

UCSF

UC San Francisco Previously Published Works

Title

Cardiopietic cell therapy for advanced ischemic heart failure: results at 39 weeks of the prospective, randomized, double blind, sham-controlled CHART-1 clinical trial

Permalink

<https://escholarship.org/uc/item/9q0918m8>

Journal

European Heart Journal, 38(9)

ISSN

0195-668X

Authors

Bartunek, Jozef
Terzic, Andre
Davison, Beth A
[et al.](#)

Publication Date

2017-03-01

DOI

10.1093/eurheartj/ehw543

Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NonCommercial License, available at <https://creativecommons.org/licenses/by-nc/4.0/>

Peer reviewed

Cardiopoietic cell therapy for advanced ischaemic heart failure: results at 39 weeks of the prospective, randomized, double blind, sham-controlled CHART-1 clinical trial

Jozef Bartunek^{1*}, Andre Terzic^{2*}, Beth A. Davison³, Gerasimos S. Filippatos⁴, Slavica Radovanovic⁵, Branko Beleslin⁶, Bela Merkely⁷, Piotr Musialek⁸, Wojciech Wojakowski⁹, Peter Andreka¹⁰, Ivan G. Horvath¹¹, Amos Katz¹², Dariouch Dolatabadi¹³, Badih El Nakadi¹³, Aleksandra Arandjelovic¹⁴, Istvan Edes¹⁵, Petar M. Seferovic¹⁶, Slobodan Obradovic¹⁷, Marc Vanderheyden¹, Nikola Jagic¹⁸, Ivo Petrov¹⁹, Shaul Atar^{20,21}, Majdi Halabi²¹, Valeri L. Gelev¹⁹, Michael K. Shochat²², Jaroslaw D. Kasprzak²³, Ricardo Sanz-Ruiz²⁴, Guy R. Heyndrickx¹, Noémi Nyolczas²⁵, Victor Legrand²⁶, Antoine Guédès²⁷, Alex Heyse²⁸, Tiziano Moccetti²⁹, Francisco Fernandez-Aviles²⁴, Pilar Jimenez-Quevedo³⁰, Antoni Bayes-Genis³¹, Jose Maria Hernandez-Garcia³², Flavio Ribichini³³, Marcin Gruchala³⁴, Scott A. Waldman³⁵, John R. Teerlink³⁶, Bernard J. Gersh², Thomas J. Povsic³⁷, Timothy D. Henry³⁸, Marco Metra³⁹, Roger J. Hajjar⁴⁰, Michal Tendera⁹, Atta Behfar², Bertrand Alexandre⁴¹, Aymeric Seron⁴¹, Wendy Gattis Stough⁴², Warren Sherman⁴¹, Gad Cotter³, and William Wijns^{1,43} for the CHART Program

¹Cardiovascular Center, Onze-Lieve-Vrouweziekenhuis OLV Hospital, Moorselbaan 164, Aalst, B-9300, Aalst, Belgium; ²Mayo Clinic, Center for Regenerative Medicine, Department of Cardiovascular Diseases, 200 First Street SW, Rochester, Minnesota 55905, USA; ³Momentum Research, Inc, Durham, NC, USA; ⁴National and Kapodistrian University of Athens, School of Medicine, Attikon University Hospital, Athens, Greece; ⁵University Hospital Center Bezanjska Kosa, Belgrade, Serbia; ⁶Cardiology Clinic, Clinical Centre of Serbia, Medical School, University of Belgrade, Belgrade, Serbia; ⁷Semmelweis University Heart and Vascular Center, Budapest, Hungary; ⁸Jagiellonian University Department of Cardiac and Vascular Diseases, John Paul II Hospital, Krakow, Poland; ⁹Third Division of Cardiology, Medical University of Silesia, Katowice, Poland; ¹⁰Gottsegen Gyorgy Hungarian Institute of Cardiology, Budapest, Hungary; ¹¹Heart Institute, University of Pécs, Pécs, Hungary; ¹²Department of Cardiology, Barzilai Medical Center, Israel Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel; ¹³Division of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium; ¹⁴Cardiology Department, Clinical Hospital Zvezdara, Belgrade, Serbia; ¹⁵Department of Cardiology, University of Debrecen, Debrecen, Hungary; ¹⁶University of Belgrade School of Medicine, Belgrade University Medical Center, Belgrade, Serbia; ¹⁷Clinic of Emergency Medicine, Military Medical Academy, School of Medicine, University of Defense, Belgrade, Serbia; ¹⁸Clinical Center Kragujevac, Kragujevac, Serbia; ¹⁹Department of Cardiology, Angiology, and Electrophysiology, City Clinic Heart and Vascular Institute, Sofia University, Sofia, Bulgaria; ²⁰Department of Cardiology, Galilee Medical Center, Nahariya, Israel; ²¹Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel; ²²Heart Institute, Hillel Yaffe Medical Center, Hadera, Rappaport School of Medicine, Haifa, Israel, Technion; ²³Department of Cardiology Medical University of Lodz, Lodz, Poland; ²⁴Hospital General Universitario Gregorio Marañón, Madrid, Spain; ²⁵Medical Centre, Hungarian Defense Forces, Budapest, Hungary; ²⁶Department of Cardiology, Centre Hospitalier Universitaire de Liège, Liège, Belgium; ²⁷Department of Cardiology, Université Catholique de Louvain, CHU Ucl Namur, Yvoir, Belgium; ²⁸Department of Cardiology, AZ Glorieux, Ronse, Belgium; ²⁹Cardiocentro Ticino, Lugano, Switzerland; ³⁰Department of Cardiology, Hospital Clínico San Carlos, Madrid, Spain; ³¹Hospital Universitari Germans Trias I Pujol, Universitat Autònoma, Barcelona, Spain; ³²Hospital Clínico Universitario Virgen de la Victoria, Malaga, Spain; ³³Department of Cardiology, University of Verona, Italy; ³⁴Department of Cardiology, Medical University of Gdansk, Gdansk, Poland; ³⁵Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA; ³⁶School of Medicine, University of California San Francisco and Section of Cardiology, San Francisco Veterans Affairs Medical Center, San Francisco, CA, USA; ³⁷Duke Clinical Research Institute and Duke Medicine, Durham, NC, USA; ³⁸Cedars Sinai Heart Institute, Los Angeles, CA, USA; ³⁹Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University and Spedali Civili, Brescia, Italy; ⁴⁰Mount Sinai School of Medicine, New York, NY, USA; ⁴¹Celyad, Mont Saint Guibert, Belgium; ⁴²Departments of Clinical Research and Pharmacy Practice, Campbell University College of Pharmacy and Health Sciences, Cary, NC, USA; and ⁴³The Lambe Institute for Translational Medicine and Curam, National University of Ireland Galway and Saolta University Healthcare Group, Galway, Ireland

Received 25 August 2016; revised 22 September 2016; editorial decision 18 October 2016; accepted 2 November 2016; online publish-ahead-of-print 20 December 2016

* Corresponding authors. Tel: +32 53 72 4447, Fax: +32 53 72 4550, Email: jozef.bartunek@olvz-aalst.be; Tel: +1 507 2842747, Fax: +1 507 2669636, Email: terzic.andre@mayo.edu

© The Author 2016. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

See page 661 for the editorial comment on this article (doi: 10.1093/eurheartj/ehw626)

Aims

Cardiopoietic cells, produced through cardiogenic conditioning of patients' mesenchymal stem cells, have shown preliminary efficacy. The Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART-1) trial aimed to validate cardiopoiesis-based biotherapy in a larger heart failure cohort.

Methods and results

This multinational, randomized, double-blind, sham-controlled study was conducted in 39 hospitals. Patients with symptomatic ischaemic heart failure on guideline-directed therapy ($n=484$) were screened; $n=348$ underwent bone marrow harvest and mesenchymal stem cell expansion. Those achieving > 24 million mesenchymal stem cells ($n=315$) were randomized to cardiopoietic cells delivered endomyocardially with a retention-enhanced catheter ($n=157$) or sham procedure ($n=158$). Procedures were performed as randomized in 271 patients ($n=120$ cardiopoietic cells, $n=151$ sham). The primary efficacy endpoint was a Finkelstein–Schoenfeld hierarchical composite (all-cause mortality, worsening heart failure, Minnesota Living with Heart Failure Questionnaire score, 6-min walk distance, left ventricular end-systolic volume, and ejection fraction) at 39 weeks. The primary outcome was neutral (Mann–Whitney estimator 0.54, 95% confidence interval [CI] 0.47–0.61 [value > 0.5 favours cell treatment], $P=0.27$). Exploratory analyses suggested a benefit of cell treatment on the primary composite in patients with baseline left ventricular end-diastolic volume 200–370 mL (60% of patients) (Mann–Whitney estimator 0.61, 95% CI 0.52–0.70, $P=0.015$). No difference was observed in serious adverse events. One (0.9%) cardiopoietic cell patient and 9 (5.4%) sham patients experienced aborted or sudden cardiac death.

Conclusion

The primary endpoint was neutral, with safety demonstrated across the cohort. Further evaluation of cardiopoietic cell therapy in patients with elevated end-diastolic volume is warranted.

Keywords

Regenerative medicine • Cardiopoiesis • Cardiovascular disease • Stem cell • Target population • Disease severity • Marker • Precision medicine

Introduction

Heart failure is a leading cause of mortality and morbidity; it limits quality of life and imposes a major societal burden.¹ Ischaemic heart disease underpins two-thirds of all systolic heart failure.² Extensive myocardial remodelling and chamber enlargement portend poor outcomes, and standard treatments are often insufficient in such patients.³ Cardiac transplantation or destination mechanical circulatory support remains high-risk therapeutic options that are further limited by donor availability, patient eligibility, and cost.⁴

By targeting myocardial restoration, cell-based therapies are alleged paradigm-shifting alternatives.^{5,6} Clinical trials document reassuring feasibility and safety yet inconsistent efficacy, ascribed in part to unpredictable potency of cell products and limited retention.^{7,8} These shortcomings impede advancement into cardiovascular practice.

