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SHORT REPORT

Iron deficiency and supplementation in patients with heart failure: Results from the IRON-HF international survey

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Aims Iron deficiency (ID) is common in patients with heart failure (HF) and is associated with poor outcomes, regardless of anaemia status. Iron supplementation has been demonstrated to improve exercise capacity and quality of life in patients with HF with an ejection fraction <50% and ID. This survey aimed to provide data on real-world practices related to ID screening and management.

Methods and results We designed and distributed an online survey (23 questions) regarding ID screening and management in the HF setting. Overall, 256 cardiologists completed the survey (59.8% male, mostly between 30 and 50 years). The majority of physicians defined ID according to the most recent HF recommendations (98.4%) and reported screening for ID in more than half of their patients (68.4%). However, only 54.3% of the respondents performed periodic screening (every 6 months to 1 year). A total of 93.0% of participants prescribed and/or administered iron supplementation, using intravenous iron as the preferred method of administration (86.3%). After iron supplementation, 96.1% of the respondents reassessed ID, most frequently at 3–6 months (67.6%). Most physicians (93.8%) perceived ID as an underestimated comorbidity in HF. Cardiologists' age, training status, subspecialty and work setting (academic vs. non-academic hospitals) were associated with heterogeneity in the answers.

Conclusions The results of this survey highlight the need for more consistent strategies of ID screening and treatment for patients with HF.

Keywords Heart failure • Iron deficiency • Iron supplementation • International survey • Heart Failure Guidelines

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Introduction

Iron deficiency (ID) is common in patients with cardiovascular diseases.[1] It is associated with higher mortality and recurrent hospitalizations in patients with heart failure (HF), independently of haemoglobin levels.[1] Notably, compared to placebo, supplementation with intravenous iron has been demonstrated to reduce the risk of HF hospitalization and mortality in numerous randomized clinical trials,[2–7] leading to the introduction of ferric compounds in published HF recommendations.[8–11] These results were further confirmed by recent meta-analyses, highlighting the beneficial effects on functional capacity and quality of life in patients with HF and an ejection fraction <50%.[12–15] The implementation of guideline recommendations in the real world remains challenging,[16] and early data from nationwide European registries show low rates of ID screening and inadequate treatment with intravenous iron in patients with HF.[17,18]

Recognizing that there is often a lag phase between guideline recommendations and their clinical implementation, we conducted a survey to better understand cardiologists' knowledge, attitudes, and willingness to screen for ID and prescribe intravenous iron compounds to patients with HF.

Methods

This survey was designed by a group of participants to the 5th Postgraduate Course in HF (PCHF), held by the University of Zürich between 2022 and 2023 with the endorsement of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). The survey was revised and approved by members of the Italian Society of Cardiology, Italian Association of Hospital Cardiologists (ANMCO), the Young Community of the HFA, and numerous alumni of the Zürich PCHF. The survey consisted of 23 questions (online supplementary *Table S1*), encompassing practices related to ID screening and supplementation, and respondents' perspectives on the issue of ID. The survey was published on the Google Form platform and shared via email by the aforementioned scientific organizations. The survey was available for 3 months (from 1 March 2023 to 1 June 2023) on the web platform. A reminder to complete the survey was sent twice via email.

Statistical analysis

Categorical variables were expressed as numbers and percentages, while continuous variables were expressed as median and interquartile range (IQR). The following subgroup comparisons were systematically performed using Fisher's exact test: age strata (<30, 30–50, and >50 years), HF specialists (with proven experience in managing patients with HF or having a master/postgraduate diploma in HF) versus non-HF specialists, and board-certified cardiologists versus cardiology fellows. Working in an academic versus non-academic hospital, and sex differences were also evaluated. All tests were two-sided, and a p-value <0.05 represented statistical significance. All analyses were performed using the R statistical software (the R Foundation for Statistical Computing, Vienna, Austria) version 4.1.2.

Results

A total of 256 board-certified cardiologists (77.7%) and cardiology fellows (22.3%) completed the survey. Respondents' characteristics are presented in *Table 1*. HF specialists accounted for half of the total participants, and more than two-thirds (75.2%) had attended a master/postgraduate course in HF.

