International Journal of Cardiology 448 (2026) 134152

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Baseline clinical profile of patients with obstructive hypertrophic cardiomyopathy in the Italian Mavacamten early access program

G. Bonacchi [a,*], A. Del Franco [a], P. Agostoni [b], E. Agricola [c], E. Ammirati [d,e], P. Baratta [f], F. Barocelli [g], E. Bertero [h], E. Biagini [i,j], G. Boriani [k], P. Calabrò [l], L. Calò [m], C. Calore [n], S. Carigi [o], E. Carluccio [p], N. Cerrato [q], C. Chimenti [r], A. Chinaglia [s], C. Chiriatti [t], L. Crotti [u,v], R. De Caterina [w], M. Di Marco [x], F. Di Spigno [y], A. Evangelista [z], G. Galasso [aa], F. Graziani [ab], W. Grosso Marra [ac], A.I. Guaricci [ad], F. Guerra [ae], C. Leuzzi [af], G. Limongelli [ag], C. Lofiego [ah], M.A. Losi [ai], B. Mabritto [aj], S. Marazia [ak], M. Merlo [al], I. Monte [am], M. Moretti [an], R. Murzilli [ao], M.B. Musumeci [ap], F. Negri [aq], D. Pasqualucci [ar], G. Patti [as,at], E. Perugini [au], M.F. Piepoli [av], G. Pontone [aw], G. Quarta [ax], C. Raineri [ay], F. Re [az], F. Ricci [ba,bb], R. Ruggieri [bc], E. Saletti [bd], C. Santolamazza [d], L. Scelsi [be], R. Spoladore [bf], G. Todiere [bg], M. Pieroni [a], G. Sinagra [al], I. Olivotto [a], On behalf of the partecipating Centers of the Early Access Program for Mavacamten, Italy

[a] *Cardiomyopathy Unit, Careggi University Hospital, Florence, Italy*
[b] *Centro Cardiologico Monzino, IRCCS, Milan, Italy*
[c] *Department of Cardiology, IRCCS San Raffaele Hospital, Milan, Italy*
[d] *De Gasperis Cardio Center, Niguarda Hospital, Milan, Italy*
[e] *School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy*
[f] *Cardiology Department, Misericordia Hospital, Grosseto, Italy*
[g] *Cardiology Division, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy*
[h] *Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy*
[i] *Cardiology Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy*
[j] *European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart-ERN GUARD-Heart, Bologna, Italy*
[k] *Cardiology Division, Department of Biomedical Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy*
[l] *Division of Cardiology, A.O.R.N. 'Sant'Anna e San Sebastiano', Caserta, Italy*
[m] *Department of Motor, Human and Health Sciences, "Foro Italico" University of Rome, Division of Cardiology Policlinico Casilino, Rome, Italy*
[n] *Department of Cardio-Thoracic & Vascular Sciences, Public Health, University Hospital of Padova, Pauda, Italy*
[o] *Cardiology Unit, Infermi Hospital, AUSL Della Romagna, Rimini, Italy*
[p] *Cardiology and Cardiovascular Pathophysiology, Santa Maria della Misericordia Hospital, University of Perugia, Perugia, Italy*
[q] *Division of Cardiology, Cardinal G. Massaia Hospital, Asti, Italy*
[r] *Department of Cardiovascular, Respiratory, Nephrologic, Anesthesiologic and Geriatric Sciences, La Sapienza University, Italy*
[s] *Division of Cardiology, A.O.U San Luigi Gonzaga, Orbassano, Turin, Italy*
[t] *Cardiology, Nuovo Ospedale Del Mugello, Borgo San Lorenzo, Italy*
[u] *Istituto Auxologico Italiano IRCCS, Cardiomyopathy Unit, Center for Cardiac Arrhythmias of Genetic Origin and Laboratory of Cardiovascular Genetics, Milan, Italy*
[v] *University of Milano-Bicocca, Department of Medicine and Surgery, Milan, Italy*
[w] *Division of Cardiology, University of Pisa and Pisa University Hospital, Pisa, Italy*
[x] *Department of Cardiology, 'Santo Spirito' Hospital, Pescara, Italy*
[y] *Cardiology Unit of Emergency Department, Guglielmo da Saliceto Hospital, Piacenza, Italy*
[z] *Cardiology Division, Isola Tiberina Gemelli Isola Hospital, Roma, Italy*
[aa] *Department of Medicine, Surgery and Dentistry, University of Salerno, Baronissi, Italy*
[ab] *Department of Cardiovascular Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy*

Abbreviations:: BB, beta-blockers; EAP, Early access program; HCM, Hypertrophic Cardiomyopathy; IRCCS, Istituto di Ricovero e Cura a carattere Scientifico; LAVI, Left atrial volume index; LVEF, Left ventricular ejection fraction; LVOTob, Left Ventricular outflow tract obstructrion; MWT, Maximal wall thickness; nHCM, Non-obstructive Hypertrophic Cardiomyopathy; NDCCB, Non-dihydropyridine calcium channel blockers; NYHA, New York heart association; NTproBNP, N terminal pro brain natriuretic peptide; oHCM, Obstructive Hypertrophic Cardiomyopathy; pVO2, Peak oxygen consumption; SRT, Septal reduction therapy; Hs-cTnI, High-sensitivity cardiac troponin I; Hs-cTnT, High-sensitivity cardiac troponin T..

* Corresponding author.
E-mail address: bonacchig@aou-careggi.toscana.it (G. Bonacchi).