Strategies for cell therapy optimization⁹ include myocardial priming to improve cell homing,¹⁰ exploiting resident cell populations¹¹ or leveraging combined cell regimens.^{12,13} Guided cardiopoiesis is a recent option that enhances the cardioreparative functionality of patient-derived mesenchymal stem cells (MSC) and induces a restorative response in failing hearts.¹⁴ The cardiopoietic phenotype demonstrated promise in proof-of-concept studies¹⁵ and in the Cardiopoietic Stem Cell Therapy in Heart Failure (C-CURE) clinical trial.¹⁶

The Congestive Heart Failure Cardiopoietic Regenerative Therapy (CHART-1) trial was executed to validate the efficacy and safety of cardiopoietic cells delivered via an enhanced retention performance catheter¹⁷ in a larger population with advanced symptomatic heart failure of ischaemic aetiology.¹⁸

Methods

Study design

The CHART-1 study is a prospective, multicentre, randomized, sham-controlled, patient- and evaluator-blinded clinical trial. Investigators at 39 centres in Europe and Israel participated (Figure 1 and Supplementary material online, Section 1). Ethics committee approvals were obtained for each participating centre. The CHART-1 trial was registered with clinicaltrials.gov (NCT01768702) and EudraCT (2011-001117-13). The study design has previously been described,¹⁸ and the study protocol is provided in Supplement 2.

Patients

Eligible patients gave written informed consent prior to any study-related procedures. Patients were not compensated for participation except for travel expenses. Patients were ≥ 18 to < 80 years old with left ventricular ejection fraction (LVEF) $\leq 35\%$ (locally interpreted echocardiograms were used for screening), ischaemic heart failure without need for revascularization, heart failure hospitalization, or outpatient vasoactive heart failure therapy (e.g. vasodilators, positive inotropic agents, vasopressors or diuretics) within 12 months, in New York Heart Association (NYHA) class II or greater at screening, and with NYHA class III or IV or Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) class ≥ 4 within 12 months.¹⁸ Guideline-directed medical therapy, a 6-min walk distance > 100 to ≤ 400 m and Minnesota Living with Heart Failure Questionnaire (MLHFQ) score > 30 were required. Acute coronary syndrome or percutaneous coronary intervention within 90 days, or coronary artery bypass graft surgery within 180 days were exclusions.¹⁸ Eligible patients were scheduled for bone marrow harvest and MSC expansion.

Approximately 2 weeks after screening, bone marrow (~ 65 – 85 mL) was collected from the iliac crest and shipped to a central production

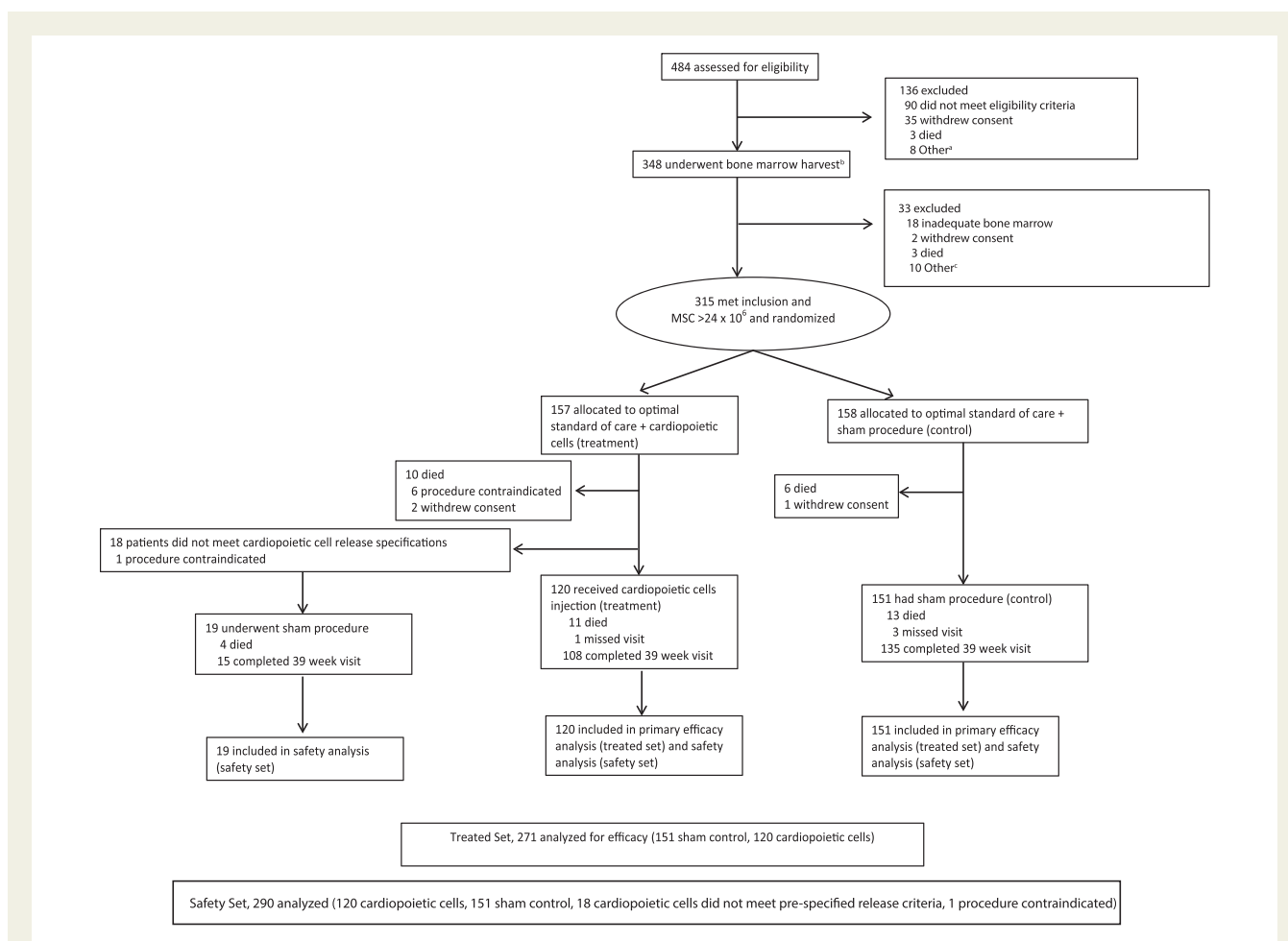


Figure 1 Consolidated standards of reporting trials diagram of the CHART-1 study. This figure depicts the patient flow through the trial. Eighteen (11.5%) patients randomized to active treatment and 7 (4.4%) patients randomized to control did not undergo the study procedure: 10 (6.4%) and 6 (3.8%) patients died, and 2 (1.3%) and 1 (0.6%) patients withdrew consent in the active and control groups, respectively. Six (3.8%) patients randomized to active treatment were discontinued because of procedural contraindications including left ventricular thrombus and aortic stenosis not identified at screening. Cell release specifications were not achieved in 18 (11.5%) patients randomized to active treatment; these patients and one additional patient for whom the injection procedure was deemed unsafe underwent a sham procedure and were followed separately. The remaining 120 patients underwent injection of cardiopoietic cells.

^aOther reasons patients were withdrawn after screening but before bone marrow harvest included: withdrawal from the study by investigator or sponsor; patient missing or lost to follow-up; or other miscellaneous.

^bForty-eight (13.8%) patients who failed the first bone marrow harvest (1 due to inadequate sample volume, 8 due to improper harvesting or transport process, 21 because the sample was contaminated, and 18 because of inadequate expansion of MSCs) were eligible for a repeat harvest. Thirty-two patients underwent the second bone marrow harvest. Of the 16 who did not have a repeat, 5 were because the patient refused, 2 were due to SAEs (1 patient had a stroke and another was hospitalized for heart failure), and the rest for sponsor reason (either cell-process related or because study enrollment was nearing completion).

^cOther reasons patients were withdrawn after bone marrow harvest but before randomization included: withdrawal from the study by sponsor or other miscellaneous.

facility (Celyad, Mont-Saint-Guibert, Belgium). If the bone marrow was of insufficient quantity, contaminated, or did not reach pre-specified cell production criteria, the harvest could be repeated. Patients with a second inadequate cell expansion or those who refused a second bone marrow harvest were discontinued from further participation.

Randomization and masking

Patients were randomized 1:1 to cardiopoietic cell injection or a sham control procedure after confirmation by the central production facility that > 24 million MSCs were achieved according to pre-specified release

criteria. An Interactive Web Randomization Service was used according to a central randomization scheme (produced by Harvard Clinical Research Institute, Boston, Massachusetts) stratified by study centre with random permuted blocks within each centre. Patients and evaluators were blinded to study group assignment (eMethods in Supplementary material online, Section 2.1).

Procedures

MSCs for patients randomized to active treatment were processed for lineage specification to derive cardiopoietic cells (eMethods in

Supplementary material online, Section 2.2).¹⁶ Patients whose cell product did not meet release criteria because of inadequate identity, potency, content, purity, homogeneity, or microbiological content (eMethods in Supplementary material online, Section 2.2.2) received a sham procedure (Figure 1). Cryopreserved cardiopoietic cell batches meeting release criteria (C3BS-CQR-1 manufactured by Celyad, Mont-Saint-Guibert, Belgium) were shipped frozen to sites and reconstituted within 6 h before injection. Cardiopoietic cells were delivered using standard cardiac catheterization procedures and a cell retention-enhanced injection catheter (C-Cath_{ez}TM; Celyad, Mont-Saint-Guibert, Belgium).¹⁷ Intramyocardial injections (~0.5 mL each, ~1 cm apart) were made into left ventricle areas with wall thickness \geq 8 mm, avoiding the apex and segments adjacent to the mitral or aortic valves. Target zones were mapped using biplane left ventricular angiography integrating preceding echocardiography information regarding wall thickness. A sham procedure, incorporating insertion of an introducer sheath, left ventricular angiography and pigtail catheter movements, was performed for patients randomized to the control group and in the patients whose cell product did not meet pre-specified release criteria.

