

RESEARCH

Open Access



HFpEF as the predominant and underrecognized heart failure phenotype in type 2 diabetes: evidence from the DIABET-IC study

P. Gil-Millan^{1,2*}, JA. Gimeno-Orna³, L. Rodriguez-Padial⁴, J. Muniz⁵, V. Barrios⁶, M. Anguita⁷ and A. Perez^{8*}

Abstract

Background Heart failure (HF) is a major complication of type 2 diabetes (T2D), with HF with preserved ejection fraction (HFpEF) now representing the most frequent phenotype. However, its clinical profile, prognosis, and treatment patterns compared with HF with reduced ejection fraction (HFrEF) remain insufficiently characterized.

Objectives To compare characteristics, outcomes, and longitudinal management of HFpEF versus HFrEF in T2D patients. **Methods:** This prespecified subanalysis of the nationwide, prospective DIABET-IC cohort included 1517 patients with T2D recruited across 58 Spanish centers and followed for three years. HF phenotypes were defined according to the 2016 ESC guidelines criteria. Baseline characteristics, outcomes (mortality, hospitalizations, and progression), and therapeutic patterns were assessed.

Results At baseline, 490 patients had HF (50.2% HFrEF, 30.6% HFpEF, 19.2% HFmrEF). HFpEF patients were older, more often female, and had higher prevalence of obesity, hypertension, and metabolic syndrome, whereas HFrEF was more strongly associated with ischemic heart disease, prior ST-elevation myocardial infarction (STEMI), and conduction disturbances. During follow-up, HFpEF was the predominant incident phenotype (46.6% of new cases), and 4.7% progressed to HFrEF. Mortality was similarly elevated in both phenotypes; HF hospitalizations tended to be higher in HFrEF, while acute coronary syndromes were more frequent in HFpEF. HFrEF patients more often received guideline-directed therapies, whereas the pre-guideline era for HFpEF, with greater uptake of SGLT2 inhibitors over time, limited use of GLP-1 receptor agonists. Notably, > 20% of HFpEF patients had natriuretic peptide levels below diagnostic thresholds, highlighting underdiagnosis.

Conclusions HFpEF is the most frequent HF phenotype in the T2D population, with outcomes comparable to HFrEF yet frequently underdiagnosed and undertreated. Improved screening strategies and broader adoption of evidence-based therapies—particularly SGLT2 inhibitors—are urgently needed for this high-risk population.

Keywords Type 2 diabetes, Heart failure, HFpEF, HFrEF, Cardiometabolic risk, Obesity, SGLT2i

*Correspondence:

P. Gil-Millan
pedroalejandrogil@vallhebron.cat
A. Perez
aperez@santpau.cat

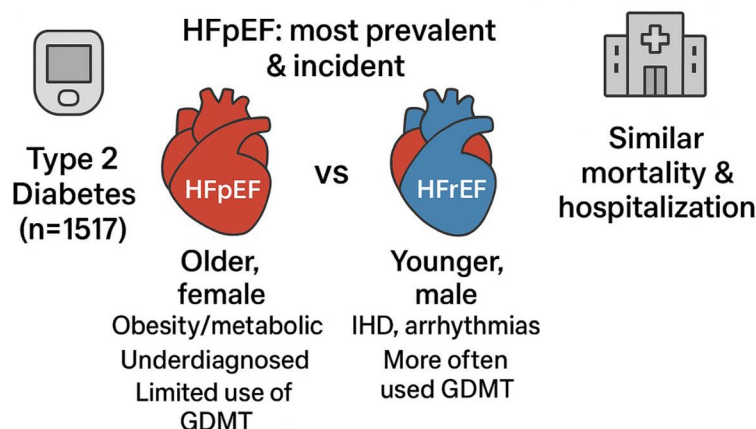
Full list of author information is available at the end of the article



© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Graphical Abstract

HF in Type 2 Diabetes: HFpEF vs HFrEF



Gil-Millán P, Gimeno-Orna JA, Rodríguez-Padial L, Muñiz J, Barrios V, Anguita M, Pérez A on behalf of DIABET-IC Investigators. HFpEF as the Predominant and Underrecognized Heart Failure Phenotype in Type 2 Diabetes: Evidence from the DIABET-IC Study.

Research in context

What is currently known about this topic?

- T2D markedly increases HF risk, with HFpEF now predominant.
- Diagnosis is often missed in obesity due to low natriuretic peptides.
- Evidence-based therapies are established for HFrEF, while effective options for HFpEF have only recently emerged with SGLT2i, GLP1RA, and finerenone.

What is the key research question?

- What are the differences in prevalence, clinical profile, prognosis, and treatment patterns between HFpEF and HFrEF in patients with T2D in real-world practice?

What is new?

- HF affected ~40% of T2D patients, with HFpEF being the leading incident phenotype.
- HFpEF showed high comorbidities, arrhythmias, and 4.7% progression to HFrEF.
- **HFpEF was the predominant incident HF phenotype in T2D and carried similar mortality and HF hospitalization to HFrEF over follow-up. A subset of HFpEF progressed to HFrEF, and >20% of HFpEF presented NT-proBNP below diagnostic**

thresholds, highlighting under-recognition—especially with obesity.

How might this study influence clinical practice?

- Supports systematic HFpEF screening in T2D with weight-independent biomarkers.
- Reinforces HFpEF as high-risk and progressive.
- Stresses the need to close the treatment gap by expanding SGLT2i, GLP1RA use in routine care.

Introduction

Cardiovascular disease has long been the leading cause of morbidity and mortality in type 2 diabetes (T2D) patients, with myocardial infarction and stroke traditionally considered the dominant complications. In recent years, however, heart failure (HF) has emerged as the most frequent and prognostically relevant cardiovascular outcome in this population, conferring a two-to-five-fold higher risk compared with individuals without diabetes [1–4]. Current data indicate that up to 40% of patients with T2D may develop HF, yet nearly one third of cases remain underdiagnosed [3, 5, 6].

Contemporary evidence indicates that HFpEF is *not* a benign phenotype. Large registries and nationwide cohorts show a persistent burden of mortality and rehospitalization across the EF spectrum, with a higher share of non-cardiovascular deaths in HFpEF compared with HFrEF [7–9].

Among HF phenotypes, HF with preserved ejection fraction (HFpEF) has become the most prevalent presentation in patients with T2D, particularly among women, elderly patients, and those with obesity [6, 10–12]. Importantly, HFpEF is not a benign condition as it is associated with a large number of comorbidities—including hypertension, atrial fibrillation, obesity, renal dysfunction, and microvascular complications—together with high rates of hospitalizations, arrhythmias, and even progression to reduced Ejection Fraction (EF) in a subset of patients [6, 12–16]. Despite this adverse profile, diagnosis is often missed, since natriuretic peptides may remain below diagnostic thresholds in obese individuals, leading to false negatives and delayed recognition [6, 17, 18]. Recent HFA-ESC guidance proposes age-tiered NT-proBNP thresholds and a “heart-stress” screening approach for at-risk patients (e.g., T2D), which may mitigate under-recognition despite obesity-related NP suppression [19].

Therapeutic advances have markedly improved outcomes in HF with reduced ejection fraction (HFrEF) through the implementation of evidence-based therapies such as renin–angiotensin system blockers, mineralocorticoid receptor antagonists, beta-blockers, and more recently sodium–glucose cotransporter-2 inhibitors (SGLT2i) [20–22]. Temporal trends reinforce this disparity: 1-year mortality declined in HFrEF but not in non-HFrEF (HFpEF/HFmrEF) in contemporary cohorts, and long-term projections still estimate substantial 10-year risks in HFpEF/HFmrEF despite modern care [23, 24]. In contrast, patients with HFpEF have historically remained undertreated, with very low real-world uptake of cardioprotective antidiabetic drugs including SGLT2i and glucagon-like peptide-1 receptor agonists (GLP1RA) [15, 20, 25–29]. Only recently have randomized trials demonstrated the benefits of SGLT2i in HFpEF, leading to updated international guidelines that now recommend their use irrespective of diabetes status [6, 30–34]. Nevertheless, significant evidence practice gap persists in clinical practice [25, 35].