https://doi.org/10.1016/j.ijcard.2025.134152
Received 30 July 2025; Received in revised form 27 December 2025; Accepted 31 December 2025
Available online 8 January 2026
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[ac] Division of Cardiology, Ivrea Hospital, ASLTO4, Ivrea, Italy
[ad] Interdisciplinary Department of Medicine, University Hospital of Bari, Bari, Italy
[ae] Cardiology and Arrhythmology Clinic, Marche Polytechnic University, University Hospital Umberto I-Lancisi-Salesi, Ancona, Italy
[af] Cardiology Unit, IRCCS Arcispedale S. Maria Nuova, Reggio Emilia, Italy
[ag] Department of Translational Medical Science, University of Campania Luigi Vanvitelli, Naples, Italy
[ah] Department of Cardiology, Lancisi Cardiovascular Center, Marche University Hospital, Ancona, Italy
[ai] Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy
[aj] Division of Cardiology, Torino Mauriziano Hospital, Turin, Italy
[ak] Cardiology Department V. Fazzi Hospital, Lecce, Italy
[al] Cardiothoracovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina (ASUGI), University of Trieste, Member of ERN-Guard Heart, Italy, Trieste
[am] Unit of Cardiology, G.Rodolico-S.Marco University Hospital, Catania, Italy
[an] Cardiology Department, Santa Chiara Hospital, Trento, Italy
[ao] Ospedale SS Filippo e Nicola, Avezzano, Italy
[ap] Department of Clinical and Molecular Medicine, Sapienza University of Roma, Italy
[aq] Cardiology Department, University Hospital Santa Maria della Misericordia, Azienda Sanitaria Universitaria Integrata Friuli Centrale, Udine, Italy
[ar] Department of Cardiology, Azienda Ospedaliera Brotzu, Cagliari, Italy
[as] Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy
[at] Division of Cardiology, Maggiore della Carità Hospital, Novara, Italy
[au] Cardiology Department, Ospedale Maggiore, Bologna, Italy
[av] Clinical Cardiology, IRCCS Policlinico San Donato, San Donato Milanese, Italy
[aw] Department of Perioperative Cardiology and Cardiovascular Imaging, Centro Cardiologico Monzino, IRCCS, Milan, Italy
[ax] Cardiovascular Department, ASST Papa Giovanni XXIII Hospital, Bergamo, Italy
[ay] Division of Cardiology, Cardiovascular and Thoracic Department, Città della Salute e della Scienza, Turin, Italy
[az] Division of Cardiology, Cardiac Arrhythmia Center and Cardiomyopathies Unit, San Camillo-Forlanini Hospital, Rome, Italy
[ba] Department of Neuroscience, Imaging and Clinical Sciences, G. D'Annunzio University of Chieti-Pescara, Chieti, Italy
[bb] University Cardiology Division, SS Annunziata Polyclinic University Hospital, Chieti, Italy
[bc] Cardiology Department, ASL Bari, Ospedale Di Venere, Bari, Italy
[bd] Cardiovascular Department, San Donato Hospital, Arezzo, Italy
[be] Heart Failure, Transplant, Pulmonary Hypertension Unit, Division of Cardiology, Fondazione IRCCS Policlinico San Matteo Pavia, Italy
[bf] Department of Cardiology, Heart Failure Clinic, Alessandro Manzoni Hospital, ASST Lecco, Lecco, Italy
[bg] Cardiothoracic Department, Fondazione Toscana Gabriele Monasterio Pisa, Italy

ARTICLE INFO

Keywords:
HCM
Mavacamten
Early access program
Baseline characterization

ABSTRACT

Background: Obstructive hypertrophic cardiomyopathy (oHCM) has recently seen the introduction of mavacamten, a disease-specific therapy that alleviates obstruction and symptoms with potential effects on disease expression. Since most patients remain symptomatic with conventional therapies, mavacamten constitutes an efficacious treatment strategy

Methods: The early access program (EAP) for mavacamten treatment ran from September 2023 to September 2024. We collected clinical and echocardiographic data prospectively

Results: 337 patients with oHCM (53% male, mean age 61.4 ± 12.3 years) were receiving mavacamten treatment from 54 centers in Italy. The EAP cohort was older and showed a more advanced cardiac phenotype, showing lower left ventricular ejection fraction (LVEF) (66 ± 6% vs 74 ± 6% in EXPLORER-HCM cohort, $p < 0.0001$) and higher left atrial volume index (51.1 ± 16.4 ml/m^2 vs 40.5 ± 12.3 ml/m^2, $p < 0.0001$. Only 74 (22%) patients in the EAP group were candidates for septal reduction therapy (SRT). Echocardiographic parameters like LVEF, maximal wall thickness and LAVI as well as pharmacologic therapy showed no difference between subgroups, while LVOT obstruction gradient was higher in SRT candidates (40 vs 63 mmHg, $p < 0.0001$)..

Conclusion: The compassionate use program for mavacamten in Italy demonstrated significant engagement. The Italian oHCM cohort were older and exhibited more advanced disease stages compared to those in the EXPLORER-HCM trial. Only one-quarter of the patients were eligible for SRT, they did not show a more severe biomarker or echocardiographic parameters compared to those without indication. Mavacamten provides an additional option for oHCM patients unresponsive to standard therapy, especially those symptomatic but ineligible for SRT

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease characterized by hypertrophy of left ventricle and left ventricular outflow tract obstruction (LVOTob) in the hypertrophic stage, which progressed to heart failure due to adverse remodelling and overt dysfunction stages [1]. HCM had no disease-specific pharmacological therapy for a long time. For many years the management of obstructive HCM (oHCM) relied on cardiovascular drugs developed for other indications [2]. While these agents have provided symptomatic relief and improved quality of life for many patients, they have not produced consistent benefits across the whole population of oHCM and the broader population of non-obstructive (nHCM) patients. The recent development of cardiac myosin inhibitors marks a paradigm shift, offering a targeted therapeutic approach for patients with obstructive disease [3]. Otherwise, randomized clinical trials on nHCM patients are still ongoing [4]. Mavacamten is the first molecule of the myosin inhibitors class and received regulatory approval from the U.S. Food and Drug Administration in 2022 and from the European Medicines Agency in 2023. In randomized clinical trials mavacamten showed to reduce left ventricular outflow tract obstruction (LVOTob), improvement in peak oxygen consumption (pVO2) at cardiopulmonary exercise test, New York Health Association (NYHA) functional class, and to reduce NTproBNP and troponin levels [5,6]. While these results are promising, real-world data are essential to validate these findings across a broader, more diverse patient population. Post-marketing surveillance and analyses of REMS (Risk Evaluation and Mitigation Strategy) data have confirmed the safety of mavacamten and provided insights into dose distribution, patient characteristics, and treatment patterns in the United States [7]. A recent survey of major Italian Cardiology Centers exploited 2 key points: the unmet need for new treatment strategies and the high eligibility for mavacamten in patients with oHCM [9]. Access to

these therapies is currently limited in several countries. In Italy has been launched an Early Access Program (EAP) for mavacamten (Camzyos). The current treatment strategy for patients with LVOTob who did not respond to optimal medical treatment, is septal reduction therapy (SRT); however this approach alone does not encompass the full spectrum of patients who may benefit for myosin inhibition [10]. Rather than being mutually exclusive, these therapeutic approaches (pharmacological and surgical) should be considered complementary within a modern, individualised management strategy for oHCM. The EAP is a valuable opportunity to characterize the real-world oHCM population and to assess demand beyond specialist cardiomyopathy Centers. This study aims to characterize the clinical profile of all Italian patients affected by oHCM who were indicated to mavacamten therapy and enrolled in EAP, and to compare this population whit the phase III randomized clinical trial cohort. Furthermore, we analyzed the subgroup of patients eligible for SRT and we compared it to the patients who were not eligible.

