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ORIGINAL ARTICLE

Two-year outcomes of a cardiac microcurrent device in chronic heart failure: A first-in-human pilot study

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Abstract

Aims In heart failure patients, altered myocardial electrical fields linked to oedema may impair left ventricular function. While short-term use of implanted microcurrent generators (C-MIC) has shown promise, long-term effects remain unclear. This study assessed the safety and efficacy of C-MIC use beyond the initial 6 month pilot period.

Methods Patients from the initial C-MIC pilot study who were alive at 6 months were screened for 2 year follow-up. The primary endpoint included rates of all-cause, cardiac- and device-related mortality, all-cause, cardiac and device related hospitalizations, along with adverse events, device malfunctions and exchanges. Secondary endpoints evaluated device performance via left ventricular ejection fraction (LVEF), 6 min walk distance, New York Heart Association (NYHA) class and SF-36 quality-of-life scores and the need for prolonged therapy.

Results Of the 10 patients enrolled in the initial study, 7 were enrolled in follow-up (mean age 52.4 ± 7.6 years, NYHA Class III and mean LVEF 31.7 ± 3.7%). No device-related adverse events occurred. One non-cardiac, non-device related death was reported at 18 months. Improvement in LVEF of 11.60% [95% confidence interval (CI): 5.64–17.56, $P < 0.001$] from baseline to 6 months was maintained at 2 years post-C-MIC deactivation, with a sustained increase of 12.56% from baseline (95% CI: 4.67–20.45, $P = 0.002$). Similarly, the 6 min walk distance improved by 206.35 m at 6 months (95% CI: 161.32–251.39, $P < 0.0001$) and remained at 191 m above baseline at 2 years (95% CI: 131.83–250.99, $P < 0.0001$). Improvements in NYHA functional class and SF-36 quality-of-life scores observed at 6 months were also preserved throughout the 2 year follow-up. One patient required C-MIC reactivation.

Conclusions Long-term use of the C-MIC device appears safe with sustained improvements in NYHA class, LVEF, 6 min walk distance and quality of life, supporting the long-term therapeutic potential of microcurrent therapy.

Keywords cardiac fibroblast; cardiovascular disease; fibrosis; microcurrent; myofibroblasts

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Introduction

Heart failure (HF) with reduced ejection fraction (HFrEF) is a complex clinical syndrome resulting from a variety of underlying causes, including ischaemic, genetic, inflammatory and idiopathic conditions. It is characterized by impaired left ventricular systolic function, often accompanied by ventricular dilation and neurohormonal activation, and affects millions of individuals worldwide. HFrEF is associated with significant morbidity, mortality and healthcare burden, frequently progressing despite optimal medical therapy.[1] In patients with a left ventricular ejection fraction (LVEF) ≤ 35% despite optimal medical therapy, device-based interventions such as implantable cardioverter-defibrillators (ICDs), cardiac

resynchronization therapy (CRT), cardiac contractility modulation (CCM) and left ventricular assist devices (LVADs) may be indicated. Prognosis remains poor, with mortality rates reaching 26% within 20 months and up to 76% at 8 years.[2,3] For patients with end-stage HF, such devices may serve as a bridge-to-transplant, particularly in those classified as NYHA Class III–IV.[4,5]

Among ambulatory patients with advanced HF, direct microcurrent therapy has emerged as a novel investigational approach aimed at reversing maladaptive remodelling.[6] This therapy aims to enhance myocardial function by modulating cardiac fibrosis.[7,8] Preclinical studies suggest that microcurrent stimulation may exert anti-inflammatory effects and promote reverse remodelling.[9–11] A first-in-human SPOT (Safety and the Performance of the Cardiac Microcurrent Therapy System) C-MIC study evaluated the C-MIC device (Berlin Heals GmBH, Germany), which delivers subthreshold microcurrent therapy directly to the myocardium. Between May 2019 and April 2020, 10 patients with NYHA Class III HF and LVEF ≤35% enrolled in the SPOT C-MIC study underwent surgical implantation of the device.[12] The C-MIC implantation procedure is a minimally invasive approach in which an epicardial patch is positioned on the anterior surface of the left ventricle through a limited thoracotomy under general anaesthesia. The patch is connected to a subcutaneous pulse generator that delivers continuous microcurrent therapy to the heart. A detailed description of the device and implantation technique has been published previously.[12] Over a 6 month follow-up period, cardiac function was assessed using echocardiography, the 6 min walk test, NYHA classification and SF-36 quality-of-life scores. The study demonstrated significant improvements in LVEF, ventricular size, functional capacity and symptom burden, with no device-related adverse events reported. At the 6 month follow-up visit, the device was switched off but left in situ. To evaluate the long-term safety of retaining the device and the durability of the observed clinical benefits, participants from the initial study were enrolled in a 2 year follow-up study. We herein present the findings of that follow-up investigation.

Methods

The SPOT C-MIC Follow-Up (SPOT C-MIC FU) study is a single-arm, single-centre, with both retrospective and prospective data collection; some data were retrospectively obtained due to mandatory COVID-19 lockdown restrictions. The key inclusion criteria were (1) patients from the per-protocol treatment group who underwent surgical implantation of a C-MIC device during the first-in-human SPOT C-MIC study[12] and (2) patients who provided written informed consent. The primary exclusion criterion was the unwillingness or inability to attend follow-up visits. For patients requiring extended C-MIC therapy, the C-MIC system was reactivated. If therapy was needed beyond the lifespan of the implantable device (IMD) battery, a device replacement was performed. These patients were categorized into a separate group designated for prolonged therapy. The main inclusion criteria for the first-in-human study were HFrEF due to non-ischaemic dilated cardiomyopathy (NYHA Class III), a LVEF ≤ 35% despite receiving optimal medical therapy for more than 30 days, and a HF diagnosis within the previous 5 years. Key exclusion criteria included a history of cardiac surgery and the presence of any other implantable electronic device.[12] The study complied with the Declaration of Helsinki and the protocol received approval from institutional ethics boards (Approval. No. 515-19-00122-2021-7) and competent national authorities (Approval No. 515-05-00122-21-001). All patients provided written informed consent. (Clinical Trials Register DRKS00027419).

