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RESEARCH ARTICLE

Cardiac contractility modulation improves long-term survival and hospitalizations in heart failure with reduced ejection fraction

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Aims Cardiac contractility modulation (CCM) improves symptoms and exercise tolerance and reduces heart failure (HF) hospitalizations over 6-month follow-up in patients with New York Heart Association (NYHA) class III or IV symptoms, QRS < 130 ms and 25% ≤ left ventricular ejection fraction (LVEF) ≤ 45% (FIX-HF-5C study). The current prospective registry study (CCM-REG) aimed to assess the longer-term impact of CCM on hospitalizations and mortality in real-world experience in this same population.

Methods and results A total of 140 patients with 25% ≤ LVEF ≤ 45% receiving CCM therapy (CCM-REG$_{25\text{-}45}$) for clinical indications were included. Cardiovascular and HF hospitalizations, Minnesota Living with Heart Failure Questionnaire (MLHFQ) and NYHA class were assessed over 2 years. Mortality was tracked through 3 years and compared with predictions by the Seattle Heart Failure Model (SHFM). A separate analysis was performed on patients with 35% ≤ LVEF ≤ 45% (CCM-REG$_{35\text{-}45}$) and 25% ≤ LVEF < 35% (CCM-REG$_{25\text{-}34}$). Hospitalizations decreased by 75% (from 1.2/patient-year the year before, to 0.35/patient-year during the 2 years following CCM, $P < 0.0001$) in CCM-REG$_{25\text{-}45}$ and by a similar amount in CCM-REG$_{35\text{-}45}$ ($P < 0.0001$) and CCM-REG$_{25\text{-}34}$. MLHFQ and NYHA class improved in all three cohorts, with progressive improvements over time ($P < 0.002$). Three-year survival in CCM-REG$_{25\text{-}45}$ (82.8%) and CCM-REG$_{24\text{-}34}$ (79.4%) were similar to those predicted by SHFM (76.7%, $P = 0.16$; 78.0%, $P = 0.81$, respectively) and was better than predicted in CCM-REG$_{35\text{-}45}$ (88.0% vs. 74.7%, $P = 0.046$).

Conclusion In real-world experience, CCM produces results similar to those of previous studies in subjects with 25% ≤ LVEF ≤ 45% and QRS < 130 ms; cardiovascular and HF hospitalizations are reduced and MLHFQ

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and NYHA class are improved. Overall mortality was comparable to that predicted by the SHFM but was lower than predicted in patients with 35% ≤ LVEF ≤ 45%.

Keywords Minnesota Living with Heart Failure Questionnaire • Survival • Hospitalizations • Left ventricular ejection fraction

Introduction

Despite the availability of multiple modern treatment options, morbidity and mortality from heart failure with reduced ejection fraction (HFrEF) remain high and are a major contributor to cardiovascular hospitalizations and cost of care.[1–3] There is also increasing appreciation for the burdens to the health care system in the management of patients with heart failure and higher (though still less than normal) left ventricular ejection fraction (LVEF) for which there are fewer or no specific treatment options, a group now referred to as heart failure with mid-range ejection fraction (HFmrEF).[2–4]

Cardiac contractility modulation (CCM) is a therapy for patients with heart failure and persistent symptoms despite guideline-directed medical therapy (GDMT).[5–7] CCM therapy consists of non-excitatory electrical signals delivered to the heart and is available for clinical use in many countries globally and is being evaluated in clinical trials in the United States.

Most recently, the FIX-HF-5[5,8] and FIX-HF-5C[7,8] studies have shown that in patients with persistent symptoms [New York Heart Association (NYHA) class III or IV] despite GDMT, QRS duration < 130 ms and LVEF between 25% and 45%, CCM significantly improves peak oxygen uptake (VO_2), 6-minute hall walk test, quality of life [indexed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ)] and symptoms (indexed by NYHA class). More significant clinical benefits were observed in the cohort with LVEF between 35% and 45%.[7–9] Data from these studies also showed a significant reduction in heart failure hospitalizations vs. the control group.[7] These and prior studies have been limited by relatively short durations of follow-up (6–12 months), which have restricted the ability to assess the longer-term impact of CCM.

Accordingly, we established the CCM-REG registry for enrolling patients implanted with a CCM system as part of their routine clinical care from multiple sites in Europe with the purpose of accumulating long-term outcome data. Patients enrolled in this observational registry were followed in a uniform manner for up to 3 years. In view of the positive findings of the recently completed FIX-HF-5C study,[7] this report focuses on results from the subset of those subjects who, at the time of implantation, had similar characteristics as noted above.

Methods

Study overview and patient selection

The CCM-REG prospective registry is a multicentre observational study enrolling patients in whom an Optimizer System was implanted as part of routine clinical care. All patients implanted with an Optimizer device at participating centres were offered participation in this observational registry study. Overall, 72% of patients agreed to participate and provided informed consent. Enrolment began October 2013 and continued through October 2017. A list of participating centres and local investigators and countries is provided in the *Appendix*.

This analysis focused on the results obtained from all patients who met the main entry criteria for the recently completed FIX-HF-5C study,[8] namely: NYHA class III or IV, QRS duration < 130 ms and LVEF between 25% and 45%. We refer to this group as the CCM-$REG_{25\text{-}45}$ cohort. The only other requirement for enrolment is the availability of data needed to calculate the Seattle Heart Failure Model (SHFM)[10] and the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) scores[11] within 3 months after Optimizer implantation. In addition, in accordance with prior studies, we assessed outcomes separately in the subset of these patients with LVEF ≥ 35%,[7,9] a subgroup referred to as the CCM-$REG_{35\text{-}45}$ cohort and in the complementary subgroup consisting of subjects with baseline LVEF < 35% but ≥ 25% (CCM-$REG_{25\text{-}34}$).

The registry was developed in accordance with the Declaration of Helsinki. Ethics committee approval was obtained at each participating site and 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 MLHFQ score. LVEF was obtained only if ordered as part of routine clinical care. Measurements were made according to standard protocols at each site from orthogonal two-dimensional echocardiographic views of the left ventricle, using Simpson's rule to assess changes in left ventricular volumes and ejection fraction. No central core lab readings were performed and the number of available tests decreased significantly as a function of time since implant. Every effort was made to follow each subject to assure as complete a set of data as possible. The sponsor conducted 100% source data verification on an ongoing basis by on-site monitoring. The registry protocol included provisions for interim analysis and publication of data.