Despite its growing prevalence, the clinical profile, prognosis, and treatment patterns, HFpEF remains insufficiently characterized compared with HFrEF in patients with T2D [5, 6, 15, 25, 34, 35]. Understanding these differences is crucial to improve early detection, close diagnostic gaps, and ensure timely initiation of disease-modifying therapies.

The present study, a prespecified subanalysis of the nationwide DIABET-IC cohort, sought to (i) compare baseline characteristics of HFpEF and HFrEF in patients with T2D, (ii) evaluate prognosis in terms of mortality, hospitalizations, and disease progression, and (iii) describe longitudinal treatment patterns, with particular

focus on cardioprotective therapies. These aims directly address the contemporary gaps highlighted above.

Methods

Study design and participants

The DIABET-IC study was a nationwide, multicenter, observational, and prospective cohort conducted in Spain between May 2, 2018, and February 28, 2020, with follow-up until June 30, 2022. It was prompted by the Spanish Society of Diabetes (SED) and the Spanish Society of Cardiology (SEC) and designed to reflect routine clinical practice with a pragmatic, non-interventional approach. After the baseline visit, patients were followed for three years under standard-of-care conditions. The main objective was to evaluate the prevalence and incidence of heart failure in individuals with T2D [12, 15]. This manuscript reports a pre-specified sub-analysis of the cohort, aimed at characterizing and comparing the clinical, biochemical, and echocardiographic profiles of patients with HFpEF versus HFrEF, evaluating prognosis in terms of hospitalization and mortality, and describing longitudinal treatment patterns with emphasis on disease-modifying therapies. Heart failure phenotypes were defined according to the 2016 ESC guidelines criteria [36]. Due to the small number of HFmrEF (Heart Failure Mildly Reduced Ejection Fraction) cases, analyses were restricted to comparisons between HFpEF and HFrEF.

Eligible participants were outpatients aged 18 years or older with a diagnosis of T2D for at least one year, as defined by the 2018 American Diabetes Association criteria [37]. Patients with type 1 diabetes (T1D), end-stage kidney disease (ESKD), or a life expectancy of less than three years were excluded. Recruitment took place during routine visits, without diagnostic or therapeutic interventions mandated by the protocol. All participants provided written informed consent. The study was approved by the Ethics Committee of the Hospital Complex of Toledo on March 28, 2018 (project identification code 243) and conducted in accordance with the Declaration of Helsinki.

Variables, data sources, and measurement

At baseline, patients underwent a comprehensive evaluation including medical history, physical examination, electrocardiogram, and echocardiography. Demographic variables included age and sex. Clinical assessments recorded systolic and diastolic blood pressure (SBP and DBP), heart rate (HR), and body mass index (BMI). Cardiovascular risk factors and comorbidities were documented, including hypertension, dyslipidemia, atrial fibrillation (AF), ischemic heart disease, peripheral artery disease (PAD), cerebrovascular disease (CVD), chronic kidney disease (CKD), obstructive sleep apnea (OSA), and chronic obstructive pulmonary disease (COPD). The Charlson comorbidity index was calculated for each

patient. Information on pharmacological treatment for diabetes and HF was obtained both at baseline and during follow-up.

HF was defined as a prior hospitalization with a primary diagnosis of HF or fulfillment of the 2016 ESC guidelines criteria [36]. Diagnosis required typical symptoms in addition to echocardiography (ECHO), to assess left ventricular ejection fraction (LVEF) and natriuretic peptide (NPs) levels abnormalities. In HFrEF, the LVEF of $<40\%$ together with symptoms was sufficient. In HFpEF a LVEF of $\geq 50\%$ and a LVEF of $40\text{--}49\%$ for HFmrEF, both elevated N-terminal pro B-type Natriuretic Peptide (NT-proBNP) (>125 pg/mL) and evidence of structural (left ventricular hypertrophy or left atrial enlargement) or functional (diastolic dysfunction) abnormalities were required. All diagnoses were confirmed by the site cardiologist.

Laboratory analyses included hemoglobin, fasting glucose, HbA1c, lipid profile, serum creatinine, estimated glomerular filtration rate (eGFR), urinary albumin-to-creatinine ratio (ACR), and NT-proBNP. Coronary artery disease (CAD) was defined as a history of myocardial infarction, acute coronary syndrome (ACS), coronary revascularization, or a documented stenosis $>50\%$. PAD was defined as the presence of lower extremity arterial disease, and cerebrovascular disease as a history of ischemic or hemorrhagic stroke or carotid stenosis $>50\%$.

Clinical outcomes during follow-up included hospitalization for HF, ACS and cardiovascular mortality. Final event analyses were restricted to participants with baseline HF and are presented by phenotype (HFrEF vs HFpEF); results are shown as percentages with accompanying event counts. All events were validated by investigators and adjudicated according to standardized definitions.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation or as median (interquartile range, IQR), depending on distribution. Categorical variables were presented as absolute and relative frequencies. Comparisons between groups were performed using the Student's t-test, ANOVA, or Kruskal–Wallis test for continuous variables, and the chi-square test for categorical variables. When multiple comparisons were conducted, p -values were adjusted using the Bonferroni correction. A two-sided p -value <0.05 was considered statistically significant.

Results

A total of 1517 patients with T2D were recruited between January 2018 and December 2019 across 58 Spanish tertiary hospitals, of whom 1249 (82.3%) completed the

3-year study, totaling ≥ 3747 person-years and yielding an average follow-up of ≥ 2.47 years per participant.

At baseline, 490 patients presented with HF (50.2% HFrEF, 19.2% HFmrEF, 30.6% HFpEF). By the end of follow-up, HF prevalence increased to 548 cases (47.4% HFrEF, 20.3% HFmrEF, 32.3% HFpEF) (Fig. 1a). Among incident HF cases, HFpEF predominated (46.6 vs. 24.1% HFrEF) (Fig. 1b). Systematic baseline screening identified 22 previously unrecognized HF cases, half corresponding to HFpEF (Fig. 1c). Subsequent analyses focused on HFpEF vs. HFrEF. Characteristics of the overall population have been previously published [12, 13, 15, 28] and are summarized in **Supplementary Table S1**.

Demographics and clinical profile

Compared with HFrEF, patients with HFpEF were significantly older and more frequently women. They exhibited higher rates of hypertension and metabolic syndrome, along with higher BMI and systolic blood pressure at baseline. In contrast, HFrEF patients were younger, predominantly male, and had slightly lower blood pressure values. Duration of diabetes, renal function, lipid parameters, hemoglobin, and glycemic control did not differ significantly between the groups (Table 1).

Social and educational characteristics

Analysis of social and educational variables revealed marked differences across HF phenotypes (**Supplementary Table S2**). Both HFrEF and HFpEF patients were less frequently employed compared with non-HF patients (10.7% and 10.2 vs. 27.3%, $p < 0.001$), with disability status more prevalent in HFrEF (12.6%) than in HFpEF (6.6%) or no HF (2.1%). HFpEF patients were less likely to live with a partner (63.3 vs. 74.9%, $p < 0.001$) and more likely to cohabit with relatives (23.6 vs. 13.2%, $p < 0.001$). Educational attainment also differed with HFpEF patients being more frequently unlettered (6.2 vs. 2.0% in no HF, $p < 0.001$), and both HF groups having higher proportions with only elementary level education.

Chronic diabetic complications

Diabetic nephropathy was significantly more common in HFrEF and HFpEF compared to non-HF patients (Table 2). Other chronic complications—including retinopathy, neuropathy, and foot lesions—showed no HF-related differences. HF was associated with higher stages of CKD and higher Kidney Disease: Improving Global Outcomes (KDIGO) risk categories (**Supplementary Table S3**). Serious hypoglycemia remained rare and hyperglycemic crises did not occur in any group.

