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.
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
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. Measures 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.

### 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               |              |                     |                      |                     |         |
| I                        | 0.4% (2/503)  | 0.6% (1/178)        | 0.6% (1/164)         | 0% (0/161)          | 0.0099  |
| 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/m²)              | 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% (479/503) | 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, minocycline receptor antagonist; NYHA, New York Heart Association.

*Comparing the three LVEF subgroups (ANOVA test for continuous variables, chi-square test for categorical variables).

### 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...
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,
there were improvements in the LVEF 26–34% and $\geq 35\%$ sub-groups of $4.2 \pm 8.1\%$ ($P = 0.01$) and $3.3 \pm 5.5\%$ ($P = 0.003$), 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 $\leq 25\%$ subgroup (Figure 2B). However, survival was better...
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

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**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      | 74           | 0.74   |            | 179      | 25           | 0.25   |            | <0.0001     |
| Non-heart failure events  | 152      | 30           | 0.30   |            | 108      | 15           | 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 events  | 45       | 25           | 0.25   |            | 33       | 14           | 0.16   | 0.0106     |
| LVEF 26–34%               |          |              |        |            |          |              |        |            |            |
| All cardiovascular events | 164      | 164          | 157    | 0.96       | 164      | 255          | 99     | 0.39       | <0.0001     |
| Heart failure events      | 102      | 62           | 0.62   |            | 59       | 23           | 0.23   |            | <0.0001     |
| Non-heart failure events  | 55       | 34           | 0.34   |            | 40       | 16           | 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       | 54           | 0.54   |            | 30       | 12           | 0.12   |            | <0.0001     |
| Non-heart failure events  | 52       | 32           | 0.32   |            | 35       | 14           | 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      | 66           | 0.66   |            | 130      | 25           | 0.25   |            | <0.0001     |
| Non-heart failure events  | 113      | 32           | 0.32   |            | 70       | 13           | 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      | 92           | 0.92   |            | 49       | 25           | 0.25   |            | <0.0001     |
| Non-heart failure events  | 39       | 25           | 0.25   |            | 38       | 19           | 0.19   | 0.2189     |

LVEF, left ventricular ejection fraction.
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 complete 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 trial7 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.