Outcome measures

The primary endpoint of this study was a comparison of observed survival (based on Kaplan–Meier analysis) to that predicted by the SHFM through 3 years of follow-up. We also made comparisons to the MAGGIC score but, as will be discussed, we considered predictions by SHFM more conservative. Several additional endpoints were examined, including the rate of heart failure and cardiovascular hospitalizations in comparison to those recorded during the year prior

to Optimizer implantation and changes in quality of life as indexed by NYHA functional class and MLHFQ. As noted above, these parameters were tracked through 2 years. Hospitalizations were reported and classified by local site study personnel and 100% of the source data were reviewed and verified by external monitors.

Optimizer implant

The implantation procedure was carried out according to the routine protocols for device implantation at the institution and in accordance with the Optimizer Physician's Manual. The general implantation process has been described recently.[12] CCM was programmed to be active for 5–7 h/day utilizing either one or two right ventricular septal leads. Patients were typically evaluated between 2 and 4 weeks after implantation. At that visit, the pulse generator was interrogated to assess the percentage of beats receiving CCM impulse delivery to ensure adequacy of CCM parameter programming and the need for any adjustment.

Adverse events

Serious adverse events (SAEs) were recorded during periprocedural period and during the 3-year follow-up. Categorization of SAEs was done by the site PI and reviewed by the study's Medical Director. SAEs were categorized as arrhythmic, worsening heart failure, infectious, bleeding, implantable cardioverter defibrillator (ICD)-related, lead problem, death, hospitalizations, sepsis, thromboembolism, neurological dysfunction, and renal failure. Cardiopulmonary SAEs outside the above categories were combined under the heading 'general cardiopulmonary SAE', and those related to general medical events not otherwise described above were classified as 'general medical SAE.'

Statistical analysis

Baseline characteristics are presented using descriptive statistics (*n*, mean, standard error of the mean, median, minimum, maximum, and 95% confidence intervals based on the *t*-distribution for continuous data; count and percentage for categorical data). The primary endpoint comparing observed survival to survival predicted by the SHFM was accomplished using Kaplan–Meier analysis and a modified one-sample log-rank test.[13] For other endpoints, changes from baseline at 6, 12, 18, and 24 months for NYHA class, MLHFQ, and LVEF (6 and 12 months only) were assessed with paired *t*-tests, and overall time effects were assessed with mixed linear model (PROC MIXED – with a repeated-measures approach). Pre- vs. post-implantation rates of hospitalizations (events per patient-year) were compared using a chi-square test based on the Poisson distribution.

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used to generate all analyses. Results are expressed as mean ± standard deviation unless otherwise indicated. All endpoints were assessed with two-sided tests, and statistical significance was considered for all *P*-values < 0.05.

Results

A total of 140 patients from 31 sites met the criteria for inclusion into the CCM-REG$_{25\text{-}45}$ cohort. Fifty-seven of those 140 (40%) met criteria for the CCM-REG$_{35\text{-}45}$ cohort and 83 were classified in the CCM-REG$_{25\text{-}34}$ cohort.

Baseline patient characteristics and background medications are summarized in *Table 1*. The average age was 66 ± 11 years and 79% of patients were male. Patients were well medicated with diuretics (90%), angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) (>90%) and β-adrenergic blockers (93%). At the time of enrolment, there were 102 subjects with ICD ($n = 97$), cardiac resynchronization therapy (CRT) with defibrillator ($n = 3$), or CRT with pacemaker ($n = 2$). The characteristics and background medical therapies of the CCM-REG$_{25\text{-}34}$ and CCM-REG$_{35\text{-}45}$ cohorts were similar to each other except for LVEF due to cohort selection, and a lower use of ICDs and beta-blockers in higher ejection fraction groups as expected. An ischaemic aetiology for heart failure was more frequent than a non-ischaemic aetiology in the overall cohort and in the CCM-REG$_{25\text{-}34}$ cohort ($P < 0.0001$). The sacubitril/valsartan drug combination was just being launched in Europe towards the end of the enrolment phase of this registry and was prescribed at baseline in only two patients; there were no reports of this drug being added during the follow-up period.

The primary endpoint, death from all causes compared to SHFM in the overall CCM-REG$_{25\text{-}45}$ cohort, is summarized in *Figure 1A*, with number at risk and quantitative results provided in *Table 2*. Survival was numerically higher than predicted by SHFM but this difference was not statistically significant ($P = 0.164$). Survival in the CCM-REG$_{25\text{-}34}$ cohort paralleled that predicted by the SHFM model ($P = 0.81$; *Figure 1B*). However, survival of subjects in the CCM-REG$_{35\text{-}45}$ cohort, shown in *Figure 1C* and summarized in *Table 2*, was significantly better than predicted by SHFM ($P = 0.046$). Regarding cause of death, in the overall CCM-REG$_{25\text{-}45}$ cohort there were 18 deaths, 11 cardiac, 5 non-cardiac and 2 unknown. In the CCM-REG$_{25\text{-}34}$ cohort, there were 13 deaths, 8 cardiac-related, 3 non-cardiac and 2 unknown. In the CCM-REG$_{35\text{-}45}$ cohort, there were 5 deaths, 3 cardiac-related and 2 non-cardiac.

In view of the difference in prevalence between ejection fraction subgroups (*Table 1*), we tested whether there was an impact of aetiology (ischaemic vs. non-ischaemic) on death via the Breslow–Day test. The result indicated no interaction between ejection fraction subgroups and aetiology with regard to death ($P = 0.26$).