1. Methods

All patients receiving active treatment with mavacamten in the EAP as of January 2025 were included. The enrollment window for the EAP, which allows access to mavacamten (Camzyos), began in September 2023 and ended in September 2024. Clinical and echocardiographic data were collected prospectively from the baseline. Patients eligible for SRT declined interventional therapy in favor of pharmacological treatment following an informed discussion about risk and benefit of each strategy. The compassionate use for each patient was approved by the local Ethic Committee, and all participants provided written informed consent.

1.1. Study population and protocol

Enrollment criteria for the EAP for Camzyos in Italy were affected by current oHCM local guidelines (European Society of Cardiology) [10]. The following criteria had to be documented by local echocardiography laboratory: unexplained left ventricular hypertrophy with nondilated ventricular chambers in absence of other cardiac causes (e.g., hypertension, aortic stenosis) or systemic disease, maximal left ventricular wall thickness (MWT) $\geq$ 15 mm (or $\geq$ 13 mm with positive family history of HCM), and a LVOTob defined as an instantaneous peak Doppler left ventricular outflow tract pressure gradient $\geq$30 mmHg at rest or during physiological provocation such as Valsalva manoeuvre, standing or exercise. Additionally, patients had to be over 18 years old, in NYHA functional class 2 or 3, have an LVEF over 55%, not be part of another clinical trial for LVOTob treatments or be satisfactorily treated with approved HCM drugs. Adequate acoustic windows were required for accurate transthoracic echocardiography. Women of childbearing potential could be included in the program; they needed to have a negative pregnancy test prior to starting treatment with mavacamten and to use highly effective contraception during and at least 6 months after treatment. Patients should be able to understand the program procedures and provide a written informed consent according to local and institutional guidelines and local ethical committee. Exclusion criteria included concomitant treatment with strong Cytochrome P450 (CYP) 3A4 (CYP3A4) inhibitors in patients with Cytochrome P450 (CYP) 2C19 (CYP2C19) poor or concomitant treatment with the combination of a strong CYP2C19 inhibitor and a strong CYP3A4 inhibitor. Patients should be genotyped for CYP2C19 to determine the appropriate mavacamten dose. The recommended starting dose of CYP2C19 poor metabolizer was 2.5 mg once daily, with a maximum dose of 5 mg once daily. Conversely, the recommended starting dose of CYP2C19 intermediate, rapid and ultrarapid metabolizer was 5 mg once daily, with a maximum dose of 15 mg once daily. LVOTob gradient had to be assessed after 4 and 8 weeks of treatment. The titration scheme starting from 12-week treatment permitted titration of dosage at 10 mg once daily and at 24-week treatment at 15 mg once daily. The evidence of LVOTob less than 20 mmHg during the first 8 weeks should prompt the reduction of dosage to 2.5 mg once daily. During the maintenance dose period, if LVEF is less then 50%, interruption of mavacamten therapy is required, along with revaluation after 4 weeks. Recovery of LVEF greater than 50% allowed resumption of mavacamten therapy at a lower dosage. At baseline and at each revaluation, centers collected clinical, echocardiographic, biomarker and symptom data (EQ-5D5L questionnaire), as specified in the program protocol. Physicians could prescribe cardiac magnetic resonance imaging, stress echocardiography, stress electrocardiography, and additional biomarker according to standard clinical practice. The case report form (CRF) model was included in the EAP documentation.

1.2. Statistical methods

Baseline data included: age, sex, NYHA functional class for dyspnea, ongoing pharmacological therapy, LVEF, LVOTob at rest, and during phase 2 of the Valsalva manoeuvre, left atrial volume index (LAVI), MWT, presence of mitral regurgitation and its grade, N-terminal pro-brain natriuretic peptide (NTproBNP) and high-sensitivity cardiac troponin (hs-cTn) I or T levels. Categorical data are presented as absolute numbers and percentages; normally distributed continuous variables are expressed as mean $\pm$ standard deviation. We considered the same parameters of the population of EXPLORER-HCM double-blinded randomized clinical trial [6]. To allow comparison with the baseline characteristics of EXPLORER-HCM population we considered the mean and standard deviation of the corresponding parameters. We analyzed a subgroup of patients from EAP cohort who met the criteria for SRT, in particular surgical myectomy. These criteria included NYHA class III or IV symptoms and a resting or provoked LVOTob gradient $\geq$50 mmHg. Comparisons between groups were conducted with Student's *t*-test and Mann-Whitney test for continuous parametric variables, reporting mean differences (mean Δ) and median differences (median Δ) and 95% confidence intervals (95% CI). For categorical variables we used chi-squared test, reporting odds ratio and 95% confidential interval. Statistical analyses and data visualisation were performed using R software (version 4.5.0) and R Studio software (version 2024.12.1–563).

2. Results

2.1. Epidemiology of mavacamten treatment and population characteristics

During the period of patient enrollment for the EAP, a total of 438 requests were received. At the time of writing 337 patients were on active treatment, while the rest were still waiting for approval of local Ethics Committee. Therefore, these 337 oHCM patients constituted the study population. They were enrolled from 54 centers in Italy: 159 (47.2%) patients were from centers in northern Italy, 133 (39.5%), in central Italy, and 45 (13.7%) in southern Italy and the islands. The top ten Centers had enrolled half of the patients of the cohort (47.5%). Furthermore, 45 (86%) of the prescribing Centers were University hospitals, second-level hospital, or IRCCS (Scientific Institute for Hospitalization and Treatment), while 9 (14%) were first-level hospitals. University Hospitals, second-level hospitals and IRCCS enrolled 273 (81%) patients in the EAP, while first-level Hospitals enrolled 64 (19%) patients. The number of patients treated by a single Center ranged from 23 to 1, and 17 centers had one or two patients on treatment.

Of the 337 patients undergoing mavacamten treatment, 180 (53%) were male. The average age was 61.4 $\pm$ 12.3 years old. CYP 2C19 genotype analysis showed 5 patients (1.4%) with a poor metabolizer phenotype and 331 patients (98.5%) with intermediate, rapid or ultrarapid metabolizer phenotype. One patient did not undergo genotype analysis. Overall, 243 (72.1%) patients were in class NYHA II and 94 (27.9%) patients were in class NYHA III (Table 1).

Echocardiographic parameters shown in Table 1, are presented as

Table 1
Comparison of baseline characteristics between EAP cohort and EXPLORER-HCM cohort. P-values and effect estimates with 95% confidence intervals are reported. Effect estimates, labeled in the table as Estimated effect (95% CI), include mean differences for continuous variables and odds ratios for categorical variables. BB, Beta-Blocker; CI, Confidential Intervals; EAP, Early Access Program; hs-cTn, High Sensitivity Cardiac Troponin; LAVI, Left Atrial Volume Index; LV, Left Ventricle; LVEF, Left Ventricular Ejection Fraction; LVOTob, Left Ventricular Outflow Tract Obstruction; ND-CCB, Non-Dihydropyridine Calcium Channel Blocker; NT-proBNP, N-Terminal Pro B-Type Natriuretic Peptide; NYHA, New York Heart Association.

