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ORIGINAL RESEARCH

Bridging the gap in the symptomatic heart failure patient journey: insights from the Italian scenario

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ABSTRACT

Background: The prognosis for heart failure (HF) patients remains poor, with a high mortality rate, and a marked reduction in quality of life (QOL) and functional status. This study aims to explore the ongoing needs of HF management and the epidemiology of patients followed by Italian HF clinics, with a specific focus on cardiac contractility modulation (CCM).

Research design and methods: Data from patients admitted to 14 HF outpatients clinics over 4 weeks were collected and compared to the results of a survey open to physicians involved in HF management operating in Italian centers.

Results: One hundred and five physicians took part in the survey. Despite 94% of patients receive a regular follow-up every 3–6 months, available therapies are considered insufficient in 30% of cases. Physicians reported a lack of treatment options for 23% of symptomatic patients with reduced ejection fraction (EF) and for 66% of those without reduced EF. Approximately 3% of HF population (two patients per month per HF clinic) meets the criteria for immediate CCM treatment, which is considered a useful option by 15% of survey respondents.

Conclusions: Despite this relatively small percentage, considering total HF population, CCM could potentially benefit numerous HF patients, particularly the elderly, by reducing hospitalizations, improving functional capacity and QOL.

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KEYWORDS
Heart failure; device therapy; cardiac contractility modulation; personalized medicine; quality of life

1. Introduction

Since heart failure (HF) was first been described as an emerging epidemic 25 years ago, the total number of HF patients continues to rise. An estimated 64.3 million people are living with HF worldwide. In developed countries, the prevalence of HF is estimated between 1% and 2% of the general adult population [1,2]. Notwithstanding differences in diagnostic criteria, most studies estimated that over half of all HF patients in the general population have a preserved left ventricular ejection fraction (LVEF) [3].

For decades, beta-blockers (BB), renin-angiotensin-aldosterone system inhibitors (RAASi), diuretics, and mineralocorticoid receptor antagonists (MRA) represented the only pharmacological strategies for HF. In the last decade, new drug therapies

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have been developed, such as sacubitril/valsartan, ivabradine, soluble guanylate cyclase stimulators, highly absorbable iron, and sodium-glucose cotransporter type 2 (SGLT-2) inhibitors [4]. However, the prognosis remains poor, with the mortality rate remaining as high as 50% at 5 years, and quality of life (QOL) remaining markedly reduced [5,6]. Furthermore, the improvement in prognosis has been confined to those with HF with reduced ejection fraction (HFrEF), whereas in patients with HF and LVEF > 35% only SGLT-2 inhibitors were demonstrated to have survival benefit [4,7,8].

In terms of device therapy, cardiac resynchronization therapy (CRT), either with a defibrillator (CRT-D) or without (CRT-P), is proven to reduce mortality and hospitalization, improve cardiac function, and enhance QOL [9,10]. These benefits are limited to patients with HFrEF and intraventricular conduction delay (which is less than one-third of patients with HFrEF) [11]. In addition, around one-third of CRT recipients are observed to be 'non-responders' [12]. Conduction system pacing (CSP), both His bundle pacing (HBP) and Left bundle branch area pacing (LBBAP), are emerging as a possible physiological alternative for CRT. In HF patients, CSP showed promising results in terms of better electro-mechanical ventricular synchronization and significant improvements in LVEF, NYHA functional status, and 6-min walk distance similar to those of conventional CRT with biventricular pacing [13]. CSP showed positive results in patients with non-left bundle-branch block intraventricular conduction delay, in whom the results of biventricular pacing are less promising [14]. Indeed significant clinical, electrocardiographic, and echocardiographic improvement has been observed in preliminary studies combining CSP with traditional biventricular pacing: His-optimized CRT (HOT-CRT) [15] and LBBAP-optimized CRT (LOT-CRT) [16]. However, only a few randomized control trials are currently available, and technical challenges, along with the lack of information on long-term clinical outcomes, still limit the role of CSP [13]. The latest guidelines do not consider CSP as a first-line strategy but recommend it in CRT candidates in whom coronary sinus lead implantation is unsuccessful [17].

All therapies (drugs and devices) should be initiated and optimized within 1 year from diagnosis. The new ESC guidelines indicate that all four pillars of pharmacological treatment should be initiated in the first 3–6 months from the diagnosis. In patients who remain symptomatic and have a prolonged QRS durationin particular, left bundle branch block QRS morphology, a biventricular device should be implanted [4]. The resynchronization therapy effects are visible and definitive after 6–9 months. This means that in about a year we can use all therapeutic resources and see their effects. Nevertheless, in a not negligible number of patients, the HF journey is longer than 1 year with worsening symptoms, decreasing QOL and limitations to physical activity. There is an unmet need for other therapies to treat patients along this long journey [4].

