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Iron and Heart Failure: Current Concepts and Emerging Pharmacological Paradigms

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Abstract

Background: Emerging evidence has recognized that anemia and iron deficiency are recurrent comorbidities in chronic heart failure (HF) and several trials have established that iron administration improves myocardial asset and clinical scenario in HF. **Purpose**: Recent acquisitions suggest that iron deficiency represents a concrete bias in the pathogenetic mechanism of chronic HF, so we have investigated the putative role of the hepcidin/ferroportin axis in the cardiovascular setting to advocate novel pharmacological and clinical approaches. **Methods**: Here, after an excursus on iron metabolism, we first reviewed the ongoing studies on novel iron targeted compounds. Then, we summarize large clinical interventional studies conducted on patient suffering from iron deficiency and HF which have tested the effects of drugging iron regard QoL, hospitalizations and cardiovascular death. **Results**: Novel compounds such as hepcidin agonist (PTG 300), synthetic human hepcidin (LJPC-401) and anti FPN (Vamifeport) are ongoing in iron overloaded patients, while the hepcidin blocker (PRS-080) is under investigation in anemic patients. Noteworthy, novel insights could arise from the results of a Phase IV interventional study regarding the modification of hepcidin pathway in a large cohort of HF patients (n = 1992) by sodium glucose cotransporter 2 inhibitors. To date, several studies highlight the beneficial effect of iron administration in cardiovascular setting and latest evidences consider hepcidin level as a novel biomarker of cardiac injury and atherosclerosis. **Conclusions**: We advocate that data from ongoing studies will suggest novel iron targeted

therapies for diagnosis, prognosis and therapy transferable in selected heart failed patients.

Keywords

Heart Failure, Iron, Anemia, Iron Deficiency, Hepcidin

1. Introduction

Plasma iron is carried in the erythrocytes (1 - 2 g) and circulates in the plasma (5 mg). Daily, 1 - 2 mg of iron is absorbed in the intestine, but the same amount is released by the exfoliation of the mucous membrane. The most significant amount of the iron (20 - 25 mg/day) derives by erythrophagocytosis from the discharge of iron deriving from senescent erythrocytes recycled by Kupffer cells and macrophages from the spleen [1] [2] [3] [4] [5].

After the reduction of ferric iron to ferrous iron by the duodenal cytochrome B reductase (DCYTB), non-heme iron is absorbed in the duodenum and jejunum, carried by the bivalent metal apical transporter 1 (DMT1) [6].

Once inside cells, iron is linked to chaperones like poly-(rC)-binding proteins delivering iron itself to ferritin that is the cellular iron store capable of keeping high amounts of iron atoms [1] [6] [7]. Alternatively, iron is exported to plasma from the ferroportin (FPN) by the basolateral membrane according to the needs [6].

Tissue and circulating iron levels are controlled by several genes such as Hamp, Emojuvelin (HJV) and HFE (**Table 1**) which are under post-transcriptional regulation according to the systemic iron levels [8].

During iron deficiency, the transcription of those gene messengers involved in iron absorption (TFR1 and FPN) is stimulated; on the other side, the transcription of those proteins involved in the iron storage (ferritin) is prevented [8].

The regulation between circulating and stored iron is due to the HAMP gene which encodes for Hepcidin [9] and to FPN1 gene (SLC40A1) which encodes for FPN [7] (**Table 1**).

Hepcidin is a peptide hormone playing a key role in iron homeostasis [9]-[14]. It is produced mostly by the liver and it is expressed in macrophages, gut, spleen and basically reduces iron cell uptake by inhibiting FPN, which is the main cell iron exporter [9]-[14].

Mostly, hepcidin level is influenced by two factors: iron level and inflammation [8] [10] [13]. The first acts principally by stimulating the bone morphogenetic proteins (BMPs 2 - 6) which activate iron pathways through SMAD proteins [15].

BMP6 level is strictly related to iron levels, while BMP2 is constitutively expressed allowing a basal hepcidin synthesis [15] [16] [17] [18].

BMP6 by binding its receptors BMPR1 and BMPR2 and its co-receptor hemojuvelin allows the activation of SMAD4 which translocates to the nucleus to

Table 1. Genes involved in iron metabolism.

