Supplementary Material

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

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Supplementary Table S1. Sensitivity analysis: multivariable model restricted to baseline LVEF strictly <40%.

Predictor	Adjusted OR	95% CI	p
Ischaemic aetiology (vs. non-ischaemic)	0.53	0.33–0.85	0.009
Baseline LVEF (per SD of 7.95 pp)	1.07	0.84–1.37	0.585
Pathway A (vs. Pathway B)	0.44	0.24–0.79	0.006
Log NT-proBNP (per log unit)	0.68	0.56–0.83	<0.001
Age (per SD of 12.7 yr)	0.92	0.72–1.17	0.495
Male sex (vs. female)	0.79	0.50–1.25	0.314

n = 397 with paired echocardiographic measurements; 190 HFrecEF events (47.9%). Multivariable logistic regression with multiple imputation (20 sets; Rubin's rules) for missing baseline NT-proBNP. Baseline LVEF association attenuated in this restricted cohort, consistent with the definitional constraint discussed in the main text. HFrecEF rate by aetiology in the sensitivity cohort: non-ischaemic 55.7%, ischaemic 38.9%. CI = confidence interval; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OR = odds ratio; pp = percentage points; SD = standard deviation.

Supplementary Table S2. Complete-case sensitivity model (restricted to participants with non-missing baseline NT-proBNP).

Predictor	Adjusted OR	95% CI	p
Ischaemic aetiology (vs. non-ischaemic)	0.60	0.36–1.00	0.048

Predictor	Adjusted OR	95% CI	p
Baseline LVEF (per SD of 7.95 pp)	0.80	0.63–1.02	0.074
Pathway A (vs. Pathway B)	0.36	0.19–0.68	0.001
Log NT-proBNP (per log unit)	0.68	0.57–0.82	<0.001
Age (per SD of 12.7 yr)	0.95	0.73–1.24	0.694
Male sex (vs. female)	0.84	0.52–1.35	0.482

n = 343 with paired LVEF measurements and non-missing baseline NT-proBNP. Multivariable logistic regression without multiple imputation. Ischaemic aetiology, Pathway A, and log NT-proBNP retained direction and statistical significance. Baseline LVEF retained the same direction with wider confidence intervals crossing unity, consistent with reduced power in the smaller sample. This pattern is consistent with a missing-at-random mechanism for NT-proBNP. CI = confidence interval; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OR = odds ratio; pp = percentage points; SD = standard deviation.

Supplementary Table S3. Variance inflation factors for the primary multivariable model.

Predictor	VIF
Age	1.37
Ischaemic aetiology	1.22
Log NT-proBNP	1.22
Pathway A	1.13
Baseline LVEF	1.12
Male sex	1.06
Mean VIF	1.19

VIFs computed on the complete-case multivariable model (n = 343). All VIFs are ≤1.37 (mean 1.19), well below the conventional threshold of concern (>5 or >10). No multicollinearity affecting model interpretation.

Supplementary Table S4. Interaction tests in the primary multiple-imputation model.

Interaction	Adjusted OR	95% CI	p
Pathway A × Ischaemic aetiology	0.50	0.17–1.48	0.208
Pathway A × Quadruple GDMT	0.86	0.29–2.53	0.790

Two interactions were tested in the primary multivariable model with multiple imputation (n = 466), addressing whether the effect of Pathway A assignment differs by aetiology (Pathway A × ischaemic aetiology) or by intensity of guideline-directed medical therapy (Pathway A × quadruple GDMT). Neither interaction reached statistical significance, supporting a single common model across pathway subgroups defined by aetiology or GDMT intensity. Quadruple GDMT was defined as concurrent prescription of all four pharmacological pillars (357/485 patients, 73.6%). CI = confidence interval; GDMT = guideline-directed medical therapy; OR = odds ratio.

Supplementary Table S5. Logistic model with follow-up duration as a covariate.

Predictor	Adjusted OR	95% CI	p
Ischaemic aetiology (vs. non-ischaemic)	0.59	0.37–0.94	0.027
Baseline LVEF (per SD of 7.95 pp)	0.69	0.55–0.86	0.001
Pathway A (vs. Pathway B)	0.38	0.21–0.68	0.001
Log NT-proBNP (per log unit)	0.73	0.60–0.89	0.002
Follow-up duration (standardised)	1.08	0.86–1.35	0.501

n = 426 with complete data on all covariates including follow-up duration (defined as months between baseline and last available echocardiogram; range 1.2–119.8 months, mean 40.8, SD 25.7). Multivariable logistic regression with multiple imputation (20 sets; Rubin's rules) for missing baseline NT-proBNP. Follow-up duration was standardised (mean-centred, divided by standard deviation) and was not an independent predictor of HFrecEF (p = 0.501). Its inclusion did not change the direction or significance of the four principal predictors. CI = confidence interval; HFrecEF = heart failure with recovered ejection fraction; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OR = odds ratio; SD = standard deviation.