Hospitalizations

There were 168 cardiovascular and heart failure hospitalizations in 98 of the 140 patients in the CCM-REG$_{25\text{-}45}$ cohort during the year prior to CCM activation (*Table 3*), yielding a yearly rate of 1.2 hospitalizations per patient-year. The number of hospitalizations for all causes was 195 over the same period, yielding 1.39 hospitalizations per patient-year. During the 2 years following CCM activation, there were 0.35 hospitalizations per patient-year ($P < 0.001$) for heart failure or other cardiovascular causes and a rate of 0.58 per patient-year for all hospitalizations (both less than the respective pre-hospitalization rates) ($P < 0.0001$). This reduction in events with CCM was also observed when considering heart failure hospitalizations and other cardiovascular-related hospitalizations separately (*Table 3*). In the CCM-REG$_{35\text{-}45}$ cohort, similarly significant reductions in yearly hospitalization rates were

Table 1 Baseline characteristics of patients in the CCM-REG$_{25-45}$, CCM-REG$_{35-45}$ and CCM-REG$_{25-34}$ registry cohorts

	CCM-REG$_{25-45}$ 25% ≤ LVEF ≤ 45% QRS ≤ 130 ms NYHA class ≥ III	CCM-REG$_{35-45}$ 35% ≤ LVEF ≤ 45% QRS ≤ 130 ms NYHA class ≥ III	CCM-REG$_{25-34}$ 25% ≤ LVEF < 35% QRS ≤ 130 ms NYHA class ≥ III
Patients, *n*	140	57	83
LVEF (%)	32.7 ± 5.1	37.9 ± 2.6	29.1 ± 2.7
Gender			
Male	111 (79)	43 (75)	68 (82)
Female	29 (21)	14 (25)	18 (22)
Age (years)	66 ± 11	67 ± 11	66 ± 11
Subjects with ICD	97 (69)	27 (47)	70 (84)
Aetiology of cardiomyopathy			
Ischaemic	97 (69)	32 (56)	65 (78)
Non-ischaemic	43 (31)	25 (44)	18 (22)
QRS duration (ms)	102 ± 15	102 ± 17	102.6 ± 14
NYHA class	3.2 ± 0.28	3.2 ± 0.27	3.2 ± 0.28
MLHFQ	44 ± 18	47 ± 18	43 ± 18
Sodium (mmol/L)	139 ± 3.3	140 ± 2.9	139 ± 3.6
Creatinine (mg/dL)	1.40 ± 0.60	1.46 ± 0.72	1.35 ± 0.5
Haemoglobin (g/dL)	13.2 ± 2.2	13.1 ± 2.4	13.4 ± 2.1
Systolic blood pressure (mmHg)	125 ± 19	126 ± 21	125 ± 18
Diabetes	64 (46)	24 (42)	40 (48)
COPD	39 (28)	15 (26)	24 (29)
Current smoker	36 (26)	14 (25)	22 (27)
Atrial fibrillation history	39 (28)	18 (32)	21 (26)
Presence of CRT	2 (1.4)	2 (3.5)	2 (2)
Medications			
Diuretic	126 (90)	53 (93)	77 (93)
Furosemide	21 (15)	8 (14)	10 (12)
Hydrochlorothiazide	18 (13)	8 (14)	10 (12)
Torsemide	110 (79)	42 (74)	66 (80)
Xipamid	12 (9)	4 (7)	7 (8)
ACE-i	84 (60)	35 (61)	49 (59)
ARB	45 (32)	17 (30)	28 (34)
Beta-blocker	130 (93)	50 (88)	80 (96)
Aldosterone antagonist	84 (60)	32 (56)	52 (63)
Digoxin	6 (4.3)	2 (3.5)	4 (5)
Allopurinol	36 (26)	17 (30)	19 (23)
Statin	115 (82)	45 (79)	70 (84)

Data are given as mean ± standard deviation, or *n* (%).
ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCM, cardiac contractility modulation; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association.

observed during the 2 years following CCM implantation compared to the year prior to implantation (*Table 3*). In the CCM-REG$_{25-34}$ group, a similar reduction was also observed after CCM in all groups except for cardiac non-heart failure hospitalizations ($P = 0.33$).

Minnesota Living with Heart Failure Questionnaire

Changes in quality of life assessed by MLHFQ are shown in *Figure 2* (numbers above bars indicate the number of paired subjects contributing to results at each time-point along with corresponding *P*-values from paired *t*-tests). A significant improvement was observed in the overall CCM-REG$_{25-45}$ cohort (*Figure 2A*), decreasing by 11.7 at 6 months, by 11.8 at 12 months, by 11.4 at 18 months, and by 17.1 at 24 months ($P < 0.001$ at each time-point). In the CCM-REG$_{25-34}$ cohort (*Figure 2B*) MLHFQ decreased by 10.4 at 6 months, by 7.3 at 12 months, by 7.9 at 18 months, and by 12.5 at 24 months ($P \leq 0.02$ at each time-point). Finally, in the CCM-REG$_{35-45}$ subgroup MLHFQ decreased by 13.6 at 6 months, by 18.4 at 12 months, by 16.3 at 18 months, and by 25.3 at 24 months ($P \leq 0.001$ at each time-point).