Follow-up visits were conducted by the blinded investigator team.¹⁸ Pre-procedure (baseline), 26 and 39-week echocardiograms were assessed centrally by a blinded core laboratory (eMethods in Supplementary material 1 online, Section 2.3).

Outcomes

The primary efficacy outcome was a hierarchical composite assessed at 39 weeks post-procedure comprising all-cause mortality (days to death), the number of worsening heart failure events (0, 1, or \geq 2), MLHFQ score (\geq 10 point improvement, \geq 10 point deterioration, or no meaningful change), 6-min walk distance (\geq 40 m improvement, \geq 40 m deterioration, or no meaningful change), left ventricular end-systolic volume (LVESV) change (\geq 15 mL improvement, \geq 15 mL deterioration, or no meaningful change), and LVEF change (\geq 4% absolute improvement, \geq 4% absolute deterioration, or no meaningful change as assessed by the echocardiographic core laboratory).¹⁸ Left ventricular assist device (LVAD) implantation or urgent heart transplantation was considered cardiac deaths for the efficacy analyses.

Safety assessment through Week 39 included all-cause mortality, rehospitalization, cardiac transplantation, myocardial infarction, stroke, aborted sudden death (resuscitated sudden death or appropriate implantable cardioverter defibrillator [ICD] shocks), and serious and non-serious adverse events.

Statistical analysis

The primary outcome was compared between groups using a Finkelstein-Schoenfeld approach,¹⁹ which allows mortality and morbidity components to be combined with other important aspects of the heart failure disease process in one outcome. Patients are ranked with respect to their clinical outcomes through comparing every patient to every other patient on the hierarchy of component outcomes ordered by their relative importance¹⁹ (eMethods in Supplementary material online, Section 2.4, eFigure 1 in Supplementary material online, Section 2.4.1). Missing data are accommodated in the algorithm, with limited need for imputation (eMethods in Supplementary material online, Section 2.4; Supplemental material 2 [protocol], page 40). The primary analysis was performed in patients as randomized, excluding patients whose cell product did not meet release criteria. Sensitivity analyses were performed in a modified intention-to-treat set including all patients who underwent the study procedure, and a per-protocol set excluding patients with major protocol deviations. All analyses were conducted using a two-sided significance level of 0.05.

A sample size of 120 patients per group was estimated to provide 87% power to detect a treatment effect corresponding to a Mann–Whitney estimator (the probability of a better response in the active treatment group plus half the probability of a tie) of 0.61 (values $>$ 0.5 favour active treatment).¹⁸ This treatment effect corresponds to a Mann–Whitney odds of 1.56, the relative probability of a better outcome on active treatment than on control. Homogeneity of the treatment effect across subgroups was assessed using chi-square tests computed from Mann–Whitney estimators and their corresponding variances in the subgroups. Post-hoc subgroup analyses evaluated treatment effect by baseline severity markers including left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), MLHFQ score, 6-min walk distance, and LVEF. Subpopulation Treatment Effect Pattern Plots (STEPs) were used to evaluate the potential effect of treatment by baseline severity markers.²⁰

Safety analyses included all patients according to the treatment received. Kaplan–Meier estimates of event rates through Week 39 and hazard ratios and 95% confidence intervals (CI) from Cox regression models are presented; groups were compared using log-rank tests.

Means \pm standard deviation (SD) or median, and interquartile range (IQR), are presented for continuous variables, and geometric mean and 95% CI for log-transformed variables. Analyses are based on the data when the last patient to have a study procedure reached Week 39. SAS® (Cary, North Carolina, USA) version 9.3 was used for analyses.

A blinded Clinical Events Committee (CEC) adjudicated all deaths, worsening heart failure events, strokes, myocardial infarctions, and aborted sudden deaths from randomization (eMethods in Supplementary material online, Section 2.3). An independent interventional cardiologist adjudicated the relatedness of peri-procedural serious adverse events to the injection catheter, the catheterization procedure, and the cardiopoietic cell product. An independent Data Safety Monitoring Board (DSMB) reviewed ongoing safety reports, evaluated safety of the delivery device when the first 46 patients had 4 weeks follow-up, and reviewed safety data and a futility analysis when 120 patients had at least 13 weeks follow-up (eMethods in Supplementary material online, Section 2.3).

Results

Study population

Screening began 18 December 2012 and the last injection procedure (cardiopoietic cell therapy or sham) was performed 31 July 2015. A total of 484 patients provided informed consent to undergo eligibility screening, and 348 underwent bone marrow harvest (Figure 1). Adequate MSC expansion was achieved in 315 patients, and they were randomized to cardiopoietic cell therapy ($n = 157$) or sham control procedure ($n = 158$). Of these, 120 patients underwent injection of cardiopoietic cells and 151 had the sham procedure (Figure 1).

Baseline characteristics were well-balanced between the groups (Table 1). The mean \pm SD age was 61.9 \pm 8.6 years, 89.7% were men, and all were white. Eighty-five percent of patients had been hospitalized for heart failure within the previous year, and 21.8% were in NYHA Class II at screening. The mean \pm SD centrally-assessed LVEF was 27.9 \pm 7.0%. Patients were well-treated with guideline-directed medical and device therapy (Table 1) that remained consistent during follow-up (eFigure 2 in Supplementary material online, Section 3.1).

The mean \pm SD time between randomization and the study procedure was 59.8 \pm 21.6 and 53.9 \pm 11.7 days in patients randomized to and who received the active treatment vs. the sham procedure,

Table 1 Baseline characteristics

	Cardiopietic cell treatment n = 120	Sham control n = 151
<i>Demographics</i>		
Male sex	107 (89.2)	136 (90.1)
Age (years)	61.6 (8.6)	62.1 (8.7)
Caucasian race	120 (100)	151 (100)
BMI (kg/m ²)	28.2 (3.7)	28.6 (4.4)
<i>Heart Failure History</i>		
NYHA class at screening		
I	0	0
II	23 (19.2)	36 (23.8)
III	96 (80)	114 (75.5)
IV	1 (0.8)	1 (0.7)
Time from first heart failure diagnosis to screening (months)	44.1 (12.3–100.1)	46.3 (16–97.7)
Heart failure hospitalization within 12 months	102 (85.0)	128 (84.8)
Number of heart failure hospitalizations in past 12 months	1.3 (0.8)	1.2 (0.5)
<i>Comorbidities</i>		
Chronic angina	38 (31.7)	56 (37.1)
CCSC-I	14 (11.7)	12 (7.9)
CCSC-II	20 (16.7)	36 (23.8)
CCSC-III	4 (3.3)	7 (4.6)
CCSC-IV	0	0
Percutaneous coronary intervention	98 (81.7)	103 (68.2)
Coronary artery bypass surgery	32 (26.7)	44 (29.1)
Myocardial infarction	106 (88.3)	133 (88.1)
Cerebrovascular atherosclerotic disease	13 (10.8)	13 (8.6)
Peripheral vascular disease	5 (4.2)	10 (6.6)
Atrial fibrillation	31 (25.8)	32 (21.2)
Atrial flutter	4 (3.3)	5 (3.3)
Sustained ventricular tachycardia	12 (10.0)	25 (16.6)
Ventricular fibrillation	10 (8.3)	20 (13.2)
ICD/AICD	46 (38.3)	63 (41.7)
CRT	25 (20.8)	25 (16.6)
Transplant list	1 (0.8)	0
Diabetes mellitus	45 (37.5)	71 (47)
Current smoking	12 (10)	25 (16.6)
Current alcohol abuse	4 (3.3)	7 (4.6)
Hypertension	99 (82.5)	124 (82.1)
Hypercholesterolemia	97 (80.8)	129 (85.4)
Renal impairment	25 (20.8)	36 (23.8)
Chronic lung disease	15 (12.5)	19 (12.6)

Continued

Table 1 Continued

	Cardiopietic cell treatment n = 120	Sham control n = 151
<i>Baseline Therapies</i>		
<i>Baseline concomitant medications</i>		
ACE inhibitor	96 (80)	117 (77.6)
ARB	14 (11.7)	21 (13.9)
ACE inhibitor or ARB	109 (90.8)	137 (90.7)
Beta blocker	107 (89.2)	135 (89.4)
CCB	6 (5)	27 (17.9)
Alpha blocker	36 (30)	39 (25.8)
MRA	94 (78.3)	109 (77.2)
Loop diuretic	104 (86.7)	123 (81.5)
Statin	107 (89.2)	125 (82.8)
Aspirin	76 (63.3)	100 (66.2)
Vitamin K antagonist	42 (35.0)	60 (39.7)
<i>Baseline Vital Signs, Left Ventricular Parameters, and Biomarkers</i>		
HR (bpm)	70.9 (12.5)	70.8 (10.3)
SBP (mmHg)	117 (14.4)	122.6 (15.3)
DBP (mmHg)	72.6 (8.5)	74.2 (10.3)
MLHFQ total score	48.8 (39.8–64.8)	46.5 (37–60)
6-min walk distance (meters)	332.5 (282–366.8)	332.5 (282.5–367.0)
LVESV (mL)	172.6 (140.4–224.2)	177.9 (133.3–212.4)
LVEF (%)	27 (23–32)	28 (24–32)
LVEDV (mL)	239.9 (197.4–294)	246.4 (198.2–285.6)
NT-proBNP (pg/mL)	1083.1 (450–2648.1)	1077.6 (483.7–2260.6)
SCr (μmol/L)	102.5 (85–128.6)	103 (86–128)
BUN (mmol/L)	7.6 (5.9–10.5)	7.5 (5.5–10.7)
eGFR (mL/min/1.73m ²)	60 (52–74.2)	60 (52–78)

Data are expressed as number (percent), mean (standard deviation), or median (interquartile range). There were no significant differences in baseline characteristics between groups ($P > 0.05$), except for history of percutaneous coronary intervention, calcium channel blocker use, and systolic blood pressure ($P < 0.05$). ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; bpm, beats per minute; BUN, blood urea nitrogen; CCB, calcium channel blocker; CCSC, Canadian Cardiovascular Society Classification; CRT-D, cardiac resynchronization therapy with defibrillator; CRT-P, cardiac resynchronization therapy with pacemaker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; ICD, automatic implantable cardioverter defibrillator; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SCr, serum creatinine.