GENE	*LOCATION*	PROTEIN	*PATHWAY*	*DISEASE*	*REF.*
HAMP	*19q13.12*	HEPCIDIN	*IT REDUCES IRON CELL UPTAKE BY INIBITING FERROPORTIN*	*HH type 2B*	[9] [11] [86] [87]
HFE2	*1q21.1*	EMOJUVELIN	*IT IS A POSITIVE MODULATOR OF HEPCIDIN VIA BMP2 - 4 SMAD PATWHAY*	HH type 2A, (JH)	[17] [88] [89]
HFE	6p22.2	HFE (Homeostatic iron regulator)	*IT ALLOWS THE UPTAKE OF TRANSFERRIN-BOUND IRON BY CELLS*	*HH*	[89] [90]
TFR2	*7q.22.1*	TRANSFERRIN RECEPTOR	*IT ALLOWS THE UPTAKE OF TRANSFERRIN-BOUND IRON BY CELLS*	*HH type 3*	[88] [89]
TF	*3q22.1*	TRANSFERRIN	*IT DELIVERS IRON TO CELLS BY BYNDING FE+++*	*ATRANSFERRINEMIA, CONGENITAL ATRANSFERRINEMIA*	[91]
CP	*3q24-q25.1*	CERULOPLASMINA (FERROXIDASE)	IT ALLOWS PEROXIDATION OF FE(II)TRANSFERRIN TO FE(III) BY BINDING TRANSFERRIN	*ACERULOPLASMINEMIA*	[26] [27] [92]
TMPRSS6	*22q12.3*	MATRIPTASE II	*IT IS A NEGATIVE EMOJUVELIN REGULATOR THROUGH THE CLEAVAGE OF CELL SURFACE EMOJUVELIN*	*IRIDA, MICROCYTIC ANEMIA*	[16] [19] [20] [21] [22]
SLC40A1	*2q32.2*	FERROPORTIN	IT MEDIATES IRON EFFLUX FROM CELLS INTO THE BLOOD	*HH type 1, HH type 4 IPERFERRITINEMIA*	[28] [29]

HH: Hereditary Hemocromatosis, JH: Juvenile Hemocromatosis; IRIDA; Iron Refractory Iron Deficiency Anemia.

bind specific sequences (BMP-responsive elements, BMP-REs) of the hepcidin promoter [13] [15] (**Table 1**).

On the contrary, during iron deficiency, BMP-mediated signal is suppressed by a specific hepatic inhibitor, matriptase 2 (TMPRSS6) (**Table 1**) [19] [20] [21] [22]. Matriptase II is mainly expressed in the liver and reduces BMP-mediated signal on hepcidin transcription by cleaving hemojuvelin (the BMP co-receptor protein) [21]. Mutations affecting matriptase II cause the lack of inhibition of hepcidin and the constitutive activation of hepcidin pathway, leading to a rare form of iron deficiency called "iron refractory deficiency anemia" (IRIDA) [22] [23] (**Table 1**).

Moreover, inflammation acts on hepcidin pathway mainly by lipopolysaccharides (LPS) and interleukin 6 (IL-6) (through the JAK/STAT pathway) which

prevent iron export by inhibiting FPN through its ubiquination and by its internalization in lysosomes [24]-[30].

The mutation of the FPN ubiquitination leads to a severe iron overload since mutant FPN types fail to be inhibited and they continue to export iron [27] [28] [29] [30] (**Table 1**).

These insights have suggested pharmacological strategies to manipulate iron pathways. In this regard some compounds are proven to prevent the hepcidin pathway due to inflammation, such as GDF 15, erythroferron and heparin [31]-[36].

Specifically, GDF15 has been recognized to be a strong hepcidin suppressor, reducing BMP /hepcidin pathways by inhibiting the release of IL-6 and IL-1 by macrophages [31] (**Table 2**).

Table 2. Main compounds involved in hepcidin pathway.

COMPOUND	MOLECULAR TARGET	PATHWAY	CONDITIONS	Ref
PR73 (only preclinical models) PTG300 (Rusfertide) LJPC-401	FPN	Hepcidin mimetics, ferroportin inhibitors	B-THALASSEMIA, HAEMOCHROMATOSIS	[93] [94] [95]
Anticalins PRS-080	Hepcidin	Hepcidin antagonist, ferroportin stimulation	HEALTHY VOLUNTEERS, CHRONIC KIDNEY DISEASE	[96]
Sodium-glucose cotransporter 2 inhibitors	Hepcidin, Erythropoietin	Reduction hepcidin pathway ferroportin stimulation	ANEMIA, IRIDA , HF	[97] [98] [99]
Tmprss6	Anti Matriptase-2 (antibody)	Increased emojuvelin pathway Increased hepcidin pathway	DISORDERS OF EYTHROPOIESIS AND IRON HOMEOSTASIS (IRON OVERLOAD AND DEFECTS)	[100] [101]
H5F9-AM8 (preclinical models)	Emojuvelin (antibody)	Reduced emojuvelin Pathway Reduction hepcidin pathway	IRON IN MOUSE LIVER AND TUMOR XENOGRAFTS	[102]
Anti BMP, Anti cytokines Interleukin (IL)-6 IL-1β, anti TGF 23	Cytokines	STAT 3- and SMAD/ hepcidin pathway inhibitors	ANEMIA OF INFLAMMATION	[103] [104] [105]
Vamifeport (VIT-2763)	FPN	ferroportin inibition	HEALTHY VOLUNTEERS	[106] [107]
GDF 15	Cytokines (IL6-1)	Reduction BMP/hepcidin pathway	IDA	[108]
SPIRONOLACTONE	Hepcidin	Suppression hepcidin expression	IDA	[109]
IMATINIB	Hepcidin	Suppression hepcidin expression	IDA	[109]
HEPARIN	Hepcidin/BMP	hepcidin antagonist	IDA	[110]
ERYTROFERRONE	BMP6 inibition	Reduction hepcidin pathway	IDA	[111]

