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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RESEARCH ARTICLE

Long-term clinical experience with cardiac contractility modulation therapy delivered by the Optimizer Smart system

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Aims We assessed long-term effects of cardiac contractility modulation delivered by the Optimizer Smart system on quality of life, left ventricular ejection fraction (LVEF), mortality and heart failure and cardiovascular hospitalizations.

Methods and results CCM-REG is a prospective registry study including 503 patients from 51 European centres. Effects were evaluated in three terciles of LVEF (≤25%, 26–34% and ≥35%) and in patients with atrial fibrillation (AF) and normal sinus rhythm (NSR). Hospitalization rates were compared using a chi-square test. Changes in functional parameters of New York Heart Association (NYHA) class, Minnesota Living with Heart Failure Questionnaire (MLWHFQ) and LVEF were assessed with Wilcoxon signed-rank test, and event-free survival by Kaplan–Meier analysis. For the entire cohort and each subgroup, NYHA class and MLWHFQ improved at 6, 12, 18 and 24 months ($P < 0.0001$). At 24 months, NYHA class, MLWHFQ and LVEF showed an average improvement of 0.6 ± 0.7, 10 ± 21 and 5.6 ± 8.4%, respectively (all $P < 0.001$). LVEF improved in the entire cohort and in the LVEF ≤25% subgroup with AF and NSR. In the overall cohort, heart failure hospitalizations decreased from 0.74 [95% confidence interval (CI) 0.66–0.82] prior to enrolment to 0.25 (95% CI 0.21–0.28) events per patient-year during 2-year follow-up ($P < 0.0001$). Cardiovascular hospitalizations decreased from 1.04 (95% CI 0.95–1.13) events per patient-year prior to enrolment to 0.39 (95% CI 0.35–0.44) events per patient-year during 2-year follow-up ($P < 0.0001$). Similar reductions of hospitalization rates were observed in the LVEF, AF and NSR subgroups. Estimated survival was significantly better than predicted by MAGGIC at 1 and 3 years in the entire cohort and in the LVEF 26–34% and ≥35% subgroups.

Conclusions Cardiac contractility modulation therapy improved functional status, quality of life, LVEF and, compared to patients' prior history, reduced heart failure hospitalization rates. Survival at 1 and 3 years was significantly better than predicted by the MAGGIC risk score.

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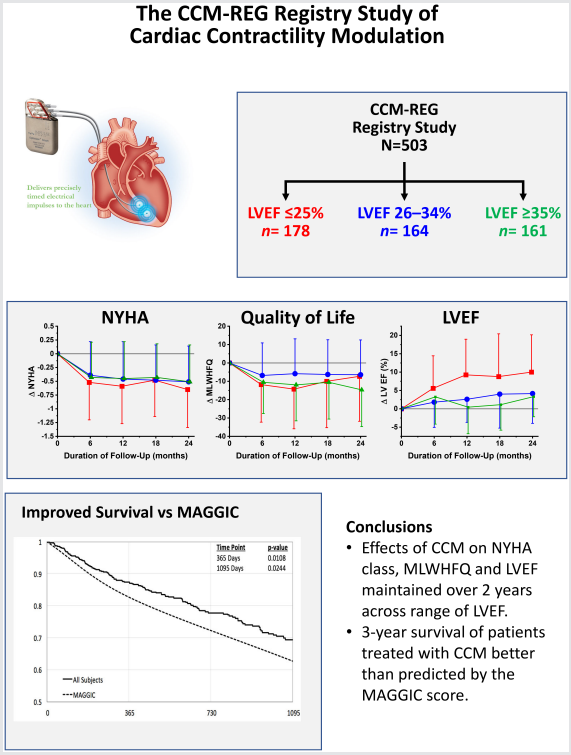
Graphical Abstract



The CCM-REG registry study of cardiac contractility modulation. CCM, cardiac contractility modulation; LVEF, left ventricular ejection fraction; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association.

Keywords Heart failure • CCM therapy

Introduction

Cardiac contractility modulation (CCM) therapy delivered by the Optimizer Smart system has been shown to improve exercise tolerance, quality of life and functional status in randomized controlled clinical trials which have also provided evidence of reduced heart failure hospitalizations.[1,2] However, currently available randomized studies of CCM have mainly been limited to a 6-month follow-up duration, limiting ability to assess the impact on mortality and other long-term effects.

In contrast to the United States, CCM is approved in CE-mark countries for use in patients with New York Heart Association (NYHA) class II, III and ambulatory IV. Accordingly, the CCM-REG registry included patients over a broader ejection fraction range. Furthermore, enrolment into the CCM-REG registry study has now expanded to include 503 patients receiving CCM based on the indications approved for clinical use in the European Union. This includes a relatively large number of patients with atrial fibrillation (AF) and a significant number of patients having reached 3-year or longer follow-up.

Accordingly, the purpose of this study was to assess the long-term clinical effects of CCM on quality of life, functional status, left ventricular ejection fraction (LVEF), hospitalizations and mortality in the overall CCM-REG cohort, in patients in different ranges of LVEF, and in patients with AF.

Methods

As detailed previously,[2] CCM-REG is a prospective, observational registry study conducted at 51 centres across the European Union. A list of participating centres and local investigators is provided in the *Appendix*. All patients who presented to a participating centre for a clinically indicated Optimizer implant were asked to enrol in the study. Study enrolment began in October 2013 and ended in October 2019.