	Italian early access program patients	EXPLORER-HCM patients	Estimated effect (95%CI)	*p*-value
Patients, n (%)	337	251		
Age, years	61.48 (±12.3)	58.5 (± 12)	2.98 (0.99 to 4.96)	0.003
Sex, n (%)			1.27 (0.91 to 1.77)	0,17
Female	157 (47)	102 (40.6)		
Male	180 (53)	149 (59.4)		
NYHA class, n (%)			0.96 (0.65 to 1.40)	0.83
II	243 (72.1)	183 (72.9)		
III	94 (27.9)	68 (27.1) 68 (27.1)		
LVEF (%)	66.0 (±5.7)	74 (± 6)	-16.3 (−8.9 to −7.0)	<0.001
Maximum LV thickness (mm)	20.2 (±4.0)	20 (± 3.5)	0.2 (−0.4 to 0.8)	0.51
LVOTob at rest (mmHg)	51.7 (±31.1)	51.5 (± 30.5)	0.07 (−4.83 to 5.23)	0.93
LVOTob Valsalva (mmHg)	79.7 (±36.6)	73 (± 32)	7.37 (1.9 to 12.8)	0.007
LAVI (ml/m^2)	51.1 (±16.4)	40.5 (± 12.3)	10.6 (8.27 to 12.92)	<0.001
Pharmacological therapy (%)				
Betablocker	294 (87)	189 (75)	2.24 (1.45 to 3.44)	<0.001
Disopyramide	100 (29)	–		
ND CCB	32 (9)	42 (17)	0.52 (0.31 to 0.85)	0.01
Beta-blocker only	184 (54)			
Disopyramide only	2 (1)			
ND CCB only	14 (4)			
Beta blocker and Dispyramide	93 (28)			
Beta-blocker and ND CCB	15 (4)			
Disopyramide and ND CCB	3 (1)			
BB and disopyramide and ND CCB	2 (1)			
None	24 (7)			
NT-proBNP (pg/ml)	1376.37 (± 1659.64)	694.9 (±882.8)	681.47 (472.8 to 890.0)	<0.001
Hs-cTn (ng/ml)	23.73 (± 27.8)	12.5 (±37.9)	11.2 (5.6 to 16.7)	<0.001

mean and standard deviation to enable comparison with EXPLORER-HCM population, as specified in the statistical methods. The median LVEF was 65% (range 55% - 90%), MWT was 20 mm, and left atrial volume indexed was 49 ml/m^2. The median LVOT gradient was 48 mmHg at rest and 75 mmHg during Valsalva manoeuvre. Mitral insufficiency was documented in 89% of patients; the severity grade was available only in 35%. In particular, 6 (6%) patients had severe mitral regurgitation, 20 (19%) had moderate regurgitation, 20 (19%) mild-to-moderate regurgitation, and 58 (55%) mild regurgitation. NTproBNP levels were available for 45% of the population with a median value of 755 pg/ml, while for hs-cTnI or hs-cTnT in the 30% of the population with a median value of 14.85 pg/ml.

At enrollment in EAP for mavacamten, pharmacological therapy comprised a wide spectrum of drugs indicated for the control of LVOTob gradient (Fig. 1). Distribution in NYHA class II and III were similar for beta-blockers (87.7% vs 87.2%), disopyramide (29.8% vs 31.9%), non-dihydropyridine calcium channel blockers (NDCCB) (8.5% and 13.8%), and for the combination therapy with at least two drugs (32.3% vs 39.4%). Similar results in pharmacological therapy, were observed when stratifying patients by sex and age groups (18–40, 41–60, 61–80, >80 years old). (See Figs. 2 and 3.)

2.2. Comparison with EXPLORER-HCM population

A comparison of baseline features of 337 oHCM patients with the population of the phase III randomized clinical trial EXPLORER-HCM, counting 251 patients, is shown in Table 1. The age of patients in the EAP cohort was significantly higher than that of the EXPLORER-HCM cohort (61.58 vs 58.5 years old, $p = 0.003$; mean Δ 2.98, 95% CI 0.99, 4.96). Further, EAP cohort showed lower LVEF (66 ± 5.7% vs 74 ± 6%, sp. <0.0001; mean Δ -16.3, 95% CI -9, −7) and higher LAVI (51.1 ± 16.4 ml/m^2 vs 40.5 ± 12.3 ml/m^2, $p < 0.0001$; mean Δ 10.6, 95% CI 8.27, 12.92). While LVOT obstruction values had similar gradients at rest, the EAP cohort showed higher gradients during phase 2 Valsalva compared to the EXPLORER-HCM cohort (79.7 ± 36.6 mmHg vs 73 ± 32 mmHg, $p = 0.007$; mean Δ 7.37, 95% CI 1.9, 12.8).

In the EXPLORER-HCM trial, only beta-blockers or ND CCB were permitted as monotherapy; in contrast, the EAP cohort received treatment with all the pharmacological drug class indicated in guidelines, often employing combination therapy [12]. A higher percentage of patients in EXPLORER-HCM trial were treated with ND CCB (32 (9%) vs 42 (17%), $p = 0.01$; OR 0.52, 95% CI 0.31, 0.85). Conversely, beta-blockers were more prescribed in the EAP cohort (294 (87%) vs 79, (75%), $p = 0.0002$; OR 2.24, 95% CI 1.45, 3.44).

We have compared means and standard deviations of biomarker of our population to EXPLORER-HCM cohort. Biomarker were markedly higher in EAP population, both for NTproBNP (1376.37 ± 1659.64 vs 694.9 (±882.8) pg/ml; *p*-value <0.0001; OR 681.47, 95% CI 472.8, 890.0) and TnI hs (23.73 ± 27.8 vs 12.5 ± 37.9 ng/l; p-value <0.0001; OR 11.2, 95% CI 5.6, 16.7).

