Regarding the included study, Impulse Dynamics is providing this information for educational purposes only. Some or all the studied uses of the Optimizer described in the article have not been approved or cleared by the FDA.

INDICATIONS

The safety and performance of the OPTIMIZER Smart System is based on clinical investigations conducted with the prior generation devices, the OPTIMIZER IVs and III Systems, given the similarities between the Systems with regard to function, intended use, design characteristics, and the CCM™ signals. Summaries of these studies are available on Impulse Dynamics' website. (http://www.impulse-dynamics.com/int/for-physicians/clinical-data/)

The OPTIMIZER Smart System, which delivers CCM™ therapy, is indicated to improve 6-minute hall walk distance, quality of life and functional status of NYHA Class III heart failure patients who remain symptomatic despite guideline directed medical therapy, who are in normal sinus rhythm, are not indicated for CRT, and have an LVEF ranging from 25% to 45%.

The OPTIMIZER Smart system delivers non-excitatory CCM™ signals to the heart and has no pacemaker or ICD functions.

CONTRAINDICATIONS AND PRECAUTIONS

Use of the OPTIMIZER Smart system is ***contraindicated*** *in:*

1. Patients with permanent or long-standing persistent atrial fibrillation or flutter
2. Patients with a mechanical tricuspid valve
3. Patients in whom vascular access for implantation of the leads cannot be obtained

WARNINGS

Potential Complications of Device Implantation

Just like any surgical procedure, implantation of an OPTIMIZER Smart IPG is associated with a certain risk. Complications of IPG implantation reported in the literature include but are not limited to: arrhythmias induced by the IPG, including life-threatening arrhythmias (e.g., ventricular fibrillation), infection, skin necrosis, device migration, hematoma formation, seroma and histotoxic reactions (also see: Potential Adverse Effects in the Appendix).

Programming high sensitivities (i.e., sensitivity settings less than 2 mV) may increase the system's susceptibility to electromagnetic interference, which could either inhibit or trigger signal delivery.

Acute and chronic complications reported in the literature include, but are not limited to: lead fracture, lead displacement, atrial or ventricular perforation, and rare cases of pericardial tamponade. Perforation of the ventricular wall can induce direct stimulation of the phrenic nerve or the diaphragm. An impedance change demonstrated on a check-up can be indicative of lead fracture, lead displacement, or perforation (also see: Potential Adverse Effects in the Appendix).

In very rare cases (<1%), transvenous lead placement can also lead to venous thrombosis and subsequent SVC syndrome.

Loss of sensing shortly after implant can be the result of lead displacement. In addition, loss of CCM™ signal delivery could be due to a lead fracture.

Atrial and Ventricular Arrhythmias Potentially Caused by Lead Implantation

As noted above, the use of transvenous leads may lead to arrhythmias, some of which may be life-threatening such as ventricular fibrillation and ventricular tachycardia. The use of screw-in leads such as those used for CCM™ signal delivery also have the potential of causing conduction disturbances such as bundle branch block. These can be minimized by performing the implant with the use of fluoroscopic guidance, ensuring that the leads are in appropriate position prior to fixation and by limiting the number of lead manipulations. Please read and follow all directions of the original Physician Manual for the leads that you intend to use to minimize adverse events connected to lead implantation.

Ventricular Arrhythmias Potentially Caused by CCM™ Signals

CCM™ signals are of greater strength than that of typical pacing pulses and are thus capable of eliciting activation of cardiac tissue when delivered outside of the absolute refractory period. CCM™ signals delivered outside of the ventricular absolute refractory period thus have the potential of causing signal-induced arrhythmias (some of which may be life-threatening, such as ventricular fibrillation and tachycardia). For this reason, it is imperative that CCM™ signal delivery parameters be chosen carefully. Most importantly, the various settings related to conditions that inhibit CCM™ signal delivery (e.g. Long AV Delay, Short AV Delay, LS Alert Window, refractory periods, and IEGM sensitivities) must be selected to allow delivery of CCM™ signals only on normally conducted (e.g. non-arrhythmic) beats, but inhibit them on beats of suspected ectopic or premature origin.