Supplementary Table S6. Cox proportional-hazards sensitivity analysis.

Panel A. Adjusted hazard ratios for time to HFrecEF

Predictor	Adjusted HR	95% CI	p
Ischaemic aetiology (vs. non-ischaemic)	0.91	0.64–1.29	0.599
Baseline LVEF (per SD of 7.95 pp)	0.86	0.73–1.00	0.052
Pathway A (vs. Pathway B)	0.59	0.37–0.95	0.031
Log NT-proBNP (per log unit)	0.88	0.76–1.00	0.058

Predictor	Adjusted HR	95% CI	p
Age (per SD of 12.7 yr)	0.77	0.65–0.92	0.005
Male sex (vs. female)	0.86	0.62–1.19	0.365

Panel B. Proportional-hazards assumption (Schoenfeld residual tests)

Variable	p (Schoenfeld)
Ischaemic aetiology	0.489
Baseline LVEF	0.811
Pathway A	0.534
Log NT-proBNP	0.580
Age	0.758
Male sex	0.133
Global test	0.806

n = 426 with complete date fields and non-missing HFrecEF status; 170 HFrecEF events. Time origin: baseline echocardiogram. Time to event: interval from baseline to the follow-up echocardiogram at which strict HFrecEF criteria were first met (event) or last available echocardiogram (censored). Cox model with multiple imputation for missing baseline NT-proBNP. Schoenfeld residual tests performed on the complete-case Cox model. The proportional-hazards assumption was not violated for any individual covariate or globally (all p > 0.13; global p = 0.806). CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SD = standard deviation.

Supplementary Table S7. Comparative summary of the four principal predictors across all models.

Predictor	Primary (n=466)	LVEF <40 (n=397)	Complete-case (n=343)	With time (n=426)	Cox HR (n=426)
Ischaemic aetiology	0.55 (0.35–0.86); p=0.008	0.53 (0.33–0.85); p=0.009	0.60 (0.36–1.00); p=0.048	0.59 (0.37–0.94); p=0.027	0.91 (0.64–1.29); p=0.599
Baseline LVEF (per SD)	0.72 (0.58–0.89); p=0.003	1.07 (0.84–1.37); p=0.585	0.80 (0.63–1.02); p=0.074	0.69 (0.55–0.86); p=0.001	0.86 (0.73–1.00); p=0.052
Pathway A	0.39 (0.22–0.68); p=0.001	0.44 (0.24–0.79); p=0.006	0.36 (0.19–0.68); p=0.001	0.38 (0.21–0.68); p=0.001	0.59 (0.37–0.95); p=0.031
Log NT-proBNP	0.68 (0.56–0.83); p<0.001	0.68 (0.56–0.83); p<0.001	0.68 (0.57–0.82); p<0.001	0.73 (0.60–0.89); p=0.002	0.88 (0.76–1.00); p=0.058

Values are adjusted OR (or HR for the Cox column) with 95% CI and p. All models adjust for age and sex in addition to the predictors shown. Ischaemic aetiology, Pathway A assignment, and log NT-proBNP retained direction and statistical significance across the restricted-cohort, complete-case, and time-adjusted logistic models. In the Cox proportional-hazards model, all predictors preserved direction, but only Pathway A reached significance; ischaemic aetiology (p=0.599), log NT-proBNP (p=0.058), and baseline LVEF (p=0.052) did not, consistent with the limited temporal resolution of a single follow-up echocardiogram. Baseline LVEF was significant in the primary and time-adjusted logistic models but was attenuated to non-significance in the restricted-cohort, complete-case, and Cox models. CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; OR = odds ratio; SD = standard deviation.

Supplementary Table S8. Re-expression of the baseline LVEF adjusted odds ratio in clinically intuitive units.

Unit of change in baseline LVEF	Adjusted OR	95% CI
Per SD (7.95 pp) higher baseline LVEF	0.72	0.58–0.89
Per 5 pp lower baseline LVEF	1.23	1.07–1.41
Per 10 pp lower baseline LVEF	1.52	1.15–2.00

Baseline LVEF was standardised for entry into the multivariable model. To improve clinical interpretability, the adjusted odds ratio is here re-expressed per clinically intuitive decrements (5 and 10 percentage points lower baseline LVEF). All estimates are derived from the same primary multivariable logistic regression model (n = 466 with paired measurements; multiple imputation for missing baseline NT-proBNP).

Supplementary Figure S1. Institutional care-pathway protocol.