2.3. Surgical candidacy

According to European Society of Cardiology guidelines for HCM, candidates for SRT are those with NYHA III or higher and a LVOT obstruction gradient greater than 50 mmHg at rest, Valsalva or exercise (Table 2) [10]. In the EAP population, 263 (78%) patients had no indication for surgical strategy due to a gradient lower than 50 mmHg or NYHA class II, whereas 74 (22%) patients were candidates for SRT. Patients eligible for SRT had a higher proportion of male (41.8% vs 63.5%, p-value = 0.001, OR 2.41, 95% CI 1.42, 4.16) and were older (63 [54.00; 69.75] vs 66 [58.25; 70.00]; p-value = 0.034; median Δ -3.00,

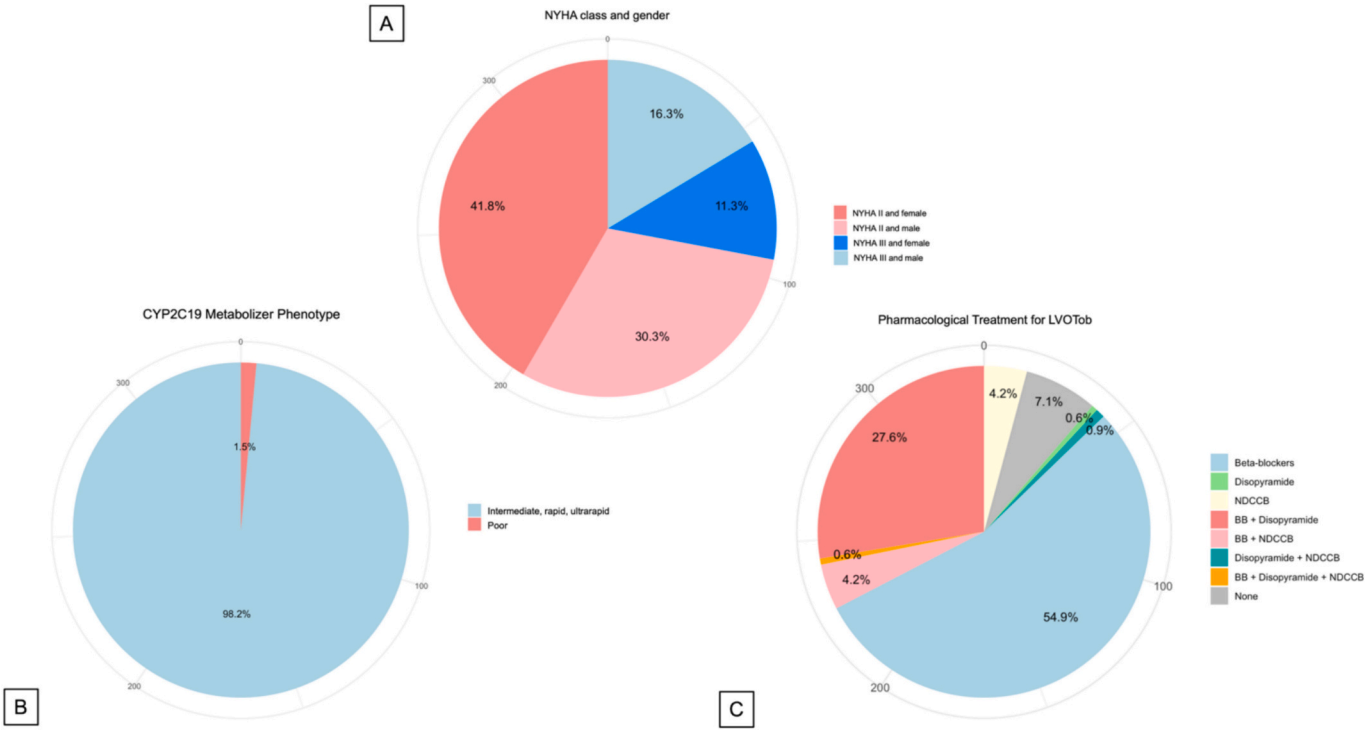

Fig. 1. A. NYHA class distribution by gender in the EAP cohort. B. CYP2C19 metabolizer phenotype in EAP cohort. Light red represents poor metabolizer phenotype, while light blue represents intermediate, rapid and ultrarapid metabolizer. C. Pharmacological treatment for LVOTob in the EAP cohort, it shows monotherapy and combination therapy. Beta-blockers and the combination of disopyramide with beta-blockers are the most frequently used treatments. A significant proportion of patients were not receiving any therapy for LVOT obstruction. A small number were treated with NDCCBs alone, and even fewer with other combination therapies. BB: beta-blocker; EAP, Early Access Program; LVOTob, left ventricular outflow tract obstruction; NDCCB: non-dihydropyridine calcium channel blocker; NYHA, New York Heart Association. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

95% CI -1.00, −4.00). Echocardiographic parameters like LVEF, MWT and LAVI showed no difference between subgroups, but LVOT obstruction gradient was higher in patients with SRT candidacy (40 vs 63.50 mmHg, $p < 0.0001$, median Δ -23.5, 95% CI -25, −16), as was the gradient measured at phase 2 Valsalva (70 vs 90 mmHg, $p < 0.0001$, median Δ -20, 95% CI -15, −22.12). There were no significant differences in pharmacologic therapy between the groups.

3. Discussion

In the EAP, 337 patients with a confirmed diagnosis of oHCM who remained symptomatic and unresponsive to conventional therapy (either as monotherapy or combination therapy) have been enrolled and received mavacamten treatment from 54 centers over a one-year enrollment period. The Italian cohort was older and exhibited a more severe phenotype at baseline compared to the baseline characteristics of patients enrolled in the EXPLORER-HCM study [6]. Only about a quarter of these patients have been eligible candidates to SRT, due to LVOTob gradient and functional classification. Conversely, most patients remained symptomatic and were not eligible for SRT, despite showing no significant differences in echocardiographic morphology, biomarker parameters or ongoing treatment compared to SRT candidates. For this subset of patients, access to the EAP represented the only opportunity for treatment.

A geographical gradient in prescribing rates was observed across Italian regions. The differences in prescribing behavior probably reflected the heterogeneous responses of the ethics committees across participating centers. This may have led to delays in program activation and, consequently, to a lower number of treated patients even in centers with a high expertise on HCM. Despite the high number of activated centers, enrolment varied significantly: the top ten enters treated almost half of all patients, while 17 centers enrolled only one or two patients. This is also attributable to Italy's extensive network of enters for treating cardiomyopathies. Unlike centralized models found in other European countries, the Italian network provides patients with a primary point of contact for new symptom occurrences and ensures rapid therapeutic management. It is not uncommon for novel pharmaceutical agents to demonstrate an imbalanced distribution of treated patients. In the initial years, medical centers with a limited number of patients often centralize to initiate new therapeutic interventions. This consolidation is driven by the objective of fostering confidence and developing the capacity to effectively manage new treatments.

In Europe, CYP2C19 genotyping is required to determine the starting dose of mavacamten. In our cohort, only 1.5% of patients were poor CYP2C19 metabolizers, consistent with estimates in the Caucasian population [11]. These data confirm the low prevalence of such profile and the minimal impact on clinical practice, where many patients do not require high doses and are effectively treated with 5 mg once daily [7].

