



Cardiac microcurrent therapy in heart failure: Mechanistic rationale, early clinical evidence, and future directions

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Abstract

Despite major advances in guideline-directed medical therapy (GDMT), many patients with heart failure with reduced ejection fraction (HFrEF) remain symptomatic, with persistent limitations in functional capacity and health status, underscoring the need for adjunctive therapeutic strategies. Direct cardiac microcurrent (C-MIC) therapy is a non-excitatory bioelectrical intervention device to modulate myocardial remodeling rather than rhythm or acute contractility. C-MIC therapy influence myocardial biology, including pathways related to fibrosis, inflammation, and cellular homeostasis by delivering continuous, subthreshold direct current. Preclinical studies across cardiomyocytes, animal models, and cardiac fibroblasts suggest that microcurrent exposure may attenuate profibrotic signaling, regulate extracellular matrix turnover, and improve calcium handling, providing a mechanistic rationale for reverse remodeling. Early clinical experience, including first-in-human studies and a randomized trial in carefully selected patients with non-ischemic HFrEF, demonstrates feasibility and a consistent signal of improvement in left ventricular function, functional capacity, and patient-reported outcomes. However, the current evidence base remains limited by small sample size, open-label designs, and the absence of sham-controlled evaluation. All available clinical data are derived from surgically implanted systems, and the effectiveness of less invasive configurations remains uncertain. Accordingly, C-MIC should be considered an investigational therapy. Future development will require rigorous mechanistic validation, optimization of device programming and delivery parameters, and confirmation of efficacy in adequately powered, sham-controlled trials to define its role in contemporary HF management.

Keywords Heart Failure with Reduced Ejection Fraction · Cardiac Microcurrent Therapy · Myocardial Remodeling · Bioelectrical Therapy · Reverse Remodeling

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Introduction

Heart failure (HF) remains a leading cause of morbidity, mortality, hospitalization, and healthcare utilization worldwide [1]. In the United States (US), an estimated 6.7 million adults are living with HF [2]. Contemporary guideline-directed medical therapy (GDMT), including renin-angiotensin system inhibitors (RAASi), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 inhibitors (SGLT2is), has substantially improved outcomes in patients with HF with reduced ejection fraction (HFrEF). However, despite receiving optimized HF therapy, many patients remain symptomatic, and continue to experience limitations in exercise capacity and health status [3]. The residual risk has driven interest in adjunctive therapies targeting pathways beyond conventional GDMT. Recent analyses have emphasized the importance of patient-reported outcomes and functional capacity as meaningful measures of therapeutic benefit, while also highlighting the relatively modest gains observed with many contemporary interventions, particularly, in HF patients with preserved ejection fraction (HFpEF) [4]. Device-based therapies, such as cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICDs) reduce sudden cardiac death (SCD) in selected patients, while left ventricular assist devices (LVADs) provide advanced circulatory support for patients with refractory end-stage HF [5]. However, each of these approaches has practical and biological limitations related to patient selection, invasiveness, procedural complexity, durability of benefit, and uncertain generalizability across heterogeneous HF populations [6].

Direct cardiac microcurrent (C-MIC) therapy represents a mechanistically distinct addition to the evolving therapeutic landscape. Unlike CRT or cardiac contractility modulation (CCM), which deliver electrical signals intended to influence activation timing or contractile performance, C-MIC delivers continuous subthreshold direct current in the microampere range without triggering myocardial depolarization. The therapeutic premise is modulation of myocardial biology over time, including pathways related to fibrosis, inflammation, tissue edema, and cellular homeostasis [7]. Early preclinical studies and first-in-human clinical investigations have positioned C-MIC therapy as a promising bioelectronic strategy for HF, particularly in non-ischemic HFpEF, where diffuse remodeling and interstitial fibrosis represent biologically plausible targets. Although clinical evidence remains preliminary and has been derived from relatively small and selected cohorts, the consistency of observed signal across ventricular function, exercise capacity, and patient-reported health status supports continued development of this platform and justifies further evaluation in rigorously controlled clinical trials [7–9].

In this review, we discuss the conceptual basis of C-MIC therapy, summarize the evolution of the C-MIC device platform, and highlight its potential role and current limitations within contemporary HF management, while situating this approach within broader discussions regarding trial design, endpoint selection, and regulatory considerations that are increasingly relevant to innovative HF therapies.