Cardiovascular history

History of CVD was markedly more prevalent in HF patients than in those without HF (Table 3). HFrEF

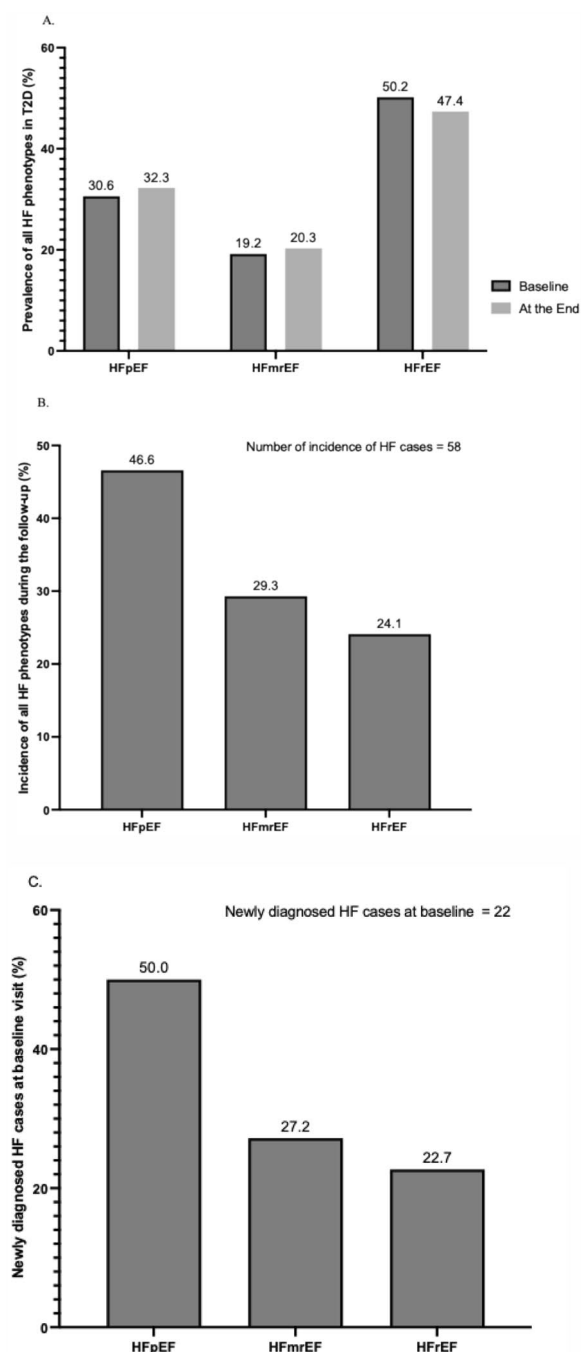


Fig. 1 Characteristics of heart-failure (HF) subtypes among patients with type 2 diabetes (T2D). **A.** Prevalence of HF phenotypes at baseline and end of follow-up. **B.** Incident HF during follow-up ($n=58$) and distribution across HFrEF, HFmrEF, and HFpEF. **C.** Newly diagnosed HF at baseline ($n=22$) and distribution across HF phenotypes. Abbreviations: HF, heart failure; HFrEF, HF with reduced ejection fraction; HFmrEF, HF with mildly reduced ejection fraction; HFpEF, HF with preserved ejection fraction; T2D, type 2 diabetes

patients had higher rates of prior cardiopathy, multivessel CAD, ST-elevation myocardial infarction (STEMI), Ventricular Fibrillation (VF), and device therapy, while HFpEF patients had higher prevalence of aortic

Table 1 Baseline characteristics of T2D patients by HF subtype (HFrEF, HFpEF)

Variables	HFrEF (n=246)	HFpEF (n=150)	p-value
Age (years)	67.9±9.73	70.5±9.64	0.008
Sex (Male/Female) (%)	79.07/20.93	63.27/36.73	<0.001
Charlson index	0.76±0.94	0.82±1.01	NS
Age at diagnosis of T2D (years)	61.71±13.44	56.63±13.04	NS
T2D duration (years)	11 (6;16)	12 (7;18)	NS
Insulin dose (U)	45.14±32.65	44.73±33.98	NS
HbA _{1c} (%) at baseline	7.45±1.36	7.41±1.44	NS
Weight (Kg) at baseline	82.65±16.51	85.10±16.02	NS
Smoking (%)	11.16	6.91	NS
Alcohol (%)	7.44	5.45	NS
HTA (%)	77.67	88	0.002
Dyslipidemia (%)	78.14	81.82	NS
Metabolic syndrome (%)	33.95	44.89	0.014
Weight (Kg)	82.34±17.34	84.45±16.12	NS
BMI (Kg/m ²)	29.44±5.22	30.75±5.81	0.03
WC (cm)	102.78±16.61	105.49±16.21	NS
SBP (mmHg)	126.15±20.05	132.57±19.31	<0.001
DBP (mmHg)	72.37±11.83	73.59±11.03	NS
Hemoglobin (g/dL)	13.88±1.9	13.49±1.9	NS
Serum creatinine (mg/dL)	1.20±0.39	1.17±0.39	NS
eGFR (mL/min/1.73 m ²)	66.1±23.4	64.7±23.4	NS
HbA _{1c} (%)	7.19±1.31	7.29±1.31	NS
Total cholesterol (mg/dL)	145.3±36.5	156.2±36.5	NS
HDL-c (mg/dL)	41.4±11.8	42.1±11.8	NS
LDL-c (mg/dL)	74.9±30.3	81.5±30.3	NS
# Atherosclerotic territories (mean)	0.88±X	0.69±X	NS
HR (bpm)	72.39±12.81	73.32±14.82	NS
COPD (%)	14.88	13.82	NS
SAHS (%)	15.81	20.73	NS
CKD (%)	32.56	35.27	NS
MAFLD (%)	5.61	9.82	NS
CHA2DS ₂ -VASc scale	4.43±1.29	4.58±1.39	NS
HAS-BLED scale	2.14±1.06	2.36±1.09	NS

Categorical variables are presented as n (%); continuous variables as mean ± SD or median (IQR). ($p<0.05$). NS: non-statistical significance. List of abbreviations: HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction; T2DM: Type 2 diabetes mellitus; HTA: Hypertension; BMI: Body mass index; WC: Waist circumference; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; COPD: Chronic obstructive pulmonary disease; SAHS: Sleep Apnea-hypopnea syndrome; CKD: Chronic kidney disease; MAFLD: Metabolic associated fatty liver disease; CHA2DS₂-VASc scale: Stroke risk prediction tool for atrial fibrillation; HAS-BLED scale: Bleeding risk prediction tool for atrial fibrillation

valvopathy, LV hypertrophy due to hypertension, AF, and coronary stents. Rates of ACS were similar across groups, whereas non-ST-elevation myocardial infarction (NSTEMI) was less frequent in HFrEF than in HFpEF or non-HF patients.

Table 2 Prevalence of chronic diabetic complications by HF phenotype

Chronic complication	No HF (1) (n = 759)	Total HF (n = 490)	HFrEF (2) (n = 246)	HFpEF (3) (n = 150)	p 1 vs 2	p 1 vs 3	p 2 vs 3
Diabetic nephropathy (%)	24.67	39.70	37.21	43.64	0.01	0.01	NS
Diabetic retinopathy (%)	14.91	12.20	11.63	13.09	NS	NS	NS
Diabetic neuropathy (%)	5.28	5.83	6.05	5.45	NS	NS	NS
Diabetic foot (%)	1.72	3.55	3.72	3.27	NS	NS	NS

Categorical variables are presented as n (%). ($p < 0.05$) NS: non-statistical significance

Table 3 Cardiovascular history among groups

History / Event	No HF (1) (n = 759)	Total HF (n = 490)	HFrEF (2) (n = 246)	HFpEF (3) (n = 150)	p 1 vs 2	p 1 vs 3	p 2 vs 3
Previous cardiopathy (%)	57.05	95.32	99.53	92.00	< 0.001	< 0.001	< 0.001
CVD (%)	43.52	83.70	91.63	77.45	< 0.001	< 0.001	< 0.001
CVD atherosclerosis (%)	43.73	59.42	67.91	52.73	< 0.001	0.010	< 0.001
CAD (%)	37.04	52.48	61.86	45.09	0.001	0.019	0.001
Affected vascular territories (> 1) (%)	7.53	16.13	18.60	14.18	< 0.001	0.002	0.003
ACS (%)	71.53	73.66	75.76	72.00	NS	NS	NS
NSTEMI (%)	38.98	36.17	30.30	40.80	0.036	NS	NS
STEMI (%)	32.54	37.48	45.45	31.20	0.036	NS	NS
Coronary stents (%)	70.85	67.87	60.61	73.60	0.037	NS	0.027
Cerebro vascular disease (%)	6.87	10.20	11.16	9.45	0.039	NS	NS
PAD (%)	8.06	15.10	15.35	14.91	0.001	0.001	NS
Aortic arteriopathy (%)	8.17	13.68	14.42	13.09	0.006	0.002	NS
Hypertrophy cardiac disease (%)	3.09	4.49	4.67	4.35	NS	NS	NS
Restrictive cardiac disease (%)	0.00	0.84	1.40	0.40	0.014	NS	NS
Congenital cardiopathy (%)	1.16	0.84	1.40	0.40	NS	NS	NS
Aortic valvulopathy (%)	9.72	15.61	9.35	20.55	NS	< 0.001	< 0.001
LV hypertrophy due to HTA (%)	22.22	20.21	10.75	27.67	< 0.001	NS	< 0.001
AF (%)	21.25	41.83	38.24	44.66	< 0.001	< 0.001	NS
VF (%)	18.75	27.69	44.44	14.49	0.033	NS	0.025

