication intake was comparable between groups at baseline (see Supplementary data online, *Table S11*) and did not differ between groups throughout the study (see Supplementary data online, *Tables S10–S14*).

Direct cardiac SWT was successfully applied in all patients. No procedural discontinuations or device malfunctions occurred.

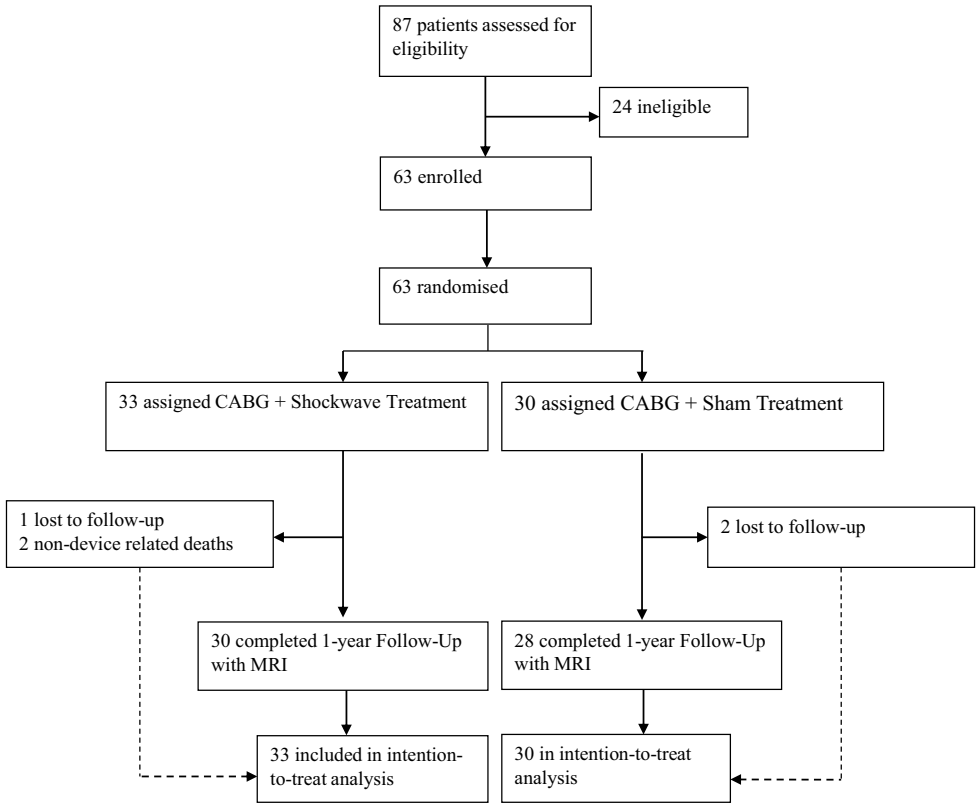


Figure 1 Trial profile

The primary efficacy endpoint, change in LVEF from baseline to 360-day follow-up, was normally distributed and differed significantly between groups, with a larger improvement in the SWT group than in the Sham group (11.3% [SD 8.8] vs. 6.3% [SD 7.4], $P = .0146$) (*Table 2*, *Figure 2A*). This effect was already visible on day 180 (*Figure 2B*). The results were confirmed by an external MRI core laboratory (see Supplementary data online, *Table S3*). No device-related adverse or serious adverse effects (primary safety endpoint) occurred. The residual SYNTAX scores were equally distributed between groups, thereby indicating that there were no differences in completeness of revascularization (see Supplementary data online, *Table S2*).

The 6-minute walking test distance at day 360 was significantly greater in the SWT group than in the Sham group (501.0 m, SD 137.7 vs. 399.6 m, SD 161.0, $P = .01$) with a delta from baseline to 360 days of 127.5 m, SD 110.6 vs. 43.6 m, SD 172.1, ($P = .028$). The MLHFQ score at day 360 was 11.0 points (SD 19.1) for the SWT group and 17.3 points (SD 15.1) for the Sham group ($P = .15$).

Renal function was similar between the SWT and Sham groups, with a GFR of 70.6 mL/min/1.73 m^2 (SD 24.8) in the SWT group, and 78.6 mL/min/1.73 m^2 (SD 23.5) in the Sham group. There was no significant difference in NT-proBNP levels between groups at baseline or at any follow-up time point. Rates of repeat angiography, re-hospitalization and survival were also similar between groups. The improvement in the NYHA functional class at one year did not differ significantly between groups (*Table 3*).