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In addition, CCM™ signals may cause changes in the electrical conduction of tissue. For this reason, the delivery of CCM™ signals to the ventricular septum has the potential of causing bundle branch block that could lead to bradycardia. Through similar mechanisms, CCM™-induced changes in the electrical conduction of the myocardium have the potential of inducing tissue refractoriness that may facilitate the induction of reentrant tachyrrhythmias. It is recommended that the patient's rhythm be monitored carefully for changes in rhythm when CCM™ signals are delivered during lead implantation, as well as during first activation of the OPTIMIZER Smart IPG and subsequent follow-up visits. Changes in ventricular rhythm caused by the delivery of CCM™ signals may require relocating the leads, as well as reprogramming the CCM™ delay and amplitude to settings that do not cause changes in the patient's ventricular rhythm.

Atrial Arrhythmias Potentially Caused by CCM™ Signals

Atrial and supraventricular arrhythmias could theoretically be initiated when CCM™-induced ventricular activity is conducted retrograde to the atria, resulting in premature atrial depolarization. The OPTIMIZER Smart IPG may sense the ventricular activation resulting from the retrograde-induced atrial event and deliver CCM™ as programmed. In addition, strong CCM™ signals delivered through leads implanted in basal position close to the atria have the potential of directly stimulating the atria. If CCM™ delivery causes atrial activation through either of these mechanisms, and the atrial signal is then conducted to the ventricles, the cycle may develop into a condition similar to pacemaker-mediated tachycardia (PMT).

The main variables that may have an impact on CCM™ events leading to atrial activation are the location of lead placement on the right ventricular septum, CCM™ amplitude, and CCM™ delay. To prevent the occurrence of atrial arrhythmias due to CCM™ signal delivery, it is recommended that basal lead implant locations be avoided. The potential for direct atrial activation by CCM™ signals can be tested during the implant by delivering the strongest possible CCM™ signal 20 to 30 ms longer than the LS-CCM delay with which the IPG will be ultimately programmed, as long as this delay places the CCM™ signal, including its 40 ms balancing phase, completely within the ventricular absolute refractory period, and monitoring for atrial activations. In such a case, the delay should be programmed to a longer value and lack of atrial activation confirmed. Besides proper lead location and CCM™ parameter programming, the "Atrial Tachycardia Rate" must be programmed to a sufficiently low value as a protective measure against atrial arrhythmias that could be induced by CCM™ signal delivery.

APPENDIX

Potential Adverse Effects

Examples of adverse effects that may occur as the result of the surgical procedure are listed below in the order of their clinical severity:

1. Death
2. Arrhythmias (brady- or tachyarrhythmias including fibrillation)
3. Stroke or TIA ("transient ischemic attack")
4. Respiratory/ventilatory failure
5. RA/RV perforation
6. Hemorrhage
7. Infection
8. Pleura or pericardial effusion
9. Pneumothorax

Examples of additional adverse effects potentially occurring secondary to CCM™ signal delivery are listed in the table below in the order of their clinical severity:

1. Abnormal cardiac function
2. Atrial and Ventricular Tachyarrhythmias
3. Atrial and Ventricular Bradyarrhythmias
4. Worsening heart failure
5. Myocardial tissue damage
6. Chest pain

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PREVENTION WILEY CLINICAL CARDIOLOGY

CLINICAL INVESTIGATIONS

Long-term results of combined cardiac contractility modulation and subcutaneous defibrillator therapy in patients with heart failure and reduced ejection fraction

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Background: Cardiac contractility modulation (CCM) is an electrical-device therapy for patients with heart failure with reduced ejection fraction (HFrEF). Patients with left ventricular ejection fraction (LVEF) ≤35% also have indication for an implantable cardioverter-defibrillator (ICD), and in some cases subcutaneous ICD (S-ICD) is selected.

Hypothesis: CCM and S-ICD can be combined to work efficaciously and safely.

Methods: We report on 20 patients with HFrEF and LVEF ≤35% who received CCM and S-ICD. To exclude device interference, patients received intraoperative crosstalk testing, S-ICD testing, and bicycle exercise testing while CCM was activated. Clinical and QOL measures before CCM activation and at last follow-up were analyzed. S-ICD performance was evaluated while both CCM and S-ICD were active.

