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Characteristics of women with type 2 diabetes and heart failure in Spain. The DIABET-IC study

Luis Rodríguez-Padial et al., Women with diabetes and heart failure in Spain

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Abstract

Background: Heart failure (HF) is the second most common initial presentation of cardiovascular disease in people with type 2 diabetes mellitus (T2DM). T2DM carries an increased risk of HF in women. The aim of this study is to analyze the clinical characteristics and the treatment received by women with HF and T2DM in Spain.
Methods: The DIABET-IC study included 1517 patients with T2DM in 2018–2019 in Spain, in 30 centers, which included the first 20 patients with T2DM seen in cardiology

and endocrinology clinics. They underwent clinical evaluation, echocardiography, and analysis, with a 3-year follow-up. Baseline data are presented in this study.
Results: 1517 patients were included (501 women; aged 67.28 ± 10.06 years). Women were older (68.81 ± 9.90 vs. 66.53 ± 10.06 years; $p < 0.001$) and had a lower frequency of a history of coronary disease. There was a history of HF in 554 patients, which was more frequent in women (38.04% vs. 32.86%; $p < 0.001$), and preserved ejection fraction being more frequent in them (16.12% vs. 9.00%; $p < 0.001$). There were 240 patients with reduced ejection fraction. Women less frequently received treatment with angiotensin converting enzyme inhibitors (26.20% vs. 36.79%), neprilysin inhibitors (6.00% vs. 13.51%), mineralocorticoid receptor antagonists (17.40% vs. 23.08%), beta-blockers (52.40% vs. 61.44%), and ivabradine (3.60% vs. 7.10%) ($p < 0.001$ for all), and 58% received guideline-directed medical therapy.
Conclusions: A selected cohort with HF and T2DM attending cardiology and endocrinology clinics did not receive optimal treatment, and this finding was more pronounced in women.
Key words: diabetes mellitus, heart failure, women, treatment

Introduction

Heart failure (HF) is one of the leading causes of illness and death in both sexes, and it is estimated that the incidence of HF will increase in the United States by 46% by 2030, affecting more than 8 million people [1]. From 40 years of age, both sexes have the same risk of developing HF throughout their lives; this pathology affects 20% of the subjects [2]. In addition, as the years go by, the incidence of HF increases, more markedly in women. Patients with HF and preserved ejection fraction (HFpEF) are more frequently female and older than those with HF and reduced ejection fraction (HFrEF) [3]. Women with HFpEF have high blood pressure more often and coronary artery disease less often than men [4]. Despite these important differences between sexes, women have been less represented in HF studies.

Heart failure is the second most common initial presentation of cardiovascular disease in people with type 2 diabetes mellitus (T2DM), and HF patients with T2DM also have a higher mortality rate compared to HF patients without T2DM. T2DM, as occurs with other risk factors and cardiovascular complications, confers a higher risk of HF in women than in men [5, 6]. In diabetics, a greater risk of coronary artery disease in

women than in men has been postulated among the possible explanations for the higher risk of HF in women with T2DM [7, 8], although the differences between sexes in the management of T2DM and other cardiovascular risk factors could also play a role [9].

Despite the importance of HF in women, this gender has been less studied in the large trials that have shown prognostic benefit of different drugs in this syndrome, especially in HFFEr [5, 10]. Similarly, whether women receive the treatments recommended by clinical practice guidelines with the same frequency as men has been little studied, although it has been shown that they also obtain a clear prognostic benefit [4]. Therefore, the objective of this preliminary study from DIABET-IC was to analyze the clinical characteristics and the treatment that women and men with HF and T2DM receive in our country.

Methods

The DIABET-IC study was designed to evaluate the prevalence and incidence of HF in patients with T2DM in our country and has a planned follow-up of 3 years. It is an observational study, without intervention, so the usual clinical practice was applied, without modifying the treatment or the examinations carried out on the patients in any case because they were included in the study. This manuscript is a preliminary work of the study and focuses on the baseline data of the patients included, emphasizing the comparison in the treatment between sexes, especially in patients who had HFrEF at baseline.