Secondary safety endpoints, including the occurrence of ventricular arrhythmia (see Supplementary data online, *Table S4*), periprocedural myocardial injury, as indicated by serum levels of cardiac biomarkers CK-MB and troponin T (see Supplementary data online, *Table S5*), and signs of infection, as indicated by an increase in CRP concentration or leukocytosis (see Supplementary data online, *Table S6*), did not differ significantly between groups during hospitalization.

Further analyses confirmed a significant improvement in LVEF in the SWT group compared to the Sham group in the per-protocol population without imputation (SWT group: 12% [SD 8.7]; Sham group: 5.7% [SD 7.2], $P = .0019$), in a complete data set analysis (SWT group: 12% [SD 8.7]; Sham group: 5.9% [SD 7.3], $P = .0025$) and in a multiple imputation technique using predictive mean matching (SWT group: 12.2% [SD 8.4]; Sham group: 6.3% [SD 7.4], $P = .004$). To rule out any surgeon's effect, the primary endpoint was as well analysed and adjusted for the *surgeon* as an interaction (see Supplementary data online, *Table S7*). Additional MRI parameters are shown in Supplementary data online, *Table S8*.

No device-related adverse or serious adverse events (primary safety endpoint) were observed. All the adverse and serious adverse events occurring during the study period are listed in the Supplementary data online, appendix.

Discussion

CAST-HF is the first randomized, single-blind, parallel-group, sham-controlled trial to evaluate the effects of direct cardiac SWT in addition to CABG surgery in patients suffering from ischaemic heart failure. The main finding of our study indicates that direct cardiac SWT in addition to CABG surgery significantly improved LVEF measured by cardiac MRI.

Table 1 Patient characteristics at baseline

Characteristic	Sham $n = 30$	SWT $n = 33$
Age, years	64.6 (8.6)	63.1 (8.5)
Female sex, no.	2 (7%)	5 (15%)
Body-mass index, kg/m^2	27.2 (4.6)	27.0 (4.7)
Heart Rate, bpm	73.0 (14.4)	74.8 (16.2)
Systolic blood pressure, mmHg	134.3 (19.7)	125.5 (15.4)
Diastolic blood pressure, mmHg	78.0 (13.9)	73.0 (10.7)
LVEF, %	30.7 (5.6)	31.5 (6.2)
≤30%, no.	14 (47%)	14 (42%)
31%–40%, no.	16 (53%)	19 (58%)
NYHA functional classification, no.		
I	1 (3%)	2 (6%)
II	8 (27%)	8 (24%)
III	18 (60%)	15 (46%)
IV	3 (10%)	8 (24%)
NT-proBNP, pg/mL	998.0 [536.0;1839.2]	1514.0 [663.0;2675.0]
Atrial fibrillation, no.	2 (7%)	4 (12%)
Diabetes, no.	18 (60%)	13 (39%)
Hypertension, no.	25 (83%)	32 (97%)
COPD, no.	7 (23%)	5 (15%)
Smoker, no.	24 (80%)	24 (73%)
Peripheral artery disease, no.	4 (13%)	3 (9%)
eGFR, mL/min/1.73 m^2	82.9 (27.6)	68.1 (22.3)
Heart failure medication, no.		
ACE-I	20 (67%)	16 (49%)
Beta-blocker	25 (83%)	27 (82%)
MRA	19 (63%)	20 (61%)
ARNI	6 (20%)	11 (33%)
ARB	7 (23%)	14 (42%)
Previous heart failure hospitalization, no.	12 (40%)	16 (49%)
Previous myocardial infarction, no.	14 (47%)	13 (39%)
Previous PCI– no.	5 (17%)	5 (15%)
SYNTAX score[a]	27.8 (8.1)	28.5 (6.9)
Low (<22)	8 (27%)	8 (24%)
Intermediate (23–32)	13 (43%)	16 (49%)
High (>32)	9 (30%)	9 (27%)
EuroSCORE II	2.9 (2.2)	2.9 (1.9)
Diseased coronaries		
2 vessel disease, no.	1 (3%)	2 (6%)
3 vessel disease, no.	29 (97%)	31 (94%)

Data are mean (SD), *n* (%) or median [IQR]. All baseline variables were well-balanced between the two groups.
ACE-I, angiotensin-converting enzyme inhibitor; ARB, Angiotensin II Receptor Blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.
[a]One patient is missing due to repeat surgery, SYNTAX score was therefore not applicable.