The registry was developed in accordance with the Declaration of Helsinki. Ethics committee approval was obtained at each participating

Table 1 Baseline demographics of patients in the CCM-REG study with comparison of patients in the different LVEF subgroups

	All (n = 503)	LVEF ≤25% (n = 178)	LVEF 26–34% (n = 164)	LVEF ≥35% (n = 161)	P-value*
Age (years)	66.2 (10.6)	64.3(11.3)	67.55 (10.16)	66.92 (10.13)	0.0098
Male sex	79.7% (401/503)	82.6% (147/178)	78.7% (129/164)	77.6% (125/161)	0.4847
Ischaemic HF aetiology	63.6% (320/503)	59.0% (105/178)	73.2% (120/164)	59.0% (95/161)	0.0083
Prior ICD	75.1% (378/503)	87.1% (155/178)	81.7% (134/164)	55.3% (89/161)	<0.0001
Diabetes	44.1% (222/503)	47.2% (84/178)	42.1% (69/164)	42.9% (69/161)	0.5875
COPD	22.5% (113/503)	24.7% (44/178)	24.4% (40/164)	18.0% (29/161)	0.2591
NYHA class					0.0099
I	0.4% (2/503)	0.6% (1/178)	0.6% (1/164)	0% (0/161)	
II	9.9% (50/503)	7.3% (13/178)	10.4% (17/164)	12.4% (20/161)	
III	81.7% (411/503)	78.1% (139/178)	83.5% (137/164)	83.9% (135/161)	
IV	8.0% (40/503)	14.0% (25/178)	5.5% (9/164)	3.7% (6/161)	
History of AF	30.6% (154/503)	28.1% (50/178)	29.9% (49/164)	34.2% (55/161)	0.4655
QRS (ms)	112.2 (24.6)	115.79 (23.19)	112.58 (25.84)	108.14 (24.25)	0.0174
LVEF (%)	29.7 (8.0)	21.25 (3.88)	30.09 (2.07)	38.68 (4.19)	<0.0001
MLWHFQ score	44.8 (19.6)	48.49 (21.71)	40.60 (17.53)	44.96 (18.53)	0.0010
BMI (kg/m^2)	29.4 (5.8)	29.28 (6.15)	28.98 (5.39)	29.79 (5.83)	0.4496
Systolic blood pressure	120.5 (18)	117.64 (17.08)	120.96 (18.00)	123.13 (18.63)	0.0180
6-min walk distance (m)	317.0 (120.6)	299.48 (127.33)	317.77 (120.13)	332.69 (115.69)	0.5297
Diuretic	90.7% (456/503)	93.3% (166/178)	92.1% (151/164)	86.3% (139/161)	0.0686
ACEi or ARB	90.7% (456/503)	92.7% (165/178)	89.6% (147/164)	89.4% (144/161)	0.5072
Beta-blocker	95.6% (479/501)	96.0% (170/177)	95.7% (157/164)	95.0% (152/160)	0.8925
MRA	68.4% (344/503)	73.6% (131/178)	65.2% (107/164)	65.8% (106/161)	0.1767

Values are given as mean (standard deviation), or % (n/N).
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.
*Comparing the three LVEF subgroups (ANOVA test for continuous variables, chi-square test for categorical variables).

site. All patients signed a separate informed consent form prior to enrolment. Demographics, medical history, laboratory and physical examination data were collected from clinical records of routine care visits. Data were available from routine follow-up conducted every 6 months after implantation through a maximum of 2 years for functional parameters and hospitalizations and for up to 3 years for vital status. Data included interim medical history (focused on the occurrence of any cardiovascular-related hospitalizations), assessment of NYHA classification and MLWHFQ score. Data collected also included all the components necessary for the calculation of the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) risk score from which predicted mortality was derived.[3] Measurements were made according to standard protocols at each site. Finally, consistent with standard practice, device interrogations and adjustments of settings were performed every 6 months to ensure optimal delivery of CCM therapy. The sponsor conducted 100% source verification of all data by external monitoring of the registry.

Endpoints included the number and rate of heart failure and cardiovascular-related hospitalizations which were compared to rates of hospitalizations in the year before Optimizer implantation. Functional status assessed by NYHA class and quality of life assessed using MLWHFQ were evaluated for the first 2 years post-implant. Observed survival curves were compared to those predicted from the validated MAGGIC risk score.

Statistical analysis

Baseline characteristics were presented using descriptive statistics [mean, standard deviation, median, minimum, maximum, and 95% confidence interval (CI) for continuous data; count and percentages for categorical data]. Hospitalization rates (events per patient-year) during the follow-up period were compared to those occurring the year prior to treatment using a chi-square test based on the Poisson distribution. This analysis accounted for the total duration of each patient's participation from enrolment to the final data cut-point for this analysis. Changes from baseline values in NYHA class, MLWHFQ and LVEF were assessed using the Wilcoxon signed-rank test. Survival (freedom from death) was presented using the Kaplan–Meier product-limit method. All P-values < 0.05 were considered statistically significant.