Patients. A total of 1517 patients with T2DM were included in 2018–2019 in Spain, in 30 centers distributed throughout all the autonomous communities. Patients were included in the Spanish provinces of A Coruña, Alicante, Asturias, Barcelona, Cáceres, Castellón, Córdoba, Ciudad Real, Granada, Guipuzcoa, Jaén, La Rioja, Las Palmas de Gran Canaria, Lugo, Lleida, Madrid, Málaga, Majorca, Murcia, Ourense, Pontevedera, Salamanca, Santa Cruz de Tenerife, Seville, Toledo, Valencia, Valladolid, Vizcaya, and Zaragoza. A cardiologist and an endocrinologist, both research collaborators, took part in the study in each center, including the first 20 patients with T2DM seen in their respective outpatient clinics. Participating centers could include more patients if desired. The patients were included in the autonomous communities of Andalusia (18.2%), Catalonia (13.5%), Madrid (13%), Castilla-La Mancha (10.9%), and Valencian Community (9.4%), with the rest of the autonomous communities having

a representation of less than 5%. Tertiary care provided 68.4% of the patients, and the rest came from secondary care.

The patients provided signed informed consent to participate in the study. Subsequently, they underwent a clinical evaluation with a detailed medical history, a physical examination, an electrocardiogram, and 2-dimensional echocardiography, following standard techniques, as well as laboratory tests (blood and urine count, NT-proBNP, glycosylated hemoglobin [HbA1c]). After the inclusion, a 3-year follow-up was conducted, with an annual check-up by the doctor responsible. If HF was suspected, the Research Collaborator from Cardiology performed the diagnosis of congestive HF and monitored the patient throughout the study. All patients with HF present or suspected were monitored by the cardiologists without any intervention, so standard of care was applied without modifying the treatment or the examinations in any case because of inclusion in the study.

The participating centers' Ethics Committees approved the study.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as proportions. The comparison between 2 variables is carried out using Pearson's chi-square tests or Student's t test, using analysis of variance for multiple comparisons. Values of $p < 0.05$ are considered significant.

Results

Baseline data are depicted in Table 1. A total of 1517 patients were included (501 women; 67.28 ± 10.06 years). At baseline, the women were older (68.81 ± 9.90 vs. 66.53 ± 10.06 years; $p < 0.001$) and had greater body mass index (BMI) (31.01 ± 5.88 vs. 29.69 ± 5.40 kg/m^2; $p < 0.001$). They also showed higher systolic blood pressure (136.57 ± 20.18 vs. 133.88 ± 18.98 mmHg; $p = 0.031$) and higher heart rates (76.59 ± 12.75 vs. 72.67 ± 13.06 bpm; $p < 0.001$) than men.

Regarding their cardiac history (Table 2), women less frequently had a history of heart disease, and especially of coronary heart disease. A total of 554 (37%) patients had a history of HF, which was more frequent in women (38.04% vs. 32.86%; $p < 0.001$), as was HFpEF (16.12% vs. 9.00%; $p < 0.001$), while a history of HFrEF (11.22% vs. 20.6%; $p < 0.001$) and mildly reduced ejection fraction (HFmrEF) (5.51% vs. 8.80%; $p < 0.001$) was more frequent in men. Women received implantable devices (cardioverter-

defibrillators-cardiac resynchronization therapy) (2.43% vs. 3.25%; $p < 0.001$) and implantable cardioverter-defibrillators (ICD) (1.01% vs. 5.42%; $p < 0.001$) less often than men, without differences in the rate of use of isolated resynchronization therapy (0.61% vs. 0.69%). There were no differences in the frequency of atrial fibrillation, valvular heart disease, and the use of pacemakers in our cohort. In patients with atrial fibrillation, the $CHAD_2DS_2$-VASc score was higher in women than in men (4.84 ± 1.37 vs. 3.93 ± 1.36 points; $p < 0.001$). Table 2 also shows the prevalence of HF in both sexes. HFrEF (< 40%) was more frequent in men (10.63% vs. 18.65%; $p < 0.001$), while HF with mild reduced or preserved ejection fraction (≥ 40%) was more prevalent in women (23.93% vs. 19.54%; $p < 0.001$).