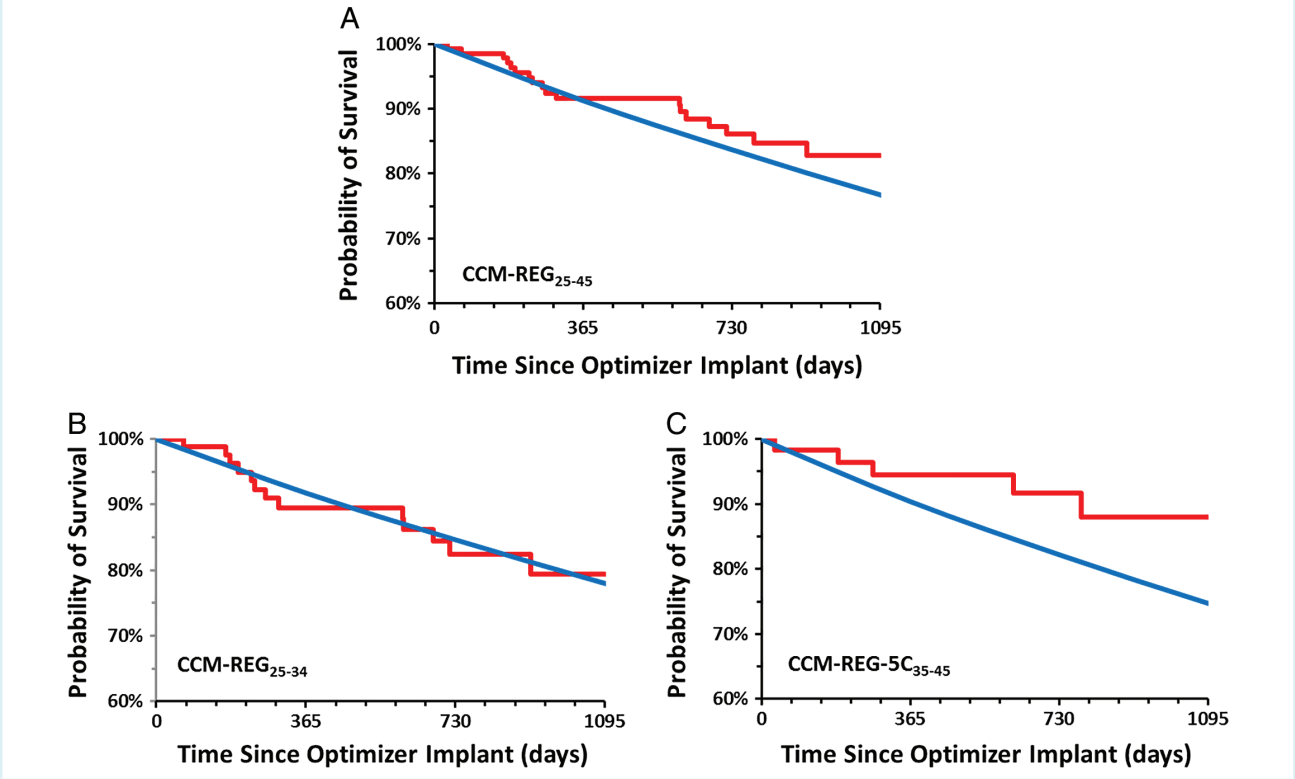

Figure 1 Kaplan–Meier survival curves over 3 years of follow-up. (*A*) Survival rates of the CCM-REG$_{25\text{-}45}$ cohort (red) which were comparable to the values predicted by the Seattle Heart Failure Model (blue). (*B*) In the CCM-REG$_{25\text{-}34}$ cohort with LVEF $< 35\%$, survival was similar to that predicted by the Seattle Heart Failure Model. (*C*) For the CCM-REG-5C$_{35\text{-}45}$ cohort with LVEF $\geq 35\%$, observed survival was greater than predicted by the model.

New York Heart Association class

Significant reductions of NYHA functional class were also observed in the entire CCM-REG$_{25\text{-}45}$ cohort as summarized in *Figure 3* (numbers above bars indicate the number of paired subjects contributing to results at each time-point along with corresponding *P*-values from paired *t*-tests). across the 2-year follow-up period, decreasing by 0.6 at 6 months, by 0.7 at 12 months, by 0.7 at 18 months, and by 0.8 at 24 months ($P < 0.001$ at each time-point). Similar, sustained improvements in NYHA class were observed in both the CCM-REG$_{25\text{-}34}$ and CCM-REG$_{35\text{-}45}$ cohorts (*Figure 3B* and *C*, respectively).

Left ventricular ejection fraction

Since LVEF measurements were not part of routine care at each follow-up time-point, the number of observations decreased more significantly than the other endpoints; accordingly, we only report paired results for the 6-month follow-up. In the entire CCM-REG$_{25\text{-}45}$ cohort, LVEF increased from 32.8 ± 4.9 at baseline to 35.8 ± 8.2 at 6 months ($n = 51$, $P = 0.003$). In the CCM-REG$_{35\text{-}45}$ cohort, LVEF trended towards an increase from 38.2 ± 2.4 at baseline to 41.0 ± 7.2 at 6 months ($n = 19$, $P = 0.081$). Finally, in the CCM-REG$_{25\text{-}34}$ subgroup, LVEF increased from 29.7 ± 2.7 at baseline to 32.8 ± 7.3 at 6 months ($n = 32$, $P = 0.021$).

Cardiac contractility modulation effectiveness by the Seattle Heart Failure Model score

In addition to ejection fraction, the SHFM score provides a measure of risk of morbidity, hospitalization and mortality. In the entire cohort, the median SHFM score was 0.4 (95% confidence interval 0.29–0.60). Consistent with that, we found that the greater the value of SHFM, the greater the actual mortality rate (c-statistic = 0.7168, regression *P*-value = 0.0035) and the greater the value of SHFM the greater the rate of hospitalizations (c-statistic = 0.6593, regression *P*-value = 0.0024). Changes in MLHFQ and NYHA from baseline were similar in patients whose SHFM score was above or below the median in the entire cohort and in the CCM-REG$_{25\text{-}34}$ and CCM-REG$_{35\text{-}45}$ cohorts individually. Patients with higher SHFM had a higher mortality (19% in the high SHFM group vs. 6% in the low SHFM group; $P = 0.025$). In patients with SHFM > 0.4, mortality was 19% compared with 35% that was predicted by the SHFM ($P = 0.041$). In patients with SHFM ≤ 0.4, mortality was 6% compared with 10% that was predicted by SHFM

Table 2 Comparison of survival observed following Optimizer implantation (cardiac contractility modulation group) to that predicted by the Seattle Heart Failure Model

	Baseline	1 Year	2 Years	3 Years	*P*-value (SHFM vs. CCM)
CCM-REG$_{25\text{-}45}$	140	104	71	29	
Number at risk	140	104	71	29	
CCM	100.0%	91.6% [85.3–95.3%]	86.2% [78.2–91.4%]	82.8% [73.4–89.1%]	
SHFM	100.0%	91.3%	83.7%	76.7%	0.1644
CCM-REG$_{35\text{-}45}$					
Number at risk	57	43	30	12	
CCM	100.0%	94.5% [83.9–98.2%]	91.7% [79.0–96.9%]	88.0% [72.5–95.1%]	
SHFM	100.0%	90.4%	82.2%	74.7%	0.0463
CCM-REG$_{25\text{-}34}$					
Number at risk	83	61	41	17	
CCM	100.0%	89.6% [80.2–94.6%]	82.5% [70.9–89.8%]	79.4% [66.3–87.9%]	
SHFM	100.0%	91.8%	84.6%	78.0%	0.8072

CCM, cardiac contractility modulation; SHFM, Seattle Heart Failure Model.
P-values from a modified one-sample log-rank test.