Data collection

In accordance with the study protocol, follow-up visits were scheduled at 6, 12, 18 and 24 months after C-MIC therapy deactivation, corresponding to 12, 18, 24 and 30 months post-implantation. However, due to COVID-19-related lockdowns, these requirements were adjusted. Data collection was conducted based on availability and aligned with the site's standard of care. Visit windows were extended to accommodate patient availability and pandemic-related disruptions. Phone and video visits were permitted, except for the final visit at 30 months post-implantation, which required an in-person assessment. Patients who received prolonged C-MIC therapy were evaluated at 1, 6, 12, 18 and up to 24 months following the conclusion of the initial therapy phase. Assessments included a general physical examination with vital signs, documentation of ongoing medical therapy, echocardiographic evaluation of LVEF, 6 min walk test, NYHA classification, SF-36 quality-of-life questionnaire, visit notes, imaging findings and any reported adverse events.

All adverse events were adjudicated by an external monitoring committee. A pseudonymized device log from the C-MIC system's portable user terminal was regularly updated and retained for study purposes. Documentation of adverse events and outcomes adhered to Good Clinical Practice and all applicable institutional, local, and national regulatory standards. Study personnel recorded key clinical parameters, including NYHA functional class, 6 min walk distance, LVEF, left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic dimension (LVEDD) measured via two-dimensional echocardiography using Simpson's rule, and SF-36 quality-of-life scores. Upon completion of the follow-up period, participants returned to routine cardiology care.

Study outcomes

The primary endpoints aimed to assess the safety of leaving the C-MIC device in situ for extended use, abandonment or removal. These included rates of all-cause mortality, cardiac- and device-related mortality, all-cause, cardiac-related and device-related hospitalizations, as well as the incidence and severity of adverse events, device malfunctions and device replacements.

The secondary endpoints evaluated the performance of the C-MIC device during prolonged use, abandonment or removal. These included changes in LVEF, LVESD, LVEDD, 6 min walk distance (6MWD), NYHA functional class, quality of life as measured by the SF-36 questionnaire and the need for extended C-MIC therapy.

Statistical method

Data analysis was conducted on an intention-to-treat basis. Descriptive statistics were used to summarize study endpoints. Normality of continuous variables was assessed using the Shapiro–Wilk test. When data were normally distributed, changes from baseline to follow-up were analysed using the Student's *t*-test given their interpretability and relative robustness to normality assumptions in small sample size. For non-normally distributed outcomes or ordinal data, the Wilcoxon signed-rank test was applied. Mixed-model repeated measures (MMRM) analysis was used to compare multiple time points outcomes to baseline. Given the very small sample size and the exploratory nature of the study, no formal adjustment for multiple comparisons was applied. Instead, exact *P* values and confidence intervals (CIs) are reported to provide transparency, and results should be interpreted as hypothesis-generating, warranting confirmation in larger controlled studies. Statistical significance was set at $P < 0.05$, and all analyses were performed using the SAS statistical software package (SAS, Cary, NC, USA).

Results

Seven of the 10 pilot study participants were enrolled in the follow-up study (*Figure* 1). One patient was excluded due to a protocol deviation during the pilot phase, one patient passed away, and one was lost to follow-up due to work related relocation. The C-MIC system was reactivated in only one of the seven patients. Baseline demographics and an overview of the medical management of study participants are summarized in *Table* 1. The study included one female and six males, with a mean age of 52.4 ± 7.6 years and a mean body mass index (BMI) of 31.0 ± 4.6 kg/m^2. HF medications were adjusted according to medical guidelines for all participants, with updates recorded at each follow-up visit. All seven patients had hypertension and a family history of HF. Three patients had a history of tobacco use, two had type 2 diabetes mellitus, one had high cholesterol and five had additional comorbidities. Throughout the follow-up study, all patients continued routine medical management for HF and associated conditions. The four planned semi-annual follow-up visits occurred at the following time points: 12.41 ± 0.38 months

Figure 1 Study consort diagram.

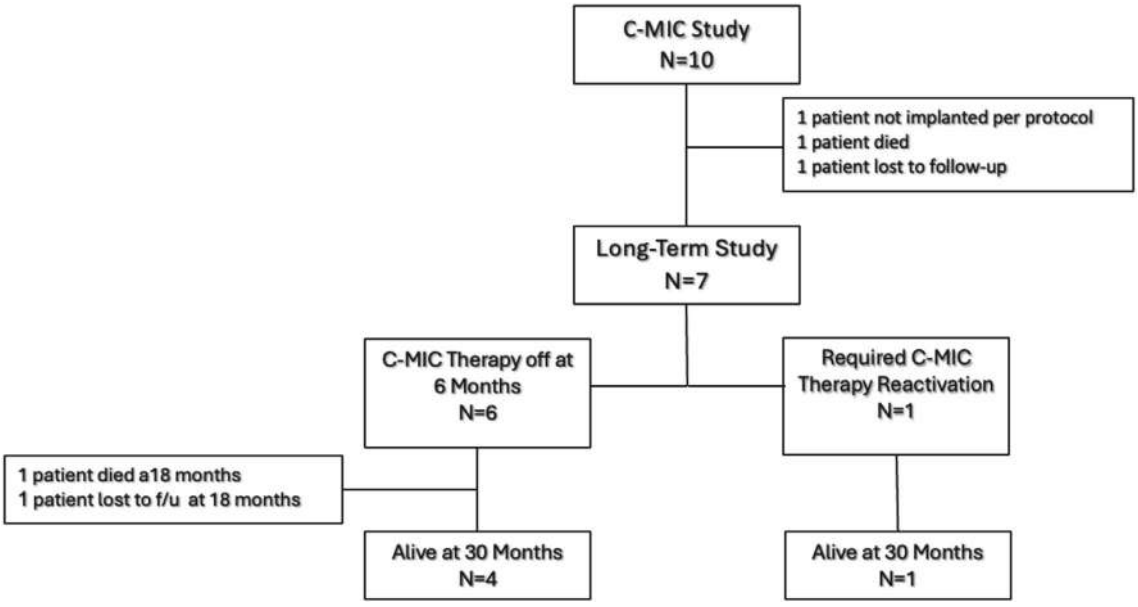

Table 1 Baseline characteristics of patients enrolled in the follow-up cohort.[a]