Categorical variables are presented as n (%). ($p < 0.05$). NS: non statistical significance. List of abbreviations: CVD, cardiovascular disease; CAD, coronary artery disease; ACS: Acute coronary syndrome; PAD, peripheral arterial disease; HTA, hypertension; HF, heart failure; HFrEF, HF with reduced ejection fraction; HFpEF, HF with preserved ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; LV, Left ventricular; AF, Atrial fibrillation; VF, Ventricular fibrillation

Antidiabetic therapy

At baseline, metformin was the most frequently prescribed drug, used more in non-HF patients than in HF subtypes (Fig. 2a). SGLT2i and GLP1RA were more common in non-HF and HFrEF groups, while pioglitazone use was rare. Insulin use was lower in HFrEF compared with both HFpEF and non-HF groups (Fig. 2b). Over follow-up, SGLT2i and GLP1RA use increased, sulfonylureas declined, and insulin use remained stable. At final follow-up, SGLT2i was more frequently prescribed in HFrEF, while GLP1RA and metformin remained more common in non-HF patients (Fig. 2c).

Antihyperlipidemic therapy

Statins were widely used across all HF phenotypes at baseline and follow-up, with ezetimibe less frequently prescribed in HFpEF. Proprotein Convertase Subtilisin/Kexin Type 9 inhibitors (PCSK9i) were rarely used, while fibrates were slightly more common in HFrEF (**Supplementary Figures S4 a–b**).

Heart failure therapy

Baseline HF therapy differed significantly between phenotypes (Fig. 3a). HFrEF patients more frequently received guideline-recommended therapies, including loop diuretics, beta-blocker (BBs), Mineralocorticoid Receptor Antagonists (MRAs), and sacubitril/valsartan. HFpEF patients showed intermediate prescription rates. By the end of follow-up, treatment patterns were largely maintained, with HFrEF patients continuing the highest use of evidence-based therapies and HFpEF patients exhibiting intermediate use (Fig. 3b).

HF biomarkers and echocardiogram

NT-proBNP levels were significantly higher in HF patients compared with non-HF patients at baseline and follow-up (Fig. 4a). HFrEF patients consistently showed the highest levels, whereas HFpEF patients had intermediate elevations. LVEF remained stable in non-HF and HFpEF patients, while it improved in HFrEF patients; 7 HFpEF patients (4.7%) progressed to HFrEF (Fig. 4b).

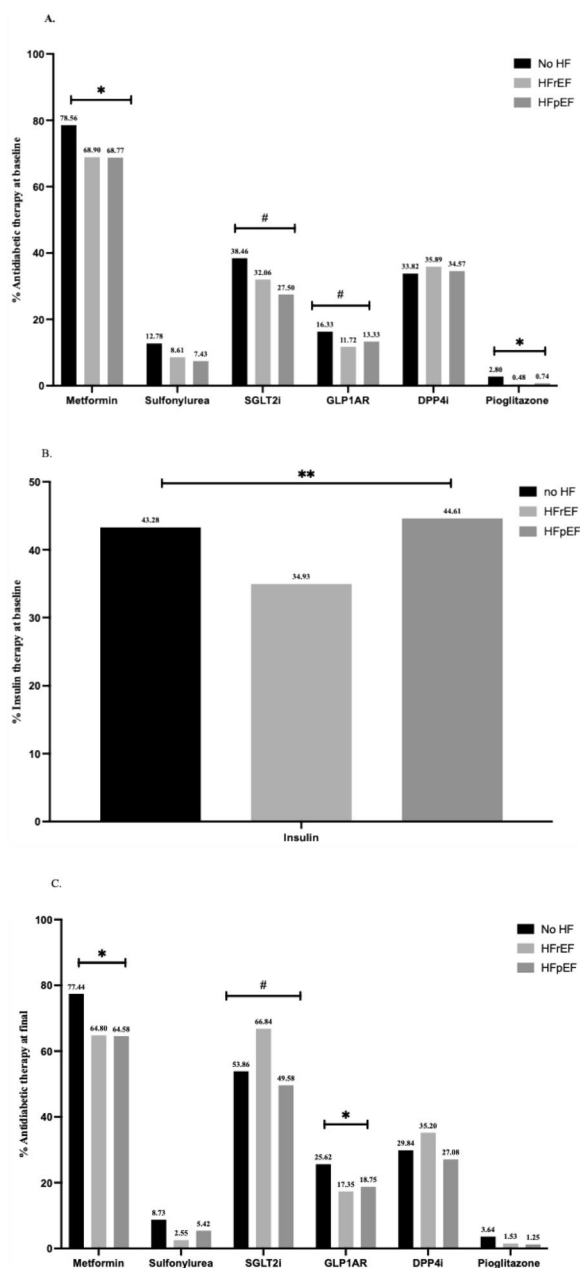


Fig. 2 Antidiabetic Therapy prescribed among T2D patients categorized by HF subtype. **A.** Antidiabetic therapy at baseline among T2D with no-HF, HFrEF and HFpEF. ($p < 0.05$) * → Statistically differences between no-HF vs HFrEF and no-HF vs HFpEF. ($p < 0.05$) # → Statistically differences across all three groups (no-HF, HFrEF, HFpEF). **B.** Insulin therapy at baseline among T2D with no-HF, HFrEF and HFpEF. ($p < 0.05$) ** Statistically differences between HFpEF vs HFrEF and no-HF vs HFrEF. **C.** Antidiabetic therapy at final among T2D with no-HF, HFrEF and HFpEF. Statistical differences were assessed using ANOVA with Bonferroni adjustment for multiple comparisons. ($p < 0.05$) *Statistically differences (No HF vs HFrEF and HFpEF). # Statistically differences (HFrEF vs no HF and HFpEF). Abbreviations: HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction

Electrocardiography

Electrocardiographic characteristics differed significantly across the three groups (no HF, HFrEF, and HFpEF). Sinus rhythm predominated in patients without HF (90.4%) but was significantly less frequent in HFrEF (65.6%) and HFpEF (62.2%) ($p < 0.001$ for all pairwise comparisons). Atrial fibrillation (AF) was more common in HFpEF (30.0%) and HFrEF (19.5%) compared with the no HF group (7.5%) ($p < 0.001$). Atrioventricular block (AVB) was uncommon and occurred at similar rates across groups (3.1% in no HF, 2.3% in HFrEF, and 3.0% in HFpEF), with no significant differences. Pacemaker implantation was more frequent in HFrEF (13.9%) compared to HFpEF (4.8%) and no HF (1.5%) ($p < 0.001$ for all comparisons). Regarding conduction abnormalities, left bundle branch block (LBBB) was significantly more prevalent in HFrEF (21.9%) than in HFpEF (12.6%) and no HF (3.1%) ($p < 0.001$), whereas right bundle branch block (RBBB) was slightly more common in no HF (7.7%) than in HFrEF (5.6%) and HFpEF (4.4%), without statistical significance. Overall, conduction and rhythm disturbances were more frequent in HF, particularly in HFrEF.

Final clinical events

During follow-up, event rates did not differ significantly between phenotypes.

