Role of Iron Deficiency in Heart Failure

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The association of chronic heart failure (CHF) and iron deficiency (ID) with or without anemia is frequently encountered in current medical practice and has a negative prognostic impact, worsening patients' exercise capacity and increasing hospitalization costs. Moreover, anemia is common in patients with chronic kidney disease (CKD) and CHF, an association known as cardio-renal anemia syndrome (CRAS) possessing a significantly increased risk of death.

: chronic heart failure | iron deficiency anemia | hemoglobin

1. Introduction

Tissue metabolism and many critical biochemical pathways involve the essential trace element *iron*. The primary consumer of iron is the erythroid bone marrow, which uses it to form new red blood cells. Iron is one of the key elements regarding oxygen homeostasis, including oxygen transport and storage processes [1][2].

Chronic heart failure (CHF) is a commonly encountered disease, with a prevalence of more than 64 million cases worldwide. Patients suffering from this affliction need continuous medical care, including frequent medical monitoring, hospitalizations, and extensive treatment.

CHF is frequently associated with iron deficiency (ID) with or without anemia, both entities representing negative independent predictors. Anemia and ID worsen therapeutical outcomes, increase the need for hospitalization, and decrease the overall quality of life in patients with CHF [3]. The contributions of anemia to heart failure, incompletely elucidated, are multiple and intricate. A series of etiopathogenic hypotheses have been described: iron deficiency, increased levels of AcSDKP (stem cell proliferation inhibitor), excessive secretion of cytokines, hemodilution, and cardiac cachexia.

Moreover, drugs commonly used in the management of CHF, such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, anticoagulants, and antiaggregants, pose a risk for anemia development through multiple mechanisms, including direct erythropoiesis inhibition, and gastrointestinal bleeding leading to absolute ID. This fact further underlines the link between anemia and CHF, and the strong likelihood of anemia onset in this group of vulnerable patients.

The association of chronic kidney disease (CKD)—incorporating a decrease in erythropoietin levels—with this condition is defined as cardio-renal anemia syndrome (CRAS). In this pathological entity, the failure of a single organ (heart or kidneys) determines the alteration of the function of the other. The overlap between physiopathological mechanisms creates a vicious cycle in which every dysfunction is perpetually amplified.

2. Iron Deficiency Anemia

Iron deficiency anemia (IDA) is characterized by decreased hemoglobin content in the red blood cells (RBCs) (hypochromia) and diminished mean corpuscular volume (MCV) (microcytosis), both abnormalities being caused by a decrease in iron levels [4].

ID is frequently encountered in medical practice. ID can be observed in any geographical area, affecting both genders and all age groups. However, some high-risk groups exist, such as young women, pregnant women, children during growth periods, and the elderly [5].

2.1. Physiology and Physiopathology

Iron is mainly present in nutrients, mainly in its ferric form (Fe^{3+}). It is reduced by gastric acid and intestinal ferric reductases (i.e., duodenal cytochrome B) to the ferrous form (Fe^{2+}). Divalent metal transporter 1 (DMT1) carries the Fe^{2+} ions inside the enterocyte through the cellular membrane. Inorganic iron absorption is facilitated by vitamin C (ascorbic acid), through the improvement of reduction processes, and the formation of soluble complexes. Organic iron is absorbed by the heme carrier protein 1 (HCP-1). Inside the cell, heme is degraded by heme oxygenase-1 (HO-1), releasing ferrous iron [5][6].

Iron can follow two paths inside the enterocyte: being exported into plasma or stored. Intracellular storage of iron uses the protein ferritin, while ferroportin (FPN) exports iron into circulation. The ferroxidase hephaestin converts ferrous iron into ferric iron, which is loaded onto transferrin—the leading plasmatic iron transporter. Besides supplying cells with iron, transferrin also limits toxic radical formation [6][7].

The are two main sub-types of ID: absolute and functional, leading to anemia. Absolute ID represents the depletion of iron stores and occurs in the presence of a decreased intake, impaired absorption, increased demand, or chronic hemorrhage. Functional ID refers to the impaired mobilization of stored iron, secondary to chronic inflammation and raised hepcidin levels, as observed in patients with cancer, obesity, inflammatory bowel disease, chronic kidney disease, and chronic heart failure. Another instance included in functional ID is the imbalance between iron supply and demand when erythropoiesis is accelerated because of elevated erythropoietin (EPO) levels (endogenous response to anemia) or treatment with erythropoiesis-stimulating agents [8].

