GLOBAL HEART

Guideline-Directed Medical Therapy and Ejection Fraction Recovery in a Specialised Heart Failure Programme in Colombia: A Registry-Based Cohort Study

ORIGINAL RESEARCH

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ABSTRACT

Background: Heart failure with reduced ejection fraction (HFrEF) carries a substantial global burden. Guideline-directed medical therapy (GDMT)—an angiotensin receptor-neprilysin inhibitor (ARNI), a beta-blocker, a mineralocorticoid receptor antagonist (MRA), and a sodium-glucose cotransporter 2 (SGLT2) inhibitor—is standard of care. Real-world implementation in Latin America and its association with left ventricular ejection fraction (LVEF) recovery remain poorly characterised.

Methods: We retrospectively analysed a prospectively maintained registry of 485 adults with HFrEF (LVEF ≤40%) enrolled in a specialised outpatient programme in Cali, Colombia. Median follow-up was 26.6 months (IQR 15.4–40.1) among 466 patients with paired baseline and follow-up LVEF measurements. Binary logistic regression identified independent predictors of strict heart failure with recovered ejection fraction (HFrecEF: baseline LVEF <40%, follow-up LVEF >40%, ΔLVEF ≥10 percentage points).

Results: Quadruple GDMT was prescribed in 73.6% of patients, with SGLT2 inhibitor use (93.8%) and beta-blocker use (94.8%) exceeding rates reported in international registries. Median LVEF increased from 32.0% to 44.0%; mean ΔLVEF +12.8 ± 12.0 pp. Strict HFrecEF was observed in 40.8% (190/466). In multivariable analysis, ischaemic aetiology (aOR 0.55, 95% CI 0.35–0.86; p = 0.008), lower baseline LVEF (aOR 0.72 per SD of 7.95 pp, 95% CI 0.58–0.89; p = 0.003), Pathway A assignment (aOR 0.39, 95% CI 0.22–0.68; p = 0.001), and higher log N-terminal pro-B-type natriuretic peptide (NT-proBNP) (aOR 0.68 per log unit, 95% CI 0.56–0.83; p < 0.001) were independently associated with HFrecEF.

Conclusions: In this sample of actively enrolled patients within a specialised Colombian heart failure programme, quadruple GDMT was documented in 73.6% and strict HFrecEF in 40.8%. Findings should be interpreted as descriptive of a structured multidisciplinary setting and are subject to survivorship bias; confirmation in cohorts followed from initial diagnosis is required.

LAY SUMMARY

- **Why we did this study.** Heart failure is a common condition in which the heart's pumping strength is reduced. In recent years, four types of medicines, given

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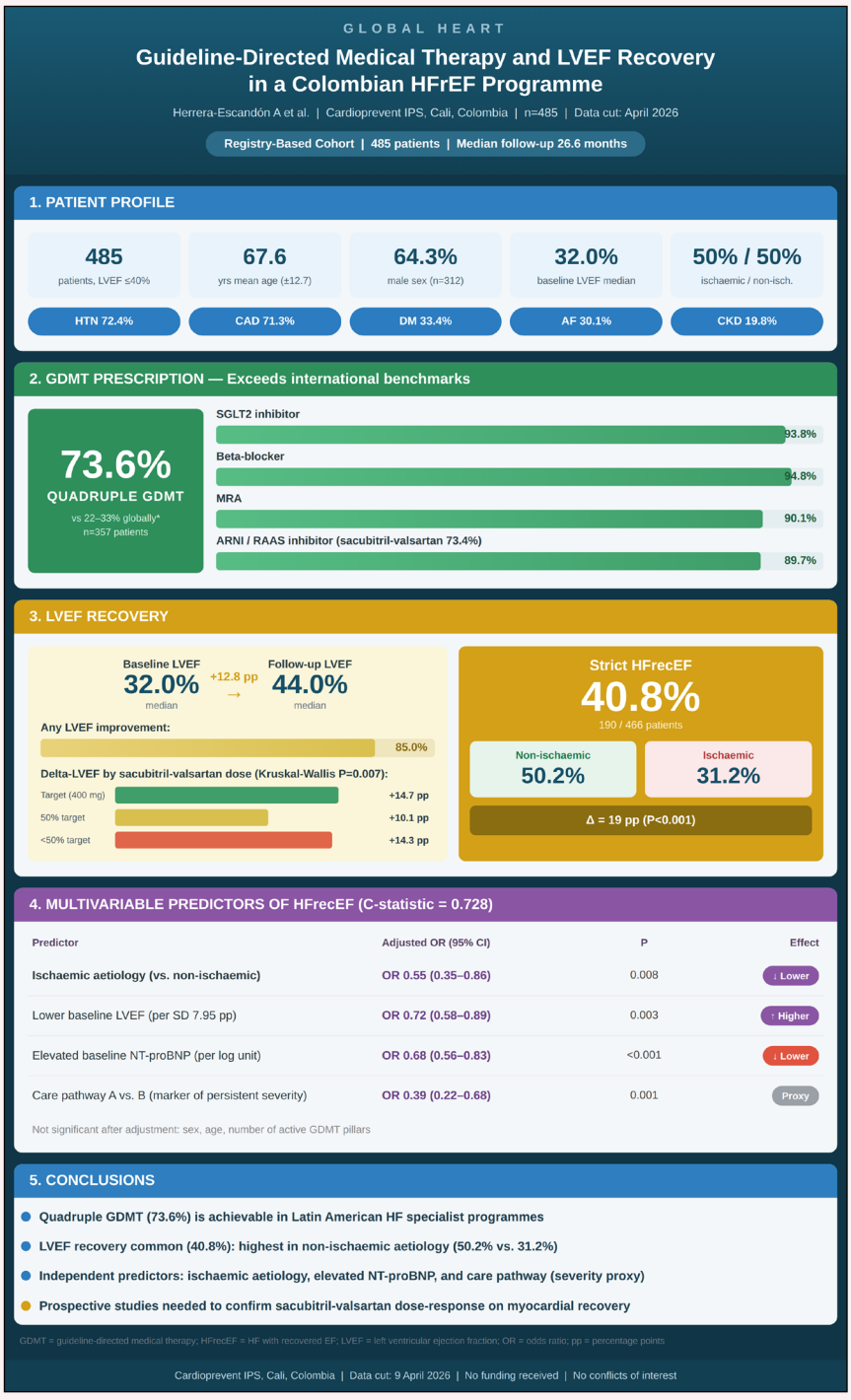
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heart failure with reduced ejection fraction; guideline-directed medical therapy; ejection fraction recovery; HFrecEF; Latin America; sacubitril-valsartan

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together, have been shown to help the heart recover some of its pumping function. We wanted to know how well this recovery works in Latin American patients treated in a specialised heart failure programme in Cali, Colombia, because very little data are available from our region.

- **What we found.** Among 485 patients followed for an average of just over two years, almost three-quarters were receiving all four recommended medicines. Four in every ten patients experienced meaningful recovery of their heart's pumping function. Recovery was more common in patients whose heart failure was not caused by blocked coronary arteries, in those with lower blood levels of a heart stress marker called NT-proBNP, and in patients with a more clinically stable disease course.
- **What this means.** In a specialised programme with structured follow-up and access to modern medicines, many patients with weakened heart pumping function can achieve important recovery. However, our patients were already stable and adherent to treatment, so these results represent what is achievable in an ideal setting rather than what routine care would deliver.