HF-related hospitalizations were slightly more frequent in HFrEF than in HFpEF, whereas new ACS episodes were numerically higher in HFpEF. Cardiovascular-related deaths were marginally more common in HFrEF. Absolute event numbers and percentages are shown in Fig. 5 (a–c). No statistically significant differences were observed for any outcome between HFpEF and HFrEF.

Summary of phenotype differences

Detailed comparison of HFpEF vs. HFrEF, including demographics, cardiovascular profile, arrhythmias, biomarkers, LVEF trajectory, renal comorbidity, and outcomes, is summarized in Supplementary Table S5.

Discussion

This sub-analysis of the DIABET-IC study provides novel insights into HF in T2D, particularly regarding prevalence, incidence, and prognosis across HF phenotypes. HFpEF emerges as the most frequent and incident form, with outcomes comparable to HFrEF. In this pre-guideline era, when HFpEF-specific disease-modifying therapies were not yet available, medication patterns show lower use of disease-modifying agents in HFpEF compared with HFrEF; by the end of follow-up, SGLT2 inhibitor uptake increased, consistent with emerging evidence and updated recommendations, but still lower used compared to HFrEF, underscoring the urgent need

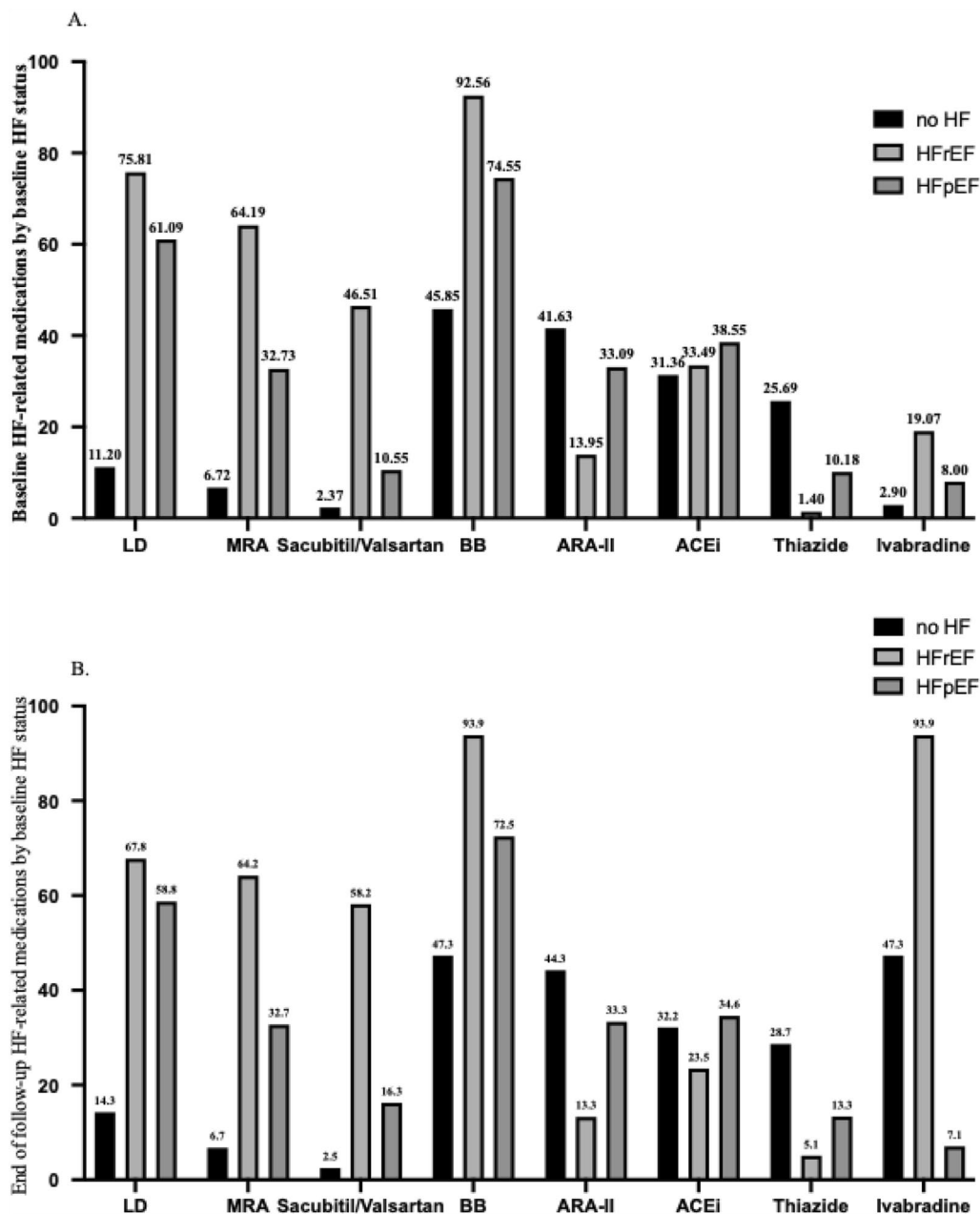


Fig. 3 Distribution of heart-failure (HF) therapies among patients with T2D. **A.** Baseline HF-related medications by baseline HF status (no-HF, HFrEF, HFpEF). **B.** End of follow-up HF-related medications by baseline HF status (no-HF, HFrEF, HFpEF). ($p < 0.05$) Statistically differences were observed in all HF-related therapy between no-HF and HFrEF groups, and between HFrEF vs HFpEF. Abbreviations: LD, loop diuretics; Thiaz, thiazide diuretics; ACEi, angiotensin-converting enzyme inhibitor; ARA-II, angiotensin II receptor blocker; ARNI, sacubitril/valsartan; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; Ivab, ivabradine; HF, heart failure; HFrEF, HF with reduced EF; HFpEF, HF with preserved EF

for improved recognition and management in this high-risk population.

In our study, HF was highly prevalent, affecting nearly 40% of outpatients, with HFpEF emerging as the most frequently newly diagnosed and incident phenotype. At baseline, HFpEF accounted for 30.6% of all HF cases and nearly half (46.6%) of incident HF during follow-up, whereas HFrEF represented 50.2% of prevalent HF but only 24.1% of new cases. Over three years, the cumulative

incidence of HF was 7.6% (≈ 3 cases per 100 person-years), underscoring the high cardiovascular burden in this population [13, 15]. Although prevalence estimates vary across populations and methodologies, similar trends have been reported in European and U.S. cohorts, where HFpEF is consistently identified as the predominant phenotype in T2D, particularly among older and obese individuals [5, 14, 38–40]. Collectively, these

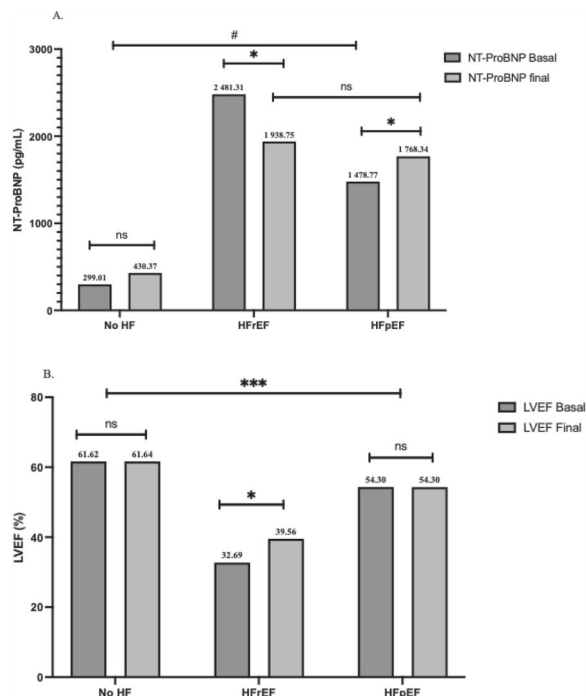


Fig. 4 HF biomarkers and echocardiography in type 2 diabetes (T2D). **A.** NT-proBNP at baseline and end of follow-up in no-HF, HFrEF, and HFpEF (pg/mL). Figure shows NT-proBNP levels measured at baseline and final visit across the three groups. ($p < 0.05$) * Statistically differences intra-group between baseline and final visit. ($p < 0.05$) # Statistically differences in NT-proBNP levels at baseline between the three groups. NS, non-significant differences. **B.** Left ventricular ejection fraction (LVEF, %) at baseline and end of follow-up in the same groups. ($p < 0.05$) *** Statistically differences intra-groups at basal and final visit. ($p < 0.05$) * Statistically differences in HFrEF between basal LVEF vs LVEF final. NS, non-significant differences in no-HF and HFpEF groups. Statistics: for between-group comparisons at baseline, Kruskal–Wallis (NT-proBNP) or ANOVA (LVEF) with Holm-adjusted post-hoc tests as appropriate. For within-group change (baseline → final), Wilcoxon signed-rank (NT-proBNP) or paired t-test (LVEF) with Holm adjustment when multiple contrasts were assessed.

findings reinforce HFpEF as the dominant and emerging form of HF in this high-risk population.