Regarding the medical treatment received for HF, significant differences were observed in some of the pharmacological groups that have shown prognostic benefit in patients with HFrEF. In the group with HF, women less frequently received treatment with angiotensin-converting enzyme inhibitors (ACEI) (26.20% vs. 36.79%; $p < 0.001$), neprilysin inhibitors (ANRI) (6.00% vs. 13.51%; $p < 0.001$), mineralocorticoid receptor antagonists (MRA) (17.40% vs. 23.08%; $p < 0.001$), beta-blockers (BB; 52, 40% vs. 61.44%; $p < 0.001$), and ivabradine (3.60% vs. 7.10%; $p < 0.001$); conversely, women received treatment with diuretics (54.80% vs. 48.82%; $p < 0.02$) and angiotensin receptor blockers (ARB) (40.00% vs. 32.94%; $p < 0.001$) more frequently than men. No differences were observed regarding the use of digoxin (5.60% vs. 4.05%; $p = 0.173$).

When analyzing only patients with HFrEF (n = 240; 21.45% women), in whom some treatments have been shown to improve prognosis (Table 3), differences were observed in the use of some drugs such as ANRI, which was used less frequently in women (30.77% vs. 50.53%; $p = 0.011$), and ARB, which, on the contrary, was used more often in women (26.92% vs. 11.17%; $p = 0.004$). Women received treatment with ACEI or ARB more often (61.54% vs. 44.15%; $p = 0.026$) than men, with no differences in the use of other drugs analyzed individually. Women with HFrEF and T2DM were treated with sodium-glucose cotransporter-2 inhibitors (i-SGLT2) as often as men (40.38% vs. 39.36%; $p = 0.894$). As for the recommended treatment combinations, in the subgroup of patients with HFrEF, women received the combination of ARB + MRA + BB more often (17.31% vs. 4.23%; $p = 0.003$), with no differences observed in the percentage of use of the rest of the drug combinations. Women with HFrEF also received ICDs (1.01% vs. 5.42%; $p < 0.001$) and cardiac resynchronization

therapy with or without associated cardioverter-defibrillator (3.04% vs. 3.94%; $p < 0.001$) less frequently than men.

Regarding T2DM (Table 1), no differences were observed in the age of T2DM diagnosis, the age of insulin therapy initiation, and HbA1c concentration at baseline. Hypothyroidism (19.56% vs. 4.43%; $p < 0.001$) and dementia (2.59% vs. 0.98%; $p < 0.02$) were more common in women. These differences, among others, made the Charlson Index higher in men than in women (0.48 ± 0.81 vs. 0.69 ± 0.91; $p < 0.001$). As for the treatment of T2DM, women received iSGLT2 less frequently (35.14% vs. 43.10%; $p < 0.001$), in contrast to insulin, which was used more often in this group (47.90% vs. 39.64%; $p < 0.01$). Finally, no differences were observed in lipid-lowering therapies with the use of statins, PCSK9 inhibitors, and fibrates, although ezetimibe was used less frequently in women than in men (13.20 vs. 18.74%; $p < 0.01$).

Discussion

The preliminary results of the DIABET-IC study show significant differences between patients' treatment for HF and for T2DM according to their sex. Also, some baseline characteristics highlight relevant results: women were older and had higher BMI and blood pressure at baseline. Although women less frequently presented a history of heart disease, and especially ischemic heart disease, they did show a higher frequency of HF and, specifically, of HFpEF. Regarding the treatment received, it was observed that just over half (58%) of these high-risk patients with HF and T2DM receive optimal medical treatment, given that they were treated with all the drugs recommended by the clinical practice guidelines (ACEI/ARB/ARNI + MRA + BB). When comparing the treatment received by women with the treatment prescribed for men, it is observed that women, partly due to the different characteristics of their clinical picture, received treatment with ACEI, ARNI, MRA, BB, and ivabradine less frequently, but they were treated more frequently with ARBs. In addition, they also received less iSGLT2 for the treatment of hyperglycemia. When only patients with HFrEF are analyzed, a lower use of ARNI is still observed in women, with no differences in the use of the other groups of drugs between both sexes.