IDA: Iron Deficiency Anemia; IRIDA: Iron Refractory Iron Deficiency Anemia; HF: Heart Failure.

Similarly, erythroferron inhibits the hepcidin pathway through the suppression of BMP/SMAD signal [32] [33] [34] (**Table 2**). Again, heparin has been recently shown to be a strong suppressor of hepcidin, by inhibiting BMP6/SMAD pathways due to blocking hepcidin receptor [35] [36] (**Table 2**).

Noteworthy, in preclinical models, rapamycin and tacrolimus inhibit hepcidin expression by binding the BMP type I receptor in hepatocytes [37].

To date, the main effort should be focused on recognizing novel compounds able to influence the major drivers involved in iron pathways such hepcidin, FPN, Matriptase2 and emojuvelin. In this regard, clinical trials are testing agonists and blockers for therapeutic use as shown in **Table 3**.

Table 3. Novel hepcidin/ferroportin axis targeted compounds: interventional ongoing studies.

TRIAL N.	STATUS	N. PATIENT	CONDITION	COMPOUND	FUNCTION	PHASE
NCT03395704	Completed	70	Haemocromatosis	LJPC-401	Synthetic human hepcidin	Phase II
NCT03381833	Terminated	84	Beta-Thalassemia	LJPC-401	Sintetic human hepcidin	Phase II
NCT04057040	Active not recruiting	80	Policitemia vera	PTG 300	Hepcidin mimetic	Phase II
NCT06033586	Not yet recruiting	50	Policitemia vera	PTG 300	Hepcidin mimetic	PhaseIII
NCT04767802	Active, not recruiting	20	Policitemia vera	PTG 300	Hepcidin mimetic	Phase II
NCT04054921	Completed	34	β-thalassemia Ineffective Erythropoiesis	PTG300	Hepcidin mimetic	Phase II
NCT05210790	Recruiting	250	Policitemia vera	PTG 300	Hepcidin mimetic	Phase III
NCT02340572	*Completed*	*48*	*Healthy*	PRS-080	Hepcidin blocker	Phase I
NCT03325621	*Completed*	*11*	*Anemia of Chronic Kidney Disease*	PRS-080	Hepcidin blocker	Phase I-II
NCT02754167	*Unknown*	*24*	*Anemia of Chronic Kidney Disease*	PRS-080	*Hepcidin blocker*	Phase I-II
NCT05499013	*Recruiting*	*65*	*Policitemia Vera*	*SLN124*	*Anti TMPRSS 6*	Phase I-II
NCT03165864	*Completed*	*36*	*Thalassemia*	*IONIS TMPRSS6-Lrx*	*Anti TMPRSS 6*	Phase I
NCT05077436	*Completed*	*28*	*Healthy*	*Vamifeport*	*AntiFPN*	Phase I
NCT04817670	*Recruiting*	*24*	*Sickle Cell Disease*	*Vamifeport* (*VIT 2763*)	*Anti FPN*	Phase II
NCT04364269	*Completed*	*25*	*Beta-Thalassemia*	*Vamifeport* (*VIT 2763*)	*Anti FPN*	Phase II
NCT04938635	*Withdrawn*	*0*	*Beta-Thalassemia*	*Vamifeport* (*VIT 2763*)	*AntiFPN*	Phase II
NCT04707261 (*ADIDAS*)	*Recruiting*	*1990*	*Anemia Heart Failure*	*Dapaglifozin*	*Reduction hepcidin pathwhay*	Phase IV

2. Iron and Cardiovascular Disease

Iron is a crucial element for hemoglobin synthesis and for heme and iron-sulfur (Fe/S) clusters production [1] [2]. It takes part in vital biological processes such as breathing, nucleic acid replication, repair, metabolic and host defense reactions [1] [2]. Thus, physiologically it is strictly controlled to avoid both deficiencies and overloads, being an example of balance between inputs and outputs [2] [3] [4]. However, despite its crucial role in many vital functions, it can result toxic if dysregulated [2] [3]. In this regard, recent acquisitions have shown that iron imbalance results critical in several heart conditions [38]-[81].