2.2. Clinical and Biological Features of Iron Deficiency Anemia

Clinically, the evolution of ID can be divided into three distinct stages:

- Iron depletion without anemia, characterized by exhaustion of iron stores, preserved serum iron, and hemoglobin levels.
- Moderate normocytic normochromic anemia is preceded by lowering serum iron and increasing total iron-binding capacity (TIBC).
- Severe microcytic hypochromic anemia, accompanied by characteristic clinical and biological features, facilitates the diagnosis.

An accurate diagnosis of IDA is supported by information provided by history and physical examination, observation of signs and symptoms of IDA (e.g., fatigue, weakness, anorexia, chest pain, headache, pallor, brittle nails, tongue swelling, cold hands and feet, etc.), and laboratory tests.

2.3. Causes of Iron Deficiency

Iron deficiency's general causes are presented in **Table 1**.

Table 1. Possible causes for iron deficiency anemia NSAID, a nonsteroidal anti-inflammatory drug. CHF, chronic heart failure. CKD, chronic kidney disease.

Causes of Iron Deficiency Anemia	
1. Anemia due to martial deficiency	
(a) insufficient reserves:	prematurity, twinship, neonatal hemorrhages, maternal anemia
(b) insufficient food intake:	diet with excess flour, exclusive diet with goat's milk, protein and vitamin deficiencies, vegetarian diet
(c) deficient absorption:	presence of inhibitory factors (phytate, phosphates, carbonates), lack of reducing factors (vitamin C, hydrochloric acid, bile acids), celiac disease, gastrectomy, Helicobacter Pylori infection, intestinal resections, bacterial overgrowths
2. Iron-loss anemia	
(a) gastro-intestinal hemorrhages:	esophageal varices (liver cirrhosis), diaphragmatic hernia, esophagitis, gastro-duodenal ulcer, cancer of the digestive tract (esophageal, gastric, colonic cancer), tumors of the small intestine, Vaterian ampulloma, hemorrhoids, rectal polyps, intestinal parasites, celiac disease, Crohn's disease, ulcerative colitis, colonic angiodysplasia, bariatric surgery, NSAIDs consumption
(b) hemorrhages of respiratory origin:	epistaxis, pulmonary tuberculosis, lung cancer, bronchiectasis, pulmonary microinfarcts, alveolar hemorrhage

Causes of Iron Deficiency Anemia	
(c) genito-urinary hemorrhages:	prolonged menstrual cycle, metrorrhagia, renal tuberculosis, renovesical cancer, hemorrhagic nephritis, hemodialysis
(d) hemorrhagic diathesis:	alteration of the capillary wall, alteration of platelets, combined alterations
(f) hypersplenism:	
(g) genetic causes:	iron-refractory iron deficiency anemia
(h) mechanical fragmentation of RBCs:	prosthetic valves
(i) endocrine diseases:	hypothyroidism, pituitary insufficiency, autoimmune polyglandular syndromes
(j) autoimmune diseases:	scleroderma, rheumatoid arthritis, lupus
(k) drugs:	anticoagulants, antiaggregants, NSAIDs
(l) CHF, CKD.	

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3. Anemia and Iron Deficiency in Heart Failure

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3.1. Causes and Etiopathogenic Mechanisms of Iron Deficiency and Anemia in Chronic Heart Failure

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3.1.1. Absolute Iron Deficiency

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Absolute ID in CHF can result from a lack of appetite, poor nutrition, gastrointestinal decrease in iron absorption, and gastrointestinal blood loss due to the use of antiaggregant and anticoagulant medication [9][10].

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CHF can determine changes in the intestinal wall, including bowel edema and consecutive enterocyte dysfunction, followed by iron malabsorption. Therefore, myocardial dysfunction contributes directly to ID development and anemia [11].

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An important number of CHF cases present cardiovascular comorbidities requiring antiplatelet and anticoagulant therapy. These therapeutical agents can induce changes in the digestive mucosa, causing chronic blood loss (**Figure 1**) [12].