Results: Mean follow-up was 34.3 months. NYHA class improved from 2.9 ± 0.4 to 2.1 ± 0.7 ($P < 0.0001$), Minnesota Living With Heart Failure Questionnaire score improved from 50.2 ± 23.7 to 29.6 ± 22.8 points ($P < 0.0001$), and LVEF improved from 24.4% ± 8.1% to 30.9% ± 9.6% ($P = 0.002$). Mean follow-up time with both devices active was 22 months. Three patients experienced a total of 6 episodes of sustained ventricular tachycardia, all successfully treated with first ICD shock. One case received an inappropriate shock unrelated to the concomitant CCM. One patient received an LVAD, so CCM and S-ICD were discontinued.

Conclusions: CCM and S-ICD can be successfully combined in patients with HFrEF. S-ICD and CCM remain efficacious when used together, with no interference affecting their function.

KEYWORDS

Cardiac Contractility Modulation, Heart Failure, Subcutaneous ICD

1 | INTRODUCTION

Cardiac contractility modulation (CCM) is an electric device therapy that applies a nonactivating electrical impulse to the cardiac muscle during the absolute refractory period.[1] Indications for CCM include patients with reduced left ventricular ejection fraction (LVEF) and normal or slightly prolonged QRS duration, thus filling a therapeutic gap among the two-thirds of patients with heart failure (HF) who do not meet criteria for cardiac resynchronization therapy.[2,3]

Two prospective, randomized, multicenter studies have demonstrated significant improvements of New York Heart Association (NYHA) functional class, quality of life indexed by Minnesota Living with Heart Failure Questionnaire (MLWHFQ), and peak oxygen uptake during cardiopulmonary exercise testing in patients with symptomatic HF with reduced LVEF (HFrEF).[4–6] Although current data show improvements in symptoms and functional cardiopulmonary capacity, data on cardiovascular outcome are limited. Randomized controlled trials were not powered to detect statistically

significant changes of cardiovascular mortality.[4,5] A recent meta-analysis of published data found that CCM did not lower the risk of severe cardiovascular adverse events[7]; nevertheless, retrospective observations suggest that mortality rates in patients treated with CCM, especially in those with normal QRS and with moderate disease stage, were lower than estimated by the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) model, by the Seattle Heart Failure Model (SHFM) model risk scores, or by a control group.[8–10] Recently, in the European Society of Cardiology (ESC) Guidelines on Acute and Chronic Heart Failure (2016), it was stated that CCM may be considered in selected patients with HF.[3]

Because many patients receiving CCM have an LVEF ≤35%, an implantable cardioverter-defibrillator (ICD) is also indicated. In most of these cases, a separate implantation procedure is performed using intracardiac defibrillation leads and a separate implantable pulse generator, as no device currently combines CCM and ICD capabilities into a single device. As a result, CCM has been extensively studied in combination with intracardiac ICDs, revealing little interference between devices. However, the need for 2 devices, both with intracardiac leads, poses the risk of additional adverse events because the cumulative risk of electrode complications, such as systemic infections or thrombosis of central venous lines, increases with the number of implanted intracardiac leads.[11]

The subcutaneous implantable cardioverter-defibrillator (S-ICD) was developed as an alternative to the transvenous ICD without the need to implant transvenous leads.[12,13] Its safety and effectiveness have been established,[14,15] and the therapy has been included in current guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death.[15,16]

In this present study, we analyzed the long-term clinical outcome of patients in whom both CCM and S-ICD were implanted.

2 | METHODS

2.1 | Patients

Twenty patients with symptomatic HF and reduced LVEF (≤35%) received CCM implantation in our tertiary university HF center between March 2009 and May 2016. Patients were required to be on stable guideline-directed medical therapy for HF, including a β-blocker, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, and mineralocorticoid receptor antagonist. Informed consent was obtained from all subjects. This study was approved by the local ethics committee.

Each of these 20 patients also received an S-ICD. In 14 cases, the S-ICD was implanted as the first ICD device, with CCM implanted during follow-up. In 6 cases, a formerly implanted transvenous ICD was replaced by the S-ICD system. After implantation of CCM, patients were followed per standard clinical practice at 3- to 4-month intervals. At each follow-up visit, clinical assessments were obtained, including NYHA class, quality of life (MLWHFQ), 12-vector electrocardiogram recordings, and NT-proBNP levels. In addition, transthoracic echocardiograms were performed every 6 months. Frequency of procedural complications or revisions, programming changes, and incidence of appropriate or inadequate device detections as well as clinical data and therapies were recorded.

