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Results: The final study cohort consisted in 215 patients. Mean age was 70 ± 12 years, mean LVEF was 43 ± 15% and 62 (29%) were women. Mean sTfR values were 1.42 ± 0.66 mg/L. In the whole cohort, median [Q1-Q3] NT-proBNP (pg/mL) was 1,125[587-2,668]. Log-transformed sTfR (log[sTfR]) showed significant correlations with log[NT-proBNP] ($r = 0.230$; p-value = 0.001), log[cTnT] ($r = 0.197$; p-value = 0.028), log[albumin]($r = -0.221$; p-value = 0.001), C-reactive protein ($r = 0.215$; p-value = 0.002), serum erythropoietin levels, MCH ($r = -0.247$; p-value <0.001) and MCHC ($r = -0.209$; p-value <0.001). As shown in *Table 1*, these findings were confirmed in multivariate age-and-sex adjusted linear regression models. In age-and-sex adjusted Generalized Additive Models (GAM) (*Figure 1*), we confirmed that higher levels of sTfR were associated with increased levels of biomarkers indicating cardiac damage (cTnT, NT-proBNP), active inflammatory status (C-reactive protein) and increased cellular stimulation in response to tissue hypoxia (endogenous erythropoietin).
Conclusions: In a cohort of HF patients without iron deficiency or anaemia, higher levels of sTfR indicating increased iron demand and tissue ID were associated with a worse biomarker profile indicating early subclinical cardiac and/or systemic damage even in the absence of overt systemic iron deficiency or anaemia.

Soluble transferrin receptor as a marker of tissue iron deficiency: impact on submaximal exercise capacity and functional class in patients with heart failure without systemic iron deficiency or anaem

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Background: Soluble receptor of transferrin (sTfR) is a marker of tissue iron status and may help to inform on subtle iron depletion and increased iron demand at tissular level even in the absence of overt systemic iron deficiency or anaemia. In this regard, the impact of raised sTfR levels as a marker of subtle tissue ID on functional limitation and submaximal exercise capacity in non-anaemic HF patients with normal systemic iron status has not been evaluated.
Purpose: To describe the association between sTfR as a marker of increased iron demand and tissue iron deficiency on submaximal exercise capacity, estimated with the distance walked in the 6-min walking test (6MWT), and symptoms of functional limitation (evaluated with the NYHA functional class) in non-anaemic patients with HF and normal systemic iron status.
Methods: We conducted an observational, prospective, cohort study of 1120 consecutive patients with chronic HF regardless the level of LVEF (DAMOCLES study). Patients included had a normal haemoglobin levels (≥12 g/dL), a normal systemic iron status (serum iron >33 μg/dL, ferritin >100ng/mL and % transferrin saturation >20%) and an available 6-min walking test data. Tissue ID was defined as levels of sTfR >75th percentile (1.63mg/L). The primary endpoint was the distance walked in the 6MWT at inclusion in the study.
The unadjusted associations between sTfR and the distance walked in the 6MWT were explored using General Additive Models (GAM), uni/multivariate linear regression models and also uni/multivariate binary regression models. All models were adjusted by age, sex, and prognostic factors such as LVEF, NYHA, NT-proBNP levels and iron status parameters among other well-known determinants of HF severity.

Figure 1. Unadjusted GAM models evaluating the association between sTfR and the distance walked in the 6-minute walking test (6MWT) as a measure of submaximal exercise capacity.

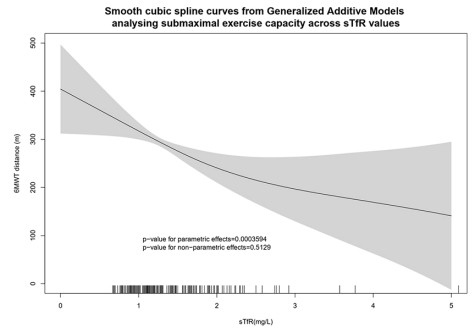

Figure 1

Table 1. Univariate and multivariate adjusted models exploring the effect on 6MWT distance, impaired submaximal exercise capacity and NYHA functional class limitations of sTfR and tissue ID in the cohort of non-anaemic patients with HF and normal systemic iron parameters.