The clinical profiles of HF phenotypes observed in DIABET-IC were consistent with contemporary Spanish cohorts: HFpEF clustered with cardiometabolic traits—female sex, obesity, hypertension, AF, and CKD—whereas HFrEF was more strongly linked to ischemic heart disease [41]. Despite these distinct characteristics, outcomes were similarly poor. In the MAGGIC meta-analysis, prognosis worsened progressively across the EF spectrum, with HFrEF showing the highest risk and HFpEF somewhat lower, though still adverse [11]. However, in our cohort of patients with T2D, outcomes were comparably poor in HFpEF and HFrEF, with both phenotypes showing similarly elevated risks of mortality and HF hospitalization relative to T2D patients without HF [8, 11]. Notably, recent data from Anguita-Gómez et al. in a contemporary general population cohort also found

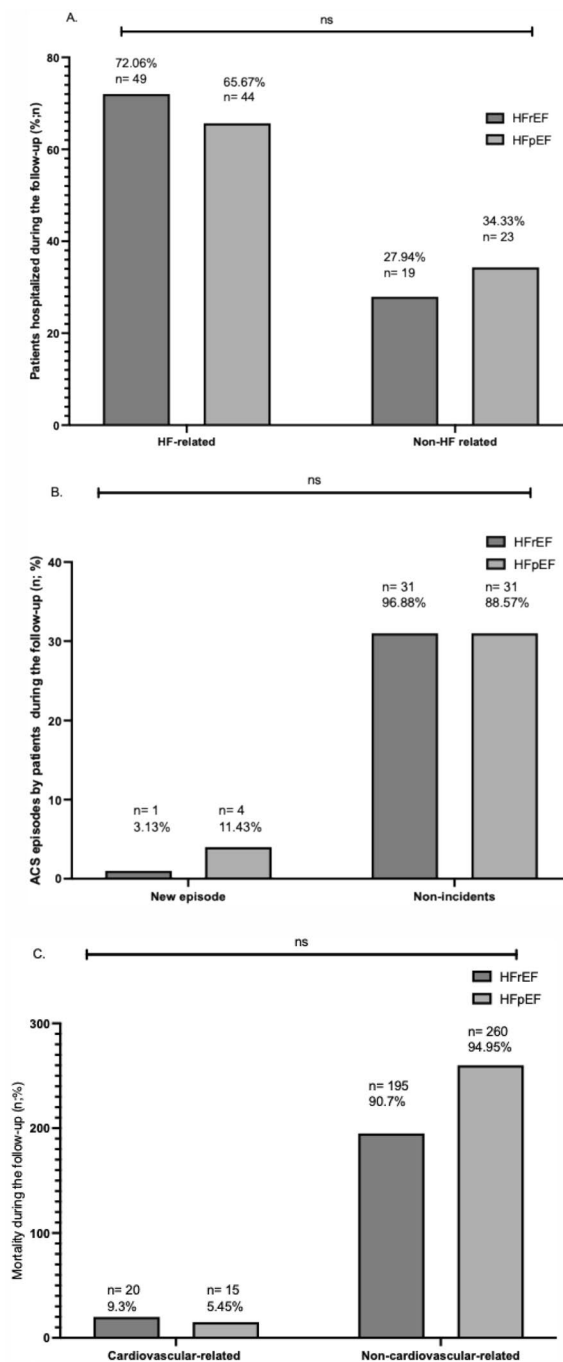


Fig. 5 Final clinical events by heart failure phenotype. **A.** HF-related vs. non-HF-related hospitalizations during follow-up. **B.** ACS incidents vs. non-incident cases. **C.** Cardiovascular-related vs. non-cardiovascular deaths. Percentages and absolute numbers (n) are shown for each phenotype. No statistically significant differences were detected between HFpEF and HFrEF for any outcome. Note: Analyses were restricted to participants with baseline HF; the non-HF group is not displayed. Abbreviations: HF = heart failure; HFrEF = HF with reduced ejection fraction; HFpEF = HF with preserved ejection fraction; ACS = acute coronary syndrome

no significant differences in 1-year outcomes across EF categories, suggesting that the prognostic gradient traditionally described may be less pronounced in current clinical practice [14]. Together, these findings reinforce that HFpEF is far from benign, particularly in T2D, and should be recognized as a major prognostic marker.

Contemporary evidence confirms that HFpEF remains a high-risk phenotype despite therapeutic gains in HFrEF. In the nationwide Swede HF analysis, Settergren et al. (2024) showed that although cardiovascular death still predominates overall, the adjusted risk of non-cardiovascular death increases with higher EF, with HFpEF exhibiting more non-CV deaths than HFrEF over 5 years [7]. Stolfo et al. (2022) further demonstrated a persistent burden across the EF spectrum, with HFpEF enriched for all-cause and non-CV hospitalizations and mortality compared with matched controls [8]. In time-trend data from Japan's WET-HF registry, Nakamaru et al. (2023) reported that age-adjusted 1-year mortality declined in HFrEF but not in non-HFrEF, underscoring slower outcome gains for HFpEF [23]. Complementing these observations, a U.S. model calibrated to contemporary HFpEF/HFmrEF trials by Sun et al. [24] estimated that ~37% of patients will be hospitalized for HF and ~26% will experience cardiovascular death within 10 years despite standard care [24]. These findings align with the state-of-the-art review by Borlaug et al. [9] highlighting persistently adverse outcomes and substantial multimorbidity in HFpEF [9]. Consistent with this modern literature, our T2D cohort showed similar mortality and HF hospitalization in HFpEF and HFrEF (differences non-significant), likely reflecting event scarcity and the heavy non-CV burden in HFpEF. These patterns also align with our prior DIABET-IC analysis, where higher KDIGO risk categories tracked with greater HF burden in T2D, supporting a shared cardiorenal-metabolic risk gradient relevant to HFpEF prognosis. However, data on CKD progression and stroke were not available for the present analysis, and results are therefore limited to HF hospitalization, ACS, and cardiovascular death.

Therapeutic patterns diverged markedly between HF phenotypes. In our cohort, HFrEF patients more frequently received guideline-directed therapies such as MRAs, sacubitril/valsartan, and beta-blockers, whereas phenotype-specific options for HFpEF were limited and remained under used. Cardioprotective antidiabetic drugs, including SGLT2i and GLP1RA, were lower uptake in the pre-guideline era, despite growing evidence of benefit in reducing HF hospitalizations [22, 26, 27, 31, 34], and current ESC guidelines now recommending SGLT2i as first-line therapy in HFpEF irrespective of diabetes status [34]. These findings are consistent with Anguita et al., who documented lower use of guideline therapies and SGLT2i in HFpEF compared with HFrEF [14], and

are further confirmed by the RED-HEART registry [25]. Beyond SGLT2i, the FINEARTS-HF trial demonstrated that finerenone significantly reduced HF hospitalizations and cardiovascular death in HFpEF [42] and recent pooled analyses from SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM trials further show that semaglutide reduces the risk of the composite endpoint of cardiovascular death or HF events and worsening HF events alone in patients with HFpEF, highlighting its potential as an efficacious therapy in this population with limited treatment options [43]. Collectively, these data underscore both the therapeutic advances and persistent gaps in HFpEF management, emphasizing the urgent need for improved implementation strategies, particularly in patients with T2D. However, therapy patterns should be interpreted in the context of the **pre-guideline era** for HFpEF, when **phenotype-specific disease-modifying options were not yet available**. The observed **increase in SGLT2 inhibitors** toward study end mirrors contemporaneous changes in practice. Emerging agents such as **finerenone** became available **after** our study period and are discussed strictly as **post-study** developments.