Physiologically, cardiac hepcidin values are lower than liver ones, but they increase during ischemia, hypoxia and inflammation, in response to the inflammatory trigger in the early phase of myocardial infarction (MI) according to IL-6 level, BMP6 level [41] and B-type natriuretic release [68]. The increased hepcidin circulating levels in MI were considered as a negative prognostic factor related to endothelial damage and plaque instability [82]. In this regard, a recent study considers the hormone hepcidin as a novel biomarker in HF, showing that circulating hepcidin levels fit with HF stage [69].

In HF patients, low hepcidin levels due to iron deficiency and low hepatocytes iron depots are predictors of mortality (AFFIRM -AHF trial) [66].

Some authors recognize that high levels of hepcidin in hemodialysed patients are considered a risk predictor for fatal and non-fatal cardiovascular events [47]. Manlov *et al.* observed a key role of iron in pathophysiology of atherosclerosis and cardiovascular disease in 63 hemodialysed patients showing that high hepcidin levels were related to plaque instability [47]. On the contrary, due to the lower hepcidin level, patients with hemochromatosis show a lower risk of atherosclerosis, despite the increased risk of iron related cardiomyopathy [48].

Again, authors show that high circulating hepcidin levels in Kawasaki patients are related to coronary atherosclerosis and lack of clinical response to therapy [49], while in Friedreich ataxia (FA) they are associated with heart dysfunction and cardiomyopathy due to the increased iron stored in mitochondria [70] [71].

Recently, increasing evidences have shown the occurrence of iron disorders such as anemia (Hb < 13 g/dl) and iron deficiency (ferritin < 100 ng/mL and transferrin saturation TSAT < 20%) in systolic HF patients [51]-[65]. These conditions affect about 50% of HF patients, increasing the risk of mortality by more than 40% [51]-[65].

HF is a chronic condition requiring lifestyle changes, an appropriate drug therapy and the possible associated use of cardiac resynchronization therapy [51]-[65].

Due to the heart's inability to pump blood effectively and to deliver oxygen to critical organs, such as kidney, brain and muscle, patients suffering from HF show several symptoms, such as dyspnea, cough, asthenia, edema and memory impairment [59] [60] [61] [65].

Patients who are asymptomatic or who respond to therapy have a long life expectancy before the decline of ventricular function, since compensation me-

chanisms maintain an adequate cardiac function [56] [57] [58].

Despite improvements in HF therapy, most patients still show progressive worsening of ventricular function with an increased risk of potentially fatal cardiac arrhythmias, showing high mortality rates.

In recent years, the management of anemia and iron deficiency are considered critical goals in patients suffering from HF [52] [54] [59] and several randomized controlled trials and meta-analyses have highlighted the beneficial effects of iron therapy in anemic HF patients, in terms of QoL and functional capacity, especially in systolic HF [59] (**Table 4**).

Despite the iron deficiency is still recognized to be a minor comorbidity in HF, the pathomechanism of this condition could be strictly influenced by anemia through two main mechanisms [53] [54] [55] [60] (**Figure 1**).

