

# Diagnosis and Treatment of Iron Deficiency in Heart Failure: OFICSel study by the French Heart Failure Working Group

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## Abstract

**Aims** Iron deficiency (ID) occurs in about 50% of patients with heart failure (HF). The European Society of Cardiology (ESC) recommends ID diagnostic testing in newly diagnosed patients with HF and during follow-up, with intravenous iron supplementation (IS) only recommended in patients with HF with reduced ejection fraction (HFrEF). This study aimed to assess prevalence, clinical characteristics, and application of ESC guidelines for ID and IS in patients with HF in the real-life clinical setting.

**Methods and results** The French transversal multicentre OFICSel registry (300 cardiologists) conducted in 2017 included patients hospitalized for HF at least once in the previous 5 years. Diverse adult patients were eligible including inpatients and outpatients and those with acute and chronic HF. Data were collected from cardiologists and patients using study-specific surveys. Data included demographic and clinical data, as well as HF and ID management data. Overall, 2822 patients, mainly male (69.3%) with a median age of 69 years (interquartile range 58–78), were included. A total of 1075 patients (38.1%) were tested for ID, with 364 (33.9%) diagnosed. Of these, 168 (46.2%) received IS: 128 (76.2%) intravenous IS and 40 (23.8%) oral. Among the 201 patients with HFrEF diagnosed with ID, 99 (49.3%) received IS: 79 (79.8%) intravenous IS and 20 (20.2%) oral.

**Conclusions** In clinical practice, only one-third of patients with HF had a diagnostic test for ID. In patients with ID with HFrEF, only 39.3% received intravenous IS as recommended. Thus, in general, cardiologists should be encouraged to follow the ESC guidelines to ensure optimal treatment for patients with HF.

**Keywords** Heart failure; Iron deficiency; Iron supplementation; Diagnosis; Guidelines

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## Introduction

Chronic heart failure (HF) is a main public health issue with a substantial economic burden. Annually in France, there are more than a million patients with HF with 165 000

hospitalizations, with the cost of hospitalization estimated to be 2.5 billion euros.<sup>1</sup>

Iron deficiency (ID) is described in approximately half of patients with HF.<sup>2</sup> ID, according to the European and American guidelines, is defined as having a ferritin level <100 µg/L, or a

level between 100 and 299  $\mu\text{g/L}$  with a transferrin saturation  $< 20\%$ .<sup>3,4</sup> ID, in patients with HF, may be associated with anaemia. Several studies have demonstrated that ID is associated with HF severity in terms of New York Heart Association (NYHA) classification, exercise performance,<sup>5,6</sup> health-related quality of life,<sup>7</sup> and higher hospitalization and death rates, irrespective of the presence of anaemia.<sup>2,6,8</sup> Iron supplementation (IS) for patients with HF with ID clinically improves exercise capacity and quality of life and reduces hospitalizations.<sup>9–11</sup> A very recent French analysis even suggests that IS could reduce hospitalization costs for worsening HF (by 35.8 million euros) and HF follow-up costs (by 2.9 million euros) for the French national health insurance.<sup>12</sup> Consequently, current guidelines published by the European Society of Cardiology (ESC) suggest systematic ID diagnostic testing in newly diagnosed patients with HF and intravenous IS only in patients with heart failure with reduced ejection fraction (HFrEF).<sup>3</sup> Currently, there is a lack of real-life data on how these guidelines are applied in terms of ID diagnosis and IS.

As part of the multicentre 'Observatoire Français de l'Insuffisance Cardiaque et du Sel' (OFICSel) registry, we aimed to describe ID prevalence in patients with HF; to assess the clinical application of the ESC guidelines, specifically concerning ID diagnosis and IS; and to investigate the epidemiological characteristics of patients with HF tested for ID and those subsequently treated.

## Methods

### Study design

OFICSel is a non-interventional, observational, transversal, multicentre registry performed by the French Heart Failure Group ['Groupe Insuffisance Cardiaque et Cardiomyopathies de la Société Française de Cardiologie' (GICC)] of the French Society of Cardiology. Overall, about 300 cardiologists from private and hospital practices participated in the registry present in each of the 13 regions of France. Patients older than 18 years, both inpatients and outpatients, with acute or chronic HF hospitalized for acute HF at least once in the previous 5 years were eligible. Patients who did not understand French were not eligible. The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee (ethics committee number, CNIL-916224; clinical trial number, CCTIRS No. 16-109). This study followed the STROBE reporting guideline for cross-sectional studies.

### Data collection

Data were collected from patients and their cardiologists using study-specific surveys. The patient's survey collected

data on socio-demographic, medical history, and quality of life (Minnesota Living with Heart Failure Questionnaire). The cardiologist's survey collected data on HF type (right, left, or global); the cause of HF; date of HF diagnosis; echocardiographic characteristics [left ventricular ejection fraction (LVEF)]; electrocardiogram data (sinus rhythm or atrial fibrillation); biological data [haemoglobin, N-terminal prohormone of B-type natriuretic peptide (NT-proBNP), and serum creatinine concentrations]; medical treatments [including the type of anticoagulant with vitamin K antagonist (VKA) or novel oral anticoagulants (NOAC) and antiplatelet therapy]; and whether a multisite and/or implantable cardioverter defibrillator had been implanted.

