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Proportion of Patients Eligible for Cardiac Contractility Modulation: Real-Life Data from a Single-Center Heart Failure Clinic

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Keywords
Chronic heart failure · Cardiac contractility modulation · Cardiac implantable electric device

Abstract
Introduction: Based on recently published randomized controlled trials, cardiac contractility modulation (CCM) seems to be an effective device-based therapeutic option in symptomatic chronic heart failure (HF) (CHF). The aim of the current study was to estimate what proportion of patients with CHF and left ventricular ejection fraction (LVEF) <50% could be eligible for CCM based on the inclusion criteria of the FIX-HF-5C trial. ***Methods:*** Consecutive patients referred and followed up at our HF clinic due to HF with reduced or mid-range LVEF were retrospectively assessed. After a treatment optimization period of 3–6 months, the inclusion criteria of the FIX-HF-5C trial (New York Heart Association (NYHA) class III/IV, 25% ≤ LVEF ≤45%, QRS <130 ms, and sinus rhythm) were applied to determine the number of patients eligible for CCM. ***Results:*** Of the 640 patients who were involved, the proportion of highly symptomatic patients in NYHA class III/IV decreased from 77.0% (n = 493) at baseline to 18.6% (n = 119) after the treatment optimization period (p < 0.001). Mean LVEF increased significantly from 29.0 ± 7.9% to 36.3 ± 9.9% (p < 0.001), while the proportion of patients with 25% ≤ LVEF ≤45% increased from 69.7% (n = 446) to 73.3% (n = 469) (p < 0.001). QRS duration was below 130 ms in 63.1% of patients, while 30.0% of patients had persistent or permanent atrial fibrillation. We found that the eligibility criteria for CCM therapy based on the FIX-HF-5C study were fulfilled for 23.0% (n = 147) of patients at baseline and 5.2% (n = 33) after treatment optimization. ***Conclusion:*** This single-center cohort study showed that 5% of patients with CHF and impaired LVEF immediately after treatment optimization fulfilled the inclusion criteria of the FIX-HF-5C study and would be candidates for CCM.

Introduction

Although several effective pharmacological and device-based therapeutic options have been developed in recent decades, chronic heart failure (HF) (CHF) is still characterized by high morbidity and mortality [1]. Car-

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diac contractility modulation (CCM) is a promising implantable device treatment option for patients with CHF who are not eligible for cardiac resynchronization therapy (CRT). The principle of CCM is the endocardial electric stimulation of the myocardium during the refractory period, resulting in the enhancement of cardiac contractility without an increase in oxygen consumption [2]. Several randomized and nonrandomized studies have shown that CCM can improve exercise tolerance, functional status, and quality of life [3–7]. In the most recent FIX-HF-5C trial, 160 patients with left ventricular ejection fraction (LVEF) ≥25% and ≤45%, sinus rhythm, New York Heart Association (NYHA) functional class III/IV, and QRS duration <130 ms were randomized to continued medical treatment versus additional CCM [5]. Using a Bayesian statistical model, the study also incorporated a subgroup of patients with the same inclusion criteria from the previous FIX-HF-5 study [4]. The results showed a significant improvement with CCM at 24 weeks in NYHA class, quality of life, and functional capacity (measured by peak VO_2 and 6-minute walk test) and a reduction in the composite of cardiovascular death and HF hospitalization. Despite the increasing evidence regarding CCM, what proportion of patients with CHF meet the eligibility criteria for CCM in real-world clinical practice has not been investigated. The aim of this study was thus to address this question using the inclusion criteria of the FIX-HF-5C study on the patient cohort of a single-center HF clinic.

Methods

Design and Study Population

Consecutive patients referred to the HF clinic of our tertiary cardiology center (Medical Centre, Hungarian Defence Forces, Budapest, Hungary) between January 01, 2013 and December 31, 2017 due to HF with reduced ejection fraction (HFrEF) or HF with mid-range ejection fraction (HFmrEF) were retrospectively assessed. HFrEF and HFmrEF were defined in accordance with the HF guidelines of the European Society of Cardiology [8]. Relevant clinical, laboratory, echocardiographic, and electrocardiographic parameters were collected at initial visit and after treatment optimization. For patients with HFrEF, guideline-recommended neurohumoral antagonist therapy consisting of β-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB), and mineralocorticoid receptor antagonist was initiated and uptitrated during follow-up visits to guideline-recommended target doses or maximal tolerated doses. If indicated, ivabradine was used. Attempts were made to minimize doses of diuretics, adjusted at each follow-up visits depending on fluid status and symptoms. Patients who met the indication criteria of current practice guidelines underwent implantation of an implantable cardioverter defibrillator or a CRT-D/P system. In treatment of patients with initial LVEF between 40 and 49%, we attempted to individually optimize therapy of both cardiovascular and noncardiovascular comorbidities with a special focus on hypertension, atrial fibrillation, and coronary artery disease. We included only patients with complete data who were followed up in our outpatient clinic during therapy optimization. LVEF was calculated using Simpson's method.