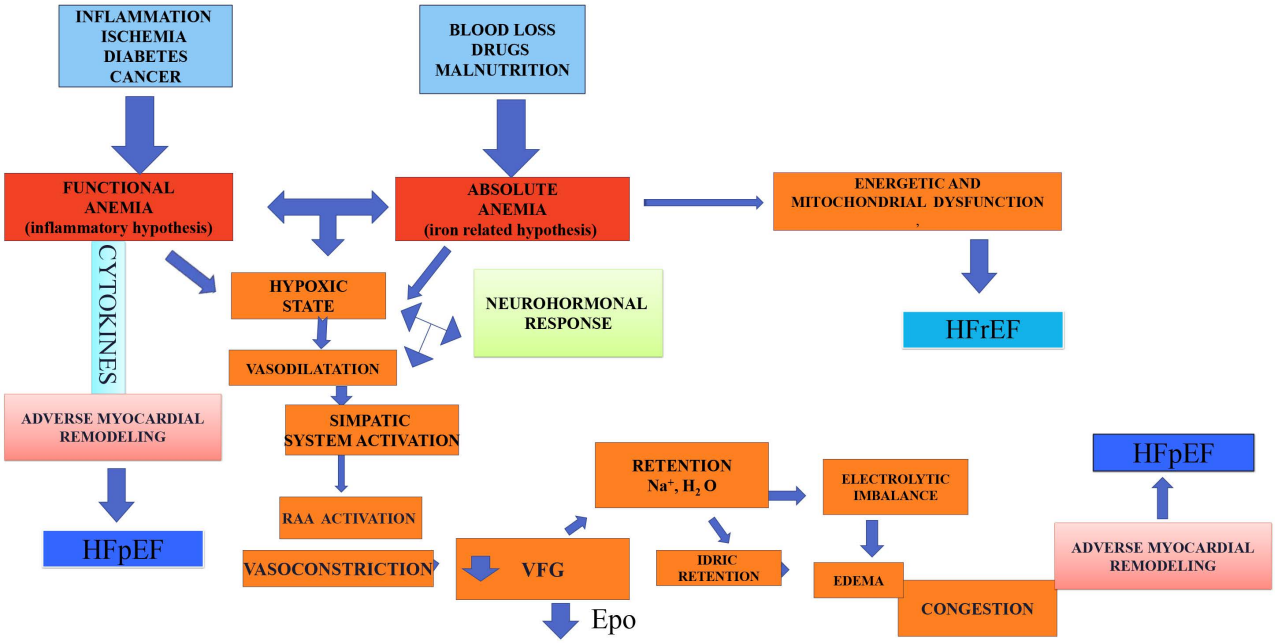

Figure 1. Putative pathomechanism of heart failure in anemic patients. Heart failure is a clinical syndrome characterized by typical signs and symptoms caused by any structural or functional cardiac disorder with reduced cardiac output (HFrEF) and/or elevated intracardiac pressures at rest or under stress (HFpEF). Anemia is involved in the pathomechanism of heart failure through two main mechanisms. According to the first hypothesis (iron-related), patients may present persistent absolute anemia due to blood loss, unbalanced diet, anticoagulant assumptions or malnutrition. Iron deficiency affects ATP production, leading by itself to cellular energetic and mitochondrial dysfunction with impairment of ventricular performance (HFrEF). On the other hand, the second "inflammatory" hypothesis asserts that cytokines, released as a result of pre-existing cardiac injury (myocarditis, ischemia, valvulopathy etc.) or other diseases (diabetes, cancer, obesity), leads to functional anemia (with iron sequestration and increased ferritinemia), by enhancing the hepcidin pathway. In addition cytokines itself induce fibrosis and adverse myocardial remodeling predisposing to HFpEF. Anemic state leads to a systemic hypoxic state which causes a neurohormonal response with peripheral vasodilation and systemic hypotension. This phenomenon produces the activation of the sympathetic system and the renin angiotensin aldosterone system (RAA) with vasoconstriction. This mechanism causes decreased blood flow to the peripheral organs and to the kidney with a decreased renal function, decreased glomerular filtration rate (VFG) and decreased Erythropoietin (Epo) release. The lower excretion of sodium (Na^+) and water produces peripheral edema, central and peripheral venous congestion thus stressing the cardiac cavities. Finally, detrimental heart remodelling due to the altered cardiac hemodynamics and pressure overload, leads to HFpEF. *HFrEF*: *heart failure with reduced ejection fraction*. *HFpEF*: *heart failure with preserved ejection fraction*. *RAA*: r*enin-angiotensin-aldosterone*.

Table 4. Iron administration in cardiovascular patients (n ≥ 50): interventional phased IV studies.