Characteristics	Patient data (N = 7)
Age (years)	51.6 ± 7.6
Women (N, %)	1 (14.3)
Body mass index (kg/m^2)[b]	31.2 ± 4.6
Diabetes type II (N, %)	2 (28.6)
Hypertension (N, %)	7 (100)
Hyperlipoproteinemia (N, %)	1(14.3)
Lung disease (N, %)	1 (14.3)
Kidney disease (N, %)	1 (14.3)
GI disease (N, %)	2 (28.6)
NYHA class III (N, %)	7 (100)
SF-36 total score	
PCS	40.7 ± 4.7
MCS	31.2 ± 9.6
Family disposition for HF (N, %)	7 (100)
Beta-blockers (N, %)	5 (71.4)
Ace inhibitors (N, %)	5 (71.4)
Diuretic (N, %)	6 (85.7)
Duration since initial HF diagnosis	2.3 (1.1)
QRS duration (ms)	101.1 (15.2)
AF/flutter (N, %)	1 (14.3%)
AV block	0 (0)
LVEF (N, %)	31.7 (3.7)
LVEDD (mm)	63.7 ± 3.5
LVESD (mm)	51.9 ± 6.9
ICD (N, %)	0 (0)
eGFR (mL/min/1.72 cm^2)	
6MWD (m)	202.9 (38.9)
Blood pressure	
Systolic (mmHg)	121.4 (12.1)
Diastolic (mmHg)	75.7 (5.3)
NT-ProBNP (pg/mL)	358.4 (335.4)
Haemoglobin (g/L)	148 (9)

Abbreviations: 6MWD, 6 min walk distance; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; AV, atrioventricular; eGFR estimated glomerular filtration; GI, gastrointestinal; HF, heart failure; ICD, intra cardiac defibrillator; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MCS, mental component summary; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association; PCS, physical component summary; SF-36, 36-Item Short-Form Health Survey Questionnaire.

[a]Plus–minus values are means ± SD.

[b]The body mass index is the weight in kilograms divided by the square of the height in metres.

Table 2 Safety assessments.

Event	Number of patients (N = 7)	Number of events (N = 11)
Adverse events	3 (42.9%)	11
Severity (maximum)		
Mild	—	7
Moderate	2	3
Severe	1	1
Serious adverse events	2 (28.6%)	3
SAE criteria (multiple entries)		
Death	1 (14.3%)	1
Cardiac related	—	—
Device related	—	—
Life-threatening illness or injury	1	2
In-patient or prolonged hospitalization	2 (28.6%)	2
Cardiac related	1 (14.3%)	1
Device related	—	—
Patient outcome:		
Resolved	1 (14.3%)	8
Persistent	1 (14.3%)	2[a]
Death	1 (14.3%)	1

[a]One patient had persistent elevated left hemidiaphragm, chronic gastritis and other chronic findings, which were evident prior to participation in the follow-up study and continued after the end of the study.

(n = 7), 17.95 ± 0.42 months (n = 6), 24.08 ± 0.53 months (n = 6) and 30.12 ± 0.25 months (n = 4) after C-MIC implantation.

The primary endpoint for evaluating the safety of leaving the C-MIC device in situ was determined by the incidence of serious adverse events (SAEs), hospitalizations and deaths associated with the device or microcurrent therapy. The device remained in situ for all seven patients, although microcurrent therapy was continued for only one. During the follow-up period, one patient died from non-cardiac, non-device-related causes. Two patients were hospitalized—one for tachyarrhythmia and another for cholecystectomy—neither of which were related to the C-MIC device. In total, 11 adverse events (AEs) were reported across three patients, none of which were attributed to the device (*Table* 2). With no device-related AEs or SAEs reported, the primary safety endpoint was achieved, supporting the long-term safety of leaving the C-MIC device in situ for extended use, abandonment or exchange.

The secondary endpoints evaluated the C-MIC device's performance during prolonged in situ use, abandonment or replacement, based on sustained cardiac and clinical improvements following the pilot study. *Figure* 2 illustrates the changes in LVEF, LVEDD, LVESD and 6MWD for individual patients while *Figure* 3 presents the least squares means of these changes based on the mixed model for repeated measures analysis. Two years after therapy deactivation, improvements in LVEF from baseline were maintained. Mean LVEF increased by 11.60% at 6 months (95% CI: 5.64–17.56, $P < 0.001$) and remained elevated with an increase from baseline of 12.56% at 2 years post-deactivation (95% CI: 4.67–20.45, $P = 0.002$) (*Figure* 3A).

Reductions in LVEDD and LVESD observed at 6 months were also sustained through 30 months post C-MIC implantation (*Figures* 3B,C). LVESD decreased from baseline by 7.0 mm at 6 months (95% CI: −9.3 to −4.7, $P < 0.0001$) and by 7.9 mm at 30 months (95% CI: −11.0 to −4.9, $P < 0.0001$). Likewise, LVEDD was reduced by 9.1 mm at 6 months (95% CI: −12.5 to −5.7, $P < 0.0001$) and by 9.6 mm at 30 months (95% CI: −14.08 to −5.15, $P < 0.0001$).

As shown by *Figure* 3D, functional capacity gains, as measured by the 6MWD, were similarly preserved. Patients experienced a mean increase of 206.35 m at 6 months (95% CI: 161.32–251.39, $P < 0.0001$), with a sustained improvement of 191 m at 30 months (95% CI: 131.83–250.99, $P < 0.0001$).

Figure 2 Changes from baseline to each follow-up visit are shown for individual patients in LVEF (A), LVEDD (B), LVESD (C) and 6MWD (D). Patient #7 underwent C-MIC reactivation. LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; 6MWD, 6 min-walk distance.