Thanks to an innovative mechanism of action, cardiac contractility modulation (CCM) could represent a new therapeutic possibility [18,19]. CCM improves the handling of calcium in cardiomyocytes through the delivery of non-excitatory high-voltage biphasic impulses during the absolute refractory period of the action potential of cardiac myocytes [20]. The delivery of electrical impulses during the plateau phase, immediately after the onset of the action potential and immediately before the maximum voltage peak in the cardiomyocyte, allows to modulate the entry of Ca2+ into the cell by increasing the contraction force of cardiomyocytes. In addition, the delivery of CCM therapy seems to allow over time a progressive reactivation of genes and proteins that regulate the release of Ca2+ in the cell, initially in the myocardial tissue around the leads and subsequently throughout the heart. An increase in the phosphorylation of Phospholamban was observed, resulting in a greater efficiency of the sarcoplasmic reticulum in sequestering intracellular Ca2+. CCM therapy showed an impact matrix remodeling, associated with upregulation and normalization of the matrix metalloproteinases, and cardiac neuro-modulation effects. CCM has been shown to activate vagal afferent fibers, reducing the excessive sympathetic activation associated with HF and resulting in an improvement in autonomic balance [21,22].

The latest version of the CCM device consists of two pacemaker leads for sensing and pacing implanted in the interventricular septum, spaced at least 2 cm apart to involve as much myocardial mass as possible. Two high-voltage biphasic pulses (4.0–7.5 V) with a duration of approximately 20 ms (10 ms for each pulse) are applied. The impulse is not excitatory, being delivered in a phase of refractoriness, and does not induce a new cardiac contraction. The septal position is determined by the need to avoid stimulation of extracardiac structures with the high current that is delivered (phrenic nerves and diaphragm). Seven 1-h therapy sessions are scheduled during the day alternated to rest periods of 2.43 h each. Considering the high energy demand, the rechargeable battery requires a weekly charging cycle lasting 1 h. Battery life is estimated at around 15 years [18,23,24].

CCM was studied in the FIX-HF patients' series [25–30], which had an LVEF 25–45% in sinus rhythm with QRS <130 ms, clinically symptomatic (NYHA class >II) despite optimized medical therapy (OMT). In this setting of patients, it was demonstrated the safety and efficacy of the device regarding the following endpoints [25–30]:

- improvement in NYHA class;
- improvement in quality of life investigated with the Minnesota Living with Heart Failure Questionnaire (MLHFQ);
- increase in functional capacity at the 6 min walk test of 6 min (6MWT);
- increase in peak oxygen consumption (VO2);
- reduction in the composite endpoint of cardiovascular death and hospitalizations for HF.

Based on the published results of these studies, particularly FIX-HF-5C and FIX-HF-5C2, CCM was awarded a labeled indication by the US Food and Drug Administration to treat heart failure patients with EF 25–45%, who have NYHA III status, are not indicated for CRT, and remain symptomatic on OMT. A large-scale real-life registry involving 503 European patients suggests that cardiac contractility modulation therapy improved functional status, quality of life, LVEF, and reduced heart failure hospitalization rates over the 24 months

following implantation. Additionally, survival at 1 and 3 years was significantly better than predicted by the MAGGIC risk score [24]. However, currently, the 2022 ACC and 2021 ESC guidelines on HF albeit acknowledging the benefits of CCM, consider the evidence insufficient to support specific recommendations, calling for new studies on the topic [4,31].

The current study aims to explore the perceived needs in the management of heart failure and to place them in the Italian context, investigating the characteristics of patients followed by Italian heart failure outpatient clinics. A particular focus was given to the role that CCM, as a new complementary therapeutic approach, may play in HF management.

2. Materials and methods

From 27 November 2021 to 1 February 2022 a survey was published on the website Cardioinfo (https://cardioinfo.it). This survey was open to physicians operating in all Italian centers involved in HF management. Participation in the survey was voluntary. The questionnaire could be completed by more than one physician from the same center. An electronic form was created on which respondents recorded their profile, the characteristics of the hospital (i.e. presence of HF clinic, number of patients with HF visited per week), and their clinical choices in different scenarios of HF management. The survey consisted of a total of 20 questions: 3 concerning the respondent's profile, 4 regarding the characteristics of the participating centers and 13 regarding the management of heart failure in different scenarios.

In addition, an analysis from the data of the registries on HF patients of 14 volume referral outpatient HF clinics was performed. The participating outpatients HF clinics were asked to collect the clinical and therapeutical characteristics of patients admitted over a four-week period (from 15 November 2021 to 15 December 2021).

The study was conducted according to the guidelines of the Declaration of Helsinki. The approval by a local ethics committee was not required as the study was based on data reported in aggregated form. In addition, the survey involved the use of records that contained only non-identifiable data about people. All the participants provided written consent for their participation in the survey and informed consent was obtained from all patients enrolled in HF registries.

The survey and the list of participating HF clinics are reported in the Appendix section.

2.1. Statistical analysis

The continuous variables are expressed as mean ± standard deviation if normally distributed; otherwise, as median and interquartile ranges. Discrete variables are expressed as frequencies and percentages. Comparisons for continuous data were made via Student's t-tests, and Chi^2 and Kruskal–Wallis tests were applied to categorical data.

We used SPSS 23.0 (SPSS Statistics/IBM Corp, Chicago IL, U.S.A.) for statistical analysis, p values < 0.05 were considered significant.