Almost all physicians (98.4%) defined ID according to current recommendation by ESC HF guidelines.[9,11] The majority (64.5%) of participants reported that the prevalence of ID in HF was approximately 50%. However, contrary to the available literature,[1] they attributed a higher prevalence of ID to HF with reduced ejection fraction compared with HF with preserved ejection fraction.

Most clinicians (68.4%) performed screening for ID in >50% of their patients. HF specialists were more likely to perform screening compared to other subspecialties (86.4% vs. 51.1%; $p < 0.001$) (*Figure 1*). More than half of participants (64.5%) also reported that their institutions/national health system covered the costs of ID screening and this finding was more frequent in HF specialists than non-HF specialists (72.1% vs. 56.9%, $p = 0.016$).

A periodic screening strategy was reported by 139 physicians (54.3%), of whom 55.4% performed screening every 6 months and 44.6% every year (*Figure 2*). Significant differences emerged among subgroup analyses (*Table 2*).

Of importance, an active role in prescribing and directly administering iron supplementation was reported only by 51.6% of physicians. Overall, 41.4% prescribed iron supplementation without directly performing administration, and 7.0% only performed screening without subsequent prescription or administration of iron. HF specialists were more likely to prescribe and administer iron supplementation compared to other physicians (*Figure 3*).

Intravenous iron was preferred over oral iron for supplementation (86.3% vs. 13.7%). However, when oral iron was proposed, non-HF specialists were more likely to prescribe this compound (22.9% vs. 4.0%; $p < 0.001$). All in all, the drug of choice for the majority of physicians (82.8%) was intravenous ferric carboxymaltose (*Figure 4*).

After iron supplementation, most participants (67.6%) reported checking for ID at 3–6 months, while 23.8% did so as early as 1 month. Early 1-month checks were more frequent among non-HF specialists, while HF specialists generally performed re-testing after 3–6 months (*Figure 5*).

Most responding physicians (93.8%) perceived ID as an underestimated issue in the treatment of HF patients, and suggested that appropriate knowledge diffusion on how to screen and treat ID is needed.

Discussion

Our survey highlighted significant heterogeneity in clinical practice across different aspects of ID screening and supplementation. This discrepancy may be attributed to the recent recognition of ID as a key factor in HF patient management, underlining the importance of knowledge dissemination and dedicated education provided by scientific societies.

Of importance, most critical issues emerged in our survey seem to relate to whether screening for ID is routinely performed in HF patients, how iron supplementation is managed once ID is diagnosed, and the timing of ID re-testing.

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Table 1 Main characteristics of the participants in the IRON-HF survey ($n = 256$)

Variables	Value	Country of practice	Counts	% of total
Age, years, median (IQR)	38.0 (32.0–44.3)	Argentina	4	1.6%
		Australia	1	0.4%
		Austria	14	5.5%
		Azerbaijan	1	0.4%
Age classes, *n*, (%)		Belgium	8	3.1%
≤30 years	42 (16.4)	Brazil	1	0.4%
30–50 years	177 (69.1)	Bulgaria	1	0.4%
≥50 years	37 (14.5)	Colombia	1	0.4%
		Croatia	1	0.4%
		Cyprus	1	0.4%
Male sex, *n*, (%)	153 (59.8)	Czech Republic	2	0.8%
		France	53	20.7%
		Germany	4	1.6%
European, *n*, (%)	238 (93.0)	Greece	6	2.3%
		Hungary	1	0.4%
		Israel	2	0.8%
Physician role, *n*, (%)		Italy	112	43.8%
Cardiologist	199 (77.7)	Japan	2	0.8%
Cardiology fellow	57 (22.3)	Mexico	2	0.8%
		Moldova	1	0.4%
		Netherlands	6	2.4%
Subspecialty, *n*, (%)		Nigeria	1	0.4%
Cardiovascular Imaging	32 (12.5)	Poland	2	0.8%
General Cardiology	42 (16.4)	Portugal	3	1.2%
Heart Failure	125 (48.8)	Romania	1	0.4%
Intensive Care	21 (8.2)	Russia	1	0.4%
Interventional Cardiology/Electrophysiology	23 (9.0)	Serbia	4	1.6%
Pediatric Cardiology	2 (0.8)	Slovenia	1	0.4%
Other	11 (4.3)	Spain	4	1.6%
		Sweden	3	1.2%
		Switzerland	5	2.0%
Academic hospital	152 (59.4)	Tunisia	1	0.4%
Non-academic hospital	66 (25.8)	Turkey	2	0.8%
Private hospital	26 (10.2)	United Kingdom	3	1.2%
Private practice only	12 (4.7)	United States	1	0.4%