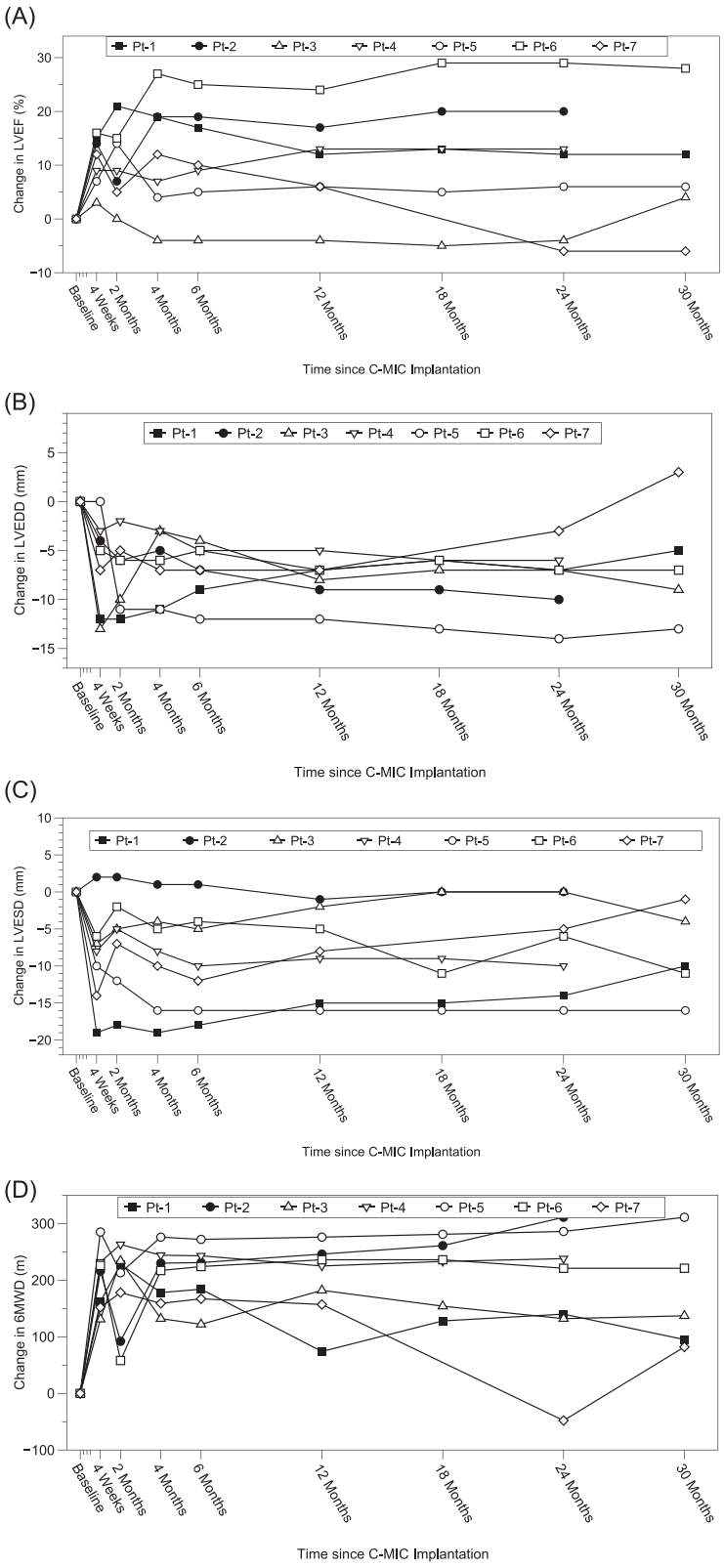

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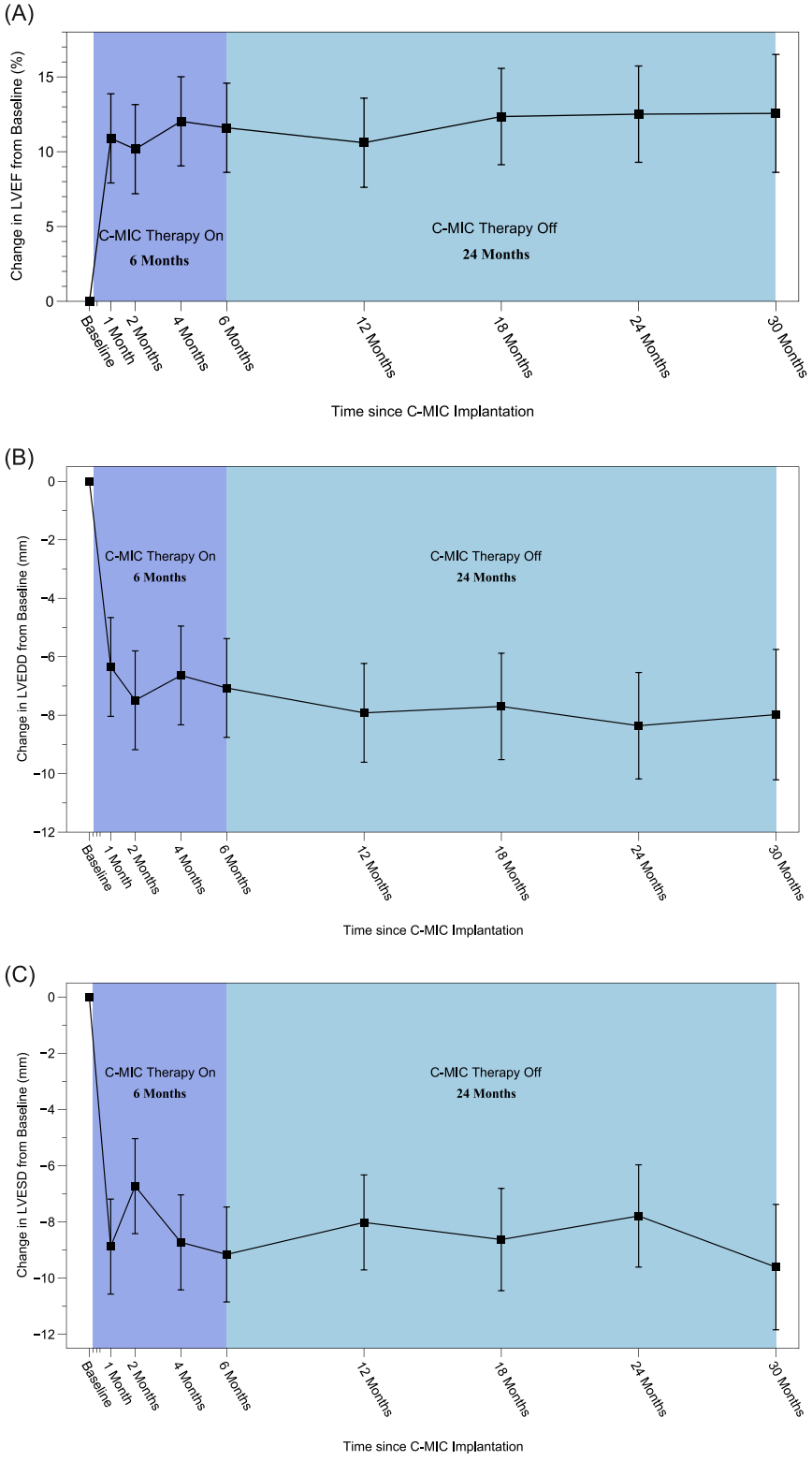
Figure 3 The figure illustrates changes in LVEF (A), LVEDD (B), LVESD (C) and 6MWD (D) from baseline to 6 months during active C-MIC therapy, and the sustainability of these changes over the following 2 years after deactivation at 6 months post-implantation. Values are based on a mixed model for repeated measures (MMRM) analysis and are presented as least squares (LS) means ± standard error (SE). Data from the patient who required therapy re-activation were excluded after the 12 month follow-up visit. LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; 6MWD, 6 min-walk distance.