Dependent variable: Distance walked in the 6MWT (submaximal exercise capacity)				
	Univariate linear regression models		Multivariate linear regression models	
Measures of Tissue ID	Standardized β coefficient	p-value	Standardized β coefficient	p-value
Log [sTfR 1 mg/L]	-0.249	<0.001	-0.135	0.001
sTfR>75th percentile (1.63mg/L)	-0.278	<0.001	-0.176	0.001
Dependent variable: Impairment in submaximal exercise capacity (6MWT distance<300 m)				
	Univariate binary logistic regression models		Multivariate binary logistic regression models	
Measures of Tissue ID	OR [95% CI]	p-value	OR [95% CI]	p-value
Log [sTfR 1 mg/L]	12.2[1.89-79.02]	0.009	10.1[1.11-91.37]	0.040
sTfR>75th percentile (1.63mg/L)	2.8[1.44-5.43]	0.002	2.9[1.25-6.77]	0.010
Dependent variable: Advanced NYHA functional class (NYHA≥III or IV)				
	OR [95% CI]		OR [95% CI]	
Measures of Tissue ID	Standardized β coefficient	p-value	Standardized β coefficient	p-value
Log [sTfR 1 mg/L]	7.4[1.04-52.54]	0.046	1.39[0.12-16.52]	0.792
sTfR>75th percentile (1.63mg/L)	2.0[1.00-4.00]	0.051	0.939[0.40-2.17]	0.889

Table 1

Results: The final study cohort consisted in 202 patients from the DAMOCLES study. Mean age was 70 ± 12 years, mean LVEF was 43 ± 15% and 57 (28%) were women. Mean sTfR values were 1.42 ± 0.66 mg/L. Tissue ID was present in 54 patients (25%). In the whole cohort, mean 6MWT distance was 287 ± 168 m. 6MWT distance was significantly worse in patients with tissue ID compared to patients without tissue ID (206 ± 179m vs. 314 ± 155, p-value <0.0001, respectively). Likewise, impaired submaximal exercise capacity was more common in patients with tissue ID (32, 64%) compared to patients without tissue ID (59, 39%, p-value = 0.003). In unadjusted GAM models (*Figure 1*) we observed a significant association between increased iron demand (higher levels of sTfR) and lower distance achieved in the 6MWT.
As shown in *Table 1*, higher sTfR levels were associated with lower distance in the 6MWT in unadjusted linear regression and binary logistic regression models.
Conclusions: In a cohort of HF patients without iron deficiency or anaemia, higher levels of sTfR indicating increased iron demand and tissue ID were associated with worse submaximal exercise capacity and tended to experience more functional limitations according to NYHA functional class.

Impact of right ventricular diastolic function on exercise tolerance in patients with chronic obstructive pulmonary disease and hypertension

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Objective: to evaluate the impact of right ventricular (RV) diastolic function on exercise tolerance in patients with chronic obstructive pulmonary disease (COPD) and hypertension (HT).
Methods: 100 COPD (GOLD 2, group B) patients in remission 54.42 ± 6.23 years old were monitored. The COPD group in combination with HT stage II included 69 patients, the isolated COPD group - 31 patients. All patients underwent general clinical and laboratory examination, 6-min walk test, pulse oximetry, spirometry, electrocardiography, echocardiography. Echocardiography was performed on ultrasound device RADMIR (Ultima PA).
Results: Analysis of RV diastolic function showed reduced early RV filling ($p < 0.05$) and the ratio between early RV filling (E-wave) and late RV filling (A-wave) (E/A ratio) ($p = 0.007$), elevated E-wave deceleration time ($p < 0.05$) and isovolumic relaxation time ($p < 0.05$) in the COPD with HT compared to the isolated COPD patients. It indicates a more pronounced relaxation disturbances and increased RV stiffness in patients with COPD combined with HT. We found RV diastolic dysfunction in the majority of comorbid patients – 78,2%, impaired relaxation (Grade I) was the predominant grade (50.7%), pseudo-normalized (Grade II) diastolic function was determined in 27,5%. In the isolated COPD group, normal diastolic function predominated (58.1%), pseudo-normalized - was less common (12,9%). Restricted (Grade III) RV diastolic dysfunction was not registered in our patients.
Among patients with COPD and hypertension significant differences ($p < 0.05$) were found in exercise tolerance parameters between patients with normal RV diastolic function ($n = 15$) and RV diastolic dysfunction ($n = 54$): the 6-min walk distance - 393.2 ± 14.61 m vs. 380.69 ± 13.85 m; exercise-induced dyspnea (Borg scale) - 3.4 ± 0.63 vs. 3.98 ± 1.0; exercise-induced oxygen desaturation - 3.4 ± 1.3 vs. 4.35 ± 1.42%. In the isolated COPD group reliable distinctions ($p < 0.05$) were found in exercise tolerance parameters between patients with normal RV diastolic function ($n = 18$) and RV diastolic dysfunction ($n = 13$): the 6-min walk distance - 402.06 ± 17.75 m vs. 386.85 ± 17.6 m; exercise-induced dyspnea (Borg scale) -