TRIAL NUMBER	STATUS	PATIENT	CONDITION	DRUG	DELIVERY ROUTE	END POINT
NCT 00520780 (FAIR-HF)	COMPLETED	456	HF, ID, IDA	FCM	i.v.	SELF-REPORTED PATIENT GLOBAL ASSESSMENT (PGA) AND NYHA FUNCTIONAL STATUS 24 WEEKS AFTER INITIATION OF THERAPY
NCT03036462	RECRUITING	1200	HF	FCM	i.v.	RECURRENT HF HOSPITALIZATIONS AND CARDIOVASCULAR DEATH (NUMBER OF EVENTS)
NCT02937454 (AFFIRM-HF STUDY)	COMPLETED	1132	HF	FCM	i.v.	HF HOSPITALIZATIONS AND CV DEATH.
NCT02642562 (IRONMAN)	COMPLETED	1160	HF, LVSD	FERRIC DERISOMALTOSE	i.v.	CV MORTALITY OR HOSPEDALIZATION FOR WORSENING HF
NCT03344523	UNKNOWN	600	HF	IRON PROTEIN SUCCINYLATE	oral	PERFORMANCE OF 6 MINUTE WALK DISTANCE
NCT05702970	NOT YET RECRUITING	258	HF	SUCROSOMIAL IRON, VIT D FCM	oral, i.v.	PERFORMANCE OF THE SIX-MINUTE WALKING TEST,
NCT01453608 (CONFIRM-HF)	COMPLETED	304	HF	FCM	i.v.	EXERCISE CAPACITY (CHANGE IN SIX MINUTE WALK TEST FROM BASELINE TO WEEK 24)
NCT05691257	NOT YET RECRUITING	300	HF, ANEMIA IN CHRONIC KIDNEY DISEASE	RECOMBINANT HUMAN EYTHROPOIETIN, FERROUS SUCCINATE, POLYSACCHARIDE IRON COMPLEX, IRON SUCROSE	oral, i.v.	CHANGE IN HEMOGLOBIN FROM BASELINE
NCT05793996	RECRUITING	100	HF	FCM	i.v.	QUALITY OF LIFE INDICATORS
NCT05759078	RECRUITING	2000	MI	FCM	i.v.	THE RISK OF CV DEATH, HF EVENTS

Continued

NCT04786769	NOT YET RECRUITING	2500	AS	FCM	i.v.	HOSPITAL ADMISSION OR CV DEATH IN TAVI OR SAVR PATIENTS
NCT05697211	RECRUITING	50	HF	FERRIC MALTOL	oral	THE SAFETY, TOLERABILITY AND EFFICACY OF ORAL FERRIC MALTOL
NCT04945707 (IRONMET-HFpEF)	RECRUITING	66	HF	FERRIC DERISOMALTOSE	i.v.	CHANGE IN PEAK OXYGEN UPTAKE FROM BASELINE TO WEEK 12
NCT03380520	COMPLETED	75	HF	FCM	i.v.	CHANGE IN LVEF FROM BASELINE
NCT03398681	*COMPLETED*	*53*	*HF*	*FCM*	*i.v.*	CHANGES IN MYOCARDIAL IRON CONTENT

In **Table 4** are illustrated interventional phased IV studies (enrolled patients n ≥ 50) which consider as primary endpoints the assessment of the clinical benefits concerning exercise capacity, QoL, recurrence of hospitalization and cardiovascular death during i.v. iron therapy (ferric carbossimaltose, derisomaltose) and/or oral iron therapy (sucrosomial) in patients with iron defects and several cardiovascular diseases (HF, MI and aortic stenosis). ID: IRON DEFICIENCY; IDA: IRON DEFICIENCY ANEMIA; MI: MYOCARDIAL INFARCTION; FCM: FERRICCARBOXYMALTOSE; AS: STENOSIS OF THE AORTA; LVSD: LEFT VENTRICULAR SYSTOLIC DYSFUNCTION; i.v.: intravenous.

Patients with HF may present pre-existing absolute anemia due to blood loss, unbalanced diet, use of anticoagulants or malnutrition [54]. Iron deficiency could affect myocardiocyte metabolism through the imbalance of the production of ATP, leading by itself to cell energetic and mitochondrial imbalance with impairment of ventricular performance and HF with reduced ejection fraction (HFrEF) [56] [62]. Indeed, according to the "iron hypothesis", iron deficiency can itself trigger HF leading to myocardial and mitochondria energetic failure in HFrEF [56] [61] [62] (**Figure 1**).

On the other hand, the second "inflammatory" hypothesis assumes that cytokines, released as a result of pre-existing cardiac injury (myocarditis, ischemia, valvulopathy, etc.) or other diseases (diabetes, cancer, obesity), could lead to a functional anemia (with iron sequestration and increased ferritinemia) by stimulating the hepcidin/ferroportin axis and by inducing a fibrotic and adverse myocardial remodeling which predisposes to HF with preserved ejection fraction (HFpEF) [63] [64] [65]. Recent evidences show that inflammatory cytokines could increase nitroxide levels which stimulate IREs and IRP1 that ultimately lead to upregulation of the Hamp gene traduction [8] [13] (**Table 1**). The consequent overload of the hepcidin level leads to the upregulation of ferritin leading to an iron cytotoxicity dose related due to NBTI (non-binding transferrin

iron) [72] [73] [74] [75]. NBTI is a free toxic species of iron which binds to low molecular weight compounds of hepatocytes, pancreatic cells and cardiomyocytes leading to liver fibrosis, chronic HF, diabetes, hypopituitarism and other severe complications [72] [73] [74] [75].

