

## Improvement of long-term survival by cardiac contractility modulation in heart failure patients: A case–control study



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### ABSTRACT

**Introduction:** Cardiac contractility modulation (CCM) has been shown to be effective in improving symptoms and cardiac function in heart failure (HF). However, there is limited data on the role of CCM on long-term survival, which was explored in the present study.

**Methodology:** Forty-one consecutive HF patients with left ventricular ejection fraction (EF) <40% received CCM and were followed for approximately 6 years. They were compared with another 41 HF patients who were enrolled into the HF registry in the same period, and had similar age, gender, EF and etiology of HF. The primary end-point was all cause-mortality. This was stratified by EF. Secondary end-points included HF hospitalization, cardiovascular death, and the composite outcome of death or heart failure hospitalization.

**Results:** The CCM and control groups were well balanced for demographic data, medications and baseline left ventricular EF ( $27 \pm 6$  vs  $27 \pm 7\%$ ,  $p = \text{NS}$ ). The mean follow-up duration was  $75 \pm 19$  months in the CCM group and  $69 \pm 17$  months in the control group. All-cause mortality was lower in the CCM group than the control group (39% vs. 71%, respectively; Log-rank  $\chi^2 = 11.23$ ,  $p = 0.001$ ). Of note, the improvement of all-cause mortality is more dramatic in patients with EF  $\geq 25$ –40% (36% vs. 80%, Log-rank  $\chi^2 = 15.8$ ,  $p < 0.001$ ) than those with EF < 25% (50% vs. 56%,  $p = \text{NS}$ ), CCM vs. control respectively. Similar results were shown for the benefit of CCM in the secondary endpoints of cardiovascular death, and the composite outcome of death or heart failure hospitalization. The occurrence of HF hospitalization showed no significant difference between CCM and control groups in the whole cohort (41% vs. 49%,  $p = \text{NS}$ ), but was significantly lower with CCM in subjects with EF  $\geq 25$ –40% at baseline (36% vs. 64%, Log-rank  $\chi^2 = 7.79$ ,  $p = 0.005$ ).

**Conclusion:** CCM resulted in significant improvement of long-term survival, in particular in those with EF  $\geq 25$ –40%. A reduction in heart failure hospitalizations was also seen in this group of patients with less severely reduced EF.

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### 1. Introduction

The incidence of heart failure is increasing in part due to more aggressive treatment of acute coronary syndromes, leaving more survivors who have had significant loss of cardiac function. The growing incidence of heart failure is expected to continue, especially in China where Westernization has propelled the prevalence of cardiovascular disease over 230 million and rank it as the commonest cause of death

[1]. As a result the number of patients in China with heart failure is expected to increase rapidly from its current prevalence of 4.2 million.

Even though therapies for chronic heart failure have advanced significantly in the past two decades, an enlarging number of patients with ejection fractions (EF) < 45% on optimal medical therapy experience life-style limiting symptoms. For these subjects, several types of device-linked therapies are potentially available including implantable cardiac defibrillators (ICD), cardiac resynchronization therapy (CRT), and cardiac contractility modulation (CCM). Although many of these patients are candidates for the life-prolonging effects of ICDs, in the subset of patients with EF < 35%, this therapy does not improve symptoms or functional status. Use of ICDs has regional variability across the globe. About one fourth of this group of patients with heart failure has left bundle branch block or otherwise prolonged QRS duration and benefits from CRT [2,3]. However for the remaining majority, who do not have

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QRS widening, CRT does not help or may be detrimental [4]. In this group, CCM (Optimizer device, Impulse Dynamics) has proven to be safe and effective, improving peak  $VO_2$ , New York Heart Association (NYHA) classification, symptoms and well-being (Minnesota Living with Heart Failure questionnaire), 6-Minute Hall Walk test and EF [5–7].