Diagnostic challenges in HFpEF remain considerable, particularly in patients with T2D and obesity. Elevated BMI, highly prevalent in this population, suppresses natriuretic peptide (NP) secretion and clearance, reducing the sensitivity of BNP and NT-proBNP and increasing the risk of false negatives [18, 44, 45]. In our cohort, over 20% of HFpEF patients had NP values below conventional diagnostic thresholds, highlighting the potential for underdiagnosis. ECHO, while central to HF evaluation, may also be limited in this setting [5, 18, 46], emphasizing the need for weight-independent biomarkers and advanced imaging tools to improve early detection and risk stratification. These diagnostic limitations have important clinical consequences, as high-risk patients may remain unrecognized and deprived of timely, evidence-based therapies. In our cohort, this gap was associated with rising NT-proBNP levels, stable or declining LVEF, and progression to HFrEF in nearly 5% of cases during follow-up. Collectively, these findings underscore that HFpEF in T2D is a dynamic and progressive phenotype that is prone to deterioration when insufficiently recognized and managed.

Building on these diagnostic gaps, Bayes-Genis et al. (2023) [19]—a Heart Failure Association (ESC) clinical consensus—provide practical NT-proBNP algorithms across settings: in the ED, 300 pg/mL rules out HF and age-adjusted rule-in thresholds of 450/900/1800 pg/mL (<50/50–74/≥75 y) apply without additional adjustment for sex, BMI, renal function, AF, or LVEF; in the outpatient setting, 125 pg/mL rules out HF, with age-tiered rule-in thresholds of 125/250/500 pg/mL (<50/50–74/≥75 y) and ≥2000 pg/mL flagged for expedited triage.

The statement also introduces “heart-stress” screening for asymptomatic high-risk patients (e.g., T2D) with rule-out 50 pg/mL and rule-in 75/150/300 pg/mL (<50/50–74/≥75 y). Adopting these weight-independent cut-points and workflows could improve early HFpEF recognition in T2D and standardize referral for echocardiography and follow-up.

While not designed to introduce new therapies, this nationwide, prospective analysis delivers granular, phenotype-level data for patients with T2D in routine care—spanning clinical characteristics, ECG features, real-world treatment patterns in the pre-guideline era, and hard outcomes. These country-level insights can help shape Spain's HF strategies in T2D (screening, referral, and implementation of evidence-based therapies) and generate hypotheses for confirmatory studies in other regions.

Conclusions

In summary, HF is highly prevalent in patients with T2D, with HFpEF emerging as the most frequent and incident phenotype, and is a high-risk, dynamic, and progressive condition. Despite this, HFpEF is often underdiagnosed due to obesity-related limitations in NP measurement and frequently undertreated, despite evidence supporting the use of SGLT2 inhibitors, GLP1 receptor agonists, and finerenone to improve outcome. The development of weight-independent biomarkers and advanced imaging, coupled with timely initiation of evidence-based therapies, is essential for early diagnosis, improved outcomes, and prevention of disease progression in this high-risk population.

Abbreviations

AF	Atrial fibrillation
ACS	Acute coronary syndrome
ACEI	Angiotensin-converting enzyme inhibitor
ARA-II	Angiotensin II receptor blocker
BB	Beta-blocker
BMI	Body mass index
BNP	B-type natriuretic peptide
CAD	Coronary artery disease
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DPP4i	Dipeptidyl peptidase-4 inhibitor
EF	Ejection fraction
ESC	European Society of Cardiology
GDMT	Guideline-directed medical therapy
GLP1RA	Glucagon-like peptide-1 receptor agonist
HF	Heart failure
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFREF	Heart failure with reduced ejection fraction
HR	Heart rate
KDIGO	Kidney disease: improving global outcomes
LD	Loop diuretics
LDL-C	Low-density lipoprotein cholesterol
LBBB	Left bundle branch block
LV	Left ventricle / left ventricular

MRA	Mineralocorticoid receptor antagonist
NPs	Natriuretic peptides
NT-proBNP	N-terminal pro B-type natriuretic peptide
OSA	Obstructive sleep apnea
PAD	Peripheral artery disease
SBP	Systolic blood pressure
SGLT2i	Sodium-glucose cotransporter-2 inhibitor
STEMI	ST-elevation myocardial infarction
TG	Triglycerides
T2D	Type 2 diabetes
VF	Ventricular fibrillation
WC	Waist circumference

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12933-025-02995-z>.

Additional file1 (DOCX 129 kb)

Additional file2 (DOCX 21 kb)

Additional file3 (DOCX 18 kb)

Additional file4 (DOCX 15 kb)

Additional file5 (DOCX 15 kb)

Acknowledgements

None.

Author contributions

PG-M and AP conceived the study. PG-M, JAG-O, and LR-P contributed to methodology. PG-M and JM curated the data. Formal analyses were performed by PG-M, JM, and VB. PG-M drafted the original manuscript. JAG-O, LR-P, JM, VB, MA, and AP critically revised the manuscript for important intellectual content. AP and MA supervised the study. All authors read and approved the final version of the manuscript.

Funding

This research was funded by the Spanish Society of Diabetes (SED) and the Spanish Society of Cardiology (SEC).

Data availability

The dataset analysed during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethics approval and consent to participate: The study was approved by the Ethics Committee of the Hospital Complex of Toledo on March 28, 2018 (project identification code 243) and conducted in accordance with the Declaration of Helsinki.

Competing interests

The authors declare no competing interests.

Author details

¹Hospital Universitari Vall d'Hebron, Barcelona, Spain

²Medicine Department, Autonomous University of Barcelona (UAB), Barcelona, Spain

³Lozano Blesa University Clinical Hospital, Zaragoza, Spain

⁴Cardiology Unit, University Hospital of Toledo, Toledo, Spain

⁵University of A Coruña & CIBERCV, La Coruña, Spain

⁶Ramon y Cajal University Hospital, Madrid, Spain

⁷Reina Sofia University Hospital, Cordoba, Spain

⁸Endocrinology & Nutrition, Hospital de La Santa Creu I Sant Pau, Barcelona, Spain