3. Results

3.1. Survey

A total of 105 physicians took part in the survey. There was at least one participant from each Italian region. Eighty-one respondents (77%) were cardiologists, of whom 22/81 (27%) were HF specialists, 21/81 (26%) were electrophysiologists and 7/81 (9%) worked in a cardiac intensive care unit; 6 respondents (6%) were internists, 2 (2%) geriatricians, and 16 (15%) had other medical specialties (i.e. critical care medicine doctors or intensivists). Sixty participants (57%) had a working experience longer than 10 years. The majority of respondents worked in a hospital with an HF clinic (85%) and/or a cardiac rehabilitation center (73%). Only 10% were private hospitals (Figure 1).

Patients with HF are followed with regular follow-up, depending on cardiac function and symptoms. The frequency of follow-up is summarized in (Figure 2A).

Despite regular clinical follow-up, the currently available medical therapy is perceived to be insufficient in stabilizing heart failure patients in 30% of cases. According to 61% of respondents, around 10–20% of patients followed for highly symptomatic heart failure do not improve despite an optimized medical therapy. About 21% of participants estimated that patients with poor symptom control despite OMT exceed 20% (Figure 2B).

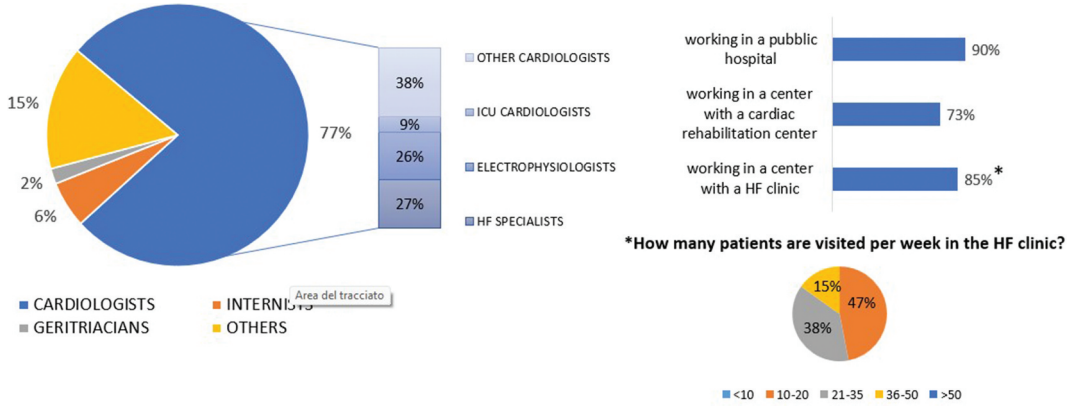

Figure 1. Characteristics of respondents. Heart failure (HF).

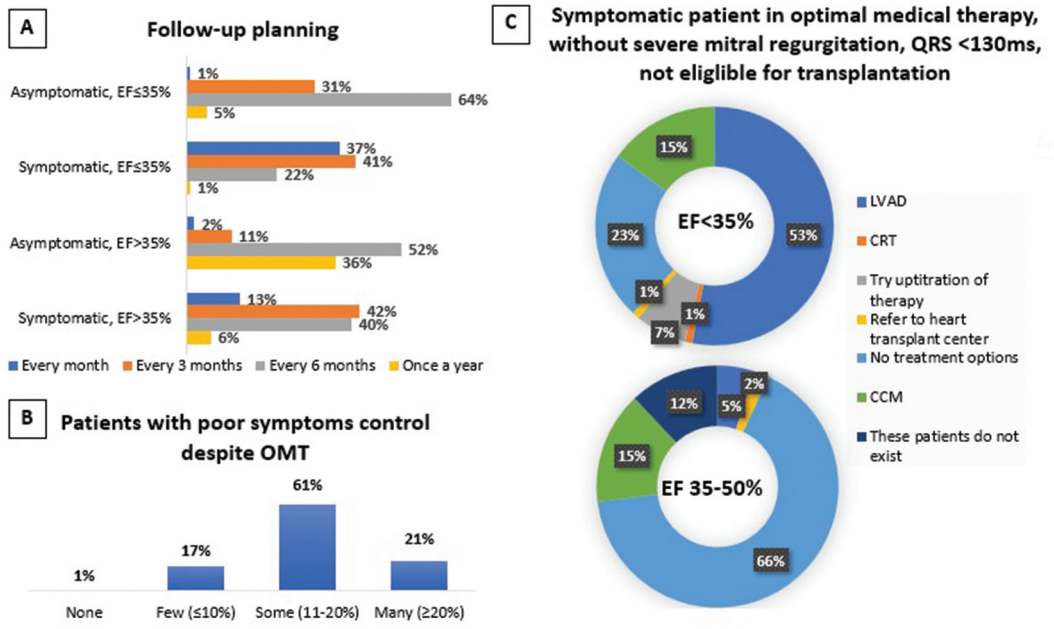

Figure 2. A) follow-up timing in different subset of patients. B) percentage of patients who are symptomatic despite OMT according to survey respondents. C) respondents' strategies adopted in symptomatic patients in OMT, without severe mitral regurgitation, QRS <130 ms, non-eligible for transplantation in two different scenarios: patients with EF<35% and patients with EF 35–50%.

Ejection fraction (EF), Optimal Medical Therapy (OMT).