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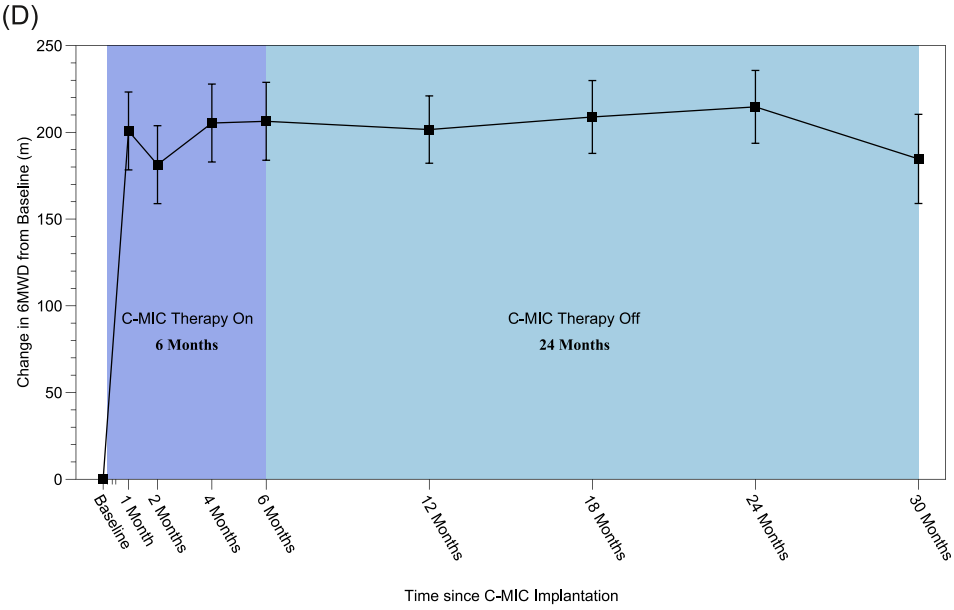


NYHA classification improvements were sustained, although due to the small size, statistical significance was not reached (*Figure* 4A). Quality-of-life outcomes on the SF-36 Physical and Mental Component Summary scores remained significantly improved at 2 years post-C-MIC deactivation (*Figure* 4B).

Table 3 shows individual patient N terminal pro brain natriuretic peptide (NT-proBNP) values from baseline through the 30 month follow-up after C-MIC implantation. *Figure* 5 displays the corresponding trajectory of NT-proBNP changes over time. While an initial rise followed by a decline is observed, these changes from baseline did not reach statistical significance.

Microcurrent therapy was reactivated in one male patient due to a decline in LVEF observed about 2 weeks after C-MIC therapy deactivation. At the time of implantation, the patient was diagnosed with hyperlipoproteinemia—a condition linked to elevated cardiovascular risk—and had a markedly elevated baseline NT-proBNP level of 1029 pg/mL, significantly higher than the group average of 358.4 pg/mL. His baseline LVEF was 33%, which improved to 43% after 6 months of C-MIC therapy. However, approximately 2 weeks after therapy deactivation, the patient was readmitted with an LVEF of 29%, prompting reactivation of the C-MIC system after IMD device exchange due to battery depletion (*Figure* 6).

After 209 days following C-MIC therapy reactivation, the system entered an error state, which was resolved 29 days later by restarting the device. Subsequently, at 385 days post-reactivation, the IMD battery was fully depleted, causing the system to transition into a safe state. To allow for the possibility of continued therapy, the patient underwent a second IMD replacement just 2 days before the study concluded. As illustrated in *Figure* 6, despite reactivation of C-MIC therapy, the improvements in LVEF and LV size observed at 6 months regressed towards baseline. The patient's 6MWD also declined slightly but remained above baseline levels (340 m vs. 258 m) (*Figure* 6C).