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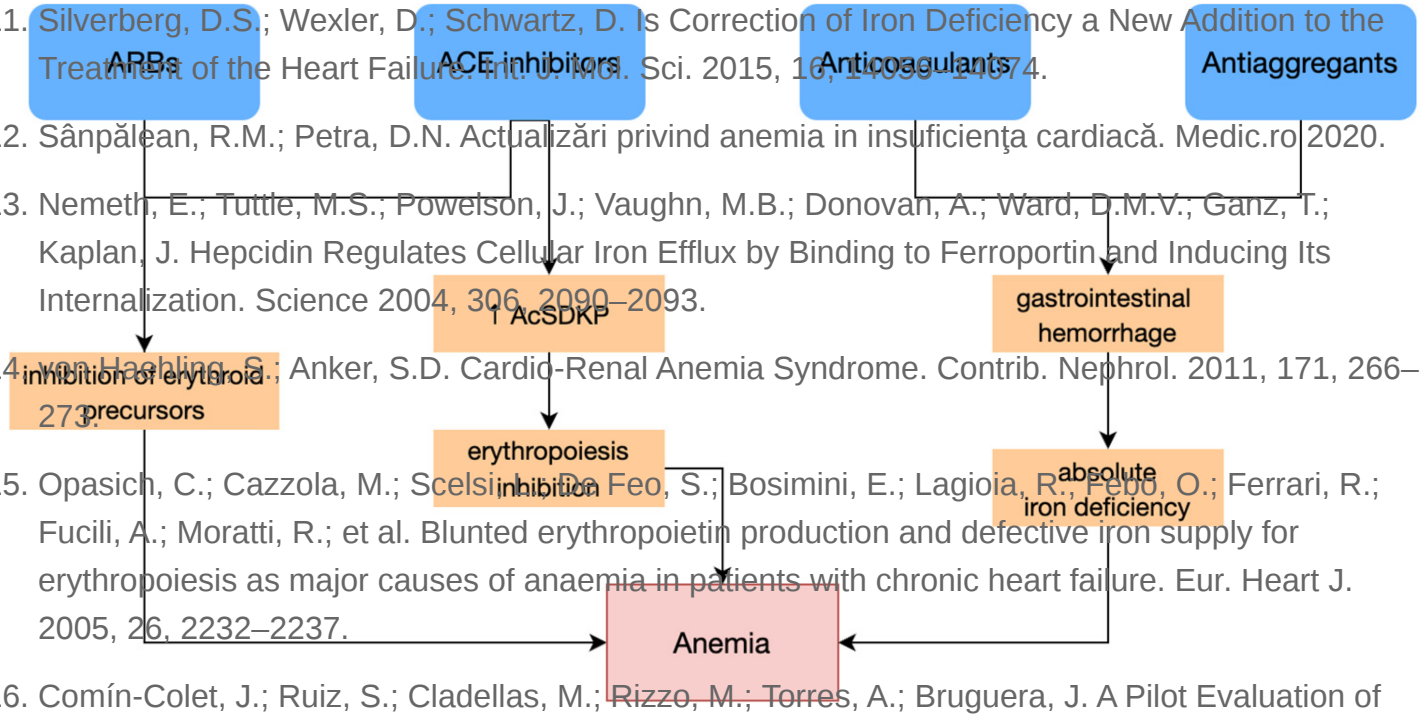

Figure 1. Therapeutical agents used in CHF management and their pathogenic mechanisms. ARB, angiotensin receptor blockers; ACE, angiotensin-converting enzyme; AcSDKP, N-Acetyl-Seryl-Aspartyl-Lysyl-Proline; ↑ = elevated value.

3.1.2. Functional Iron Deficiency

Heart failure has been associated with a systemic pro-inflammatory status that leads to functional ID. The pro-inflammatory group and the association of bacterial proliferation favor the sequestration of iron in stores by increasing the level of hepcidin, thus decreasing the iron availability for hematopoiesis [11][12][13] and chronic kidney disease are associated with poor outcomes in heart failure patients. BMC Nephrol. 2006, 7, 3.

3.1.3. Cardio-Renal Anemia Syndrome

Anemia is a common condition in both CHF and CKD. The three entities form a pathological triangle, potentiating the other entities and aggravating patient outcomes (**Figure 2**) [14].