The inclusion criteria of the FIX-HF-5C study (including NYHA class III/IV, 25% ≤ LVEF ≤45%, QRS duration <130 ms, and sinus rhythm) were applied to identify the proportion of patients eligible for CCM on optimal treatment. We assessed the number of patients who could receive CCM as primary device therapy and the proportion of those for whom CCM would be indicated alongside the use of a previously implanted cardiac implantable electronic device. This study was approved by the local Ethical Committee (approval number: KKOO/182-1/2020) and was undertaken in conformity with the Helsinki Declaration.

Statistical Analysis

Data were obtained from the hospital information system and patient records and were recorded in an anonymized form in a Microsoft Excel 2007 spreadsheet (Microsoft, Redmont, WA, USA). Statistical analysis was performed using the statistical program SPSS 21.0 (IBM, Armonk, NY, USA). The calculated values for categorical variables are represented as percentages, while continuous variables are represented by their means and standard deviations. To compare variables before and after therapy optimization, the McMahon test was used in the case of categorical variables and the paired *t* test with continuous variables. A 2-sided *p* value <0.05 was considered statistically significant.

Results

Six hundred forty patients were referred due to HFrEF or HFmrEF and followed up at our HF clinic during the study period. Of these 640 patients, 48.1% (n = 308) suffered from coronary artery disease and 28.0% had persistent or permanent atrial fibrillation (Table 1). The mean LVEF in the whole patient cohort was 29.0 ± 7.9% at baseline, and 63.1% of patients had a QRS width <130 ms. At the time of the first presentation, 43.9% of patients received a β-blocker, 38.1% ACEi/ARB, and 38.3% mineralocorticoid receptor antagonist (Table 2). Among patients with HFrEF (n = 579), this proportion was significantly increased through individual optimization of medical therapy to 88.4, 96.5, and 57.0%, respectively. The guideline-recommended target dose of β-blocker and ACEi/ARB was achieved in 46.8 and 36.8% of patients with HFrEF. After treatment optimization, 424 patients (66.3%) were found to have improved at least one NYHA class so that the proportion of severe symptomatic patients (NYHA III–IV) decreased from 77.0 to 18.6% (p < 0.001). Mean LVEF increased significantly to 36.3 ± 9.9% (p < 0.001). The proportion of patients with

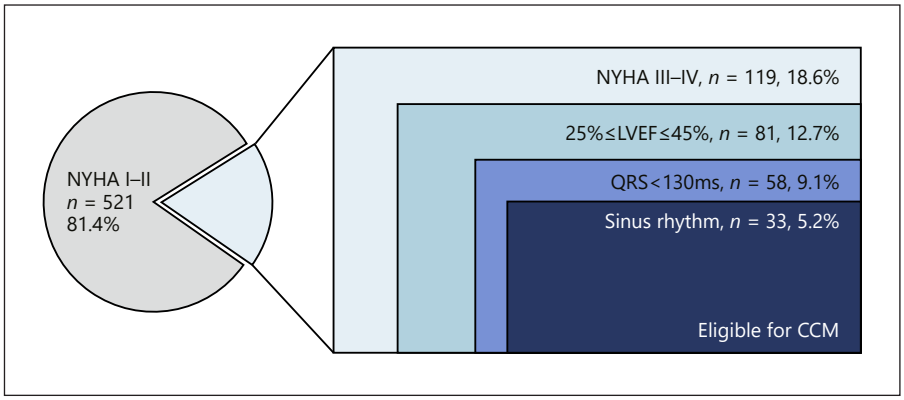

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Fig. 1. Venn diagram demonstrates the proportion of eligible patients for CCM therapy after pharmacological treatment optimization. NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CCM, cardiac contractility modulation.