Seventy-nine percent of respondents reported seeing at least one patient per week with an ICD, LVEF < 35%, QRS < 130 ms, without severe mitral regurgitation, who is not eligible for transplant, and remains symptomatic despite optimal medical therapy (OMT). In this scenario, 53% of participants would evaluate such a patient for an LVAD implantation, 15% a CCM implantation. Twenty-three percent of the participants felt that there were no other treatment options (Figure 2C).

When considering symptomatic patients with similar characteristics (with an ICD, QRS < 130 ms, without severe mitral regurgitation, who are not eligible for transplant), but with LVEF between 35% and 50%, the lack of treatment options rose to 66%. In this setting, 15% of respondents would consider a CCM implantation, and only 5% an LVAD implantation. Participants reported seeing at least once per week a patient with these characteristics in 54% of cases, and more than 3 patients per week in 18% of cases (Figure 2C).

In patients <70 years, more than 70% of the respondents considered it very important for HF treatment to improve quality of life, hospitalization reduction, and mortality reduction. When considering patients >70 years, the percentage of respondents who consider the mortality reduction very important decreases to 55%.

If a new implantable device for HF treatment was available, the parameters that would most influence its adoption are improvement of quality of life, the reduction in hospitalizations, the safety of the procedure, and the reduction in mortality (considered important or very important by 86%, 85%, 85%, and 83% respectively).

3.2. Patients characteristics in HF clinics

During the 4 weeks of data collection, a total of 1207 patients performed an examination in one of the 14 outpatients HF clinics. Five hundred and sixty-six patients (47%) had an age between 56 and 74 years, 253 (21%) were younger and 385 (32%) were older (Figure 3A). The majority of patients (56%) were in NYHA II class, 29% in NYHA III class, only 1% in NYHA IV (Figure 3B). Five hundred and seven patients (42%) had ischemic cardiomyopathy. The mean LVEF was 40% ±13,1%. LVEF distribution and its distribution according to NYHA class are described in (Figure 3C). Sixty percent of patients had a QRS interval <130 ms. Six hundred and twenty-five patients (52%) had a cardiovascular implantable electronic device (CIED): 68/625 patients (11%) had a pacemaker, 332/625 (53%) had an implantable cardioverter defibrillator (ICD), and 225/625 (36%) a cardiac resynchronization therapy device (CRT-D). Eight hundred and thirty-five patients (69%) were on optimal medical therapy (OMT) for at least 3 months. Four hundred and eight patients (34%) had at least one hospitalization for heart failure decompensation in the last year. The characteristics of the total population and different LVEF subgroups are summarized in Table 1.

Considering all the patients evaluated and using the criteria of the most representative trials on the topic, there were 31 patients on OMT (2 patients/month per HF outpatient clinic) who could be eligible for CCM. The number increases to 3 patients/month per HF outpatient clinic when patients who achieved only maximum tolerated therapy but not OMT were considered. When considering less stringent

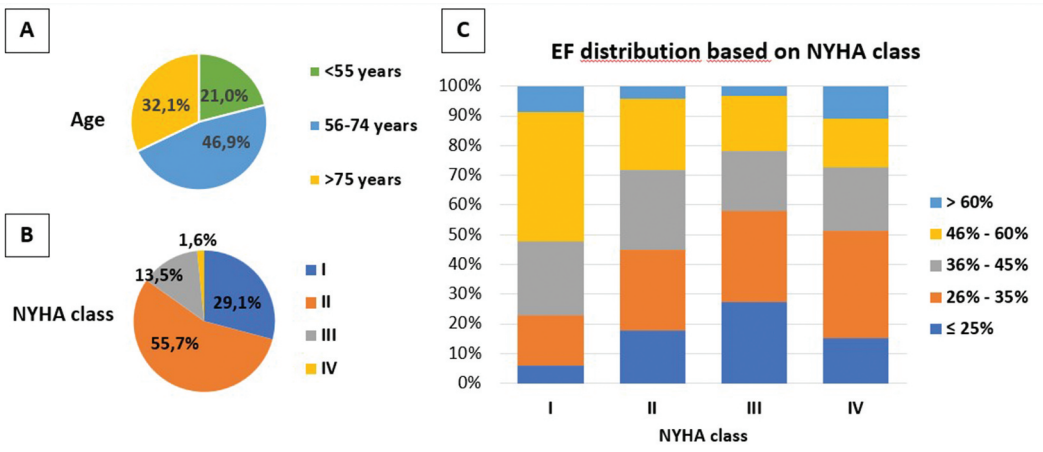

Figure 3. A: patients stratified according to age. B: patients stratified according to NYHA functional class. C: EF distribution in different NYHA classes. Ejection Fraction (EF).

criteria, such as those of the CCM Italian registry (which include patients in NYHA functional class II who have had a hospitalization for heart failure in the previous 12 months) [32], the number increased to 5–6%. See the algorithms proposed in Figure 4.