CCM delivers a biphasic high voltage signal to the right ventricular septum during the absolute refractory period, triggered by detecting the tissue depolarization within the QRS complex with a timed delay. CCM acutely increases EF by about 5% and over time improves other parameters of cardiac function and symptoms. The mechanism of action involves improvement of cardiac calcium handling through upregulation of phospholamban, sarcoendoplasmic reticulum calcium transport ATPase, and L-type calcium channels both locally near the CCM signal delivery site and remotely throughout the heart [6]. CCM use also elicits left ventricular reverse remodeling of the fetal gene program towards that seen in normal hearts with elevation of myosin heavy chain- $\alpha$  and reduction in B-type Natriuretic Peptide levels [8]. While the acute and short term benefits (months) are well-established, much less data exist regarding longer term benefits including effects on mortality and hospitalization. This report provides long-term follow-up on 41 consecutive symptomatic subjects with EF < 40% in whom an Optimizer device was implanted and compared to a matched control group from a local heart failure registry of selected patients who did not receive CCM.

## 2. Methods

The study group consisted of forty-one consecutive patients with NYHA III symptomatic heart failure and EF < 40% who were on stable doses of heart failure medications and in whom an Optimizer III device was deployed. Patients were recruited from a University teaching hospital from 2005 to 2012. The protocol was approved by the local ethics board and all study subjects provided written informed consent. The comparator group consisted of 41 heart failure patients enrolled in the same hospital's heart failure registry over the same time period and who were also receiving optimal medical therapy (non-CCM control group). Control group subjects were matched 1:1 to the CCM group by age, gender, medications at baseline, left ventricular EF at baseline, follow-up duration, and etiology of heart failure (Table 1). Based on local standards of care, ICDs were not typically implanted in the patients. Two patients had an ICD at the time the study began and none were implanted during the course of the study.

**Table 1**  
Baseline characteristics of the CCM and control groups.

Parameters	CCM (n = 41)	Control group (n = 41)	P value
<i>Demographic data</i>			
Age, years	61 ± 10	64 ± 11	0.15
Male, n (%)	35 (85)	35 (85)	1.00
Follow-up duration (months)	75 ± 19	69 ± 17	0.10
LVEF, %	27 ± 7	27 ± 6	0.95
NYHA class, n (%)	3.0 ± 0.0	3.29 ± 0.68	<0.001
I	0 (0)	1 (2)	
II	0 (0)	2 (5)	
III	41 (100)	22 (54)	
IV	0 (0)	16 (39)	
PAF <sup>a</sup> at baseline, n (%)	6 (15)	15 (37)	0.02
Ischemic causes of HF, n (%)	21 (51)	16 (39)	0.38
<i>Medications at admission</i>			
Diuretics, n (%)	29 (71)	25 (61)	0.35
Aldosterone antagonists, n (%)	6 (15)	1 (2)	0.11
ACEI/ARB, n (%)	31 (76)	26 (63)	0.34
Beta-blocker, n (%)	32 (78)	27 (66)	0.22
Digoxin, n (%)	5 (12)	6 (15)	0.75

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; HF, heart failure; ACEI, Angiotensin converting enzyme inhibitors; ARB, Angiotensin receptor blockers.

<sup>a</sup> No patients had permanent AF or any AF at the time of implantation.

The primary end-point was all cause-mortality. Secondary end-points included HF hospitalization, cardiovascular death, and the composite outcome of death or heart failure hospitalization. Endpoints were stratified by EF.

### 2.1. Device implantation and programming

CCM implantation was performed under local anesthesia. Three standard pacing leads were tunneled subcutaneously into the subclavian vein. One was advanced into the right atrium and the other two were secured into anterior and inferior aspects of the right ventricular endocardium. The generator was inserted into a subcutaneous pocket formed in the left subclavicular area. In some patients, acute LV + dP/dt(max) was measured with a Millar catheter before and during CCM activation and the physician could then decide whether to reposition the right ventricular leads based on the acute changes in + dP/dt(max).