Concept of cardiac microcurrent therapy

C-MIC therapy is based on the application of a continuous, low-intensity direct current in the microampere range that remains below the threshold required to induce myocardial depolarization [10]. Conventional electrical therapies rely on pulsatile stimulation to modify cardiac rhythm or contractility. In contrast, microcurrent delivery establishes a stable electrical field across myocardial tissue without triggering action potentials. Endogenous electrical gradients play an important role in cellular homeostasis and tissue integrity. Direct current fields in the microampere range have been shown to influence fibroblast and endothelial cell behavior, promote angiogenesis, and coordinate wound-healing responses [11, 12]. Disruption of endogenous electrical gradients and alterations in myocardial fluid homeostasis have been associated with impaired lymphatic drainage, myocardial edema, and progressive ventricular dysfunction [13, 14]. Sustained microcurrent delivery has been shown to modulate key cellular pathways involved in adverse remodeling. Preclinical studies demonstrate that exposure to low-intensity direct current alters fibroblast behavior, attenuates fibroblast-to-myofibroblast differentiation, and reduces expression of extracellular matrix components and pro-inflammatory cytokines [7, 9]. These effects are accompanied by partial restoration of intracellular calcium signaling, improved cellular viability, and distinct transcriptional reprogramming toward a less fibrotic and less activated cellular phenotype [9].

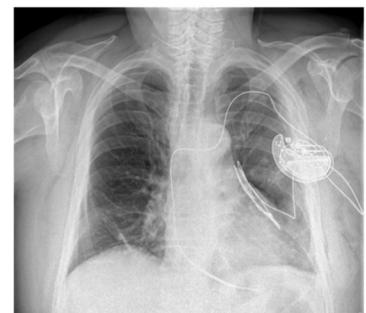
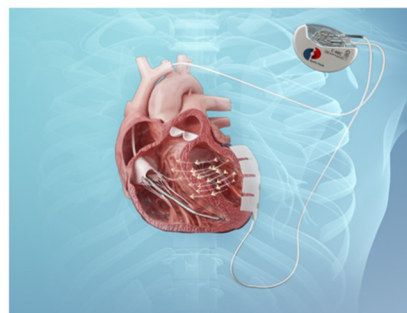
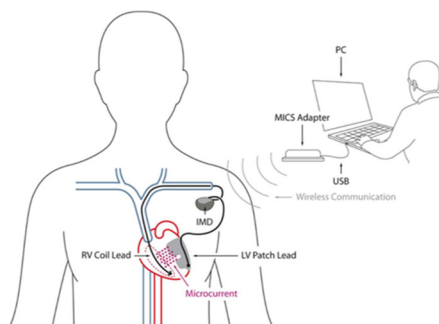
Overview of cardiac microcurrent device therapy

The C-MIC System is an implantable bioelectrical device consisting of three core components: (1) a transvenous intracardiac lead positioned within the right ventricle that functions as the cathode; (2) a left ventricular (LV) patch electrode that functions as the anode, enabling generation of a stable direct-current (DC) electrical field across the myocardium; and (3) an implantable microcurrent device (IMD) that generates the therapeutic microcurrent and to which both electrodes are connected. In contrast to alternating

current (AC) therapies, the C-MIC System delivers a constant low-amplitude direct microcurrent between the cathode and anode. Device programming allows adjustment of current amplitude as well as activation or deactivation of therapy delivery. In early and current clinical studies, microcurrent delivery parameters are standardized across patients rather than individualized.

First-Generation Surgical System

Initial clinical experience with C-MIC therapy was derived from a surgically implanted configuration requiring a limited thoracotomy for placement of an epicardial LV patch electrode [15]. A subcutaneous pocket is first created in the left subclavian region for the implantable generator, followed by transvenous access via the subclavian vein. A right ventricular (RV) lead is advanced under fluoroscopic guidance and anchored within the trabeculae of the RV apex. Subsequently, a left-sided thoracic incision (typically 5–6 cm in the fourth intercostal space) is performed to access the pericardial cavity. The LV patch electrode is then introduced into the pericardial space or positioned over the pericardial sac along the LV free wall, with its conductive surface oriented toward the epicardium. The LV lead is tunneled to the subclavian pocket, where it is connected along with the RV lead to the implantable generator. Following device placement and wound closure, system activation is typically performed 24 h after implantation. This configuration enables delivery of a continuous direct electrical field traversing the ventricular myocardium. However, the requirement for thoracic access, pericardial manipulation, and surgical implantation is associated with increased procedural complexity and a post-implant recovery period typically extending several days, thereby limiting scalability and broader clinical applicability (Fig. 1).



LV = left ventricular; **IMD** = implantable medical device; **RV** = right ventricular; **MICS** = Microcurrent Implantable Cardiac System; **USB** = universal serial bus; **PC** = personal computer.