3.22 ± 0.65 vs. 3.92 ± 0.95. There was no significant difference in exercise-induced oxygen desaturation between COPD patients with normal RV diastolic function and RV diastolic dysfunction.
Conclusions: Thus, RV diastolic dysfunction contributes to exercise intolerance and exercise-induced oxygen desaturation in patients with COPD and HT.

Characteristics of patients with heart failure and advanced chronic kidney disease (stages 4–5) not undergoing renal replacement therapy (ERCA-IC STUDY)

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Background: Despite the frequent coexistence of heart failure (HF) in patients with advanced chronic kidney disease (CKD), they are often not studied in depth and little is known about HF prevalence and its prognostic relevance.
Purpose: The aim of our study is to compare the clinical characteristics of a population with advanced chronic kidney disease with and without previous HF and determine the risk of developing heart failure, need of renal replacement therapy and risk of death in the follow up.
Methods: Retrospective study of 217 patients with advanced CKD (stages 4 and 5) not undergoing renal replacement therapy (RRT). Patients were followed up for two years. The primary outcome was all-cause death or the need for RRT.
Results: Eighty-seven patients (40%) had a history of HF. The mean age was 78.2 ± 8.8 years, 52.9% were female and mean eGFR was 18.4 ± 5.5 ml/min/1.73m^2. The presence of previous HF identified a subgroup of high-risk patients with a high prevalence of cardiovascular comorbidities. A previous HF diagnosis was significantly and independently associated with the composite endpoint of all-cause hospitalization or need for RRT (66.7% vs. 53.1%, (HR 95% CI 1.62 (1.04–2.52), $p = 0.034$). The need for RRT was not different between patients with and without previous HF (27.6% vs 32..2%, $p = 0.46$), but the modality chosen was different. Nineteen patients without HF at baseline developed HF during the 2-year follow-up. 15 patients (78.9%) required hospitalization due to HF, and 11 (57.9%) required ambulatory intravenous diuretic treatment. These patients were older (77.2 ± 7.4 vs. 71.2 ± 13.6; $p = 0.007$) and more frequently diabetic (68.4% vs. 40.5%; $p = 0.024$), and all-cause death was numerically higher (36.8 vs. 19.8%, $p = 0.1$).
Conclusion: Patients with advanced CKD have a high prevalence of HF (40%). The prognosis was poor, with a significantly higher composite of all-cause death or need for renal replacement therapy in patients with previous HF. Multidisciplinary management involving cardiologist and nephrologist have critical importance in improving these patients' prognostic.

Table 1: Baseline characteristics and basal treatment between patients with and without heart failure at inclusion.

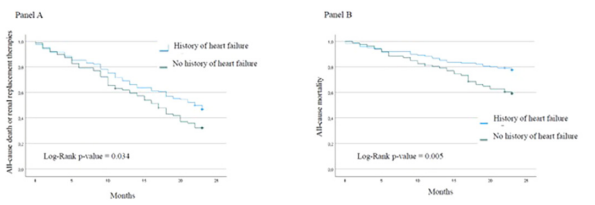
	No heart failure n=130 (60%)	Heart failure n=87 (40%)	P-Value
Baseline Characteristics			
Age (years) (mean±sd)	72.1 ± 13.1	78.2 ± 8.8	<0.001
Women n, (%)	47 (36.2)	46 (52.9)	0.015
Hypertension n, (%)	128 (98.5)	85 (97.7)	0.683
Diabetes mellitus n, (%)	58 (44.6)	61 (70.1)	<0.001
Dyslipidemia n, (%)	109 (83.8)	79 (90.8)	0.14
BMI (mean±sd)	28.0 ± 5.1	29.6 ± 5.7	0.016
Never smoker n, (%)	84 (64.6)	57 (65.5)	0.25
Active smoker n, (%)	25 (19.2)	22 (25.3)	
Previous smoker n, (%)	21 (16.2)	8 (9.2)	
Stroke/TIA n, (%)	16 (12.3)	13 (14.9)	0.58
Sleep apnea n, (%)	15 (11.5)	17 (19.5)	0.10
COPD/Asthma n, (%)	19 (14.6)	19 (21.8)	0.17
Peripheral vascular disease n, (%)	31 (23.8)	24 (27.6)	0.54
Cancer n, (%)	37 (28.5)	19 (21.8)	0.28
Myocardial infarction n, (%)	13 (10.0)	26 (29.9)	<0.001
Percutaneous coronary intervention n, (%)	7 (5.5)	23 (26.4)	<0.001
Moderate-severe valve disease n, (%)	3 (2.3)	15 (17.2)	<0.001
Atrial fibrillation/flutter n, (%)	14 (10.8)	48 (55.2)	<0.001