Greene et al. [11] recently analyzed the factors associated with non-use or sub-target dosing of drugs recommended by clinical practice guidelines in HF by analyzing studies on real-life patients targeting this problem. They found that the percentage of patients who reach the target doses recommended in the guidelines are 4–55% for

ACEI/ARB, 11–87% for sacubitril/valsartan, 4–60% for BB, and 22–80% for MRA. The use of these drugs in our patients falls within these ranges of observed real-life use, being 47.9% for ACEI/ARBs, 46.2% for ARNI, 66.2% for MRAs, and 92.1% for BBs. It is evident that there is ample room for the improvement of these treatments recommended by clinical practice guidelines. Furthermore, Greene et al. [11] indicated that advanced age and worsening renal function are associated with the non-use of drugs recommended by clinical practice guidelines, which was also observed in patients with lower body weight, hyperkalemia, and hypotension. Female sex is also associated with the non-use of ACEI/ARB, as well as with the use of sub-target dosing of ACEI/ARB, which may help explain what was found in our female patients. This finding is especially important given that Owerkerk et al. [12] observed that patients treated with lower doses of ACEI/ARB and BB tend to have a higher mortality.

Although both HF and T2DM are individually associated with considerable morbidity and mortality, both pathologies occur frequently in the same patient [14], which further worsens the health outcomes and quality of life of patients, as well as the cost for the health system [5]. Because both pathologies present a very different risk profile between both sexes [15], it is important to know in some detail the characteristics of these patients, especially in women, due to their lower representation in studies, emphasizing the aspects of improvement in their treatment, which can lead to a better prognosis. T2DM causes HF by different mechanisms, not all of which are well known [16]. In addition to the usual cardiovascular risk factors, women present some sex-specific risk conditions for HF related to their vulnerability during pregnancy, physical/emotional stress, such as the pathogenesis of Takotsubo syndrome or cardiovascular toxicity after chemotherapy, as well as some incremental pathophysiological features like the greater degree of endothelial inflammation and microvascular dysfunction and the vascular dysfunction with its impact on ventriculoarterial coupling) [5].

The profile of cardiovascular risk factors in our patients was similar to the one observed by López-Vilella et al. [7] in a Spanish population admitted with decompensated HF, a series in which 40% of patients had T2DM. These authors also observed, as described elsewhere [17, 18], that women are older than men at the time of HF presentation. They suffer from arterial hypertension more frequently, in contrast to ischemic heart disease which occurs less often, probably because women develop HF at a more advanced age when other risk factors are also more prevalent. They also

described a higher frequency of HFpEF in women, as has been pointed out by other authors [17].

Women obtain prognostic benefit from guideline-directed medical therapy, although some differences have been reported between the sexes with respect to the response to drugs used in HF [16]. In general, women obtain benefit from ACEI/ARB with lower doses than men, which probably makes it unnecessary to try to increase the dose of these drugs above 40–60% of the target dose [19], in the same way that it has been demonstrated that women are more sensitive to the side effects of cardiovascular drugs [20]. In addition, in the PARAGON study [21], which includes patients with HEpEF, a significant interaction between female sex and ARNI has been observed, such that women obtain a benefit of these drugs, with a significant reduction of 27% ($p < 0.006$) in cardiovascular death and admission for HF, but with no significant difference observed in men. Despite these findings, in our series women received treatment less frequently with these drugs. We also observed low use of iSGLT2 in the treatment of T2DM, despite the drugs having demonstrated prognostic benefit in patients with HF, whether they have T2DM or not. It is noteworthy that around 60% of the patients, with no differences between the sexes, were receiving treatment with the four pharmacological groups that have shown prognostic benefit. Although the use of iSGLT2 was lower in women when considering the entire population, in contrast to what was found by other authors [7], in patients with HFrEF we did not observe differences in the percentage of use of iSGLT2 between the sexes; however, the percentage of use (35–40%) can clearly be improved in this high-risk population.