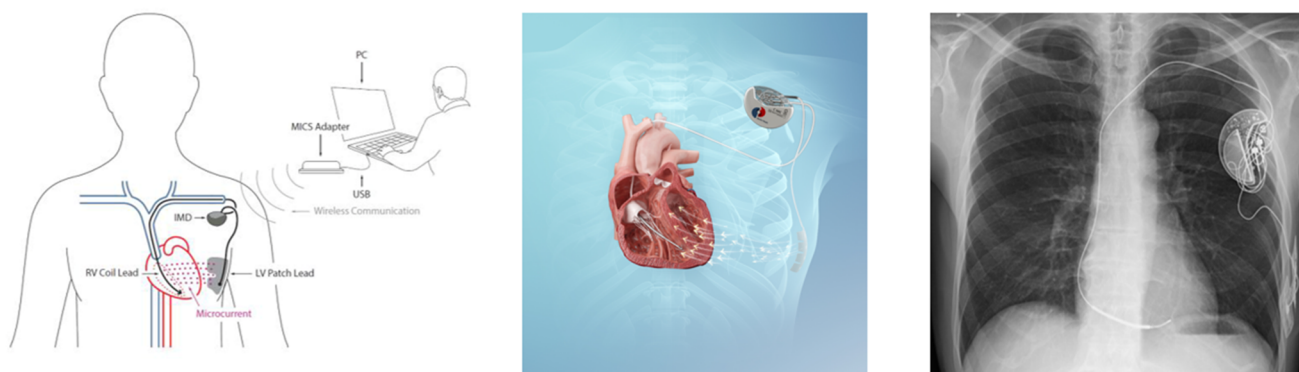
Fig. 1 Surgical Epicardial Implantation of the Left Ventricular Patch via Thoractomy. LV = left ventricular; IMD = implantable medical device; RV = right ventricular; MICS = Microcurrent Implantable Cardiac System; USB = universal serial bus; PC = personal computer

Next generation subcutaneous system

The development of a subcutaneous (SubQ) C-MIC system represents an important evolution aimed at overcoming the procedural limitations of surgically implanted configurations, including peri-procedural risks, prolonged recovery time, and limited scalability in patients with advanced HF [16]. In this approach, the implantable generator is coupled with a transvenous intracardiac lead and a subcutaneous LV patch electrode positioned along the left lateral thoracic wall, thereby eliminating the need for thoracotomy, pericardial access, and surgical lead placement. The implantation workflow is conceptually aligned with contemporary subcutaneous ICD techniques, enabling deployment in the cardiac catheterization or electrophysiology laboratory and substantially reducing procedural complexity. This strategy is currently being evaluated in an ongoing phase 2 study (C-MIC III), which investigates multiple implantation paradigms, including subcutaneous LV patch placement and alternative minimally invasive configurations, in patients with advanced HF. The study is designed to evaluate whether microcurrent therapy delivered through these configurations can improve left ventricular ejection fraction over 6 months of therapy [16]. Importantly, these approaches eliminate the need for open surgical access while preserving the ability to generate a therapeutic trans-myocardial electrical field (Fig. 2).

Preclinical evidence

Preclinical investigations of cardiac microcurrent therapy have focused on whether low-intensity direct current can modulate the structural and cellular substrate of HF (Table 1). In experimental models, this concept has been examined



LV = left ventricular; **SubQ** = subcutaneous; **IMD** = implantable medical device; **RV** = right ventricular; **MICS** = Microcurrent Implantable Cardiac System; **USB** = universal serial bus; **PC** = personal computer.

Fig. 2 Subcutaneous Implantation of the Left Ventricular Patch Using a Minimally Invasive Approach. LV = left ventricular; SubQ = subcutaneous; IMD = implantable medical device; RV = right ventricular;

MICS = Microcurrent Implantable Cardiac System; USB = universal serial bus; PC = personal computer

Table 1 Preclinical Studies of Cardiac Microcurrent Therapy

Study	Model	Intervention	Key Findings	Mechanistic Implication
Kapeller et al. ⁸	Cardiomyocytes + hypertensive rat model	Microcurrent stimulation	↑ Cardiomyocyte proliferation; modulation of MMP-2/9 and TIMP-3/4	Regulation of extracellular matrix turnover
Macfelda et al. ⁷	Hypertensive HF rat model	Continuous epicardial microcurrent (~45 days)	LVEF toward normalization; ↓ LV wall thickness; ↓ collagen I, TGF- β , IL-6	Anti-fibrotic and anti-inflammatory remodeling
Somesh et al. ⁹	Cardiac myofibroblasts (in vitro)	1–2 $\mu\text{A}/\text{cm}^2$ microcurrent	↓ myofibroblast activation; ↓ ECM genes; ↓ cytokines; improved Ca^{2+} signaling	Reversal of myofibroblast phenotype and cellular reprogramming