GRAPHIC ABSTRACT



1. INTRODUCTION

Heart failure (HF) is a clinical syndrome affecting more than 64 million people worldwide and constituting one of the leading causes of cardiovascular morbidity, hospitalisation, and mortality globally (1, 2, 3). In Latin America, registries such as BREATHE and RECOLFACA have documented region-specific features, including predominance of ischaemic aetiology, high hospitalisation rates, and significant gaps in access to evidence-based pharmacological therapy (4, 5). Current guidelines from the European Society of Cardiology (ESC 2021) and the American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA 2022) recommend quadruple guideline-directed medical therapy (GDMT) for HFrEF—comprising an ARNI (preferably sacubitril-valsartan), a cardioselective beta-blocker (6), an MRA (7), and an SGLT2 inhibitor—as Class I treatment (8, 9). Pivotal trials demonstrate that these four drug classes reduce all-cause mortality by up to 47% and cardiovascular death or HF hospitalisation by up to 62% versus conventional therapy, with progressive left ventricular ejection fraction (LVEF) improvement and N-terminal pro-B-type natriuretic peptide (NT-proBNP) reduction (10, 11).

Sacubitril-valsartan (PARADIGM-HF) reduced cardiovascular death or HF hospitalisation by 20% versus enalapril (11), and SGLT2 inhibitors (DAPA-HF, EMPEROR-Reduced) reduced HF hospitalisation by 25–30% (12, 13). Despite this evidence, real-world implementation remains suboptimal. The QUALIFY registry documented rates of triple evidence-based therapy at recommended doses (pre-SGLT2 era) ranging from 22–33% globally (14). Data from Latin America are particularly sparse.

Heart failure with recovered ejection fraction (HFrecEF) (15)—defined as baseline LVEF <40%, follow-up LVEF >40%, and absolute LVEF increase ≥10 percentage points—is a clinically meaningful outcome associated with improved prognosis (8, 16). Its contemporary characterisations derive predominantly from high-income settings. Regional registries such as BREATHE and RECOLFACA (4, 5) were not designed to capture longitudinal ejection fraction trajectories or dose-attainment data at the granularity required to identify HFrecEF; implementation of quadruple GDMT in the region is further constrained by heterogeneous access to novel therapies and the uneven availability of multidisciplinary programmes. We therefore characterise GDMT implementation, LVEF recovery, and independent predictors of HFrecEF in a specialised Colombian programme with structured GDMT protocols and echocardiographic follow-up.

2. METHODS

2.1 STUDY DESIGN AND POPULATION

This observational cohort study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and meets the minimum standards of the CODE-EHR framework for studies using electronic healthcare records. We conducted a retrospective analysis of a prospectively maintained clinical registry of patients enrolled in a specialised outpatient heart failure programme in Cali, Colombia. The registry has been continuously maintained since the programme opened in April 2018; new patients are added monthly, and patients who miss three or more scheduled encounters are formally discharged from the programme per institutional policy. The analytic sample was defined as all patients still actively enrolled at the data cut of 9 April 2026. Because patients who died, were lost to follow-up, or were discharged for non-attendance before that date are not represented, the sample over-represents patients who have continued in the programme and remained adherent to treatment. The programme provides comprehensive multidisciplinary HF management, including specialist physician visits, echocardiographic monitoring, biomarker surveillance, and structured cardiac rehabilitation. Of all patients actively enrolled at the data cut, those with a confirmed HF diagnosis, an echocardiographic LVEF ≤40% (per ESC 2021 HFrEF definition) at programme entry, and who were age ≥18 years were eligible, yielding a final analytic cohort of 485 patients (Figure 1).

Two care pathways were operationally defined at programme entry. Pathway A (high-complexity surveillance) was assigned to patients meeting at least one pre-specified criterion: hospitalisation within the preceding three months for acute decompensated heart failure; more than two cardiovascular hospitalisations within the preceding 12 months; marked

functional deterioration (NYHA class III–IV or AHA/ACC Stage D); estimated glomerular filtration rate <30 mL/min/1.73 m²; suspected infiltrative aetiology or haemodynamically unstable cardiomyopathy; or clinical deterioration despite optimised therapy. Patients meeting none were assigned to Pathway B; criteria were not mutually exclusive. Assignment was re-evaluated at each scheduled visit and could change in either direction during follow-up; the variable analysed reflects the most recent recorded assignment at the data cut. Both pathways followed a structured 12-month multidisciplinary schedule of monthly contacts (general physician, cardiology, nursing-education, and telephone), with four cardiology reviews in Pathway A (months 2, 4, 8, 11) and one in Pathway B (month 5); the full schedule is reproduced in Supplementary Figure S1. Sex was self-reported (male/female); gender, race, and ethnicity were not captured in the standardised dataset.

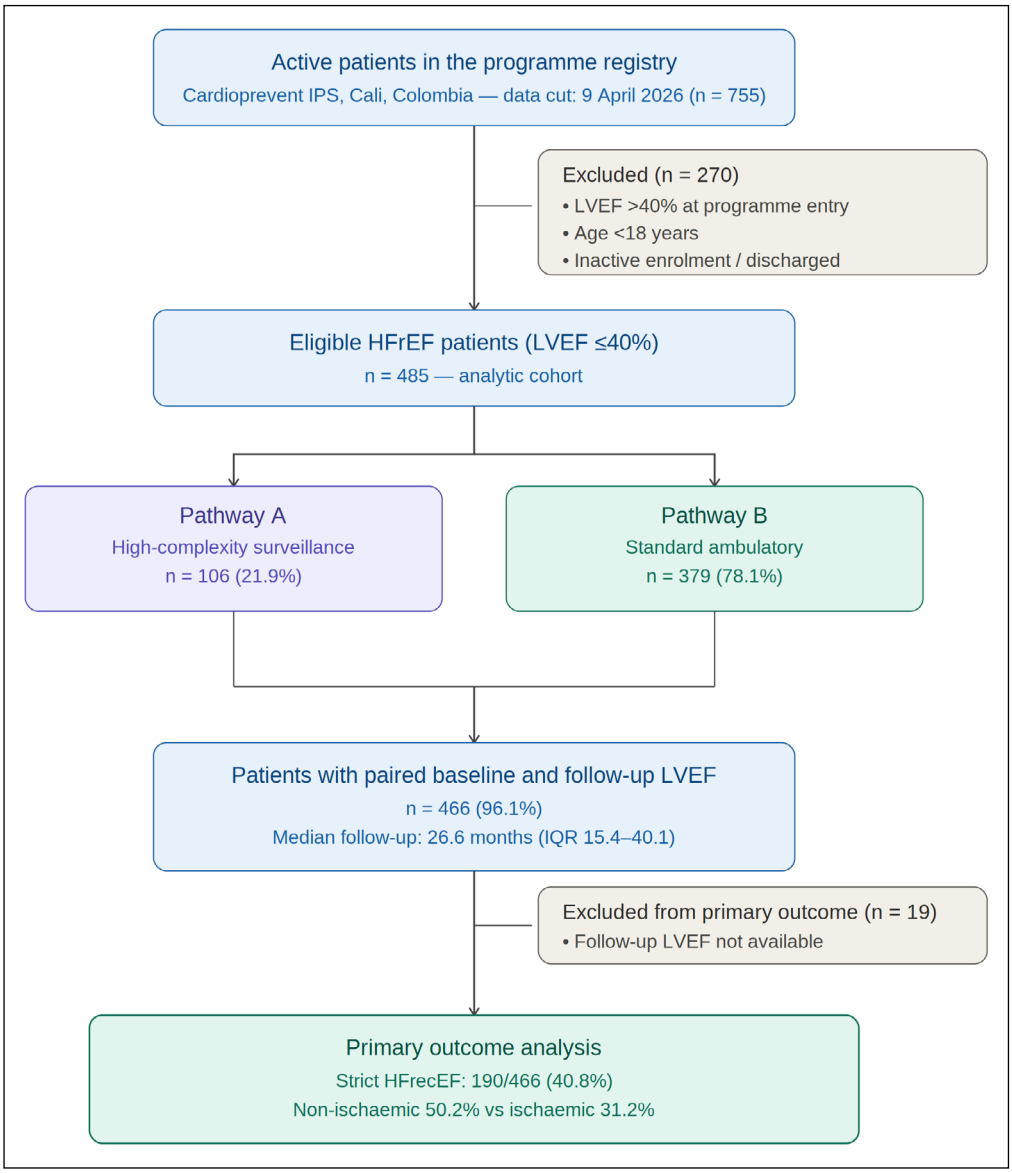


Figure 1 STROBE flow diagram of patient selection.