Categorical variables are expressed as *n*, (%), and continuous variables are expressed as median (interquartile range [IQR]).

The most recent ESC guidelines on HF treatment define ID as a serum ferritin level <100 ng/ml or a transferrin saturation (TSAT) <20% with a ferritin level of 100–299 ng/ml.[9,11] Although almost all participants in the survey aligned with this definition, recent data demonstrated a low predictive value for adverse clinical outcomes with this approach.[19] In the same population, definitions based on bone marrow biopsy comparisons appeared to be more strongly associated with adverse events, calling for further refinement of the ID diagnostic criteria. A recently proposed definition of ID in patients with chronic HF focuses on hypoferraemia alone, defined as TSAT <20%.[20,21] This proposal was driven by recent evidence that low TSAT, but not serum ferritin, predicts the effect of intravenous iron in reducing major adverse HF outcomes. Moreover, this attempt tried to address limitations of previous criteria by not differentiating between absolute (due to impaired iron intake and iron loss) and functional (due to inadequate iron supply despite normal body iron stores) ID, therefore simplifying the identification of patients with true ID, also considering that these conditions coexist in most cases.

Of note, more than half of participants to this survey affirmed to routinely screen their HF patients for ID. Real-world data from a large Swedish population, however, showed that ID screening remains underutilized, with less than 25% of HF patients being tested,[17] although a promising trend towards more frequent screening was noted.[17,22] Nonetheless, this discrepancy may be at least partly due to the selected audience answering to our survey.

Moreover, only half of clinicians reported playing an active role in all phases of screening, prescription and administration of iron compounds. A comprehensive patient management should be advisable, as different strategies may lead to discrepancies in terms of the pharmacological compounds used, management of side effects and re-screening modalities. In this context, while a

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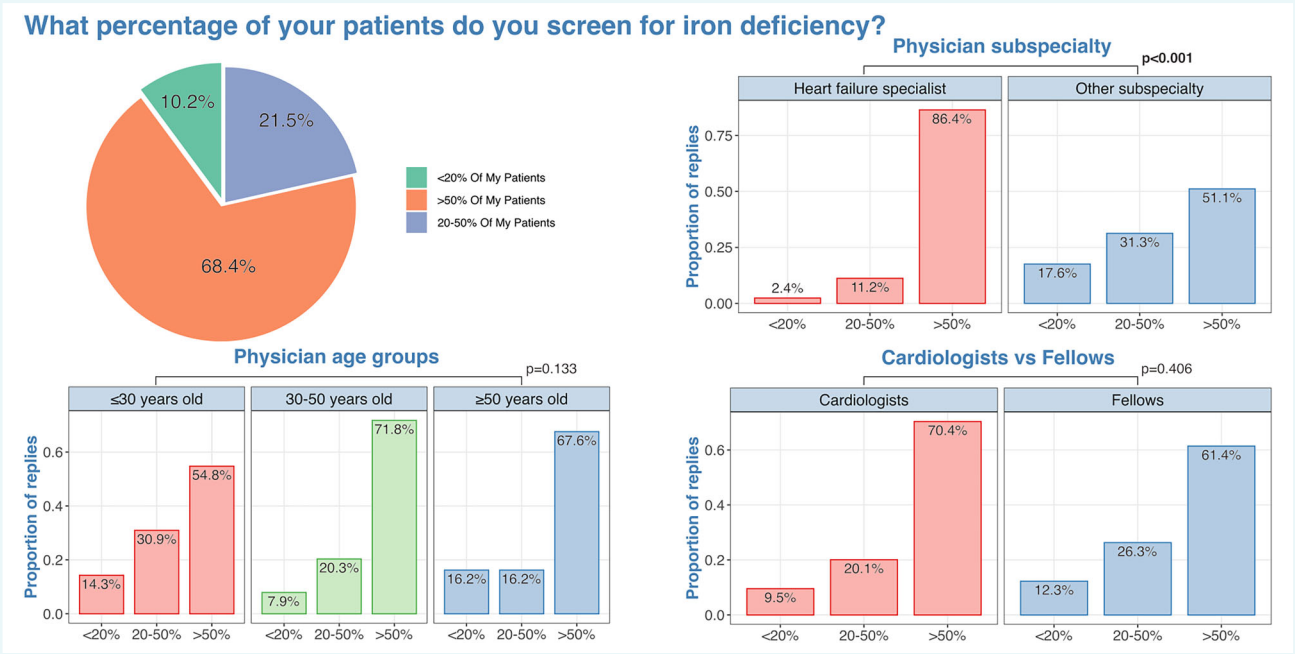