2.2 | CCM device description and implantation procedure

In 14 patients, the Optimizer IVs system (Impulse Dynamics Inc., Orangeburg, NJ) was implanted. Six patients received the prior model, the Optimizer III. The implantation procedure has been described in detail.[2] Briefly, the Optimizer device is implanted into the pectoral region in a minimally invasive procedure utilizing 3 bipolar pacemaker leads that are introduced into the right side of the heart via the subclavian vein (Tendril STS; St. Jude Medical/Abbott, St. Paul, MN). One of these leads is placed into the right atrium to detect the electrical activity as part of the algorithm for timing CCM delivery. CCM signal delivery occurs through the remaining 2 leads, positioned at the ventricular septum, after electrical activity is sensed in those leads. Active CCM treatment is typically programmed for 5 or 7 segments of 1 hour spread equally throughout the day.

2.3 | S-ICD device description, implantation procedure, and device testing

The S-ICD system (Emblem; Boston Scientific, Marlborough, MA) and its implantation procedure have been described in detail.[2,17,18] The lead is positioned parallel to the sternum (normally 1 to 2 cm to the left) and the pulse generator is positioned in the left axillary region at the level of the sixth rib. The 2 sensing electrodes of the subcutaneous lead and the IPG itself represent 3 vector projections of electrical conduction through the heart. The S-ICD automatically selects an optimal vector for adequate rhythm sensing and to avoid T-wave oversensing or double QRS counting. A conditional shock zone incorporating a feature-extraction technique can be programmed between rates of 170 and 250 bpm. S-ICD therapy within conditional shock zone and shock zone consists of an 80-J shock, with the potential for temporary transthoracic backup pacing for 30 seconds.

At the end of each S-ICD implantation procedure, device testing is performed. Ventricular fibrillation (VF) is induced by a high-voltage 50-Hz signal. During S-ICD testing, VF is terminated by a 65-J shock to ensure a margin of safety.

Every patient implanted with an S-ICD receives routine bicycle ergometer testing 1 to 7 days postoperatively. Subsequently, different provocation maneuvers are performed, which have been described previously.[17] The 3 sensing vectors of the S-ICD are monitored in real time during these tests to exclude oversensing or double counting that occurs during exercise or sinus tachycardia. In case of an unclear signal, oversensing, or double counting during exercise or provocation maneuvers, the automatically selected sensing vector can be changed manually to select the clearest signal. Characteristics of a clear signal are a stable baseline, high signal amplitude, and a high QRS/T ratio.

2.4 | Combining CCM and S-ICD

Three tests were performed upon insertion of the second device (either CCM or S-ICD) to exclude device interactions (Table 1).

TABLE 1 Safety tests for combination of Optimizer CCM and S-ICD

Test 1: Intraoperative Crosstalk Test
Activate both devices and monitor all 3 sensing configurations of S-ICD.
Temporarily program CCM to various therapy timings (ie, test longer delay of CCM signal delivery within the QRS complex) to exclude potential double counting or oversensing by the S-ICD even at extremes of CCM programming intervals.
Program S-ICD vector with the clearest result as selected sensing vector.
In case CCM is implanted after S-ICD, repositioning of CCM leads is possible during the implantation procedure to a location where the CCM signal shows fewer artifacts on the S-ICD sensing vectors.
Test 2: Intraoperative S-ICD Testing
Turn CCM signal delivery to "on" and induce VF.
CCM device contains a built-in algorithm that inhibits delivery of a CCM signal when irregular electrical activity is detected (such as premature atrial or ventricular complexes or sensing defects). This is designed to eliminate the possibility of CCM signal delivery during a T-wave.
When CCM detects ventricular arrhythmias, CCM signal delivery ceases.
S-ICD can properly recognize the arrhythmia and VF is terminated through ICD shock delivery.
Test 3: Postoperative Bicycle Ergometer Testing and Provocation Maneuvers
Turn CCM signal delivery to "on" and monitor all 3 sensing configurations of S-ICD.
Perform bicycle ergometer testing.
Perform provocation maneuvers (eg, aggregate manipulation, physical maneuvers, standing and supine posture).
Select sensing vector with the clearest signal, avoiding double counting or oversensing as well as noise that was produced by the CCM device.