Received: 1 September 2025 / Accepted: 23 October 2025

Published online: 03 November 2025

References

- Gulins GS, Athithan L, McCann GP. Diabetic cardiomyopathy: prevalence, determinants and potential treatments. *Ther Adv Endocrinol Metab* [Internet]. 2019;10:2042018819834869.
- Gulins GS, Brady EM, Swarbrick DJ, Athithan L, Henson J, Baldry E, et al. Rationale, design and study protocol of the randomised controlled trial: Diabetes Interventional Assessment of Slimming or Training to Lessen Inconspicuous Cardiovascular Dysfunction (the DIASTOLIC study). *BMJ Open*. 2019;9(3):e023207.
- Lorenzo-Almorós A, Tuñón J, Orejas M, Cortés M, Egido J, Lorenzo Ó. Diagnostic approaches for diabetic cardiomyopathy. *Cardiovasc Diabetol*. 2017;16:28.
- Park JJ, Korean Diabetes Association. Epidemiology, pathophysiology, diagnosis and treatment of heart failure in diabetes. *Diabetes Metab J*. 2021;45:146–57.
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–726.
- Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2022;145:895–1032.
- Settergren C, Benson L, Shahim A, Dahlström U, Thorvaldsen T, Savarese G, et al. Cause-specific death in heart failure across the ejection fraction spectrum: a comprehensive assessment of over 100,000 patients in the Swedish Heart Failure Registry. *Eur J Heart Fail*. 2024;26(5):1150–9.
- Stolfo D, Lund LH, Benson L, Hage C, Sinagra G, Dahlström U, et al. Persistent High Burden of Heart Failure Across the Ejection Fraction Spectrum in a Nationwide Setting. *J Am Heart Assoc*. 2022;11(22):e026708.
- Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart Failure With Preserved Ejection Fraction: JACC Scientific Statement. *J Am Coll Cardiol*. 2023;81:1810–34.
- Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, et al. Obesity and cardiovascular disease: a scientific statement from the American heart association. *Circulation*. 2021;143:E984–1010.
- Doughty RN, Cubbon R, Ezekowitz J, Gonzalez-Juanatey J, Gorini M, Gotsman I, et al. The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis: Meta-analysis Global Group in Chronic Heart Failure (MAGGIC). *Eur Heart J*. 2013;33(14):1750–7.
- Rodríguez-Padial L, Pérez A, Anguita Sánchez M, Barrios V, Gimeno-Orna JA, Muñoz J. Characteristics of women with type 2 diabetes and heart failure in Spain. The DIABET-IC study. *Cardiol J*. 2023;XX(X):1–8.
- Gimeno-Orna JA, Rodríguez-Padial L, Anguita-Sánchez M, Barrios V, Muñoz J, Pérez A. Association of the kldgo risk classification with the prevalence of heart failure in patients with type 2 diabetes. *J Clin Med*. 2021. <https://doi.org/10.3390/jcm10204634>.
- Anguita-Gámez M, Bonilla-Palomares JL, Recio-Mayoral A, González-Manzanares R, Muñoz-García J, Romero-Rodríguez N, et al. Differences in clinical features and 1-year outcomes of patients with heart failure and reduced, mildly reduced, and preserved ejection fraction in a contemporary cohort: is the clinical profile changing?. *Clinical Research in Cardiology*. 2025;114. <https://doi.org/10.1007/s00392-025-02632-5>.
- Gonzalez-Manzanares R, Anguita-Gámez M, Muñoz J, Barrios V, Gimeno-Orna JA, Pérez A, et al. Prevalence and incidence of heart failure in type 2 diabetes patients: results from a nationwide prospective cohort—the DIABET-IC study. *Cardiovasc Diabetol*. 2024;23(1):253.
- Savji N, Meijers WC, Bartz TM, Bhamhani V, Cushman M, Naylor M, et al. The Association of Obesity and Cardiometabolic Traits with Incident HFpEF and HFREF HHS Public Access. *JACC Heart Fail*. 2018;6(8):701–9.
- Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. ACCF/AHA guideline for the management of heart failure: A report of the American college of cardiology foundation/american heart association task force on practice guidelines. *J Am Coll Cardiol*. 2013;62(16):e147–239.
- Meijers WC, Bayes-Genis A, Mebazaa A, Bauersachs J, Cleland JGF, Coats AJS, et al. Circulating heart failure biomarkers beyond natriuretic peptides: review from the biomarker study group of the Heart Failure Association (HFA), European Society of Cardiology (ESC). *Eur J Heart Fail*. 2021;23(10):1610–32.
- Bayes-Genis A, Docherty KF, Petrie MC, Januzzi JL, Mueller C, Anderson L, et al. Practical algorithms for early diagnosis of heart failure and heart stress using NT-proBNP: a clinical consensus statement from the Heart Failure Association of the ESC. *Eur J Heart Fail*. 2023Nov 1;25(11):1891–8.
- Steiner S. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *Zeitschrift für Gefässmedizin*. Krause und Pachernegg GmbH. 2016;13:17–8.
- Anker SD, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, et al. Effect of Empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status: results from the EMPEROR-reduced trial. *Circulation*. 2021. <https://doi.org/10.1161/CIRCULATIONAHA.120.051824>.
- McMurray JJV, DeMets DL, Inzucchi SE, Køber L, Kosiborod MN, Langkilde AM, et al. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. *Eur J Heart Fail*. 2019Nov 1;21(11):1402–11.
- Nakamaru R, Kohsaka S, Shiraiishi Y, Kohno T, Goda A, Nagatomo Y, et al. Temporal trends in heart failure management and outcomes: insights from a Japanese multicenter registry of tertiary care centers. *J Am Heart Assoc*. 2023;12(21):e031179.
- Sun LA, Dayer VW, Hansen RN, Du Y, Williamson T, Kong SX, et al. Long-Term Outcomes of Heart Failure With Preserved or Mid-Range Ejection Fraction in the U. S. JACC: Advances. 2024;3(7):101027.
- Kocabas U, Ergin I, Yavuz V, Altın C, Kaplan M, Yılmaz Öztekin GM, et al. Real-world data on Empagliflozin and Dapagliflozin use in patients with HEART failure: The RED-HEART study. *ESC Heart Fail*. 2025Feb 28;12(1):434–46.
- Bizino MB, Jazet IM, Westenberg JJM, Van Eyk HJ, Paiman EHM, Smit JWA, et al. Effect of liraglutide on cardiac function in patients with type 2 diabetes mellitus: randomized placebo-controlled trial. *Cardiovasc Diabetol*. 2019. <http://doi.org/10.1186/s12933-019-0857-6>.
- Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7(10):776–85.
- Diabet-ic T. European Journal of Internal Medicine Risk of cardiovascular events in patients with type 2 diabetes after 3 years of follow-up.
- Belli M, Barone L, Bellia A, Sergi D, Lecis D, Prandi FR, et al. Treatment of HFpEF beyond the SGLT2-Is: Does the Addition of GLP-1 RA Improve Cardio-metabolic Risk and Outcomes in Diabetic Patients? *Int J Mol Sci*. 2022Nov 23;23(23):14598.
- Anker SD, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, et al. Evaluation of the effects of sodium–glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. *Eur J Heart Fail*. 2019Oct 1;21(10):1279–87.
- Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *New England Journal of Medicine* [Internet]. 2021 Oct 14 [cited 2022 Feb 28];385(16):1451–61. Available from: <https://www.nejm.org/doi/https://doi.org/10.1056/NEJMo2107038>
- Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387(12):1089–98.
- Hasegawa K, Lewis BS. Are SGLT2 inhibitors effective against ‘all’ heart failure with preserved ejection fraction? *Eur Heart J*. 2022. <https://doi.org/10.1093/ehjcvp/pvac004>.
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure Developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2023Oct 1;44(37):3627–39.
- Scheen AJ. Real-life underuse of SGLT2 inhibitors for patients with type 2 diabetes at high cardiorenal risk. *Diabetes Epidemiology and Management*. 2024;13:100184.
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Vol. 37, *European Heart Journal*. Oxford University Press; 2016. p. 2129–2200m.
2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2018*. *Diabetes Care*. 2018 Jan 1;41(Supplement_1):S13–27.
- Hoek AG, Dal Canto E, Wenker E, Bindraban N, Handoko ML, Elders PJM, et al. Epidemiology of heart failure in diabetes: a disease in disguise. *Diabetologia*. 2024;67:574–601.

39. Rosano GMC, Seferovic P, Savarese G, Spoletini I, Lopatin Y, Gustafsson F, et al. Impact analysis of heart failure across European countries: an ESC-HFA position paper. *ESC Heart Fail.* 2022Oct 22;9(5):2767–78.
40. Abudureyimu M, Luo X, Wang X, Sowers JR, Wang W, Ge J, et al. Heart failure with preserved ejection fraction (HFpEF) in type 2 diabetes mellitus: from pathophysiology to therapeutics. *J Mol Cell Biol.* 2022 Sep 12;14(5).
41. Li Z, Shi Y, Xia Y, Wu L, Li H, Zhou R, et al. Disparate clinical characteristics and prognosis of HFpEF versus HFrEF phenotype of diabetic cardiomyopathy. *J Clin Med.* 2023Feb 16;12(4):1565.
42. Solomon SD, McMurray JJV, Vaduganathan M, Claggett B, Jhund PS, Desai AS, et al. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med.* 2024Oct 24;391(16):1475–85.
43. Kosiborod MN, Deanfield J, Pratley R, Borlaug BA, Butler J, Davies MJ, et al. Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HFpEF, and STEP-HFpEF DM randomised trials. *Lancet.* 2024;404(10456):949–61.
44. Madamanchi C, Alhosaini H, Sumida A, Runge MS. Obesity and natriuretic peptides, BNP and NT-proBNP: mechanisms and diagnostic implications for heart failure. *Int J Cardiol.* 2014;176(3):611–7.
45. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, et al. Heart failure association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail.* 2019;21(6):715–31.
46. Pieske B, Tschöpe C, De Boer RA, Fraser AG, Anker SD, Donal E, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur Heart J.* 2019;40(40):3297–317.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.