Figure 1 Distribution of the answers regarding the proportion of patients screened for iron deficiency in the entire population and in subgroup analyses.

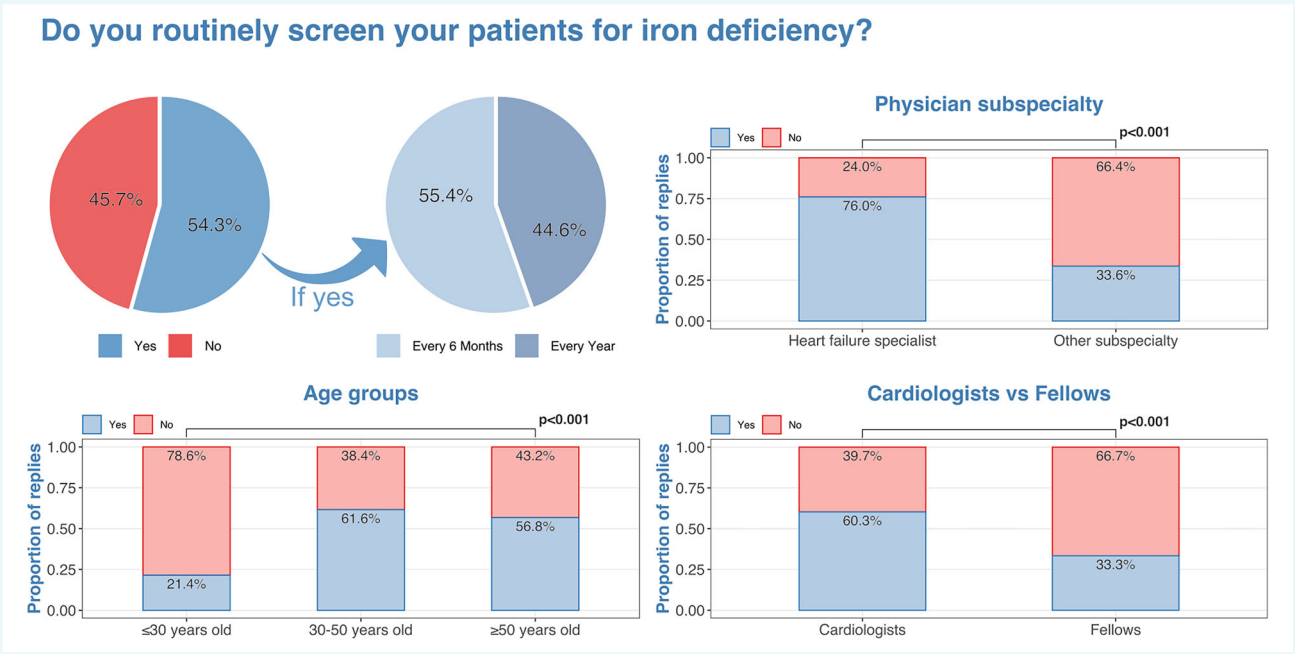

Figure 2 Distribution of replies regarding the percentage of physicians who perform periodic screening for iron deficiency, in the entire population and in subgroup analyses, along with the respondents' preferences for timing of screening.