4. Discussion

This data gives an overall picture of an Italian cardiology practice attentive to the needs of HF patients, with dedicated outpatient clinics, and frequent follow-ups based on the patients' clinical complexity profiles. Though several advancements occurred in HF treatment over the past years [4], 30% of the respondents are dissatisfied with the results of HF treatment: 82% reported that more than 10% of patients do not improve despite OMT and regular clinical follow-up at 3–6 months in 94% of cases. These data are not surprising as in recent studies, despite the introduction of new therapeutic drugs such as SGLT2 inhibitors, event rates remain high both in patients with reduced or preserved LVEF (HF hospitalization 5.6%–6.9% per year, overall mortality 7.2%–7.9% per year) [7,33].

Patients who remain symptomatic despite OMT remain a challenge, particularly those with preserved or moderately reduced ejection fraction. Indeed, in this patient setting, more than two-thirds of the respondents feel that they have no treatment options. This percentage is reduced to 23% in patients with HFrEF, as most of the respondents consider LVAD may be a valid treatment option as destination therapy in these patients when not eligible for transplantation. Over the past 20 years, therapeutic advances in the field of heart failure have been modest compared to the number and complexity of patients' clinical profiles, and the improvement in prognosis had been confined to patients

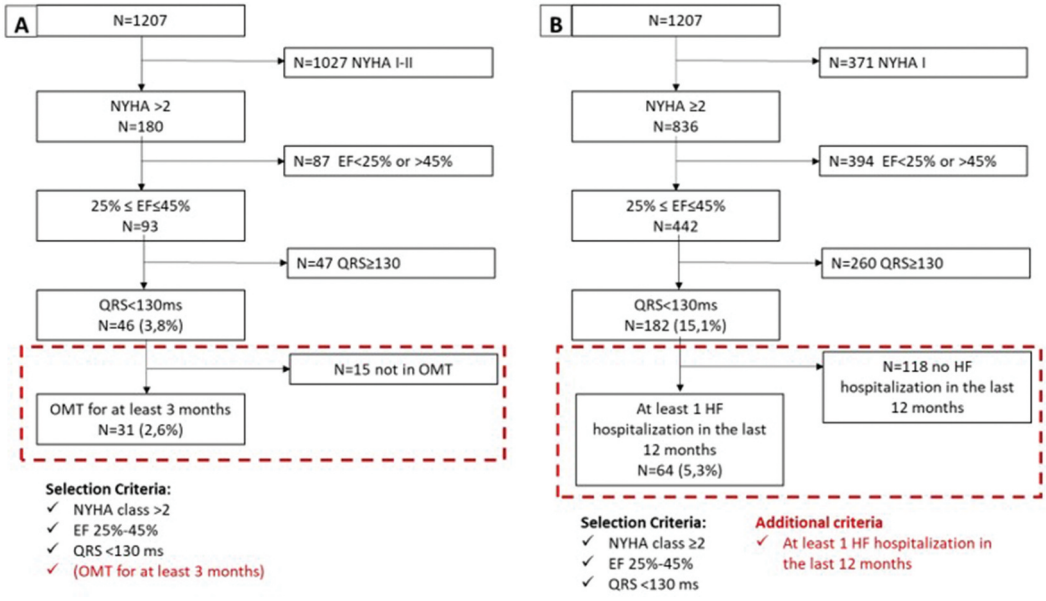

Figure 4. Patients eligible to CCM implant according to different selection criteria. A: patients selection according to FDA selection criteria. B: patients selection according to CCM Italian registry criteria (NYHA>3 or NYHA 2 + HF hospitalization in the last year).

Table 1. Characteristics of the total population of survey B and of different LVEF subgroups.

Characteristics	Totali (n° 1207)	LVEF <25% (n° 189)	LVEF 25%-35% (n° 295)	LVEF 36%-45% (n° 302)	LVEF 46%-60% (n° 355)	LVEF >60% (n°66)	p-value
NYHA							<0.001
I	344 (29.5%)	22 (11.2%)	60 (20.3%)	86 (28.5%)	148 (41.7%)	28 (42.6%)	
II	658 (54.5%)	116 (61.4%)	178 (60.3%)	172 (57.0%)	166 (46.8%)	26 (39.4%)	
III	160 (13.3%)	44 (23.3%)	49 (16.6%)	32 (10.6%)	30 (8.5%)	5 (7.6%)	
IV	19 (1.6%)	3 (1.6%)	7 (2.4%)	4 (1.3%)	3 (0.8%)	2 (3.0%)	
AGE							0.047
<55 years	254 (21.0%)	33 (17.5%)	60 (20.3%)	60 (19.9%)	87 (24.5%)	14 (21.2%)	
56–74 years	566 (46.9%)	104 (55.0%)	152 (51.5%)	137 (45.4%)	146 (41.1%)	27 (40.9%)	
>75 years	387 (32.1%)	52 (27.5%)	83 (28.1%)	105 (34.8%)	11 (34.4%)	25 (37.9%)	
Creatinine (mg/dl)	1.3 ±0.7	1.4 ±0.6	1.4 ±0.6	1.3 ±0.8	1.2 ±0.7	1.1 ±0.4	<0.001
GFR (ml/min)	63 ±28	59 ±29	62 ±28	61 ±27	69 ±26	66 ±28	<0.001
Diabetes	316 (26.2%)	61 (32.3%)	94 (31.9%)	78 (25.8%)	74 (20.8%)	9 (13.6%)	<0.001
CAD	507 (42.0%)	116 (61.4%)	159 (53.9%)	146 (48.3%)	74 (20.8%)	12 (18.2%)	<0.001
OMT for at least three months	835 (69.2%)	120 (63.5%)	203 (68.8%)	219 (72.5%)	256 (72.1%)	37 (56.1%)	<0.001
QRS <130 ms	727 (60.2%)	99 (52.4%)	171 (58.0%)	177 (58.6%)	231 (65.1%)	49 (74.2%)	<0.001
Diuretics	1.4 ±0.6	1.6 ±0.6	1.4 ±0.7	1.4 ±0.6	1.3 ±0.6	1.3 ±0.5	<0.001
Sacubitril/Valsartan	446 (37.0%)	107 (56.6%)	178 (60.3%)	117 (38.7%)	44 (12.4%)	0 (0%)	<0.001
SGLT2	118 (9,8%)	34 (18.0%)	39 (13.2%)	27 (8.9%)	15 (4.2%)	3 (4.5%)	<0.001
At least one HF hospitalization in the last 12 months	408 (33.8%)	75 (39.7%)	121 (41.0%)	100 (33.1%)	95 (26.8%)	17 (25.8%)	<0.001
Other device implanted	625 (51.8%)	155 (82%)	215 (72.9%)	92 (30.5%)	151 (42.5%)	12 (18.2%)	<0.001
• PM	51 (4.2%)	6 (3.2%)	8 (2.7%)	26 (8.6%)	22 (6.2%)	6 (91%)	
• ICD	332 (27.5%)	82 (43.4%)	134 (45.4%)	33 (10.9%)	77 (21.7%)	6 (9.1%)	
• CRT-D	225 (18.6%)	65 (34.4%)	72 (24.4%)	26 (8.6%)	45 (12.7%)	0 (0%)	
• CRT-P	17 (1.4%)	2 (1.1%)	1 (0.3%)	7 (2.3%)	7 (2.0%)	0 (0%)	