Abbreviations: CCM, cardiac contractility modulation; ICD, implantable cardioverter-defibrillator; S-ICD, subcutaneous implantable cardioverter-defibrillator; VF, ventricular fibrillation.

2.5 | Statistical analysis

Changes in each tested parameter were calculated for each patient comparing baseline to last follow-up visit. Data are reported as mean ± SD, and the *t* test was used for the univariate analysis.

3 | RESULTS

3.1 | Patient population

Baseline characteristics of the 20 CCM patients are given in Table 2. Mean age at CCM implant was 54.3 ± 11.5 years, and mean baseline LVEF was 24.4% ± 8.1%. Thirty-five percent of patients had ischemic cardiomyopathy.

In the course of their treatment all 20 patients received an S-ICD (Figure, A). In 14 patients, the S-ICD was the first implanted ICD device. Thirteen of these 14 patients had a primary preventive ICD indication because LVEF was ≤35% for ≥3 months of optimal medical treatment. One of these 14 patients had a secondary preventive ICD indication because he had a history of life-threatening sustained ventricular tachyarrhythmias in addition to LVEF ≤35%. These 14 patients received their S-ICDs before CCM implantation.

In 6 patients, a formerly implanted transvenous ICD was replaced by an S-ICD due to ICD lead defects. In 3 of these 6 patients, the first transvenous device was implanted for primary prevention and in the other 3 patients for secondary prevention.

Taken together, 80% of the study subjects underwent implantation of their first ICD for primary prevention and 20% for secondary prevention (Table 2).

3.2 | Operation results

S-ICD and CCM implantations were successfully performed in all patients.

TABLE 2 Characteristics of the study population before CCM implantation

Characteristic	Value
Age, y	54.3 ± 11.5
Male sex	18 (90)
Weight, kg	103.5 ± 23.7
BMI, kg/m^2	32.5 ± 7.2
SBP, mm Hg	118.2 ± 15.7
LVEF, %	24.4 ± 8.1
DM	4 (20)
CKD	8 (40)
Current smoker	8 (40)
Chronic lung disease	7 (35)
QRS width, ms	108.9 ± 19.4
HF etiology	
Ischemic	7 (35)
DCM	13 (65)
NYHA class	
II	3 (15)
III	16 (80)
IV	1 (5.0)
Medications	
ACEI/ARB	20 (100)
β-Blocker	19 (95)
MRA	17 (85)
Ivabradine	4 (20)
Diuretic	20 (100)
Amiodarone	4 (20)
Cr, mg/dL	1.37 ± 0.83
NT-proBNP, pg/mL	2882.7 ± 5456.6
ICD indication	
Primary preventive	16 (80)
Secondary preventive	4 (20)
Patients with former transvenous ICDs	6 (30)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCM, cardiac contractility modulation; CKD, chronic kidney disease; Cr, creatinine; DCM, dilated cardiomyopathy; DM, diabetes mellitus; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation. Data are presented as n (%) or mean ± SD.

TABLE 3 CCM efficacy results

	Before CCM Implantation	At Last Follow-up	*P* Value
NYHA class	2.9 ± 0.4	2.1 ± 0.7	<0.0001
MLWHFQ score	50.2 ± 23.7	29.6 ± 22.8	<0.0001
LVEF, %	24.4 ± 8.1	30.9 ± 9.6	0.002
LVEDD, mm	66.6 ± 7.1	64.4 ± 6.5	0.087
LVESD, mm	59.2 ± 7.2	54.8 ± 7.3	0.012
LVEDV, mL	230.0 ± 49.2	207.8 ± 65.0	0.029
LVESV, mL	175.8 ± 46.1	147.2 ± 60.1	0.011
QRS duration, ms	108.9 ± 19.4	110.0 ± 22.0	0.663
NT-proBNP, pg/mL	2882.7 ± 5456.6	2460.7 ± 7575.6	0.561
Cr, mg/dL	1.37 ± 0.83	1.32 ± 0.51	0.278
Paroxysmal AF events, %	5	15	0.163

Abbreviations: AF, atrial fibrillation; CCM, cardiac contractility modulation; Cr, creatinine; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation. Data are presented as mean ± SD unless otherwise noted.