HF Heart Failure, *LVEF* Left Ventricular Ejection Fraction, *LV* Left Ventricle/Left Ventricular, *MMP* Matrix Metalloproteinase, *TIMP* Tissue Inhibitor of Metalloproteinases, *TGF- β* Transforming Growth Factor Beta, *IL-6* Interleukin-6, *ECM* Extracellular Matrix, $\mu\text{A}/\text{cm}^2$ Microampere per square centimeter, Ca^{2+} Calcium ion

in isolated cardiomyocytes, animal models of adverse remodeling, and more recently, cultured rat cardiac myofibroblasts. These studies suggest that microcurrent exposure can influence extracellular matrix turnover, inflammatory signaling, calcium homeostasis, and cell survival, thereby providing a mechanistic rationale for reverse remodeling. In an early mechanistic study using isolated rat cardiomyocytes and in vivo hypertensive rat models, microcurrent stimulation significantly enhanced cardiomyocyte proliferation in vitro in young rats without apparent morphologic disruption with a more modest effect in adult cardiomyocytes, and altered expression of matrix metalloproteinases (MMP-2 and MMP-9) and their tissue inhibitors (TIMP-3 and TIMP-4). These findings suggest not only a proliferative benefit but also a protective effect on cardiac cells. These findings provided early evidence that microcurrent therapy may influence myocardial remodeling through modulation of matrix turnover and tissue homeostasis, while also underscoring that its biological effects are likely context- and disease-stage dependent [8]. Subsequent experimental work applied continuous epicardial microcurrent to spontaneously hypertensive rats for approximately 45 days. Microcurrent therapy was associated with significant improvements in cardiac structure and function, including normalization of left ventricular ejection fraction (LVEF) and reduction in left ventricular posterior wall thickness. Treatment was accompanied by downregulation of collagen I, transforming growth factor- β , interleukin-6, and selected connexins, consistent with attenuation of inflammatory and profibrotic signaling. Changes in MMP-2 and MMP-9 were not significant in this model, suggesting that the biological effects of microcurrent extends beyond simple MMP suppression and may reflect broader modulation of extracellular

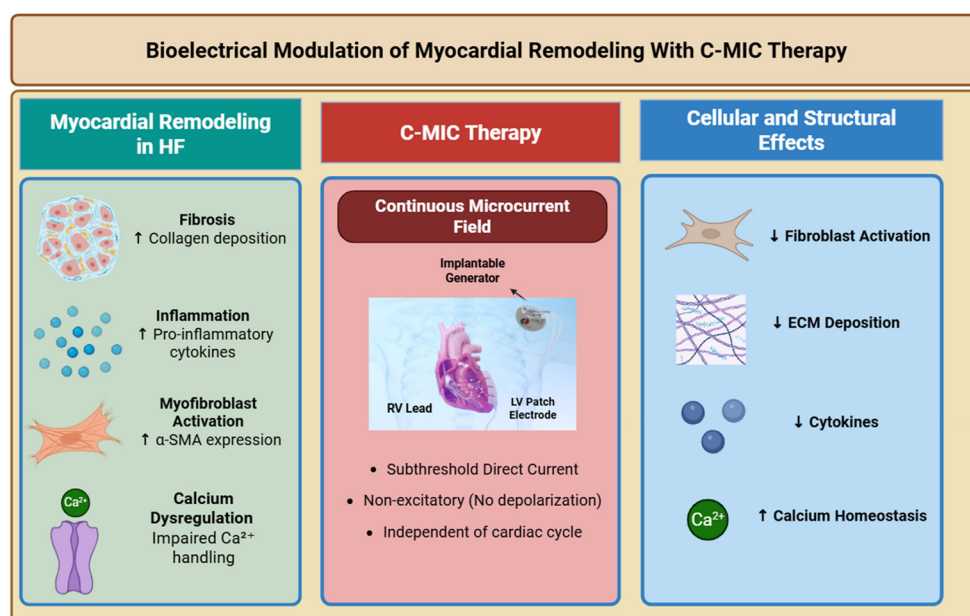
matrix composition, inflammatory activity, and intercellular signaling [7]. More recent work using differentiated rat cardiac myofibroblasts has provided mechanistic insights into the cellular effects of microcurrent stimulation. Exposure to low-intensity direct current (1–2 $\mu\text{A}/\text{cm}^2$) resulted in reduced myofibroblast activation markers, suppressed extracellular matrix components and pro-inflammatory cytokines, and partially restored intracellular calcium signaling, while also decreasing apoptosis and improving cell viability. Transcriptomic profiling further demonstrated that microcurrent induced gene expression signatures characterized by a shift from pro-inflammatory and profibrotic pathways toward cell cycle and repair-associated processes, consistent with partial reversal of the activated myofibroblast state toward a more reparative phenotype [9] (Fig. 3).