Structured English translation of the Cardioprevent IPS institutional heart failure care-pathway protocol (2023). The protocol standardises the initial assessment, the criteria for high-complexity (Pathway A) assignment, the initial pharmacological plan, and the 12-month monitoring schedule for each pathway.

Panel A. First-visit assessment (general practitioner).

Component	Requirement
Echocardiogram	Performed within last 12 months; classify by LVEF (preserved ≥50%, mildly reduced 41–49%, reduced ≤40%)
Functional status	NYHA class assessment

Component	Requirement
Laboratory	Creatinine and potassium within last 3 months
Hospitalisation history	Ask about hospitalisations in last 6 months with decompensated heart failure as principal diagnosis; ascertain whether optimal medical therapy was in place prior to admission
Aetiology	Attempt to define whether ischaemic or non-ischaemic component

Panel B. Criteria for Pathway A (high-complexity) assignment. Any single criterion assigns the patient to Pathway A; otherwise, Pathway B.

#	Criterion
1	Hospitalisation within the last 3 months for acute heart failure
2	More than 2 cardiovascular hospitalisations within the last 12 months
3	Marked functional deterioration (NYHA III or IV) or AHA stage D
4	eGFR <30 ml/min/1.73 m²
5	Suspected infiltrative cardiomyopathy or clinical instability from another cardiomyopathy
6	Clinical deterioration despite optimal medical therapy

Panel C. Initial pharmacological plan for patients with reduced LVEF, if blood pressure, eGFR, and potassium levels permit.

Drug class	Agent	Starting dose
ACE inhibitor	Enalapril	5 mg every 12 h
Beta-blocker	Carvedilol	3.125 mg every 12 h
MRA	Spironolactone or eplerenone	25 mg every 24 h
SGLT2 inhibitor	Empagliflozin or dapagliflozin	10 mg every 24 h
Loop diuretic (only if congestive)	Furosemide	40 mg every 24 h

Panel D. 12-month monitoring schedule by pathway.

Months 1–6:

Pathway	M1	M2	M3	M4	M5	M6
Pathway A	GP	Cardiologist / Nurse ed.	GP	Cardiologist	Phone	GP
Pathway B	GP	GP / Nurse ed.	GP	Phone	Cardiologist	Phone

Months 7–12:

Pathway	M7	M8	M9	M10	M11	M12
Pathway A	Nurse ed.	Cardiologist	Phone	Nurse ed.	Cardiologist	GP
Pathway B	GP	Phone	Nurse ed.	Phone	Phone	GP

Visit types (colour code):

GP	General practitioner visit	**Cardiologist**	Cardiology visit
Nurse ed.	Nurse-led education session	**Phone**	Telephone follow-up

Structured English translation of the Cardioprevent IPS Heart Failure Programme institutional protocol (2023). Non-pharmacological measures apply to both pathways: limit alcohol intake and psychoactive substances, maintain body mass index <30 kg/m², encourage physical activity, and manage cardiovascular risk factors. Titration of guideline-directed medical therapy proceeds at each scheduled visit within predefined haemodynamic and biochemical limits. Pathway A patients receive four cardiology reviews within the first 12 months (months 2, 4, 8, 11); Pathway B patients receive one cardiology review (month 5). ACE = angiotensin-converting enzyme; AHA = American Heart Association; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter 2.

STROBE Statement—checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	**1**	(a) Indicate the study's design with a commonly used term in the title or the abstract	1. Abstract submitted as separate file
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract (separate file)
Introduction			
Background/rationale	**2**	Explain the scientific background and rationale for the investigation being reported	2
Objectives	**3**	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	**4**	Present key elements of study design early in the paper	3
Setting	**5**	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	**6**	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3-4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	**7**	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4–5
Data sources/ measurement	**8***	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4–5
Bias	**9**	Describe any efforts to address potential sources of bias	5-6, 12-13
Study size	**10**	Explain how the study size was arrived at	3
Quantitative variables	**11**	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	**12**	(a) Describe all statistical methods, including those used to control for confounding	5-6
		(b) Describe any methods used to examine subgroups and interactions	5-6
		(c) Explain how missing data were addressed	5-6
		(d) If applicable, explain how loss to follow-up was addressed	5-6, 12-13
		(e) Describe any sensitivity analyses	5-6
Results			
Participants	**13***	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	6, Figure 1

	Item No	Recommendation	Page No
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	**14***	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	5-6, 8
Outcome data	**15***	Report numbers of outcome events or summary measures over time	8-9, Tables 4, 6
Main results	**16**	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, Table 4
		(b) Report category boundaries when continuous variables were categorized	5-6, 7-8
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	**17**	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	**18**	Summarise key results with reference to study objectives	10
Limitations	**19**	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	**20**	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-13
Generalisability	**21**	Discuss the generalisability (external validity) of the study results	13
Other information			
Funding	**22**	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the websites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.