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## Appendix

| Study user site ID | Site name                                               | Title                  | First name | Last name |
|-------------------|---------------------------------------------------------|------------------------|------------|-----------|
| 01                | Universitätsmedizin Mannheim                            | Prof. Dr. med.         | Martin     | Borggrefe |
| 02                | KVZ Darmstadt                                          | Dr. med.               | Harald     | Kux       |
| 05                | Maerckische Kliniken Luedenscheid                       | Prof. Dr. med.         | Bernd      | Lemke     |
| 07                | Medizinisches Versorgungszentrum am Kuechwald GmbH     | Dr. med.               | Wilfried   | Daenschel |
| 08                | Universitätsklinikum Leipzig AöR                       | Dr. med.               | Martin     | Neef      |
| 09                | St. Agnes Krankenhaus Bocholt                           | Dr. med.               | Franz      | Kalscheur |
| 11                | Krankenhaus Maria Hill GmbH Warstein                   | Dr. med.               | Christian  | Fastnath  |
| 12                | Universitätsklinikum Frankfurt                          | Prof. Dr. med.         | Stefan     | Hohnloser |
| 100               | Klinikum Kempten                                       | PD Dr. med.            | Martin     | Karch     |
| 13                | Herz- und Gefaellzentrum Bad Bevens                     | Prof. Dr. med.         | Bjorn-Andres| Remppis   |
| 15                | ASklepios Klinik Hamburg St. Georg                     | PD Dr. med.            | Carsten    | Schneider |
| 17                | Heidelberger Privatklinik fuer Innere Medizin, Kardiologie| Dr. med.               | Mohammed   | Natour    |
| 18                | ASklepios Klinik Hamburg Nord                           | Dr. med.               | Ralph      | Metlakao  |
| 19                | Nucleo per la ricerca Clinica                          | Dr.                    | Paolo      | China     |
| 20                | Kreiskliniken GuenzburgKrumbach                        | Dr. med.               | Michael    | Reitmayer |
| 21                | Herzzentrum Dresden GmbH                               | Prof. Dr. med.         | Ruth       | Strasser  |
| 22                | St. Vincenz Krankenhaus Paderborn                      | Prof. Dr. med.         | Andreas    | Goette    |
| 23                | Praxis fuer Innere Medizin / KardiologieDr. A. Horowitz| Dr. med.               | Avner      | Horowitz  |
| 24                | Zentralklinik Bad Berka GmbH                           | Dr. med.               | Marc-Alexander | Ohlow   |
| 25                | Heinrich-Braun-Klinikium Zwickau gGmbH                 | Dr. med.               | Magdalena  | Szczesny  |
| 26                | Krankenhaus Landschut-Achdorf                          | Prof. Dr. med.         | Bernhard   | Zrenner   |
| 27                | Katholisches Krankenhaus 'St. Johann Nepomuk' Erfurt   | PD Dr. med.            | Henning    | Ebel      |
| 28                | Charité Berlin- Campus Benjamin Franklin                | Dr. med.               | Martin     | Huener    |
| 29                | Herzzentrum Leipzig GmbH                               | Prof. Dr. med.         | Gerhard    | Hindricks |
| 30                | Praxisklinik Herz und Gefaesse Dresden                 | Dr. med.               | Laszlo     | Karolyi   |
| 36                | Helios Klinikum Erfurt                                 | Dr. med.               | Frank      | Steinborn |
| 38                | DRK Klinikum Koepenick                                 | Dr. med.               | Sebastian  | Spencer   |
| 41                | SRH Waldklinikum Gera gGmbH                            | Dr. med.               | Martin     | Winterhalter |
| 42                | Elbe Klinikum Stade                                    | Dr. med.               | Oliver     | Marx      |
| 43                | Universitaets Herzszentrum Freiburg GmbH               | Dr. med.               | Johannes   | Steinfurt |
| 45                | Klinikum Niederlausitz GmbH Senftenberg                | Dr. med.               | Torsten    | Ropke     |
| 46                | Universitaetsklinikum Aachen                           | PD Dr. med.            | Sebastian  | Reith     |
| 47                | Sana Kliniken Luebeck GmbH                             | Prof. Dr. med.         | Joachim    | Wei       |
| 48                | Medizinische Hochschule Hannover                       | PD Dr. med.            | Christian  | Veltmann  |
| 53                | Juedisches Krankenhaus Berlin                           | Dr. med.               | Andreas    | Greissinger |
| 54                | Universitaetsklinikum Magdeburg                        | Prof. Dr. med.         | Rudiger    | Braun-Dullaeus |
| 55                | Karolinska Universitas Solna                            | Dr. med.               | Cecilia    | Linde     |
| 56                | HELIOS St. Marienberg Klinik Helmsdetz                 | Dr. med.               | Samir      | Said      |
| 57                | Hufeland Klinikum Muehlhausen                          | Dr. med.               | Sibylle    | Kaisar    |
| 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 Soemmernda                             | Dr. med.               | Corinna    | Mueller   |
| 73                | Kardiologische Praxis Papenburg                        | Dr. med.               | Andreas    | Wilke     |
| 75                | Krankenhaus Maria-Hil Stadllohn                        | Dr. med.               | Alessandro | Cuneo     |
| 76                | Krankenhaus Buchholz und Winsen gGmbH                  | Dr. med.               | Klaus      | Hersting  |
| 78                | 4 Wojoskowy Szpital Kliniczny z Poliklinika SPZO        | Dr. med.               | Bartek     | Kraskowisk |
| 79                | Chirurgisches Klinikum Muenchen Sued                   | Dr. med.               | Helmut     | Mair      |
| 80                | St.-Marien-Hospital Luken / Werne                      | Prof. Dr. med.         | Christian  | Perings   |
| 81                | Klinikum Fuert                                        | Dr. med.               | Dirk       | Bastian   |
| 82                | ASklepios Klinik Hamburg Barmbek                        | PD Dr. med.            | Gerian     | Groenefeld |
| 83                | Universitaetsklinikum Schleswig-Holstein Kiel         | Prof. Dr. med.         | Hendrik    | Bonnemeier|
| 85                | Universitaetsklinikum Wuerzburg                       | PD Dr. med.            | Peter      | Nordbeck  |
| 89                | Cardio Centrum Ludwigsburg-Bietigheim                  | PD Dr. med.            | Ralph      | Bosch     |
| 91                | Marienhaus Klinikum Neuwied                            | Dr. med.               | Burkhard   | Hugl      |
| 94                | Klinikum Neumark                                      | Dr. med.               | Steffen    | Heyes     |
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