Table 2 Primary outcome, intention-to-treat last-observation-carried-forward

Characteristic	Sham $n = 30$	SWT $n = 33$	Difference	*P*-value
LVEF at 360 days, %	37.4 (8)	42.5 (9.3)	5 (1 to 9)	.0146
Δ from baseline to 360 days, %	6.3 (7.4)	11.3 (8.8)		
LVEF at 180 days, %	36.8 (7.7)	41.7 (8.5)	4.9 (1.4 to 8.3)	.0068
Δ from baseline to 180 days, %	5.7 (6.3)	10.5 (7.5)		

Data are mean (SD), *n* (%) or median [IQR].
LVEF was measured by cardiac magnetic resonance imaging.
ITT, intention-to-treat; LOCF, last-observation-carried-forward; LVEF, left ventricular ejection fraction.

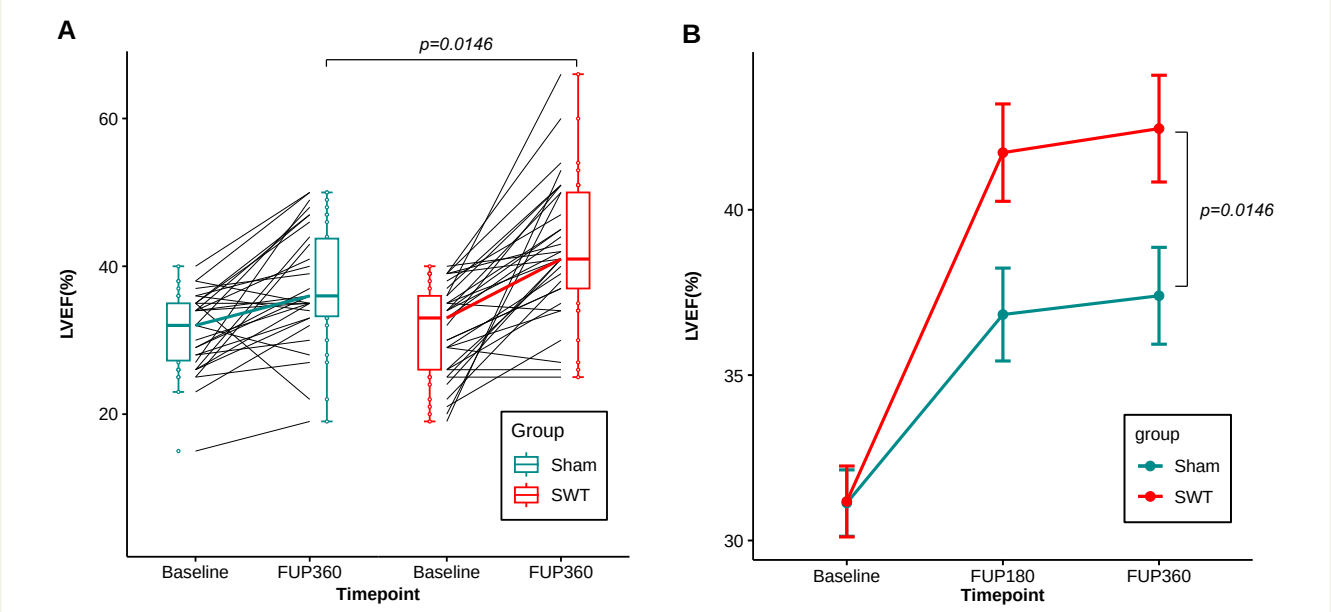


Figure 2 (*A*) Improvement in left ventricular ejection fraction for each patient, from baseline to day 360 follow-up. (*B*) Improvement in left ventricular ejection fraction from baseline to day 180 and day 360

A significant improvement in LVEF was already evident six months after the procedure and remained stable for up to one year. The application of direct cardiac SWT was both feasible and safe. Patients of the SWT group also demonstrated significant improvements in the 6MWT results (*Structured Graphical Abstract*).