### Iron deficiency assessment

The cardiologist provided information on whether or not an ID diagnostic test had been performed. In patients who had ID diagnostic testing, the cardiologist specified whether or not the patient had ID: defined as ferritinaemia  $< 100 \mu\text{g/L}$  or ferritinaemia between 100 and 299  $\mu\text{g/L}$  and a transferrin saturation  $< 20\%$ .<sup>3</sup> The first assay performed was ferritinaemia; then only if the ferritinaemia value was between 100 and 299  $\mu\text{g/L}$  was a transferrin saturation assay carried out. For patients diagnosed with ID, the cardiologist noted if IS was implemented. Data concerning anaemia were collected. Anaemia, using the laboratory test closest to registration, was defined as a haemoglobin level  $< 12.0 \text{ g/dL}$  in women and  $< 13.0 \text{ g/dL}$  in men, according to the World Health Organization recommendations.<sup>13</sup>

### Statistical analysis

Continuous variables are expressed as medians [interquartile ranges (IQRs)], and categorical variables as numbers or frequencies (%). Patient characteristics were compared using the  $\chi^2$  test for categorical data or using the Student's unpaired *t*-test for continuous data. Multivariable logistic regression modelling was used to identify variables independently associated with ID diagnosis and with IS and to compute adjusted odds ratios (ORs) with 95% confidence intervals (CIs). The multivariable models were built using backward stepwise variable selection, with exit criteria set at  $P \leq 0.1$  to limit model overfitting. A two-sided *P*-value  $< 0.05$  was considered statistically significant. All statistical analyses were performed using STATA software, Version 15.1 (StataCorp, College Station, TX, USA).

## Results

### Participants of OFICSel study

From March to June 2017, 2822 patients were included. The study participant flow chart is shown in *Figure 1*. The clinical and biological characteristics of the patients with HF in the study are provided in *Table 1*. Overall, patients with HF were mostly male (69.1%), the median age was 69 years (IQR 58–78), and the median LVEF was 36% (IQR 29–50). Of the 2680 patients with data, 53.8% had HFrEF, 21.0% heart failure with mid-range ejection fraction (HFmEF), and 25.2% heart failure with preserved ejection fraction (HFpEF). Moreover, 427 (16.4%) patients were diagnosed with HF within the previous 3 months. Also, HF was acute in 783 (27.7%) patients and chronic stable in 2039 (72.3%).

Regarding HF treatment, 2440 patients (86.5%) were treated with either an angiotensin-converting enzyme inhibitor, an angiotensin receptor blocker, or an inhibitor of angiotensin and neprilysin; 2311 (81.9%) were treated with a beta-blocker; 1269 (45.0%) received a mineralocorticoid antagonist; 2144 (76.0%) received a diuretic; 725 (25.7%) had an implantable cardioverter defibrillator; and 411 (14.6%) had received cardiac resynchronization therapy. Concerning anticoagulant and antiplatelet therapy, of the 2822 patients, 986 (34.9%) received VKA, 413 (14.6%) NOAC, and 1330 (47.1%) antiplatelet therapy.

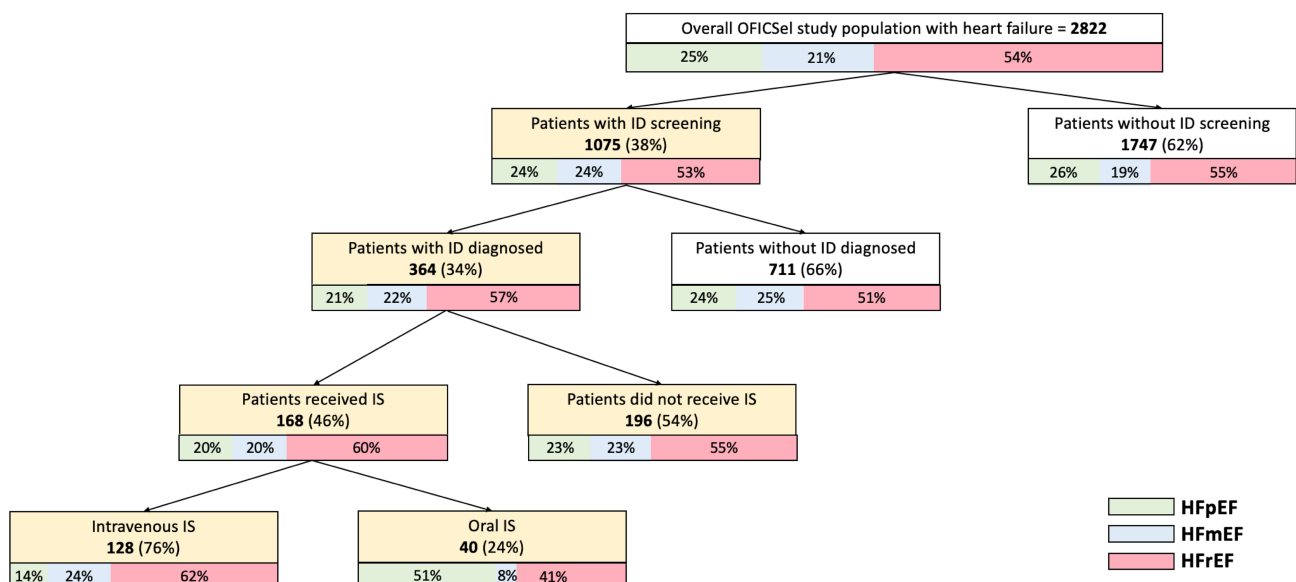
### Prevalence of iron deficiency and clinical characteristic of the patients according to iron deficiency status

Among the 2822 patients, 1075 (38.1%) patients had ID diagnostic testing within the previous year. Among those, 364 (33.9%) were diagnosed with ID.

Compared with patients without ID diagnostic test, patients with ID diagnostic test were younger (median age 67 vs. 69 years;  $P = 0.0002$ ) and were less frequently smokers ( $P = 0.035$ ). Regarding the type of HF, patients with ID diagnostic testing had ischaemic heart disease more frequently ( $P = 0.027$ ). There were no differences between groups (patients with diagnostic testing vs. those without testing) regarding the median LVEF ( $P = 0.723$ ), time from last decompensation ( $P = 0.507$ ), and diagnosis of HF within the previous 3 months ( $P = 0.283$ ). Similarly, concerning disease severity, there were no differences between groups for the rates of NYHA class III or IV ( $P = 0.231$ ), median NT-proBNP plasma concentration ( $P = 0.332$ ), nor diuretic use ( $P = 0.117$ ). Patients with ID diagnostic testing had beta-blocker ( $P < 0.0001$ ) and mineralocorticoid antagonist treatment ( $P = 0.003$ ) more frequently than those without ID diagnostic testing (*Table 1*).