Effects of CCM on parameters of clinical effectiveness, hospitalizations and mortality were considered in five non-exclusive patient cohorts: the total cohort (n = 503); patients with AF at baseline (n = 154); patients with LVEF ≤25% (n = 178); patients with LVEF 26–34% (n = 164); and patients with LVEF ≥35% (n = 161). These thresholds for LVEF ranges were chosen to yield approximately equivalent sample sizes for each of the subgroups; notably, these coincide precisely with cutoffs used to examine clinical effectiveness in prior studies.[1,4] We also compared the Kaplan–Meier survival curve

Table 2 Baseline demographics of patients in the CCM-REG study with comparison of patients with atrial fibrillation and those with normal sinus rhythm

	All (n = 503)	AF (n = 154)	NSR (n = 349)	P-value*
Age (years)	66.2 (10.6)	69.9 (9.7)	65.0 (10.8)	<0.0001
Male sex	79.7% (401/503)	82.5% (127/154)	78.5% (274/349)	0.3375
Ischaemic HF aetiology	63.6% (320/503)	55.8% (86/154)	67.0% (234/349)	0.0206
Prior ICD	75.1% (378/503)	67.5% (104/154)	78.5% (274/349)	0.0101
Diabetes	44.1% (222/503)	42.9% (66/154)	44.7% (156/349)	0.7702
COPD	22.5% (113/503)	27.3% (42/154)	20.3% (71/349)	0.1043
NYHA class				
I	0.4% (2/503)	0.0% (0/154)	0.6% (2/349)	0.4890
II	9.9% (50/503)	9.7% (15/154)	10.0% (35/349)	
III	81.7% (411/503)	79.9% (123/154)	82.5% (288/349)	
IV	8.0% (40/503)	10.4% (16/154)	6.9% (24/349)	
History of AF	30.6% (154/503)	100% (154/154)	0.0% (0/349)	<0.0001
QRS (ms)	112.2 (24.6)	117.8 (29.5)	109.8 (21.7)	0.0028
LVEF (%)	29.7 (8.0)	30.6 (8.6)	29.3 (7.7)	0.1057
MLWHFQ score	44.8 (19.6)	44.8 (18.9)	44.8 (20.0)	0.9908
BMI (kg/m^2)	29.4 (5.8)	29.5 (6.0)	29.3 (5.7)	0.7443
Systolic Blood Pressure	120.5 (18)	119.4 (17.5)	121.0 (18.2)	0.3780
6-min walk distance (m)	317.0 (120.6)	272.7 (106.1)	333.8 (122.2)	0.0180
Diuretic	90.7% (456/503)	91.6% (141/154)	90.3% (315/349)	0.7407
ACEi or ARB	90.7% (456/503)	92.9% (143/154)	89.7% (313/349)	0.3195
Beta-blocker	95.6% (479/501)	96.1% (148/154)	95.4% (331/347)	0.8168
MRA/eplerenone or spironolactone	68.4% (344/503)	68.2% (105/154)	68.5% (239/349)	>0.9999

Values are given as mean (standard deviation), or % (n/N).
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MLWHFQ, Minnesota Living with Heart Failure Questionnaire; MRA, mineralocorticoid receptor antagonist; NSR, normal sinus rhythm; NYHA, New York Heart Association.
*Comparing the AF and NSR subgroups (ANOVA test for continuous variables, chi-square test for categorical variables).

for each of the five groups to survival as predicted by the MAGGIC score.

Results

Baseline characteristics

Baseline characteristics and medication use for the entire cohort of CCM-REG patients (n = 503) are summarized in *Table 1*. The mean age was 66.2 ± 10.6 years and approximately 80% of patients were male. Ischaemic heart disease was the aetiology for 64% of patients and 75% of patients had an implantable cardioverter-defibrillator (ICD). The majority of patients (81.7%) were in NYHA functional class III. AF was present in 30.6% of patients at the time of enrolment. LVEF averaged 29.7 ± 8.0% and the mean 6-min walk distance was 317 ± 121 m. Over 90% of patients were on diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and beta-blockers at study enrolment. Comparison of baseline demographics among patients with different LVEF ranges (*Table 1*) revealed several significant differences; however, none of these were clinically meaningful except for the expected differences in LVEF and for lower ICD use in patients with LVEF ≥35%.

A comparison of baseline demographics and medication use among patients with AF and those with normal sinus rhythm (NSR) is provided in *Table 2*. Notable differences included that AF patients were older, had a lower prevalence of ischaemic cardiomyopathy and a lower use of ICDs.

Clinical effectiveness

Effectiveness results for the entire CCM-REG cohort and subgroups are provided in *Figure 1* (showing changes from baseline based on paired observations) and detailed further in online supplementary *Table S1* which indicates the number of paired observations contributing to each parameter and each timepoint. In brief, significant improvements in NYHA class, MLWHFQ score and LVEF were observed for the entire cohort at 6, 12, 18 and 24 months following initiation of CCM therapy compared to baseline (P < 0.0001; *Figure 1*). At 24 months, NYHA class showed an average class improvement of 0.6 ± 0.7, MLWHFQ an average point improvement of 10 ± 21, and LVEF and average improvement of 5.6 ± 8.4% (all P < 0.001).