At the time of implantation of the second device (either CCM or S-ICD), intraoperative crosstalk testing was performed. No patient had double counting due to a concomitant CCM. In 9 patients, ≥1 of the 3 S-ICD vectors showed "noise-free" ventricular sensing during active CCM therapy. In 11 patients, "noise" was recognized in all 3 S-ICD sensing vectors when CCM was activated. Nevertheless, during the S-ICD testing with CCM activated, the CCM signal delivery stopped immediately during ventricular tachycardia (VT)/VF, and the S-ICD properly recognized the arrhythmia with no undersensing or undue delay (Figure, B,C). In all cases VF was terminated by the first ICD shock and within an adequate time window (time to shocks, 12 to 20 seconds).

During the ergometric testing with activated CCM therapy, none of the 20 patients showed double counting or T-wave oversensing. Therefore, both devices could be activated appropriately in all 20 patients.

Other than postimplantation and postergometry configuration, no reprogramming of the S-ICD device was required. Later follow-up processes were routinely done as with any other ICD and/or CCM device cases.

3.3 | Complications

One patient had postoperative wound-healing delay of the S-ICD pocket that required a prolonged hospital stay. One patient suffered from thrombosis of the subclavian vein after implantation of CCM, requiring oral anticoagulation for 3 months.

With regard to long-term complications, 3 patients required lead-revision procedures of CCM ventricular leads at a mean follow-up of 30 months. One patient with a body mass index of 40 kg/m^2 and a history of recurrent skin infections had a skin abscess on the thoracic wall that affected the tip of the subcutaneous lead, requiring temporary removal of the subcutaneous ICD at 22 months. The device was successfully re-implanted 3 months later.

3.4 | Efficacy of CCM therapy

The mean duration of follow-up from CCM implantation was 34.3 ± 30.6 months (range, 7–94 months; median, 19 months).

There were significant improvements of NYHA class as well as MLWHFQ (Table 3). LVEF also improved significantly, by 6.5%, and there was a trend toward a decrease in left ventricular end-diastolic diameter. Additionally, there were significant decreases of left ventricular end-systolic diameter, and left ventricular end-diastolic and end-systolic volumes. There were no significant changes seen in N-terminal pro brain natriuretic peptide or creatinine levels. Furthermore, QRS duration remained unchanged.

3.5 | Arrhythmias

Mean follow-up after dual device implantation was 22.0 ± 15.3 months (range, 5–61 months; median, 17 months). During this time, 3 patients experienced a total of 6 episodes of sustained VT at a mean follow-up of 7.2 ± 2.5 months with both devices active. Each episode was adequately treated with a single ICD shock. Patients' electrophysiological characteristics are described in Table 4.

One patient (male, age 75 years, ischemic cardiomyopathy) received an inappropriate shock (see Supporting Information, Figure S1, in the online version of this article). The patient had non-sustained VT for 11 seconds that was then followed by a phase of T-wave oversensing for 15 seconds. The T-wave oversensing led to the inappropriate shock. During the inappropriate shock event, CCM therapy was in an "off" phase, and therefore the inappropriate shock is unrelated to CCM. The patient received antiarrhythmic therapy with amiodarone and had no further ventricular tachyarrhythmias.

TABLE 4 Details of appropriate S-ICD therapies

Patient	VT Date	VT Cycle Length, ms	Shock	Shock Successful?	Time to Shock, s
Male, 70 years, ICM	January 9, 2015	320	1 × 80 J	Yes	19
Male, 75 years, ICM	December 13, 2015	260	1 × 80 J	Yes	24
Male, 48 years, DCM	July 8, 2016	300	1 × 80 J	Yes	30
	August 21, 2016	300	1 × 80 J	Yes	53
	August 22, 2016	260	1 × 80 J	Yes	53
	August 22, 2016	300	1 × 80 J	Yes	19

Abbreviations: DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; S-ICD, subcutaneous implantable cardioverter-defibrillator; VT, ventricular tachycardia.