In multivariable analysis, ID diagnostic testing was more frequently performed in younger patients (OR 0.991, 95% CI 0.985–0.998;  $P = 0.013$ ), non-smokers (OR 0.65, 95% CI

**Figure 1** Flow diagram of patients included in the OFICSel study ( $n = 2822$ ). HFmEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ID, iron deficiency; IS, iron supplementation.



**Table 1** Clinical and biological characteristics of the study population depending on whether iron deficiency diagnostic testing was performed or not (*n* = 2822)

	<i>n</i> <sup>a</sup> (%)	All 2822	ID diagnostic test performed		<i>P</i> -value
			Yes 1075 (38.1)	No 1747(61.9)	
<b>Baseline characteristics</b>					
Age, years (IQR)	2729	69 (58–78)	67 (56–77)	69 (60–79)	0.0002
Male sex, <i>n</i> (%)	2788	1956 (70.2)	725 (68.0)	1231 (71.5)	0.051
BMI, kg/m <sup>2</sup> (IQR)	2668	26.1 (23.2–30.1)	26.1 (23.1–30.1)	26.2 (23.2–30.1)	0.577
NYHA III–IV vs. I–II, <i>n</i> (%)	2530	971 (38.4)	350 (36.0)	621 (39.9)	0.049
Current decompensation, <i>n</i> (%)	2577	789 (30.6)	313 (31.6)	476 (30.0)	0.507
MLWHF total score (IQR)	1090	48 (31–62)	50 (31–65)	46 (31–59)	0.035
Serum creatinine, μmol/L (IQR)	2459	99.0 (76.0–128.0)	99.0 (77.0–128.0)	99.0 (76.0–127.0)	0.830
Haemoglobin, g/dL (IQR)	2581	12.9 (11.6–14.2)	12.9 (11.5–14.3)	12.9 (11.7–14.1)	0.434
Anaemia, <i>n</i> (%)	2581	1087 (42.1)	439 (42.2)	648 (42.1)	0.935
<b>Baseline medical history, <i>n</i> (%)</b>					
Diabetes	2822	816 (28.9)	297 (27.6)	519 (29.7)	0.237
Hypertension	2822	1578 (55.9)	611 (56.8)	967 (55.4)	0.440
Dyslipidaemia	2822	1072 (38.0)	416 (38.7)	656 (37.6)	0.542
Smoking	2822	321 (11.4)	105 (9.8)	216 (12.4)	0.035
AF	2822	767 (27.2)	271 (25.2)	496 (28.4)	0.065
SAS	2822	231 (8.2)	88 (8.2)	143 (8.2)	1.000
COPD	2822	199 (7.1)	70 (6.5)	129 (7.4)	0.379
Renal dialysis	2822	17 (0.6)	10 (0.9)	7 (0.4)	0.077
<b>Clinical features of HF</b>					
ICM	2639	1162 (44.0)	416 (40.9)	746 (46.0)	0.010
LVEF, % (IQR)	2680	36 (29–50)	37 (28–48)	35 (30–50)	0.723
HFrEF, <i>n</i> (%)		1442 (53.8)	554 (52.7)	888 (54.5)	} 0.009
HFmEF, <i>n</i> (%)		563 (21.0)	251 (23.9)	312 (19.2)	
HFpEF, <i>n</i> (%)		675 (25.2)	246 (23.4)	429 (26.3)	
Newly diagnosed HF < 3 months, <i>n</i> (%)	2680	427 (16.4)	173 (17.4)	254 (15.8)	0.283
<b>Last decompensation, <i>n</i> (%)</b>					
<3 months		1068 (44.1)	412 (43.6)	656 (44.4)	} 0.507
3 months to 1 year		535 (22.1)	220 (23.3)	315 (21.3)	
>1 year		821 (33.9)	313 (33.1)	508 (34.3)	
NT-proBNP, pg/mL (IQR)	1739	1811 (703–4384)	1783 (663–4342)	1855 (734–4405)	0.332
BNP, pg/mL (IQR)	828	438 (177–855)	351 (140–732)	517 (214–948)	0.020
<b>NT-proBNP or BNP quartiles, <i>n</i> (%)</b>					
1st		615 (25.1)	277 (27.4)	338 (23.5)	} 0.074
2nd to 3rd		1214 (49.6)	493 (48.8)	721 (50.2)	
4th		619 (25.3)	241 (23.8)	378 (26.3)	
<b>Treatments, <i>n</i> (%)</b>					
Diuretic	2822	2144 (76.0)	834 (77.6)	1310 (75.0)	0.117
ACE inhibitor or ARB	2822	1855 (65.7)	694 (64.6)	1161 (66.5)	0.302
ARNi	2822	427 (15.1)	179 (16.7)	248 (14.2)	0.077
Beta-blocker	2822	2311 (81.9)	925 (86.0)	1386 (79.3)	<0.0001
MRA	2822	1269 (45.0)	521 (48.5)	748 (42.8)	0.003
VKA	2822	986 (34.9)	361 (33.6)	625 (35.8)	0.235
NOAC	2822	413 (14.6)	160 (14.9)	253 (14.5)	0.769
Antiplatelet therapy <sup>b</sup>	2822	1330 (47.1)	489 (45.5)	841 (48.1)	0.171
ICD	2822	725 (25.7)	275 (25.6)	450 (25.8)	0.917
CRT		411 (14.6)	158 (14.7)	253 (14.5)	0.875
<b>Recruitment site</b>					
Hospitalization	2822	1350 (47.8)	544 (56.7)	806 (51.0)	} 0.001
Consultation		908 (32.2)	300 (31.3)	608 (38.5)	
Cardiac rehabilitation		283 (10.0)	116 (12.0)	167 (10.5)	