Moreover, the systemic anemic state sustains a hypoxic condition which triggers a neurohormonal reaction leading to a peripheral vasodilation and systemic hypotension. These phenomena produce the reactive activation of the sympathetic system and the renin angiotensin aldosterone system (RAA) with consequent vasoconstriction which causes decreased blood flow to the peripheral organs and to the kidney with a decreased renal function, decreased glomerular filtration rate (VFG) and decreased Erythropoietin (Epo) release. The consequent lower excretion of sodium and water produces peripheral edema, central and peripheral venous congestion thus stressing the cardiac cavities by producing an altered cardiac hemodynamics and pressure overload leading to a detrimental heart condition and to HFpEF (**Figure 1**).

3. Literature Search Strategy

We performed a computerized literature search on studies and trials by using the following search terms (also combining them): (anemia, iron, iron deficiency, hepcidin, hepcidin agonist, hepcidin blocker, emojuvelin, matriptase II, ferroportin, heart, heart disease).

This search was achieved in the following databases: PubMed and clinicaltrials.gov. We have selected clinical trials published in the last five years (2018-2023).

4. Discussion

Iron is crucial for several biologic functions [1]. Thus, the maintenance of the iron metabolism is strictly controlled at several levels by various genes and encoded proteins. The most important known genes involved in iron regulation, encode for key players of the hepcidin/ferroportin axis (**Table 1**). Mutations affecting these genes are involved in congenital or acquired iron disorders such as anemia or hemochromatosis (**Table 1**).

In **Table 2** are summarized synthetic and physiologic compounds involved in hepcidin/ferroportin axis modulation. Hepcidin activity is inhibited by several compounds, including GDF-15, heparin and erytroferrone which act through the inhibition of inflammation mediated by BMP and cytokines, as shown in **Table 2**. Most of these compounds are considered in patients suffered from IDA and anemia of inflammation (**Table 2**). Furthermore, preclinical studies have evaluated minihepcidins PR73 which are small peptides more effective than hepcidin to inhibit FPN (**Table 2**). Noteworthy, sodium glucose cotransporter 2 inhibitors largely used in HF patients are considered in patients with IRIDA (**Table 2**). In **Table 3**, we have reviewed interventional ongoing studies which have assessed safety profile and efficacy of hepcidin/ferroportin targeted compounds. As shown, most of them are phased I - II ongoing studies. The hepcidin

blocker PRS-080 is evaluated in anemic conditions, while hepcidin mimetic, FPN blockers and anti TMPRSS6 are tested in iron overload (Table 3). Specifically, PRS-80 is evaluated in 2 phased I - II ongoing studies conducted in healthy and anemic subjects.

To date, the hepcidin mimetic PTG 300 is tested in 5 phased II - III ongoing studies, while the synthetic human hepcidin LJPC-401 is evaluated in 2 phased II ongoing studies. Moreover, two anti TMPRSS6 molecules (SLN124 and IONIS TMPRSS6-Lrx) are under investigation in phased I - II ongoing studies which are conducted in iron overloaded patients. To date, Vamifeport (VIT 2763) is the only FPN blocker which is considered, and it is under investigation in 4 phased I - II studies.

As reported in Table 3, two clinical trials have enrolled healthy subjects (NCT-02340572-NCT05077436), N. 8 trials have enrolled anemic patients (NCT03388133-NCT04054921-NCT03325621-NCT02754167-NCT03165864-NCT04817670-NCT04364269-NCT04938635). N. 5 clinical trials are conducted on patients with iron overloaded diseases, such as hemochromatosis (NCT03395704) and polycythemia vera (NCT04057040-NCT04767802-NCT06033586-NCT05499013).

Noteworthy, a phased IV study (NCT04707261) on the reduction of the hepcidin pathway by Dapaglifozin has enrolled a large cohort of anemic HF patients (n = 1990).

Preliminary data, supported by clinical evidence, have proven that iron stabilization is effective in improving cardiac failure in patients with anemia and HF (Table 4).

Most of the reviewed interventional phased IV studies are conducted on intravenous (i.v.) iron (Table 4).

Iron administrated was largely ferrocarboxymaltose (FCM), but IRONMAN and IRONMET-HFpEF studies were conducted on ferric derisomaltose. Several clinical interventional phased IV studies conducted on large populations ($n \geq 50$) including FAIR-HF(NCT00520780) and CONFIRM-HF (NCT01453608) show that the administration of FCM i.v. improves QoL in patients with HF associated with iron deficiency (Table 4). Noteworthy AFFIRM-HF study proved that that FCM i.v. reduces the hospitalizations by 21% (NCT02937454) (Table 4). As reported in Tab.4, at least n.15 interventional phased IV studies (enrolled patients $n. > 50$) have assessed the clinical benefits concerning exercise capacity, QoL, recurrence of hospitalization and cardiovascular death after intravenous (i.v.) iron administration (ferric carbossimaltose, derisomaltose) or after oral iron administration (sucrosomial) in patients with iron defects and cardiovascular diseases (HF, MI and aortic stenosis).