Clinical evidence

Initial clinical experience with C-MIC therapy was established in a first-in-human, single-arm pilot study enrolling 10 patients with NYHA Class III non-ischemic dilated cardiomyopathy and LVEF $\leq 35\%$ who underwent surgical implantation of an epicardial LV patch via limited thoracotomy together with a transvenous right ventricular coil lead, connected to a subcutaneous generator (Table 2). Procedural feasibility was achieved in all patients, with no device-related or treatment-related adverse events. Early signals of efficacy were observed within weeks of therapy initiation, including a rapid increase in LVEF (from 32% to 42% at 6 months),

reduction in LV dimensions, and marked improvement in functional capacity. Six-minute walk distance increased substantially (mean ~ 210 m to > 400 m), and the majority of patients improved from NYHA class III to class I. Quality of life scores (SF-36) improved significantly and in parallel with functional measures [10]. Long-term follow-up of the initial cohort ($n = 7$) demonstrated sustained improvements in cardiac function and clinical status up to 2 years after device deactivation following 6 months of active microcurrent therapy. Mean LVEF improvement of approximately 11–12% from baseline was maintained at 2 years, with persistent reductions in LV dimensions, and sustained gains in 6-minute walk distance (~ 190 m above baseline). Improvements in NYHA class and quality of life also remained durable over time. Importantly, no device-related adverse events were reported during extended follow-up, and only one patient required reactivation of therapy [17]. Although limited by sample size and single-arm design, the magnitude and rapidity of improvement across echocardiographic, functional, and quality-of-life measures provided an early proof-of-concept that continuous subthreshold microcurrent delivery could translate into clinically meaningful reverse remodeling. The durability of benefit after device deactivation is particularly noteworthy, as it supports the hypothesis that C-MIC may modify the myocardial substrate rather than simply provide an on-treatment hemodynamic effect. The C-MIC II trial represents the first randomized evaluation of microcurrent therapy in HFrEF. In this open-label, multi-center trial, 70 patients with non-ischemic cardiomyopathy (LVEF 25–35%, NYHA III–IV) were randomized

Fig. 3 Bioelectrical Modulation of Myocardial Remodeling With C-MIC Therapy in Heart Failure
C-MIC= Cardiac Microcurrent; HF = Heart Failure; ECM = Extracellular Matrix; α -SMA = Alpha-Smooth Muscle Actin; Ca^{2+} = Calcium ion; RV = Right Ventricle; LV = Left Ventricle



C-MIC = Cardiac Microcurrent; HF = Heart Failure; ECM = Extracellular Matrix; α -SMA = Alpha-Smooth Muscle Actin; Ca^{2+} = Calcium ion; RV = Right Ventricle; LV = Left Ventricle.

Table 2 Clinical Studies of Cardiac Microcurrent Therapy

Study	Registration ID	Design	Population	N	Implant Approach	Follow-up	Key Outcomes
C-MIC I	DRKS00015708	First-in-human (single-arm)	Non-ischemic HFrEF (NYHA III)	10	Surgical (thoracotomy)	6 months	↑ LVEF (~+10%); ↑ 6MWD (210 → 418); improved QoL (via SF-36)
C-MIC I Follow-up	DRKS00027419	Long-term observational	Same cohort post deactivation	7	Surgical (Existing Implant)	2 years	Sustained ↑ LVEF (~+11–12%); durable ↑ 6MWD (~+191 m); preserved NYHA and QoL gains
C-MIC II	NCT04662034	Open-label RCT	Non-ischemic HFrEF (NYHA III–IV); LVEF 25–35%	70	Surgical (thoracotomy)	6 months	↑ LVEF (+5.1% vs. control); ↑ KCCQ (+41 points); ↑ 6MWD (~+165 m) vs. 20 m in control; 81% vs. 13% > 1 NYHA class improvement
C-MIC II Extension	NCT05189860	Long-term observational follow-up	Post-RCT device cohort	31 (planned)	Surgical	Ongoing	Mortality, hospitalizations, adverse events at 2 years
C-MIC III	NCT06920030	Feasibility/exploratory	Advanced HF	22 (planned)	Subcutaneous (SubQ)	Ongoing	LVEF change from baseline at 6 months