Our cohort exhibited a moderate HCM phenotype, a non-hypercontractile LVEF, and severe left atrial enlargement, indicating advanced disease phenotype (HCM with adverse remodelling, stage III) [1]. According to that, NT-proBNP and TnI-hs levels were markedly elevated. These features make our cohort distinct from the EXPLORER-HCM cohort, particularly due to the absence of hypercontractile phenotype. This is in line with the differences observed when comparing results from randomized clinical trials with real-word data. Real-world patients often exhibit a more severe phenotype, different disease expression, and broader demographic representation for subpopulations that are

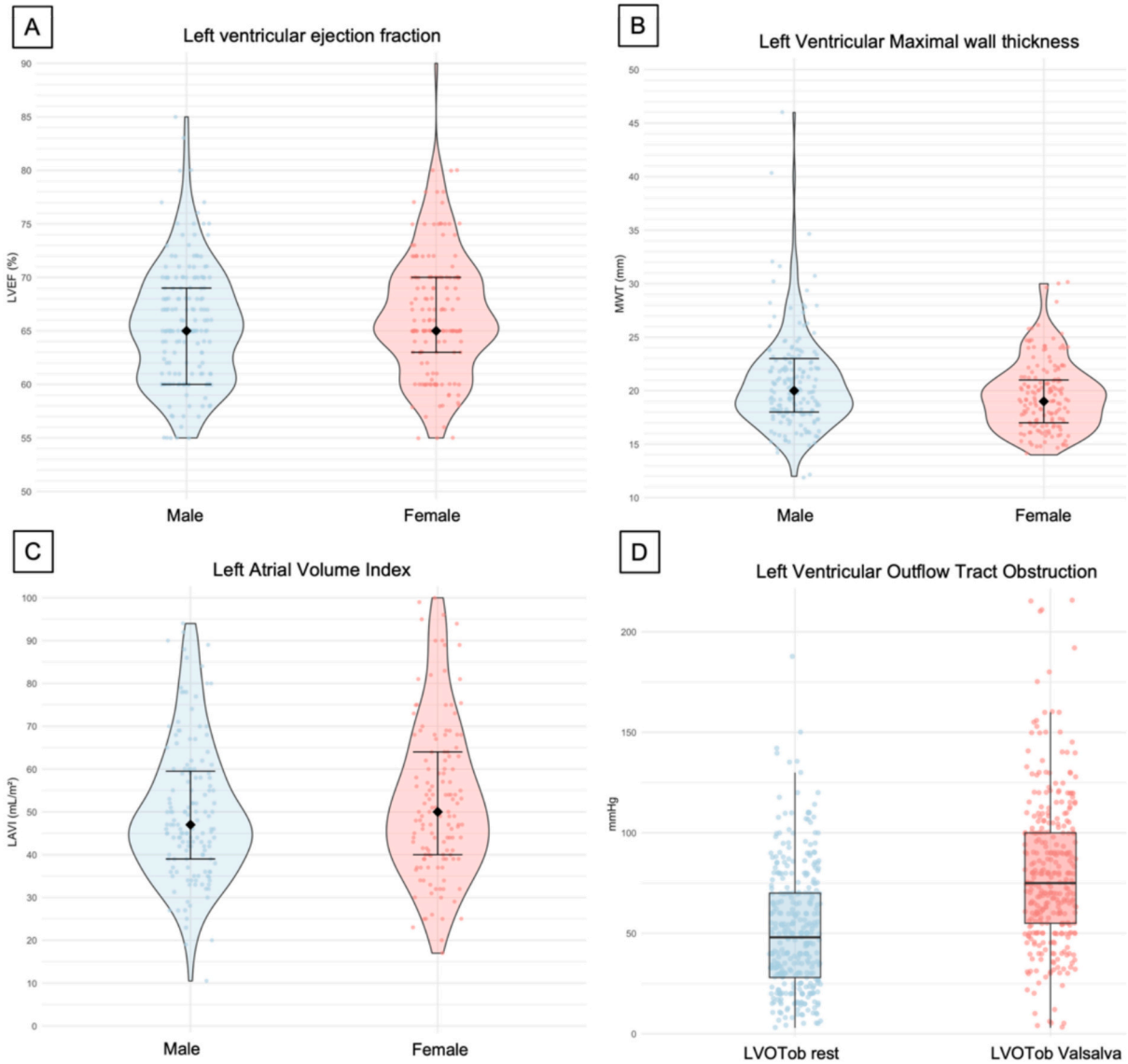

Fig. 2. The four graphs represent echocardiographic parameters at baseline of EAP cohort: A. LVEF, B. MWT, C. LAVI, D. LVOTob at rest and with Valsalva. LVEF, MWT and LAVI are stratified by gender; light blue represents male patients, while light red represents female patients. EAP, Early Access Program; MWT, maximal wall thickness; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVOTob, left ventricular outflow tract obstruction. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

underrepresented in trials. Conversely, real-world registries allow testing treatments in advanced disease stages and reassessing their safety [13].

An important consideration can be inferred from our cohort: only 22% of patients with oHCM met the criteria for SRT at baseline and many patients continued to experience obstruction even with combination therapy involving 2 drugs. The low eligibility for SRT was primarily attributable to the fact that most patients were in NYHA class II. Additional exclusion criteria such as high operative risk or advanced age were not considered in this analysis. The persistent obstruction in these individuals may adversely affect their long-term outcomes [14,15]. This suggests that myosin inhibition should not be viewed merely as an alternative to SRT, but rather as a strategy to treat patients even in the early stages or in less severe symptomatic stages of the disease. In preclinical studies in induced pluripotent stem cells (iPSC) and murine models, early administration of mavacamten prevented disease progression by attenuating myocardial hypertrophy, fibrosis and diastolic dysfunction [8]. This data supports mavacamten as a disease-modifying therapy, which could be a class property of myosin inhibitors. Therefore, longitudinal real-world data are necessary to determine whether myosin inhibitors can modify the natural history of oHCM and reduce cardiovascular outcomes [8,16,17]. While SRT has been shown to improve outcomes in oHCM in performed in high-volume and experienced cardiac surgery centers, the non-invasive nature of mavacamten allows for broader use of this therapeutic option, although its long-term safety and efficacy still require further confirmation [17,18]. Additional data are needed to understand its potential as a disease-modifying therapy and to identify patients who may not respond adequately to such treatment.