... respectively. The median duration was 112.0 (IQR 78.0–157.5) minutes for the injection procedure and 36.0 (IQR 17.0–66.0) minutes for the sham procedure. The treatment group received a median of 19 (IQR 17–20) injections with a median injection volume of 9.6 (IQR 8.5–10) mL.

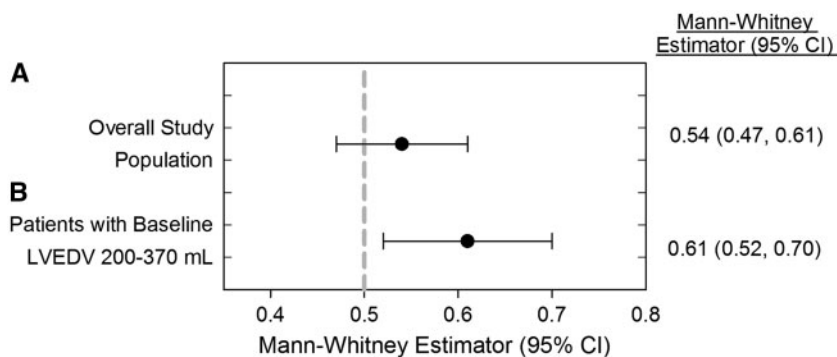


Figure 2 Primary efficacy outcome. Panel A depicts the primary efficacy outcome in the total population. The Mann–Whitney estimator, or the probability that the treatment group had a better outcome on the composite primary endpoint, was 0.54 (95% CI 0.47–0.61), $P = 0.27$ (a value > 0.5 favours the active treatment). The corresponding Mann–Whitney odds was 1.17 (95% 0.89–1.55). Panel B depicts the primary efficacy outcome in the subgroup of patients with LVEDV 200–370 mL. The Mann–Whitney estimator, or the probability that the treatment group had a better outcome on the composite primary endpoint, was 0.61 (95% CI 0.52–0.70), $P = 0.015$ (a value > 0.5 favours the active treatment). The corresponding Mann–Whitney odds was 1.57 (95% 1.09–2.35).

Primary end-point

The hierarchical composite primary endpoint across the total study cohort was neutral (Mann–Whitney estimator 0.54, 95% CI 0.47–0.61, $P = 0.27$) (Figure 2, panel A, eTable 1 in Supplementary material online, Section 2.4.2), corresponding to a Mann–Whitney odds of 1.17 (95% CI 0.89–1.55). No significant between-group differences were noted for individual components of the primary outcome, but a signal for a benefit was observed across the categories of change in 6-min walk distance ($P = 0.07$) (Table 2).

Subgroup analysis

The response was similar according to sex (homogeneity $P = 0.43$), age (homogeneity $P = 0.25$), NYHA class (homogeneity $P = 0.69$), and geographic region (homogeneity $P = 0.71$). The effect of active treatment according to baseline heart failure severity was examined in post-hoc, exploratory analyses. A suggestion of efficacy for the active treatment was noted in patients with LVEDV, LVESV, or MLHFQ score greater than the median, and in those with 6-min walk distance less than the median (Figure 3). Subpopulation treatment effect pattern plots were used to further explore the pattern of treatment effect on the composite primary endpoint as a function of increasing, overlapping intervals of severity markers. The observed response patterns are shown in Figure 4. Patients with baseline LVEDV 200–370 mL receiving cardiopoietic cell treatment had a greater probability of a better outcome on the composite primary endpoint compared to the sham control group (Mann–Whitney estimator 0.61, 95% CI 0.52–0.70, $P = 0.015$; Mann–Whitney odds 1.57, 95% CI 1.09–2.35) (Figure 2, panel B). Patients with baseline LVEDV 200–370 mL (cardiopoietic cell therapy $n = 66$, sham control $n = 96$) treated with cardiopoietic cell therapy had a greater improvement in MLHFQ score from baseline that was of nominal significance. A greater absolute proportion had improvement in 6-min walk distance compared to sham control, and the absolute proportion with LVESV improvement was greater and with deterioration lesser in the active

treatment vs. the sham control group, but these differences were not significant (Table 2). All components of the composite, including all-cause mortality and worsening heart failure events, were directionally consistent (Table 2).

Safety

Of the 120 patients undergoing study injections, 106 were without incident and 14 experienced catheter-procedure related serious adverse events. Of the 14 patients, each developed one of the following: ventricular tachyarrhythmia (4 sustained, responsive to cardioversion), left bundle branch block (3 sustained, 2 receiving cardiac resynchronization therapy [CRT] for persistent heart failure 2 and 4.5 months after injection, respectively), dissection of the ascending aorta requiring surgery (in a patient with known calcific and dilated thoracic aorta, occurring prior to the procedure while catheter was introduced), transient ischaemic attack (1 with aphasia; normal head computerized tomography [CT] scan and resolution by 48 h), femoral artery stenosis (1 with claudication; sub-total occlusion at site of closure device implantation, managed medically), and pericardial effusion (4, three with tamponade responsive to drainage, 1 without hemodynamic consequences resolving spontaneously). No cases of pericardial tamponade occurred in the final 72 active cases after additional procedural training and oversight.

Cardiac markers (CK-MB and high-sensitivity cardiac troponin T [hs-cTnT]) were increased at 6 and 24 h following the cell injection procedure. At 6 h, CK-MB had increased a median of 3.35 (IQR -0.600–59.800) $\mu\text{g/L}$ in the active treatment group, compared to a median change of -0.20 (IQR -11.200–8.800) $\mu\text{g/L}$ in the control group. At 24 h, median changes were 0.90 (IQR 0.1–1.8) and -0.30 (IQR -0.80–0.00) $\mu\text{g/L}$ in patients treated with active and sham control, respectively, a ratio of 2.08 ($P < 0.001$). The median change in hs-cTnT at 6 h was 0.088 (IQR 0.04–0.151) $\mu\text{g/L}$ in the cardiopoietic cell treatment group and 0.001 (IQR -0.002–0.003) $\mu\text{g/L}$ in the sham control. At 24 h, the median change from baseline was 0.059 and

Table 2 Components of the primary efficacy endpoint in the total cohort and subpopulation with elevated left ventricular end-diastolic volume

	Total cohort				Patients with baseline left ventricular end-diastolic volume 200–370 mL			
	n = 271		HR or M-W odds (95% CI)	P-value	n = 162		HR or M-W odds (95% CI)	P-value
	Cardiopoietic cell treatment n = 120	Sham control n = 151			Cardiopoietic cell treatment n = 66	Sham control n = 96		
All-cause mortality through Week 39 (Kaplan–Meier %)	11 (9.2)	12 (7.9)	1.18 (0.52, 2.67)	.70	3 (4.5)	6 (6.2)	0.73 (0.18, 2.93)	0.66
Worsening heart failure events								
0	100 (83.3)	128 (84.8)			58 (87.9)	79 (82.3)		
1	11 (9.2)	14 (9.3)	1.03 (0.87, 1.23)	.72	4 (6.1)	9 (9.4)	0.90 (0.71, 1.12)	0.34
≥2	9 (7.5)	9 (6)			4 (6.1)	8 (8.3)		
Change in MLHFQ total score from baseline	^a n = 108	^a n = 136			^a n = 63	^a n = 89		
≥10-point improvement (decrease)	64 (59.3)	66 (48.5)			43 (68.3)	44 (49.4)		
No meaningful change	37 (34.3)	60 (44.1)	0.84 (0.68, 1.04)	.12	15 (23.8)	39 (43.8)	0.74 (0.55, 0.99)	0.04
≥10-point deterioration (increase)	7 (6.5)	10 (7.4)			5 (7.9)	6 (6.7)		
Change in 6-min walk distance from baseline	^a n = 108	^a n = 131			^a n = 63	^a n = 85		
≥40 m improvement (increase)	50 (46.3)	40 (30.5)			27 (42.9)	21 (24.7)		
No meaningful change	39 (36.1)	69 (52.7)	0.82 (0.66, 1.02)	.07	25 (39.7)	51 (60)	0.79 (0.59, 1.06)	0.12
≥40 m deterioration (decrease)	19 (17.6)	22 (16.8)			11 (17.5)	13 (15.3)		
Change in LVESV from baseline	^a n = 102	^a n = 124			^a n = 63	^a n = 85		
≥15 mL improvement (decrease)	51 (50)	56 (45.2)			36 (57.1)	41 (48.2)		
No meaningful change	33 (32.4)	36 (29)	0.89 (0.73, 1.09)	.26	18 (28.6)	23 (27.1)	0.81 (0.60, 1.09)	0.17
≥15 mL deterioration (increase)	18 (17.6)	32 (25.8)			9 (14.3)	21 (24.7)		
Change in LVEF from baseline	^a n = 102	^a n = 124			^a n = 63	^a n = 85		
≥4% absolute improvement (increase)	69 (67.6)	82 (66.1)			42 (66.7)	56 (65.9)		
No meaningful change	28 (27.5)	33 (26.6)	0.97 (0.81, 1.15)	.73	19 (30.2)	22 (25.9)	0.96 (0.74, 1.25)	.76
≥4% absolute deterioration (decrease)	5 (4.9)	9 (7.3)			2 (3.2)	7 (8.2)		

Data are expressed as number (percent). Hazard ratio (HR) for active treatment vs. control is provided for mortality. The Mann–Whitney (M-W) odds for worse outcome in active vs. control is given for ordered categories. Values <1.0 favour active treatment.

LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MLHFQ, Minnesota Living with Heart Failure Questionnaire.

^an reflects the number of patients with data.

0.001 µg/L in the active treatment and sham control group patients, respectively ($P < 0.001$). At Week 39, hs-cTnT levels were comparable: the median change was 0.001 µg/L in both groups, treatment ratio 1.014, 95% CI 0.901–1.142.