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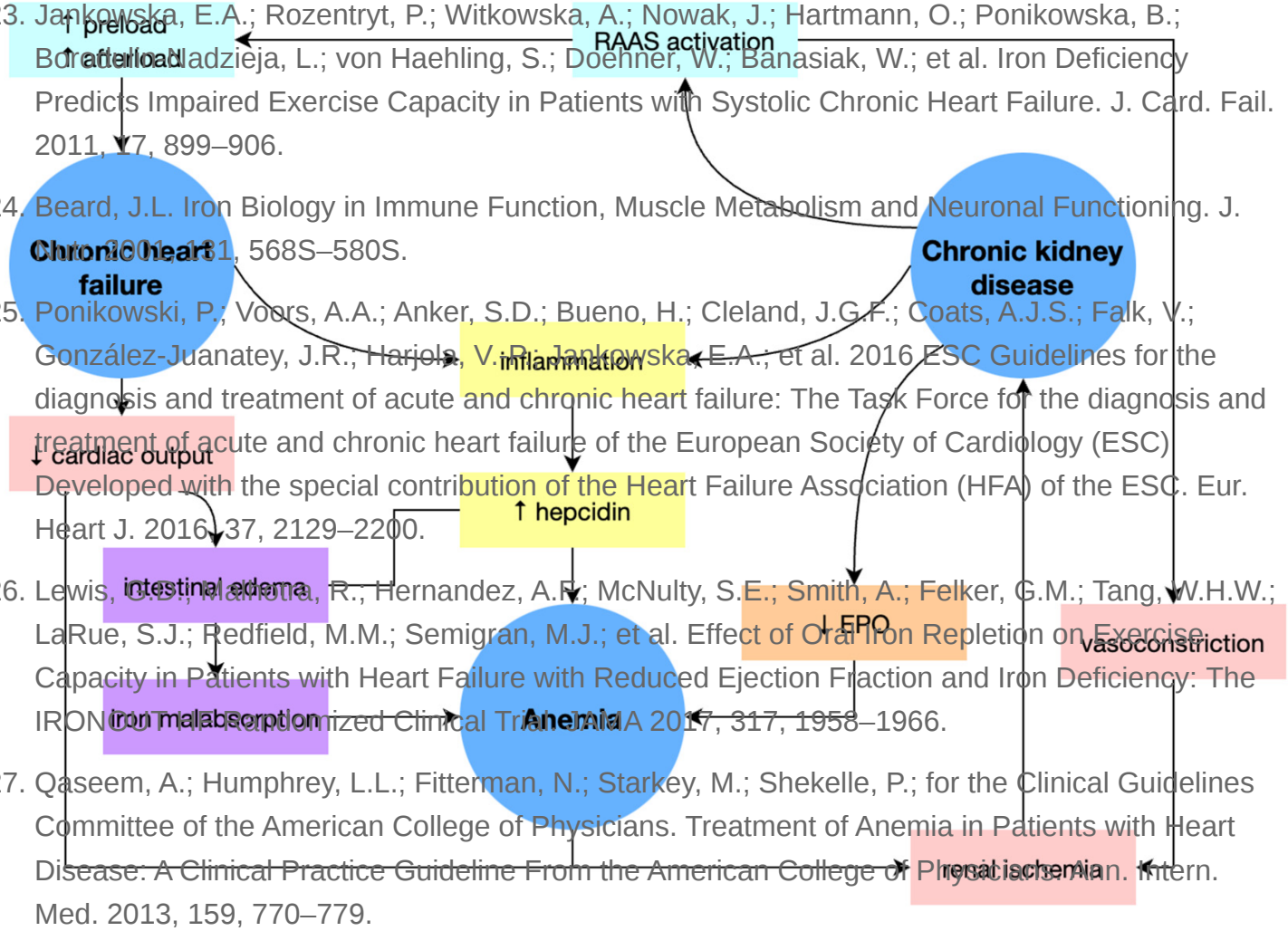

Figure 2. Physiopathology of cardio-renal anemia syndrome. EPO, erythropoietin; RAAS, renin-angiotensin-aldosterone system. ↑ = elevated value, ↓ = decreased value.