Similarly, functional status, quality of life and LVEF were all improved at 6, 12, 18 and 24 months after initiation of CCM therapy in the LVEF ≤25% subgroup (*Figure 1*). Most notable was the average 10 ± 10% (P < 0.0001) improvement of LVEF by 24 months in this subgroup. Changes in NYHA class and MLWHFQ were similarly improved in the other LVEF subgroups and, at 24 months,

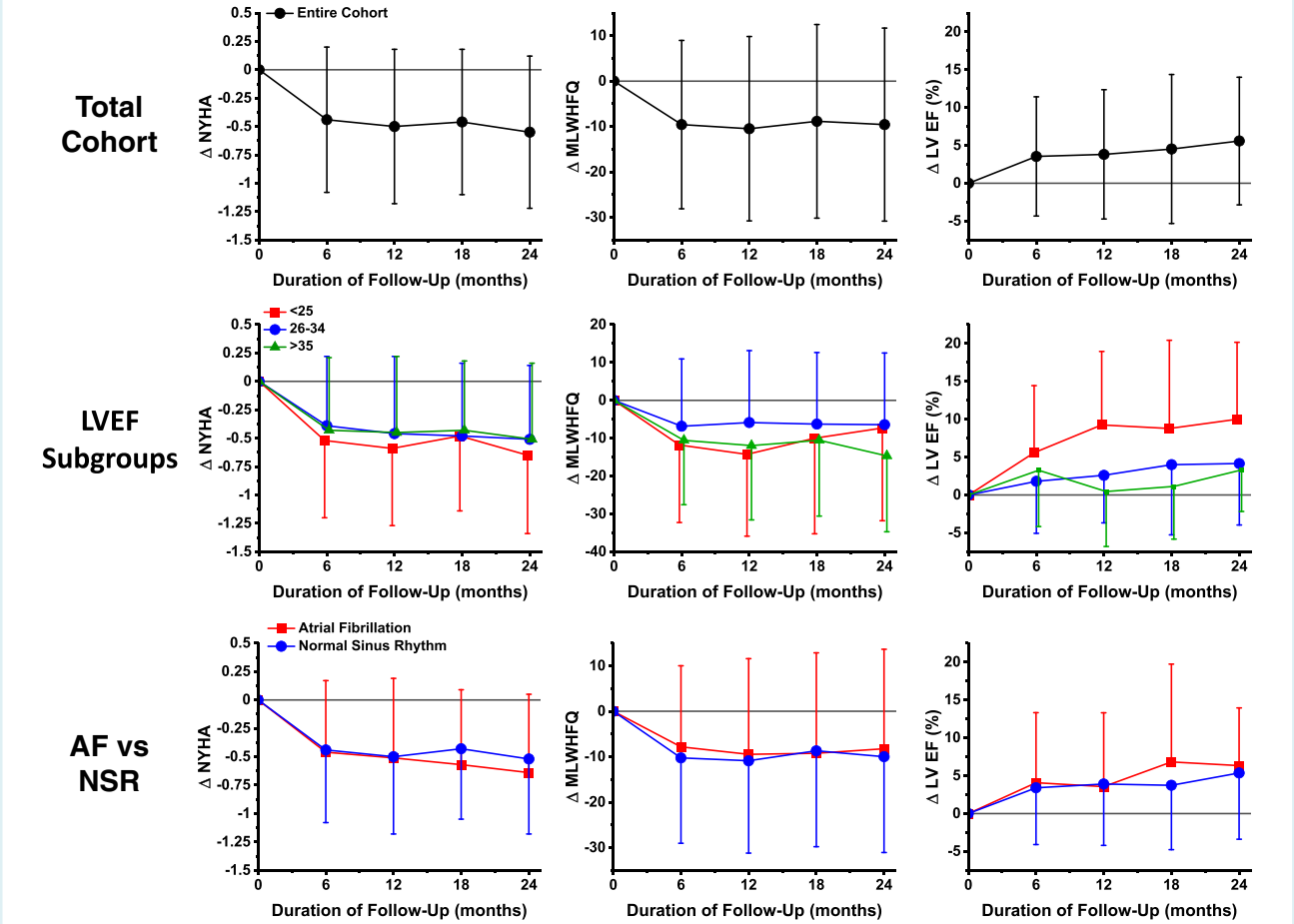


Figure 1 Change in effectiveness measures [New York Heart Association (NYHA) class, Minnesota Living with Heart Failure Questionnaire (MLWHFQ) and left ventricular ejection fraction (LVEF)] as a function of the duration of follow-up in months. The upper set of graphs shows these results for the total cohort, while the middle set of graphs provides the results for the LVEF subgroups. In the bottom set of graphs, the results for subgroups with atrial fibrillation (AF) and normal sinus rhythm (NSR) are shown. Decreases in NYHA class and MLWHFQ depict improvement in these measures. Data show consistent improvements in all effectiveness measures for all groups over the 24 months of follow-up after Optimizer implant.

there were improvements in the LVEF 26–34% and ≥35% subgroups of 4.2 ± 8.1% ($P = 0.01$) and 3.3 ± 5.5% ($P = 0.003$), respectively.

Finally, clinical effects were similar in patients with NSR and AF (*Figure 1* and online supplementary *Table S1*).

Hospitalizations

The rates of overall cardiovascular, heart failure-related, and non-heart failure cardiovascular-related hospitalizations the year prior to study enrolment and for the 2 years following enrolment and initiation of CCM therapy are summarized in *Table 3* for the overall cohort and the five subgroups of interest. For the entire cohort, the rate of overall cardiovascular-related hospitalizations decreased from 1.04 (95% CI 0.95–1.13) events per patient-year the year prior to study enrolment to 0.39 (95% CI 0.35–0.44) events per patient-year during the 2-year period following initiation of CCM therapy ($P < 0.0001$). Heart failure-related events decreased from 0.74 (95% CI 0.66–0.82) to 0.25 (95% CI 0.21–0.28; $P < 0.0001$) events per patient-year. The rate of non-heart failure-related cardiovascular hospitalization events (0.30 events per patient-year, 95% CI 0.26–0.35) decreased to 0.15 (95% CI 0.12–0.18; $P < 0.0001$) events per patient-year.