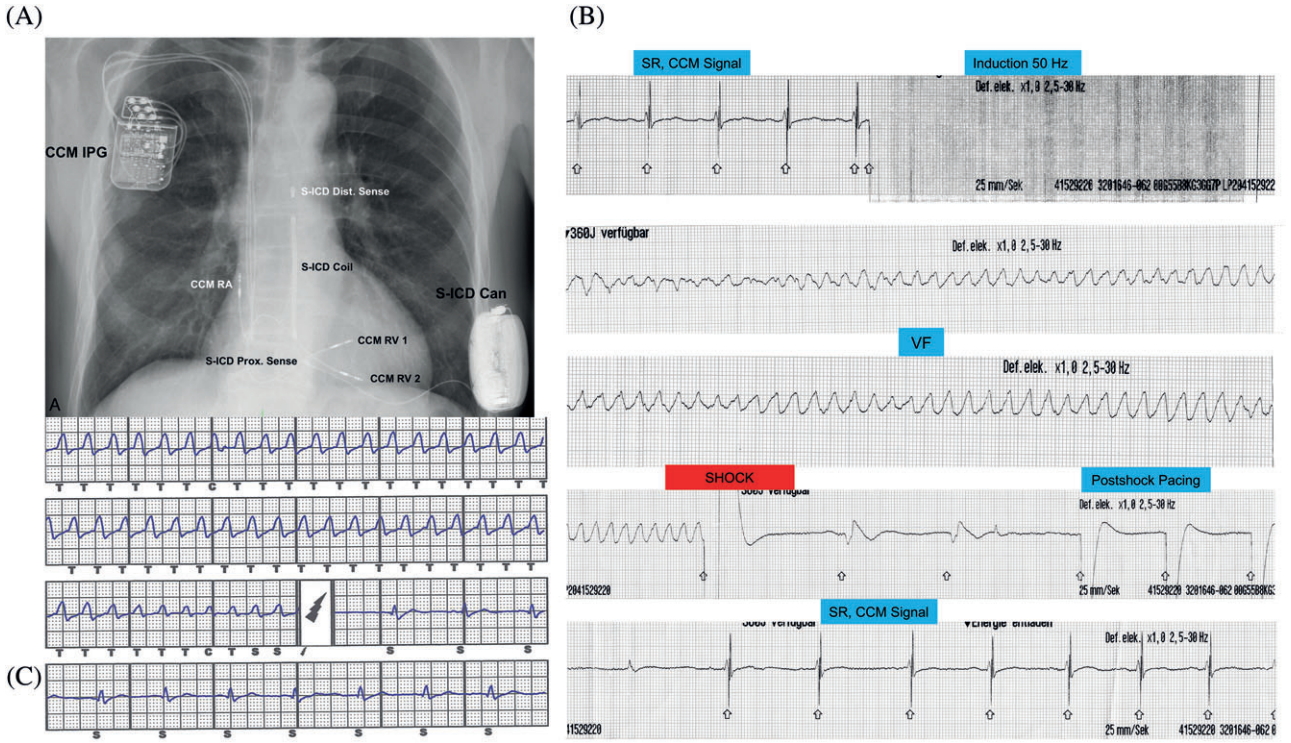

FIGURE 1 (A) Chest x-ray of patient with CCM and S-ICD. (B) Intraoperative S-ICD testing with activated CCM: rhythm strip ECG. (C) S-ICD report of the same test from the same patient. Abbreviations: CCM, cardiac contractility modulation; ECG, electrocardiogram; IPG, implantable pulse generator; RA, right atrium; RV, right ventricle; S-ICD, subcutaneous implantable cardioverter-defibrillator; VF, ventricular fibrillation

During the 22 months of follow-up with both devices active, none of the 20 patients had syncope.

3.6 | Survival

For this patient population at the time of CCM implantation, the MAGGIC score estimated mean 1-year and 3-year death rates of 13.2% and 30.2%, respectively. The SHFM score predicted mean 1-year, 2-year, and 5-year death rates of 5.1%, 10.1%, and 24.6%, respectively, for this same group of subjects. At the time of last follow-up, 19 of the 20 patients were alive. No patient died while being treated with CCM. One 54-year-old female patient had received a left ventricular assist device after 14 months of follow-up due to progressive HF; thus, CCM and S-ICD were switched off. That patient died subsequently of postoperative complications.