ACE, angiotensin-converting enzyme; AF, atrial fibrillation/flutter; ARB, angiotensin receptor blocker; ARNi, inhibitor of angiotensin and neprilysin; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; HFmEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; ICM, ischaemic cardiomyopathy; ID, iron deficiency; IQR, interquartile range; LVEF, left ventricular ejection fraction; MLWHF, Minnesota Living with Heart Failure Questionnaire with ≥18 items completed; MRA, mineralocorticoid antagonist; NOAC, novel oral anticoagulants; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; SAS, sleep apnoea syndrome; VKA, vitamin K antagonist.

<sup>a</sup>Number of data available.

<sup>b</sup>Corresponded to aspirin, clopidogrel, ticagrelor, or prasugrel.

0.48–0.87;  $P = 0.004$ ), patients with lower body mass index (OR 0.80, 95% CI 0.67–0.96;  $P = 0.015$ ), and those with beta-blocker (OR 1.44, 95% CI 1.13–1.83;  $P = 0.003$ ). Moreover, ID diagnostic testing occurred more frequent during hospitalizations than during consultations (Table 2).

## Patients with iron deficiency

The clinical and biological characteristics of the 1075 patients tested for ID according to ID are shown in Supporting Information, Table S1. Patients with ID were older (median age 69 vs. 66 years;  $P = 0.028$ ), were more frequently women (36.0% vs. 29.9%;  $P = 0.044$ ), had a higher median LVEF ( $P = 0.039$ ), and had ischaemic heart disease ( $P = 0.0004$ ) compared with those without ID. Patients with ID had more severe HF disease: higher rates of NYHA class III or IV and acute HF, a higher median NT-proBNP plasma concentration, increased diuretic use, and a shorter time interval from the last decompensation (all  $P < 0.0001$ ). Figure 2 shows the prevalence of ID according to NYHA and LVEF classes. The prevalence of ID increases with NYHA class severity. HF times of onset were similar in patients with or without ID ( $P = 0.44$ ). Patients with diagnosed ID had more anaemia and kidney dysfunction (both  $P < 0.0001$ ). Also, patients with ID were more frequently treated with beta-blockers ( $P = 0.003$ ) and VKA ( $P = 0.001$ ). There was no difference between groups regarding the prescription of NOAC ( $P = 0.565$ ) or antiplatelet therapy ( $P = 0.567$ ). The ID prevalence was higher in patients with anaemia than patients without anaemia ( $P < 0.001$ ; Figure 3).

In multivariable analysis, the presence of ID was independently associated with a higher rate of current acute HF (OR 2.83, 95% CI 2.09–3.83;  $P < 0.0001$ ), with lower haemoglobin levels (OR 0.76, 95% CI 0.71–0.83;  $P < 0.0001$ ), and lower LVEF (OR 0.98, 95% CI 0.96–0.98;  $P = 0.0006$ ) (Table 2).

## Patients receiving iron supplements

Clinical and biological characteristics of 364 patients diagnosed with ID according to IS are shown in Table 3. Among those, 168 (46.2%) received IS of whom 128 (76.2%) were treated with intravenous IS (Table S2) and 40 (23.8%) with oral iron. Among the patients diagnosed with ID, there were 91/213 patients (42.7%) treated with IS during hospitalizations, 41/82 patients (50.0%) during consultations, and 22/36 patients (61.1%) during cardiac rehabilitations. Regarding the LVEF value, of those patients diagnosed with ID, there were 33/75 patients with HFpEF (44.0%), 34/76 patients with HFmEF (44.7%), and 99/201 patients with HFrfEF (49.3%) treated with IS. Compared with patients with no IS, patients with IS more frequently had anaemia ( $P = 0.040$ ), treatment with VKA ( $P < 0.0001$ ), higher serum creatinine levels ( $P = 0.011$ ), and higher rates of renal dialysis ( $P = 0.030$ ). There was no difference between groups regarding the median LVEF ( $P = 0.423$ ), recruitment site ( $P = 0.095$ ), or number of patients recently diagnosed with HF within 3 months of registration ( $P = 0.992$ ). Among the 201 patients with HFrfEF with diagnosed ID, only 99 (49.3%) received IS: 79 (79.8%) intravenously and 20 (20.2%) orally.