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Table 2 **Main survey results according to subgroup analyses**

	Sex (%)			Physician subspecialty (%)			Career status (%)			Hospital setting (%)		
	M	**F**	***p*-value**	**HF specialist**	**Other**	***p*-value**	**Cardiologists**	**Fellows**	***p*-value**	**Academic**	**Non-academic**	***p*-value**
Iron deficiency screening			0.337			**<0.001**			0.406			**0.046**
<20% of my patients	7.8	13.6		2.4	17.6		9.5	12.3		6.6	15.4	
20–50% of my patients	21.6	21.4		11.2	31.3		20.1	26.3		24.3	17.3	
>50% of my patients	70.6	65.0		86.4	51.1		70.4	61.4		69.1	67.3	
Periodic screening			0.250			**<0.001**			**<0.001**			0.899
No	42.5	50.5		24.0	66.4		39.7	66.7		46.1	45.2	
Yes	57.5	49.5		76.0	33.6		60.3	33.3		53.9	54.8	
Supplementation role			0.443			**0.013**			0.867			0.436
Prescription only	44.4	36.9		41.6	41.2		40.7	43.9		38.2	46.2	
Prescription and administration	48.4	56.3		56.0	47.3		51.8	50.9		53.9	48.1	
No active role	7.2	6.8		2.4	11.5		7.5	5.2		7.9	5.8	
Preferred route of administration			0.194			**<0.001**			0.189			0.355
Intravenous iron	88.9	82.5		96.0	77.1		87.9	80.7		88.2	83.7	
Oral iron	11.1	17.5		4.0	22.9		12.1	19.3		11.8	16.3	
Assessment after supplementation			0.708			**0.008**			0.409			0.435
After 1 month	21.6	27.2		15.2	32.0		22.1	29.8		23.7	24.0	
After 3–6 months	68.6	66.0		75.2	60.3		68.9	63.2		67.8	67.3	
After 1 year	5.2	3.9		6.4	3.1		5.5	1.8		5.9	2.9	
No further checks	4.6	2.9		3.2	4.6		3.5	5.3		2.6	5.8	
Underestimated issue?			1000			**0.038**			0.760			0.443
Yes	93.5	94.2		96.9	90.4		94.0	93.0		94.7	92.3	
No	6.5	5.8		3.1	9.6		6.0	7.0		5.3	7.7	

HF, heart failure.
Bold indicates signifciant *p* values.

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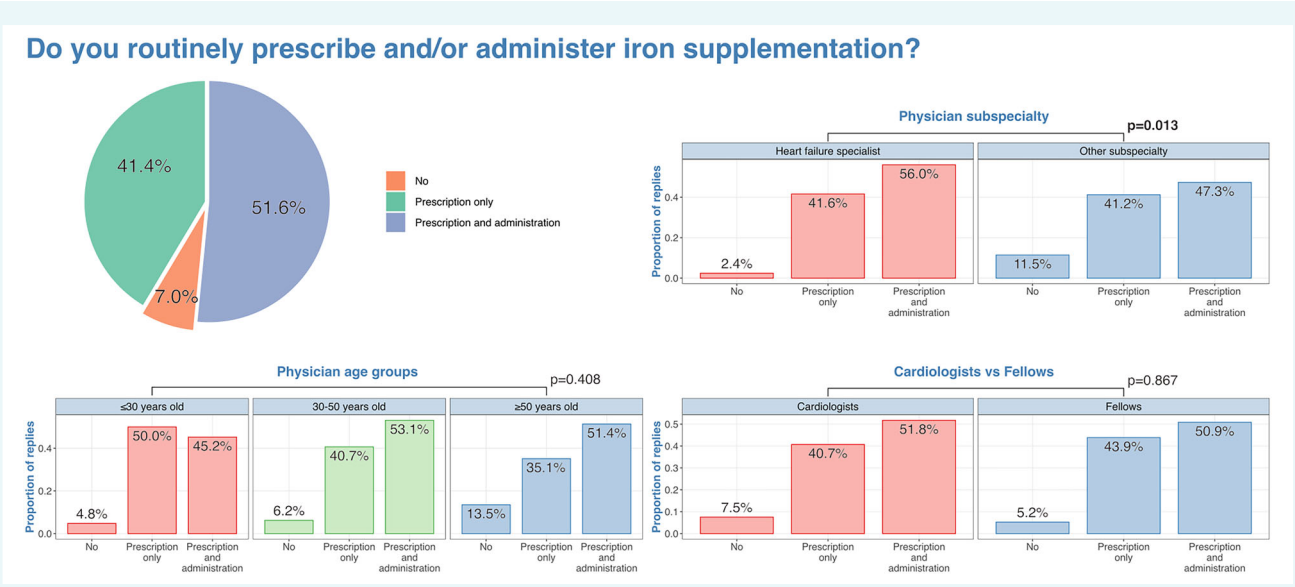