Adjudicated clinical endpoints and investigator-reported adverse events through Week 39 according to the actual treatment received (i.e. the 19 patients randomized to active who received a sham procedure are included in the sham group) are shown in Table 3. Similar

proportions of patients died who underwent the active treatment and sham procedure (HR 1.02, 95% CI 0.45–2.29). The adjudicated causes of death were similar, although sudden cardiac death occurred in no patient in the cardiopoietic cell treatment group and in 4 patients who underwent the sham procedure. Aborted or sudden cardiac death occurred in 1 (0.9% [Kaplan–Meier estimated risk]) cardiopoietic cell treatment patient and 9 (5.4%) of sham control patients (HR 0.16, 95% CI 0.02–1.23, $P = 0.04$). One patient who received active

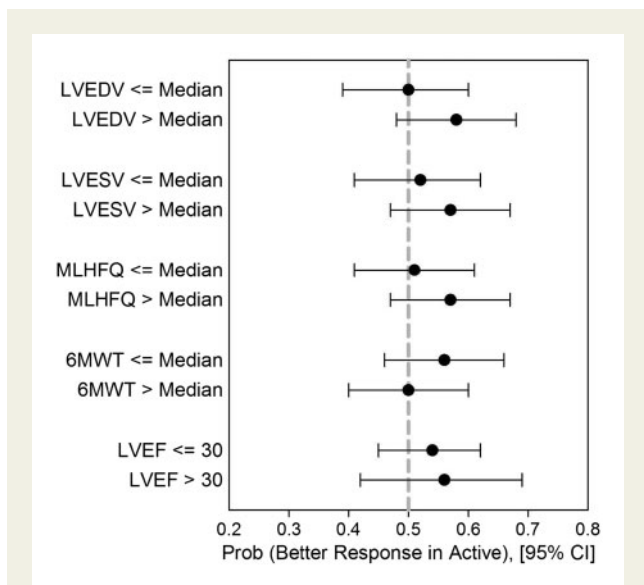


Figure 3 Primary efficacy outcome by markers of disease severity. This figure shows the Mann–Whitney estimator, or the probability that the treatment group had a better outcome on the composite primary endpoint, for patients above and below the median values for LVEDV, LVESV, MLHFQ score, and 6-min walk distance, and for LVEF above and below a cutpoint of 30%.

treatment had a cardiac transplantation. Occurrence of other adjudicated clinical endpoints including myocardial infarction and stroke were similar in the groups (Table 3). Similar hospitalization rates after the index procedure were observed through Week 39 (26.2% for active treatment vs. 27.4% for control, HR 1.01, 95% CI 0.64–1.59, $P = 0.96$), most often due to heart failure (15.2% for active and 18.1% for control) (eTable 2 in Supplementary material online, Section 3.2).

Discussion

The CHART-1 study is the largest cardiovascular regenerative medicine trial to date addressing the effect of cardiopoiesis-based cell therapy in ischaemic heart failure patients with moderate to severe symptoms. In this at-risk population with limited therapeutic options, the trial was neutral regarding the primary endpoint, a hierarchical composite encompassing all-cause mortality, worsening heart failure events, MLHFQ score, 6-min walk distance, LVESV and LVEF assessed at 39 weeks. Exploration of the primary composite endpoint according to baseline heart failure severity revealed a clinically relevant population that appeared to benefit from cardiopoietic cell therapy. This sizable target population, representing 60% of the whole study cohort, was characterized by severe heart enlargement (baseline LVEDV 200–370 mL). These patients had greater improvement in 6-min walk distance consistent with favourable effects on myocardial structure (i.e. LVESV). Directionally similar treatment effects on all-cause mortality and worsening heart failure events were also observed in this subset. Patients displaying a lower (< 200 mL) or greater (> 370 mL) LVEDV did not appear to respond to cell therapy in this study. These data suggest that targeted patient selection using disease severity

markers should be considered for future clinical trials and/or potential clinical application of cell therapy in patients with heart failure. Indeed, a call for a focus on precision medicine has been issued, where clinical studies would target well-defined patient populations to improve development of effective cardiovascular treatments.²¹

The CHART-1 study corroborates, in a larger heart failure cohort, the feasibility, safety and initial efficacy signals detected in the C-CURE trial.¹⁶ Clinical surveillance documented safety through 39 weeks without excess adverse events attributable to cardiopoietic cell therapy. Peri-procedural events in the CHART-1 trial were consistent with well-established complications of left heart catheterization and/or intramyocardial injection, which can spike with the introduction of a new device but generally recede as interventional experience and procedural volume accrue.²² Notably, a significantly lower incidence of sudden or aborted sudden deaths was documented in cardiopoietic cell-treated patients compared to controls, underpinning clinical safety across both C-CURE¹⁶ and CHART-1 trials.

Heart failure clinical trial experience points to inter-trial and inter-patient variability in cell therapy outcomes.^{23–25} Recognizing that only a limited number of patients with ischaemic heart disease harbors reparative stem cells, processes have been introduced to optimize reparative outcome.²⁶ The ixCELL-DCM trial is a recent example where a reduction in adjudicated clinical cardiac events in ischaemic cardiomyopathy was documented after delivery of an expanded multicellular product.¹³ Leveraging the cardiopoiesis platform in conjunction with a novel catheter fitted with a curved needle delivery system,¹⁵ the CHART-1 clinical experience advances current knowledge by identifying disease severity as a potential modifier of cell therapy benefit.

In this regards, heart failure is a progressive and heterogeneous syndrome where conventional symptoms or ejection fraction often fail to identify patients that optimally respond to a therapy. Non-uniform responses in advanced heart failure have been reported in a spectrum of therapies including revascularization,²⁷ interventions targeting functional mitral regurgitation²⁸ or CRT.²⁹ Of note and consistent with the CHART-1 findings, the degree of baseline LV enlargement has previously been detected as a modifying factor influencing therapeutic responsiveness to patients undergoing CRT, where the response was most robust in patients with LV end-diastolic volume index >125 mL/m².²⁹ The relationship between left ventricular volumes and clinical outcomes in heart failure is well recognized.³ The CHART-1 study extends these findings by defining a range of LVEDV that appeared to segregate heart failure patients with the highest potential to benefit from cell-based therapy. Evidence from the CHART-1 experience, in the context of prior knowledge with other therapies^{27–29} and recent proposals to streamline clinical development,²¹ suggests that heart failure management should be patient-tailored based on disease severity markers, such as degree of left ventricular dilation.

The present data should be interpreted in the context of the following limitations. Use of a composite primary endpoint was intended to increase the statistical precision of the trial, yet if an important component of the composite outcome is not substantially modified by the treatment then the statistical power to detect effects on the overall composite may be reduced.³⁰ Indeed, neutrality in the primary hierarchical composite endpoint within the overall study population was related primarily to a neutral effect on all-cause mortality or worsening heart failure. This finding may reflect the 39-week

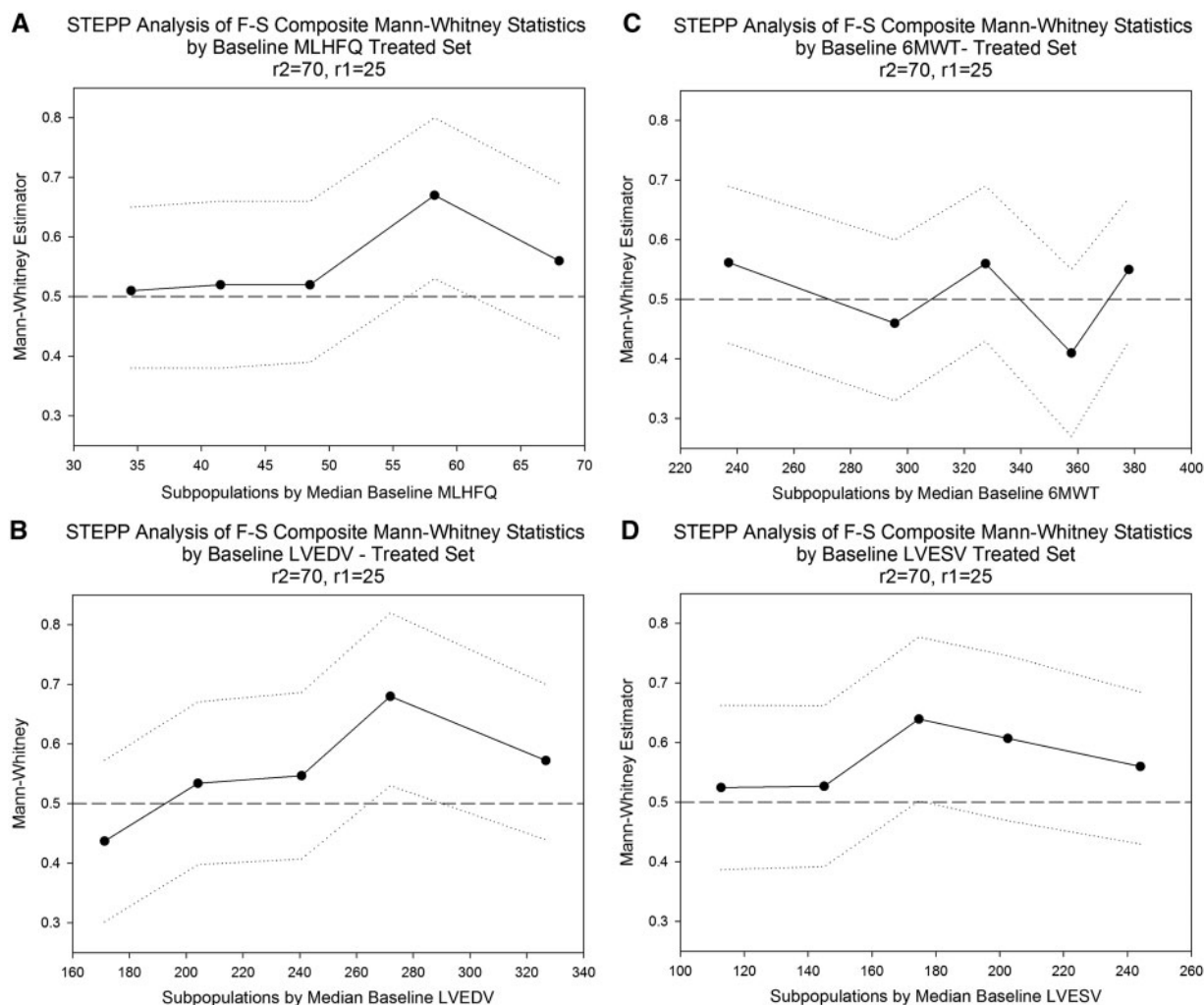


Figure 4 Subpopulation treatment effect pattern plot by markers of disease severity. Subpopulation Treatment Effect Pattern Plots (STEPPs) were used to further evaluate the potential effect of treatment according to baseline markers of disease severity. This figure shows the STEPP results according to baseline MLHFQ score (panel A), baseline LVEDV (panel B), baseline 6-min walk distance (panel C), and baseline LVESV (panel D).