4 | DISCUSSION

The major new finding from this study is that combination of CCM with S-ICD in patients with an indication for both is feasible and that it was safe and successful in this study cohort during long-term follow-up. The benefit of CCM therapy, as demonstrated by improvements of NYHA class, quality-of-life scores, and echocardiographic parameters, seems consistent with prior publications in larger populations.[5,8,19]

Recent retrospective single-center observational studies have suggested prolonged survival of HF patients treated with CCM therapy.[8–10] In most of these studies, patients receiving CCM therapy had LVEF ≤35%; therefore, they also had ICD devices with intracardiac leads in place. To date there is no device combining CCM with ICD functions; thus, multiple intracardiac leads are required (for the CCM and for the ICD), raising the risk of lead- and implantation-related adverse events. Although CCM has been studied with patients receiving intravenous ICD in multiple studies,[4–6,8] and its safety, functionality, and efficacy were demonstrated, it is clearly also desired to have a future combined device to address this population with an integrated solution. The recent introduction of S-ICD eliminates the need for intracardiac leads to deliver defibrillation shocks, and thus reduces the risk of lead-related events.

Prior studies have reported successful combination of the S-ICD with transvenous pacemakers[14] in patients with need for pacing after implantation of an S-ICD. Recently, Tjong et al. reported that combined leadless pacing and S-ICD therapy appeared feasible in animal experiments and in 1 human subject.[20] In a recent case series, we demonstrated that the S-ICD can be combined with a variety of cardiac implantable electronic devices that require intracardiac or epicardial leads, including CCM, and that the devices can be programmed and tested to achieve efficacy and avoid interference when used in the same patient.[17] This testing includes postprocedural ergometry and provocative maneuvers with the concomitant device active, while monitoring sensing vectors in real time. This enables observation of interference or malfunction that might appear only during exercise or tachycardia.

In this study, we present the first long-term results of combined CCM and S-ICD devices. Using our established algorithm, the chances for detrimental crosstalk between CCM and S-ICD can be

minimized, allowing both devices to function properly and safely. All device implantations were successfully performed, even in those 6 patients who had suffered complications with prior transvenous ICDs. Postprocedural and long-term complications were successfully handled. This group of patients showed significant improvements in HF symptoms and LVEF. S-ICD shock delivery was effective during device testing. In 3 patients, 6 ventricular arrhythmias that occurred during follow-up were terminated properly. No patient died of arrhythmia or of unknown reasons during a mean follow-up of 22 months of combined therapy.

A major requirement for successfully combining CCM and S-ICD is the absence of significant bradycardia requiring cardiac pacing (neither of the 2 devices has a pacing function). Furthermore, the S-ICD has no antitachycardia pacing functions. Patients with HFrEF requiring ventricular pacing or patients with a wide QRS complex should receive cardiac resynchronization therapy.[3]

The new-generation Optimizer, the Optimizer Smart, includes an algorithm that does not require the implantation of an atrial lead (keeping the 2 ventricular leads only), thereby further simplifying the implantation procedure. The new mode also allows the delivery of CCM therapy in patients with permanent atrial fibrillation, which was considered a contraindication for the prior-generation Optimizer device.[21] In a recent study, it was demonstrated that efficacy and safety of CCM were similar when the signal was delivered through either 1 or 2 ventricular leads.[22] These results support the potential future use of a single ventricular lead for delivery of CCM, further reducing device implantation–associated risk.

4.1 | Study limitations

This study presents experience with the combination of CCM and S-ICD in a small cohort of patients from a single site. It presents limited data on clinical outcome in a nonrandomized, noncontrolled manner. Further multicenter studies are needed to evaluate the long-term impact of combining these 2 technologies in support of patients with HFrEF and LVEF ≤35%, who comprise a large segment of the chronic HF population.

5 | CONCLUSION

S-ICD and CCM can be successfully combined to work efficaciously and safely in HFrEF patients who do not require cardiac pacing. A careful intraprocedural crosstalk test and postoperative exercise testing with both devices activated is recommended to identify and abate any functional interactions between the 2 devices.

With the long-term follow-up, it can be concluded that S-ICD therapy and CCM therapy can be safely used together, thereby decreasing risk by reducing the number of intracardiac leads implanted. A future device that combines CCM and ICD functions is desirable.

Conflicts of interest

Susanne Röger has received speaker fees from Impulse Dynamics. Jürgen Kuschyk has received speaker fees from Impulse Dynamics and serves on the international advisory board of Boston Scientific. Martin Borggrefe has received speaker fees from Impulse Dynamics and serves on their international advisory board. The authors declare no other potential conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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