Figure 3 Distribution of replies regarding prescription and administration of iron supplements in patients diagnosed with iron deficiency, in the entire population and in subgroup analyses.

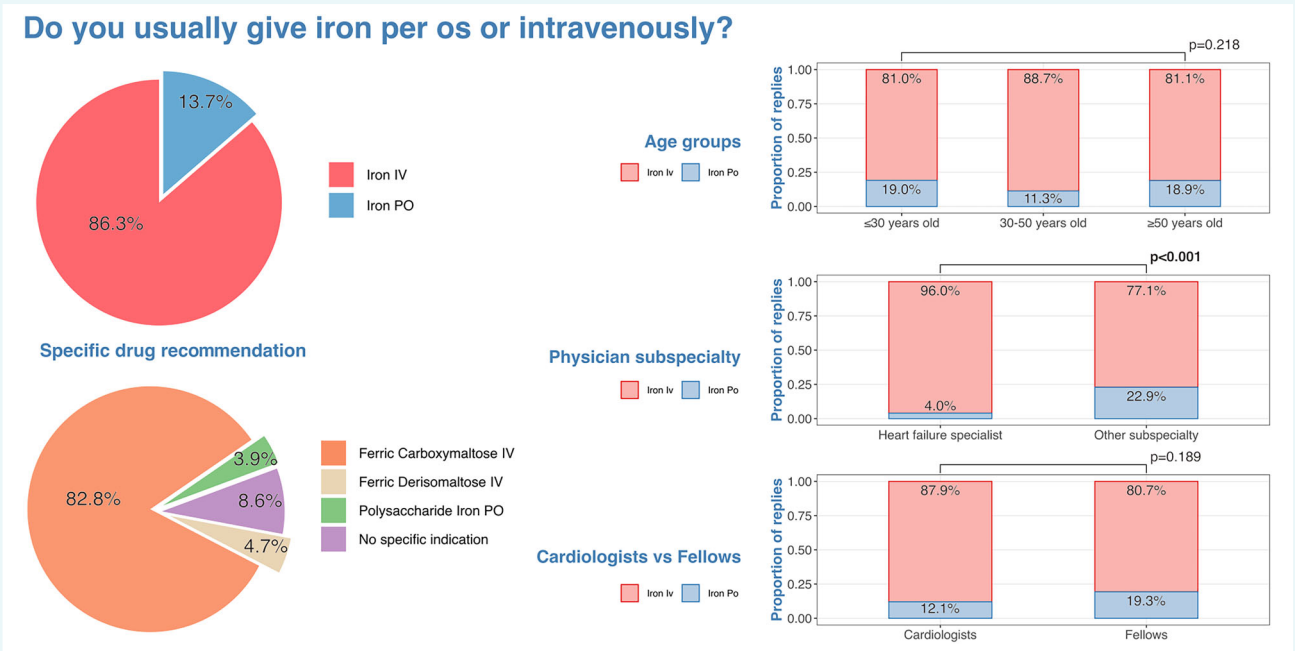

Figure 4 Distribution of replies regarding the preferred method of supplementation (oral [PO] vs. intravenous [IV]), in the entire population and in subgroup analyses, along with the respondents' preference for specific drug recommendations.