time point for the primary outcome. In this context, longer follow-up is planned to evaluate the effect of cardiopoietic cell therapy. Eighteen patients initially randomized to the cardiopoietic cell group did not meet cardiopoietic cell release criteria and the procedure was contraindicated in one patient; these patients received a sham procedure and were not included in the primary efficacy analysis. This approach assesses the effect of cardiopoietic cells in those patients who actually received them. The result of an analysis in a modified intent-to-treat set, which included the process failures who underwent a sham procedure in the active group for analysis, was nearly identical (Mann–Whitney estimator 0.54, $P=0.283$) to that of the primary endpoint (Mann–Whitney estimator 0.54, $P=0.27$). STEPP was used to identify the influence of LVEDV on the primary endpoint. This approach is methodologically preferred compared to conventional post-hoc analysis, as STEPP constructs overlapping subpopulations along the continuum of the covariate, improving the precision of the estimated treatment effects.³¹ LV volumes and function

were assessed by transthoracic echocardiography using established guidelines.¹⁸ To minimize reproducibility issues, measurements were performed by a trained single echocardiographer per center with central core analyses. Although inadequate bone marrow aspiration or suboptimal outcome of the production process preventing cell product release occurred, these are expected to diminish as the technology and procedural experience matures. Finally, the study population was Caucasian and predominantly male. The present findings should be confirmed in subsequent studies with broader representation of women and non-Caucasian racial groups.

Conclusions

The CHART-1 study is the largest cardiovascular regenerative medicine clinical trial to date that addresses the efficacy and safety of cardiopoiesis-based cell therapy in ischaemic heart failure. The trial

Table 3 Mortality and cardiovascular events and adverse events through 39 weeks^a

	Cardiopoietic cell treatment n = 120	Sham control n = 170 ^b
Total deaths ^c	10 (8.3)	14 (8.2)
During hospitalization for study procedure		
Cardiovascular – other CV cause	1 (0.8)	0
After hospitalization for study procedure		
Cardiovascular death	9 (7.6)	12 (7.1)
Heart failure/cardiogenic shock	6 (5.0)	7 (4.2)
Sudden cardiac death	0	4 (2.4)
Acute MI	1 (0.9)	0
Stroke	1 (0.9)	0
Undetermined cause	1 (0.9)	1 (0.6)
Non-cardiovascular death	0	2 (1.2)
Infection	0	2 (1.2)
Non-fatal events		
Cardiac transplantation	1 (0.9)	0
Myocardial infarction		
During hospitalization for study	0	0
After hospitalization for study	1 (0.9)	1 (0.6)
Stroke		
During hospitalization for study	1 (0.8)	0
After hospitalization for study	2 (1.8)	2 (1.2)
Aborted sudden cardiac death		
During hospitalization for study	0	0
After hospitalization for study	1 (0.9)	5 (3.0)
Adverse Events Reported by interventional investigators (not blinded)		
Any AE	25 (20.8)	9 (5.3)
AE related to cardiopoietic cells or sham as reported by investigator	10 (8.3)	2 (1.2)
AE related to the catheter as reported by investigator	12 (10)	1 (0.6)
Any serious AE	17 (14.1)	3 (1.8)
Serious AE with fatal outcome	2 (1.7)	0
Adverse Events Reported by evaluator investigators (blinded)		
Any AE	62 (52.5)	90 (53.0)
AE related to cardiopoietic cells or sham as reported by investigator	5 (4.2)	2 (1.2)
AE related to the catheter as reported by investigator	4 (3.4)	2 (1.2)
Any serious AE	44 (37.2)	63 (37.1)
Serious AE with fatal outcome	8 (6.8)	17 (10)

Data are expressed as number (percent).

AE, adverse event; CV, cardiovascular; MI, myocardial infarction.

^aKaplan–Meier %.

^bSafety set comprised of 151 sham control and 19 patients who did not meet cardiopoietic cell release specifications or had a contraindication but underwent sham procedure.

^cNote the number of deaths shown in *Figure 1* is different from the values shown in this table, because *Figure 1* includes 4 deaths (1 in patients randomized to and treated with active, 2 randomized to and treated with sham, and 1 randomized to active and treated with sham) who died after day 273 but before a Week 39 visit could be performed. Thus, they are included in the patient disposition figure based on visit completion, but they are not included in calculation of Week 39 (or day 273) event rates. There were a total of 24 deaths by day 273: 10 in patients randomized to and treated with active, 11 randomized to and treated with sham, and 3 randomized to active and treated with sham. There were 2 additional patients who had an urgent LVAD placed, but who did not die by day 273: 1 patient randomized to and treated with active, and 1 patient randomized to and treated with sham. These urgent LVAD placements were considered deaths in the efficacy analyses.

was neutral regarding the primary endpoint. Using markers of heart failure severity, the CHART-1 trial identified a clinically relevant patient population characterized by severe heart enlargement (LVEDV 200–370 mL) that appeared to derive consistent benefit from cardiopoietic cell treatment as regards the primary endpoint. Insights from the CHART-1 trial, namely targeting the patient population using indices of disease severity, should be considered for cardiopoietic cell therapy in future clinical trials. This application of the CHART-1 results could be an effective step towards cell-based precision medicine in patients with advanced ischaemic heart failure.³²

Collaborators

Clinical investigators and sites

Belgium: Ziekenhuis Oost-Limburg: J. Dens (Principal Investigator), M. Dupont, W. Mullens, M. Janssens; Hôpital Civil de Charleroi: D. Dolatabadi (Principal Investigator), Y. De Bruyne, J. Lalmand, P. Dubois, B. El Nakadi, A. Aminian, E. De Vuyst, P. Gurnet, M. Gujic, I. Blankoff; CHU Mont-Godinne UCL: A. Guedes (Principal Investigator), L. Gabriel, S. Seldrum, C. Doyen, M. André; AZ Glorieux: A. Heysse (Principal Investigator), F. Van Durme, J. Verschuere; Domaine Universitaire du Sart Tilman: V. Legrand (Principal Investigator), O. Gach, V. D'Orio, L. Davin, P. Lancellotti, E. Baudoux, A. Ancion, R. Dulgheru; OLV Ziekenhuis Aalst – Cardiologie: M. Vanderheyden (Principal Investigator), J. Bartunek, W. Wijns, S. Verstreken, M. Penicka, P. Meeus

Bulgaria: Tokuda Hospital Sofia: V. Gelev (Principal Investigator), I. Zheleva-Kichukova, R. Parapunova, R. Melamed, S. Sardovski, O. Radev, A. Yordanov, A. Radinov, D. Nenov, I. Amine; City Hospital Clinic Cardiology Center: I. Petrov (Principal Investigator), K. Kichukov, L. Nikitasov, Z. Stankov, H. Stoyanov, I. Tasheva-Dimitrova, M. Angelova, E. Dimitrov, M. Minchev, I. Garvanski, C. Botev, P. Polomski; Alexandrovska University Hospital, Sofia: D. Vassilev (Principal Investigator), K. Karamfiloff, R. Tarnovska-Kadreva, L. Vladimirova, G. Dimitrov, E. Hadzhiev, G. Tzvetkova, M. Atanasova

Hungary: Gottsegen György Országos Kardiológiai Intézet: P. Andreka (Principal Investigator), G. Fontos, J. Fabian, A. Csepregi, G. Uzonyi, A. Gelei; Debreceni Egyetem Orvos- és Egészségtudományi Centrum Általános Orvostudományi Kar Kardiológia Intézet: I. Edes (Principal Investigator), L. Balogh, G. Vajda, A. Darago, S. Gergely, T. Fulop, C. Jenei; Pécsi Tudományegyetem Klinikai Központ Szívgyógyászati Klinika: I. Horvath (Principal Investigator), B. Magyar, A. Nagy, A. Cziraki, R. Faludi, B. Kittka, H. Alizadeh; Semmelweis Egyetem Városmajori Szív- és Érgyógyászati Klinika: B. Merkely (Principal Investigator), L. Geller, P. Farkas, G. Szombath, G. Foldes, J. Skopal, A. Kovacs, A. Kosztin, E. Gara, N. Sydo; MH Egészségügyi Központ Kardiológiai Osztály: N. Nyolczas (Principal Investigator), G. Kerecsen, A. Korda, M. Kiss, T. Borsányi, B. Polgár; B. Muk, Z. Bári

Ireland: HRB Clinical Research Facility: F. Sharif (Principal Investigator), Y. M. Smyth

Israel: Western Galilee Hospital: S. Atar (Principal Investigator), A. Shturman, L. Akria, M. Kilimnik, M. Brezins; Ziv Medical Center: M. Halabi (Principal Investigator), N. Dally, a. Goldberg, K. Aehab, I. Rosenfeld, T. Levinas, D. Saleem; Barzilai Medical Center: A. Katz (Principal Investigator), T. Plaev, T. Drogenikov, A. Nemetz, Y. Barshay, J. Jafari, I. Orlov; Nazareth Hospital EMMS: M. Omory (Principal Investigator), N. Kogan Nielsen; Hillel Yaffe Medical