HF heart failure, HFrEF heart failure with reduced ejection fraction, NYHA New York Heart Association, LVEF left ventricular ejection fraction, RCT randomized controlled trial, 6MWD six-minute walk distance, QoL quality of life, SF-36 36-item Short Form Health Survey, KCCQ Kansas City Cardiomyopathy Questionnaire, SubQ subcutaneous

to C-MIC plus GDMT versus medical therapy alone.¹⁵ At 6 months, C-MIC therapy resulted in a significant improvement in LVEF compared with control (mean treatment difference + 5.1%; $p < 0.001$). Consistent improvements were observed across secondary endpoints, including functional capacity and patient-reported outcomes. The proportion of patients achieving ≥ 1 NYHA class improvement was markedly higher in the device group ($\approx 81\%$ vs. 13%), with substantial gains in KCCQ score and 6-minute walk distance (mean increase ~ 165 m vs. ~ 20 m in controls). No device-related mortality was observed. However, procedural complications and serious adverse events were reported in the device group, including hemothorax in two patients, pericardial effusion in one patient, and worsening renal function in one patient. Importantly, the randomized C-MIC II experience moved the field beyond feasibility by demonstrating that the observed signal was not confined to uncontrolled pilot experience. The concordant improvement in LVEF, symptoms, exercise capacity, and KCCQ supports a clinically coherent treatment effect, even though the absence of blinding and sham control precludes definitive estimation of its magnitude.

From a mechanistic standpoint, direct C-MIC therapy may be more relevant to non-ischemic cardiomyopathy, where diffuse myocardial remodeling, interstitial fibrosis, and altered cellular signaling play a central role in disease progression. In this context, modulation of extracellular matrix turnover and fibroblast activation may possibly

translate into reverse remodeling. In contrast, ischemic cardiomyopathy is characterized by focal scar burden, regional scar formation, and irreversible myocardial injury, factors that may limit responsiveness to bioelectric modulation [18, 19]. The extent to which microcurrent therapy can influence established scar tissue or border-zone remodeling remains uncertain. To date, clinical experience with C-MIC therapy has been limited to carefully selected patients with non-ischemic HFrEF. The clinical effects of microcurrent therapy in patients with ischemic HF remains unknown and has not yet been systematically evaluated. Accordingly, any extrapolation of potential benefit to ischemic populations should be considered speculative. Future studies will be required to determine whether microcurrent therapy provides meaningful benefit in ischemic HF, whether treatment effects differ according to HF etiology, and which patient subgroups are most likely to respond. These questions are particularly important given the high prevalence of ischemic HF in routine clinical practice and underscore the need for etiology-specific analyses in subsequent controlled trials. Available clinical experience with C-MIC therapy is notable for the consistency of benefit observed across independent studies and across multiple domains of HF status. Improvements have been reported in ventricular structure and function, functional capacity, NYHA class, and patient-reported health status, including in randomized clinical experience. Particularly notable is the persistence of structural and clinical improvement in some patients despite discontinuation

of active therapy, a finding that raises the possibility that C-MIC may exert disease-modifying effects rather than merely transient symptomatic benefit. Although these observations remain hypothesis-generating and require confirmation in adequately powered, sham-controlled trials, the consistency of signal across mechanistic, structural, and clinical domains supports continued investigation of C-MIC as a promising emerging bioelectrical therapy for HF. Persistence of benefit following device deactivation in early follow-up further supports the hypothesis that C-MIC may act through durable remodeling rather than temporary physiological support.

Future directions

Despite encouraging early results of C-MIC therapy, several fundamental questions remain before its role in HF management can be clearly defined. Current clinical evidence is limited to carefully selected patients with non-ischemic HFrEF. Whether response to microcurrent therapy is substrate-dependent remains unknown. Given its proposed mechanism of action targeting diffuse myocardial remodeling, patients with non-ischemic cardiomyopathy may represent the most biologically plausible responders. However, the potential role of C-MIC therapy in ischemic cardiomyopathy, HFpEF, or earlier stages of HF requires systematic evaluation. Identification of patient phenotypes most likely to benefit will be essential to avoid dilution of treatment effect within heterogeneous HF populations. Moreover, given the substantial improvements observed in patient-reported outcomes, functional capacity, and early changes in left ventricular function, distinguishing true biological effects from placebo response is critical. This consideration is particularly important in device-based therapies, where invasive procedures and patient expectations may amplify perceived benefit. Future studies should incorporate blinded endpoint assessment, sham procedures when feasible, and standardized optimization of background GDMT to ensure accurate estimation of treatment effect.

Optimal parameters of C-MIC delivery, including current amplitude, spatial field distribution, duration of therapy, and the potential need for re-treatment, remain undefined. Initial clinical studies employed standardized programming without individualized titration. Future investigations should explore whether treatment response is dose-dependent and whether patient-specific optimization can enhance therapeutic efficacy. Integration of imaging modalities, such as cardiac magnetic resonance imaging to quantify fibrosis, may help guide therapy targeting and monitor biological response. Although transition from surgically implanted

epicardial systems to minimally invasive subcutaneous configurations represents an important step toward broader clinical application, all currently available efficacy data have been derived from surgical implanted systems. Whether less invasive approaches can reproduce similar therapeutic effects remains unknown. Comparative evaluation of device configurations, procedural safety, and long-term durability will therefore be necessary.