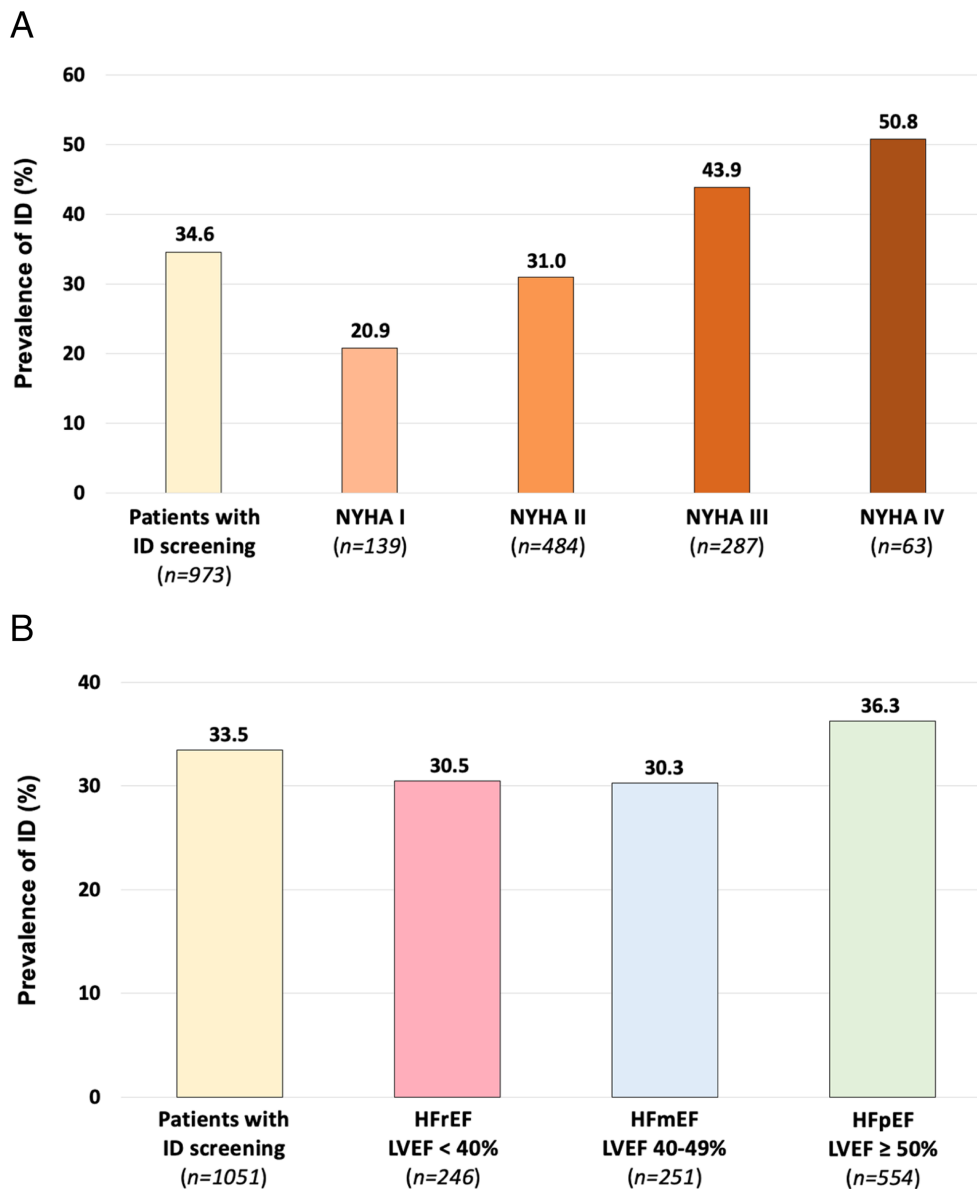
In multivariable analysis, IS treatment was independently associated with a higher prescription rate of VKA or NOAC

**Table 2** Multivariable logistic regression analysis for iron deficiency performed, iron deficiency diagnosed, and iron supplementation performed

	ID performed		ID diagnosed		IS performed	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Gender, male	—	—	0.55 (0.75–1.03)	0.075	—	—
Age	0.991 (0.985–0.998)	0.013	—	—	—	—
BMI	0.80 (0.67–0.96)	0.015	—	—	—	—
Smoking	0.65 (0.48–0.87)	0.004	—	—	—	—
Beta-blocker	1.44 (1.13–1.83)	0.003	—	—	—	—
VKA	—	—	—	—	2.40 (1.48–3.88)	0.0004
Recruitment site						
Hospitalization	1 (ref)	—	—	—	1 (ref)	—
Consultation	0.68 (0.56–0.82)	<0.0001	—	—	1.89 (1.06–3.39)	0.032
Cardiac rehabilitation	0.94 (0.71–1.25)	0.673	—	—	2.95 (1.34–6.49)	0.007
Current decompensation	—	—	2.83 (2.09–3.83)	<0.0001	—	—
LVEF, %	—	—	0.98 (0.96–0.99)	0.0006	—	—
Haemoglobin	—	—	0.76 (0.71–0.83)	<0.0001	0.88 (0.78–0.99)	0.031
NT-proBNP or BNP quartiles						
1st	—	—	—	—	1 (ref)	—
2nd to 3rd	—	—	—	—	1.23 (0.60–2.51)	0.574
4th	—	—	—	—	2.39 (1.09–5.21)	0.029

BMI, body mass index; BNP, B-type natriuretic peptide; CI, confidence interval; ID, iron deficiency; IS, iron supplementation; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; VKA, vitamin K antagonist.

**Figure 2** Prevalence of ID in patients stratified by NYHA class (A) and LVEF value (B). Bar chart of the ID prevalence in the 973 patients received ID diagnostic test and with NYHA status assessed ( $n = 973$  of 1075), stratified by NYHA class (A), and the 1051 patients received ID diagnostic test and with LVEF value assessed, stratified by LVEF value (B). HFmEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ID, iron deficiency; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