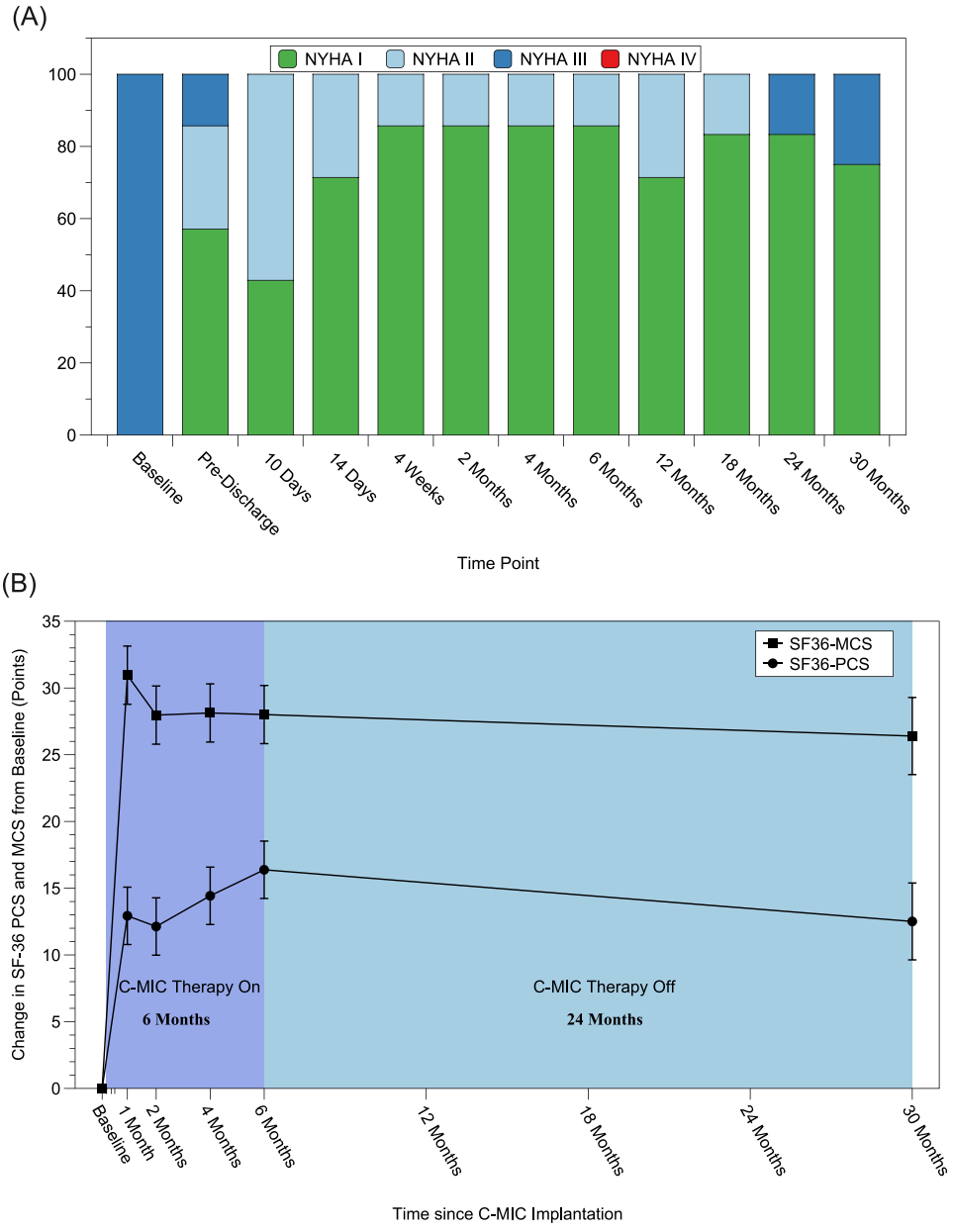
At final follow-up, the patient remained in NYHA Class II. His SF-36 Mental Component Score (MCS) had declined below baseline (40.8 vs. 51.2) while the SF-36 Physical Component Score (PCS) remained elevated (48.1 vs. 32.9).

Discussion

In this 2 year follow-up study of the first-in-human pilot study, no device-related AEs were reported in either the initial pilot or follow-up study. Initial improvement in LVEF, NYHA functional class, exercise capacity and patient-reported quality-of-life (QoL) outcomes after 6 months of C-MIC therapy were sustained through the 2 year follow-up period in all participants except one, who required reactivation of microcurrent therapy.

The relatively low baseline NT-proBNP levels in this cohort likely reflect the demographic profile of the study population, which consisted predominantly of younger male patients—a

Figure 4 The figure shows changes in (A) NYHA class and (B) health status as measured by the mental (MCS) and physical (PCS) component scores of the S-36 questionnaire, from baseline to 6 months during active C-MIC therapy, and the relative sustainability of these changes over the subsequent 2 years following therapy deactivation at 6 months post-implantation. SF-36 data are based on a mixed model for repeated measures (MMRM) analysis and presented as least squares (LS) means ± standard error (SE). Data from the patient who required therapy reactivation were excluded after the 12 month follow-up visit. MCS, Mental Component Summary; NYHA, New York Heart Association; PCS Physical Component Summary; SF-36, 36-Item Short-Form Health Survey Questionnaire.



group known to have lower NT-proBNP concentrations compared to older adults and women, even in the presence of HF.[13] Given these baseline characteristics and the limited sample size, large post-treatment changes in NT-proBNP were not observed. The impact of C-MIC therapy on NT-proBNP remains uncertain and warrants further investigation in larger, more diverse populations.

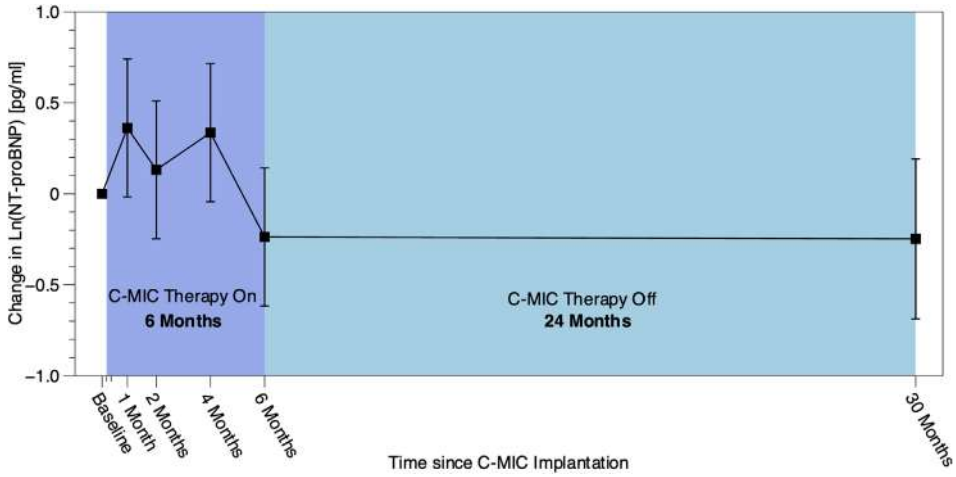
C-MIC therapy is an emerging bioelectronic approach that delivers direct microcurrents to myocardial tissue through an IMD. The therapy is designed to promote functional recovery of myocardium by leveraging the bioelectric properties of cells and tissues, with the goal of improving left ventricular function in patients with chronic HF. The precise mechanism by which C-MIC therapy exerts its therapeutic effects remains

Table 3 Trend in NT-proBNP for each patient from baseline to 30 months.