Although preclinical data support a role for microcurrent therapy in modulating fibrosis, inflammation, and cellular signaling, the dominant mechanism of action in human HF remains uncertain. Future studies should incorporate mechanistic endpoints, including imaging-based assessment of myocardial fibrosis, circulating biomarkers of extracellular matrix turnover, and transcriptomic or proteomic profiling where feasible. Establishing a clear mechanistic link between microcurrent delivery and reverse remodeling will be important for broader clinical acceptance. Additionally, device-related complications, including infection risk, and management following completion of therapy, remain incompletely characterized over longer term follow-up and will become increasingly important as therapy is evaluated in broader and more comorbid patient populations. Potential adverse events associated with the C-MIC system are not limited to procedural or surgical complications related to device implantation. Theoretical non-surgical risks associated with chronic microcurrent delivery to the myocardium may include adverse effects on myocardial tissue, electrical stability, arrhythmogenesis, myocardial inflammation or fibrosis, lead-tissue interface changes, or other unforeseen long-term biologic effects related to continuous current application. To date, however, neither the preclinical studies nor the cumulative clinical experience across C-MIC investigations has identified a specific safety signal suggesting harmful myocardial effects associated with chronic microcurrent therapy.

To further assess the long-term safety of leaving the C-MIC System implanted in situ following completion of therapy, extended clinical follow-up studies and long-term registry programs are currently ongoing. Preliminary longer-term observations following discontinuation of active therapy have been encouraging and have not identified evidence of device-related myocardial injury, progressive electrical instability, or clinically meaningful late safety concerns attributable to chronic microcurrent exposure. Nevertheless, continued long-term surveillance remains important given the novel mechanism of action and the relatively limited cumulative clinical experience to date.

At present, the duration of continuous active C-MIC therapy is primarily limited by current device battery longevity, which supports approximately 8–12 months of therapy

delivery. Future generations of the C-MIC System are expected to incorporate improvements in battery technology, energy efficiency, and overall device design to support longer treatment duration and broader therapeutic application. Future investigations should also evaluate the implications of chronic implantation, device extraction, and potential need for therapy reactivation. Given the high prevalence of implantable cardioverter-defibrillators (ICDs), cardiac resynchronization therapy (CRT) devices, pacemakers, and other cardiac implantable electronic devices (CIEDs) in patients with heart failure, additional testing and evaluation of potential interactions between the C-MIC system and concomitantly implanted CIEDs are planned. These activities are intended to further characterize potential electrical, sensing, telemetry, and functional interactions, and to define appropriate implantation techniques, lead positioning strategies, and device programming recommendations to support safe concomitant device use.

At present, concomitant implantation of the C-MIC system with other active cardiac implantable electronic devices is not permitted, as compatibility and interaction testing have not yet been fully completed. C-MIC therapy introduces a novel paradigm of bioelectrical modulation of myocardial remodeling that is distinct from traditional rhythm- or contractility-based interventions. Current evidence remains insufficient to establish clinical efficacy or define its role within contemporary HF treatment algorithms. Future adoption of C-MIC therapy will depend on rigorous validation of its mechanism of action, reproducibility of effectiveness in controlled trials, and clear identification of the patient populations most likely to derive meaningful clinical benefit.

Conclusion

C-MIC therapy represents a novel bioelectrical approach to HF treatment that is mechanistically distinct from conventional rhythm- or contractility-based device therapies. Preclinical studies support a biologically plausible role in modulating fibrosis, inflammation and myocardial remodeling. Early clinical studies suggest feasibility and a consistent signal of improvement in left ventricular function, symptoms, and functional capacity in carefully selected patients with non-ischemic HFrEF. However, current evidence remains limited by small sample sizes, open-label study designs, and the absence of sham-controlled evaluation. The future role of C-MIC therapy will depend on rigorous mechanistic validation, confirmation of efficacy in adequately powered controlled clinical trials and identification of the patient phenotypes most likely to derive meaningful clinical benefit.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests 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 Kallel and Somesh are Berlin Heals employees.