After closing incisions, the Optimizer III was wirelessly programmed to deliver impulses only when atrial sensed signal is followed by ventricular signal occurring at a pre-specified interval. CCM is designed to be active only in heart beats when ventricular arrhythmias are absent. Treatment was delivered during several one hour periods spread throughout the day for 7 h/day.

### 2.2. Baseline measurements and follow-up

Patients who received CCM were followed up prospectively and were monitored as an outpatient approximately every 6 months with device interrogation performed with each visit. During the peri-implantation period subjects underwent history and physical examination, echocardiography, laboratory testing, and assessments of symptoms. Patients included in the study arm had 1) NYHA Class III or IV heart failure with left ventricular EF ≤ 40% and 2) were required to be on a stable medical regimen for heart failure (appropriate doses of a beta-adrenergic blocker, ACE-inhibitor or angiotensin receptor blocker, aldosterone antagonist, and/or diuretic) for at least 1 month. Other inclusion criteria were 3) age > 18, and 4) QRS < 130 ms (unless not appropriate for CRT). Patients were excluded for 1) permanent atrial fibrillation or atrial flutter (some had paroxysmal atrial fibrillation but were in sinus rhythm at the time of implantation), 2) severe symptomatic heart failure appropriate for transplantation, 3) treatment with intravenous inotropic medications within the past 3 weeks, 4) baseline peak  $VO_2$  known to be < 9 ml/min × kg, 5) clinically significant angina pectoris (Canadian Cardiovascular Society Angina score of II or more) or an episode of unstable angina or myocardial infarction within 30 days of enrollment, or resting ischemia by ECG or symptoms of angina, 6) potentially correctable cause of heart failure, 7) ICD firing within 1 month of enrollment, 8) > 8900 premature ventricular contraction per 24 h by Holter, 9) inability to complete a 6 min walk test or non-cardiac condition that markedly reduces exercise capacity (e.g. chronic obstructive pulmonary disease, peripheral vascular disease, orthopedic disease, orthopedic disease), 10) scheduled or completed coronary artery bypass grafting or percutaneous coronary intervention within the past 3 months, 11) indication for CRT therapy, 12) prior cardiac transplant, mechanical tricuspid or aortic valves, 13) inability to provide informed consent, or 14) participation in another simultaneous experimental protocol. The analysis is based on data from 41 patients who were followed until the end of the study or until a primary endpoint was reached. Three of these subjects failed to complete the follow up. Among them, one failed to return for testing 3 months after implantation and two had explanation as explained below.

### 2.3. Statistical analysis

All data are presented as mean ± standard deviation. Statistical significance was defined as p < 0.05. Groups were assigned in the analysis per intention-to-treat, independent of CCM therapy being active for the

entire or part of the follow-up period per CCM case. T-test was used to compare the baseline characteristics. Z-test was used to compare the baseline characteristics which were presented as proportions of populations. Kaplan–Meier analysis was performed for all-cause mortality events per group, and the groups were compared by Log-rank analysis. Similarly, Kaplan–Meier and Log-rank analyses were performed separately for the subgroups of patients with baseline EF < 25% and of patients with baseline EF ≥ 25%. Similar analysis was performed for the secondary endpoints.

### 3. Results

Forty-one patients implanted with CCM between July 6, 2005 and June 6, 2012 were enrolled and followed through 31st August 2013. Baseline characteristics of these subjects and the matched controls are shown in the Table. There were no differences between groups within the matching criteria (age, gender, medications at baseline, left ventricular EF at baseline, follow-up duration, and etiology of heart failure). Only two subjects had an ICD implanted and both were in the group receiving CCM. Other than for ICD utilization rates, both groups were representatives of other studies in patients with similarly advanced heart failure [9–11].