Similar significant reductions of hospitalization event rates were observed in the three LVEF subgroups and the AF and NSR subgroups. The only exception was that non-heart failure cardiovascular-related hospitalizations were not reduced in the AF subgroup.

Survival analysis

Estimated survival was significantly better than that predicted by the MAGGIC score at 1 and 3 years after initiation of CCM therapy in the entire cohort (*Figure 2A*). No survival benefit was detected in the LVEF ≤25% subgroup (*Figure 2B*). However, survival was better

Table 3 Hospitalization rates the year prior to Optimizer implant compared to the 2 years following Optimizer implant in the entire cohort and in the five subgroups of interest

Subgroup	Pre-treatment (1 year prior)				Post-treatment (0–730 days)				
	Patients	Patient-years	Events	Event rate	Patients	Patient-years	Events	Event rate	*P*-value
All patients									
All cardiovascular events	503	503	523	1.04	503	729	287	0.39	<0.0001
Heart failure events			371	0.74			179	0.25	<0.0001
Non-heart failure cardiovascular events			152	0.30			108	0.15	<0.0001
LVEF ≤25%									
All cardiovascular events	178	178	227	1.28	178	233	123	0.53	<0.0001
Heart failure events			182	1.02			90	0.39	<0.0001
Non-heart failure cardiovascular events			45	0.25			33	0.14	0.0106
LVEF 26–34%									
All cardiovascular events	164	164	157	0.96	164	255	99	0.39	<0.0001
Heart failure events			102	0.62			59	0.23	<0.0001
Non-heart failure cardiovascular events			55	0.34			40	0.16	0.0002
LVEF ≥35%									
All cardiovascular events	161	161	139	0.86	161	242	65	0.27	<0.0001
Heart failure events			87	0.54			30	0.12	<0.0001
Non-heart failure cardiovascular events			52	0.32			35	0.14	0.0002
Normal sinus rhythm									
All cardiovascular events	349	349	342	0.98	349	530	200	0.38	<0.0001
Heart failure events			229	0.66			130	0.25	<0.0001
Non-heart failure cardiovascular events			113	0.32			70	0.13	<0.0001
Atrial fibrillation									
All cardiovascular events	154	154	181	1.18	154	198	87	0.44	<0.0001
Heart failure events			142	0.92			49	0.25	<0.0001
Non-heart failure cardiovascular events			39	0.25			38	0.19	0.2189

LVEF, left ventricular ejection fraction.

than predicted by the MAGGIC score in the other LVEF subgroups (*Figure 2C*, *D*).

As for the overall cohort, survival in the AF subgroup was highly dependent on LVEF (*Figure 3*; $P = 0.004$), improving with LVEF. Although trends for survival were better than predicted by MAGGIC, the number of patients was too small, precluding meaningful statistical comparisons.

Discussion

The current study describes the largest series of patients treated with CCM therapy ($n = 503$), followed for the longest duration (3 years), over the broadest range of LVEF, also including the largest number of patients with AF. Results show CCM-associated improvements in quality of life and NYHA functional class over the 2 years post-implant follow-up period, as well as reductions of hospitalization rates compared to the year prior to implant. Improvements in LVEF were seen in patients with baseline LVEF ≤25%. Moreover, survival was significantly better for the total cohort than predicted by the MAGGIC risk score. This large and long-term registry confirms effectiveness and benefits of CCM therapy in patients with moderate to severe heart failure consistent with the results of prior shorter-term and smaller randomized and registry studies.[5,6]

Similar improvements in functional status and quality of life were shown for the AF and LVEF subgroups. LVEF improvements were also seen in all subgroups, with the largest improvements in patients of the lowest LVEF subgroup (≤25%). Patients with AF fared equally well with regard to these metrics as those in NSR. In all subgroups, 2-year hospitalization rates were significantly reduced from the rates obtained 1 year prior to CCM therapy; this applied to total cardiovascular hospitalizations, heart failure-related hospitalizations and non-heart failure cardiovascular-related hospitalizations with the exception that non-heart failure cardiovascular hospitalizations were not reduced in the AF subgroup. In addition, estimated survival for all patients included in the present analysis was significantly better at 1 and 3 years than predicted by the MAGGIC score. This was especially apparent for the LVEF 26–34% and LVEF ≥35% subgroups. In the AF subgroup, survival was impacted by baseline LVEF similar to the NSR group.