Flow of participants from the active programme registry to the primary outcome analysis. Among 755 patients in the registry at the data cut, 270 were excluded (LVEF >40% at entry, age <18 years, or inactive enrolment), yielding 485 eligible patients with HFrEF (LVEF ≤40% per ESC 2021 definition) at programme entry. Patients were assigned to Pathway A (high-complexity surveillance, n = 106) or Pathway B (standard ambulatory, n = 379). Paired baseline and follow-up LVEF were available in 466 (96.1%) and constituted the analytic sample for the strict HFrecEF outcome (190/466, 40.8%).

Abbreviations: HFrecEF: heart failure with recovered ejection fraction; LVEF: left ventricular ejection fraction.

Follow-up echocardiograms were clinically indicated rather than scheduled at fixed intervals; the follow-up ejection fraction was the most recent transthoracic echocardiogram in the electronic record as of the data cut (institutional imaging archive or digitised external report when performed elsewhere).

2.2 DEFINITIONS

LVEF was measured by two-dimensional transthoracic echocardiography using the biplane Simpson method per American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) recommendations (17). Strict HFrecEF required all three criteria: baseline LVEF strictly <40%, follow-up LVEF >40%, and absolute ΔLVEF ≥10

percentage points (8, 16). Quadruple GDMT was the concurrent prescription of all four pillars: an angiotensin receptor-neprilysin inhibitor (ARNI) or renin-angiotensin-aldosterone system (RAAS) inhibitor, a cardioselective beta-blocker, a mineralocorticoid receptor antagonist (MRA) (7), and a sodium-glucose cotransporter-2 (SGLT2) inhibitor (8, 9). Sacubitril-valsartan dose categories were target (400 mg/day), 50% (200 mg/day), and <50% (<200 mg/day) of target dose (data in 294 of 356 users, 82.6% coverage); bisoprolol categories were target (10 mg/day), 50% (5 mg/day), and <50% (<5 mg/day). These two agents were stratified by dose given their established titration targets and dose-dependent effects on reverse remodelling (8, 18); SGLT2 inhibitors were prescribed at a single approved dose (10 mg/day) and were not stratified.

2.3 OUTCOMES

The primary outcome was strict HFrecEF, defined per ESC 2021 criteria and Section 2.2. Secondary outcomes were: any LVEF improvement (ΔLVEF >0 percentage points); hospitalisation during follow-up; and NYHA functional class III–IV at data cut. The primary outcome and candidate predictors were specified prior to data extraction; the analytical plan was not formally pre-registered in a public protocol repository.

2.4 STATISTICAL ANALYSIS

Continuous variables are presented as means ± SD or medians (IQR); categorical variables are presented as frequencies and percentages. Follow-up time was the interval between baseline and the most recent available LVEF measurement (median 26.6 months, IQR 15.4–40.1 among the 466 paired patients). A binary logistic regression model for strict HFrecEF used a priori-selected candidate predictors: therapy intensity, sacubitril-valsartan and bisoprolol dose categories, age (per SD), sex, ischaemic aetiology, baseline LVEF (per SD), care pathway, and log-transformed baseline NT-proBNP. Missing baseline NT-proBNP (27%; n = 131) was handled by multiple imputation by chained equations (20 sets, pooled by Rubin's rules). Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) are reported, and discrimination assessed by the C-statistic. Baseline NT-proBNP was heavily right-skewed (median 730 pg/mL, IQR 244–1,840) and natural-log transformed to satisfy the linearity-of-log-odds assumption. Multicollinearity was evaluated by variance inflation factors (Supplementary Table S3). Two interactions (Pathway A × ischaemic aetiology; Pathway A × quadruple GDMT) and the following six sensitivity analyses were performed:

- **i.** restricted cohort excluding baseline LVEF exactly 40%
- **ii.** complete-case model with measured baseline NT-proBNP
- **iii.** logistic model with follow-up duration as a covariate
- **iv.** a Cox proportional-hazards model using programme enrolment as time origin, with the proportional-hazards assumption examined by Schoenfeld residual tests
- **v.** re-expression of the baseline LVEF odds ratio per 5 and 10 percentage-point decrements
- **vi.** a comparative summary across models (Supplementary Tables S1–S8)

LVEF differences across sacubitril-valsartan dose groups were assessed by Kruskal-Wallis with post-hoc Mann-Whitney U test and Bonferroni correction, and the pillar-count-ΔLVEF association by Spearman correlation. Two-sided $p < 0.05$ was significant. Analyses used Python 3.12 and STATA 19.5.

2.5 ETHICS

The study complied with the Declaration of Helsinki and was approved by the Cardioprevent IPS Institutional Ethics Committee (Approval No. CP2026-001). Under Colombian Resolution 8430 of 1993, this analysis was classified as research without risk. The requirement for written informed consent was waived by the ethics committee, given the retrospective, observational, registry-based design and the use of de-identified data.

3. RESULTS

3.1 PATIENTS

A total of 485 patients with HFrEF met eligibility criteria (Table 1). Mean age was 67.6 ± 12.7 years, and 64.3% (n = 312) were male. Aetiology was balanced between ischaemic (49.9%) and non-ischaemic (50.1%) causes. The most prevalent coexisting conditions were systemic hypertension (72.4%), coronary artery disease (71.3%), diabetes mellitus (33.4%), and atrial fibrillation (30.1%); 21.9% (n = 106) were in Pathway A. Paired baseline and follow-up echocardiograms were available in 466 of 485 patients (96.1%); the 19 without a follow-up study were retained in descriptive analyses but excluded from the HFrecEF analysis. At data cut, 72.8% were in NYHA class I, 25.0% in class II, and 2.3% (n = 11) in class III–IV. Over a median programme observation of 41.9 months, we recorded any clinical events during follow-up: cumulative hospitalisation was 12.4% (n = 60; 3.6 per 100 patient-years), and 15.9% (n = 77; 4.7 per 100 patient-years) had emergency visits. Cardiac rehabilitation was completed by 37.7% (n = 183), with median attendance of 65.0% (IQR 40.0–84.6%) (Table 1).

VARIABLE	STUDY COHORT (N = 485)	
	No. (%)	MISSING
Demographic Characteristics		
Age: yr., mean ± SD	67.6 ± 12.7	0
Median (IQR)	68 (59–77)	–
Male sex	312 (64.3)	0
Age Groups		
< 40 yr.	18 (3.7)	–
40–59 yr.	104 (21.4)	–
60–79 yr.	277 (57.1)	–
≥ 80 yr.	86 (17.7)	–
Care Pathway		
Pathway A: high-complexity	106 (21.9)	0
Pathway B: standard ambulatory	379 (78.1)	–
Aetiology		
Ischaemic	242 (49.9)	0
Non-ischaemic	243 (50.1)	–
Coexisting Conditions		
Systemic hypertension	351 (72.4)	0
Coronary artery disease	346 (71.3)	0
Prior myocardial infarction	39 (8.0)	0
Angioplasty/stent	317 (65.4)	0
CABG/Revascularisation	74 (15.3)	0
Diabetes mellitus	162 (33.4)	0
Atrial fibrillation	146 (30.1)	0
Dyslipidaemia	125 (25.8)	0
Chronic kidney disease	96 (19.8)	0
Stroke or TIA	54 (11.1)	0
Left Ventricular Ejection Fraction		
Baseline LVEF: %, median (IQR)	32.0 (25.0–37.0)	0
Mean ± SD	30.5 ± 7.9	–
Follow-up LVEF: %, median (IQR)	44.0 (35.0–51.0)	19 (3.9)
Mean ± SD	43.1 ± 11.3	–
Change in LVEF (ΔLVEF): pp, mean ± SD	+12.8 ± 12.0	19 (3.9)
Improvement in LVEF (ΔLVEF >0): n/N (%)	396/466 (85.0)	–

(Contd.)