#### 3.1. Outcomes

Patients treated with CCM were followed for an average of  $75 \pm 19$  months (11–97 months). Follow-up for controls averaged  $69 \pm 17$  months (14–86 months). The primary outcome of all-cause mortality was significantly lower in the CCM group than in the controls (41% vs. 71%, respectively; Log-rank  $\chi^2 = 11.23$ ,  $p = 0.001$ ) for the entire cohort (Fig. 1a). When stratified by baseline EF, CCM-treated patients with EF < 25% had no survival benefit compared to controls (Fig. 1b). On the other hand, those with baseline EF between 25 and 40% had a significant survival benefit with CCM (Fig. 1c).

The secondary outcome of heart failure hospitalization was no different over the course of the study between CCM and control groups in the full cohort of patients or in the subset with EF < 25% (Fig. 2a & b). However in the subset of patients with EF between 25 and 40%, heart failure hospitalization rate was significantly lower in the CCM group (Fig. 2c). The composite outcome of all-cause mortality or heart failure hospitalization was worse in the control than the CCM group for the entire cohort (Fig. 3a) and for the subset with EF between 25 and 40% (Fig. 3c). When considering only cardiovascular deaths, CCM

had a survival advantage over control in both the entire group (Fig. 4a) and in the subset of patients with EF between 25 and 40% (Fig. 4c).

Two patients suffered a wound infection and underwent explantation of the Optimizer device, one after 5 months and one after 2 months. Based on the intention to treat analysis, data from both subjects was included in the analysis. No other major adverse events were recorded.

### 4. Discussion

The primary finding in this case–control study is that CCM added to medical therapy is associated with better survival than medical therapy alone. This is the first demonstration of long-term benefit of CCM in a population of Chinese patients. Cumulative survival at 80 months was 29% in the control group and 61% in the CCM treated group. The separation in survival curves occurred within the first few months and was maintained throughout the study thus the benefit of CCM starts early and is sustained. When stratifying subjects by EF, those with poorer pre-implantation function (EF < 25%) showed similar survival whether CCM was implanted or not. The mortality benefit was observed only in those with an EF of 25% or greater. This is consistent with the prior observation that while the whole cohort shows improvement in symptoms and function, the earlier in the disease process that CCM is initiated, the better the outcomes are (FIX-HF-5 study subgroup [11]). These findings help target which patients receive the most benefit from CCM with less severely damaged hearts being most capable of substantially responding to therapy.

Our finding of better long-term survival with CCM vs. optimal medical treatment alone is consistent with the recent findings of Kuschyk et al. [12] who followed patients also recruited from a single center, for an average of 3 years. Patients in that study had similar age and slightly lower baseline EF than patients in the present study, and a few of them were CRT-non-responders before receiving CCM therapy. During follow up at 3 years, 30% died in the CCM group which was less than the expected mortality based on the MAGGIC risk score calculator. In their study, most patients concurrently had an ICD implanted while data from MAGGIC was mostly derived from patients before ICD implantation was more routine. Thus the mortality benefit from CCM alone in the study by Kuschyk vs. the MAGGIC data may reflect the greater use of ICD in Kuschyk's study. The authors therefore analyzed their data by considering all ICD discharges as “deaths” (worst case scenario) and found 3 year survival at just under 70%, similar to that observed in the present study. Thus the presence of an ICD does not appear necessary to contribute to the observed survival benefit from CCM therapy [7,13].