The present study also summarizes clinical effects in the largest number of AF patients treated with CCM. The improved health status and reduced hospitalization rates observed in this cohort in the absence of an apparent excess of mortality suggest that CCM

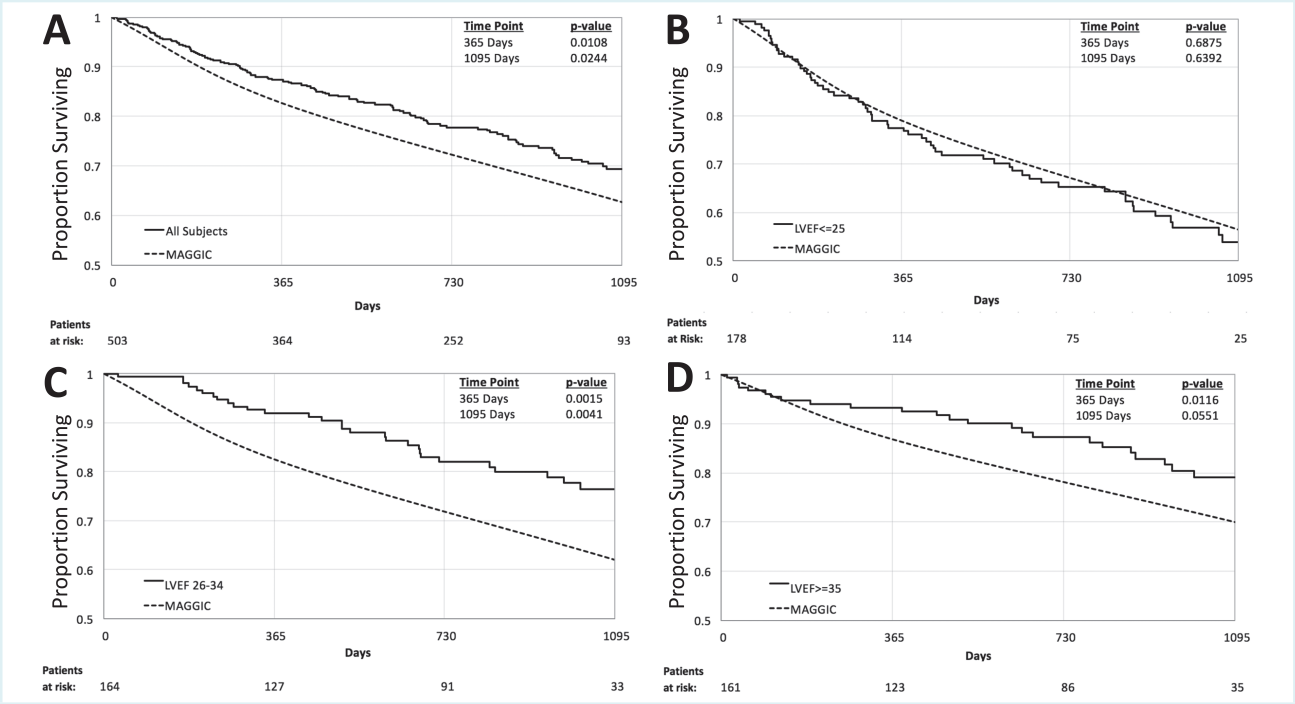


Figure 2 Kaplan–Meier survival curves for the total cohort and each LVEF group compared to the predicted survival curves for the MAGGIC heart failure risk score. The proportion surviving is presented for 3 years (1095 days) of follow-up. Patients at risk at each time interval are shown at the bottom of each graph. *P*-values provided in the upper right hand corner of each individual graph demonstrate that observed survival was statistically better than survival predicted by the MAGGIC risk score for the total cohort (*A*), the LVEF 26–34% group (*C*) and the LVEF ≥35% group (*D*). There was no difference between observed and predicted survival in the LVEF ≤25% group (*B*).

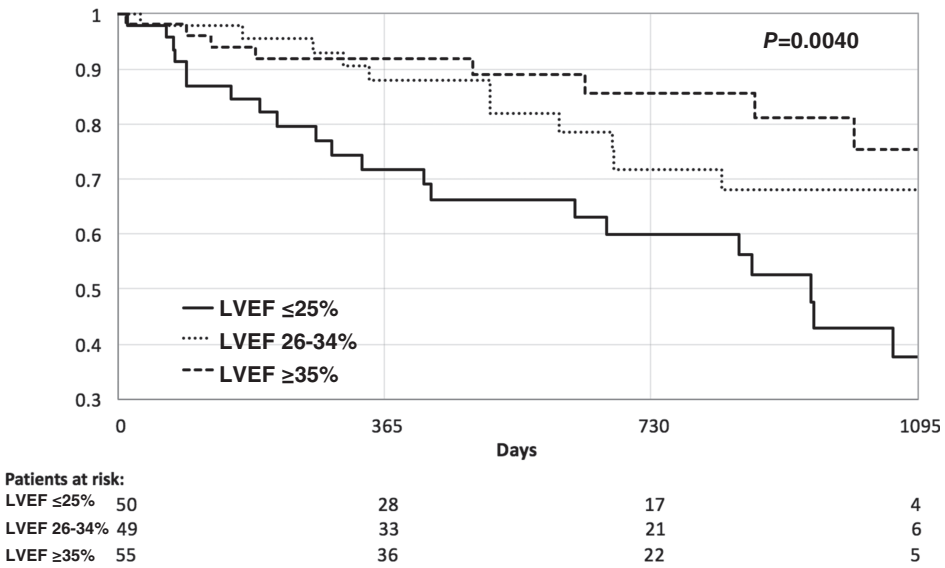


Figure 3 Kaplan–Meier survival curves for each left ventricular ejection fraction (LVEF) tercile in the group of patients with atrial fibrillation. Survival in the atrial fibrillation subgroup was highly dependent on LVEF ($P = 0.004$).

therapy is safe and effective in this highly prevalent subgroup. Also, importantly, better outcomes than predicted by MAGGIC risk score observed in AF patients with LVEF >25% suggests that LVEF, and not the presence of AF, is the major driving factor for survival.