notable transition from oral to intravenous compound prescriptions has been observed in real-word practice following the publication of the 2021 HF guidelines,[16,22] our data highlight that a non-negligible proportion of physicians, primarily those without a HF specialization, still prescribe oral supplements to correct ID. Therefore, our results reinforce the critical value of specialized HF clinics and training programmes.[23]

Intravenous ferric carboxymaltose was the most frequently chosen compound among the respondents. This result may likely stem from the longer-track record of ferric carboxymaltose clinical trials published over the past decades, consistently highlighting a favourable risk–benefit profile.[1] However, ferric derisomaltose has recently shown similar efficacy and safety in the IRONMAN randomized study.[7] As a result, current guidelines equally

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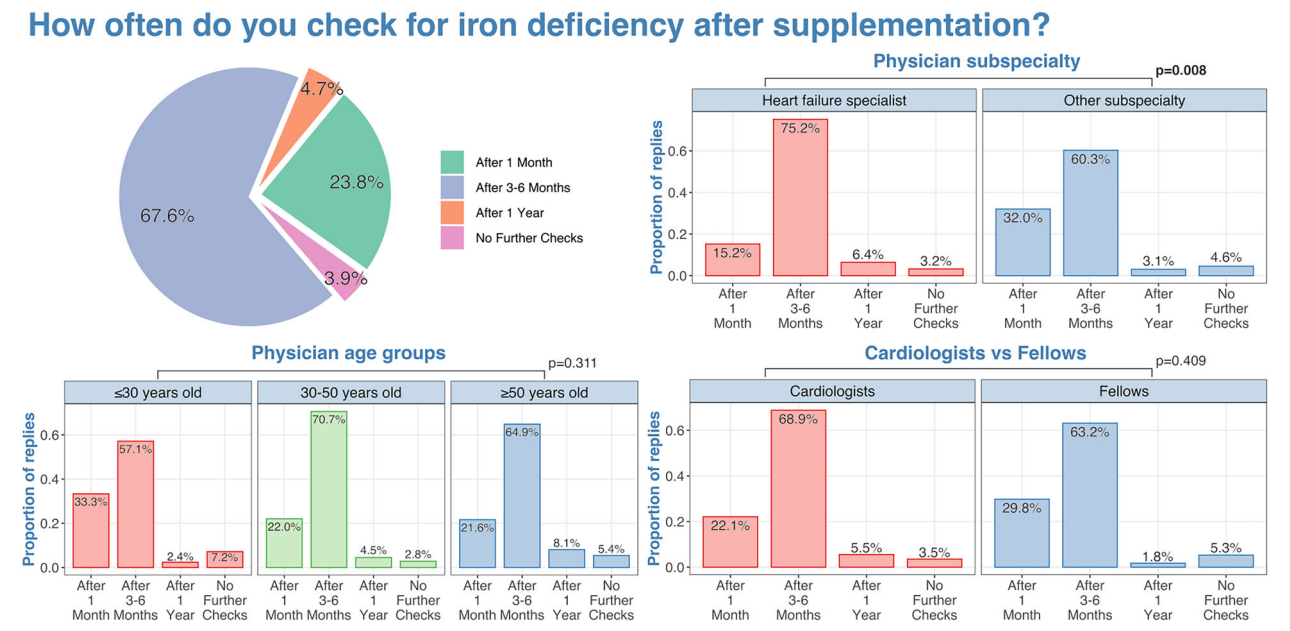

Figure 5 Distribution of replies regarding the preferred timing to check for iron deficiency after administration of iron supplements, in the entire population and in subgroup analyses.

recommend either preparation for intravenous iron supplementation.[11] It should be noted that this survey preceded the publication of the aforementioned guideline update and recommendations in this field may change in future.