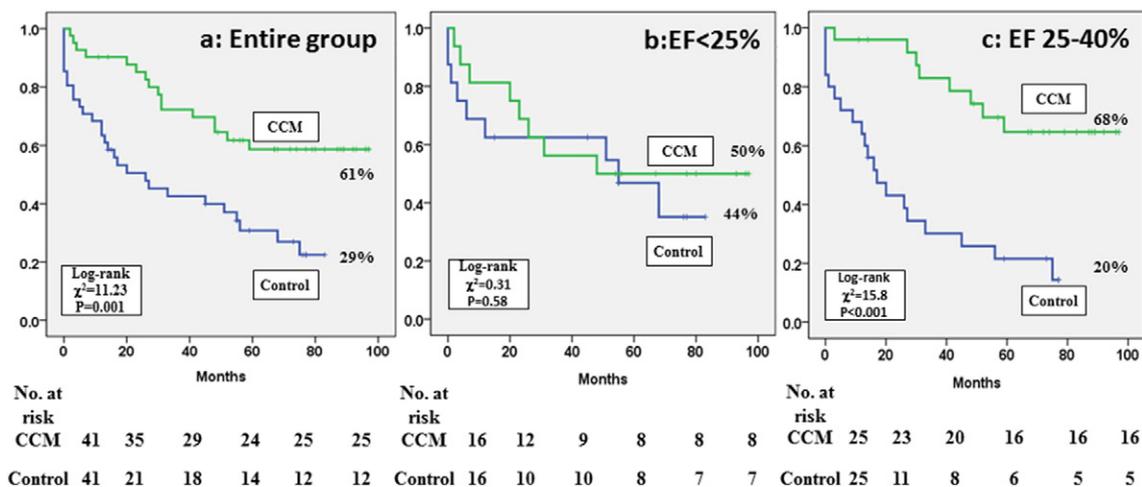
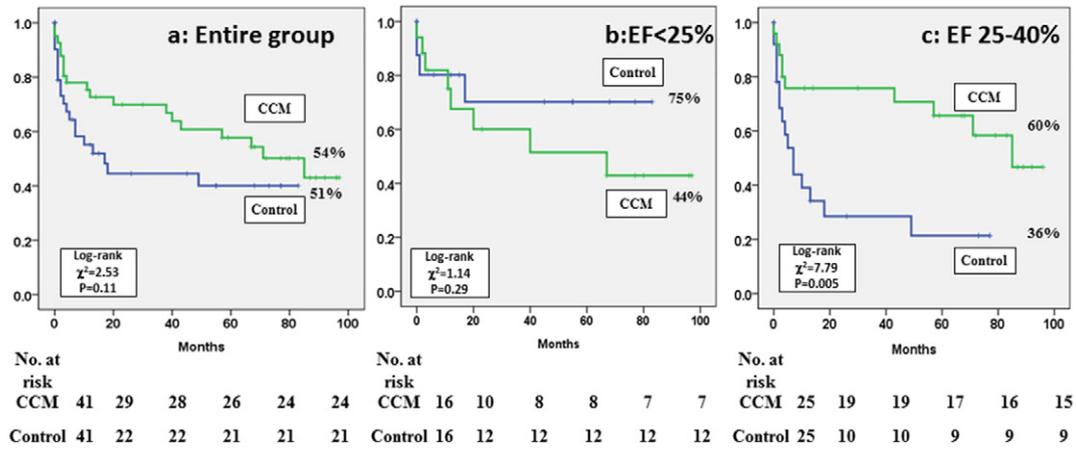


Fig. 1. All-cause mortality rates (Kaplan–Meier analysis) in CCM vs. control groups across the entire study cohort (a), and for the subgroups with EF < 25% (b) and (c) EF 25–40% (c). A significant improvement in survival was observed in the CCM group when compared to Controls for the entire cohort (Fig. 1a) and for those with EF between 25 and 40% (Fig. 1c). The improvement began at about 4 months and extending through the end of the study period (>80 months).



**Fig. 2.** Heart failure hospitalization rates (Kaplan–Meier analysis) for the entire study cohort (a), and for the subgroups with EF <25% (b) and (c) EF between 25 and 40% (c). In patients with EF <25%, CCM had no apparent effect on heart failure hospitalization (Fig. 2a). However in subjects with EF between 25 and 40% at baseline, CCM significantly reduced heart failure hospitalization throughout the study period (Fig. 2c). If there were more than one hospitalization for heart failure, only the first was used for this analysis.