Electrohydraulic shock waves are created via the application of high voltage to two electrodes surrounded by water. The emerging shockwave is a well-defined sonic wave with a very specific wave profile. A high peak positive pressure amplitude (up to 120 MPa) is followed by a wave of negative pressure (up to 10 MPa). Shockwave therapy has been shown effective in the treatment of various pathologies including tendonitis, non-healing bone fractures, chronic leg ulcers and soft tissue wounds, post-stroke spasticity and spinal cord injury.[8] Three different parameters can be adjusted when creating a shockwave: (i) the EFD, the energy applied per unit area, measured in millijoules per square millimetre (mJ/mm^2), (ii) the number of impulses applied per treatment area, and (iii) the frequency of shockwaves applied per minute. Preclinical trials assessing cardiomyocyte morphology after direct SWT using transmission electron microscopy showed no signs of mechanical damage on a cellular or subcellular level.[23] Safety assessment of SWT showed no differences in postprocedural cardiac biomarkers in our trial (see Supplementary data online, *Table S5*). The mechanistic effects of SWT on the myocardium have been thoroughly investigated in preclinical studies. In a mouse model, it was shown that SWT triggers the release of microvesicles from endothelial cells.[24] Both, the microvesicles and their cargoes stimulate the innate immune receptor Toll-like receptor 3 (TLR3) in neighbouring cells, causing these cells to secrete angiogenic cytokines and growth factors. In TLR3 knock-out mice the effects were almost completely abolished, proving the TLR3-dependency of SWT.[25] Toll-like receptor 3 activation induces inflammatory signalling which causes global changes in epigenetic modifiers to increase DNA accessibility and cellular plasticity.[26–30] In addition, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and placental growth factor (PlGF) are released by the mechanical stimulus.[9–11,31,32] Subsequent stimulation of VEGF receptor 2 causes endothelial cell proliferation and tube formation, resulting in efficient angiogenesis and arteriogenesis in the border zone of the ischaemic myocardium.[10] The induction of new vessel formation improves LVEF in mice, rats and pigs with acute and chronic ischaemic heart failure.[9–11] These experimentally proven effects on LVEF were also observed in the CAST-HF

Table 3 **Secondary outcomes, intention-to-treat last-observation-carried-forward**

	FUP 90 days			FUP 180 days			FUP 360 days		
	Sham $n = 30$	SWT $n = 33$	*P*-value	Sham $n = 30$	SWT $n = 33$	*P*-value	Sham $n = 30$	SWT $n = 33$	*P*-value
6MWT, m	354.6 (160.3)	438.0 (137.5)	.031	391.2 (163.8)	471.2 (129.3)	.037	399.6 (161.0)	501.0 (137.7)	.010
Δ from baseline	−1.5 (147.0)	62.6 (114.9)	.062	35.2 (133.7)	96.8 (116.9)	.059	43.6 (172.1)	127.5 (110.6)	.028
MLHFQ Overall	28.5 (19.6)	18.9 (17.5)	.046	23.0 (20.4)	14.3 (18.3)	.081	17.3 (15.1)	11.0 (19.1)	.150
GFR, mL/min/1.73 m^2	79.7 (23.7)	70.8 (23.4)	.140	79.9 (22.5)	64.7 (22.1)	.009	78.6 (23.5)	70.6 (24.8)	.196
NT-proBNP, pg/mL	1865.6 (3368.1)	2702.1 (5896.1)	.488	1524.0 (2964.4)	1979.2 (4234.1)	.621	1133.0 (1529.0)	1631.2 (3925.4)	.503
NYHA class			.072			.160			.214
I	2 (6.7%)	7 (21.2%)		5 (16.7%)	12 (36.4%)		10 (33.3%)	17 (51.5%)	
II	18 (60.0%)	21 (63.6%)		19 (63.3%)	18 (54.5%)		15 (50.0%)	14 (42.4%)	
III	10 (33.3%)	4 (12.1%)		6 (20.0%)	3 (9.1%)		5 (16.7%)	2 (6.1%)	
IV	0 (0.0%)	1 (3.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Survival	30 (100.0%)	32 (97.0%)	1.000	30 (100.0%)	32 (97.0%)	1.000	30 (100.0%)	31 (93.9%)	.493
SAQ Summary	87.8 (10.4)	86.1 (17.0)	.638	89.4 (12.1)	88.6 (16.4)	.825	91.0 (10.5)	92.9 (16.0)	.571
SF36 General	67.2 (19.3)	69.1 (18.9)	.692	62.3 (22.6)	69.5 (22.3)	.208	68.2 (20.9)	72.6 (22.5)	.422

Data are mean (SD), *n* (%) or median [IQR].
FUP, follow-up; 6MWT, 6-minute walk test; MLHFQ, Minnesota Living with Heart Failure Questionnaire; GFR, glomerular filtration rate; NYHA, New York Heart Association Classification; SAQ, Seattle Angina Questionnaire; SF36, Short Form-36 Questionnaire; SWT, shockwave therapy.

trial. In the trial, direct cardiac SWT was applied after CABG surgery, since we consider complete revascularisation and global reperfusion a prerequisite to render the ischaemic myocardium susceptible to a regenerative trigger. The fundamental underlying mechanism of SWT is *mechanotransduction*, a term describing that a physical stimulus translates into a specific biologic signal,[8] in this case most probably the release of microvesicles. We assume that this targeted physical stimulus to the application area explains the favourable side-effect profile of SWT. Shockwave therapy resulted in an improved ejection fraction overall, however, the improvement was not unitary. RNA sequencing of intraoperative myocardial biopsies will be conducted to reveal further insights into the underlying molecular mechanisms.