with HFrEF [4]. SGLT2 inhibitors represent the latest advances in medical therapy and their effectiveness in terms of reducing hospitalization and mortality is not limited to patients with HFrEF [7,8]; however, their use in clinical practice is still very limited [34, 35]. In the Italian HF clinics cohort, only 10% of patients were treated with SGLT2 inhibitors. This is partly due to the fact that SGLT2 inhibitors could not be prescribed in non-diabetic HF patients [35] at the time surveys were conducted, and the benefit in patients without HFrEF was not clear yet [7,8].

LVAD is a valid option in selected HF patients, improving quality of life and extending survival [4,36]. However, it should be reserved for selected patients with advanced HF. Its efficacy in elderly patients, who, in our survey, represent almost 30% of the patients admitted to HF outpatients clinics, is supported by some studies [37,38]; however, its applicability should be subject to a careful assessment of comorbidities and frailty, which may affect outcomes [39,40].

In addition, in elderly patients, an improvement in clinical status, functional capacity, and QOL may be more relevant than reducing mortality [41,42]. According to our survey respondents, the pursuit of mortality reduction is considered to be more important in patients <70 years, while in patients >70 years reducing hospitalizations and improving quality of life take on greater relevance. In addition, according to the respondents, the efficacy evaluation paradigm for the adoption of a new HF device must focus not only on mortality but also on QOL improvement. HF treatment should be personalized, and end-points may acquire different weights depending on patients' characteristics and personal choices [41,42]. The arbitrary cutoff of 70 years for deeming survival as a primary goal in patients' management is very likely a biased opinion based on historical data of HF populations, that are currently outdated as observed by the survival of octogenarians treated by CRT or ICD, whose prognosis is dependent on biological age rather than on chronological age [43–45].

Fifteen percent of respondents felt that CCM could be a valuable tool in patients with symptomatic HF despite OMT, both in those with severe and mildly reduced ejection fraction. CCM improves QOL, NYHA class, functional capacity, and increases peak oxygen consumption [25–30]. Some studies suggested a positive impact on cardiovascular outcomes such as mortality and hospitalizations [29,46,47] but specifically designed studies are needed in order to confirm the potential role of CCM in reducing these adverse outcomes in HF. CCM expands the indication beyond the traditional LVEF cutoff of 35% to patients who fall in the midrange LVEF group up to 45% [29,46]. A recent real-world study showed an even more impressive effect in the subgroup of patients with an ejection fraction between 35% and 45% [46]. On these bases, a new trial is exploring the impact of CCM in HF patients with preserved ejection fraction [48]. CCM could potentially play a relevant role in patients who are symptomatic despite OMT, reducing the actual therapeutic gap [49]. Given the results of the FIX series studies [25–30], in 2019 Food and Drug Administration (FDA) approved the use of CCM in NYHA Class III HF patients who remain symptomatic despite OMT, are not indicated for cardiac resynchronization therapy, and have a left ventricular ejection fraction ranging from 25% to 45%. Based on these indications, it is estimated that twice as many patients are indicated for CCM than are currently indicated for CRT. In the cohort of patients visited in the HF clinics, considering the limitations of the selection criteria, around 3% of patients were found to be suitable for CCM implantation.

However, even if the relative number of candidates is low, the absolute value (two patients a month per heart failure outpatient clinic) is high, with potentially relevant effects.