Patients in the control (optimal medical therapy) and CCM groups were matched by age, gender, medications at baseline, left ventricular ejection fraction, etiology of heart failure, and duration of follow-up. Despite the similarity between groups with respect to these assessments of cardiac function and other baseline parameters, NYHA classification was higher by approximately 7% in the control group. When the CCM cohort (all NYHA FC III) was compared only to those control patients with baseline NYHA FC III, event-free survivals were similar to data presented in Figs. 1–4 for overall cohort comparisons and for comparisons between control and CCM groups with EF < 25% or between 25 and 40%.

There were more frequent paroxysmal episodes of atrial fibrillation in the control group although none of the patients (by design) had persistent atrial fibrillation at the time of enrollment. Even though most of the recorded baseline characteristics were similar between groups, we cannot exclude an effect of the higher NYHA classification in the control group on outcomes.

This was a single site study thus the number of subjects enrolled was relatively small for mortality outcome comparison. Nevertheless we did observe a significant reduction in long term mortality with CCM. This suggests a robust effect but must be tempered by potential confounding effects of baseline differences between groups (NYHA classification and incidence of atrial fibrillation).

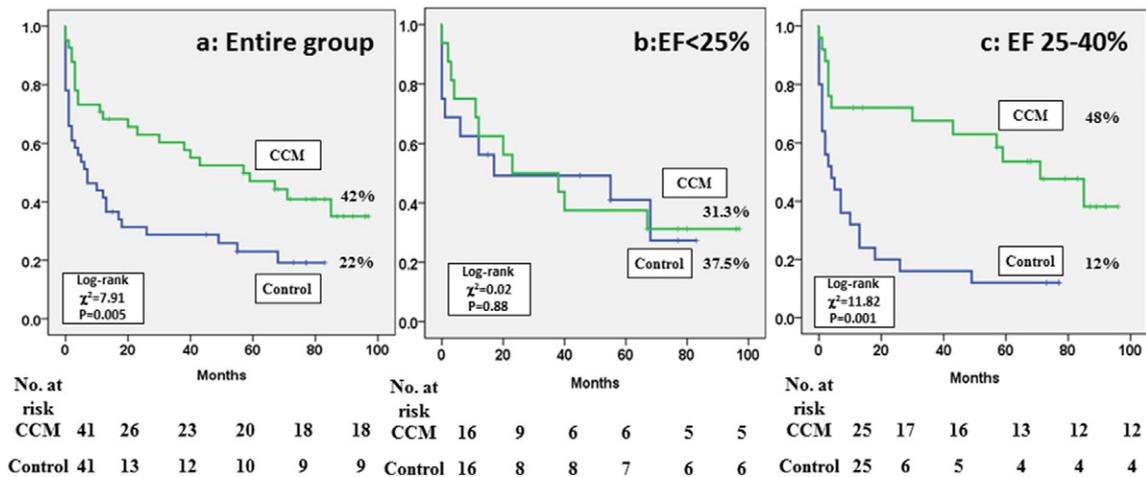
Most patients were regularly using guideline-recommended medical therapy for heart failure as used in other analyses of medical

compliance (beta-adrenergic blockers and ACE-I or ARBs) [14], and diuretics. The rate of compliance with these medications (70–75%) is not dissimilar to what has been reported in the literature for post-hospitalization compliance with CHF medications [15,16].