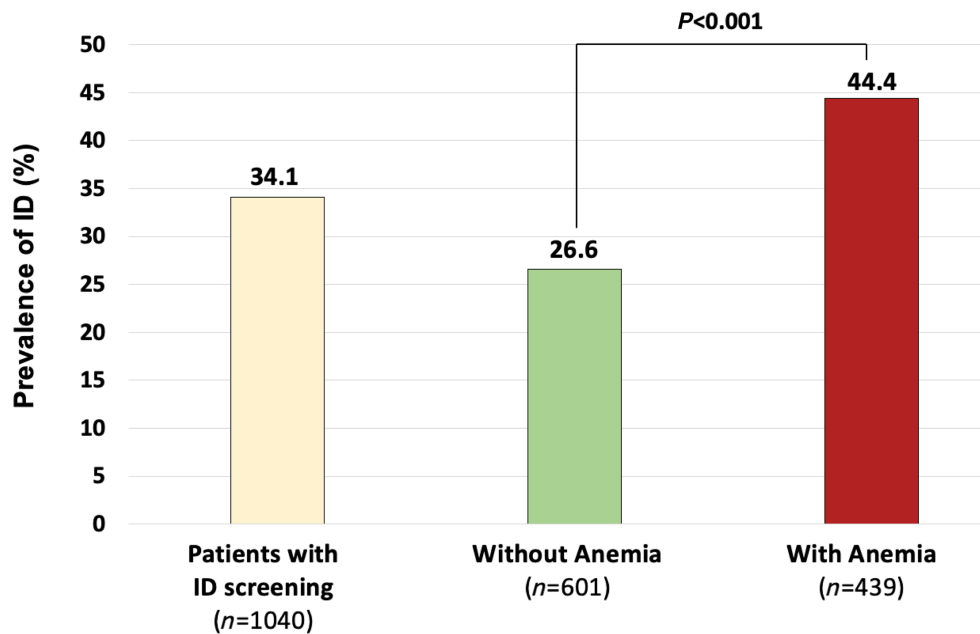


(OR 2.05, 95% CI 1.26–3.32;  $P = 0.004$ ), a higher NT-proBNP plasma concentration (OR 2.26, 95% CI 1.02–4.99;  $P = 0.044$ ), a lower haemoglobin level (OR 0.86, 95% CI 0.76–0.97;  $P = 0.012$ ), and a lower LVEF (OR 0.98, 95% CI 0.96–0.99;  $P = 0.030$ ) than those without IS (Table 2).

## Discussion

The OFICSel registry obtained data that are highly representative of the French HF population. Patients were included from various healthcare structures throughout France. Our results show that ESC recommendations that ID diagnostic

**Figure 3** Prevalence of ID in patients stratified by the presence of anaemia. Bar chart of the ID prevalence in the 1040 patients received ID diagnostic test and with anaemia status assessed, stratified by the presence of anaemia. ID, iron deficiency.



testing be performed in all patients with HF and intravenous IS be administered in those patients with HFrEF diagnosed with ID are not being followed.<sup>3</sup> Furthermore, the prevalence of ID in patients tested was 34%. Multivariate analyses found that patients' age, non-ischaemic cardiomyopathy, non-smoking, beta-blocker treatment, and the recruiting healthcare centre were associated with increased ID diagnostic testing, while LVEF, haemoglobin levels, anticoagulant treatment, and NT-proBNP levels were associated with prescription of IS (intravenous or oral).

The population included in this study was approximately a decade younger than the European HF population in the community<sup>14</sup> but similar to the large French ODIN cohort study.<sup>15</sup> Indeed, in this type of study using a self-administered questionnaire, patients are often younger than in registry studies. In our study, the subgroup of patients with reduced LVEF were generally well treated, medically, with results similar to data from European registers for patients receiving an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (90.1% and 93.2%, respectively), a beta-blocker (92.3% and 92.2%, respectively), or a mineralocorticoid antagonist (61.0% and 67.8%, respectively).<sup>14</sup> Moreover, the distribution of LVEF was fairly similar in our study and the European register [median 36% (29–50%) and median 39% (30–52%), respectively].<sup>14</sup>

In our study population, only 38.1% of patients with HF underwent ID diagnostic testing as recommended by the current guidelines.<sup>3,16</sup> Although the ESC guidelines recommend ID diagnosis in stable patients, 31.6% of patients underwent

ID diagnostic testing during a hospitalization for HF decompensation. These findings are surprising because cardiologists participating in the OFICSel registry routinely treat patients with HF. It is unlikely that ID test effectiveness nor regulatory hurdles hamper prescription. Several reasons may explain the non-systematic ID diagnostic testing. Firstly, the study was performed only 1 year after the guidelines were published: perhaps more time is required for these to be applied in real life. However, a more recent study published in 2018 reported similar results.<sup>17</sup> Secondly, HF is a complex disorder with various treatment strategies available. Although several treatments are known to decrease mortality, there is no evidence that IS reduces mortality. Consequently, ID and IS may not be of primary concern for HF treatment. However, IS may be beneficial and may result in sustainable improvement in functional capacity, symptoms and quality of life, and a significant reduction in hospitalizations for worsening HF.<sup>10</sup> Very recently, the AFFIRM-AHF trial, in patients with HFrEF with ID who were stabilized after an episode of acute HF, showed that IS was safe and reduced the risk of HF hospitalizations, with no apparent impact on the risk of cardiovascular death.<sup>18</sup> For these reasons, expert working groups have published position papers to increase awareness among cardiologists concerning ID and interpretation of the ID test results.<sup>16,17</sup>

In our study, the prevalence of ID, in patients tested, was 33.9%, lower than the 40–70% previously reported.<sup>2</sup> This is probably due to the non-systematic ID diagnostic testing in our study. Our results are similar to those previously

**Table 3** Clinical and biological characteristics of patients diagnosed with iron deficiency ( $n = 364$ ) according to whether iron supplementation was performed