Women with HFrEF also less frequently received advanced HF therapy, such as ICDs, and cardiac resynchronization therapy, with or without associated cardioverter-defibrillator. This lower use of advanced therapies for HF in women has been described by other authors, even after adjusting for confounding factors [22]. Although there are data that women, who have underlying ischemic heart disease less frequently, obtain less benefit from the use of the ICD and have a higher rate of complications [23], the truth is that, on the contrary, they benefit more from the use of cardiac resynchronization therapy [24], probably because they less frequently have areas of necrosis in the myocardium. For all the above, it can be concluded that there is a significant margin for improvement in the treatment received by all patients with HF and T2DM in our setting, both pharmacological and non-pharmacological. This

deficiency in the treatment of HF, which is observed especially in women, can lead to a worse prognosis for these patients.

Limitations of the study

There are several limitations concerning our study. Of interest, the lack of randomization at baseline, and the overrepresentation of participant hospitals interested in their results and willing to provide the best care for the patients presenting the 2 conditions explored (T2DM and HF), might have led to a selection bias compromising the external validity of our results. Also, we highlight the low rate of devices used, although we cannot provide any information about the percentage of left bundle branch block/QRS data.

Conclusions

In conclusion, a selected cohort attending cardiology and endocrinology clinics because of HF and T2DM did not receive optimal treatment for their conditions, and this finding is more pronounced in women. Therefore, there is scope for improvement in the treatment of this high-risk population.

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Table 1. Baseline characteristics.

	Men (n = 1016)		**Women (n = 501)**		**P**
Diagnostics	**Mean**	**SD**	**Mean**	**SD**	
Age [year]	66.53	10.06	68.81	9.9	< 0.001
SBP [mmHg]	133.88	18.98	136.57	20.18	0.031
DBP [mmHg]	75.57	11.34	75.96	11.87	0.539
Heart rate [bpm]	72.67	13.06	76.59	12.75	< 0.001
Weight [kg]	86.38	16.4	76.82	14.58	< 0.001
Height [cm]	169.81	7.14	157.32	6.88	< 0.001
BMI [kg/m^2]	29.69	5.4	31.01	5.88	< 0.001
Waist circumference [cm]	105.42	13.72	103.81	14.81	0.159
LVEF [%]	53.54	14.04	57.8	11.59	< 0.001
BNP [pg/mL]	203.34	318.25	359.74	837.05	0.994
NTproBNP [pg/mL]	975.72	2405.75	1115.91	2972.66	0.832
Hemoglobin [g/dL]	14.4	1.81	13.24	1.48	< 0.001
Creatinine [mg/100 mL]	1.1	0.39	0.9	0.39	< 0.001
eGFR	73.64	22.3	71.98	23.51	0.211
Cholesterol [mg/dL]	148.34	35.82	163.78	35.54	< 0.001
LDL-C [mg/dL]	77.56	30.16	85.86	29.59	< 0.001
Triglycerides [mg/dL]	153.94	96	149.72	76.27	0.772
HDL-C [mg/dL]	41.85	11.32	49.05	13.04	<0.001
Glucose [mg/dL]	141.05	48.11	143.23	44.94	0.110
HbA1c [%]	7.27	1.3	7.38	1.31	0.088
Age at T2DM diagnosis [year]	53.13	12.65	53.48	14.13	0.512
Age of insulin therapy [year]	57.46	13.23	57.59	13.49	0.835
Insulin dose [U/day]	46.92	31.91	46.82	35.25	0.237

BNP — B-type natriuretic peptide; BMI — body mass index; DBP — diastolic blood pressure; HbA1c — glycosylated hemoglobin; HDL-C — high-density lipoprotein cholesterol; eGFR — estimated glomerular filtration rate; LDL-C — low-density lipoprotein cholesterol; NT-proBNP — N-terminal prohormone B-type natriuretic peptide; LVEF — left ventricle ejection fraction; SBP — systolic blood pressure; SD — standard deviation

Table 2. Comorbidities and risk factors in the total population and by sex.