Center: M. Shochat (Principal Investigator), A. Shotan, A. Frimerman, S. Meisel, A. Asif, O. Sofer, D. S. Blondheim, A. Vazan, L. Arobov

Italy: A.O. Spedali Civili di Brescia: M. Metra (Principal Investigator), I. Bonadei, L. Inama, E. Chiari, C. Lombardi, M. Magatelli, D. Russo, V. Lazzarini, V. Carubelli; AOUI Verona – Borgo Trento Hospital: C. Vassanelli (Principal Investigator), F. Ribichini, C. Bergamini, M. Krampera, M. A. Cicoria, L. Zanolla, D. Dalla Mura, A. Gambaro, A. Rossi, G. Pesarini

Poland: Jagiellonian University Department of Cardiac and Vascular Diseases at John Paul II Hospital in Krakow: P. Musialek (Principal Investigator), A. Mazurek, L. Drabik, A. Kądzelski, Z. Walter, M. Dzieciuch-Rojek, P. Rubiś, W. Plazak, L. Tekieli, J. Podolec, W. Orczyk, U. Sutor, K. Zmudka, M. Olszowska, P. Podolec; Uniwersyteckie Centrum Kliniczne: M. Gruchala (Principal Investigator), D. Ciećwierz, M. Mielczarek, S. Burakowski, M. Chmielecki, M. Zielinska, A. Frankiewicz, J. Wdowczyk, I. Stopczynska, J. Bellwon, K. Mosakowska, R. Nadolna, J. Wroblewska, M. Rozmyslowska, M. Rynkiewicz, I. Marciniak, G. Raczak, M. Tarnawska, M. Taszner; Biegański Hospital: J. Kasprzak (Principal Investigator), M. Plewka, D. Fiutowska, T. Rechcinski, P. Lipiec, M. Sobczak, P. Weijner-Mik, M. Wraga, R. Krecki, M. Markiewicz, D. Haval Qawoq; Górnośląskie Centrum Medyczne Śląskie j Akademii Medycznej: W. Wojakowski (Principal Investigator), J. Ciosek, S. Dworowy, E. Gaszewska-Zurek, A. Ochala, W. Cybulski, T. Jadczyk, W. Wanha, Z. Parma, M. Kozłowski, M. Dzierzak, M. Markiewicz

Serbia: Clinical Hospital Center Zvezdara, Cardiology Clinic: A. Arandjelovic (Principal Investigator), N. Šekularac, D. Boljević, A. Bogdanović, S. Živković, N. Cvetinovic, G. Lončar; Clinical Centre of Serbia, Cardiology Clinic: B. Beleslin (Principal Investigator), M. Nedeljkovic, D. Trifunovic, V. Giga, M. Banovic, A. Bogdanovic, I. Nedeljkovic, J. Stepanovic, V. Vukcevic, A. Djordjevic-Dikic, M. Dobrić, B. Obrenovic-Kircanski; Clinical Centre of Serbia, Cardiology Clinic: P. Seferovic (Principal Investigator), D. Orlic, M. Tesic, O. Petrovic, A. Bogdanović, I. Milinković, D. Simeunovic; Clinical Center of Kragujevac: N. Jagic (Principal Investigator), M. Tasic, D. Nikolic, V. Miloradovic, P. Djurdjevic, M. Sreckovic, N. Zornic; Clinical Hospital Center Bezanijska Kosa, Cardiology Department: S. Radovanović (Principal Investigator), J. Šarić, S. Hinić, A. Djokovic, S. Đorđević, V. Bisenić, O. Marković, S. Stamenković, V. Malenkovic, J. Trešnjak, G. Mišić, D. Čotra, L. Tomović, M. Banović, V. Vučković; Clinic of Emergency Internal Medicine, Military Medical Academy: S. Obradović (Principal Investigator), Z. Jovic, S. Vukotic, D. Markovic, N. Djenic, A. Ristić-Andjelkov, D. Ljubinka

Spain: Hospital Universitario Germans Trias I Pujol: A. Bayes Genis (Principal Investigator), O. Rodriguez Leor, C. Labata, N. Vallejo, E. Ferrer, M. Batlle; Hospital General Universitario Gregorio Marañón: F. Fernandez-Aviles (Principal Investigator), R. Sanz Ruiz, A. Casado, G. Loughlin, E. Zatarain, J. Anguita, M. E. Fernández-Santos, C. Pascual, J. Bermejo; Hospital Clinico Universitario Virgen de la Victoria: J. M. Hernandez-Garcia (Principal Investigator), M. Jimenez Navarro, A. Dominguez, F. Carrasco, A. Muñoz, J. M. Garcia Pinilla, J. Ruiz, M. P. Queipo de Llano, A. Hernandez, A. Fernandez; Hospital Clinico San Carlos: P. Jimenez-Quevedo (Principal Investigator), R. Guerra, C. Biagioni, R. A. Gonzalez, J. J. Gomez de Diego, L. Perez de Isla

Sweden: Karolinska University Hospital: A. Mansson-Broberg (Principal Investigator), C. Sylvé, K. LeBlanc, R. Winter, P. Blomberg, E. Gunyeli, A. Ruck, C. Silva, J. Förstedt

Switzerland: CardioCentro Ticino, Switzerland: T. Moccetti (Principal Investigator), M. Rossi, E. Pasotti, I. Petrova, C. Crljenica, C. Monti, R. Murzilli, D. Sürder, M. Moccetti, L. Turchetto, V. Locicero, L. Chiumiento, S. Maspoli, M. Mombelli, A. Anesini, M. Biggiogero, G. Ponti, C. Camporini, S. Polledri, G. Dolci

United Kingdom: Kings College Hospital: J. Hill (Principal Investigator), C. Plymen, G. Amin Youssef, T. McDonagh, E. Drasar, A. Mijovic, F. Jouhra, D. McLoman, R. Dworakowski, I. Webb, J. Byrne, V. Potter

Funding

This work was supported by Celyad, SA (Mont-Saint-Guibert, Belgium). Celyad has received research grants from the Walloon Region (Belgium, DG06 funding).

Conflict of interest: Dr. Bartunek: Employed by an institution (Cardiovascular Centre, OLV Hospital) which has been co-founder of Cardio3Biosciences (now Celyad); all consultancy/speakers fees and research contracts are directed to Cardiovascular Onderzoek and Cardiac Research Institute, Aalst, Belgium.

Dr. Terzic: Research grants, administered by Mayo Clinic, from Marriott Foundation, Michael S. and Mary Sue Shannon Family, Russ and Kathy VanCleve Foundation, Leducq Fondation, Florida Heart Research Institute, Celyad, and National Institutes of Health. Dr. Terzic is listed as a co-inventor on patents US 20080019944 and US 20120100533. Mayo Clinic has rights to future royalties from Celyad.

Dr. Davison: Research grants from Celyad, Novartis, Singulex, ChanRx, Laguna Pharmaceuticals, Sorbent Therapeutics, Trevena, Inc.; personal fees from Novartis.

Dr. Filippatos: Personal fees from committee participation from Novartis, Bayer, Vifor, Servier.

Dr. Merkely: Research grant from Boston Scientific; personal fees from Boston Scientific and Novartis.

Dr. Wojakowski: Proctoring fees from Celyad.

Dr. Horvath: Personal fees from University of Pecs, Pecs, Hungary.

Dr. Katz: Research support from Celyad as a participating center in CHART-1.

Dr. Arandjelovic: Research support from Celyad as a participating center in CHART-1.

Dr. Vanderheyden: Employed by an institution (Cardiovascular Centre, OLV Hospital) which has been co-founder of Cardio3Biosciences (now Celyad). All consultancy/speakers fees and research contracts are directed to Cardiovascular Onderzoek and Cardiac Research Institute, Aalst, Belgium.

Dr. Jagic: Research grants from Celyad paid to institution and research team for conducting the study.

Dr. Kasprzak: Fees received from Celyad as trial investigator.

Dr. Sanz Ruiz: Personal fees from Celyad.

Dr. Heyndrickx: Employed by an institution (Cardiovascular Centre, OLV Hospital) which has been co-founder of Cardio3Biosciences (now Celyad). All consultancy/speakers fees and research contracts are directed to Cardiovascular Onderzoek and Cardiac Research Institute, Aalst, Belgium.

Dr. Jimenez-Quevedo: Research support from Celyad as a participating center in CHART-1.

Dr. Gruchala: None declared.

Dr. Waldman: Research grants from NIH, Scynexis, Merck, Targeted Diagnostics & Therapeutics, Inc. (Scientific Advisory Board), Synergy Pharmaceuticals; Personal fees (Data Monitoring Board) from Celyad, Immunovative Therapies LTD (Scientific Advisory Board), US Food and

Drug Administration (Advisory Committees), American Society for Clinical Pharmacology and Therapeutics (editor), NIH (reviewer), Scientific Foundation Ireland (reviewer), Synergy Pharmaceuticals (consultant); Non-financial support from Ironwood Pharmaceuticals (Biologic reagents).

Dr. Teerlink: Research grant from Celyad (chairperson, CHART-1 Clinical Events Committee); Research grants from Amgen, Bayer, BMS, Cytokinetics, Mast Therapeutics, Medtronic, Novartis, Trevena; Personal fees and non-financial support from Amgen, Bayer, BMS, Mast Therapeutics, Novartis, Relypsa, Trevena, ZS Pharma; Non-financial support from Medtronic.

Dr. Gersh: Consultant for Celyad.

Dr. Povsic: Research grant from Celyad to Duke Medicine (employer); Research grant from Baxter Healthcare; personal fees from Pluristem, Capricor.

Dr. Henry: Steering committee member, CHART-1 trial.

Dr. Metra: Personal fees for consulting honoraria as advisory board of Scientific Committee member from Amgen, Bayer, Novartis, Servier, Relypsa.

Dr. Tendra: Personal fees from Celyad (Steering Committee activities), Bayer (consulting and lecture fees), Janssen Cilag (consulting fees), Novartis (consulting fees), Servier (consulting and lecture fees); research grants from Polish National Center for Research and Development and EU Framework program VII (related to cell therapy and research outside the area of interest).