<i>n</i> (%)	ID diagnosed		<i>P</i> -value
	With IS 168 (46.2)	Without IS 196 (53.8)	
<b>Baseline characteristics</b>			
Age, years (IQR)	69 (58–78)	69 (58–78)	0.920
Male sex, <i>n</i> (%)	101 (60.5)	128 (67.0)	0.199
BMI, kg/m <sup>2</sup> (IQR)	26.1 (23.3–30.8)	25.4 (22.6–30.0)	0.167
NYHA III–IV vs. I–II, <i>n</i> (%)	70 (47.0)	85 (45.2)	0.747
Current decompensation, <i>n</i> (%)	75 (48.3)	90 (48.6)	0.962
MLWHF total score (IQR)	52 (40–69)	51 (35–65)	0.416
Serum creatinine, mg/dL (IQR)	108 (80–150)	105 (77–136)	0.011
Haemoglobin, g/dL (IQR)	11.9 (10.3–13.1)	12.4 (11.0–13.9)	0.005
Anaemia, <i>n</i> (%)	98 (60.9)	97 (50.0)	0.040
<b>Baseline medical history, <i>n</i> (%)</b>			
Diabetes	65 (38.7)	62 (31.6)	0.159
Hypertension	107 (63.7)	117 (59.7)	0.435
Dyslipidaemia	81 (48.2)	81 (41.3)	0.187
Smoking	13 (7.7)	28 (14.3)	0.049
AF	51 (30.4)	49 (25.0)	0.254
SAS	12 (7.1)	21 (10.7)	0.237
COPD	14 (8.3)	21 (10.7)	0.442
Renal dialysis	4 (2.4)	0 (0.0)	0.030
<b>Clinical features of HF</b>			
ICM, <i>n</i> (%)	83 (51.2)	84 (45.4)	0.278
LVEF % (IQR)	35 (25–45)	35 (27–46)	0.423
HFrEF, <i>n</i> (%)	99 (59.6)	102 (54.8)	0.659
HFmEF, <i>n</i> (%)	34 (20.5)	42 (22.6)	
HFpEF, <i>n</i> (%)	33 (19.9)	42 (22.6)	
Newly diagnosed HF < 3 months, <i>n</i> (%)	26 (16.0)	28 (16.1)	0.992
<b>Last decompensation, <i>n</i> (%)</b>			
<3 months	84 (54.2)	96 (54.2)	0.024
3 months to 1 year	42 (27.1)	30 (16.8)	
>1 year	29 (18.7)	51 (28.8)	
NT-proBNP, pg/mL (IQR)	3169 (1250–9000)	2059 (850–4353)	0.003
BNP, pg/mL (IQR)	361 (193–1011)	468 (233–748)	0.130
<b>NT-proBNP or BNP quartiles, <i>n</i> (IQR)</b>			
1st	23 (14.0)	36 (18.9)	0.007
2nd to 3rd	80 (48.8)	112 (58.9)	
4th	61 (37.2)	42 (22.1)	
<b>Treatments, <i>n</i> (%)</b>			
Diuretic	145 (86.3)	166 (84.7)	0.063
ACE inhibitor or ARB	105 (62.5)	130 (66.3)	0.447
ARNi	27 (16.1)	24 (12.2)	0.294
Beta-blocker	142 (84.5)	155 (79.1)	0.182
MRA	91 (54.2)	92 (46.9)	0.169
VKA	104 (61.9)	42 (21.4)	<0.0001
NOAC	22 (13.1)	29 (14.8)	0.641
Antiplatelet therapy <sup>a</sup>	73 (43.5)	97 (49.5)	0.250
ICD	54 (32.1)	43 (21.9)	0.028
CRT	28 (16.7)	28 (14.3)	0.530
<b>Recruitment site, <i>n</i> (%)</b>			
Hospitalization	91 (59.1)	122 (68.9)	0.095
Consultation	41 (26.6)	41 (23.2)	
Cardiac rehabilitation	22 (14.3)	14 (7.9)	

ACE, angiotensin-converting enzyme; AF, atrial fibrillation/flutter; ARB, angiotensin receptor blocker; ARNi, inhibitor of angiotensin and neprilysin; BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; HFmEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; ICM, ischaemic cardiomyopathy; ID, iron deficiency; IQR, interquartile range; IS, iron supplementation; LVEF, left ventricular ejection fraction; MLWHF, Minnesota Living with Heart Failure Questionnaire with  $\geq 18$  items completed; MRA, mineralocorticoid antagonist; NOAC, novel oral anticoagulants; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; NYHA, New York Heart Association; SAS, sleep apnoea syndrome; VKA, vitamin K antagonist.

<sup>a</sup>Corresponded to aspirin, clopidogrel, ticagrelor, or prasugrel.



reported<sup>19,20</sup> and highlight the importance of ID, not only a predisposing factor for HF but also a consequence of HF severity.<sup>21,22</sup>

There was no difference in ID diagnostic rates in patients newly diagnosed with HF, that is, within the last 3 months. However, current acute HF status was independently associated with ID diagnosis, as previously reported.<sup>23,24</sup> This suggests that ID diagnostic test during decompensation or worsening of the disease may be valuable, even in patients without ID at HF diagnosis. It is unlikely that the high incidence of ID in patients with acute HF in our study is related to initial haemodilution of the iron parameters, as reported for plasma haemoglobin.<sup>25</sup> Indeed, Androne *et al.* reported that in patients with anaemic chronic HF, 46% had haemodilution and 54% true anaemia.<sup>25</sup> Inflammation and ID may be associated, given that HF is an inflammatory condition, especially when decompensated. Iron levels are known to fluctuate as HF evolves: patients may become ID even if they had normal levels at HF diagnosis,<sup>26,27</sup> and ID prevalence for acute HF decreases from hospital admission to 30 days after discharge.<sup>28</sup> HF evolution is a complex process with several co-morbidities,<sup>21</sup> especially in patients with HFpEF.<sup>29</sup> Current guidelines recommend ID diagnostic test at HF diagnosis.<sup>3</sup> However, patients with HF may benefit from more regular follow-up and monitoring of ID, and when required IS, particularly during HF evolution, for example, the onset of AF or anaemia. The guidelines need to be updated to include continuous ID monitoring.<sup>3</sup> Practical recommendations that complement the guidelines have been published. They suggest that iron levels be evaluated in patients with existing chronic HF, particularly when HF is severe and symptomatic despite optimal HF treatment.<sup>17</sup> They also suggest that iron levels be assessed once or twice a year, as well as after hospitalization for patients with decompensated HF.<sup>17</sup> Our results show that there is a need for implementing these practical recommendations. We also suggest that studies be developed to assess evidence-based strategies for clinicians to support recommendations. Furthermore, specifically in patients with HFpEF, large morbimortality trials adapted to the evolution of co-morbidities and specific risk factors should be proposed.