Table 1 Baseline characteristics of the study population.

All patients met criteria for HFrEF (LVEF ≤40%) at programme entry. Percentages may not sum to 100 due to rounding. Coronary artery disease is defined as the presence of prior myocardial infarction, percutaneous coronary intervention with a stent, or coronary artery bypass grafting; components are not mutually exclusive. Subtypes of non-ischaemic aetiology were not available as discrete variables in the analytic database and are not reported. Conventional units (mg/dL for creatinine; mEq/L for potassium) are reported, consistent with the laboratory reporting standard used in Colombia. Approximate SI conversions: creatinine mg/dL × 88.4 = µmol/L; potassium mEq/L = mmol/L (equivalent at this physiological range).

Abbreviations: CABG: coronary-artery bypass grafting; CRT-D: cardiac resynchronisation therapy-defibrillator; ICD: implantable cardioverter-defibrillator; IQR: interquartile range; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; SD: standard deviation; TIA: transient ischaemic attack.

VARIABLE	STUDY COHORT (N = 485)	
	No. (%)	MISSING
Biomarkers and Renal Function		
NT-proBNP, baseline: pg/mL, median (IQR)	730 (244–1840)	131 (27.0)
Serum creatinine, baseline: mg/dL, median (IQR)	1.09 (0.93–1.34)	14 (2.9)
Mean ± SD	1.32 ± 1.16	–
Serum potassium: mEq/L, mean ± SD	4.45 ± 0.54	22 (4.5)
Hyperkalaemia (K+ > 5.5 mEq/L)	14 (3.0)	–
Hypokalaemia (K+ < 3.5 mEq/L)	9 (1.9)	–
NYHA Functional Class at Data Cut-off		
Class I	353 (72.8)	0
Class II	121 (25.0)	0
Class III	9 (1.9)	0
Class IV	2 (0.4)	0
Implantable Devices		
CRT-D (resynchronisation + defibrillator)	66 (13.6)	0
ICD alone	44 (9.1)	0
CRT alone	15 (3.1)	0
Permanent pacemaker	17 (3.5)	0
Chronic inotropic support	19 (3.9)	0
Clinical Events During Follow-up		
Hospitalisation	60 (12.4)	0
Emergency department visit	77 (15.9)	0
Composite CV event (hospitalisation or ED)	89 (18.4)	0
Cardiac Rehabilitation		
Enrolled	183 (37.7)	0
Attendance: %, median (IQR)	65.0 (40.0–84.6)	302 (62.4)

3.2 GDMT PRESCRIPTION AND DOSE ATTAINMENT

Quadruple GDMT was prescribed simultaneously in 73.6% of patients (n = 357; Table 2). Triple therapy was documented in 22.3% (n = 108), dual in 3.3% (n = 16), and monotherapy or no pillar in 0.8% (n = 4). Among patients receiving triple therapy, the most frequently absent class was the RAAS/ARNI (33.3%), followed by MRA (31.5%), beta-blocker (17.6%), and SGLT2 inhibitor (17.6%).

DRUG CLASS/AGENT	STUDY COHORT (N = 485) N (%)
RAAS Inhibitors/ARNI	
Any RAAS agent	435 (89.7)
Sacubitril-valsartan (ARNI)	**356 (73.4)**
Target dose: 400 mg/day	160 (44.9*)
50% target dose: 200 mg/day	111 (31.2*)
<50% target dose: < 200 mg/day	23 (6.5*)
Dose not documented	62 (17.4*)
Valsartan	29 (6.0)
Enalapril	28 (5.8)
Losartan	14 (2.9)
Candesartan/Other	8 (1.6)
Beta-Blockers	
Any beta-blocker	460 (94.8)

(Contd.)

Table 2 Guideline-directed medical therapy—Detailed prescription profile (N = 485).

*Percentage calculated among users of the respective drug class. **Percentage calculated among triple-therapy patients. One patient received lovastatin and is included in statin (any) but not in individual agent counts. Dose data for sacubitril-valsartan were extracted from clinical records with 82.6% coverage (294/356 users).

Abbreviations: ARNI: angiotensin receptor-neprilysin inhibitor; MRA: mineralocorticoid receptor antagonist; RAAS: renin-angiotensin-aldosterone system; SGLT2: sodium-glucose cotransporter 2.

DRUG CLASS/AGENT	STUDY COHORT (N = 485) N (%)
Bisoprolol	**306 (63.1)**
Target dose: ≥10 mg/day	36 (11.8*)
50% target dose: 5 mg/day	152 (49.7*)
<50% target dose: <5 mg/day	32 (10.5*)
Dose not documented	86 (28.1*)
Carvedilol	105 (21.6)
Target dose: 50 mg/day	0 (0.0*)
25 mg/day	40 (38.1*)
<25 mg/day	38 (36.2*)
Dose not documented	27 (25.7*)
Metoprolol	36 (7.4)
Nebivolol	13 (2.7)
Mineralocorticoid Receptor Antagonists	
Any MRA	437 (90.1)
Spironolactone	330 (68.0)
Eplerenone	107 (22.1)
SGLT2 Inhibitors	
Any SGLT2 inhibitor	455 (93.8)
Dapagliflozin	239 (49.3)
Empagliflozin	216 (44.5)
Therapy Intensity	
Quadruple therapy (all 4 pillars)	**357 (73.6)**
Triple therapy (3 pillars)	108 (22.3)
Without RAAS/ARNI	36 (33.3**)
Without MRA	34 (31.5**)
Without beta-blocker	19 (17.6**)
Without SGLT2 inhibitor	19 (17.6**)
Dual therapy (2 pillars)	16 (3.3)
Monotherapy or no pillar	4 (0.8)
Other Cardiovascular Agents	
Oral anticoagulant (any)	194 (40.0)
Apixaban	90 (46.4*)
Rivaroxaban	63 (32.5*)
Warfarin	25 (12.9*)
Dabigatran	2 (1.0*)
Not documented	14 (7.2*)
Aspirin	215 (44.3)
Clopidogrel	42 (8.7)
Loop diuretic (furosemide)	103 (21.2)
Statin (any)	339 (69.9)
Rosuvastatin	240 (70.8*)
Atorvastatin	98 (28.9*)
Amiodarone	30 (6.2)
Ivabradine	44 (9.1)
Digoxin	0 (0.0)
Thiazide diuretic	15 (3.1)

By individual drug class: SGLT2 inhibitors were prescribed to 93.8% of patients (dapagliflozin 49.3%, empagliflozin 44.5%); beta-blockers 94.8% (bisoprolol 63.1%, carvedilol 21.6%); MRAs 90.1% (spironolactone 68.0%, eplerenone 22.1%); RAAS/ARNI agents 89.7% (sacubitril-valsartan 73.4%). Among sacubitril-valsartan users (n = 356), target dosing was achieved in 44.9% (n = 160), 50% target dose in 31.2% (n = 111), and less-than-50% target dose in 6.5% (n = 23); dose data were available in 294 of 356 users (82.6% coverage, Figure 4). Among bisoprolol users (n = 306), the target dose was reached in 11.8% (n = 36), 50% target dose in 49.7% (n = 152), and less-than-50% target dose in 10.5% (n = 32; Figure 4).

Additional cardiovascular agents included statins (69.9%; rosuvastatin 70.8%), oral anticoagulants (40.0%; predominantly apixaban 46.4%), aspirin (44.3%), and loop diuretics (21.2%) (Table 2).