	No heart failure n=130 (60%)	Heart failure n=87 (40%)	P-Value
Baseline Treatment			
ACEI/ARB2/ARNI n, (%)	40 (30.8)	18 (20.7)	0.1
Beta blockers n, (%)	52 (40.0)	56 (64.4)	<0.001
MRA n, (%)	4 (3.1)	2 (2.3)	0.74
iSLGT2 n, (%)	1 (0.8)	3 (3.4)	0.15
Insulin n, (%)	27 (20.8)	40 (46.0)	<0.001
Other oral anti-diabetic drugs n, (%)	24 (18.5)	23 (26.4)	0.16
Antiplatelet therapy n, (%)	43 (33.1)	36 (41.1)	0.21
Statins n, (%)	98 (75.4)	68 (78.2)	0.64
Loop diuretic n, (%)	66 (50.8)	78 (89.6)	<0.001
HCTZ/bigrotone n, (%)	7 (5.4)	14 (16.1)	0.009
Anti-vitamin K n, (%)	12 (9.2)	21 (24.1)	0.003
Direct-acting anticoagulants n, (%)	1 (0.8)	14 (16.1)	<0.001
Intravenous iron n, (%)	21 (16.2)	20 (23.0)	0.21
Oral iron n, (%)	75 (57.7)	56 (64.4)	0.32
Eritropoyetin n, (%)	52 (40.0)	46 (52.9)	0.062

Abbreviations: BMI: body mass index. TIA: transient ischemic attack. COPD: chronic obstructive pulmonary disease. ACEi: Angiotensin-converting-enzyme inhibitors. ARB2: Angiotensin II receptor blockers. ARNI: angiotensin receptor-neprilysin inhibitor. MRA: mineralocorticoid receptor antagonists. iSLGT2: sodium-glucose cotransporter type 2 inhibitors. HCTZ: hydrochlorothiazide.

Baseline characteristics

Figure 1: Kaplan–Meier curves for long-term outcome divided by a history of HF. Panel A: All-cause death or renal replacement therapies. Panel B: All-cause mortality.



Kaplan–Meier curves

Clinical experience and safety of ferric carboxymaltose for treating iron deficiency in heart failure patients with mildly reduced and preserved left ventricular ejection fraction.

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Background: Iron deficiency (ID) is common in heart failure (HF) patients and has been related to exercise impairment, worse quality of life, and HF hospitalization. Clinical practice guidelines recommend checking and correcting ID with ferric carboxymaltose (FCM). However, there is a lack of evidence in patients with left ventricular ejection fraction (LVEF) > 40%.
Purpose: This study aims to evaluate the effectiveness and safety of ID correction with FCM at 3-month follow-up in a cohort of HF outpatients across the whole spectrum of LVEF.
Methods: We included all HF outpatients treated with FCM after being diagnosed with ID according to clinical guidelines. We analyzed clinical and analytical parameters before FCM administration and at 3 months. The analysis was performed according to LVEF: preserved (>50%), mildly reduced (41-49%), and reduced (<40%).
Results: We included 235 patients (51.5% female) aged 73.5 ± 10.7 years. Ninety-six patients have reduced LVEF (40.8%), 41 mildly reduced (17.4%), and 98 preserved (41.7%). Patients with preserved LVEF have more anemia (42.6 vs.26.8 vs. 52.6%; $p = 0.02$), with no other differences between groups. The mean dose of FCM was 947.0 ± 154.2 mg, with < 50% of patients receiving the correct dose of FCM, especially in patients with preserved LVEF ($p = 0.004$). One patient (0.4%) presented a local exanthema with no other adverse effects.
At 3 months, all analytical parameters significantly improved, except hemoglobin (12.9 vs. 13.0 mg/dL; $p = 0.95$) and natriuretic peptides (3261 vs. 3471 pg/mL; $p = 0.56$) in mildly reduced LVEF patients which did not change. The functional class did not improve in preserved LVEF patients, but it did in the rest of the groups (*Table 1*).
Conclusions: FCM is safe and effective in correcting ID in HF patients regardless of LVEF. Natriuretic peptides are reduced during the follow-up in all patients except those with mildly reduced LVEF. Functional class improvement is less likely in patients with preserved LVEF.