Furthermore, we must consider that the concept of OMT is complex and the definition is often elusive as it is not supported by the achievement of real end-points (e.g. HR, reduction of fluid congestion, and improvement of cardiac index). It is important to use all available strategies to achieve therapeutic optimization, limiting clinicians' inertia or 'lazy up-titration' and treating all reversible conditions and comorbidities (e.g. hyperkalemia) which may limit OMT [50,51]. In our survey population, 372 patients (31%) did not have at least 3 months of OMT at the time of the statistical analysis. However, it is reasonable to assume that participating centers with experience in HF management, wherever possible, will pursue optimized therapy in all patients in a short period. Therefore, more patients will fulfill the CCM implant criteria within a few months of the initial analysis. Including these patients, the percentage of subjects eligible for CCM in our cohort rises to 3.8% (3–4 patients a month per heart failure outpatient clinic).

More data are needed to establish which patients are most likely to benefit from device implantation [52]. Many gray zones still exist on the effect of CCM in different patient settings. However, promising results have been obtained in patients with atrial fibrillation [30,53] and in CRT non-responders [54,55]. After some promising data in patients with cardiac amyloidosis, an Italian registry on the use of CCM in patients with heart failure with medium or reduced EF and a diagnosis of TTR amyloidosis has recently been initiated [56].

The 2021 ESC HF guidelines urged for early and comprehensive therapy already for heart failure patients with NYHA class II to improve their symptom burden [4]. Actually, the FDA approved the use of CCM for NYHA Class III-IV patients; CE mark-related approval is less stringent and allows implantation in all HF patients who remain symptomatic despite OMT. Indeed, in clinical practice CCM has been used in patients with NYHA Class II: in CCM-REG, a prospective registry study including 503 European patients with CCM, 9.9% of patients had a NYHA Class II at time of implant [24]. Exploratory data on the use of CCM in Italy can be derived from the CCM Italian registry, which is a prospective registry enrolling patients with symptomatic HF (NYHA functional class >II or class II with previous episodes of acute decompensation). A preliminary analysis of 42 patients implanted with CCM device in 10 Italian centers showed an improvement in left ventricle ejection fraction, NYHA functional status and MLHFQ score at 12 months follow-up [32]. In patients with mildly symptomatic heart failure in NYHA class II, the MAnnheim cardlac coNtracTility modulation obsErvational study (MAINTAINED) observational study showed a significant improvement in LVEF, but not in NYHA class under CCM therapy [57]. By broadening the eligibility criteria for CCM therapy to encompass all symptomatic HF patients patients despite OMT who are not candidates for CRT and have a LVEF between 25% and 45%, the patient population increases substantially (15.1%).

However, expanding the pool of beneficiaries, the need to better stratify which factors may be associated with greater CCM benefits emerges. Similar to the inclusion criteria of the ongoing CCM trial in HF patients with preserved ejection fraction [48], we explored the use of the history of HF hospitalization in the previous year as additional selection criteria. By applying these new criteria, the percentage of patients eligible for CCM was around 5–6%. A follow-up analysis collecting the data of heart failure hospitalizations in the 6–12 months after baseline, the decline of NYHA class, and the trend of EF in our population could help to test the new algorithms and to identify which patients are most likely to benefit from CCM implantation.

5. Conclusions

Heart failure can be defined as the pandemic of our century, with alarming data for the next several years. Despite the significant attention paid to HF in Italian hospitals and regular follow-ups, there is a lack of improvement for a non-negligible number of patientsin particular, those without reduced ejection fraction. CCM is a new promising therapeutic option, helpful in reducing hospitalizations, improving functional capacity, and QoL. Only a small percentage of the Italian HF population fulfills the indication for immediate CCM treatment; nonetheless, given the large size of the total HF population, CCM may be helpful for many HF patients, particularly the elderly.

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Author contributions

Conceptualization, M. Ziacchi, M. Biffi, and G. Sinagra; methodology, L. Potena, P. Marchese, F. Clemenza, and D. Masarone; software, M. Merlo, C. Ghiglieno, and A. Alonzo; validation, S. Ghio, M. Pellegrino, and C. Inserra; formal analysis, A. Spadotto, R. Rordorf, and M. Senni; investigation, D. Stolfo, G. Patti, A. D'Onofrio, G.B. Forleo, and G. Pacileo; resources, M.M. Caracciolo, D. Pini, F. Ammirati, F. Rametta, and G. Arcidiacono; data curation, F. Adamo, M. Mariani, M. Ruzzolini, M. Ciccarelli, and G.M. De Ferrari; writing – original draft preparation, A. Spadotto, N. Aspromonte, and M. Grimaldi; writing – review and editing, M. Ziacchi and M. Biffi; visualization, F. Colivicchi, G. Firetto, F. Giallauria, and S. Bianchi; supervision, G. Sinagra, M.G. Bongiorni, C.

Tondo, and F. Oliva; project administration, M. Cipriani and M. Ziacchi. All authors have read and agreed to the published version of the manuscript.

Data availability statement

Digital database available from the corresponding author, M Ziacchi: matteo.ziacchi@gmail.com.