Time point	Pt-1	Pt-2[a]	Pt-3	Pt-4[b]	Pt-5	Pt-6	Pt-7[c]
Baseline NT-proBNP (pg/mL)	381.2	46.0	92.7	408.0	134.0	418.3	1029.0
4 weeks NT-proBNP (pg/mL)	90.6	98.7	374.9	1203.0	267.7	284.4	1540.0
2 months NT-proBNP (pg/mL)	83.9	128.8	271.8	1558.0	275.0	99.1	757.0
4 months NT-proBNP (pg/mL)	221.4	68.1	170.6	1954.0	217.3	267.1	1349.0
6 months NT-proBNP (pg/mL)	112.7	61.2	201.2	824.8	203.9	38.6	790.2
30 months NT-proBNP (pg/mL)	175.1	—	142.7	—	102.0	111.0	1720.0

Abbreviation: NT-proBNP, N-terminal pro–B-type natriuretic peptide.
[a]Pt-2 lost to follow-up at 18 months.
[b]Pt-4 died at 18 months.
[c]Pt-7 required C-MIC reactivation.

Figure 5 N terminal pro brain natriuretic peptide (NT-proBNP) mean change from baseline to 30 months for the overall cohort on a natural log scale (b). Values are derived from a mixed model for repeated measures (MMRM) and presented as least squares (LS) means ± standard error (SE).

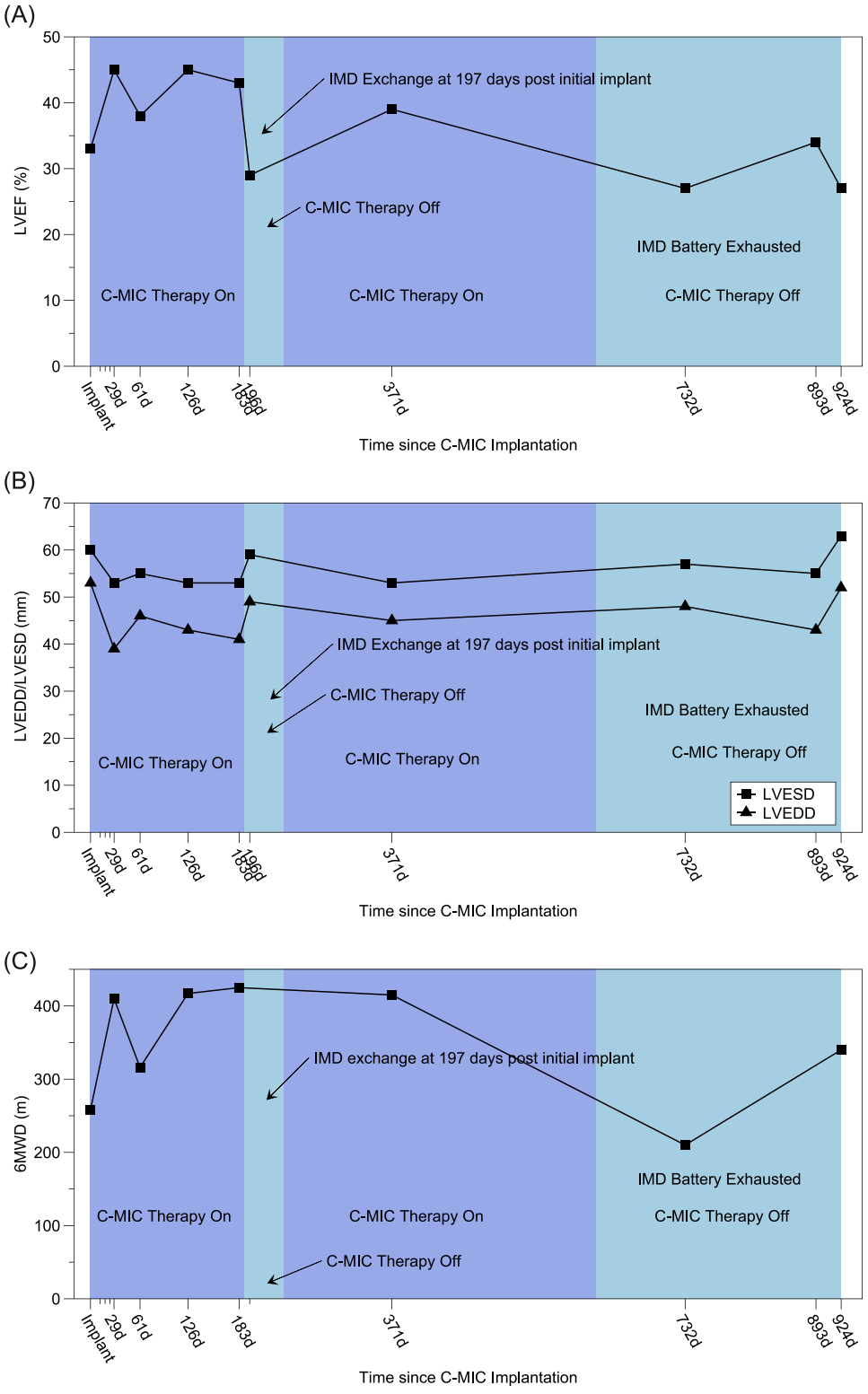


under investigation, but several hypotheses have been proposed.[7,9,14–16] Low-level DC microcurrents may help restore disrupted myocardial bioelectric signalling, stabilizing cardiomyocyte membrane potential and enhancing synchronization of myocardial contraction. This may be an important reason for the improved ejection fraction, especially the changes seen in the early phase of microcurrent application. Future studies should confirm the improvement in load-independent measures of myocardial function such as contractility and cardiac efficiency.