Table 1. Clinical and analytical parameters at 3-month follow-up according to LVEF

Parameter	HFrEF			HFmrEF			HFpEF		
	Basal (n=96)	3 months (n=96)	p-value	Basal (n=41)	3 months (n=39)	p-value	Basal (n=98)	3 months (n=92)	p-value
Hemoglobin (mg/dL)	12.7 (1.5)	13.2 (1.6)	0.001	12.9 (1.5)	13.0 (1.3)	0.95	12.1 (1.4)	12.7 (1.8)	0.001
MCHC (pg)	29.2 (3.1)	30.6 (2.0)	0.001	29.8 (2.7)	31.1 (2.1)	0.04	28.9 (2.5)	30.1 (2.2)	0.001
MCV (fL)	90.7 (9.4)	95.2 (5.9)	0.001	89.7 (11.2)	95.2 (5.8)	0.001	90.9 (6.9)	94.5 (5.2)	0.001
Serum iron (mcg/dL)	57.0 (28.4)	86.8 (26.0)	0.001	50.4 (21.9)	77.9 (28.0)	0.001	55.1 (25.4)	76.3 (35.4)	0.001
Ferritin (ng/mL)	86.2 (122.4)	312.1 (535.2)	0.001	83.1 (109.9)	245.1 (166.2)	0.001	58.5 (72.5)	255.1 (143.4)	0.001
Transferrin (mg/dL)	267.7 (51.4)	225.8 (48.8)	0.001	272.1 (59.9)	226.8 (48.3)	0.001	293.8 (63.1)	232.4 (50.9)	0.001
TSAT (%)	14.9 (7.5)	27.1 (9.8)	0.001	13.1 (5.7)	24.5 (11.6)	0.001	13.7 (6.5)	22.7 (11.8)	0.001
TSAT<20%-n (%)	72 (81.8)	13 (13.5)	0.001	38 (95.0)	9 (23.0)	0.001	73 (82.0)	21 (22.8)	0.001
Creatinin (mg/dL)	1.7 (3.3)	1.3 (0.5)	0.30	1.2 (0.4)	1.3 (0.5)	0.25	1.2 (0.5)	1.2 (0.5)	0.66
GFR (mL/min)	54.4 (23.7)	55.1 (24.5)	0.75	65.0 (22.7)	62.7 (24.6)	0.02	57.7 (21.4)	59.8 (20.3)	0.55
GFR<40 mL/min-n (%)	29 (35.4)	22 (22.9)	1	5 (13.9)	7 (17.9)	0.30	19 (23.2)	13 (14.1)	0.82
NTproBNP (pg/mL)	6229.1 (9929.2)	4133.0 (5070.2)	0.04	3260.6 (3524.0)	3470.9 (4622.6)	0.56	3182.2 (5141.7)	2389.7 (3198.3)	0.04
Anemia-n (%)	40 (42.6)	19 (19.8)	0.03	11 (26.8)	6 (15.4)	0.75	50 (52.6)	25 (27.2)	0.03
Absolute iron deficiency-n (%)	72 (76.6)	14 (14.5)	0.001	32 (78.0)	4 (10.3)	0.03	80 (85.1)	10 (10.9)	0.001
NYHA I-n (%)	3 (3.2)	15 (15.6)	0.03	1 (2.4)	10 (25.6)	0.03	4 (4.1)	9 (9.8)	0.150
NYHA II-n (%)	79 (82.3)	72 (75.0)		35 (85.4)	28 (71.8)		55 (56.1)	71 (77.2)	
NYHA III-n (%)	14 (14.5)	9 (9.4)		3 (7.3)	1 (2.6)		22 (22.4)	12 (13.0)	
Improved NYHA 1 grade-n (%)		20 (20.8)			11 (28.2)			19 (20.7)	
No changes in NYHA-n (%)		73 (76.0)			28 (71.8)			69 (75.0)	
Reported improvement after FCM-n (%)		69 (71.9)			30 (73.2)			63 (64.3)	

The impact of advanced chronic kidney disease on therapeutic management of chronic heart failure with reduced ejection fraction

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