3.3 LVEF CHANGE AND PHENOTYPIC RECLASSIFICATION

Baseline median LVEF was 32.0% (IQR 25.0–37.0; mean 30.5 ± 7.9%). Among the 466 patients with paired measurements, mean follow-up LVEF was 43.1 ± 11.3% (median 44.0%, IQR 35.0–51.0) and mean absolute ΔLVEF was +12.8 ± 12.0 percentage points (one-sample t-test vs. zero, $p < 0.001$). Any LVEF improvement (ΔLVEF >0) occurred in 396 of 466 patients (85.0%), and strict HFrecEF per ESC 2021 criteria was met in 190 of 466 patients (40.8%; Table 6; Figures 2 and 3)—a prevalence estimate within the actively enrolled cohort at the data cut. The strict HFrecEF rate was substantially higher in non-ischaemic than ischaemic aetiology (50.2% vs. 31.2%; absolute difference 19 percentage points).

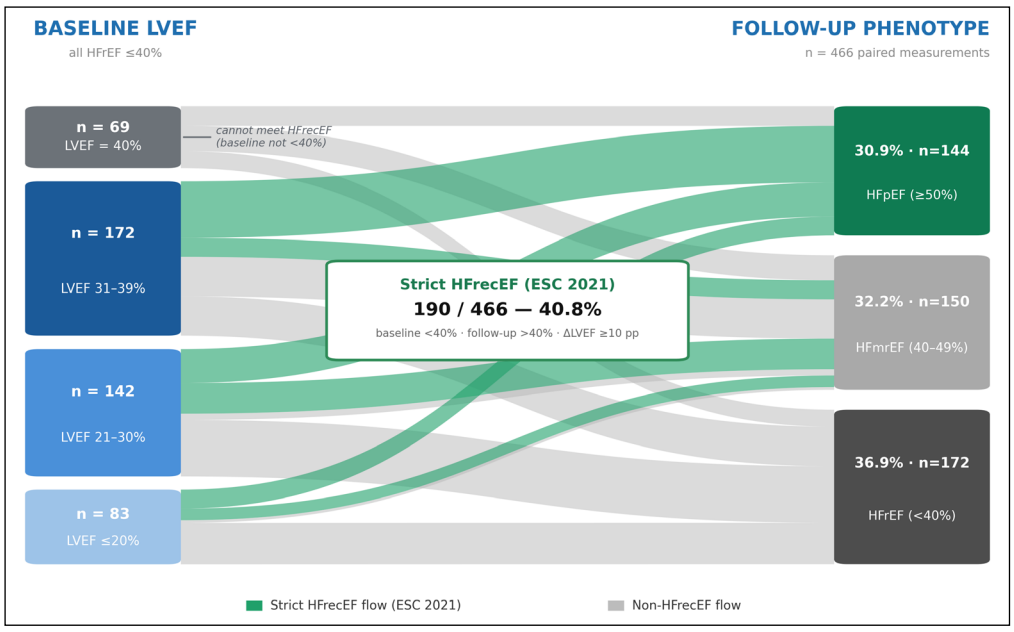


Figure 2 Phenotypic LVEF reclassification—Overall cohort.

Sankey diagram showing the distribution of left ventricular ejection fraction (LVEF) strata from baseline (all patients with LVEF ≤40%) to follow-up phenotypic categories. Green flows represent trajectories meeting the strict ESC 2021 HFrecEF criteria (baseline LVEF <40%, follow-up LVEF >40%, ΔLVEF ≥10 pp); grey flows represent all other trajectories. Patients with a baseline LVEF of exactly 40% (n = 69) cannot meet the strict definition and therefore are shown entirely in grey irrespective of their follow-up phenotype. Overall strict HFrecEF rate: 190/466 (40.8%). n = 466 patients with paired measurements. Cali, Colombia. Data cut: 9 April 2026.

Abbreviations: HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrecEF: heart failure with recovered ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; pp: percentage points.

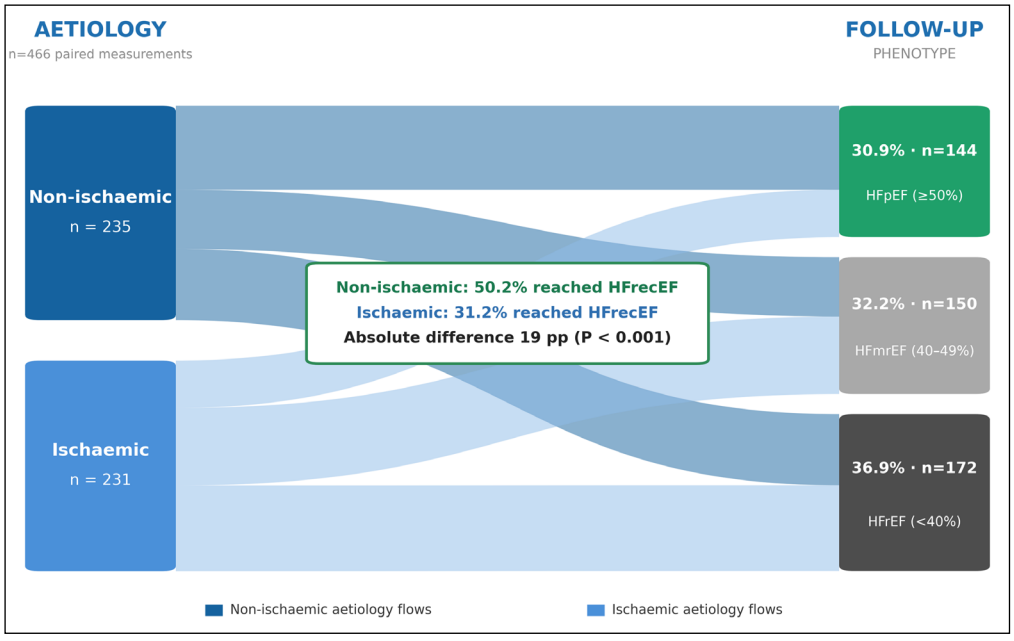


Figure 3 Phenotypic LVEF reclassification by aetiology.

Sankey diagram of the 466 patients with paired measurements, stratified by non-ischaemic (n = 235) and ischaemic (n = 231) aetiology on the left and follow-up phenotype (HFpEF ≥50%, HFmrEF 40–49%, HFrEF <40%) on the right; ribbons are coloured by aetiology. Strict HFrecEF (ESC 2021) was reached by 50.2% of non-ischaemic versus 31.2% of ischaemic patients (absolute difference 19 percentage points; P < 0.001). Definitions and abbreviations as in Figure 2. Data cut: 9 April 2026.

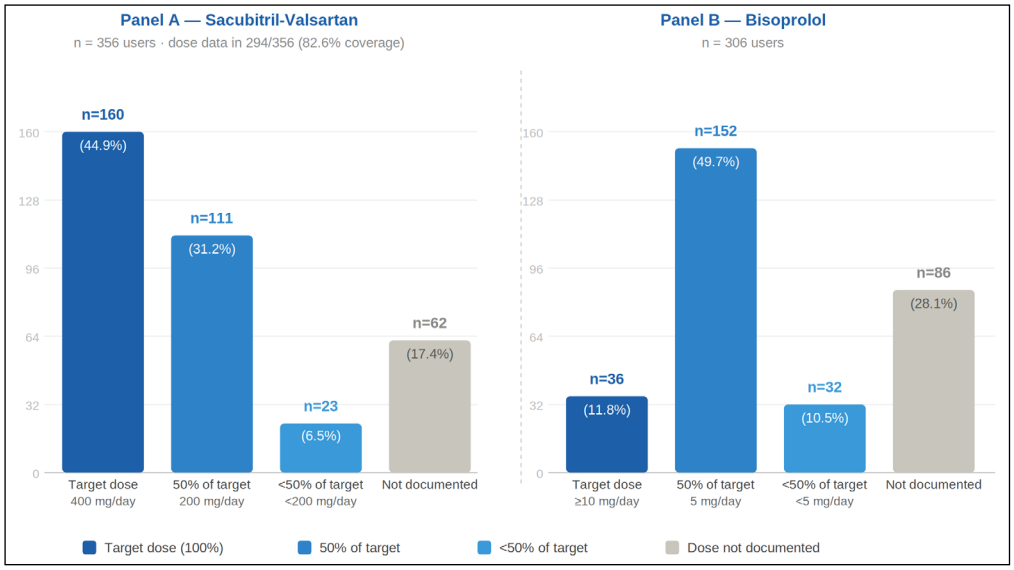


Figure 4 Achieved doses: Sacubitril-valsartan (Panel A) and bisoprolol (Panel B).