Results of a prior randomized trial of CCM showed that exercise tolerance (both 6-min hall walk and peak oxygen consumption) was improved to a greater extent in patients with LVEF ≥35% than in those with LVEF <35%.[1] The reason(s) for enhanced response to CCM therapy in the higher LVEF range are likely multifactorial but may include the presence of a greater amount of viable myocardium and smaller heart sizes at the higher LVEF which can be positively affected by the molecular and cellular effects of CCM.[7,8]

Anker *et al.*[2] recently reported on the clinical effects of CCM from 140 subjects participating in the prospective CCM-REG registry study having an LVEF between 25% and 45%, which was chosen to match the range approved by the Food and Drug Administration for use in the United States.[2] Sustained CCM-related improvements of quality of life (measured by the MLWHFQ) and NYHA functional class were reported over a 2-year follow-up period. This study also found significant reductions of heart failure and cardiovascular hospitalization rates in the 2-year period following initiation of CCM therapy compared to the prior year. Finally, 1-, 2- and 3-year survival rates were higher than those predicted by the Seattle Heart Failure Model (SHFM),[9] though the number of patients followed for 2 or more years was limited and the number of patients with complete information to assign an SHFM score was limited.

In contrast, the present study which included a larger number of patients was able to demonstrate better than predicted survival even in the subgroup of patients with LVEF ranging from 26–34%.

Limitations

The current results are subject to the limitations of an observational, non-randomized study including the potential role of placebo effect. However, sustained improvements over 2 years in NYHA class, MLWHFQ and, more objectively, LVEF, and the consistency of these findings among different patient subgroups suggest that clinical effects beyond placebo are operative. Additionally, LVEF data were available only when this test was performed as part of routine care, which accounts for the lower number of observations compared to NYHA class and MLWHFQ which were collected at each visit. It should also be recognized that these results are derived from completer analyses over time, which do not account for patients lost to follow-up or who have died.

Similarly, effects of CCM on hospitalization rates were based on comparison of patients' historical rates rather than on a parallel control group. However, similar findings were observed in the prior randomized clinical trial[2] and have also been used as the primary analysis for other studies of heart failure therapies.[10,11]

Additionally, changes in medications were not tracked during the follow-up period. However, as detailed in *Table 1*, there was very high usage of diuretics (90.7%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (90.7%), beta-blockers (95.6%) and mineralocorticoid receptor antagonists (68.4%). Accordingly, there would have been very little opportunity for meaningful additions of drugs to the population as a whole; changes in medications would therefore not likely have contributed to the sustained improvements in clinical status and hospitalizations noted during follow-up. Also note that during the period of data collection neither sacubitril/valsartan nor sodium–glucose co-transporter 2 inhibitors were in widespread use, so these medications do not factor into the results.

Finally, interpretation of effects on survival was based on the MAGGIC risk score, not a parallel control group. However, the MAGGIC score incorporates values of 13 independent, readily obtained clinical parameters. This is the most comprehensive and generalizable risk score currently available in the literature which has been based on 39 372 patients from 30 studies with a median follow-up of 2.5 years.[3] Furthermore, the score was prospectively validated in a study of 51 043 patients.[12] The MAGGIC score does not reflect the use of ICDs.

Patients were enrolled in this study prior to approval and incorporation of sacubitril/valsartan into heart failure guidelines. However, a vast majority of patients were treated with angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Accordingly, like other previously approved devices (e.g. cardiac resynchronization therapy and ICD), the effects of CCM have not been evaluated in the presence of this drug combination. Nevertheless, based on current understanding of the CCM mechanisms of action,[7] there is no reason for effects to be decreased by the presence of a neprilysin inhibitor.

Conclusion

This study summarized the largest experience to date of real-world, long-term use of CCM therapy in patients meeting CE-mark approved criteria for the use of CCM therapy. The results demonstrate that CCM improves functional status, quality of life, LVEF and, compared to patients' prior history, reduces heart failure hospitalization rates. In the overall cohort, survival at 1- and 3-year follow-up was significantly better than predicted by the MAGGIC risk score. Additional ongoing studies and further device refinements continue to support the use of CCM in patients with LVEF ≤45% who remain symptomatic despite guideline-directed medical therapy.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: J.K. reports receiving lecture and consultancy fees from Impulse Dynamics. P.F. reports past membership on the Impulse Dynamics Medical Advisory Board. T.D. reports receiving lecture and consultancy fees from Impulse Dynamics. O.M. reports receiving fees for participation in the CCM-REG study and lecture fees from Impulse Dynamics. D.M. and I.R. are paid employees of Impulse Dynamics. D.B. is a paid consultant to Impulse Dynamics.