Table 3 Rate of hospitalizations for heart failure and other cardiovascular causes 2 years following cardiac contractility modulation activation compared to 1 year prior

Subgroup/category	Pre-enrolment			Post-enrolment			*P*-value*
	Patient-years	Events	Event rate	Patient-years	Events	Event rate	
CCM-REG$_{25\text{-}45}$							
All[a]	140	195	1.39	279.6	162	0.58	<0.0001
HF[b]		134	0.96		73	0.26	<0.0001
CV not HF[c]		34	0.24		24	0.09	<0.0001
All CV[d]		168	1.20		97	0.35	<0.0001
CCM-REG$_{35\text{-}45}$							
All[a]	57	83	1.46	113.5	51	0.45	<0.0001
HF[b]		47	0.82		18	0.16	<0.0001
CV not HF[c]		23	0.40		9	0.08	<0.0001
All CV[d]		70	1.23		27	0.24	<0.0001
CCM-REG$_{25\text{-}34}$							
All[a]	83	112	1.35	166.1	111	0.67	<0.0001
HF[b]		87	1.05		55	0.33	<0.0001
CV not HF[c]		11	0.13		15	0.09	0.3309
All CV[d]		98	1.18		70	0.42	<0.0001

CCM, cardiac contractility modulation; CV, cardiovascular; HF, heart failure.
[a]All hospitalizations regardless of cause.
[b]HF-related.
[c]CV but not related to HF.
[d]CV-related.
*P-value comparing post-vs. pre-enrolment.

($P = 0.53$). Thus, the benefits of CCM on quality of life were similar across the spectrum of SHFM scores; the impact of CCM on mortality was greatest in patients at higher risk.

Serious adverse events

There were 18 device- or procedure-related adverse events reported in 14 patients during the first 30 days following device implantation. These included bleeding ($n = 1$), supraventricular arrhythmias ($n = 2$), pericardial effusion ($n = 1$), worsening heart failure ($n = 5$), Optimizer pocket infection ($n = 1$), Optimizer lead dislodgement ($n = 2$), and other general medical events ($n = 6$).

Serious adverse events were tracked over the 3-year follow-up period. During this period, 201 events were reported in 82 patients. Of these, 10 events (nine subjects) were classified as an Optimizer device- or Optimizer lead-related adverse event. These

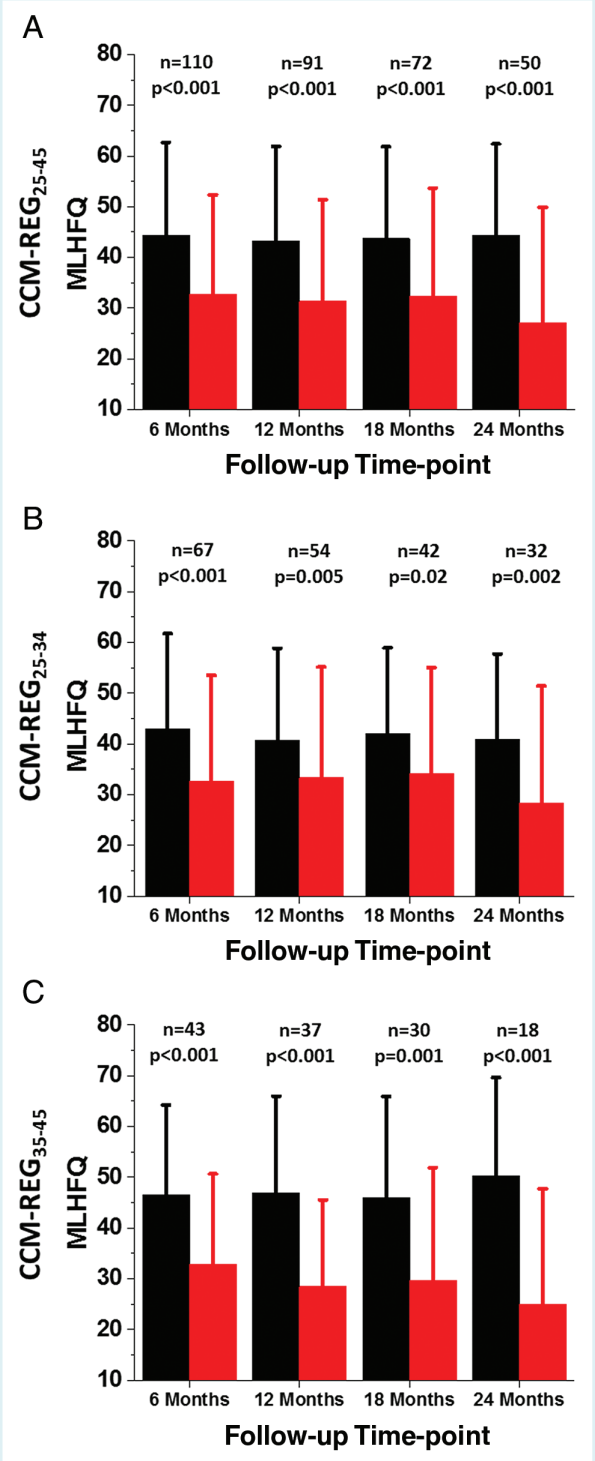

Figure 2 Effect of cardiac contractility modulation (CCM) on Minnesota Living with Heart Failure Questionnaire (MLHFQ) score. Paired baseline (black) and follow-up (red) mean (standard deviation) values shown at each time-point for the entire CCM-REG$_{25-45}$ (*A*), for the CCM-REG$_{25-34}$ cohort (*B*), and for the CCM-REG$_{35-45}$ cohort (*C*). Numbers above symbols indicate the number of paired contributing subjects at each time-point along with *t*-test for each comparison.