Distribution of daily dose categories among drug users. Panel A: sacubitril-valsartan (n = 356 users; dose extracted from clinical records with 82.6% coverage, 294/356 users). Target dose defined as 400 mg/day. Target dose achieved in 160 (44.9%), 50% of target dose in 111 (31.2%), less than 50% of target dose in 23 (6.5%), and dose not documented in 62 (17.4%). Panel B: bisoprolol (n = 306 users). Target dose defined as ≥10 mg/day per guideline-recommended titration targets. Target dose achieved in 36 (11.8%), 50% of target dose in 152 (49.7%), less than 50% of target dose in 32 (10.5%), and dose not documented in 86 (28.1%). Percentages calculated among drug users. 'Dose not documented' refers to records in which dose data were not available for extraction.

3.4 LVEF RECOVERY BY DOSE

Kruskal-Wallis testing across sacubitril-valsartan dose groups showed a statistically significant difference in ΔLVEF (p = 0.007) among 287 patients with documented dose and follow-up LVEF: mean ΔLVEF was 14.7 ± 12.7 percentage points at target dose (400 mg/day), 10.1 ± 11.0 percentage points at 50% target dose (200 mg/day), and 14.3 ± 11.8 percentage points at less than 50% target dose (<200 mg/day; Table 3). Post-hoc pairwise comparisons with Bonferroni correction (α = 0.0167) showed a significant difference between target dose and 50% target dose groups (p = 0.002); comparisons involving the less-than-50% target dose group did not reach significance after correction (p = 0.906 for target vs. <50% target; p = 0.141 for 50% target vs. <50% target). In the multivariable model (Section 3.5, Table 4), sacubitril-valsartan dose was not an independent predictor of HFrecEF after adjustment for baseline severity. For bisoprolol, an unadjusted trend was observed (Kruskal-Wallis p = 0.069), and bisoprolol dose was not an independent multivariable predictor. The Spearman correlation between the number of active GDMT pillars and ΔLVEF was weak (r = 0.09, p = 0.058), and the number of active pillars was not an independent predictor of HFrecEF.

THERAPY TYPE	n	BASELINE LVEF%, MEAN ± SD	FOLLOW-UP LVEF%, MEAN ± SD	ΔLVEF pp, mean ± SD
Quadruple (4 pillars)	344	30.0 ± 7.9	42.7 ± 11.1	+12.7 ± 12.0
Triple (3 pillars)	104	30.9 ± 8.5	43.8 ± 11.8	+12.9 ± 12.5
Dual (2 pillars)	15	32.5 ± 6.3	47.7 ± 9.7	+15.2 ± 9.4
Monotherapy/None	3	32.7 ± 1.2	39.7 ± 18.2	+7.0 ± 17.1
Sacubitril-Valsartan Dose Subgroup Analysis (Kruskal-Wallis P = 0.007)				
Target dose (400 mg/day)	156	28.9 ± 8.8	43.7 ± 11.0	**+14.7 ± 12.7**
50% target dose (200 mg/day)	108	31.0 ± 7.1	41.0 ± 11.4	+10.1 ± 11.0
<50% target dose (<200 mg/day)	23	27.5 ± 6.1	41.9 ± 9.5	+14.3 ± 11.8

Table 3 Change in left ventricular ejection fraction according to therapy intensity and sacubitril-valsartan dose.

Kruskal-Wallis test for ΔLVEF across sacubitril-valsartan dose groups: P = 0.007. Analysis restricted to 287 patients with documented dose and follow-up LVEF.

Abbreviations: LVEF: left ventricular ejection fraction; pp: percentage points; SD: standard deviation.

3.5 MULTIVARIABLE PREDICTORS OF HFrecEF

In the multivariable logistic regression model for strict HFrecEF (n = 466, 190 events, C-statistic 0.728), four independent predictors were identified. Ischaemic aetiology was associated with lower odds of HFrecEF versus non-ischaemic (adjusted OR 0.55, 95% CI 0.35–0.86; p = 0.008). Lower baseline LVEF was independently associated with HFrecEF (adjusted OR 0.72 per SD of 7.95 percentage points, 95% CI 0.58–0.89; p = 0.003); in clinically intuitive units this corresponds to adjusted OR 1.23 (95% CI 1.07–1.41) per 5-percentage-point lower baseline LVEF and 1.52 (95% CI 1.15–2.00) per 10-percentage-point lower baseline value (Supplementary Table S8). Elevated baseline log NT-proBNP was inversely associated with HFrecEF (adjusted OR 0.68 per log unit, 95% CI 0.56–0.83; p < 0.001), corresponding to adjusted OR 0.76 per doubling. Pathway

A assignment was associated with lower odds of HFrecEF versus Pathway B (adjusted OR 0.39, 95% CI 0.22–0.68; p = 0.001); assigned on pre-specified high-complexity criteria, it functions as a marker of persistent disease severity and was retained to adjust for case-mix. Sex, age, and number of active GDMT pillars were not independent predictors after adjustment (Table 4).

VARIABLE	CRUDE OR	P	ADJUSTED OR*	P	95% CI	INTERPRETATION
Therapy Intensity (ref = quadruple, 4 pillars)						
Triple therapy (3 pillars) vs. quadruple	0.75	0.222	0.85	0.544	0.50–1.44	Not significant
Dual/mono (≤2 pillars) vs. quadruple	1.17	0.747	1.50	0.472	0.50–4.49	Not significant
Sacubitril-Valsartan Dose (ref = target dose, 400 mg/day)						
50% target dose (200 mg/day)	0.66	0.087	**0.68**	**0.110**	0.42–1.09	Not significant
<50% target dose (<200 mg/day)	0.78	0.226	0.74	0.289	0.42–1.29	Not significant
No ARNI (other RAAS or none)	1.05	0.817	1.03	0.909	0.61–1.75	Not significant
Bisoprolol Dose (ref = target dose, ≥ 10 mg/day)						
50% target dose (5 mg/day)	1.05	0.793	0.89	0.667	0.51–1.54	Not significant
<50% target dose (<5 mg/day)	0.51	0.110	0.58	0.279	0.22–1.55	Not significant
No bisoprolol (other BB or none)	1.32	0.155	1.07	0.822	0.62–1.84	Not significant
Clinical Covariates						
Ischaemic aetiology (vs. non-ischaemic)	0.45	<0.001	**0.55**	**0.008**	0.35–0.86	Lower HFrecEF odds
Baseline LVEF (per SD = 7.95 pp)	0.76	0.004	**0.72**	**0.003**	0.58–0.89	Lower with higher LVEF
Pathway A vs. B	0.32	<0.001	**0.39**	**0.001**	0.22–0.68	Confounding by indication
Log NT-proBNP baseline (per log unit)	0.64	<0.001	**0.68**	**<0.001**	0.56–0.83	Lower with higher NT-proBNP
Age (per SD = 12.7 yr.)	0.73	0.001	0.93	0.527	0.73–1.17	Not significant
Male sex (vs. female)	0.82	0.302	0.86	0.487	0.56–1.32	Not significant

Table 4 Multivariable predictors of strict heart failure with recovered ejection fraction (HFrecEF).

CI = 95%; Outcome: n = 466 with paired measurements, 190 events (40.8%). Model: AIC = 422.3; McFadden R2 = 0.123. *Adjusted for all variables listed. Bold values: P < 0.05 in multivariable model.