To explain the long-term sustained effects on cardiac function, microcurrent therapy has been shown in preclinical studies to enhance cellular ATP production, increase protein synthesis and upregulate key growth factors involved in tissue repair (e.g., VEGF and IGF-1).[14] These effects may support angiogenesis, reduce fibrosis and promote cardiomyocyte survival in chronic failing myocardium known to be associated with capillary rarefaction, progressive interstitial fibrosis and cardiomyocyte apoptosis. Through angiogenic signalling, C-MIC may enhance myocardial perfusion due to capillary rarefaction, supporting better oxygen and nutrient delivery to metabolically stressed regions of the chronically failing heart.[16–18] The microcurrents may modulate inflammatory pathways by reducing pro-inflammatory cytokine expression and oxidative stress, which also attenuate fibrotic remodelling and progressive myocardial dysfunction.[9,14]

Another proposed mechanism by which microcurrent therapy exerts its effects is through the impact on electroosmosis —the movement of interstitial fluid in response to applied electrical fields.[7] In the context of chronic cardiomyopathic failure, this process may facilitate the clearance of excess myocardial fluid and reduce tissue oedema, thereby improving myocardial compliance and contractile function. Prior studies have demonstrated that chronic cardiomyopathy is associated with myocardial oedema and that systolic function can be significantly compromised with the induction of myocardial oedema via coronary sinus ligation.[19] The time frame observed in C-MIC I study where changes in myocardial function were observed was within 1 month.[12] Given the observed improvement in myocardial function as early as 2–4 weeks, an important mechanism to explore is whether myocardial oedema—commonly present in chronic cardiomy-

Figure 6 Changes in LVEF (A), LVEDD/LVESD (B) and 6MWD (C) from baseline to 930 days in the patient who required C-MIC therapy reactivation.



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opathy—may favourably affected by electroosmosis, a process associated with microcurrent therapy in the healing of other tissues.[14,15]

Future studies incorporating advanced imaging and biomarker analyses will be essential in translating these mechanisms into clinical insight. These tools will not only help validate the therapy's mode of action but may also enable more accurate identification of patients most likely to benefit, ultimately enhancing the precision and impact of C-MIC therapy. Incorporating mechanistic endpoints into future trials will be critical for understanding how C-MIC exerts its effects at the tissue and cellular levels.

In summary, data from this early feasibility C-MIC clinical study demonstrate that C-MIC therapy is associated with statistically significant and sustained improvements in left ventricular function, as measured by increases in LVEF and reductions in end-systolic and end-diastolic dimensions. These improvements were accompanied by enhanced functional capacity—reflected in gains in 6 min walk distance—and better patient-reported outcomes, including NYHA functional class and SF-36 scores.[12] Notably, some of these benefits persisted even after therapy was deactivated, suggesting the potential for long-term restoration of myocardial function rather than a transient physiological response.

The precise mechanisms for recurrent HF in the one patient who was reactivated on the C-MIC device are not yet fully understood, although progression of the underlying disease despite the long-term potential benefits of microcurrent therapy may be a contributing factor. Larger sample sizes are needed to better understand the phenotype of recurrent HF after therapeutic application of microcurrent and assess the potential benefits of microcurrent reapplication to the myocardium.

Cardiac magnetic resonance (CMR) imaging offers a highly accurate and reproducible modality for assessing changes in left ventricular function and remodelling. Incorporating CMR into future C-MIC studies could provide valuable insights into the structural and functional impact of microcurrent therapy. Moreover, an 'on/off' CMR protocol—similar to that used in CRT research—may help determine the sustainability and reversibility of C-MIC's therapeutic effects.[20] To enable this, MR compatibility studies of the C-MIC system are currently underway, with the goal of expanding the imaging modalities available for mechanistic and longitudinal evaluation of device performance.

Limitations

This study has several important limitations. Most notably, the very small sample size and absence of a control group significantly constrain the ability to draw definitive conclusions regarding the long-term safety of leaving the device in situ and the durability of treatment effects following C-MIC therapy. The observed improvements may be influenced by background medical therapy, natural disease progression or placebo effects, and no causal inferences should be made. As an exploratory study in predominantly male cohort, it was not powered to assess clinical outcomes such as mortality. Future studies, including a sham-controlled trial, will be necessary to more rigorously evaluate the safety and clinical impact of C-MIC therapy.

Additionally, the timing of follow-up visits varied across patients, largely due to disruptions from the COVID-19 pandemic, which may have introduced inconsistencies in data collection. Although flexible visit windows were used to mitigate this effect, the potential for residual bias remains.

The current exclusion of patients with other implantable cardiac devices—such as CRT, CCM and ICD systems—was based on safety considerations. Because C-MIC delivers a continuous microcurrent via an epicardial patch, devices capable of sensing electrical activity may be susceptible to interference. Until further safety testing confirms compatibility and ensures reliable signal discrimination, these patients remain excluded. Nonetheless, the C-MIC device does not rely on electrical resynchronization and does not require a specific QRS duration, potentially supporting broader applicability across HFrEF phenotypes. Future studies should investigate whether specific subgroups, such as those defined by scar burden or prior device history, may derive greater benefit from this therapy.

To address the limitations of this pilot study, a larger randomized controlled trial (C-MIC II) was subsequently conducted, including a control group receiving guideline-directed medical therapy and blinded core lab analysis of imaging endpoints. The findings of C-MIC II, recently presented at the ESC-HFA 2025 conference, provide additional evidence regarding the safety and potential efficacy of C-MIC therapy.[21] In parallel, a long-term follow-up study of C-MIC II patients post-treatment deactivation is ongoing (NCT05189860) and will offer further insight into the durability of treatment effects beyond the initial trial period.

In light of these limitations, the current findings should be considered hypothesis-generating and interpreted with appropriate caution.

Conclusions

C-MIC therapy represents a novel and promising approach to cardiac function improvement in HF patients, with early data suggesting favourable effects on ventricular function and patient outcomes. However, additional research is needed to further expand the mechanistic understanding, optimize patient selection and enhance the therapy's safety and durability. Future pivotal trials and mechanistic studies will be essential to unlocking the full potential of this bioelectronic

therapy. The findings from this follow-up study are encouraging and indicate that keeping the C-MIC system in place for up to 30 months after initial implantation is safe. There were no reported AEs related to the device or treatment, and the initial improvements in LVEF, NYHA class, functional capacity and QoL were sustained.

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Conflict of interest statement

Dr Rame reports receiving consulting fees from Berlin Heals and Abbott Laboratories. Dr Fudim reports receiving consulting fees from Berlin Heals. Dr Anker reports receiving research support from Abbott Vascular and Vifor Pharma and personal fees from Abbott Vascular, Berlin Heals, Bayer, BRAHMS, Boehringer Ingelheim, Cardiac Dimensions, Impulse Dynamics, Novartis, Servier and Vifor Pharma. Drs Goettel, Brandes, Kallel and Mueller are Berlin Heals employees.

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