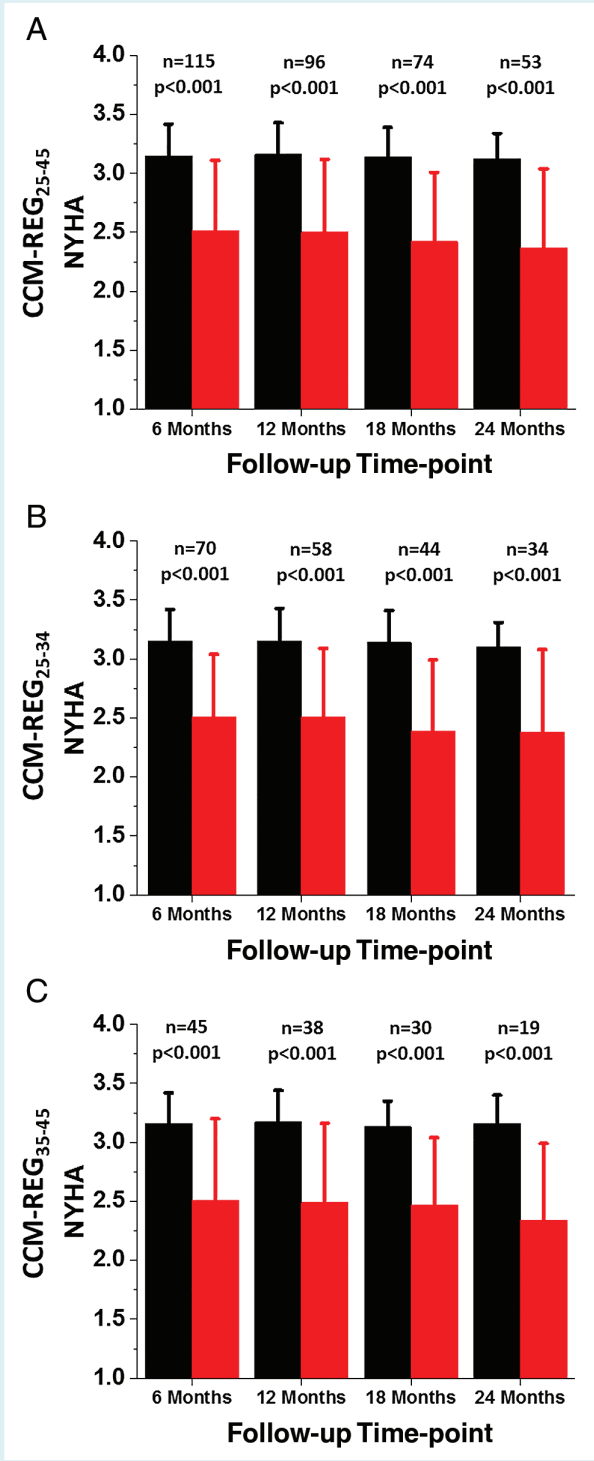

Figure 3 Effect of cardiac contractility modulation (CCM) on New York Heart Association (NYHA) functional class. Paired baseline (black) and follow-up (red) mean (standard deviation) values shown at each time-point for the entire CCM-REG$_{25-45}$ (*A*), for the CCM-REG$_{25-34}$ cohort (*B*), and for the CCM-REG$_{35-45}$ cohort (*C*). Numbers above symbols indicate the number of paired contributing subjects at each time-point along with *t*-test for each comparison.

included Optimizer lead fracture ($n = 1$), pocket stimulation ($n = 2$), ventricular lead dislodgement ($n = 5$), pocket erosion ($n = 1$), and thoracic muscle contraction ($n = 1$).

An overview of all reported SAEs are summarized in *Table 4* (including the 10 device-related events described above) and are stratified by ejection fraction grouping. The most frequent SAE was worsening heart failure, which occurred in 32 subjects, representing 23% of the total number enrolled. The rate of SAEs is comparable to that seen in other studies enrolling similar patient populations. General medical SAEs included uncontrolled diabetes, renal insufficiency/failure, neurological dysfunction, epilepsy/seizure, gastrointestinal disease, orthopaedic disorders, trauma, peripheral artery disease, hyperthyroidism, benign prostatic hypertrophy, sleep apnoea, hypoglycaemia, and other non-cardiovascular or non-specific medical abnormalities.

Discussion

The current analysis represents the largest longer-term prospective analysis of survival and hospitalizations in patients with heart failure treated with CCM. The results provide important new insights into the sustainability of the clinical effects of CCM when applied in addition to GDMT in this population (patients with 25% ≤ LVEF ≤ 45%, QRS < 130 ms and persistent NYHA class III or IV symptoms). First, over the 2-year period during which secondary endpoints were obtained, CCM showed similar positive effects in reducing heart failure hospitalizations to those observed in the shorter randomized studies.[8] Specifically, CCM use was associated with a 75% reduction in the rate of cardiovascular and heart failure hospitalizations in the CCM-REG$_{25\text{-}45}$ cohort, an approximately 80% reduction in the CCM-REG$_{35\text{-}45}$ cohort and a roughly 65% reduction in the CCM-REG$_{25\text{-}34}$ cohort when compared with the year prior to CCM therapy. Further, symptoms and quality of life (NYHA class, MLHFQ) showed sustainable improvement and of similar magnitude to the ones observed in the randomized studies.[5–7] LVEF also improved during the early follow-up period, as in prior studies.[14,15] Finally, 3-year survival was comparable to that predicted by SHFM in the overall group and the CCM-REG$_{25\text{-}34}$ group, whereas in the subset of patients with 35% ≤ LVEF ≤ 45%, survival was significantly better than predicted by SHFM. Collectively, these data both confirm and extend the evidence for the safety and efficacy of CCM.

Hospitalization is a frequent and major source of morbidity and expense for patients with heart failure and there are mandates within the medical community to identifying treatments that reduce heart failure-related hospitalizations.[1,16] Importantly, the reduction in rates of hospitalizations we observed in the CCM-REG cohort was comparable to that reported for CRT,[17] albeit in a different patient population.

Relief of symptoms and improvements of functional capacity identified in randomized studies of CCM have consistently been more pronounced in patients with less severely compromised left ventricular function.[5,7,15,18] The FIX-HF-5 study[5] initially identified better effects in patients with LVEF ≥ 25% and even more pronounced improvements in those with LVEF ≥ 35%. These findings have now been confirmed in the follow-on FIX-HF-5C study.[7] The results of the current study not only confirm these findings again in a similar patient population, but also add important complementary data related to the impact of CCM on hospitalizations and mortality in the LVEF ≥ 35% cohort by recruitment of patients receiving CCM for clinical indications, thus minimizing the potential for selection bias in controlled prospective trials.