Dr. Behfar: Research grants, administered by Mayo Clinic, from Russ and Kathy VanCleve Foundation, Michael S. and Mary Sue Shannon Family, Marriott Foundation, and Celyad. Dr. Behfar is listed as co-inventor on patents US 20080019944 and US 20120100533. Mayo Clinic has rights to future royalties from Celyad.

B. Alexandre: Employee of Celyad.

Dr. Seron: Employee of Celyad.

Dr. Stough: Personal fees for consulting to European Society of Cardiology, Heart Failure Association of the European Society of Cardiology, European Drug Development Hub, Relypsa, CHU Nancy, Heart Failure Society of America, Overcome, Stealth BioTherapeutics, University of North Carolina, Respicardia, and Celyad.

Dr. Sherman: Employee of Celyad; consulting fees from Ventrix, Inc.

Dr. Cotter: Research grants from Celyad, Novartis, Singulex, ChanRx, Laguna Pharmaceuticals, Sorbent Therapeutics, Trevena, Inc.; personal fees from Novartis.

Dr. Wijns: Institutional grants and support for research from Celyad. Cardiovascular Research Center Aalst was a co-founder of Cardio3Biosciences, now Celyad. Shareholder and non-executive Board member of Argonauts and Genae Inc. Past Board member and past shareholder of Cardio3Biosciences. Cardiovascular Research Center Aalst has received research grants on behalf of W. Wijns from several device companies (outside the submitted work).

Trial Registration: clinicaltrials.gov (NCT01768702) and EudraCT (2011-001117-13).

References

- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de FS, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER III, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation* 2016;**133**:e38–360.
- Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. *J Am Coll Cardiol* 2010;**56**:392–406.
- Braunwald E. The war against heart failure: the Lancet lecture. *Lancet* 2015;**385**:812–824.
- Behfar A, Crespo-Diaz R, Terzic A, Gersh BJ. Cell therapy for cardiac repair—lessons from clinical trials. *Nat Rev Cardiol* 2014;**11**:232–246.
- Menasche P, Vanneau V. Stem cells for the treatment of heart failure. *Curr Res Transl Med* 2016;**64**:97–106.
- Cogle CR, Wise E, Meacham AM, Zierold C, Traverse JH, Henry TD, Perin EC, Willerson JT, Ellis SG, Carlson M, Zhao DX, Bolli R, Cooke JP, Anwaruddin S, Bhatnagar A, da GC-H, Grant MB, Lai D, Moye L, Ebert RF, Olson RE, Sayre SL, Schulman IH, Bosse RC, Scott EW, Simari RD, Pepine CJ, Taylor DA. Detailed analysis of bone marrow from patients with ischaemic heart disease and left ventricular dysfunction: BM CD34, CD11b, and clonogenic capacity as biomarkers for clinical outcomes. *Circ Res* 2014;**115**:867–874.
- Marban E, Malliaras K. Mixed results for bone marrow-derived cell therapy for ischaemic heart disease. *JAMA* 2012;**308**:2405–2406.
- Terzic A, Behfar A. Regenerative heart failure therapy headed for optimization. *Eur Heart J* 2014;**35**:1231–1234.
- Assmus B, Walter DH, Seeger FH, Leistner DM, Steiner J, Ziegler I, Lutz A, Khaled W, Klotsche J, Tonn T, Dimmeler S, Zeiher AM. Effect of shock wave-facilitated intracoronary cell therapy on LVEF in patients with chronic heart failure: the CELLWAVE randomized clinical trial. *JAMA* 2013;**309**:1622–1631.
- Malliaras K, Makkar RR, Smith RR, Cheng K, Wu E, Bonow RO, Marban L, Mendizabal A, Cingolani E, Johnston PV, Gerstenblith G, Schuleri KH, Lardo AC, Marban E. Intracoronary cardiosphere-derived cells after myocardial infarction: evidence of therapeutic regeneration in the final 1-year results of the CADUCEUS trial (Cardiosphere-Derived autologous stem Cells to reverse ventricular dysfunction). *J Am Coll Cardiol* 2014;**63**:110–122.
- Heldman AW, DiFede DL, Fishman JE, Zambrano JP, Trachtenberg BH, Karantalis V, Mushtaq M, Williams AR, Suncion VY, McNiece IK, Ghersin E, Soto V, Lopera G, Miki R, Willens H, Hendel R, Mitrani R, Pattany P, Feigenbaum G, Oskouei B, Byrnes J, Lowery MH, Sierra J, Pujol MV, Delgado C, Gonzalez PJ, Rodriguez JE, Bagno LL, Rouy D, Altman P, Foo CW, da SJ, Anderson E, Schwarz R, Mendizabal A, Hare JM. Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischaemic cardiomyopathy: the TAC-HFT randomized trial. *JAMA* 2014;**311**:62–73.
- Patel AN, Henry TD, Quyyumi AA, Schaer GL, Anderson RD, Toma C, East C, Remmers AE, Goodrich J, Desai AS, Recker D, DeMaria A. Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial. *Lancet* 2016;**387**:2412–2421.
- Terzic A, Behfar A. Stem cell therapy for heart failure: ensuring regenerative proficiency. *Trends Cardiovasc Med* 2016;**26**:395–404.
- Behfar A, Yamada S, Crespo-Diaz R, Nesbitt JJ, Rowe LA, Perez-Terzic C, Gausson V, Homsy C, Bartunek J, Terzic A. Guided cardiopoiesis enhances therapeutic benefit of bone marrow human mesenchymal stem cells in chronic myocardial infarction. *J Am Coll Cardiol* 2010;**56**:721–734.
- Bartunek J, Behfar A, Dolatabadi D, Vanderheyden M, Ostojic M, Dens J, El NB, Banovic M, Beleslin B, Vrolix M, Legrand V, Vrints C, Vanoverschelde JL, Crespo-Diaz R, Homsy C, Tendra M, Waldman S, Wijns W, Terzic A. Cardiopoietic stem cell therapy in heart failure: the C-CURE (Cardiopoietic stem Cell therapy in heart failure) multicenter randomized trial with lineage-specified biologics. *J Am Coll Cardiol* 2013;**61**:2329–2338.
- Behfar A, Latere JP, Bartunek J, Homsy C, Daro D, Crespo-Diaz RJ, Stalboerger PG, Steenwinckel V, Seron A, Redfield MM, Terzic A. Optimized delivery system achieves enhanced endomyocardial stem cell retention. *Circ Cardiovasc Interv* 2013;**6**:710–718.
- Bartunek J, Davison B, Sherman W, Povsic T, Henry TD, Gersh B, Metra M, Filippatos G, Hajjar R, Behfar A, Homsy C, Cotter G, Wijns W, Tendra M, Terzic A. Congestive heart failure Cardiopoietic Regenerative Therapy (CHART-1) trial design. *Eur J Heart Fail* 2016;**18**:160–168.
- Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. *Stat Med* 1999;**18**:1341–1354.
- Bonetti M, Gelber RD. Patterns of treatment effects in subsets of patients in clinical trials. *Biostatistics* 2004;**5**:465–481.
- Jackson N, Atar D, Borentain M, Breithardt G, van Eickels M, Endres M, Fraass U, Friede T, Hannachi H, Janmohamed S, Kreuzer J, Landray M, Lautsch D, Le Floch

- C, Mol P, Naci H, Samani N, Svensson A, Thorstensen C, Tijssen J, Vandzhura V, Zalewski A, Kirchhof P. Improving clinical trials for cardiovascular diseases: a position paper from the Cardiovascular Roundtable of the European Society of Cardiology. *Eur Heart J* 2016;**37**:747–754.
22. Bartunek J, Sherman W, Vanderheyden M, Fernandez-Aviles F, Wijns W, Terzic A. Delivery of biologics in cardiovascular regenerative medicine. *Clin Pharmacol Ther* 2009;**85**:548–552.
 23. Fisher SA, Doree C, Mathur A, Martin-Rendon E. Meta-analysis of cell therapy trials for patients with heart failure. *Circ Res* 2015;**116**:1361–1377.
 24. Janssens S. Stem cells in the treatment of heart disease. *Annu Rev Med* 2010;**61**:287–300.
 25. Karantalis V, Hare JM. Use of mesenchymal stem cells for therapy of cardiac disease. *Circ Res* 2015;**116**:1413–1430.
 26. Behfar A, Terzic A. Stem cell in the rough: repair quotient mined out of a bone marrow niche. *Circ Res* 2014;**115**:814–816.
 27. Bax JJ, Schinkel AF, Boersma E, Elhendy A, Rizzello V, Maat A, Roelandt JR, van der Wall EE, Poldermans D. Extensive left ventricular remodeling does not allow viable myocardium to improve in left ventricular ejection fraction after revascularization and is associated with worse long-term prognosis. *Circulation* 2004;**110**:1118–1122.
 28. Braun J, Bax JJ, Versteegh MI, Voigt PG, Holman ER, Klautz RJ, Boersma E, Dion RA. Preoperative left ventricular dimensions predict reverse remodeling following restrictive mitral annuloplasty in ischaemic mitral regurgitation. *Eur J Cardiothorac Surg* 2005;**27**:847–853.
 29. Goldenberg I, Moss AJ, Hall WJ, Foster E, Goldberger JJ, Santucci P, Shinn T, Solomon S, Steinberg JS, Wilber D, Barsheshet A, McNitt S, Zareba W, Klein H. Predictors of response to cardiac resynchronization therapy in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation* 2011;**124**:1527–1536.
 30. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? *JAMA* 2003;**289**:2554–2559.
 31. Lazar AA, Bonetti M, Cole BF, Yip WK, Gelber RD. Identifying treatment effect heterogeneity in clinical trials using subpopulations of events: STEPP. *Clin Trials* 2016;**13**:169–179.
 32. Terzic A, Pfenning MA, Gores GJ, Harper CM Jr. Regenerative medicine build-out. *Stem Cells Transl Med* 2015;**4**:1373–1379.