	Men		**Women**		**P**
Diagnosis	**N**	**%**	**N**	**%**	
Hypertension	832	81.89	411	82.04	0.945
Dyslipidemia	816	80.31	409	81.64	0.539
Tobacco	132	13.02	32	6.4	< 0.001
Alcohol	59	5.81	0	0	< 0.001
Heart disease	657	64.92	218	43.83	< 0.001
Ischemic heart disease	523	51.58	125	21.15	< 0.001
STE-ACS	187	19.72	44	8.06	< 0.001
NST-ACS	200	18.94	40	8.87	< 0.001
Coronary by-pass surgery	100	9.86	16	3.23	< 0.001
PCI	356	31.86	81	15.52	< 0.001
Stroke	93	9.26	39	7.78	0.626
PAD	143	14.12	21	4.21	< 0.001
Atrial fibrillation	223	22.01	104	20.88	0.616
CKD (stages 3–5)	229	22.56	122	24.35	0.437
COPD	133	13.9	33	6.59	< 0.001
Obstructive sleep apnea	175	17.22	57	11.38	0.003
Thyroid disease	71	7.10	112	22.15	< 0.001
Dementia	10	0.98	13	2.59	0.016
Type of heart failure					
LVEF reduced (< 40%)	188	18.65	52	10.63	< 0.001
LVEF midrange-preserved (≥ 40%)	197	19.54	117	23.93	

CKD — chronic kidney disease; COPD — chronic obstructive pulmonary disease; LVEF — left ventricular ejection fraction; PAD — peripheral artery disease; PCI — percutaneous coronary intervention; NSTE-ACS — non-ST-segment elevation acute coronary syndrome; STE-ACS — ST-segment elevation acute coronary syndrome

Table 3. Treatment in patients with heart failure with reduced ejection fraction.

	Total		**Men**		**Women**		**P**
Drugs	**N**	**%**	**N**	**%**	**N**	**%**	
Diuretics	200	75	142	75.53	38	73.07	0.819
ACEI	81	33.75	63	33.51	18	34.72	0.881
ARB	35	14.58	21	11.17	14	26.92	**0.004**
ACEI or ARB	115	47.92	83	44.15	32	61.54	**0.026**
ARNI	111	46.25	95	50.53	16	30.77	**0.011**
ACE or ARB or ARNI	224	93.23	177	94.15	47	90.38	0.335
Beta-blockers	221	92.08	170	90.43	51	98.08	0.084
MRA	159	66.25	123	65.43	36	69.23	0.608
Ivabradine	43	17.92	35	18.62	8	15.38	0.591
Digoxin	21	8.79	15	8.02	6	11.54	0.414
iSGLT2	95	39.58	74	39.36	21	40.38	0.894
ACE+MRA+BB	49	20.42	38	20.21	11	21.15	0.848

ARB+MRA+BB	17	7.08	8	4.26	9	17.31	**0.003**
ACEI or ARB or ARNI+MRA+BB	140	58.43	107	56.91	33	63.46	0.397

ACEI — angiotensin-converting enzyme inhibitor; ARNI — angiotensin receptor II blocker-neprilysin inhibitor; ARB — angiotensin receptor blocker; BB — beta-blockers; iSGLT2 — sodium-glucose cotransporter 2 inhibitor; MRA — mineralocorticoid receptor antagonist

Figure 1. Medical treatment of heart failure with reduced ejection fraction in women and men; *p < 0.05; ACEI — angiotensin-converting enzyme inhibitor; ARNI — angiotensin receptor II blocker-neprilysin inhibitor; ARB — angiotensin receptor blocker; BB — beta-blockers; iSGLT2 — sodium-glucose cotransporter 2 inhibitor; MRA — mineralocorticoid receptor antagonist.

Figure 1. Treatment of HFrEF