A broad divergence across participants was observed in terms of the timing of repeated screening. These uncertainties may stem from limited existing data on ID natural progression and biomarker trajectories,[1] as well as from the lack of specific guideline recommendations regarding the frequency of ID screening in patients with chronic HF.[8–11] In a multicentre study enrolling 1563 patients with HF, 20% developed *de novo* ID within 6 months of observation, whereas in subjects with ID at baseline more than 50% had persistent ID.[24] These findings may suggest a pragmatic approach to check ID markers every 6 months, although dedicated studies are warranted.

Nearly 68% of physicians reported re-checking for ID 3–6 months after supplementation, whereas a considerable proportion preferred testing after only 1 month. Limited data on ID natural progression and biomarker trajectories exist.[1] For instance, in the AFFIRM-AHF trial,[6] ferritin levels increased by an average of ~20 ng/ml and TSAT by 5% after 6 weeks from baseline. The initial increase in ferritin levels may have overestimated long-term correction, reflecting a protective mechanism that leads to ferritin synthesis to mitigate the oxidative stress provided by cytosolic iron overload. After the initial steep raise, ferritin levels remained persistently high (albeit lower than the first weeks) at 6 months, with little change at 1 year.[6,21]

Our survey faces limitations. Despite the international nature of the survey, the majority of answers came from Europe, particularly Italy and France; therefore, results may not be generalizable to other countries in which practice and clinicians' attitudes may differ. Additionally, there is a potential for selection bias, as the respondents may disproportionately represent cardiologists with an interest in HF and/or who attended a master's degree in HF. Lastly, since the last update of ESC guidelines was released after the survey conclusion, we should acknowledge that clinical practice may have been modified so far, as well as answers given.

In conclusion, ID is an established treatment target in patients with HF. However, real-world implementation of evidence-based iron supplementation strategies is still affected by areas of uncertainty. Commitment by scientific societies to the diffusion of standardized screening and treatment protocols, as well as the development of comprehensive HF education programmes, are pivotal to bridge these gaps in care.

Supplementary Information

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

Conflict of interest: N.G. declares honoraria from AstraZeneca, Bayer, Boehringer, Lilly, Roche Diagnostics, and Novartis. A.J.F. declares fees from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Fresenius, Imedos Systems, Medtronic, MSD, Mundipharma, Novartis, Pierre Fabre, Pfizer, Roche, Schwabe Pharma, Vifor, and Zoll, as well as grant support by Novartis, AstraZeneca and Berlin Heart, unrelated to this article. G.S. reports grants and personal fees from Vifor, Boehringer Ingelheim, AstraZeneca, Servier, Novartis, Cytokinetics, PHARMACOSMOS, personal fees from Medtronic, TEVA, grants from Boston Scientific, Merck, Bayer. F.R. has not received personal payments by pharmaceutical companies or device manufacturers in the last 3 years (remuneration

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for the time spent in activities, such as participation as steering committee member of clinical trials and member of the Pfizer Research Award selection committee in Switzerland, were made directly to the University of Zurich). The Department of Cardiology (University Hospital of Zurich/University of Zurich) reports research, educational and/or travel grants from Abbott, Amgen, AstraZeneca, Bayer, Berlin Heart, B. Braun, Biosense Webster, Biosensors Europe AG, Biotronik, BMS, Boehringer Ingelheim, Boston Scientific, Bracco, Cardinal Health Switzerland, Corteria, Daiichi, Diatools AG, Edwards Lifesciences, Guidant Europe NV (BS), Hamilton Health Sciences, Kaneka Corporation, Kantar, Labormedizinisches Zentrum, Medtronic, MSD, Mundipharma Medical Company, Novartis, Novo Nordisk, Orion, Pfizer, Quintiles Switzerland Sarl, Roche Diagnostics, Sahajanand IN, Sanofi, Sarstedt AG, Servier, SIS Medical, SSS International Clinical Research, Terumo Deutschland, Trama Solutions, V- Wave, Vascular Medical, Vifor, Wissens Plus, ZOLL. All other authors have nothing to disclose.

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