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- **The MANTAINED observational study suggested that NYHA class II patients may benefit from cardiac contractility modulation therapy in terms of LVEF improvement.**

Appendix

The survey and the list of participating HF clinics are reported in the appendix section.

SURVEY

1. **Sex**
(male/female)

2. **How many years you have been working?**
- <5 years
- 5–10 years
- 10–15 years
- 15–20 years
- >20 years

3. **What's your medical specialty?**
- General cardiologist
- Cardiologist specialized in HF management
- Electrophysiologist
- Interventional cardiologist
- Cardiologist working in an intensive care unit
- Internal Medicine physician
- Geriatrician
- Other

4. **The hospital where you work is**:
(public/private)

5. **Does your hospital have or is connected with a cardiac rehabilitation center?**
(yes/no)

6. **Does your hospital have an HF clinic?**
(yes/no)

7. **How many patients are visited per week in the HF clinic of your hospital?**
- <10 patients
- 10–20 patients
- 21–35 patients
- 36–50 patients
>50 patients

8. **How important are to you the following endpoints in heart failure (HF) management in patients younger than 70 years old?** (1 = somewhat important, 3 = very important)
- Mortality
- Reduction in hospitalization for HF
- Improvement of quality of life

9. **How important are to you the following endpoints in heart failure (HF) management in patients older than 70 years old?** (1 = somewhat important, 3 = very important)
- Mortality
- Reduction in HF hospitalization
- Improvement of quality of life

10. **How important are to you the following parameters for the use of a new implantable device for the management of HF patients older than 70 years old?** (1 = unimportant, 5 = very important)
- Clinical evidence of improved quality of life
- Clinical evidence of a reduction in HF hospitalization
- Clinical evidence of mortality reduction
- Approval by the guidelines
- Cost of the device
- Remuneration according to the diagnosis-related group (DRG)
- Safety of implant

11. **Do you believe that current medical therapy is sufficient to stabilize most patients with heart failure?**
(yes/no)

12. **How many HF patients of your center are highly symptomatic and/or limited in their daily lives despite optimal medical therapy?**
- >20%
- 10%-20%
- 1%-10%
- <1%

13. **How often do you visit on average a clinically stable HF patient with EF < 35%, ICD recipient, in optimal medical therapy?**
- Every month
- Every 3 months
- Every 6 months
- Every year

14. **How often do you visit on average a symptomatic HF patient with EF < 35%, ICD recipient, in optimal medical therapy?**
- Every month
- Every 3 months
- Every 6 months
- Every year

15. **What therapeutic approach would you adopt for a symptomatic patient with EF < 35%, ICD recipient, without severe mitral regurgitation, QRS < 130 ms, not eligible for heart transplantation?**
- Left Ventricular Assist Device (**LVAD)**
- Cardiac Resynchronization Therapy Upgrade
- Try uptitration of therapy
- Refer to a heart transplant center
- Implant cardiac contractility modulation (CCM) device
- This patient does not exist
- No treatment options

16. **Last week how many people corresponding to the previous question characteristics have you visited?**
- 0
- 1-2
- 3-5
> 5

17. **How often do you visit on average a clinically stable HF patient with EF 35%–50% in optimal medical therapy?**
- Every month
- Every 3 months
- Every 6 months
- Every year

18. **How often do you visit on average a symptomatic HF patient with EF 35%–50% in optimal medical therapy?**
- Every month
- Every 3 months
- Every 6 months
- Every year

19. **What therapeutic approach would you adopt for a symptomatic patient with EF 35%–50%, ICD recipient, without severe mitral regurgitation, QRS < 130 ms, not eligible for heart transplantation?**
- Left Ventricular Assist Device (**LVAD)**
- Cardiac Resynchronization Therapy Upgrade
- Try uptitration of therapy
- Refer to a heart transplant center
- Implant cardiac contractility modulation (CCM) device
- This patient does not exist
- No treatment options

20. **Last week how many people corresponding to the previous question characteristics have you visited?**
- 0
- 1-2
- 3-5
- > 5

PARTICIPATING HF CLINICS

- Cardiology Unit, Anonymized, Bologna, Italy
- Cardiology Unit, Ospedale Garibaldi, Catania, Italy
- De Gasperis Cardio Center, Anonymized, Milan, Italy
- Department of Cardiology, Azienda Ospedaliera – Anonymized 'Anonymized,' Milan, Italy
- Heart Failure Unit, AORN dei Colli, Anonymized, Naples, Italy
- Department of Cardiovascular Disease, Unit of Cardiology, Ospedale Civile di Legnano, Legnano, Italy.
- Anonymized, Anonymized 'Maggiore Della Carita,' Novara, Italy
- Division of Cardiology, Fondazione Anonymized San Matteo, Pavia, Italy
- Cardiology Division, Anonymized, Anonymized, Rome, Italy
- UOC Cardiologia, Anonymized, Rome, Italy.
- Division of Cardiology, Hospital 'S. Filippo Neri,' Rome, Italy
- Cardio Center, Anonymized, Rozzano-Milan, Italy
- Department of Medicine, Surgery and Dentistry, Anonymized, Salerno, Italy
- Cardiothoracovascular Department, Azienda Sanitaria Anonymized (Anonymized) and University of Anonymized, Anonymized, Italy