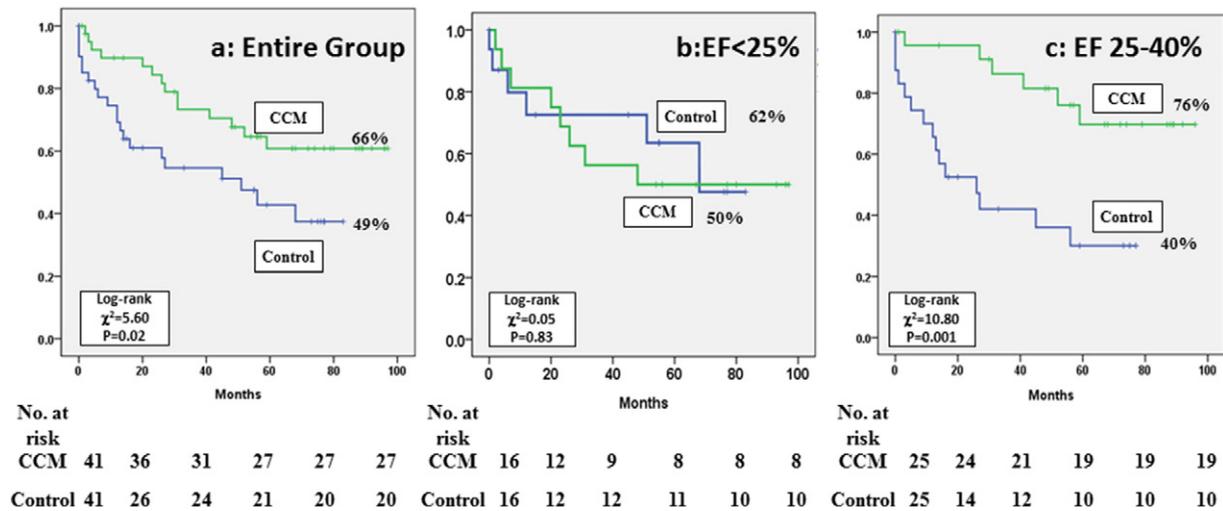
The lack of ICD utilization in the present cohort might have reduced the observed benefit of CCM in the lower EF group. Indeed the CCM benefit was greater in the higher EF subgroup even though a benefit was still apparent in the overall cohort. CCM also showed a benefit in HF hospitalizations in the higher EF subgroup, an endpoint that is independent of ICD utilization.

The CCM group also demonstrated reductions in LV end-diastolic pressure, LV end-systolic volume and LV end-diastolic volume [7] which suggest alleviation of strain on the left atrium, providing an avenue for reducing the propensity for atrial fibrillation. The improved LV dimensions are also predictive of reduced mortality risk as seen in the present study.

In summary, CCM in patients with moderate to severe heart failure demonstrates marked reductions in long-term all-cause mortality when compared to a matched cohort. The reduction in mortality occurs early and is sustained for 7 years of follow-up. Heart failure hospitalization rate was similar in both groups, but significantly lower in the CCM subgroup with higher baseline EF. These data are consistent with a sustained improvement in long-term survival with CCM in a Chinese cohort with moderate to severe heart failure. These findings support the



**Fig. 3.** Kaplan–Meier analysis for the composite endpoint of all-cause mortality or HF hospitalization in the entire study cohort (a), and for the subgroups with EF <25% (b) and (c) EF between 25 and 40% (c). The composite endpoint was significantly less frequently observed in patients with CCM across the entire cohort (Fig. 3a) and among those with EF between 25 and 40% (Fig. 3c). If there were more than one hospitalization for heart failure, only the first was used for this analysis.



**Fig. 4.** Kaplan–Meier analysis for cardiovascular mortality in the entire study cohort (a), and for the subgroups with EF < 25% (b) and (c) EF between 25 and 40% (c). Cardiovascular mortality was significantly lower in CCM when compared to Controls across the entire cohort (Fig. 4a) and in the subgroup with EF between 25 and 40% (Fig. 4c).

idea that in addition to reducing mortality, long-term CCM treatment delays heart failure hospitalizations in moderate heart failure and reduces cardiovascular mortality, two potentially very important benefits for the growing clinical problem of persistent symptomatic heart failure in patients on medical therapy.

#### Conflict of interest

Dr. Shlomo is the founder of Impulse Dynamics. Dr. Burkhoff and Dr. Gutterman are consultants to Impulse Dynamics. Dr. Rousso is an employee of Impulse Dynamics.

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