The renal synthesis of EPO is stimulated by tissue hypoxia. In CHF, plasma levels of EPO increase when the hemoglobin value decreases, but not proportionally. It has also been highlighted that the bone marrow develops a certain degree of resistance to the action of EPO. However, the most critical alteration in EPO's activity is CKD, an affliction frequently associated with CHF. Long-term renal ischemia and CKD directly reduce the secretion of EPO [15].

The decrease in serum levels of EPO in CHF is also correlated with the excessive secretion of cytokines (TNF alpha, IL6). These cytokines interfere with EPO's action, reducing iron availability by inhibiting absorption at the gastrointestinal level and blocking it in the reticuloendothelial system [16].

ACE inhibitors and angiotensin receptor blockers (ARBs), therapeutical agents often used in CHF treatment, inhibit erythroid precursors [17]. One of the ACEI mechanisms of action contributing to anemia is mediated by N-Acetyl-Seryl-Aspartyl-Lysyl-Proline (AcSDKP), a tetrapeptide with an antiproliferative effect that acts by inhibiting erythropoiesis. The action of the converting enzyme normally metabolizes AcSDKP. By using ACEIs, the enzyme is inhibited, thus increasing AcSDKP activity and inhibiting erythropoiesis.

Renal hypoperfusion caused by CHF determines kidney injury. Decreases in cardiac output, renal blood flow, efferent arteriole vasoconstriction, and neurohormonal activation are followed by changes in intrarenal circulation and increased sodium and water reabsorption. Central venous pressure and its expression in the renal veins lead to a decrease in the glomerular filtration rate, with consequent worsening of renal dysfunction. Increased levels of renin, angiotensin, and aldosterone cause damage directly to cardiac cells, thus exacerbating existing damage. Low renal blood flow also causes an increase in antidiuretic hormone secretion, exacerbating renal vasoconstriction and sodium and water retention [18].

3.2. Diagnosis of Iron Deficiency

There is a relatively high rate of underdiagnosis of ID because anemia is often not clinically evident. Furthermore, anemia may be completely absent, as it needs a specific time frame to develop after the appearance of ID.

Diagnostic criteria for ID in CHF patients, with or without anemia, refer to serum ferritin <100 µg/L, or ferritin between 100 µg/L and 299 µg/L, and transferrin saturation <20% [19].

3.3. Clinical Consequences of Iron Deficiency in Heart Failure

ID caused an increase in the length of hospitalization in patients with heart failure [20]. The association of ID with heart failure also determined a significant decrease in the health-related quality of life (HRQL), assessed by the Minnesota standardized questionnaire. A European multi-observational study of 1278 heart failure patients showed that iron deficiency affected the quality of life and human life, independent of anemia. In the study, 58% of patients were diagnosed with ID, and 35% had anemia. HRQL in patients with iron deficiency and anemia was lower than in those with heart failure but without iron deficiency or anemia [21].

ID also has a negative impact on exercise capacity in heart failure patients, based on the fact that non-hematopoietic tissues, including skeletal and cardiac muscle tissue, depend on the presence of iron as a critical element in the constitution of proteins involved in vital cellular processes, namely oxygen storage (a component of myoglobin) and oxidative energy metabolism methods (part of oxidative enzymes) [22][23][24].

3.4. Management of Iron Deficiency in Heart Failure

3.4.1. Intravenous Iron Supplementation Therapy

The 2016 European Society of Cardiology (ESC) guidelines for heart failure address the clear benefit of treating ID in patients with heart failure, where ID is defined as an essential entity independent of the presence of anemia [25].

Treatment options for correcting iron deficiency in the general population are intravenous (IV) or oral iron. In patients with heart failure with low ejection fraction (LVEF), however, the 2016 ESC guidelines specifically recommended that ID should be treated by prescribing iron compounds with parenteral administration, such as IV ferric carboxymaltose (**Figure 3**), as oral iron therapy is ineffective for replenishing iron stores (**Table 2**) [26].