As shown in Table 5, ongoing observational studies have recognized hepcidin level as a novel specific biomarker of iron deficiency (NCT02889133-NCT-02637102-NCT04986033-NCT004437866), iron overload (NCT00512564), iron loss (NCT00338234) and acute inflammatory state (NCT01589874) in several conditions.

Table 5. Hepcidin as a biomarker of iron imbalance: studies.

NCT Number	*State*	*Study Type*	*Conditions*	*Number Enrolled*	*Endpoint*
NCT00338234 (FAIRe)	Completed	Observational	ICU And Post-Operative Patients	153	Iron loss
NCT00437866	Completed	Observational	HF	100	Anemia
NCT04986033	Not Yet Recruiting	Observational	CAD	162	Perioperative anemia
NCT01589874	Unknown	Observational	Anemia of acute inflammation	100	Inflammation and anemia
NCT00512564	Completed	Observational	Sickle Cell Anemia/Sickle Cell Thalassemia	50	Iron overload
NCT02637102 (UK CAVIAR STUDY)	Completed	Observational	Patients Awaiting Vascular And Cardiac Surgery	425	Iron deficiency
NCT02889133	Active, Not Recruiting	Interventional	Blood Donors	85	Iron deficiency

ICU: Intensive Care Unit; CAD: Coronary Artery Disease.

5. Conclusions

Iron plays a crucial role in supporting main vital functions and the latest recommendations have recognized that iron check and iron correction are mandatory in patients with HF [71].

Iron sustains the myocardiocyte metabolism and several pieces of evidences report that iron defects are involved in pathomechanism of several cardiovascular diseases, including HF [61] [71] (**Figure 1**).

In the light of the main genes taking part in iron regulation (**Table 1**), we considered those compounds potentially involved in the modulation of hepcidin/ferroportin axis, which is the main pathway for iron signaling (**Table 2**). In our opinion, these hepcidin targeted compounds should be largely tested in cardiovascular patients. The major goal should be the improvement of iron levels in cardiomyocytes, inducing few changes in systemic iron levels.

The emerging evidence on synthetic hepcidin agonists, hepcidin blockers, anti FPN and anti TMPRSS6 are supplying new insight to modulate iron pathways in iron defected/overloaded patients [82]-[96] (**Table 2** and **Table 3**). To date, the hepcidin agonist PTG300 results in an advanced state of investigation (phased III ongoing studies NCT05210790) in a large cohort of patients suffering from policitemia vera.

Furthermore, sodium glucose co-transport2 (SGLT2) inhibitors have been proven to reduce the risk of cardiovascular death and hospitalization in HF patients with a beneficial effect on hemoglobin level by decreasing the hepcidin pathway [97] [98] [99]. Noteworthy, the hepcidin modulation capability by dapaglifozin is under investigation in ADIDAS study conducted on a large cohort

of anemic HF patients (NCT04707261) (Table 3).

HF has long been recognized as an irreversible disease but in recent years this concept has been revised and recent studies show that an early diagnosis associated with an appropriate therapy could improve the clinical scenario of HF [67]. Recent clinical trials (2018-2023) conducted in patient suffering from HF and iron deficiency have proved the beneficial clinical effects of drugging iron regard QoL, hospitalizations and cardiovascular death (Table 4).

Table 5 shows those studies which have evaluated hepcidin as a novel disease specific biomarker of iron imbalance. Actually, authors have proven that circulating hepcidin level could also improve diagnosis of cardiac damage and atherosclerosis achieving an enhanced classification and a more accurate stratification of HF patients effective in clinical practice [43] [47] [49].

In our opinion, the issue that iron deficiency in cardiovascular patients is underestimated and untreated, represents the major limitation of the reviewed literature. Consequently, novel hepcidin/ferroportin targeted compounds are not tested in cardiovascular patients (Table 3). In addition, the evidence of the critical role of iron administration in cardiovascular setting comes from few studies conducted in heterogeneous populations (Table 4).

We consider crucial to answer to this clinical gap. We advocate that results on novel compounds will provide new skills to modulate hepcidin/ferroportin axis by suggesting a personalized approach with translatable findings in the cardiovascular setting.

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Declarations

Ethics approval and consent to participate.

Consent for Publication

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Conflicts of Interest

The authors declare that they have no competing financial interests or personal relationships that could appear to have influence the content of this paper.

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