This study provides an overview of Italy's real-world experience with prescribing mavacamten to patients with oHCM. The results reflect the drug's availability through a compassionate use programme, which required extensive documentation for each patient, thus limiting enrolment based on administrative capacity at each center. Despite

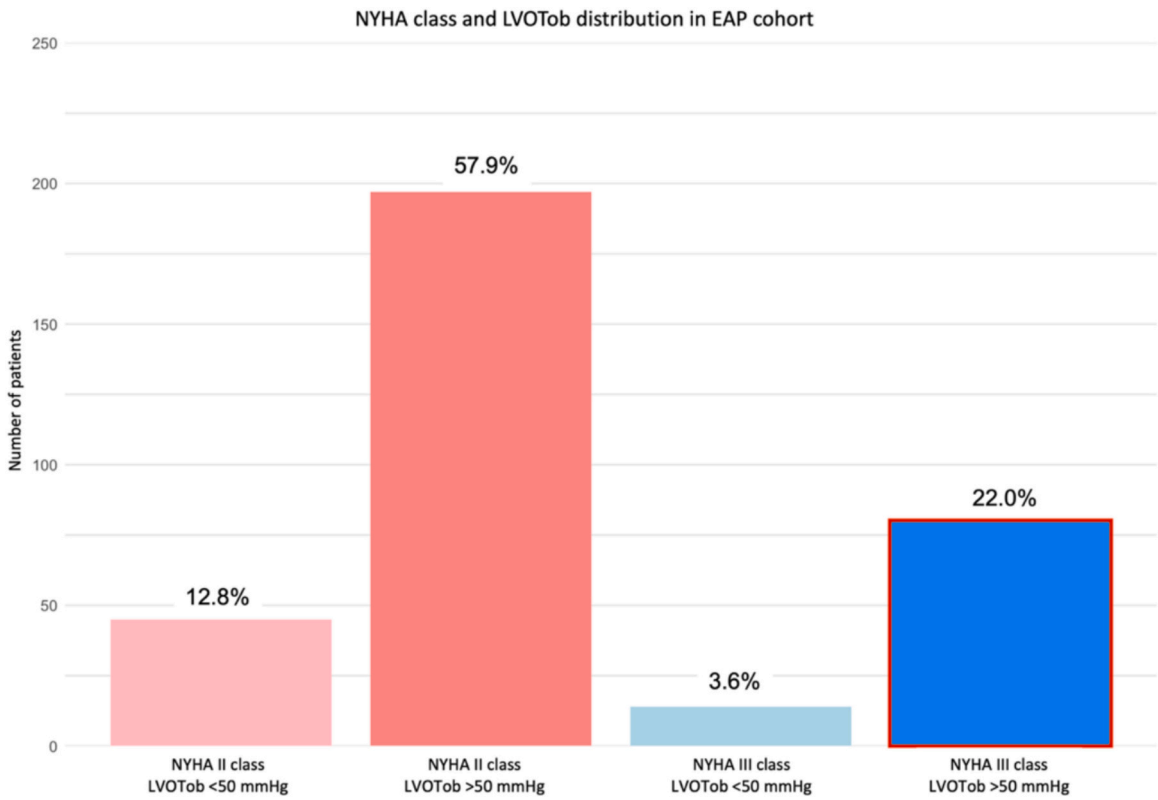

Fig. 3. The bar graph represents the EAP cohort stratified by NYHA class (II or III) and by the severity of LVOT obstruction (≤50 mmHg or > 50 mmHg). According to the 2023 ESC Guidelines for the management and treatment of cardiomyopathies, patients in NYHA class III with LVOT obstruction >50 mmHg meet the indication for septal reduction therapy. EAP, Early Access Program; NYHA, New York Heart Association; LVOTob, left ventricular outflow tract obstruction.

these constraints, the findings offer valuable insights into the characteristics of the initial patients selected for mavacamten therapy.

4. Limitations and future perspective

It should be noted that variability in ethics committees criteria may have influenced the number of patients enrolled across centers that activated the EAP. Italy has a well-established network of HCM referral centers, which would theoretically allow for widespread and equitable access to care, including the complex and resource-intensive management required for mavacamten treatment. However, this potential may not have been fully realized due to multiple factors unrelated to the clinical expertise or organizational structure of HCM centers, but rather to the unique nature of a compassionate use program. Furthermore, imaging data were not centrally analyzed in a dedicated core laboratory. This may have contributed to discrepancies in certain echocardiographic parameters when compared with randomized clinical trials of mavacamten, such as LVEF. This limitation is partially mitigated by the substantial experience of all participating centers in the diagnosis and management of HCM, including the evaluation of disease-defining features such as LVOTo. Certain echocardiographic parameters, such as the severity of mitral regurgitation, and biomarker data, including NT-proBNP and hs-cTnI or hs-cTnT, were reported in a limited proportion of the study cohort, restricting the robustness of some comparisons. Nevertheless, given the overall size of the study population, the available dataset was considered sufficient to support the analyses performed.

In the future, the aim will be to investigate the impact of mavacamten on the prognosis of patients with HCM, which will require real-world data from large cohorts, potentially supported by national registries. In addition, predictors of response or non-response to myosin inhibitors will be the focus of further studies, aiming to support clinical decision-making on the optimal strategy to manage LVOTo and symptoms on an individual basis.

5. Conclusion

The compassionate use program for mavacamten in Italy showed engagement, enrolling many patients despite time constraints and administrative requirements. A large number of centers participated, with a few high-volume centers treating over half of the patients. The Italian cohort of oHCM was older and exhibited more advanced disease stages compared to those in the EXPLORER-HCM trial. Almost three-quarters did not meet criteria for SRT, suggesting that pharmacological treatments like mavacamten and interventional approaches should be complementary. Mavacamten provides an additional option for oHCM patients unresponsive to standard therapy, especially those symptomatic but ineligible for SRT.

CRediT authorship contribution statement

G. Bonacchi: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **A. Del Franco:** Writing – review & editing, Writing – original draft. **P. Agostoni:** Writing – review & editing. **E. Agricola:** Writing – review & editing. **E. Ammirati:** Writing – review & editing. **P. Baratta:** Writing – review & editing. **F. Barocelli:** Writing – review & editing. **E. Bertero:** Writing – review & editing. **E. Biagini:** Writing – review & editing. **G. Boriani:** Writing – review & editing. **P. Calabrò:** Writing – review & editing. **L. Calò:** Writing – review & editing. **C. Calore:** Writing – review & editing. **S. Carigi:** Writing – review & editing. **E. Carluccio:** Writing – review & editing. **N. Cerrato:** Writing – review & editing. **C. Chimenti:** Writing – review & editing. **A.**

Table 2
Comparison of baseline characteristics between subgroup without septal reduction therapy candidacy and subgroup with candidacy, in EAP cohort. Patients with SRT candidacy had NYHA class ≥3 and LVOTob ≥50 mmHg. P-values and effect estimates with 95% confidence intervals are reported. Effect estimates, labeled in the table as Estimated effect (95% CI), include mean differences for continuous variables and odds ratios for categorical variables. BB, Beta-Blocker; CI, Confidential Intervals; EAP, Early Access Program; hs-cTn, High Sensitivity Cardiac Troponin; LAVI, Left Atrial Volume Index; LV, Left Ventricle; LVEF, Left Ventricular Ejection Fraction; LVOTob, Left Ventricular Outflow Tract Obstruction; ND-CCB, Non-Dihydropyridine Calcium Channel Blocker; NYHA, New York Heart Association; N-Terminal Pro B-Type Natriuretic Peptide; SRT, Septal Reduction Therapy.