Abbreviations: ARNI: angiotensin receptor-neprilysin inhibitor; BB: beta-blocker; CI: confidence interval; HFrecEF: heart failure with recovered ejection fraction (ESC 2021: baseline LVEF <40%, follow-up LVEF >40%, ΔLVEF ≥10 pp); LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-B-type natriuretic peptide; OR: odds ratio; pp: percentage points; RAAS: renin-angiotensin-aldosterone system; SD: standard deviation.

Sensitivity analyses (Supplementary Tables S1–S8) supported the robustness of the principal associations. Ischaemic aetiology, Pathway A assignment, and higher log NT-proBNP retained their direction and statistical significance across the restricted-cohort, complete-case, and follow-up-time-adjusted logistic models. In the time-to-event Cox proportional-hazards model all four predictors preserved their direction, but only Pathway A assignment (adjusted HR 0.59, 95% CI 0.37–0.95; p = 0.031) reached statistical significance; ischaemic aetiology (adjusted HR 0.91; p = 0.599), log NT-proBNP (adjusted HR 0.88; p = 0.058), and baseline LVEF (adjusted HR 0.86, 95% CI 0.73–1.00; p = 0.052) did not—an attenuation consistent with the limited temporal resolution of a single follow-up echocardiogram, which cannot date the moment of ejection-fraction recovery. The proportional-hazards assumption was not violated (global Schoenfeld p = 0.806). The baseline LVEF association was likewise attenuated (adjusted OR 1.07, 95% CI 0.84–1.37; p = 0.585) in the sensitivity cohort restricted to baseline LVEF strictly <40% (n = 397; HFrecEF rate 47.9%), consistent with the definitional constraint that participants with baseline LVEF exactly 40% cannot, by construction, meet strict HFrecEF criteria. Two interactions (Pathway A × ischaemic aetiology; Pathway A × quadruple GDMT) were not statistically significant (Supplementary Table S4).

4. DISCUSSION

In this registry-based cohort of 485 patients with HFrEF in a specialised Colombian outpatient programme, we identified three principal findings. First, quadruple GDMT rates substantially exceeded most international registries, with SGLT2 inhibitor and beta-blocker use both exceeding 93%. Second, strict HFrecEF was documented in 40.8% of patients with paired measurements and was markedly higher in non-ischaemic aetiology (50.2% vs. 31.2%). Third,

ischaemic aetiology, elevated baseline NT-proBNP, and Pathway A assignment (as a marker of persistent disease severity) were independently associated with lower odds of HFrecEF; the additional association with lower baseline LVEF in the primary model was attenuated in a sensitivity analysis and is best interpreted as a definitional constraint.

The quadruple GDMT rate (73.6%) substantially exceeds the QUALIFY registry (22–33% for triple therapy, pre-SGLT2 era) (14), the ESC-HF-LT registry (19), and contemporary post-DAPA-HF analyses from Europe and North America (15–40%) (20, 21). Comparison with population-based registries requires caution, as those span heterogeneous health systems. Against the more appropriate benchmark of specialised clinics (quadruple GDMT 50–70% in high-volume European and North American centres), the 73.6% rate and 93.8% SGLT2 inhibitor use remain notably high, and are particularly relevant in Latin America, where access to novel therapies has historically lagged (20).

Several structural features help explain these rates: a prospectively maintained registry that formally discharges patients missing three or more encounters (so the analytic sample is, by construction, adherent continuers); a multidisciplinary structure with monthly alternating contacts that provides repeated opportunities for dose titration; guideline-recommended therapy initiated at the first visit whenever tolerated, with structured review when target dose is not reached; and system-level access to sacubitril-valsartan and SGLT2 inhibitors within the Colombian health system. These features account for the high therapy rates, but also mean the sample is not a random group followed from diagnosis; the rates represent an upper bound achievable in a structured specialist programme, not routine care.

The strict HFrecEF rate (40.8%) is consistent with contemporary GDMT-treated cohorts (22, 23), and landmark analyses show HFrecEF carries an intermediate prognosis between persistent HFrEF and HFpEF, underscoring the relevance of this reclassification (8, 24).

The association between lower baseline LVEF and higher odds of HFrecEF requires cautious interpretation. Because participants with baseline LVEF exactly 40% cannot, by construction, meet the strict criterion (which requires <40%), their inclusion in the primary cohort mechanically inflated the recovery gradient at the upper end of the LVEF distribution; accordingly, the association attenuated to non-significance in the cohort restricted to baseline LVEF <40% (adjusted OR 1.07, 95% CI 0.84–1.37; p = 0.585, Supplementary Table S1), while ischaemic aetiology, Pathway A assignment, and log NT-proBNP were essentially unchanged. The three robust predictors reflect biological determinants of myocardial plasticity and disease severity, unaffected by this constraint.

In multivariable analysis, sacubitril-valsartan dose was not an independent predictor of HFrecEF; once baseline severity was accounted for, the unadjusted dose signal was largely explained by other factors. The unadjusted ΔLVEF difference across dose groups probably reflects that patients reaching target dose had better haemodynamic tolerance and less advanced disease, consistent with the difficulty of up-titrating higher-risk patients (18). The <50% target dose group contains only 23 patients, so the absence of a monotonic gradient reflects small subgroup size rather than a biological signal, and dose documentation was incomplete for 17.4% of sacubitril-valsartan users (with MRA dose not extracted), reflecting the state of the records rather than a true gradient. The biological rationale remains plausible—neprilysin inhibition potentiates natriuretic-peptide signalling favouring reverse remodelling (11, 25)—but whether reaching target dose independently accelerates recovery requires prospective testing with pre-specified titration protocols and complete dose data.

The higher HFrecEF rate in non-ischaemic aetiology reflects greater myocardial plasticity in neurohormonal-driven cardiomyopathies than in ischaemic disease, where scar limits structural recovery (26, 27), supporting phenotype-stratified HFrecEF surveillance and patient counselling on recovery expectations.

Elevated baseline NT-proBNP was independently associated with lower odds of HFrecEF, consistent with its role as a marker of wall stress and neurohormonal activation (25); a high baseline value reflects the severity of the remodelling substrate before treatment, distinct from the NT-proBNP reduction seen with GDMT. Whether the degree of NT-proBNP reduction mediates this association warrants prospective study, particularly given that follow-up NT-proBNP was available in only 11.1% of patients.

Among triple therapy patients, RAAS/ARNI (33.3%) and MRA (31.5%) were the most commonly omitted classes, likely reflecting concerns about hyperkalaemia and renal function in the 19.8% with CKD.

The inverse association between Pathway A and HFrecEF (adjusted OR 0.39) is not causal. The pathway variable reflects the most recent recorded assignment, and Pathway A criteria define a subgroup with greater persistent haemodynamic compromise at that time; its inclusion served as a proxy for current disease severity dimensions not captured by the other covariates. Because it is time-proximal to the outcome, the association may partly reflect patients whose LVEF had already recovered transitioning to Pathway B by the data cut (discussed as a limitation below). Notably, the number of active GDMT pillars was not an independent predictor, and its correlation with ΔLVEF was weak ($r = 0.09$, $p = 0.058$): where 95.9% received triple or quadruple therapy, variability in pharmacological intensity is insufficient to drive a detectable gradient. Taken together, the robust predictors—ischaemic aetiology and higher NT-proBNP, alongside Pathway A as a severity marker—reflect biological determinants and case-mix rather than pharmacological intensity per se. However, this should not be read as evidence against GDMT intensification, but as a consequence of the uniformly high treatment standard achieved here.

Cardiac rehabilitation enrolment (37.7%, median attendance 65.0%) exceeds Latin American averages but leaves room for improvement, given meta-analytic evidence that structured exercise training reduces HF hospitalisation by 20–30% and improves quality of life (28).