A randomized blinded controlled trial of CCM with mortality as the primary outcome has not been performed. However, data from the randomized controlled FIX-HF-5 and FIX-HF-5C trials of CCM vs. optimal medical therapy have shown a reduction in the composite 24-week outcome of cardiovascular death and heart failure hospitalization.[7] The enrolment criteria were similar to those for the current registry (NYHA class > III, QRS duration < 130 ms, 25% ≤ LVEF ≤ 45%). In that study of 160 patients, significant improvements were also observed in peak VO_2, symptoms and quality of life. The present study supports these findings in a practical real-life population receiving CCM followed for a longer period of time.

Several relevant prior but smaller retrospective studies show either no detriment in survival or suggest a survival benefit. Schau *et al.*[19] retrospectively evaluated 54 patients with moderate to severe heart failure treated with CCM. When compared to the SHFM predicted mortality, no difference was observed. Kuschyk *et al.*[20] conducted a single site study in Germany enrolling 81 subjects treated with CCM for heart failure. Analysis of the Kaplan–Meier curves revealed a significant reduction in mortality at 3 years compared to the MAGGIC predicted value. Kloppe *et al.*[21] conducted a mortality study of 68 subjects at two sites in Germany. Survival at 1, 2, and 5 years was better than predicted by SHFM modelling. In a more recent study, Liu *et al.*[18] reported on 41 consecutive patients with LVEF < 40% treated for heart failure with CCM and followed for 75 months. Control subjects were matched from the same clinical practice. All-cause mortality was less in those treated with CCM. When subjects were stratified by LVEF, those with LVEF between 25% and 40% had significantly reduced mortality compared to control. Those with LVEF < 25% had no difference in mortality. Most recently, Muller *et al.*[15] reported results of a registry that included 143 patients treated with CCM with LVEFs up to 45% (no lower limit; mean ± standard deviation LVEF of 28.3 ± 6.4) who were followed for 2 years; there were only 28 patients with LVEF > 35%. Overall survival estimated by Kaplan–Meier analysis was 94.2% at 1 year and 86.4% at 2 years, which are very similar to those reported in the current overall CCM-REG$_{25\text{-}45}$ cohort.

The current registry is the first to prospectively examine survival over a 3-year period with real-world experiences across multiple sites in patients implanted for clinical indications and followed in routine fashion by their primary care providers. As indicated in Methods, we compared observed mortality to that predicted by SHFM. We also calculated the MAGGIC score.[11,22] Overall, we found that survival predicted by the MAGGIC score was significantly lower than that of the SHFM. For example, in the entire CCM-REG$_{25\text{-}45}$ cohort, where observed survival at 3 years was 82.8% and SHFM predicted 76.7%, survival predicted by the MAGGIC score was only 63.3%, which was a statistically

Table 4 Serious adverse events over 3 years stratified by patient subgroup according to ejection fraction

Category	25% ≤ LVEF ≤ 34% (*n* = 83)			35% ≤ LVEF ≤ 45% (*n* = 57)			25% ≤ LVEF ≤ 45% (All) (*n* = 140)		
	Events	Pts.	%	Events	Pts	%	Events	Pts	%
Optimizer lead fracture or failure	0	0	0.0	1	1	1.8	1	1	0.7
Optimizer related – other	6	6	7.2	3	3	5.3	9	9	6.4
Bleeding (clinically significant)	1	1	1.2	1	1	1.8	2	2	1.4
Infection (other than Optimizer pocket)	12	9	10.8	1	1	1.8	13	10	7.1
ICD-related	2	2	2.4	0	0	0.0	2	2	1.4
Cardiac – arrhythmias	5	5	6.0	5	4	7.0	10	9	6.4
Cardiac – worsening HF	49	24	28.9	12	8	14.0	61	32	22.9
Cardiac – other	5	5	6.0	7	4	7.0	12	9	6.4
General cardiopulmonary	24	15	18.1	11	9	15.8	35	24	17.1
Sepsis	1	1	1.2	0	0	0.0	1	1	0.7
TIA/stroke	3	2	2.4	0	0	0.0	3	2	1.4
Thromboembolism (non-neurologic)	1	1	1.2	0	0	0.0	1	1	0.7
General medical	30	21	25.3	21	14	24.6	51	35	25.0
Total	**139**	**49**	**59.0**	**62**	**33**	**57.9**	**201**	**82**	**58.6**

Device-related and medical condition-related events are listed.
HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; TIA, transient ischaemic attack.

significant difference ($P < 0.001$). For the CCM-REG$_{35\text{-}45}$ cohort, where observed survival at 3 years was 88.0% and SHFM predicted 74.7% ($P = 0.046$), survival predicted by the MAGGIC score was 67.7%; again, observed survival was significantly better than predicted by MAGGIC ($P < 0.001$). Consistent with our observations, one prior study also showed that the MAGGIC score tended to overestimate mortality in comparison to the SHFM.[23] Accordingly, we chose the more conservative SHFM predications on which to base the present study and conclusions. While the SHFM is not as powerful as a true control group, it has been developed from and validated across a large number of randomized clinical trials.

The similarity of survival in both the entire CCM-REG$_{25\text{-}45}$ and the CCM-REG$_{25\text{-}34}$ cohorts to those predicted by the SHFM, and the superior survival in the CCM-REG-5C$_{35\text{-}45}$ compared to that predicted by the SHFM cohort are both very encouraging findings. However, even when overall survival seems significantly better on a statistical basis vs. a prediction model, such findings should not be over-interpreted as proving a mortality benefit. Nevertheless, we believe these findings do provide important information regarding the long-term safety of CCM therapy.

Cardiac contractility modulation offers a device therapy option to patients who are ineligible for CRT because of the presence of a narrow QRS complex.[24–27] The fact that the results of CCM in this study were even better in those with more mildly reduced LVEF, close to the range of the recently described HFmrEF with LVEFs between 40% and 49%,[28–31] offers a new alternative treatment to consider for this 'middle group' of heart failure patients.