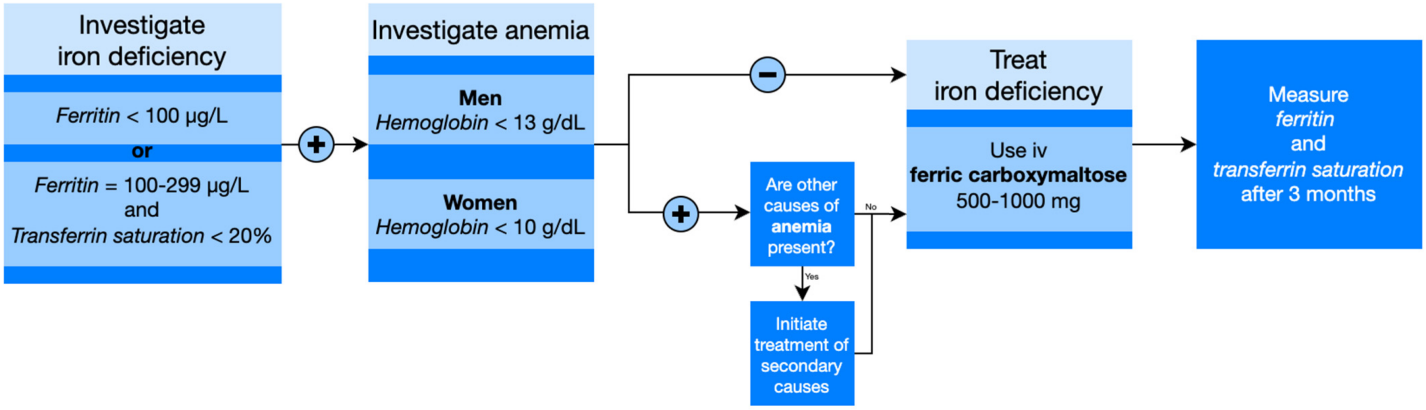

Figure 3. Therapeutical management of iron deficiency.

Table 2. Comparison of the efficacy and side effects of ferric carboxymaltose versus oral iron supplements.

Ferric Carboxymaltose	Parameter	Oral Iron Supplements
Significant	↑ Hemoglobin levels	Minimal
+	NYHA class improvement	−
+	HRQL improvement	−
+	↑ Exercise capacity	−
+/−	Gastro-intestinal adverse effects	+

HRQL, health-related quality of life. ↑ high value, + present, − absent.

3.4.2. Oral Iron Supplementation Therapy

Oral iron supplementation therapy offers some practical advantages, which are limited where absorption in the gastrointestinal tract is reduced. The IRONOUT-HF study concluded that there was a minimal increase in iron stores in CHF patients with reduced LVEF who followed oral iron therapy. Additionally, no improvement in exercise capacity was recorded [26]. Moreover, oral iron is poorly tolerated in patients with CHF, who may present digestive symptoms and gastrointestinal side effects in up to 60% of cases. Oral iron is less effective than IV iron, and a relatively long duration of oral iron therapy is always necessary (in some cases > 6 months) to refill iron stores, thus being a therapy often limited by gastrointestinal adverse effects [23].

3.4.3. Blood Transfusion

Red blood cell transfusion is recommended under careful monitoring in cases of severe anemia (hemoglobin value below 7 g/dL) [27]. The therapy must be strictly individualized considering the cost–benefit ratio because the procedure presents risks and possible immunological (hemolysis, hyperthermia, allergic reactions, purpura, etc.) and non-immunological (fluid overload, electrolyte disturbances, infections) complications.

3.4.4. Erythropoiesis-Stimulating Agents

The use of erythropoietin in treating moderate anemia associated with heart failure can beneficially affect cardiac function, improving both NYHA functional class and LVEF, decreasing atrial natriuretic peptide values, and improving kidney function. However, recombinant human erythropoietin is associated with unfavorable side effects: increased blood pressure due to increased hematocrit and micro vascularization damage, risk of deep vein thrombosis due to increased blood viscosity, and risk of aplastic anemia secondary to the production of anti-rHuEpo antibodies [28].

A human EPO analog, darbepoetin, may also be used, with proven clinical benefits such as exercise capacity and quality of life improvement. However, a randomized, double-blind trial conducted in 2008 (STAMINA-HeFT) claims that darbepoetin alfa treatment, administered subcutaneously every two weeks for 12 months, is well tolerated and increases hemoglobin, while associated morbidity and mortality are lowered [29].