Regarding the cause of ID, several studies have reported that iron in patients with HF may be depleted by gastrointestinal bleeding from or exacerbated by anticoagulants.<sup>21,30</sup> Indeed, in our study, patients receiving VKA, as anticoagulants, had ID diagnosed more frequently. Interestingly, there was no difference in ID diagnostic rates in patients prescribed NOAC, compared with those prescribed VKA, even though lower rates of gastrointestinal bleeding are reported with NOAC.<sup>31</sup> As expected, patients diagnosed with ID more often had anaemia and kidney dysfunction.<sup>27</sup> In patients with ID and anaemia, the guidelines suggest investigating the underlying causes of anaemia and excluding other pathologies.<sup>3,17</sup>

The current ESC guidelines recommend intravenous IS for treating ID in patients with symptomatic HFpEF.<sup>3</sup> Indeed, several studies have shown that oral IS is not as effective as intravenous IS in these patients.<sup>32</sup> Oral IS does not replenish iron stores nor improve the clinical status of patients with HF.<sup>32</sup> Moreover, oral IS is poorly tolerated in patients with HF, with more than 50% experiencing gastrointestinal side effects.<sup>33</sup>

In our study, 1442 patients (53.8%) had HFpEF. Of these, 554 (38.4%) had a diagnostic test for ID. ID was diagnosed in 201 patients, with 36.3% of patients with HFpEF tested. Finally, of the 201 patients with HFpEF diagnosed with ID, 99 patients (49.3%) received IS: 39.3% received the recommended intravenous IS, and 10.0% oral IS. Overall, despite the potential benefit of intravenous IS, only a small proportion of patients with HFpEF benefited from optimal treatment with intravenous IS.

Perhaps clinicians are unaware of the superiority of intravenous IS. These findings suggest that guidelines are not consistently been applied in the real-life clinical setting, as previously reported.<sup>34</sup> In the clinical setting, there are not only ethical, societal, and organizational constraints but also logistic issues. Indeed, as previously mentioned, intravenous IS, in France, requires a short-stay hospitalization to manage possible hypersensitivity.<sup>9</sup> Consequently, intravenous IS is more expensive than oral IS. Interestingly, rules and regulations concerning the administration of intravenous IS vary among countries.<sup>17</sup>

What about IS in patients other than those with HFpEF? The ESC guidelines recommend IS only in patients with HFpEF.<sup>3</sup> However, in patients with HFpEF, ID is associated with worse functional capacity compared with patients with HFpEF.<sup>35,36</sup> Interestingly, of the 76 patients with HFmEF diagnosed with ID, 34 (44.7%) received IS. Similarly, of the 75 patients with HFpEF diagnosed with ID, 33 (44.0%) received IS. Currently, in France, the use of IS for ID for patients with HFpEF is not established. In contrast, the American guidelines suggest that IS may be reasonable in all patients with symptomatic HF.<sup>4</sup> Hopefully, the ongoing Phase II FAIR-HFpEF trial (NCT03074591) assessing intravenous IS in patients with HFpEF will determine the usefulness of IS in this population.

## Study limitations

Our study has several limitations. Firstly, there is a possible selection bias. Furthermore, patients with consecutive HF were prospectively enrolled at each centre. However, for logistical reasons, each centre or cardiologist was initially only provided with 10 study-specific surveys, with further surveys supplied on request. Secondly, our study population was on average younger (by about 10 years) and with more optimal treatment compared with most published HF registers.<sup>3</sup> Enrolled patients had to complete a lengthy study-specific

survey, which may have deterred older patients from participating. Thirdly, data concerning ID diagnostic testing and IS were based on declarative data from the patient's referring cardiologist. We assume that the cardiologist participating in the study would be aware of ID diagnostic testing or IS previously performed. The definition of ID was reported in the questionnaire to avoid any bias of interpretation of the presence or not of ID, and this definition was in accordance with the guidelines.<sup>3</sup> Moreover, the presence of a history of inflammatory disease that could influence the prevalence of ID was not collected in this study. Fourthly, we are unable to distinguish between absolute and functional ID in our data.<sup>3</sup> However, according to the guidelines, patients with HFrEF, with either absolute or functional ID, should be treated with intravenous IS.<sup>37</sup> Fifthly, the recommended intravenous IS is not easily accessible. In France, intravenous IS requires hospitalizations. Thus, cardiologists may be reluctant to test for ID because a diagnosis would imply that intravenous IS is not easily accessible. Sixthly, the result suggesting a significant association between VKA uptake and ID is limited by the lack of data on the international normalized ratio (INR) value in the study. Moreover, we did not collect details concerning the specific intravenous IS administered. Indeed, both ferric carboxymaltose and iron sucrose complex are available, but only ferric carboxymaltose is recommended by the ESC. Finally, as OFICSel is a large registry including physicians from different practices and patients with different type of HF, it might be representative of HF population in France. However, the extrapolation of these findings to other countries or specialists could be limited.

## Conclusions

Of the 2822 patients with HF included in the multicentre OFICSel registry, only 38% of patients had an ID diagnostic test. This is despite the current ESC guidelines that recommend ID diagnostic testing in all patients with HF. Among the patients tested, more than a third were diagnosed with ID. Regarding IS, fewer than half of patients with HFrEF with diagnosed ID received IS. Our results suggest that cardiologists should be encouraged to follow the ESC guidelines, concerning ID testing and IS, to ensure optimal treatment for patients with HF.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Clinical and biological characteristics of patients with iron deficiency in patients with ID diagnostic testing ( $n = 1075$ ).

**Table S2.** Clinical and biological characteristics of patients diagnosed with iron deficiency according to whether intravenous iron supplementation was performed. ( $n = 364$ ).

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