4.1 LIMITATIONS

Several of this study's limitations warrant discussion. First, the analytic sample was defined by active enrolment at the data cut, with patients missing three or more scheduled encounters being formally discharged; those who died, were lost to follow-up, or were discharged earlier are not represented, which likely inflates the HFrecEF rate and overstates GDMT adherence relative to the source population—findings describe the currently enrolled sample rather than an unselected group followed from diagnosis. Second, several dimensions of drug exposure were not captured: individual exposure duration was not recorded (a key gap for HFrecEF, which depends on cumulative treatment time), adherence was inferred from active prescription, sequencing of GDMT initiation was not extracted, MRA dose was not extracted, and sacubitril-valsartan dose was incomplete in 17.4% of users; a structured re-extraction of dose data across all four classes is planned. Third, baseline NT-proBNP was missing in 27.0% of patients and handled by multiple imputation (20 sets, Rubin's rules); a complete-case analysis (Supplementary Table S2) was consistent with the imputed model, though missing-not-at-random cannot be excluded, and follow-up NT-proBNP was available in only 11.1%, precluding analysis of biomarker change. Fourth, follow-up echocardiograms were clinically indicated rather than fixed intervals, producing heterogeneity in observation time (median 26.6 months, IQR 15.4–40.1); this was addressed by a logistic model with follow-up duration as a covariate (Supplementary Table S5, non-significant) and a Cox model (Supplementary Table S6), and the Pathway A odds ratio reflects the most recent rather than baseline assignment. Fifth, 69 patients (14.8%) had a baseline LVEF of exactly 40% and were structurally ineligible for the strict criterion; the restricted analysis (Supplementary Table S1) attenuated the baseline LVEF association while leaving the other three predictors essentially unchanged. Sixth, the multidisciplinary structure, drug availability, and echocardiographic surveillance may not be reproducible in routine settings; paired comprehensive structural echocardiographic data were available in only 67 of 485 patients (13.8%), limiting longitudinal structural inference (Table 5), and cardiac rehabilitation was captured as a binary variable.

4.2 CONCLUSIONS

In this sample of actively enrolled patients within a specialised Colombian heart failure programme, quadruple guideline-directed medical therapy was documented in 73.6% and strict HFrecEF in 40.8% of those with paired measurements. Ischaemic aetiology, elevated baseline NT-proBNP, and Pathway A assignment—a marker of persistent disease severity at the data cut—were independently associated with lower odds of HFrecEF; the apparent association

PARAMETER	Initial echo, median (IQR)	Last echo, median (IQR)	n (initial/last)
LV Systolic Function			
LVEF (%)	43.0 (35–50)	44.0 (35–54)	269/67
LV end-diastolic diameter (mm)	54.0 (49–61)	55.0 (49–63)	269/67
LV end-systolic diameter (mm)	41.0 (36–49)	41.0 (35–52)	269/67
LV end-diastolic volume (mL)	129.5 (98–181)	123.0 (98–187)	248/65
LV end-systolic volume (mL)	73.0 (46–113)	65.0 (44–114)	245/65
Interventricular septum thickness (mm)	10.0 (8–12)	10.0 (8–12)	269/67
Posterior wall thickness (mm)	9.0 (8–11)	9 (8–11)	269/67
Relative wall thickness	0.36 (0.29–0.44)	0.36 (0.28–0.44)	268/67
Left Atrium and Diastolic Function			
LA volume index (mL/m^2)	40.0 (35–50)	44.0 (36–55)	269/67
E/e' ratio	11.0 (8–14)	11.0 (8–14)	213/51
Right Ventricular Function			
RV end-diastolic diameter (mm)	37.0 (34–40)	37.0 (34–40)	269/67
TAPSE (mm)	20.0 (17–23)	19.0 (17–22)	269/67
Pulmonary Pressures and IVC			
Estimated PASP (mmHg)	35.0 (30–40)	34.0 (30–47)	201/53
IVC diameter (mm)	14.0 (13–16)	15.0 (13–17)	267/67

Table 5 Echocardiographic parameters at baseline and follow-up.

The 'Initial echo' column reports values from the earliest echocardiogram within the programme that included full chamber quantification (median 16 months post-enrolment). These do not represent the enrolment echocardiogram, which captured LVEF only and is the baseline LVEF used throughout the rest of the manuscript. Paired comprehensive structural data were available in 67 of 485 patients (13.8%), limiting longitudinal structural inference.

Abbreviations: IQR: interquartile range; IVC: inferior vena cava; LA: left atrium; LVEF: left ventricular ejection fraction; PASP: pulmonary artery systolic pressure; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion.

PHENOTYPE	Follow-up (%)	Strict HFrecEF*n (%)
HFrEF (LVEF <40%)	172 (36.9)	0 (0.0)
HFmrEF (LVEF 40–49%)	150 (32.2)	68/150 (45.3)
HFpEF (LVEF ≥50%)	144 (30.9)	122/144 (84.7)
Total	466 (100.0)	190/466 (40.8)
Strict HFrecEF by Aetiology (ESC 2021)		
Non-ischaemic aetiology	235 (50.4)	118/235 (50.2)
Ischaemic aetiology	231 (49.6)	72/231 (31.2)

Table 6 Phenotypic reclassification of left ventricular ejection fraction.

*Strict HFrecEF per ESC 2021: baseline LVEF <40%, follow-up LVEF >40%, and ΔLVEF ≥10 pp. All patients entered the programme with HFrEF (inclusion criterion LVEF ≤40%); follow-up phenotype boundaries (HFrEF <40%, HFmrEF 40–49%, HFpEF ≥50%) follow ESC 2021. The analytic cohort comprised 485 patients; 19 without a follow-up measurement were excluded, leaving 466 with paired measurements, over which all percentages are calculated. Of these 466, 294 reached a follow-up LVEF ≥40% (150 HFmrEF +144 HFpEF) and 190 met all three strict HFrecEF criteria. Patients with a baseline LVEF of exactly 40% (n = 69) were ineligible for strict HFrecEF, which requires a baseline below 40%.

Abbreviations: HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrecEF: heart failure with recovered ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; pp: percentage points.

with lower baseline LVEF was attenuated when participants with baseline LVEF exactly 40% were excluded and is best read as partly a definitional constraint. These findings are descriptive of a structured multidisciplinary setting and are subject to survivorship bias. Confirmation in cohorts followed from initial diagnosis—with standardised follow-up echocardiography, complete dose ascertainment, and prospective evaluation of dose-response and time-to-recovery relationships—will be required.

DATA ACCESSIBILITY STATEMENT

The de-identified individual-level dataset analysed in this study is held by the Cardioprevent IPS Heart Failure Programme Registry. The data are not publicly available due to institutional and ethical restrictions, but are available from the corresponding author upon reasonable request and with the approval of the Cardioprevent IPS Institutional Ethics Committee.

ADDITIONAL FILE

The additional file for this article can be found as follows:

- **Supplementary Material.** Institutional care-pathway protocol (Figure S1) and supporting sensitivity, interaction and diagnostic analyses for the primary model (Tables S1–S8). DOI: https://doi.org/10.5334/gh.1606.s1

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COMPETING INTERESTS

All authors confirm that they have no competing interests to declare. None of the authors is currently a member of the editorial team or editorial board of Global Heart, nor has held such a position within the last three years.

AUTHOR CONTRIBUTIONS

Conceptualisation: A.H.-E. and G.A.C.-B. Methodology: A.H.-E., M.A.P.-L. and G.A.C.-B. Data curation: M.A.P.-L., C.M.-G., and D.B. Formal analysis: A.H.-E. and M.A.P.-L. Investigation: A.H.-E. and M.A.P.-L. Project administration: A.H.-E. and M.A.P.-L. Supervision: G.A.C.-B. Visualisation: A.H.-E. and M.A.P.-L. Writing—original draft: A.H.-E. Writing—review and editing: all authors. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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