	EAP patients without SRT indication	EAP patients with SRT indication	Estimated effect (95%CI)	p-value
Patients, n (%)	263 (78)	74 (22)		
Age, years	63.00 [54.00; 69.75]	66.00 [58.25; 70.00]	3.0 (1.0 to 4.0)	0.034
Sex, n (%)			2.41 (1.42 to 4.16)	0.001
Female	153 (58.2)	27 (36.5)		
Male	110 (41.8)	47 (63.5)		
NYHA class, n (%)				<0.001
II	243 (92.4)	–	–	
III	20 (7.6)	74 (100)		
LVEF (%)	65.0 [61.00; 70.00]	65.0 [60.10; 70.00]	0.0 (−0.5 to 0.0)	0.808
Maximum LV thickness (mm)	19.0 [18.00; 22.00]	20.0 [18.00; 22.00]	1.0 (0.0 to 1.0)	0.251
LVOTob at rest (mmHg)	40.0 [24.50; 65.50]	63.5 [40.00; 82.75]	23.5 (16.0 to 25.0)	<0.001
LVOTob Valsalva (mmHg)	70.0 [50.00; 95.00]	90.0 [69.25; 113.75]	20.0 (15.0 to 22.12)	<0.001
LAVI (ml/m^2)	48.5 [39.60; 59.25]	50.0 [40.00; 64.00]	1.50 (0.0 to 6.0)	0.321
Pharmacological therapy (%)				
Betablocker	229 (87.1)	65 (87.8)	0.90 (0.42 to 2.0)	1.0
Disopyramide	76 (28.9)	24 (32.4)	0.84 (0.48 to 1.47)	0.65
ND CCB	26 (9.9)	8 (10.8)	0.9 (0.39 to 2.09)	0.98
Association therapy	85 (32.8)	28 (36)	0.78 (0.45 to 1.34)	0.45
Beta-blocker only	147 (56.7)	37 (47)		
Disopyramide only	0 (0)	2 (3)		
ND CCB only	12 (4.6)	2 (3)		
Beta blocker and disopyramide	71 (27.4)	22 (28)		
Beta-blocker and ND CCB	9 (3.4)	6 (8)		
Disopyramide and ND CCB	3 (1.1)	0 (0)		
BB and disopyramide and ND CCB	2 (0.7)	0 (0)		
None	19 (7.3)	5 (6)	1.07 (0.38 to 2.98)	1.0
NT-proBNP (pg/ml)	676 [347.50; 1437.25]	1128 [492.50; 2508.50]	−452 (−1513 to −3)	0.059
Hs-cTnI (pg/ml)	17.90 [9.55; 27]	13 [10; 20]	−4.9 (−5.3 to −1.7)	0.326

Chinaglia: Writing – review & editing. **C. Chiriatti:** Writing – review & editing. **L. Crotti:** Writing – review & editing. **R. De Caterina:** Writing – review & editing. **M. Di Marco:** Writing – review & editing. **F. Di Spigno:** Writing – review & editing. **A. Evangelista:** Writing – review & editing. **G. Galasso:** Writing – review & editing. **F. Graziani:** Writing – review & editing. **W. Grosso Marra:** Writing – review & editing, Conceptualization. **A.I. Guaricci:** Writing – review & editing. **F. Guerra:** Writing – review & editing. **C. Leuzzi:** Writing – review & editing. **G. Limongelli:** Writing – review & editing. **C. Lofiego:** Writing – review & editing. **M.A. Losi:** Writing – review & editing. **B. Mabritto:** Writing – review & editing. **S. Marazia:** Writing – review & editing. **M. Merlo:** Writing – review & editing. **I. Monte:** Writing – review & editing. **M. Moretti:** Writing – review & editing. **R. Murzilli:** Writing – review & editing. **M.B. Musumeci:** Writing – review & editing. **F. Negri:** Writing – review & editing. **D. Pasqualucci:** Writing – review & editing. **G. Patti:** Writing – review & editing. **E. Perugini:** Writing – review & editing. **M.F. Piepoli:** Writing – review & editing. **G. Pontone:** Writing – review & editing. **G. Quarta:** Writing – review & editing. **C. Raineri:** Writing – review & editing. **F. Re:** Writing – review & editing. **F. Ricci:** Writing – review & editing. **R. Ruggieri:** Writing – review & editing. **E. Saletti:** Writing – review & editing. **C. Santolamazza:** Writing – review & editing. **L. Scelsi:** Writing – review & editing. **R. Spoladore:** Writing – review & editing. **G. Todiere:** Writing – review & editing. **M. Pieroni:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **G. Sinagra:** Writing – review & editing. **I. Olivotto:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Conceptualization.

Funding

This study did not receive external funding.

Declaration of competing interest

Dr. Giacomo Bonacchi, MD, has received speaker honoraria and advisory board honoraria from Bristol-Myers Squibb. Prof Iacopo Olivotto, MD, has received speaker, consultant and advisor honoraria from Bristol-Myers Squibb; he has received research support from Bristol-Myers Squibb. Prof Piergiuseppe Agostoni, MD, PhD, has received speaker, consultant and advisor honoraria from Bristol-Myers Squibb. Dr. Ammirati, MD, PhD, has received a grant from the Italian Ministry of Health (GR-2019-12,368,506; principal investigator of the investigator-driven MYTHS [Myocarditis Therapy With Steroids]) and a grant from Italian Ministry of Health and NextGenerationEU (PNRR-MAD-2022-12,376,225); and he is a consultant for Lexeo. Prof. Massimo Piepoli, MD, PhD, received consultant fees and advisory honoraria from Novo-Nordisk and Astra Zeneca. Prof Maurizio Pieroni, MD, PhD, has received speaker, consultant and advisor honoraria from Bristol-Myers Squibb. Prof Gianfranco Sinagra, MD, has received speaker, consultant and advisor honoraria from Bristol-Myers Squibb.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2025.134152.

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