Appendix

Study user site ID	Site name	Title	First name	Last name
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02	KVZ Darmstadt	Dr. med.	Harald	Küx
05	Maerkische Kliniken Luedenscheid	Prof. Dr. med.	Bernd	Lemke
07	Medizinisches Versorgungszentrum am Kuechwald GmbH	Dr. med.	Wilfried	Daenschel
08	Universitaetsklinikum Leipzig AöR	Dr. med.	Martin	Neef
09	St. Agnes Krankenhaus Bocholt	Dr. med.	Franz	Kalscheur
11	Krankenhaus Maria Hilf GmbHWarstein	Dr. med.	Christian	Fastenrath
12	Universitaetsklinikum Frankfurt	Prof. Dr. med.	Stefan	Hohnloser
100	Klinikum Kempten	PD Dr. med.	Martin	Karch
13	Herz- und Gefaeßzentrum Bad Bevensen	Prof. Dr. med.	Björn-Andrew	Remppis
15	Asklepios Westklinikum Hamburg	PD Dr. med.	Carsten	Schneider
16	Asklepios Klinik Hamburg St. Georg	Dr. med.	Nils	Gosau
17	Heidelberger Privatklinik fuer Innere Medizin, Kardiologie	Dr. med.	Mohammed	Natour
18	ASKLEPIOS Klinik Hamburg Nord	Dr. med.	Ralph	Mletzko
19	Nucleo per la ricerca Clinica	Dr.	Paolo	China
20	Kreiskliniken GuenzburgKrumbach	Dr. med.	Michael	Reitmayer
21	Herzzentrum Dresden GmbH	Prof. Dr.	Ruth	Strasser
22	St. Vincenz Krankenhaus Paderborn	Prof. Dr. med.	Andreas	Goette
23	Praxis fuer Innere Medizin / KardiologieDr. A. Horowitz	Dr. med.	Avner	Horowitz
26	Zentralklinik Bad Berka GmbH	Dr. med.	Marc-Alexander	Ohlow
27	Heinrich-Braun-Klinikum Zwickau gGmbH	Dr. med.	Magdalena	Szczesny
28	Krankenhaus Landshut-Achdorf	Prof. Dr. med.	Bernhard	Zrenner
29	Katholisches Krankenhaus 'St. Johann Nepomuk' Erfurt	PD Dr. med.	Henning	Ebelt
30	Charité Berlin- Campus Benjamin Franklin	Dr. med.	Martin	Huemer
33	Herzzentrum Leipzig GmbH	Prof. Dr. med.	Gerhard	Hindricks
35	Praxisklinik Herz und Gefaesse Dresden	Dr. med.	Laszlo	Karolyi
36	Helios Klinikum Erfurt	Dr. med.	Frank	Steinborn
38	DRK Klinikum Koepenick	Dr. med	Sebastian	Spencker
41	SRH Waldklinikum Gera gGmbH	Dr. med.	Martin	Winterhalter
42	Elbe Klinikum Stade	Dr. med.	Oliver	Marx
43	Universitaets Herzzentrum Freiburg GmbH	Dr. med.	Johannes	Steinfurt
45	Klinikum Niederlausitz GmbH Senftenberg	Dr. med.	Torsten	Röpke
46	Universitaetsklinikum Aachen	PD Dr. med.	Sebastian	Reith
47	Sana Kliniken Luebeck GmbH	Prof. Dr. med	Joachim	Weil
48	Medizinische Hochschule Hannover	PD Dr.	Christian	Veltmann
53	Juedisches Krankenhaus Berlin	Dr. med.	Andreas	Greissinger
54	Universitaetsklinikum Magdeburg	Prof. Dr. med.	Rüdiger	Braun-Dullaeus
55	Karolinska Universitaet Solna	Prof. Dr. med.	Cecilia	Linde
56	HELIOS St. Marienberg Klinik Helmstedt	Dr. med.	Samir	Said
57	Hufeland Klinikum Muehlhausen	Dr. med.	Sibylle	Kaiser
58	HELIOS Klinikum Aue	Dr. med.	Ulrike	Wetzel
61	Herzzentrum Dresden GmbH	PD. Dr. med.	Christopher	Piorkowski
63	Evangelisches Krankenhaus Koeln Kalk gGmbH	PD Dr. med.	Frank	Eberhardt
68	Klinikum Coburg	Prof. Dr. med.	Johannes	Brachmann
69	Universitaetsklinikum Goettingen	Prof. Dr. med.	Lars	Luethje
70	Internistisches Klinikum Muenchen Sued GmbH	Prof. Dr. med.	Torsten	Lewalter
71	DRK Krankenhaus Soemmerda	Dr. med	Corinna	Mueller
73	Kardiologische Praxis Papenburg	Dr. med	Andreas	Wilke
75	Krankenhaus Maria-Hilf Stadtlohn	Dr. med.	Alessandro	Cuneo
76	Krankenhaus Buchholz und Winsen gGmbH	Dr. med.	Klaus	Hertting
78	4 Wojskowy Szpital Kliniczny z Poliklinika SPZO	Dr. med	Bartek	Krakowiak
79	Chirurgisches Klinikum Muenchen Sued	Dr. med	Helmut	Mair
80	St.-Marien-Hospital Luenen / Werne	Prof. Dr. med.	Christian	Perings
81	Klinikum Fuerth	Dr. med	Dirk	Bastian
82	Asklepios Klinikum Hamburg Barmbek	PD Dr. med.	Gerian	Groenefeld
83	Universitaetsklinikum Schleswig-Holstein Kiel	Prof. Dr. med.	Hendrik	Bonnemeier
85	Univeritaetsklinikum Wuerzburg	PD Dr. med	Peter	Nordbeck
89	Cardio Centrum Ludwigsburg-Bietigheim	PD Dr. med.	Ralph	Bosch
91	Marienhaus Klinikum Neuwied	Dr. med.	Burkhard	Hügl
94	Klinikum Neumarkt	Dr. med.	Steffen	Heyes

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