Table 1. Clinical, echocardiographic, and laboratory characteristics of the study population at the time point of referral to HF clinic

Patients, *n*	640
Age, mean ± SD, years	61.3±13.1
>75 years, *n* (%)	95 (14.8)
Males, *n* (%)	487 (76.1)
Hypertension, *n* (%)	464 (72.5)
Diabetes mellitus, *n* (%)	220 (34.4)
Ischemic heart disease, *n* (%)	308 (48.1)
Heart rate, mean ± SD, min^{-1}	86±20
Atrial fibrillation, *n* (%)	179 (28.0)
QRS width, mean ± SD, ms	122±37
QRS <130 ms, *n* (%)	404 (63.1)
Hemoglobin, mean ± SD, g/dL	14.0±1.8
Serum potassium >5.5 mmol/L, *n* (%)	17 (2.7)
Serum creatinine, mean ± SD, µmol/L	116±59
eGFR, mean ± SD, mL/min/1.73 m^2	64±23
eGFR ≤30 mL/min/1.73 m^2, *n* (%)	39 (6.1)

eGFR, estimated glomerular filtration rate.

Table 2. Changes in NYHA class, LVEF, and medical and device-related treatment at timepoint of referral versus after therapy optimization

	Baseline, *n* = 640	After treatment optimization, *n* = 640	*p* value
NYHA III–IV, *n* (%)	493 (77.0)	119 (18.6)	<0.001
LVEF, mean±SD, %	29.0±7.9	36.3±9.9	<0.001
25% ≤ LVEF ≤35%, *n* (%)	327 (51.1)	270 (42.2)	0.001
35% < LVEF ≤45%, *n* (%)	119 (18.6)	199 (31.1)	<0.001
Use of β-blocker, *n* (%)	281 (43.9)	569 (88.9)	<0.001
Use of ACEi/ARB, *n* (%)	244 (38.1)	615 (96.1)	<0.001
Use of MRA, *n* (%)	245 (38.3)	371 (58.0)	<0.001
ICD, *n* (%)	35 (5.5)	69 (10.7)	0.004
CRT-P/D, *n* (%)	42 (6.6)	175 (27.3)	<0.001
Eligible for CCM, *n* (%)	147 (23.0)	33 (5.2)	<0.001

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ICD, implantable cardioverter defibrillator, CRT-P/D, cardiac resynchronization therapy pacemaker/defibrillator; CCM, cardiac contractility modulation.

25% ≤ LVEF ≤45% increased from 69.7% (*n* = 446) to 73.3% (*n* = 469) (*p* < 0.001). We found that the eligibility criteria for CCM therapy based on the FIX-HF-5C study were fulfilled for 23.0% (*n* = 147) of our patient population at baseline and 5.2% (*n* = 33) after treatment optimization (shown in Fig. 1). Ten of the 33 potential CCM candidates would receive CCM as a second device in addition to a pacemaker or implantable cardioverter defibrillator implanted previously.

Discussion

The basis of CCM is a nonexcitatory, relatively high-voltage (~7.5 V), long-duration (~20 millisecond), biphasic electrical signal delivered during the absolute refractory period of the ventricle. The device (Optimizer system, Impulse Dynamics, Orangeburg, NY, USA) is typically implanted in the right pectoral region and is connected to 2 standard pacemaker leads that are placed through venous access into the right ventricular septum at a distance of at least 2 cm from each other [9]. The beneficial effects of CCM manifest at the molecular, cellular, and extracellular levels [10]. Positive changes in the remodeling of intracellular Ca^{2+} regulatory proteins and increasing sensitivity of myofilaments to Ca^{2+} appear to be the most important molecular changes, leading to improvement not only in regional but also in global LV contractility [11, 12].

Three prospective randomized trials proved that CCM in addition to optimal medical therapy is effective in reducing symptoms and improving exercise capacity and quality of life in patients with NYHA class III/IV, 25% ≤ LVEF ≤45%, QRS <130 ms, and sinus rhythm versus optimal medical therapy alone [3–5]. Additionally, the most recent FIX-HF-5C study showed an approximately 50% reduction in the composite endpoint of cardiovascular death and HF hospitalizations at 6 months [5]. The clinical effectiveness of CCM is most convincing in patients with LVEF between 35 and 45%, while patients with LVEF below 25% do not appear to benefit from this therapy [13]. Due to the invasive nature and costs of this therapy, careful patient selection and thorough follow-ups are necessary.

To the best of our knowledge, this is the first report to describe an assessment of the proportion of patients who would be eligible for CCM therapy based on current evidence in a real-world patient population. We found that 5.2% (n = 33) of our patients met the indication criteria, and about one-third (n = 10) of them would be eligible for a CCM as a second device additional to another cardiac implantable electronic device implanted previously. A previous review article from Abi-Samra estimated that 79% of patients with NYHA II/III and LVEF <35% could be eligible for CCM [14]. The reason for this apparent discrepancy in eligibility is that this rough estimation ignored some important eligibility criteria derived from the results of former RCTs.