The observed effects of SWT on myocardial function are meaningful and have important clinical implications. In our study, direct cardiac SWT was associated with an 11.3% increase in LVEF after 1 year compared to baseline. Such changes in LVEF are known to cause significant improvements in survival and reductions in heart failure hospitalizations.[33] In a recent study of 10 071 patients who underwent revascularization by either percutaneous coronary intervention or CABG surgery each 5% improvement in LVEF was associated with a 10% reduction of mortality and heart failure hospitalizations.[34] The extent of improvement of LVEF shown in the CAST-HF trial therefore is of clinical relevance and reflected in patient-reported outcomes. Intraoperative application of direct cardiac SWT is technically a straightforward and short procedure that takes <15 min and can be performed during the usual reperfusion time after opening the aortic cross-clamp. As a result, neither anaesthesia nor operating times are affected by the addition of SWT to CABG surgery.

Left ventricular ejection fraction assessments were performed by cardiac MRI which is considered the gold-standard.[16] Patients had to be on stable, optimized heart failure medication for at least 30 days prior to each follow-up MRI scan. Left ventricular ejection fraction assessments were validated post-hoc by an independent core laboratory, which confirmed our findings. The control group received a sham treatment with an inactive applicator to mimic the exact same manipulation of the heart as in the SWT group. An interim analysis was performed according to the study protocol when at least 20 patients per group had finished their 360-day follow-up to assess the primary safety endpoint. The superiority of direct cardiac SWT over sham treatment at one-year follow-up led the DSMB to halt the recruitment of additional patients for this study as pre-defined in the study protocol.

The limitations of our study should be recognized. First, our study was performed in a single centre with a limited number of patients. Efficacy data on repeat heart failure hospitalization and mortality need to be generated in a larger multicentre trial with a longer follow-up period. Second, a cardiac MRI evaluation was performed at our institution. However, the investigators were blinded to the study assignment. In addition, the results were validated by an external MRI core laboratory. Third, the timing of the surgeon's break blind was changed during the study by an amendment to the study protocol to prevent potential surgeon bias. From this date onwards, envelopes were opened at the end of the CABG procedure, after the aortic cross-clamp had been released (bypasses fully established). However, analysis with adjustment for amendment as an interaction showed no effect on the study results (see Supplementary data online, *Table S9*).

In summary, we found that direct cardiac SWT in addition to CABG surgery in patients with ischaemic heart failure resulted in a significant improvement of LVEF at 12 months after the intervention compared to patients undergoing CABG surgery and sham treatment. Direct cardiac SWT was associated with improvements in the physical capacity of patients. The treatment was both feasible and safe. The results of the CAST-HF trial suggest that this treatment strategy could contribute to solving the unmet clinical need for myocardial regeneration in patients suffering from ischaemic heart failure. Further trials with larger sample sizes in this patient population are therefore warranted to evaluate whether the beneficial effects of direct cardiac SWT on myocardial function translate into better clinical outcomes, as suggested by the current trial.

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Role of the funding source

The study was partly funded by an unrestricted grant from Heart Regeneration Technologies GmbH, Innsbruck, Austria, which is a spin-off company from the Medical University of Innsbruck, Austria. Investigators J.Ho, M.Gri, and J.P.C. are shareholders of this company and have been involved in study design, data collection, data analysis, data interpretation, and writing of the report. The sponsor and all other funding sources had no involvement in the before-mentioned activities.

Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

The study was partly funded by an unrestricted grant from Heart Regeneration Technologies GmbH, Innsbruck, Austria, which is a spin-off company from the Medical University of Innsbruck, Austria. Investigators JHo, MGri and JPC are shareholders of this company and have been involved in study design, data collection, data analysis, data interpretation, and writing of the report. The sponsor and all other funding sources had no involvement in the before-mentioned activities.

Data Availability

The detailed study protocol and statistical analysis plan are provided in the supplementary appendix. Anonymised participant source data are available from the corresponding author upon reasonable request.

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Ethical Approval

Prior to the study start, the study protocol and all other appropriate documents were approved by the Ethics Committee of the Medical University of Innsbruck and competent authorities. IRB Number: 1118/2018. Written, informed consent to participate was obtained from all participants prior to inclusion.

Pre-registered Clinical Trial Number

The trial is registered at ClinicalTrials.gov (NCT03859466).

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