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References

1. Writing Committee Members (2026) HF STATS 2025: heart failure epidemiology and outcomes statistics an updated 2025 report from the Heart Failure Society of America. *J Card Fail* 32(2):439–498. <https://doi.org/10.1016/j.cardfail.2025.07.007>
2. Bozkurt B, Ahmad T, Alexander KM et al (2023) Heart failure epidemiology and outcomes statistics: a report of the Heart Failure Society of America. *J Card Fail* 29(10):1412–1451. <https://doi.org/10.1016/j.cardfail.2023.07.006>
3. Greene SJ, Xu H, Chiswell K et al (2026) Residual risk despite quadruple medical therapy for men vs women hospitalized for heart failure with reduced ejection fraction. *JACC Heart Fail.* <https://doi.org/10.1016/j.jchf.2026.102939>

4. Rasool W, Siddiqi AK, Khan LA (2025) Importance of patient-reported outcomes in cardiovascular illnesses. *Glob Cardiol* 3(2). <https://doi.org/10.4081/cardio.2025.69>
5. Mody R, Nee Sheth AB, Dash D et al (2024) Device therapies for heart failure with reduced ejection fraction: a new era. *Front Cardiovasc Med* 11:1388232. <https://doi.org/10.3389/fcvm.2024.1388232>
6. Pinto FJ, Anker SD, Abraham WT et al (2025) The Global Implementation Guidelines Initiative: how to optimize cardio-renal-metabolic care worldwide. *Glob Cardiol* 3(1). <https://doi.org/10.4081/cardio.2025.68>
7. Macfelda K, Kapeller B, Holly A et al (2017) Bioelectrical signals improve cardiac function and modify gene expression of extracellular matrix components. *ESC Heart Fail* 4(3):291–300. <https://doi.org/10.1002/ehf2.12169>
8. Kapeller B, Mueller J, Losert U, Podesser BK, Macfelda K (2016) Microcurrent stimulation promotes reverse remodelling in cardiomyocytes. *ESC Heart Fail* 3(2):122–130. <https://doi.org/10.1002/ehf2.12080>
9. Bachamanda Somesh D, Jürchott K, Giesel T et al (2024) Microcurrent-mediated modulation of myofibroblasts for cardiac repair and regeneration. *Int J Mol Sci* 25(6):3268. <https://doi.org/10.3390/ijms25063268>
10. Kosevic D, Wiedemann D, Vukovic P et al (2021) Cardio-microcurrent device for chronic heart failure: first-in-human clinical study. *ESC Heart Fail* 8(2):962–970. <https://doi.org/10.1002/ehf2.13242>
11. Li X, Kolega J (2002) Effects of Direct Current Electric Fields on Cell Migration and Actin Filament Distribution in Bovine Vascular Endothelial Cells. *J Vasc Res* 39(5):391–404. <https://doi.org/10.1159/000064517>
12. Lu C, Kolbenslag J, Nüssler AK et al (2021) Direct current electrical fields improve experimental wound healing by activation of cytokine secretion and Erk1/2 pathway stimulation. *Life Basel* 11(11):1195. <https://doi.org/10.3390/life11111195>
13. Kiseleva DG, Kirichenko TV, Markina YV, Cherednichenko VR, Gugueva EA, Markin AM (2024) Mechanisms of Myocardial Edema Development in CVD Pathophysiology. *Biomedicines* 12(2):465. <https://doi.org/10.3390/biomedicines12020465>
14. Pu Z, Shimizu Y, Hayashi T et al (2023) Cardiac lymphatic insufficiency leads to diastolic dysfunction via myocardial morphologic change. *JACC Basic Transl Sci* 8(8):958–972. <https://doi.org/10.1016/j.jacbs.2023.01.008>
15. Rame JE, Schmitt JD, Kosevic DN et al (2025) Cardio-microcurrent device treatment for heart failure with reduced ejection fraction: results from the C-MIC II open-label randomized controlled trial. *Eur J Heart Fail* 27(10):1837–1849. <https://doi.org/10.1002/ehf2.3763>
16. Berlin Heals GmbH. Pilot Study to Investigate the Performance of the Cardiac Microcurrent (C-MIC) System With a Less Invasively Placed Left Ventricular Lead. *clinicaltrials.gov* (2026) Accessed March 26, 2026. <https://clinicaltrials.gov/study/NCT06920030>
17. Kosevic DB, Radak U, Vukovic P et al (2025) Two-year outcomes of a cardiac microcurrent device in chronic heart failure: a first-in-human pilot study. *ESC Heart Fail* 12(5):3264–3275. <https://doi.org/10.1002/ehf2.15369>
18. Cabac-Pogorevici I, Muk B, Rustamova Y, Kalogeropoulos A, Tzeis S, Vardas P (2020) Ischaemic cardiomyopathy. Pathophysiological insights, diagnostic management and the roles of revascularisation and device treatment. Gaps and dilemmas in the era of advanced technology. *Eur J Heart Fail* 22(5):789–799. <https://doi.org/10.1002/ehf2.1747>
19. Del Buono MG, Moroni F, Montone RA, Azzalini L, Sanna T, Abbate A (2022) Ischemic Cardiomyopathy and Heart Failure After Acute Myocardial Infarction. *Curr Cardiol Rep* 24(10):1505–1515. <https://doi.org/10.1007/s11886-022-01766-6>

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