The relatively small proportion of eligible patients in our patient cohort is due to several reasons. The main cause is that through accurate optimization of guideline-recommended therapy, the proportion of highly symptomatic patients was reduced and LVEF increased significantly. The fact that the proportion of HFrEF patients receiving a target dose of neurohumoral antagonist therapy was fairly large (higher than reported in the ESC Heart Failure Long-Term Registry [15]) can explain this impressive improvement in NYHA class and LVEF. The relatively large proportion of CRT recipients could also have contributed to clinical improvement. Of course, our single-center data cannot be automatically extrapolated to the whole CHF patient population, although we found that the baseline characteristics and prevalence of comorbidities in our cohort were very similar to those of the Hungarian and other large multicentric HF registry data [16–20]. The mean age was 61.3 years in our patient cohort, 63 years in the Qualify registry, 64.4 years in the Hungarian Heart Failure Registry, and 66 years in the ESC HF Long-term Registry in CHF patients. The proportion of males was 76% in BIOSTAT-CHF and EVITA-HF registries, 74% in the Qualify registry, 72.3% in the Hungarian Heart Failure Registry, and 76.1% in our patient population. The incidence of diabetes was 38.7, 34, and 34.4%, and the incidence of hypertension was 75.8, 64, and 72.5% in EVITA-HF and QUALIFY registries and in our patient cohort, respectively. Therefore, a similar eligibility proportion can be assumed in other HF patient populations. Our eligibility data are also in line with patient selection data from the FIX-HF-5C study, where only about one-third of patients who had signed informed consent passed baseline testing and underwent randomization [5].

There are presently several gaps in the evidence about CCM. If these are filled, the proportion of patients eligible for CCM is likely to increase in the future.

First, in the aforementioned RCTs, it was predominantly patients with NYHA class III/IV who were included; there is a lack of evidence concerning whether NYHA class II patients would also benefit from this therapy. We found that by ignoring this criterion, the number of suitable patients increased to 13.3%. It is also important to note that in single-center studies and in CCM-REG, the proportion of NYHA II patients was 8–20% [6, 21, 22], but this finding should be verified through further prospective studies. Second, since the previous-generation CCM signal delivery algorithm required the sequential intracardiac sensing of a P-wave and ventricular signal, patients with permanent or persistent atrial fibrillation were excluded from the randomized trials. The new-generation Optimizer Smart does not require the implantation of an atrial lead and contains an algorithm which also delivers a signal during atrial fibrillation. As approximately half of all patients with HF develop atrial fibrillation at some point [23], further studies are required to assess the effect of CCM in this patient population. Third, while the effects of CCM therapy have primarily been tested in patients with narrow or mildly prolonged QRS (<130 ms), 2 studies with low patient numbers evaluated the efficacy of CCM among patients who had a wide QRS and were nonresponders to CRT [24, 25]. The authors found an improvement in quality of life and exercise tolerance, similar to the results of earlier randomized trials. Since about 20–40% of patients who receive CRT do not obtain benefit from CRT [26], CCM could be an alternative therapeutic option for them [13]. Finally, it is also important to mention that although the proportion of patients eligible for CCM was relatively small in our patient cohort, thus regarding the wide prevalence of disease, this may mean a high total number of CCM candidates in the whole population.

Beyond the single-center character of the study, the main limitation of our work is that none of the patients received sacubitril/valsartan in our patient population because the drug was not available during the study period in Hungary. The further limitation is that the short follow-up period of the current analysis involved only the period of treatment optimization of 3–6 months, and due to the progressive nature of the disease, it is likely that the clinical state of some patients would have worsened over time, despite optimized medical therapy, thereby becoming candidates for CCM.

Conclusions

This short-term single-center cohort study showed that nearly 5% of patients with HFrEF and HFmrEF immediately after treatment optimization fulfilled the inclusion criteria of the FIX-HF-5C study and would be candidates for CCM.

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Statement of Ethics

This retrospective observational study was approved by the local Ethical Committee and was undertaken in conformity with the Helsinki Declaration.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.P. and B.M. conceived the study, performed data collection, analyzed the data, and drafted the manuscript. Zs.M., D.V., M.Sz., and E.Sz. contributed to data collection and revised the manuscript. M.D. and R.G.K. supervised data collection and contributed substantially to manuscript revision. N.Ny. coordinated the study and was involved in interpreting data, drafting the manuscript, and revising it critically for important intellectual content.

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