The mechanisms underlying better clinical responses to CCM in higher ejection fraction patients, a consistent finding across several studies,[7,32] are not yet defined. CCM signals are delivered locally to the right ventricular septum (which is an anatomic equivalent to the left ventricular epicardium); their acute molecular effects are only observed in the local area of signal delivery.[33] Over time, effects appear in remote areas.[33,34] It is therefore hypothesized that the smaller the heart, the greater the ability to impact on remote areas. Since LVEF is mainly an index of heart size (lower LVEF associated with larger left ventricular size), CCM may be able to influence a greater proportion of myocardium in hearts with higher LVEFs. Another factor may be that hearts with lower ejection fractions likely have more scar and less muscle mass; CCM can only exert effects on viable myocardium. Nevertheless, if correct, these concepts offer an opportunity for further device development aimed at multisite CCM signal delivery; original attempts at left ventricular free wall signal delivery were unsuccessful due to sensation experienced by patients when signals were delivered via leads in the epicardial coronary veins.

Limitations

The limitations of the present study have already been largely acknowledged. First, this was not a randomized study and there was no separate control group. Our choice of the SHFM to provide a basis for interpreting observed survival, while not as ideal as a control group, has been detailed above and was chosen over the MAGGIC score since it provided more conservative estimates. We also do not report any measure of functional capacity since this was not a standard clinical test and was required for the present registry study. Furthermore, the fact that this study was a voluntary registry collecting data from routine clinical visits imposed at least two limitations. First, study participation was offered to all patients implanted with an Optimizer at each participating centre, ~30% of patients did not agree to participate; there is no way to determine the characteristics of those that did not participate compared

to those that did participate, and whether this created selection bias in the results. Second, several clinical parameters including hospitalizations, NYHA class and MLHFQ scores were difficult to collect over the past 2 years. Interpretation of the changes in LVEF was limited by lack of an adjudicating echocardiography core (each site calculated this parameter separately) and by the relatively small number of LVEF values at later time-points, which increases the possibility of a type II error and of selection bias. For this reason, we only report changes for paired observations at 6 months. For similar reasons, we did not attempt to collect measures of exercise tolerance that are not performed in the course of routine clinical care such as 6-minute hall walk or peak VO_2.

In the context of randomized studies, core labs are used for analysis of endpoints such as LVEF, and adjudication committees are used to examine clinical endpoints; these were not utilized in the present study and are typically not used in real-world registry studies.

Conclusions

In summary, this is the largest long-term prospective evaluation of CCM in heart failure with moderately reduced ejection fraction and persistent symptoms. After 3 years of follow-up, CCM was associated with a reduction in heart failure hospitalizations similar to that observed in a previous, randomized study of less duration. Improvements in functional status and quality of life extended at least through 24 months. There was no detriment in 3-year survival compared to that predicated by SHFM in the overall cohort; patients with LVEF between 35% and 45% may derive a survival benefit from CCM. Thus, consistent with previous smaller studies, the cohort of subjects with LVEF between 25% and 45% appears to derive significant clinical benefit from CCM with improvement in quality of life and functional capacity over extended periods of time.

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Appendix

The following centres, cities and principal investigators enrolled patients in this registry study: Universitätsmedizin Mannheim, Mannheim, Germany, Prof. Dr. Martin Borggrefe. Märkische Kliniken GmbH Lüdenscheid, Prof. Dr. Bernd Lemke. MVZ am Kuechwald GmbH, Chemnitz, Dr. Wilfried Daenschel. Universitätsklinikum Leipzig, Leipzig, Dr. med. Martin Neef. St. Agnes Hospital Bocholt, Bocholt. Internistenteam Kamen, Kamen, Dr. Fastenrath. Universitätsklinikum Frankfurt, Frankfurt am Main, Prof. Dr. Stefan Hohnloser. Herz- und Gefäßzentrum Bad Bevensen, Bad Bevensen, Prof. Dr. med. Bjoern Remppis. Asklepios Westklinikum Hamburg, Hamburg, PD Dr. Schneider. AK St. Georg, Hamburg, Prof. Dr. med. Karl-Heinz Kuck. HPK- Heidelberger Privatklinik, Heidelberg, Dr. med. Mohammed Natour. Kreisklinikum Günzburg-Krumbach, Krumbach, Dr. Cornelia Monat. St. Vincenz-Krankenhaus, Paderborn, Prof. Dr. med. Andreas Goette. Zentralklinik Bad Berka, Bad Berka, PD Dr. med. Marc-Alexander Ohlow. Katholisches Krankenhaus, Erfurt, Prof. Dr. med. Henning Ebelt; Charité Campus Benjamin Franklin (CBF), Berlin, Dr. med. Martin Huemer. Praxisklinik Herz- und Gefaesse Dresden, Dresden, Dr. Laszlo Karolyi; Helios Klinikum Erfurt, Erfurt, Dr. med. Frank Steinborn; SRH Wald-Klinikum Gera, Gera, Dr. med. Jana Hoffmann. Elbe Klinikum Stade, Stade, Dr. med. Oliver Marx. Helios Vogtland-Klinikum Plauen, Plauen, Dr. med. Hans Neuser. Klinikum Niederlausitz, Senftenberg. Universitätsklinikum der RWTH Aachen, Aachen, PD Dr. med. Sebastian Reith. Medizinische Hochschule Hannover, Hannover, PD Dr. med. Christian Veltmann. Jüdisches Krankenhaus Berlin, Berlin, Dr. med. Andreas Greissinger. Universitaetsklinik Magdeburg, Magdeburg, Prof. Dr. med. R. Braun-Dullaeus. Helios St. Marienberg Klinik, Helmstedt, Dr. med. Samir Said; Hufeland Klinikum GmbH, Thüringen. Dr. Kaiser Köln. Evangelisches Krankenhaus Köln Kalk gGmbH, Köln, PD Dr. med. Frank Eberhardt. DRK Krankenhaus Sömmerda, Sömmerda, Dr. Corinna Müller. Krankenhaus Buchholz und Winsen gemeinn. GmbH, Buchhohlz i. d. Nordheide, Dr. Klaus Hertting.

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